ISSN 1591-223X
DOSSIER
199-2010

Agenzia sanitaria e sociale regionale

RegioneEmilia-Romagna

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

Innovative radiation treatment in cancer: IGRT/IMRT

Health Technology Assessment

ORIentamenti 2

Osservatorio regionale per l'innovazione

ISSN 1591-223X
DOSSIER
199-2010

Agenzia sanitaria e sociale regionale

RegioneEmiliaRomagna
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

Innovative radiation treatment in cancer: IGRT/IMRT

(Image Guided Radiation Therapy - Intensity Modulated Radiation Therapy)

Health Technology Assessment

ORIentamenti 2

Osservatorio regionale per l'innovazione

The report has been prepared by / Il rapporto è stato redatto da

Luciana Ballini	Agenzia sanitaria e sociale regionale dell'Emilia-Romagna
Filippo Cipriani	Agenzia sanitaria e sociale regionale dell'Emilia-Romagna
Gabriele Guidi	Azienda ospedaliero-universitaria di Modena
Tiziana Giovannini	Agenzia sanitaria e sociale regionale dell'Emilia-Romagna
Silvia Minozzi	Agenzia sanitaria e sociale regionale dell'Emilia-Romagna
Antonella Negro	Agenzia sanitaria e sociale regionale dell'Emilia-Romagna
Paolo Pertile	Dipartimento di Scienze economiche - Università degli studi di Verona
Giampiero Pirini	Assessorato alle politiche per la salute, Regione Emilia-Romagna
Elisa Stivanello	Agenzia sanitaria e sociale regionale dell'Emilia-Romagna
Rosanna Trisolini	Agenzia sanitaria e sociale regionale dell'Emilia-Romagna

The literature search was carried out by / La ricerca in lettaratura è stata effettuata da

Maria Camerlingo	Agenzia sanitaria e sociale regionale dell'Emilia-Romagna

This report has been peer-reviewed by / Il rapporto è stato revisionato da

Vincenzo Valentini	Policlinico universitario A. Gemelli - Roma, Italy
Maurizio Dondi	International Atomic Energy Agency - Vienna, Austria
Frank Hulstaert	Belgian Healthcare Knowledge Centre - KCE - Brussels, Belgium
David Jaffray	Ontario Cancer Institute, Princess Margaret Hospital Toronto, Canada
Craig Tim	Princess Margaret Hospital Toronto, Canada

The working group is very grateful to our peer-reviewers for their thoughtful and useful comments.

La collana Dossier è curata dal Sistema comunicazione, documentazione, formazione dell'Agenzia sanitaria e sociale regionale dell'Emilia-Romagna

responsabile Marco Biocca

redazione e impaginazione Federica Sarti

Stampa Regione Emilia-Romagna, Bologna, novembre 2010

Copia del volume può essere richiesta a

Federica Sarti - Agenzia sanitaria e sociale regionale dell'Emilia-Romagna - Sistema CDF
viale Aldo Moro 21 - 40127 Bologna
e-mail fsarti@regione.emilia-romagna.it

oppure può essere scaricata dal sito Internet

http://asr.regione.emilia-romagna.it/wcm/asr/collana_dossier/doss199.htm

Panel members list / Gruppo di lavoro

Luciana Ballini	Coordinator, Agenzia sanitaria e sociale regionale dell'Emilia-Romagna
Enza Barbieri	Radiotherapist, Azienda ospedaliero-universitaria di Bologna
Filippo Bertoni	Radiotherapist, Azienda ospedaliero-universitaria di Modena
Alba Brandes	Oncologist, Azienda USL di Bologna
Giancarlo Candini	Medical Physicist, Azienda ospedaliero-universitaria di Ferrara
Francesco Cartei	Radiotherapist, Azienda ospedaliero-universitaria di Ferrara
Filippo Cipriani	Health Economist, Agenzia sanitaria e sociale regionale dell'Emilia-Romagna
Ferdinando Cusmano	Radiologist, Azienda USL di Parma
Ermanno Emiliani	Radiotherapist, Azienda USL di Ravenna
Andrea Ferri	Medical Physicist, Azienda USL di Ravenna
Silvano Filice	Medical Physicist, Azienda ospedaliero-universitaria di Parma
Giovanni Piero Frezza	Radiotherapist, Azienda USL di Bologna
Marco Fumagalli	Radiotherapist, Azienda ospedaliero-universitaria di Parma
William Gaiba	Medical Physicist, Azienda ospedaliero-universitaria di Bologna
Gabriele Guidi	Medical Physicist, Azienda ospedaliero-universitaria di Modena
Bruno Iacopino	Radiotherapist, Azienda ospedaliero-universitaria di Bologna
Mauro Iori	Medical Physicist, Azienda ospedaliera di Reggio Emilia
Cinzia Iotti	Radiotherapist, Azienda ospedaliera di Reggio Emilia
Francesco Leonardi	Oncologist, Azienda ospedaliero-universitaria di Parma
Lucia Mancini	Medical Physicist, Azienda USL di Rimini
Giorgio Mazzi	Health Director, Azienda ospedaliera di Reggio Emilia
Carlo Milandri	Oncologist, IRST Meldola (FC)
Silvia Minozzi	Epidemiologist, Agenzia sanitaria e sociale regionale dell'Emilia-Romagna
Maria Morelli	Medical Physicist, Azienda USL di Ravenna
Antonella Negro	Health Statistician, Agenzia sanitaria e sociale regionale dell'Emilia-Romagna
Francesco Perini	Radiotherapist, Azienda USL di Rimini
Giampiero Pirini	Clinical Engineer, Assessorato alle politiche per la salute, Regione Emilia-Romagna
Rolando Polico	Radiotherapist, IRST Meldola (FC)
Ruggero Ruggieri	Medical Physicist, IRST Meldola (FC)
Elisa Stivanello	Epidemiologist, Agenzia sanitaria e sociale regionale dell'Emilia-Romagna
Pierenrico Sverzellati	Medical Physicist, Azienda USL di Piacenza
Rosanna Trisolini	Economist, Agenzia sanitaria e sociale regionale dell'Emilia-Romagna
Carlo Vanzo	Radiotherapist, Azienda USL di Piacenza
Annibale Versari	Nuclear Physician, Azienda ospedaliera di Reggio Emilia

Index

Glossary and acronyms

Acronym / Terminology	Description	Definition
3D-CRT	Three Dimensional Conformal Radio Therapy	Technique obtained with the use of an MLC to shape as much as possible the beam to the pattern of the area to be irradiated. This allows to orient a higher dose of radiation on the tumour. Surrounding healthy cells and adjacent structures are therefore exposed to lower doses, reducing the possibility of side effects.
CTV	Clinical Target Volume	It represents the tissue volume containing the GTV and/or the sub clinical disease. In the case of differential doses, there are so many different CTVs as the prescribed dose levels.
DMLC	Dynamic MLC	IMRT technique that uses special MLCs, allowing full intensity modulation during gantry rotation.
EPID	Electronic Portal Imaging Device	Electronic system for portal image acquisition.
FAD	Focal to axis distance	Distance of focal spot from the axis. Term equivalent to SAD.
Gantry		It houses the X-ray tube, detector system, collimators and rotational circuitry.
GTV	Gross Target Volume	Macroscopic extension of the tumour. It almost always corresponds to that part of the tumour whose cell density is higher. It can be classified into: GTV T (primary tumour), GTV N (lymph nodes), GTV M (metastasis).
Helical Tomotherapy		IMRT technique guided by tomographic images, developed for the first time at the University of Wisconsin (USA). Provides the combined use of a "Megavoltage" CT and a LINAC. The technique is realised through the simultaneous movement of the gantry and the couch (bed). It represents an evolution of SST - Sequential Segmented Tomotherapy.
Hyperfractionation		Method of radiation where the same total dose is delivered in the same timeframe, but employing a major number of fractions and a minor dose per fraction.
Hypofractionation		Dose delivered in a shorter time with fewer fractions and higher dose per fraction. The overall dose delivered is lower for a similar biological effect.

Acronym / Terminology	Description	Definition
IMRT	Intensity Modulated Radio Therapy	A type of 3-dimensional radiation therapy that uses computer-generated images to show the size and shape of the tumour. Thin rays (thin beam) of radiation of varying intensity are sent to the tumour from different angles. This type of radiation therapy reduces the damage to healthy tissue near the tumour. This technique adds also fluence rate modulation to a three-dimensional conformal radiation therapy, allowing the irradiation of concave forms of tumours. The technique is generally obtained through the use of a specific planning software indicated under the term "inverse planning".
LINAC	LINear ACcelerator	A medical device that uses electricity to form a beam of high-speed subatomic particles. This creates a high-energy radiation that can be used to treat cancer. Equivalent terms are: "Mega Voltage Linear Accelerator", "MeV Linear Accelerator".
MLC	Multileaf Collimator	A device with individual "leaves" made of high atomic number material (e.g. tungsten). It can be operated independently and is able to hinder the path of the particle beam generated by a LINAC. Patented for the first time in 1959 and then developed commercially in the 80s by Scanditronix.
MSF-MLC IMRT	Multiple Static Field MLC delivery IMRT	IMRT technique using an MLC, generating a multiple static field. It is similar to the "step-and-shoot" technique. Segmental IMRT is an equivalent term.
PTV	Planning Target Volume	A Planning Target Volume takes into account safety margins outside a CTV. The margins of safety are due to physiological movements (respiration, peristalsis, heart rate, etc.) and to the impossibility to perfectly reproduce the alignment and positioning of a patient in the same session or among different sessions.
R&V	Record and Verify	System for verification of a treatment plan.
SAD	Source to axis distance	Distance of the source from the axis. Term equivalent to FAD.
S-IMRT	Standard IMRT	IMRT technique used in conjunction with an MLC, employed with a relatively small number of gantry angles (about 7).
Single Arc IMRT		IMRT technique that delivers the entire dose within a single rotation of the gantry.
Step-and-shoot		IMRT technique obtained by dividing the area corresponding to a given position of the gantry in a series of small fields of irregular shape having different Monitor Units. The dose is released while the gantry is in a static position and after the leaves have been conformed.

Sommario

Trattamento radiologico innovativo per i tumori

IGRT / IMRT (Radioterapia guidata da immagini / Radioterapia con modulazione di intensità del fascio)

Quesito di politica sanitaria e obiettivo

Questo rapporto di *health technology assessment* è stato commissionato all'Agenzia sanitaria e sociale regionale dell'Emilia-Romagna con lo scopo di informare decisioni relative all'utilizzo clinico e alla diffusione dei nuovi sistemi di *Image Guided Radiation Therapy*[1] (tomoterapia e acceleratori con TC *Cone-Beam*) associati all'*Intensity Modulated Radiation Therapy*[2] (IGRT-IMRT).

Gli obiettivi del presente rapporto consistono nel valutare i benefici clinici potenziali, stabilire i criteri di appropriatezza d'uso, analizzare i risultati della ricerca clinica condotta sino ad oggi, valutare l'impatto economico e organizzativo della tecnologia e identificare le raccomandazioni per la ricerca clinica.

1. Introduzione

Fino alla fine degli anni '70, prima che la tomografia computerizzata (TC) si rendesse disponibile, risultava difficile delimitare chiaramente il tumore dai tessuti sani circostanti e la radioterapia comportava l'irradiazione del tumore e dei tessuti sani limitrofi alla più alta dose tollerabile. Grazie all'introduzione della TC, vi è stata una importante evoluzione nell'*imaging* e nella pianificazione del trattamento che comporta la delimitazione, sulle scansioni TC, dei tessuti bersaglio da irradiare e di quelli sani da salvaguardare. Un ulteriore sviluppo nella tecnologia di erogazione della dose, la *Intensity Modulated Radiotherapy* (IMRT), ha aggiunto la possibilità di variare l'intensità della dose all'interno dell'area bersaglio, consentendo una migliore conformazione oltre a un più ampio *range* di distribuzione di dose. La pianificazione IMRT permette un migliore rapporto rischio/beneficio tra il controllo del tumore e gli effetti collaterali indesiderati.

La possibilità di erogare dosi radianti alte ed efficaci, risparmiando gli organi critici adiacenti, ha aumentato la necessità di localizzare in modo più preciso il volume bersaglio e di operare il contornamento geometrico prima e durante l'irradiazione. Alcuni tumori e

[1] Radioterapia guidata da immagini.

[2] Radioterapia con modulazione di intensità del fascio.

organi a loro adiacenti, infatti, mostrano un considerevole grado di mobilità e le masse tumorali tendono a subire variazioni durante il corso del trattamento radioterapico. La tecnologia *Image Guided Radiation Therapy* (IGRT) rappresenta quindi una svolta importante. I dispositivi designati a tale scopo (ad esempio la tomoterapia e gli acceleratori con TC *Cone-Beam*) consentono di delineare il tumore, di apportare, prima e durante il trattamento, una correzione per eventuali errori di posizionamento del paziente e/o per l'erogazione del fascio radiante. La moderna radioterapia guidata da immagini potrebbe offrire i seguenti benefici tangibili:

- una maggiore precisione nell'irradiazione dei siti tumorali, con conseguente riduzione di irradiazione indesiderata ai tessuti sani adiacenti;
- una diminuzione dell'incidenza di effetti collaterali associati alla terapia radiante tradizionale;
- la possibilità di utilizzare dosaggi più alti con efficacia presumibilmente maggiore;
- l'estensione dell'utilizzo terapeutico a un maggior numero di tumori, possibilmente come trattamento radicale alternativo alla chirurgia.

2. Metodi e risultati

Definizione del problema e dei quesiti di ricerca

Un panel multidisciplinare di esperti regionali (comprendenti le discipline di radioterapia, fisica medica, oncologia, medicina nucleare, radiologia, statistica, economia, epidemiologia e metodologia di ricerca clinica) è stato riunito per stabilire le informazioni necessarie a determinare il ruolo clinico dell'IGRT/IMRT, per valutare criticamente i risultati disponibili dalla letteratura scientifica e lo stato delle conoscenze e per identificare le lacune della ricerca che sarebbe necessario colmare per informare le decisioni sull'adozione e la diffusione della tecnologia nella pratica clinica.

Per realizzare questi obiettivi il panel ha condiviso la seguente definizione del razionale clinico per l'IGRT/IMRT:

> *una migliore correzione degli errori di set up e di movimento degli organi, con conseguente* dose targeting *più accurato, può diminuire la tossicità e/o aumentare l'efficacia clinica dei trattamenti radioterapici con intento radicale su tumori situati in prossimità di organi vitali.*

Qualsiasi terapia conformazionale con sistema bi-dimensionale di acquisizione delle immagini è stata indicata come trattamento di confronto, o *comparator*.

Sulla base del razionale clinico sopra definito, che prende in considerazione solo i trattamenti radianti a scopo radicale di tumori in prossimità di organi vitali, il panel ha deciso di effettuare la valutazione del ruolo dell'IGRT/IMRT sui seguenti tumori: prostata, testa e collo, polmone, cervello e pancreas. L'elenco dei quesiti di ricerca è riportato in Tabella 1.

Tabella 1. Quesiti di ricerca

Sito tumorale	Quesiti di ricerca
Prostata	• In pazienti con tumore alla prostata a rischio basso o intermedio, il trattamento radioterapico IGRT/IMRT con intento radicale diminuisce la tossicità, se confrontato con la radioterapia conformazionale con acquisizione bi-dimensionale delle immagini? • In pazienti con tumore alla prostata a rischio basso o intermedio, il trattamento radioterapico IGRT/IMRT con intento radicale, somministrato con dosi più alte per frazione o ipofrazionato, diminuisce la tossicità e incrementa l'efficacia clinica, se confrontato con la radioterapia conformazionale con acquisizione bi-dimensionale delle immagini?
Polmone	• In pazienti con tumore polmonare inoperabile di stadio T1 T2 N0 MO, o in pazienti con tumore polmonare di stadio IIA, IIIA+B, o in pazienti con tumore polmonare metastatico (max 5 cm), il trattamento radioterapico radicale IGRT/IMRT con ipofrazionamento incrementa l'efficacia clinica senza aumentare la tossicità, se confrontato con la radioterapia conformazionale con acquisizione bi-dimensionale delle immagini?
Testa e collo	• In pazienti con qualsiasi tipo di tumore della testa e del collo, ad esclusione di quelli della laringe, il trattamento radioterapico IGRT/IMRT con intento radicale e con ipofrazionamento - esclusivo o associato alla chemioterapia - aumenta l'efficacia clinica e diminuisce la tossicità, se confrontato con la radioterapia conformazionale con acquisizione bi-dimensionale delle immagini?
Cervello	• In pazienti con tumore cerebrale primario, il trattamento radioterapico IGRT/IMRT con intento radicale e ipofrazionamento diminuisce la tossicità, se confrontato con la radioterapia conformazionale con acquisizione bi-dimensionale delle immagini? • In pazienti con tumore cerebrale metastatico, il trattamento radioterapico IGRT/IMRT con intento radicale e ipofrazionamento diminuisce la tossicità, se confrontato con la radioterapia conformazionale con acquisizione bi-dimensionale delle immagini?
Pancreas	• In pazienti con tumore pancreatico, il trattamento radioterapico pre-operatorio IGRT/IMRT aumenta l'efficacia clinica e diminuisce la tossicità, se confrontato con la radioterapia conformazionale con acquisizione bi-dimensionale delle immagini? • In pazienti con tumore pancreatico, il trattamento radioterapico post-operatorio IGRT/IMRT diminuisce la tossicità, se confrontato con la radioterapia conformazionale con acquisizione bi-dimensionale delle immagini? • In pazienti con tumore pancreatico inoperabile, il trattamento radioterapico IGRT/IMRT con ipofrazionamento aumenta l'efficacia clinica e diminuisce la tossicità, se confrontato con la radioterapia conformazionale con acquisizione bi-dimensionale delle immagini?

Da una rapida panoramica della letteratura pubblicata è emerso che lo stato delle conoscenze sviluppate finora è tutt'altro che robusto. Il gruppo di lavoro ha concordato di stabilire un criterio che potesse guidare la classificazione e l'interpretazione di evidenze deboli. Il principio adottato per differenziare i livelli di incertezza consiste nella probabilità che ulteriori studi di migliore qualità metodologica possano modificare i risultati. Utilizzando questo criterio è stato delineato un profilo di incertezza in grado di classificare i risultati in quattro categorie:

- **risultati stabili**: risultati che è improbabile possano essere modificati da studi successivi;
- **risultati plausibili**: risultati coerenti su stime di dimensione e di direzione dell'effetto, che probabilmente non cambierebbero significativamente se valutati mediante studi clinici randomizzati;
- **risultati incerti**: risultati su stime di dimensione e di direzione dell'effetto che molto probabilmente cambierebbero, se valutati mediante studi clinici randomizzati;
- **risultati ignoti**: assenza di risultati.

Lo scopo di questa mappatura delle evidenze basata sul livello di incertezza è stato quello di definire lo stato delle conoscenze sulla tecnologia e di comprendere quanto la ricerca attuale sia sufficiente o meno a rispondere ai quesiti clinicamente rilevanti. L'esito di questa valutazione consiste nel tracciare un percorso di ricerca e nel definire l'utilizzo sperimentale della tecnologia nell'ambito del Sistema sanitario**.**

Il panel ha definito il profilo delle evidenze della tecnologia; in esso vengono riportate tutte le dimensioni da valutare, gli esiti sulla base dei quali intraprendere la valutazione, e il tipo di studi inclusi (*Tabella 2*).

Tabella 2. Profilo dell'evidenza della tecnologia IGRT/IMRT e criteri di inclusione degli studi

Attributo	Esito	Studi inclusi
Performance tecnica	Errore di *set up* Movimento dell'organo	Revisione sistematica di RCT o CCT RCT CCT Serie di casi controllate Serie di casi non controllate Studi sulla pianificazione del trattamento
Fattibilità	Adesione dei pazienti Curva di apprendimento Costi	Revisione sistematica di RCT o CCT RCT CCT Serie di casi controllate Serie di casi non controllate
Sicurezza	Effetti avversi acuti / tossicità acuta Effetti avversi tardivi / tossicità tardiva	Revisione sistematica di RCT o CCT RCT CCT Serie di casi controllate Serie di casi non controllate
Efficacia clinica	Esiti surrogati Risposta tumorale Controllo locale Controllo loco-regionale Esiti secondari Sopravvivenza libera da malattia Sopravvivenza libera da progressione Qualità della vita	Revisione sistematica di RCT o CCT RCT CCT Serie di casi controllate
	Esiti primari Sopravvivenza malattia-specifica Sopravvivenza globale	Revisione sistematica di RCT o CCT RCT CCT

Revisione sistematica della letteratura

L'obiettivo principale della revisione è stato quello di valutare la *performance* tecnica e l'efficacia clinica della tecnologia IGRT/IMRT per i tumori del polmone, di testa e collo, del cervello, del pancreas e della prostata, che rappresentano le indicazioni cliniche concordate dal gruppo di lavoro.

La ricerca è stata condotta, senza limiti temporali di inizio e fino a gennaio 2009 - con un successivo aggiornamento a giugno 2010, sui principali siti *web* contenenti rapporti di *Health Technology Assessment* (HTA) e sulle banche dati *Medline* e *Cochrane Library* per gli studi primari e le revisioni sistematiche.

Per valutare la *performance* tecnica, sono state inclusi i rapporti di *Health Technology Assessment*, le revisioni sistematiche (SR), gli studi clinici randomizzati (RCT), gli studi clinici controllati (CCT), gli studi osservazionali controllati, le serie di casi controllate e non controllate, sui metodi IGRT/IMRT basati sulla ricostruzione volumetrica mediante TC 3D KV o MV, utilizzati in uno degli scenari clinici identificati e riportanti almeno uno dei seguenti esiti: gli errori di *set up* e il movimento dell'organo. Nessun limite relativo al numero di pazienti reclutato è stato applicato.

Per valutare l'efficacia clinica sono stati inclusi i rapporti di HTA, le SR, gli RCT, i CCT, gli studi osservazionali controllati, le serie di casi controllate e non controllate sui metodi IGRT/IMRT basati sulla ricostruzione volumetrica con TC 3D KV o MV, utilizzati in uno degli scenari clinici sopra menzionati e riportanti almeno uno dei seguenti esiti: sopravvivenza globale e sopravvivenza malattia-specifica, sopravvivenza libera da malattia e sopravvivenza libera da progressione, controllo locale e loco-regionale, tossicità acuta e tardiva. Sono stati esclusi gli studi con meno di 10 pazienti.

Le revisioni sistematiche e i rapporti di HTA sono stati valutati mediante i criteri della *checklist* AMSTAR (1); gli studi clinici controllati randomizzati sono stati valutati con i criteri raccomandati dalla *Cochrane Collaboration* (2); gli studi di coorte prospettici sono stati valutati con la scala *NewCastle-Ottawa* (3). Le serie di casi non sono state valutate in modo formale poiché non esistono criteri standardizzati e gli elementi presi in considerazione sono stati: la dimensione campionaria delle serie, se i pazienti erano stati reclutati in modo consecutivo (sì, no, non chiaro), se lo studio era prospettico, retrospettivo o se questo aspetto non risultava chiaro.

I dati di ciascuno studio sono riportati in tabelle delle evidenze (*Appendice 2*), mentre le sintesi dei risultati sono incluse nel corpo del documento.

La ricerca ha prodotto 989 citazioni, di cui 715 escluse in fase iniziale a causa di doppia pubblicazione (8), sulla base dei criteri di esclusione linguistica (9), e dei criteri di esclusione per il tema trattato e il tipo di studio (698). È stato esaminato il testo completo di 274 articoli, sono stati quindi esclusi 203 studi ulteriori (6 rapporti di HTA, 23 studi su esiti clinici e 166 studi sulla *performance* tecnica) poiché il tema trattato o la tipologia degli studi non corrispondeva ai criteri di inclusione predefiniti. Ulteriori 8 studi su esiti clinici sono stati eliminati poiché essi includevano meno di 10 pazienti. Il testo completo non era disponibile per ulteriori 16 articoli.

Sono stati inclusi 55 studi: 6 rapporti di HTA, 34 studi sulla *performance* tecnica e 15 studi sugli esiti clinici.

Prima della pubblicazione del rapporto è stato effettuato un aggiornamento della letteratura tramite una ricerca degli studi sull'efficacia clinica pubblicati tra gennaio 2009 e giugno 2010. A seguito di questo aggiornamento 11 ulteriori studi sono stati inclusi nella revisione sistematica: 6 sul tumore del polmone, 2 sul tumore alla prostata e 3 sul tumore del testa e collo.

Sintesi dei risultati

Tumore del polmone

Sono state incluse 6 serie di casi sulla tomoterapia e 7 sull'acceleratore CBCT, quasi tutti senza un confronto con trattamenti standard. Solamente uno studio, serie di casi controllata, ha confrontato la resezione chirugica con la *Stereotactic Body Radiation Therapy* (SBRT) in pazienti con T1-2NO NSCLC riportando differenze non statisticamente significative tra i due trattamenti. Gli studi forniscono solo informazioni preliminari e la qualità metodologica degli studi è bassa, con campioni piccoli e regimi di trattamento eterogenei. Studi di migliore qualità metodologica, come confronti randomizzati con trattamenti standard e *follow up* adeguati, sono necessari.

Non è possibile trarre conclusioni sulla tossicità, sul controllo tumorale, sulla sopravvivenza libera da recidiva e sulla sopravvivenza globale.

Tumore del cervello

Sono state incluse solo 2 serie di casi sulla tomoterapia senza confronto con il trattamento standard. Non sono stati rinvenuti studi sull'efficacia dell'acceleratore CBCT su esiti clinici. La qualità degli studi rinvenuti era bassa con campioni di piccole dimensioni e senza confronto tra tomoterapia e altre tecnologie. I regimi di trattamento erano eterogenei, le dosi e le frazioni variavano e l'intento era sia curativo che palliativo. Gli studi fornivano soltanto informazioni preliminari. Non è possibile trarre conclusioni né sulla sicurezza né sulla efficacia clinica del trattamento.

Tumori del testa e collo

Sono state incluse 4 serie di casi sulla tomoterapia. I pazienti inclusi sono eterogenei a differenti stadi della malattia e i campioni sono di piccole dimensioni. Si tratta di informazioni molto preliminari provenienti da prime esperienze di pochi centri e non è possibile trarre conclusioni sulla sicurezza ed efficacia di questa tecnologia. Sono necessari studi di migliore qualità metodologica come confronti randomizzati con trattamenti standard e *follow up* adeguati.

Tumore della prostata

Le evidenze sono limitate: sono state rinvenute soltanto serie di casi e i gruppi di confronto utilizzati nei 3 studi erano rappresentati da coorti storiche. Tutti gli studi, ad eccezione di uno, limitano la loro analisi ad esiti relativi alla sicurezza.

Gli studi forniscono soltanto informazioni preliminari e da essi non possono essere tratte conclusioni né sulla sicurezza, né tanto meno sull'efficacia di questa tecnologia. Non è possibile trarre conclusioni neppure su tossicità, controllo tumorale, sopravvivenza libera da recidiva e sopravvivenza globale.

Tumore del pancreas

Non sono stati rinvenuti studi sul tumore del pancreas.

Classificazione dell'incertezza e identificazione dei gap della ricerca

I risultati della revisione della letteratura sono stati riportati ai profili delle evidenze definiti per ciascun quesito e i risultati per ogni dimensione ed esito sono stati classificati in base al loro livello di incertezza.

La letteratura disponibile è stata giudicata sufficiente nel fornire informazioni sulla *performance* tecnica per tutti i quesiti di ricerca, ad eccezione di quelli riguardanti il tumore del pancreas, mentre l'informazione su sicurezza ed efficacia clinica è stata giudicata molto scarsa.

Sono state rinvenute:

- informazioni sulla sicurezza in pazienti con cancro alla prostata;
- alcune informazioni sulla sicurezza e pochissime informazioni sull'efficacia per l'utilizzo in pazienti affetti da cancro del polmone, della testa e collo e del cervello (tumore metastatico);
- nessuna informazione sull'utilizzo in pazienti con cancro pancreatico e tumori primari del cervello.

La quantità e qualità degli studi di ricerca esistenti sono state incluse tra i criteri applicati per la prioritizzazione dei quesiti per la futura ricerca clinica.

Analisi del contesto regionale e implicazioni organizzative

I volumi stimati per le 5 indicazioni cliniche che potrebbero potenzialmente beneficiare dell'utilizzo della tecnologia IGRT/IMRT (ottenuti da un *database* regionale in cui sono stati inseriti tutti i trattamenti radioterapici effettuati in un periodo di 2 mesi durante il 2004) risultano essere approssimativamente il 20% di tutti i trattamenti radioterapici erogati in un anno per le 5 tipologie di tumore. La proporzione di casi incidenti elegibili al trattamento IGRT/IMRT per le 5 tipologie di tumore è risultata essere: 23% per il tumore primario del cervello; 20% per il tumore del cervello metastatico; 24% per il tumore del testa e collo; 10% per il tumore primario del polmone; 21% per il tumore della prostata; 18% per il tumore del pancreas. Sulla base di queste stime è stata calcolata l'attività di un centro dotato di sistema IGRT/IMRT secondo la seguente ipotetica ripartizione: 45% dell'attività dedicata a pazienti con cancro della prostata, 19% a pazienti con cancro del polmone, 11% a pazienti con tumori del testa e collo, 6% a pazienti con tumore del cervello, primario o metastatico, 5% a pazienti con tumore del pancreas e il rimanente 9% a pazienti con altre indicazioni cliniche. Prendendo in considerazione soltanto i trattamenti con finalità radicale, il numero dei pazienti è stimato a 1 338 l'anno.

La distribuzione e le percentuali descritte sopra possono essere utilizzate dai singoli centri di radioterapia per valutare il loro utilizzo della tecnologia IGRT/IMRT e per stimare i volumi attesi di attività.

Sette degli 11 centri di radioterapia della regione Emilia-Romagna sono dotati di sistema IGRT/IMRT, per un totale di 8 apparecchiature, che è un numero adeguato per la stima attesa di pazienti candidati al trattamento, con una distribuzione geografica delle apparecchiature in grado di coprire la maggior parte del territorio regionale.

L'analisi del percorso dei pazienti che conduce alla radioterapia presenta una certa variabilità in funzione della presenza o meno di un approccio multidisciplinare alla valutazione e decisione terapeutica. Qualora ulteriori valutazioni della tecnologia IGRT/IMRT dovessero confermare le indicazioni cliniche di cui sopra, l'accesso al trattamento dovrebbe essere garantito a tutti i pazienti candidati al trattamento. Per via della variabilità dei percorsi, si raccomanda che i protocolli di riferimento siano concordati da tutti i centri di radioterapia dell'Emilia-Romagna con la responsabilità al radioterapista di porre l'indicazione al trattamento con IGRT/IMRT. Sarebbe opportuno istituire una lista unica di prenotazione per Area vasta per assicurare ai pazienti candidati al trattamento l'accesso al centro IGRT/IMRT più vicino entro un appropriato lasso di tempo. Diventa quindi necessaria una stretta collaborazione fra i centri in modo da assicurare al paziente una presa in carico da parte del centro IGRT/IMRT, che non disorienti i pazienti e non ne comprometta il rapporto con il centro di cura di riferimento. Tale stretta collaborazione, che sembra esistere da tempo fra i centri radioterapici della regione, garantirebbe anche tempi di attesa uniformi e appropriati per i pazienti provenienti da aree geografiche differenti e un supporto reciproco in caso di guasti di sistema o macchinari.

Per un presumibile futuro sviluppo di questa tecnologia, i centri che prendono in considerazione l'acquisizione dei sistemi IGRT/IMRT più innovativi dovrebbero avere presente il fatto che questi richiedono spazio dedicato, consistente in due stanze, una delle quali climatizzata, e che spesso è necessaria la costruzione di un *bunker* dedicato. Per quanto riguarda il personale, la tecnologia richiede un radioterapista, un fisico medico e un dosimetrista. Dovrebbe essere programmata anche l'implementazione di un programma di formazione dedicato, orientato soprattutto al fisico medico che dovrà diventare particolarmente esperto nelle tecniche di pianificazione inversa. Tale addestramento, che può essere offerto da qualsiasi centro IGRT/IMRT con esperienza, richiede un periodo di un mese a tempo pieno, mentre è necessario un periodo di 6 mesi per diventare formatore.

Implicazioni economiche e finanziarie

È stata condotta una valutazione delle principali implicazioni finanziarie ed economiche determinate dall'acquisizione e dalla successiva utilizzazione di un approccio *image-guided* in radioterapia, mediate le seguenti analisi:

- stime, basate su tariffe regionali correnti, di un aumento teorico della remunerazione e, di conseguenza, del carico finanziario per il Servizio sanitario regionale dell'Emilia-Romagna;

- applicazione del modello di analisi *Break Even* per stimare il numero minimo di pazienti che garantisca la copertura dei costi annui totali.

Stima della remunerazione per il trattamento

Attraverso il contributo di tutte le unità radioterapiche dell'Emilia-Romagna è stato mappato il percorso di trattamento radioterapico. L'analisi è stata limitata ai trattamenti con intento radicale, non tenendo conto di quelli palliativi. È stato definito uno scenario di riferimento e applicato al trattamento con radioterapia conformazionale 3D. La remunerazione per un trattamento completo è risultata essere di € 697,55 + (€ 113,60 * N), dove N rappresenta il numero di sedute richieste per raggiungere la dose totale di trattamento pianificata. Per stimare il rimborso per un trattamento IGRT/IMRT, lo stesso calcolo è stato applicato alle tecnologie IGRT/IMRT, risultando in € 922,55 + (€ 266 * N).

Dal calcolo della spesa incrementale determinata dalla tecnologia IGRT/IMRT rispetto alla radioterapia conformazionale 3D per ciascuna delle 5 tipologie di tumore è risultato un incremento che va da un massimo di € 5 559 (per un trattamento del tumore del testa e collo), a un minimo di € 4 340 (per un trattamento del tumore del pancreas).

Quindi, assumendo che 1 338 pazienti/anno vengano sottoposti a trattamento radicale con tecnologia IGRT/IMRT (702 per trattamento alla prostata, 168 a testa e collo, 294 a polmone, 78 a pancreas, 96 a cervello), la spesa aggiuntiva per il Sistema sanitario regionale sarebbe approssimativamente di 6,6 milioni di Euro.

Analisi Break Even

Il costo del capitale delle tecnologie in questione è stato definito sulla base dei listini-prezzo dell'anno 2008 e il costo dell'ammortamento annuale è stato stimato sotto l'assunto che un'apparecchiatura rimanga in uso per 8 anni, mentre i costi di *set up* e di formazione sono stati inclusi nel costo del capitale della tecnologia.

Grazie alla collaborazione di varie unità radioterapiche, è stata ottenuta una stima regionale del costo annuo di ciascun professionista coinvolto nella pianificazione/ erogazione del trattamento radioterapico.

L'analisi *break even* è stata applicata sia alla tomoterapia sia all'acceleratore con TC *Cone-Beam*, in quanto entrambi i sistemi IGRT/IMRT sono presenti in Emilia-Romagna, e ha dato come risultato 209 trattamenti l'anno per la tomo terapia e 150 trattamenti l'anno per il TC *Cone-Beam*. Avendo stimato un numero di pazienti elegibili di 1 560 l'anno, le 8 apparecchiature IGRT/IMRT presenti in regione potrebbero trattare circa 195 pazienti all'anno, cifra compatibile con entrambi i punti di *break even* e con la capacità produttiva dei sistemi.

Prioritizzazione dei quesiti di ricerca clinica

Uno degli scopi del gruppo di lavoro è stato quello di sviluppare le raccomandazioni di ricerca per una successiva valutazione del ruolo e dell'impatto clinico della tecnologia IGRT/IMRT.

La priorità dei temi di ricerca clinica è stata definita utilizzando un pecorso strutturato. I partecipanti sono stati coinvolti in procedimenti *Delphi* e RAND (modificati) e hanno ricevuto una scheda di votazione per ogni scenario clinico, contenente le seguenti informazioni:

- la popolazione beneficiaria stimata;
- la stima dei costi del trattamento;
- un elenco degli esiti clinici rilevanti (identificatii dal gruppo di lavoro);
- le stime di *performance* della terapia standard (conformazionale 3D) e di quella IGRT/IMRT (quando disponibile) per ogni esito clinico.

Ai partecipanti è stato chiesto di assegnare un voto per ciascun esito clinico, esprimendone la rilevanza in termini sia clinici che di ricerca. Ad essi è stato chiesto inoltre di dare un punteggio a ciascuna indicazione di ricerca, in riferimento alle seguenti dimensioni determinanti la priorità:

- gravità della patologia in termini di morbidità e mortalità;
- impatto della tecnologia sulla morbidità e mortalità della patologia;
- fattibilità di uno studio clinico.

In ultima battuta ai partecipanti è stato chiesto di dare un punteggio alla priorità globale di ogni quesito di ricerca clinica.

Il processo strutturato ha dato come risultato la seguente graduatoria dei temi di ricerca:

1. trattamento radioterapico con intento radicale in pazienti con tumore alla prostata a rischio basso o intermedio;
2. trattamento radioterapico con intento radicale in pazienti con tumore del polmone inoperabile di stadio T1-T2, III A e B;
3. trattamento radioterapico per i tumori di testa e collo, esclusivi o associati alla chemioterapia;
4. trattamento radioterapico delle metastasi del polmone;
5. trattamento radioterapico del cancro del pancreas in stadio avanzato;
6. trattamento radioterapico delle metastasi del cervello;
7. trattamento radioterapico pre-operatorio del tumore del pancreas;
8. trattamento radioterapico post-operatorio del tumore del pancreas;
9. trattamento radioterapico del tumore primario del cervello.

Tenendo in considerazione la quantità e qualità degli studi di ricerca clinica pubblicati a oggi, il panel ha concordato che la futura ricerca sulla tecnologia IGRT/IMRT non dovrebbe limitarsi a valutarne l'impatto su effetti avversi e tossicità, ma che la tecnologia è sufficientemente matura per essere sottoposta a una valutazione di efficacia clinica su esiti di lungo termine. Il gruppo di lavoro ha quindi raccomandato che il ruolo della tecnologia IGRT/IMRT in trattamenti con *dose escalation* e/o ipofrazionamento sia valutato attraverso studi clinici controllati randomizzati.

Conclusioni

Obiettivi principali di questo rapporto sono stati:

- valutare i benefici clinici potenziali della *Image Guided Radiotherapy* with *Intensity Modulated Radiation Therapy* (IGRT/IMRT);
- identificare le indicazioni cliniche per le quali questa tecnologia appare particolarmente promettente;
- delineare un futuro programma di valutazione idoneo a fornire risultati clinici robusti.

La *Image Guided Radiotherapy* rappresenta una reale svolta nel trattamento radioterapico per via della sua capacità di delineare i contorni tumorali, di introdurre correzioni nel posizionamento del paziente e nell'erogazione dell'irradiazione prima e durante il trattamento. Pertanto i potenziali e tangibili benefici della moderna tecnologia IGRT/IMRT sono:

- una maggiore precisione nell'irradiamento dei siti tumorali con conseguente riduzione di irradiazione indesiderata ai tessuti sani adiacenti;
- una diminuzione dell'incidenza di effetti collaterali associati alla terapia radiante tradizionale;
- la possibilità di utilizzare dosaggi più alti con efficacia presumibilmente maggiore;
- l'estensione dell'utilizzo terapeutico a un maggior numero di tumori, anche in alternativa alla chirurgia.

Nonostante questo promettente razionale teorico, mancano ad oggi robuste evidenze cliniche a sostegno dei benefici ipotizzati. Per l'utilizzo della IGRT/IMRT nei 5 tumori selezionati dal panel - polmone, testa e collo, prostata, cervello e pancreas - vi sono sufficienti evidenze sulla *performance* tecnica, pochi dati sulla sicurezza, pochissime informazioni sull'efficacia clinica e nessun dato sulla costo-efficacia.

Il gruppo di lavoro ha definito la ricerca clinica necessaria a ridurre l'incertezza sull'efficacia clinica della IGRT/IMRT e, attraverso un processo strutturato di prioritarizzazione dei quesiti di ricerca, ha individuato i tre quesiti più importanti che costituiscono le raccomandazioni per la ricerca.

RACCOMANDAZIONI PER LA RICERCA

1. Valutare se il trattamento radioterapico IGRT/IMRT con intento radicale, con dose biologica più alta, in regime di ipofrazionamento, in pazienti con tumore alla prostata a rischio basso o intermedio, migliori la ricaduta biochimica e la sopravvivenza libera da malattia senza che risulti aumentata la tossicità, quando confrontato con il trattamento 3D-CRT/IMRT.
2. Valutare se il trattamento radioterapico IGRT/IMRT con una dose biologica più alta, in regime di ipofrazionamento, in pazienti con tumore primario del polmone, migliori il controllo locale o loco-regionale senza che risulti aumentata la tossicità, quando confrontato con il trattamento 3D-CRT/IMRT.
3. Valutare se il trattamento radioterapico IGRT/IMRT con una dose biologica più alta (non in regime di ipofrazionamento), in pazienti con tumore della testa e collo, migliori il controllo locale senza che risulti aumentata la tossicità, quando confrontato con il trattamento 3D-CRT/IMRT.

Executive summary

Policy question and objective

This HTA report has been commissioned to the Agency for Health and Social Care of the Emilia-Romagna Region (ASSR-RER) by its Health Authority in order to inform decisions on clinical use and diffusion of new systems of Image Guided Radiation Therapy (Tomotherapy and Accelerators with Cone-Beam CT) associated with Intensity Modulated Radiation Therapy (IGRT/IMRT).

Objectives of the present HTA report are to assess potential clinical benefits and establish criteria of appropriate use, to critically appraise results of published research, to evaluate economic and organisational impact of the technology and to identify recommendations for clinical research.

1. Background

Until the late 70s, before Computed Tomography (CT) became available, clear delineation of tumour affected from healthy tissues was difficult to achieve and radiation treatment of tumours involved irradiation of neighbouring healthy tissues at the highest tolerable dosage. Since the introduction of CT, evolution in imaging has occurred and treatment planning involves delineation on computed tomography scans of target issues to be irradiated and of healthy tissues to be spared. A further development in dose delivery, the Intensity Modulated Radiotherapy (IMRT), added the possibility to vary the dose intensity within the targeted area, allowing a higher conformality as well as a broader range of dose distribution. IMRT planning has introduced a trade-off between tumour control and unwanted side-effects.

The opportunity to deliver effective high radiation doses, while sparing critical neighbouring organs, increased the need for more precise target volume localisation and for geometrical contouring before and during irradiation. Organs and tumours, in fact, show an important degree of mobility and tumour masses tend to undergo variations during the course of the radiation treatment. A real breakthrough is thus represented by the Image Guided Radiation Therapy (IGRT) technology. Equipments designed for this purpose (e.g. Tomotherapy and CBCT, i.e. Accelerators with Cone-Beam CT) allow to delineate the tumour, correct for patient positioning and/or delivery of irradiation dose before and during treatment. Modern image guided radiotherapy could therefore offer the following tangible benefits:

- greater precision in irradiation of tumour sites with consequent reduction in unwanted irradiation of neighbouring healthy tissues;
- lower incidence of side-effects associated with traditional radiation therapy;

- possibility to use higher dosage with presumed higher efficacy;
- extension of therapeutic use to a larger number of tumours, possibly as a therapeutic option in alternative to surgery.

2. Methods and results

Definition of the problem and research questions

A panel of regional experts from several disciplines (radiotherapy, medical physics, oncology, nuclear medicine, radiology, statistics, economics, epidemiology and health research methodology) was convened to establish the information necessary to determine the clinical role of IGRT/IMRT, assess results of scientific literature, identify research gaps that need to be filled to complete the technology's evidence profile.

To achieve these tasks the panel agreed on the following definition of the clinical rationale for IGRT/IMRT:

> *A better correction for set up errors and organs' motion and a consequent more accurate dose targeting can decrease toxicity and/or increase clinical effectiveness of radiation treatments with radical intent of tumours in proximity of vital organs.*

The comparator was chosen to be any conformal radiotherapy with bi-dimensional image acquisition.

Based on the above defined clinical rationale, which considers only radiation treatments with radical intent of tumours in proximity of vital organs, the panel agreed to evaluate the role of IGRT/IMRT only for the following tumours: prostate, head and neck, lung, brain and pancreas. The specific research questions identified are listed below (*Table 1*).

Table 1. Research questions

Tumour site	Research questions
Prostate	• Does IGRT/IMRT radical radiation treatment for patients with low or intermediate risk prostate cancer decrease toxicity compared to conformal radiotherapy with bi-dimensional image acquisition? • Does IGRT/IMRT radical radiation treatment, with a higher dose per fraction or hypofractionation, for patients with low or intermediate risk prostate cancer decrease toxicity and increase clinical efficacy compared to conformal radiotherapy with bi-dimensional image acquisition?
Lung	• Does IGRT/IMRT radical radiation treatment with hypofractionation for patients with T1 T2 N0 MO inoperable lung cancer, or patients with stage IIA,IIIA+B lung cancer, or patients with metastatic lung cancer (max 5cm) increase clinical efficacy without increasing toxicity compared to conformal radiotherapy with bi-dimensional image acquisition?
Head and neck	• Does IGRT/IMRT radiation treatment with radical intent with hypofractionation - exclusive or associated with chemotherapy - in patients with any type of head and neck cancer, excluding those of the larynx, increase clinical efficacy and decrease toxicity compared to conformal radiotherapy with bi-dimensional image acquisition?
Brain	• Does IGRT/IMRT radiation treatment with radical intent with hypofractionation for primary brain tumour decrease toxicity compared to conformal radiotherapy with bi-dimensional image acquisition? • Does IGRT/IMRT radiation treatment with hypofractionation for metastatic brain tumour decrease toxicity compared to conformal radiotherapy with bi-dimensional image acquisition?
Pancreas	• Does IGRT/IMRT pre-operative radiation treatment with hypofractionation for pancreatic tumour increase clinical efficacy and decrease toxicity compared to conformal radiotherapy with bi-dimensional image acquisition? • Does IGRT/IMRT post-operative radiation treatment for pancreatic tumour decrease toxicity compared to conformal radiotherapy with bi-dimensional image acquisition? • Does IGRT/IMRT radiation treatment with hypofractionation for inoperable pancreatic tumour increase clinical efficacy and decrease toxicity compared to conformal radiotherapy with bi-dimensional image acquisition?

From a quick overview of the published literature it was ascertained that the body of knowledge developed to date is far from robust. The panel therefore agreed on criteria for the classification and interpretation of weak evidence. The principle adopted to differentiate levels of uncertainty was the likelihood that further studies of better methodological quality would change the results. Using this criterion an uncertainty profile has been outlined that distinguishes results in four categories:

- **Steady results**: results that are highly unlikely to be changed by further studies.
- **Plausible results**: consistent results on estimate of size and direction of effect, which would probably not change significantly if evaluated through randomised clinical trials.
- **Uncertain results**: results on estimates of size and direction of effect that would most probably change, if evaluated through randomised clinical trials.
- **Unknown results**: absence of results.

The purpose of this evidence mapping according to levels of uncertainty, was to define the state of knowledge of the technology and to understand how current research is far from, or close to, answering clinically relevant questions. Expected outcome of this appraisal was to chart a future research course of action and define the experimental use of the technology within the regional health system.

An evidence profile of the technology was outlined by the panel, specifying all dimensions to be evaluated, relevant outcomes and study design (*Table 2*).

Table 2. Evidence profile of IGRT/IMRT and criteria for the inclusion of the studies

Attribute	Outcome	Included studies
Technical performance	Set up error Organ motion	SR of RCTs or CCTs RCT CCT Controlled case series Uncontrolled case series Studies on treatment planning
Feasibility	Patients' compliance Learning curve Costs	SR of RCTs or CCTs RCT CCT Controlled case series Uncontrolled case series
Safety	Acute adverse effect / toxicity Late adverse effect / toxicity	SR of RCTs or CCTs RCT CCT Controlled case series Uncontrolled case series
Clinical efficacy	Surrogate outcomes Tumour response Local control Loco-regional control Secondary outcomes Disease free survival Progression free survival Quality of life	SR of RCTs or CCTs RCT CCT Controlled case series
	Primary outcomes Disease specific survival Overall survival	SR of RCTs or CCTs RCT CCT

Systematic review of literature

The main objective of the review was to assess the technical performance and the clinical efficacy of IGRT/IMRT for the clinical indications agreed upon by the panel: lung, head and neck, brain, pancreatic, and prostate cancer.

The search was carried out, with no limits for starting date and up to January 2009 with a further update to June 2010, on main international websites for Health Technology Assessment (HTA) reports and on Medline and the Cochrane Library for primary studies and systematic reviews.

To assess technical performance, we included systematic reviews (SRs), HTA reports, RCTs, CCTs, observational controlled studies, controlled and uncontrolled case series on IGRT/IMRT methods based on volumetric reconstruction employing 3D KV or MV CT, used in one of the clinical scenarios identified and reporting any of the following outcomes: set up errors and organ motion. No limits for number of patients included were applied.

To assess clinical efficacy we included SRs, HTA reports, RCTs, CCTs, observational controlled studies, controlled and uncontrolled case series on IGRT/IMRT methods based on volumetric reconstruction employing 3D KV or MV CT, used in one of the above mentioned tumours and reporting any of the following outcomes: overall and disease specific survival, disease free and progression free survival, local and loco-regional control, acute and late toxicity. Studies recruiting less than 10 patients were excluded.

Systematic reviews and HTA reports have been assessed using the criteria reported in the AMSTAR checklist (1); randomised controlled trials have been assessed using the criteria recommended by the Cochrane Collaboration (2); prospective cohort studies have been assessed using the Newcastle-Ottawa scale (3). Case series were not formally assessed for methodological quality as no standardized criteria are available. Elements considered were: sample size of the series, whether patients were consecutively recruited (yes, no, unclear) and whether the study was prospective (yes, no, unclear).

Data for each study are reported in separate evidence tables (*Appendix 2*), while summary of their results are included in the full document.

The search resulted in 989 citations, 715 of which were excluded for double publication (8), on the basis of language exclusion criteria (9), topic and type of study exclusion criteria (698). We reviewed the full text of 274 articles and we excluded 203 studies (6 HTA reports, 23 studies on clinical outcomes and 166 studies on technical performance) because the topic or type of study was not matching our inclusion criteria. Eight further studies on clinical outcomes were excluded as they enrolled less than 10 patients. The full text was not available for another 16 articles.

Fifty-five studies were included: 6 HTA reports, 34 studies on technical performance and 15 studies on clinical outcomes.

Prior to the report's publication an update of literature search was performed in June 2010, to retrieve primary studies on clinical efficacy published between January 2009 and June 2010.

Eleven further studies were included in the systematic review of the literature: 6 on lung cancer, 2 on prostate cancer and 3 on head and neck cancer.

Summary of results

Lung cancer

Six case series on Tomotherapy and seven on CBCT, most of them without comparison with the standard treatment have been retrieved. Only one controlled case series was found, comparing wedge resection and SBRT in patients with TI-2NO NSCLC and showing

no statistically significant differences between the two treatments. The studies only provide preliminary information and their methodological quality is generally low: small sample sizes and heterogeneous treatment regimens. Studies of higher methodological quality, i.e. randomised parallel comparisons with the standard treatment with longer follow up, are needed.

No conclusions can be drawn on toxicity, tumour control, relapse free survival and overall survival.

Brain cancer

Only two case series on Tomotherapy without comparison with the standard treatment have been retrieved. No studies assessing the efficacy of Cone Beam CT Accelerators on clinical outcomes were found. The quality of the retrieved studies was low, with small sample sizes and no study compared the safety and efficacy of Tomotherapy with other technologies. Treatment regimens were heterogeneous, the doses and fractions varied and the intent were either curative or palliative. The studies only provided preliminary information and no definitive conclusions could be drawn on either the safety or the efficacy of this technique.

Head and Neck Cancer

Four case series on Tomotherapy have been included. Sample sizes were small and patients were heterogeneous and at different stages of disease. Only preliminary information on initial clinical experience of very few centres was provided and no definitive conclusions could be drawn on either the safety or the efficacy of this technique. Studies of higher methodological quality, i.e. randomised parallel comparisons with the standard treatment with longer follow up, are needed.

Prostate cancer

The evidence retrieved is limited: only case series were found and the comparison groups used in three studies were historical cohorts. All studies but one limited their analyses to safety outcome.

The studies only provide preliminary information and no definitive conclusions can be drawn on either safety or efficacy of this technique. Studies of higher methodological quality, i.e. randomised parallel comparisons with the standard treatment with longer follow up, are needed.

Pancreatic cancer

No studies were found on pancreatic cancer.

Classification of uncertainty and identification of research gaps

Results of the literature review were charted on the evidence profiles defined for each research question and results for each dimension and outcome were classified according to their level of uncertainty.

Available literature was judged to give sufficient information on technical performance for all research questions, with the exception of those related to pancreatic cancer. However the information on safety and clinical efficacy was judged to be very scarce.

Overall we found:

- some information on safety for use in patients with prostate cancer;
- some information on safety and very little on efficacy for use in patients affected by lung, head and neck and metastatic brain cancer;
- no information on use in patients with pancreatic cancer and with primary brain tumours.

Quantity and quality of existing research were among the criteria applied for the prioritisation of future clinical research questions.

Analysis of regional context and organisational implications

The estimated volumes for the 5 clinical indications that could potentially benefit from the use of IGRT/IMRT were obtained from a regional survey carried out on all radiotherapy treatments provided during a two months period in 2004 and it resulted in approximately 20% of all radiation treatments provided in one year for the 5 tumours. The proportion of incident cases eligible for IGRT/ IMRT for the 5 tumours resulted to be 23% of patients with primary brain cancer; 20% of patients with metastatic brain cancer; 24% of patients with head & neck cancer; 10% of patients with primary lung cancer; 21% of patients with prostate cancer and 18% of patients with pancreatic cancer. Based on these estimates the activity of an IGRT/IMRT service was calculated as comprising of 45% of its activity dedicated to patients with prostate cancer, 19% to patients with lung cancer, 11% to patients with head & neck cancer, 6% to patients with primary or metastatic brain cancer, 5 % to patients with pancreatic cancer and the remaining 9% for other clinical indications. Considering only the radical treatments the number of patients to be treated in one year resulted to be 1 338.

The above distribution and percentages, calculated on the basis of current activity of radiation therapy services of Emilia-Romagna, can be used by radiotherapy centres to asses their use of IGRT/IMRT and estimate their expected volumes.

Seven of the eleven regional radiotherapy centres are at the moment equipped with an IGRT/IMRT system, for a total of 8 IGRT/IMRT systems, which is an adequate number for the expected eligible patients, and the geographical distribution of the systems covers most of the region's territory.

Analysis of patients' pathways leading to radiation therapy treatment showed a certain degree of variability depending on whether a multidisciplinary approach for evaluation and therapeutic decision is established and secured to the patient. Should further

evaluations of IGRT/IMRT confirm the above clinical indications for this type of treatment, access to the technology would have to be guaranteed for all eligible patients. Given the variability in pathways, it is suggested that referral protocols should be agreed upon by all radiotherapy centres of the Emilia-Romagna Region (RER), requiring that the radiotherapist places an indication for IGRT/IMRT treatment. Single waiting lists for patients eligible for IGRT/IMRT treatments could be set up in each regional sub-area to ensure admittance to the nearest IGRT/IMRT centre within the appropriate time interval. A close collaboration between centres is recommended ensuring a smooth take over of the patient by the IGRT/IMRT centre, that neither disorients the patient nor undermines the relationship between patients and their local health centre. Such close collaboration, which appears to be long-standing between RER radiotherapy centres, will also guarantee uniform and appropriate waiting times for patients coming from different geographical areas as well as reciprocal support, should system or machines' failures occur. Centres considering acquisition of latest IGRT/IMRT systems should take into account that such systems require dedicated space, consisting in two rooms, one of which acclimatised, often involving the construction of a dedicated bunker. In terms of staff, the technology requires one radiotherapist, one medical physicist and a dosimetrician. A dedicated training programme should also be taken into account, targeted primarily at the medical physicist who needs to become particularly skilful in techniques of invert treatment planning. Such training, which can be offered by any experienced IGRT/IMRT centre, requires a full-time training period of one month, while a 6 month course is necessary to become a trainer.

Economic and financial implications

An assessment of the main financial and economic implications was carried out, related to the acquisition and subsequent utilisation of an image-guided approach in radiotherapy, through the following analyses:

- estimates, based on current regional tariffs, of a theoretical cost increase and, consequently, of the increase in expenditure for the Regional Health Service of Emilia-Romagna;
- application of the Break Even Analysis model to estimate the minimum number of patients that ensures coverage of total annual costs.

Treatment reimbursement estimates

An analysis based on the regional reimbursement's scheme was carried out to estimate the increase in expenditure due to the use of IGRT/IMRT. A radiation treatment pathway was mapped out with the contribution of all Emilia-Romagna radiation therapy units. The analysis was limited to radical treatments, ignoring palliative ones. A "reference-case" scenario was defined and applied to treatment with 3D conformal radiotherapy. Reimbursement for a complete treatment resulted in € 697.55 + (€ 113.60 * N), where N is the number of sessions required to reach the total planned dose. To estimate the reimbursement for IGRT/IMRT, the same calculations were applied to the IGRT/IMRT

workflow, resulting in € 922.55 + (€ 266 * N), where N is the number of sessions required to reach the total planned dose.

The incremental expenditure for IGRT/IMRT over 3D conformal radiotherapy for each of the five tumours was calculated, showing a range of increment between € 4 340 (for treating one patient with pancreatic cancer), to € 5 559 (for treating one patient with head and neck cancer).

Therefore, assuming 1 338 patients/year (702 treated for prostate cancer, 168 for head & neck cancer, 294 for lung cancer, 78 for pancreatic cancer, 96 for brain cancer) the additional expenditure for the Regional Health System would be of approximately 6.6 million Euros.

Break Even Analysis

Capital cost of the relevant technologies was based on 2008 prices and the annual depreciation cost was estimated assuming the equipment remains in use for 8 years, while set up and training costs were included in the technology capital cost.

An estimate of full yearly cost and time absorption for all personnel involved in planning and delivery of treatments was obtained from the regional radiotherapy centres. Following this, costs of single sessions and of complete treatments were calculated to build a theoretical scenario. Break Even Analysis was applied to both Tomotherapy and to Cone-Beam CT accelerator, as both systems of IGRT/IMRT are present in the Emilia-Romagna Region, and resulted in 209 treatments for Tomotherapy and 150 treatments for Cone-Beam CT. Having estimated the eligible patients to be 1 569 per year, the 8 IGRT/IMRT systems present in our region would be treating around 195 patients each per year, which is compatible both with break even points and with the production capacity of the systems.

Prioritisation of clinical research questions

One of the aim of the panel's work was to develop research recommendations for further evaluation of the role and clinical impact of IGRT/IMRT.

The priority for clinical research topics was defined using a structured process. Participants were involved in modified Delphi and RAND processes and presented with a voting form for each clinical scenario, related to the 5 tumours. The voting forms provided the following information:

- estimated target population;
- estimated treatment costs;
- a list of relevant clinical outcomes (suggested by the panel);
- estimates of performance of standard therapy (3D conformal) and of IGRT/IMRT (when available) for each clinical outcome.

Participants were asked to place a vote next to each clinical outcome, expressing relevance in both clinical and research terms. They were then asked to rate each research indication in terms of the following priority's determinants:

- severity of disease in terms of morbidity and mortality;
- impact of the technology on the morbidity and mortality of the disease;
- feasibility of a clinical trial.

As a final step participants were asked to rate overall priority of each clinical research question.

The structured process resulted in the following ranking of research topics:

1. radiation treatment with radical intent in low and intermediate risk prostate cancer;
2. radiation treatment with radical intent in inoperable T1-T2, III A and B lung cancer;
3. radiation treatment of head & neck cancer, exclusive or associated with chemotherapy;
4. radiation treatment of lung metastasis;
5. radiation treatment of advanced pancreatic cancer;
6. radiation treatment of brain metastasis;
7. pre-operative radiation treatment of pancreatic cancer;
8. post-operative radiation treatment of pancreatic cancer;
9. radiation treatment of primary brain cancer.

Taking in consideration the quantity and quality of the clinical research published this far, the panel agreed that further research on IGRT/IMRT should not aim at assessing just its impact on adverse effects and toxicity, as the technology is mature enough to undergo evaluation of clinical effectiveness on long-term clinical outcomes. The panel therefore recommended that the role of IGRT/IMRT in treatments with dose escalation and/or hypofractionation should be assessed through randomised controlled clinical trials.

Conclusions

The main objectives of this report were:

- evaluate potential clinical benefits of Image Guided Radiotherapy with Intensity Modulated Radiation Therapy;
- identify in which clinical indications this technology appears to be particularly promising;
- map a future programme of evaluation suitable to provide robust clinical results.

Image Guided Radiotherapy represents a real breakthrough in radiation treatment for its capacity to delineate the tumour contours, correct for patient positioning and delivery of irradiation beam before and during treatment. The tangible potential benefits of modern IGRT/IMRT are therefore:

- greater precision in irradiating tumour sites with consequential reduction in unwanted irradiation of neighbouring healthy tissues;
- lower incidence of side-effects associated with traditional radiation therapy;
- possibility to use higher dosage with presumed higher efficacy;

- extension of therapeutic use to a larger number of tumours, even as an alternative to surgery.

Despite this convincing theoretical rationale, robust research evidence in support of its promising clinical benefits is still lacking. For the use of IGRT/IMRT in the 5 tumours selected by the panel - lung, head & neck, prostate, brain and pancreatic cancer - there is sufficient evidence on technical performance, some but not yet conclusive information on safety, very scarce information on clinical effectiveness and none on cost-effectiveness.

Research gaps and research needs to reduce uncertainty on clinical effectiveness of IGRT/IMRT have been identified and the structured process for the prioritisation of research topics, undertaken by the panel, produced a list of research questions, ranked according to priority.

The resulting top three recommendations for research are reported below.

RECOMMENDATIONS FOR FUTURE RESEARCH

1. To assess whether radical radiation treatment with IGRT/IMRT with a higher biological dose in hypofractionation regimen in patients with low and intermediate risk prostate cancer improves biochemical recurrence and disease free survival without increasing toxicity, compared to treatment with 3D-CRT/IMRT.
2. To assess whether radical radiation treatment with IGRT/IMRT with a higher biological dose in hypofractionation regimen in patients with primary lung cancer increases local and loco-regional control without increasing toxicity, compared to treatment with 3D-CRT/IMRT.
3. To assess whether radical radiation treatment with IGRT/IMRT with higher dose (not in hypofractionation regimen) in patients with head & neck cancer increase local control without increasing toxicity, compared to treatment with 3D-CRT/IMRT.

1. Objective and background

Policy question and objective

This HTA report has been commissioned to the Agency for Health and Social Care of the Emilia-Romagna Region (ASSR-RER) by its Health Authority in order to inform decisions on clinical use and diffusion of new systems of Image Guided Radiation Therapy (Tomotherapy and Accelerators with CT Cone Beam) associated with Intensity Modulated Radiation Therapy (IGRT/IMRT).

Objectives of the present HTA report are to assess potential clinical benefits and establish criteria of appropriate use, to critically appraise results of published research, to evaluate economic and organisational impact of the technology and to identify recommendations for clinical research.

1.1. Epidemiological background

In Western countries the incidence of cancer is growing among both men and women, while mortality is decreasing. In Italy it is estimated that 250 000 new diagnoses of cancer are made each year and approximately 122 000 deaths are due to cancer-related diseases. Ten years ago these estimates were 225 000 and 130 000 respectively.

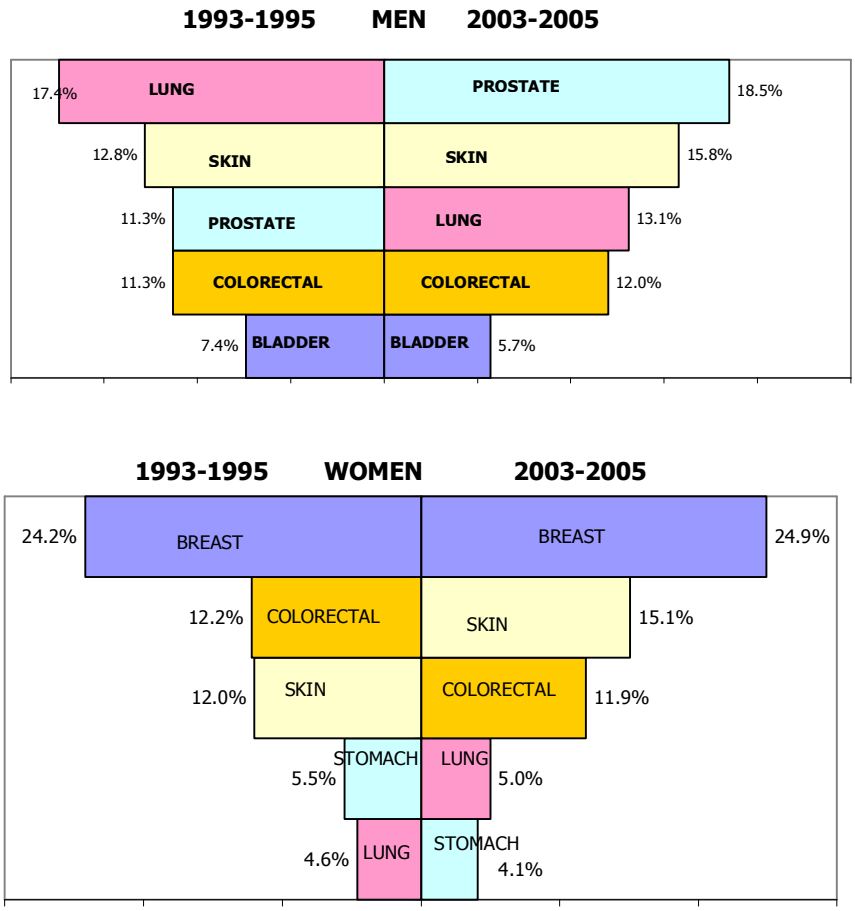
This increase in number of cancer diagnoses is largely due to the aging of the population, screening programmes and early detection, which contribute to anticipate the time of diagnosis. If the aging effect is removed, and tumours undergoing screening programmes are excluded, the remaining tumours show an average decrease in new diagnosis, which is masked by the aging effect.

Mortality is decreasing for all cancer types. Among men over the age of 45 the most frequent diagnosis is for prostate cancer, which is rising above that for lung cancer. Among women, the most frequent diagnosis is for breast cancer (one third of tumours diagnosed each year), while lung cancer is among the 5 most frequently diagnosed cancers for women, showing a growing trend.

As directly observable data covering the whole of the Italian population are lacking, the number of new diagnosed cancers is quantified through estimates (http://www.tumori.net). In 2008 the new cases of cancer in people aged between 0 and 84 years were estimated to be 132 141 for men and 122 052 for women. According to the AIRTUM Register (Italian Association of Tumour Registers), between 2003-2005 there were 7 new cases per 1 000 inhabitants among men and 5 new cases per 1 000 among women.

The 5 most frequently diagnosed cancer between 2003 and 2005 are reported in Figure 1.1.

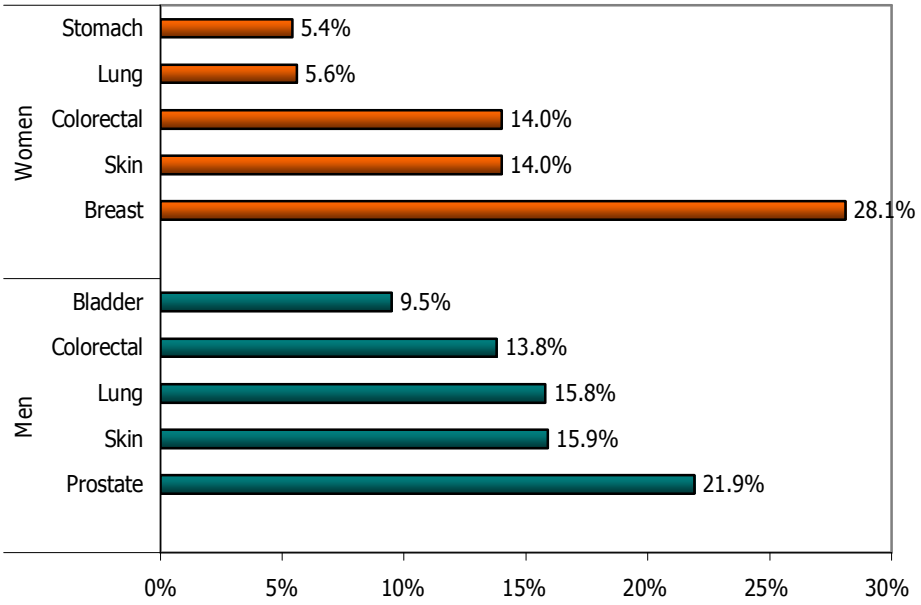
Figure 1.1. Five most frequently diagnosed cancers in Italy - 1993-1995 versus 2003-2005 (AIRTUM Register)



Survival from cancer at 5 years after diagnosis has increased from 33%, for patients whose tumour was diagnosed in the late 70's, to 39%, for those diagnosed in the late 80s. Further increases in survival rates are estimated for most recently diagnosed cases, suggesting a continuous improvement in cancer prognosis. In Italy this increase in survival, together with the aging of the population, has resulted in a sharp increase in prevalence. In 1970 prevalent cases were around 820 000 and in the year 2000 they are estimated to have risen to 1.3 million.

The Emilia-Romagna Region data from 2004 show an incidence of 30 733 cases (18 588 males and 15 091 females). Nine new cases per 1 000 men and 7 per 1 000 women are detected each year. The distribution of tumours, reported in Graph 1.1, shows proportions in line with the national data, except for breast cancer, for which the proportion appears to be higher, and regional mortality rates (16.2%) do not differ from national ones (17.1%).

Graph 1.1. Five most frequently diagnosed cancer in Emilia-Romagna - 2004 - Men and women (Emilia-Romagna Tumour Register)



1.2. The use of radiation therapy in the Emilia-Romagna Region (RER)

The analysis of radiation therapy's use in the 11 radiotherapy centres of the Emilia-Romagna Region (RER) was performed using data of the Regional Outpatient Database (ASA - *Assistenza Specialistica Ambulatoriale*) and the Hospital Discharge Records Database (SDO - *Schede Dimissione Ospedaliera*) from 2004 to 2008. Codes used for extracting data are reported in Table 1.1.

Table 1.1. Selected ICD9-CM codes

	ICD9-CM Diagnostic Codes		
Outpatient Database (ASA) codes	92.23.1	92.23.2	92.23.3
	92.24.1	92.24.2	92.24.3
	92.24.4	92.25.1	92.25.2
	922440	922401	922402
Hospital Discharge Records Database (SDO) codes	V58.0		

	ICD9-CM Procedure Codes	
Hospital Discharge Records Database (SDO) codes	92.23	92.29

Graph 1.2 reports the number of patients treated between 2004 and 2008, including treatment for non-RER residents. There is a slight upward trend in the use of radiotherapy, with an apparent inversion of this trend for the year 2007, probably due to the breakdown of a linear accelerator in one of the main radiotherapy services.

Graph 1.2. Volumes of radiotherapy in RER

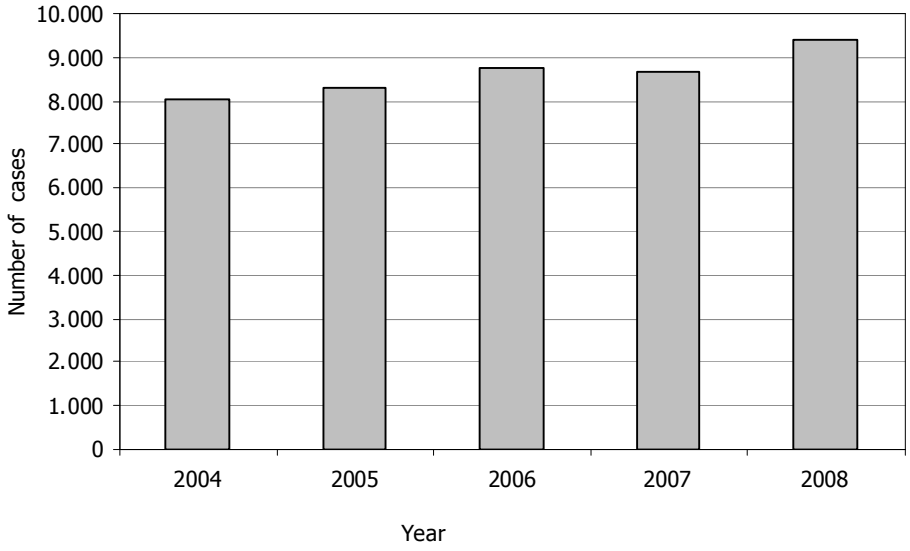


Table 1.2 reports the number of patients treated and use of radiotherapy in relation to incident cases. In the year 2008 the number of patients affected by cancer and receiving radiation therapy in the Emilia-Romagna Region represents 30% of incident cases.

Table 1.2. Emilia-Romagna Region's residents treated with radiotherapy, 2004-2008

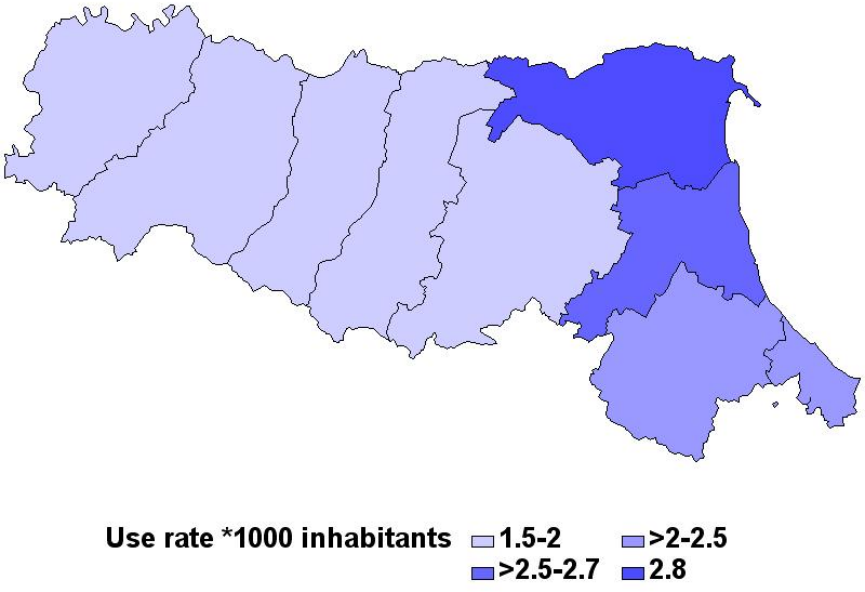
Year	RER incident cases (from RER Tumour Register)	Emilia-Romagna residents treated (from ASA + SDO RER databases)	% of incident cases
	N	N	%
2004	28 625	7 553	26
2005	28 625	7 762	27
2006	28 625	8 185	29
2007	28 625	7 908	28
2008	28 625	8 597	30

For the year 2008 the rate of use of radiotherapy (volumes of treatments / number of residents) across provinces shows a minimum rate of 1.5 per thousand residents and a maximum rate of 2.6 per thousand residents, with a regional rate of 2.0 per thousand inhabitants (*Table 1.3* and *Figure 1.2*).

Table 1.3. Rate of use of radiation therapy - year 2008

Province	Resident population	Use rate * 1 000 inhabitants
Parma	425 690	1.5
Piacenza	281 613	1.7
Reggio Emilia	510 148	1.8
Bologna	964 065	1.9
Ferrara	355 809	2.5
Modena	677 672	1.9
Forlì-Cesena	383 046	2.3
Ravenna	379 467	2.6
Rimini	298 333	2.3
E-R Region	***4 275 843***	***2.0***

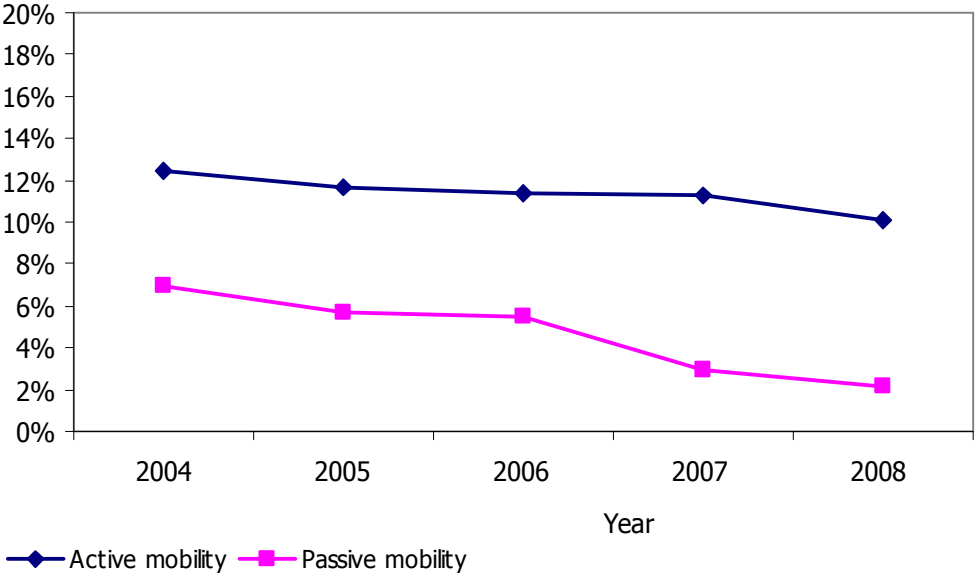
Figure 1.2. Rate of use of radiation therapy by province - year 2008



1.3. Patient mobility for radiotherapy

Passive mobility has undergone a decrease from 7% to 2% in the last four years (*Graph 1.3*), probably due to the increase in technology's availability, showing capacity to satisfy internal treatment request. Active mobility, which had stabilised around 12%, has recently undergone a slight decrease.

Graph 1.3. Emilia-Romagna Region's patient mobility - year 2008



Figures 1.3 and 1.4 show the intra-regional mobility (among provinces) and extra-regional mobility by province, while Table 1.4 reports a focus on patients' flow between provinces. Overall, the relative low rate of mobility shows that local health centres are able to fulfil treatment's requests for their own residents.

Figure 1.3. Intra-regional mobility (%)

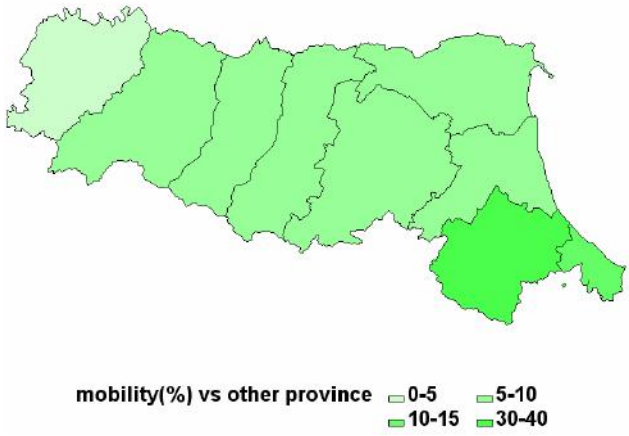


Figure 1.4. Extra-regional mobility (%)

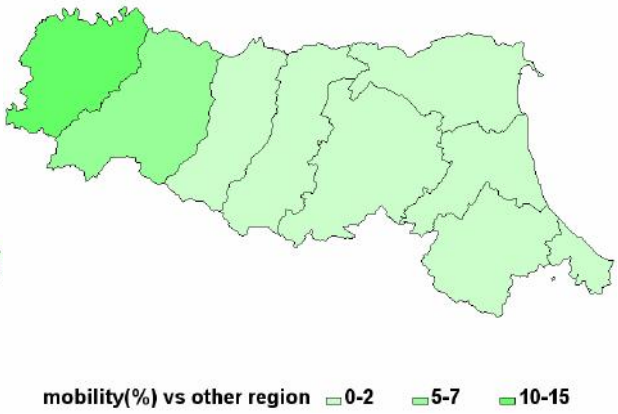


Table 1.4. Mobility flow - year 2008

Province of treatment	Province of patients' residence									Total
	PC	RA	FC	RN	PR	RE	MO	BO	FE	
	N	N	N	N	N	N	N	N	N	N
Other region	69	5	5	8	37	10	16	12	20	182
PC	391	0	0	0	6	0	0	0	0	397
RA	0	899	291	34	0	2	2	106	39	1 373
FC	0	70	551	23	3	5	4	33	5	694
RN	0	0	19	599	1	0	1	2	0	622
PR	16	0	0	0	574	21	3	0	0	614
RE	1	0	0	0	24	830	38	0	2	895
MO	1	0	1	2	1	24	1 169	28	3	1 229
BO	1	21	11	14	2	1	34	1 683	42	1 809
FE	0	0	0	0	0	0	5	13	764	782
Total	***479***	***995***	***878***	***680***	***648***	***893***	***1 272***	***1 877***	***875***	***8 597***

1.4. Advances in Image Guided Radiation Therapy

Until the late 70s, before Computed Tomography (CT) became available, clear delineation of tumours from healthy tissues was difficult to achieve and radiation treatment of tumours involved irradiation of neighbouring healthy tissues at the highest tolerable dosage. Since the introduction of CT, evolution in imaging has occurred and treatment planning involves delineation on computed tomography scans of target issues to be irradiated and of healthy tissues to be spared. A further development in dose delivery, the Intensity Modulated Radiotherapy (IMRT), has added the possibility to vary the dose intensity within the targeted area, allowing a higher conformality as well as a broader range of dose distributions. IMRT planning has introduced a trade-off between tumour control and unwanted side-effects.

The opportunity to deliver effective high radiation doses while sparing critical neighbouring organs, increased the need for more precise target volume localisation and for geometrical contouring before and during irradiation. Organs and tumours, in fact, show an important degree of mobility and tumour masses tend to undergo variations during the course of the radiation treatment. A real breakthrough is thus represented by the Image Guided Radiation Therapy (IGRT) technology. Equipments designed for this purpose (e.g. Tomotherapy and Accelerators with CT Cone Beam) allow to delineate the tumour, correct for patient positioning and/or delivery of irradiation beam before and during treatment. Modern IGRT could then offer the following tangible benefits:

- greater precision in irradiating tumour sites with consequent reduction in unwanted irradiation of neighbouring healthy tissues;
- lower incidence of side-effects associated with traditional radiation therapy;
- possibility to use higher dosage with presumed higher efficacy;
- extension of therapeutic use to a larger number of tumours, even as an alternative to surgery.

2. Brief technical description of the technology

2.1. Description of the technology

Linear accelerators and cobalt therapy units are used in the treatment of cancer through the application of a ray beam to the patient's body.

Linear accelerators are emitting ray beam (X-rays), of uniform intensity, whose energy varies depending on the type of accelerator.

Low energy linear accelerators are primarily used to treat bone cancer and tumours of the head, shoulder and breast. High energy linear accelerators are used to treat neoplasms located in depth and also pelvic and thoracic tumours.

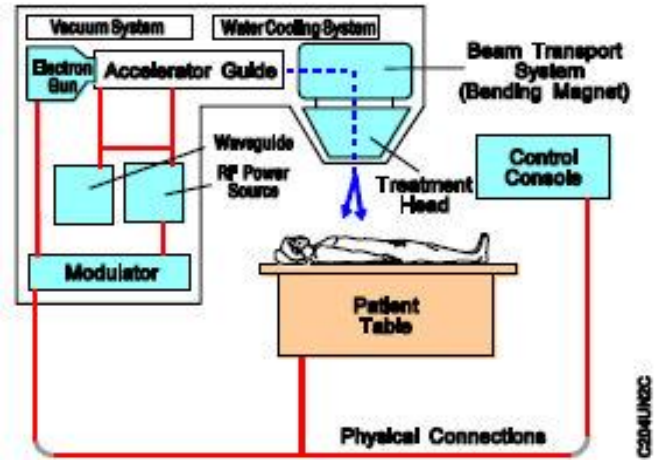
Thanks to the latest technology developments, radiation therapy has become one of the primary ways of treating cancer, together with chemotherapy and surgery.

Radiation therapy is used to treat at least 50% of tumour cases and many patients often receive a combination of all three methods; depending on the disease stage, it can be either curative or palliative. For a successful treatment, the area to be irradiated must be well defined, to avoid the irradiation of healthy tissues.

The components directly involved in the generation of ray beams are *(Figure 2.1*):

- a modulator,
- an electron gun,
- a radio frequency source,
- an acceleration guide.

Figure 2.1. LINAC components - ECRI 2008



The modulator, installed on the gantry or in a separate cabin, generates a rectified voltage that feeds a circuit capable of producing high voltage pulses. These pulses are the synchronized input signal for the electron gun and the radiofrequency source.

The electron gun injects electrons into the acceleration guide through pulses of appropriate duration, speed and position, to maximise the acceleration. The electron gun can be connected to the acceleration guide with a removable sealed flange that allows easy replacement of the gun itself. There are also solutions that provide the electron gun permanently connected to the acceleration guide: in that case the whole accelerator must be replaced upon burning of the gun filament.

The radiofrequency source (RF), whether a Klystron or Magnetron, provides electromagnetic waves at a high frequency (3 GHz) that accelerate the electrons injected by the electron gun into the acceleration guide.

Linear accelerators are labelled as follows, according to their energy levels:

- low-energy units, producing 4 or 6 MV photons;
- medium energy units, producing 8 to 10 MV photons and 9 to 15 MeV electron beams;
- high energy units, producing 15 to 25 MV photons and 4 to 22 MeV electron beams.

Most linear accelerators are capable of operating at different levels of energy: many systems can operate at two energy levels offering both low energy (typically 6 MV) and high energy (10 MV at least). Many of them are multi-level units offering both photon and electron beams.

The higher the energy that the accelerator is able to provide, the more expensive it is, as more powerful radiofrequency source and longer and more complex acceleration guide are required. The treatment room is also more expensive, as it must protect from the neutrons generated when energy levels higher than 10 MeV are employed.

Linear accelerators are implemented in a way that allows easy positioning of the patient. They are equipped with a motorised bed, capable of moving along the x, y and z axes of rotation (one of the movements is isocentric, relative to the beam axis). The bed should be featured so that it can accommodate patients with above average physical characteristics. Some treatments, named "arc therapy" or "commuting therapy", are made in a moving gantry. In this case rotation is allowed in both directions.

Most accelerators have blind spots of 2-3 mm in diameter, lower than a cobalt source (diameters between 1 and 2 cm). Many linear accelerators offer, all-included or optional, a system for the production of radiographic images (e.g. using an amorphous silicon detector), to control the correct pointing location during treatment. Images obtained are generally of poor quality, since the X-ray source is of high-energy (MegaVolt), making soft tissues less distinguishable from hard ones.

All accelerators are controlled remotely from a console placed outside the treatment room, where the intensity of the radiation beam dose can also be controlled.

2.2. Planning systems for radiotherapy treatments

A planning system is composed of specialised hardware, a module for data import and export, and several software modules for planning.

The intended use of these systems is to allow proper planning of radiotherapy treatment on the basis of the information (mainly imaging) previously acquired.

Data is imported telematically via standard DICOM interface.

Some planning systems are supplied as individual workstations; a recently expanding different paradigm providing remote access to client workstations allows the different specialists involved to collaborate more effectively.

Another advantage of this configuration is its ability to distribute the computational load across multiple systems, so as to decrease the processing time.

The first step in the system's use is the definition of the "planning target volume" (PTV) and of "organs at risk" (OAR). These tasks are performed by physicians with tools that enable to contour the anatomical areas of interest and automatically select the volumes showing a similar density.

For some types of lesions it is very important to simultaneously use images acquired with different modalities. The recording system allows to align the anatomical information of the different image sets via the anatomical markers used to capture the images, whereas the fusion system allows the simultaneous viewing of different sets.

The system for calculating the dose is the main part of the radiotherapy planning system. Two planning techniques are used: forward and inverse planning.

In forward planning the operator selects the beam and the collimation, then the system automatically calculates the dose. Planning is then recalculated in order to reach a satisfactory result.

In inverse planning the operator specifies the target volume and the system calculates backwards the best beam angle and the collimation. This is the system that probably provides better performance, even if it requires more computational resources.

All planning systems must model the interaction between a radiation beam and a patient.

The choice of the final treatment plan stays in the selection of the best trade-off between different factors, i.e. the dose irradiated to the lesion, the dose to organs at risk and the available time slot.

Typically, a physician bases his/her decision on a comparison of dose-volume histograms among target and organs at risk, which provide an indication about the extent to which the treatment planning fits the prescription.

There are planning systems capable of giving a clinician immediate feedback and of showing the effects of changes in the input parameters almost in real time.

Some systems also provide really advanced features, such as: the comparison of treatments carried out on different systems; the scheduling of treatment plans that include the treatment through several different therapy systems; the recording of the effectiveness of the treatments performed.

Once completed, the plan is exported to the treatment device and the planning system generates further information to get the best positioning of a patient.

2.3. Simulation systems in radiation therapy (TPS)

A radiotherapy simulation system is a device that replicates the movement of a radiotherapy treatment device to outline (by means of fluoroscopic X-ray or CT images) the localisation of the tumour and the volume that needs to be treated.

The two main objectives of the therapy planning system are the definition of the tumour volume (the region of the current tumour and surrounding tissue that has to be considered at risk) and the development of a treatment technique that provides a uniform dose of radiation to the tumour, while minimising the dose given to surrounding healthy tissues.

By combining therapeutic and diagnostic technologies, a simulation system represents the movements of the linear accelerator or the cobalt therapy device in a virtual way. Instead of emitting high-energy radiation, the system delivers radiofrequency-based images to determine, document and mark the boundaries of the area that needs to be treated. Once the potential field of radiation is established, the areas and organs that should be excluded from the radiotherapy treatment are outlined.

Prior to the first treatment's session, the position of the patient on the radiotherapy field is verified.

Systems based on the use of CT

With systems based on CT simulation, the tumour area is identified through the acquisition of CT images and subsequently characterised by defining the target volume and by selecting the treatment area using a TPS. The simulation system is then used to mark the patient for irradiation. Stages of acquisition, treatment planning, definition of the area of treatment and patient marking can be achieved in a single session. The CT - based systems are also used to verify the tumour margins and anatomy near the lesion, to trace the regression of the tumour after treatment, for a three-dimensional analysis, in view of a conformal therapy and use of multi leaves collimators.

The simulation through CT allows the possibility to plan three-dimensional treatments and volumetric images, which, together with verification images, can be compared with portal images. This type of simulation requires a CT scan of the patient, followed by a virtual simulation, which does not require the patient's presence. The purpose of the CT simulation is to combine the accuracy of the simulation of a conventional treatment with the added benefit of the three-dimensional display.

The acquired CT data are transferred for the 3-D reconstruction to the post-processing workstation. The workstation is used to locate the tumour, to outline the target volume and calculate the coordinates necessary to place tattoos on the patient. The computer also controls the laser pointers that indicate the areas to be tattooed. Digitally reconstructed radiographs (DRRs) are generated according to several beam orientations

to verify or change the patient positioning, the collimators angles, the beam width, the SAD and the position of the gantry during the treatment. Data are then made available to the PACS (Picture Archiving and Communications System) or other applications.

"Record and verify" and EPID systems

"Record and verify" systems used in radiotherapy are aimed at carrying out quality control during treatment, by controlling the dose administered, verifying the treatment parameters and blocking radiation if errors are encountered. Portal imaging (EPID) provides real-time and on-line images of the area involved by radiation before, during and after therapy. The positioning of the patient, the alignment of the area to be irradiated and the positioning of the collimator can be verified before irradiation, in order to improve accuracy of the dose distribution and reduce errors during treatment. Real-time imaging systems are faster and reduce costs by eliminating the need to recover "port films". These systems can also be used to verify the procedures of intensity modulated radiotherapy (IMRT) and 3D conformal radiotherapy (CRT), where high doses and complex set up are usual.

Networking

All systems can be networked and connected to software packages of the Hospital Information System (HIS): this is particularly useful in radiotherapy departments where multiple linear accelerators and simulators are present, as in this way the access to the treatment data of all patients is allowed on each workstation. The use of a DICOM RT standard enables the standardization of the transmission of radiotherapy data, maintaining in this way compatibility among the systems.

2.4. The evolution of the technology

Figures 2.2 and 2.3 provide a graphical representation of recent evolution in radiotherapy infrastructures.

3D-CRT

"Conformal" 3D Radio Therapy realised together with the use of a MLC (Multi Leaf Collimator) allows to adapt the dose distribution to all tumour convex shapes.

IMRT

It may differ in relation to planning techniques, and, in particular, it is possible to distinguish between forward planning and inverse planning. The first one is consisting of an empirical process where fields of treatment and methods of irradiation are iteratively modified (often manually), in order to achieve optimal therapeutic solutions. The process is usually used in the design of 3D-CRT plans, even if it can also be employed to create the so-called "field-in-field" treatments, simple and intensity modulated. Inverse planning is the term used to describe the optimisation of the process

that translates the mathematical formalism of clinical requirements to a mode of irradiation closest to the solution required.

IGRT

In such technique an image captured in the treatment room is compared with a reference image of the same patient, usually acquired 15 days before the actual treatment; it is later used to elaborate the dose distribution. IGRT is thus used to adjust the set up at the first session and also in further ones. The use of this technique allows a substantial improvement of the overall process, also in terms of safety to the patient: in particular it permits the reduction of ballistic errors concerning OAR (Organ at Risk) overdosage and target area underdosage. Moreover, it enables the reduction of PTV (Planning Tumour Volume) margins, given that the movement of a tumour during each session is exactly known. Therefore it allows to control and correct:

- the set up errors;
- the "inter-fractions" movement of an organ, that leads to inaccurate sets;
- the "intra-fractions" organ movement, i.e. during a treatment.

The terms IGRT and 2D-3D-IGRT conventionally refer to the treatment planning.

Bi-dimensional (or planar) treatment planning systems

The current two-dimensional treatment planning system is based on standardised processing techniques applied to "homogeneous" disease classes (e.g. tumours of lung, brain, etc.).

This process makes use of an X-ray simulator, a computerised bi-dimensional treatment planning system (used to calculate the dose distribution, if X-rays and electron beams are employed), a system of portal images (film-based or digital) and a system for the verification of the treatment.

The computerised system for the planning of a bi-dimensional treatment simply generates the dose distributions relative to the patient target volume in a single or a few plans.

Tri-dimensional treatment planning systems

Current technologies provide a tri-dimensional view of the patient tumour anatomy that enables physicians to be more accurate in identifying the tumour itself. These systems are also called 3D-CRT. 3D-CRT treatment techniques are based on the specific size and location of the tumour area and also on the patient anatomy. They are made of an integrated process that consists in the following steps:

1. patient immobilisation, anatomical localisation and CT images acquisition;
2. identification of the precise volume of the tumour/target and definition of the isocentre;
3. virtual simulation;
4. evaluation and optimisation of the treatment plan;
5. implementation of a treatment plan and verification of the treatment provided.

DGRT

It allows the adjustment of a treatment plan according to the dose distribution, not only as a function of the ballistic feature.

Figure 2.2. The history of HT systems

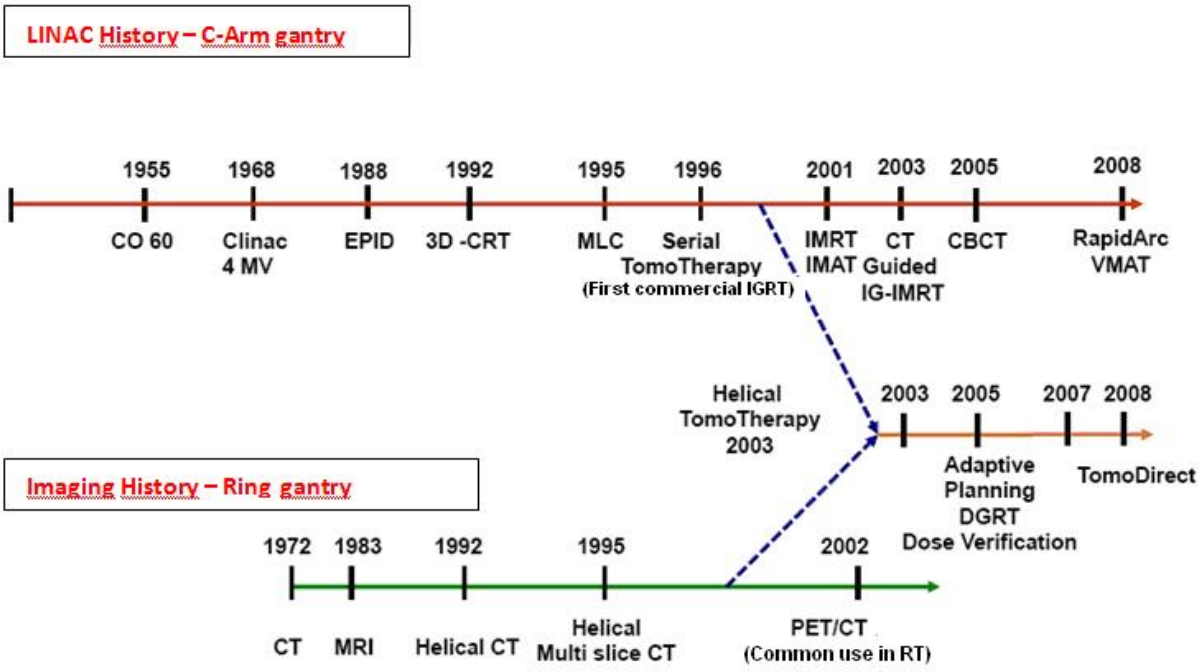
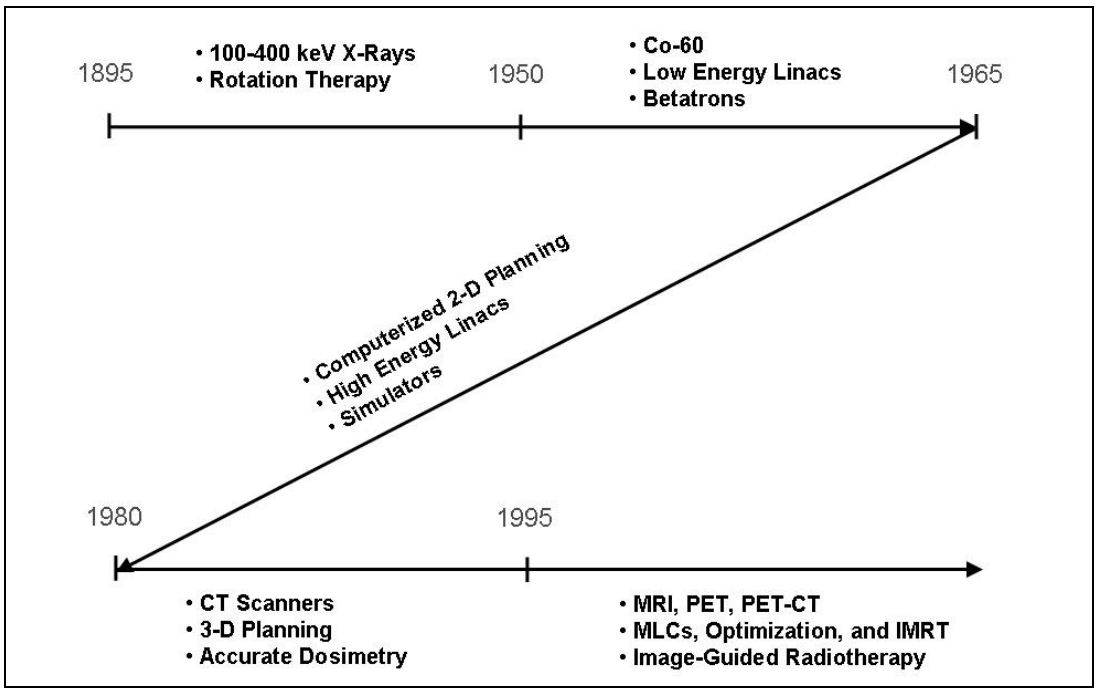


Figure 2.3. The evolution of techniques



2.5. Innovative treatment techniques

The new features in IMRT, IMAT and VMAT are obtained by adding an MLC, controlled by additional computerised systems, to the classical structure of a linear accelerator.

Similarly, the IGRT (Image Guided Radiotherapy) feature is obtained by adding a system consisting of an X-ray tube and on the other side an amorphous silicon detector, both mounted, respectively, on 2 robotic arms, solidly connected to the gantry. The IGRT is working on an axis arranged at 90° with respect to the axis of the therapeutic radiation.

Verification of the patient positioning is realised with a hand device called EPID (Electronic Portal Imaging Device), placed in an opposed position to the axis of the therapeutic beam, formed by an imaging detector.

In particular:

- IMAT Intensity Modulated Arc Therapy (Varian and Elekta)
- VMAT Volumetric Modulated Arc Therapy (Elekta)
- Rapid Arc (Varian)

IMAT

The IMAT (Intensity Modulated Arc Therapy) technique is used in conventional linear accelerators and mainly consists in the management of the MLC movement during the arc rotations of a gantry.

This technique was proposed in the mid-90s, but did not obtain a great success due to its complexity and the limited improvements obtained in the dose distribution compared to conventional IMRT.

The physical complexity of the technique, due to the slow movement of the MLC, and the complexity of the software needed to calculate the dose distribution limit its utilisation.

Elekta and Varian offer a commercial IMAT version together with a device produced by 3D line added on to an MLC.

The technique is performed with multiple rotations of a gantry (complete or partial arcs) and can create dose distributions more complex than those obtained by conventional IMRT treatments realised with conventional accelerators.

V-MAT

Elekta announced its VMAT (Volumetric Modulated Arc Therapy) solution as a WIP (Working In Progress), during ESTRO 2007. This WIP started its commercialisation in April 2008.

Using VMAT, according to Elekta, would enable to irradiate the patient with a continuous rotation of the gantry of a linear accelerator, and vary the fluence rate of the beam (through the continuous movement of the collimator leaves), the speed of gantry rotation and the dose-rate. This technique, used in combination with 3D-CBCT/IGRT (3D Cone Beam Computerised Tomography Image Guided Radiation Therapy) has been announced as the fastest and most precise radiation therapy in the field of conventional linear accelerators.

The beam-on time of the treatment session will be around 5 minutes, thus increasing IMRT productivity. This will also cause less patient discomfort and a greater biological efficacy of the treatment.

RapidArc™ (Radiotherapy Technology for Volumetric Arc Therapy)

In October 2007 Varian announced to have developed a new technology that uses an IMRT much faster than conventional IMRT. Such technology would decrease the 10 min average time typical of IMRT to 2 minutes only, thanks to the single arc of rotation with a continuous emission of the radiation beam, instead of the fixed angle radiation.

According to Varian, this new technique, named RapidArc, should be more precise than a traditional IMRT, it should have a higher capacity of dose conformation and be able to protect healthy tissues and surrounding organs at risk.

RapidArc uses a complex algorithm which works in the same way as a VMAT. The IMRT treatment is carried out with a single gantry revolution, through the simultaneous variation of the following 3 parameters:

- the rotation speed;
- the beam opening, through the movement of the MLC leaves (each 2 rotation degrees, for a total of 180 projections);
- the dose-rate.

Varian obtained in January 2008 the FDA 510 (k) approval with 2 licenses: the first one for the treatment hardware and the second one for the software module dedicated to the Eclipse planning system.

2.6. Imaging in radiotherapy processes

"Imaging" systems in radiotherapy processes are fundamental to provide the visualization of the body internal structure with the same reference of the treatment unit (*Figure 2.4*)

There are four main methods used for this aim:

1. Ultrasound
2. Megavoltage Computed Tomography (MVCT)
3. Kilovoltage Radiography (X-ray kV)
4. Cone-beam Computed Tomography (both megavoltage and kilovoltage)

1. Ultrasound imaging has been available as a device in radiation image-guided therapy since the late 1970s. Traditional ultrasound systems are combined with tracking systems (optical or robotic) to correlate ultrasound images with the isocentre of the treatment unit. These units are used for different applications, but are predominantly employed for prostate cancer treatments. They offer various advantages: low-cost, easy integration with the radiotherapy process and X-ray free. Nevertheless there are some controversies: the reliance on operators' skills for precision and accuracy and potential errors due to the shift of relevant organs during probe's placement.

However, there are on-going improvements in this system which allow the manufacturer to suggest the use of ultrasound in both simulation and treatment, avoiding the variation in interpretation of clinical data associated with tomography-ultrasound registration.

2. Megavoltage CT has been present for twenty years. The development of Tomotherapy units provided the ideal platform for progress of this technology. In the Tomotherapy the X-ray beam is generated by the same system that generates the treatment beam. The transmitted fluence rate is acquired by a conventional Xenon-based detector and stored for helical reconstruction. The images created are registered as treatment unit references and used to adjust the patient position according to delivered fluence pattern. The use of MV beam causes a loss in contrast by comparison with kilovoltage systems with equal doses (about 3 cGy to isocentre). However, the images generated are of remarkably high quality with excellent 3-D visualization of bony anatomy and detection of soft tissue structures, such as rectum, bladder and lung lesions. The geometric accuracy of these images allows a precise and accurate patient positioning. The Megavoltage Beam provides accurate estimate of electron density and reduces the magnitude of artefact related to metal implants. Possible drawbacks are a lower spatial resolution in the longitudinal direction (typically about 3 mm), limited possibility to register movements during the treatment and lower contrast/noise ratio at the megavoltage energies.

3. Kilovoltage radiography has originated for an adaptation of kV X-ray tubes to linear accelerators. These systems disappeared from the radiation therapy treatment room by the 1990s, but later developments in detectors have allowed their return. Initial systems used a flat-panel amorphous silicon detector installed on the treatment table below the patient, connected to X-ray tubes to the isocentre of the treatment unit. Thanks to high geometric precision, to low dose and high integration level, these systems allow to acquire multiple localisations during a single fraction used to verify the correct and stable positioning of treatment beam. The potential for acquisition frequency increase (about 15 fps) is given by the development of high-performance fluoroscopic modes of the flat-panel amorphous silicon detector. These systems allow the automated tracking of markers or high-contrast anatomical structure (focal lung lesions) during radiation delivery.

4. The same technological development that allowed the re-introduction of kilovoltage radiography has also consented the creation of volumetric "Cone-Beam" Computed Tomography. Both kilovoltage and megavoltage approaches have quickly adapted to conventional linear accelerator. With these approaches, a series of high-quality and low-dose radiographs are stored during the gantry rotation (190° to 360°) around the patient. This approach allows the operator to detect, localise and correct the anatomical position with respect to the treatment beam just before the irradiation. The main advantage of this approach is the localisation of soft tissues and the anatomical visualisation of patient in the treatment position. It is estimated that about 80% of linear accelerators are equipped with kilovoltage imaging capabilities

(radiographic and cone-beam computed tomography). Main problems are: movements during the acquisition, X-ray scatter, detector delay and detector's limited field of view. Megavoltage "Cone-Beam" CT systems owe their advantages to the common isocentre of treatment unit and to unrequested additional hardware. However, the presence of the treatment collimator limits the field of view of the imaging systems to a 400 mm diameter cylinder.

Imaging is envisaged in radiotherapy processes in a wide variety of forms. The approach chosen basically depends on: the type of imaging, the availability of the imaging technology (directly at the radiotherapy department, or at an adjacent radiological department) and the clinical objective.

Figure 2.4. Image-based radiation therapy

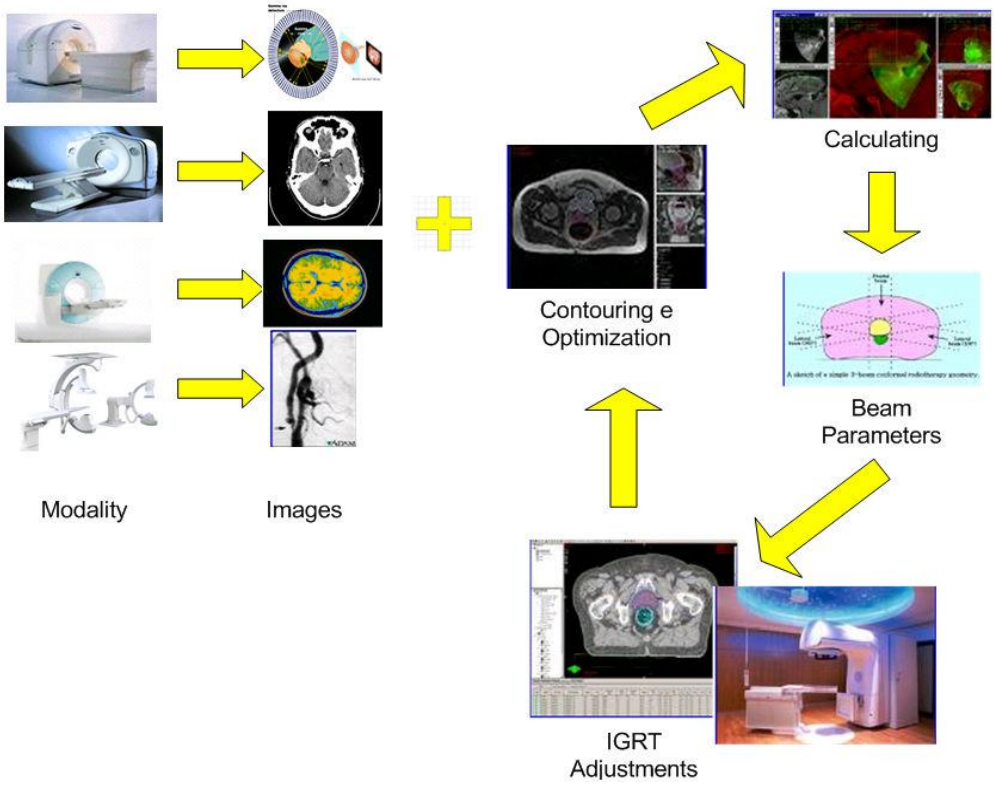


Image Guided Radiation Therapy has laid the foundation for the evolution of therapeutic treatments that address the daily morphological and anatomical changes of tumours and normal tissues. The molecular imaging will be soon integrated with the opportunity to observe, during the treatment, all clinical changes compared with the initial treatment planning.

IGRT could become a necessary tool for new therapeutic strategies, such as Adaptive Radiation Therapy (ART) bringing new perspectives for on-line and off-line post-processing and for dose delivery sparing healthy tissues. These activities will determine

the need for more specialists qualified in clinical, physics and technology and prospective of new activities.

A comparison sheet of technical characteristics of linear accelerators and treatment planning systems is provided in Appendix 1.

Sources

- Bortfeld T., Schimdt-Ulrich R., de Neve W., Wazer D.E. *Image-Guided IMRT: Concepts and Clinica Applications*. 2005.
- Bortfeld T., Webb S. Single-Arc IMRT. *Phys Med Biol*, 54: N9-N20, 2009.
- Clifford Chao K.S., Apisarnthanarax S., Ozyigit G. *Practical essentials of intensity modulated radiation therapy*. Edition: 2, Ed. Lippincott Williams & Wilkins, 2004.
- ECRI Institute. Computers, Radiotherapy Planning Systems - Healthcare Product Comparison System. ECRI Institute, August 2008.
- ECRI Institute. Computers, Radiotherapy Record and verify, Digital Imaging Systems, Portal - Healthcare Product Comparison System. ECRI Institute, August 2008.
- ECRI Institute. Linear Accelerators, Radiotherapy Units, Cobalt - Healthcare Product Comparison System. ECRI Institute, August 2008.
- ICRU. *Report 50. Prescribing, recording and reporting photon beam therapy*. Bethesda (MD): International Commission on Radiation Units and Measurements, 1993.
- ICRU. *Report 62. Prescribing, recording and reporting photon beam therapy*. Bethesda (MD): International Commission on Radiation Units and Measurements, 1999.
- IHE. *Radiation Oncology - Technical Framework* - Volumes 1-2. 2007.
- IHE. *Radiation Oncology - Technical Framework* - Volumes 1-2 - Image Registration (REG) Integration Profile - Addenda for Version 2.0. 2008.
- IHE. *Radiation Oncology - Technical Framework* - Volumes 1-2 - Managed Delivery Workflow Addenda for Version 2.0. 2008.
- National Cancer Institute - U.S. National Cancer Institutes of Health
http://www.cancer.gov
- Ragona R. Tecniche innovative "modulate" con LINAC. *XVII Convegno regionale AIRO Piemonte Valle d'Aosta, 2008.*
http://www.congressiairo.it/russi/Ragona_TecnicheinnovativemodulateconLINAC.pdf
(pdf, 3,4 Mb)
- Sterzing F., Schubert K., Sroka-Perez G., Kalz J., Debus J., Herfarth K. Helical Tomotherapy. Experiences of the first 150 patients in Heidelberg. *Strahlenther Onkol*, 184: 8-14, 2008.
- Yang J.N., Mackie T.R., Reckwerdt P., Deasy J.O., Thomadsen B.R. An investigation of Tomotherapy beam delivery. *Med Phys*. 24 (3), March 1997.

3. Definition of the problem and research questions

IGRT/IMRT has been introduced in clinical practice fairly recently and it is not equipped with a robust body of knowledge. The scientific literature available comprises mainly of uncontrolled and controlled case series evaluating technical performance and, sometimes, safety. Although the technology seems to be supported by a fairly strong theoretical and technical rationale, rigorous evaluations of clinical impact, proving the theoretically expected benefits, are still lacking.

For these reasons the main objective of this assessment has been to define the clinical rationale of IGRT/IMRT, in order to identify potentially clinically effective use and to develop research recommendations for further evaluation of the role and clinical impact of IGRT/IMRT.

A multidisciplinary panel of regional experts was convened with representatives of the following disciplines: radiotherapy, medical physics, oncology, nuclear medicine, radiology, statistics, economics, epidemiology and health research methodology. All 11 radiotherapy services of the Emilia-Romagna Region were represented.

As the paucity of evidence supporting the technology was known at the outset of the work, the main tasks of the panel consisted in:

- establishing the information necessary to determine the clinical role for IGRT/IMRT;
- assessing the results of scientific literature and state of knowledge;
- identifying research gaps that need to be filled in order to inform decisions on adoption and diffusion in clinical practice.

Given these main objectives, the work of the panel proceeded as follows:

- definition of the clinical rationale for IGRT/IMRT and outline of a broad evidence profile stating the dimensions and the outcomes of interest that need evaluation;
- selection of clinical indications for IGRT/IMRT and definition of research questions;
- outline of evidence profiles for each research question.

3.1. Rationale and evidence profile of IGRT

Considering the specific technological progress and development that the IGRT/IMRT presents, the panel agreed to define the rationale for its use as follows:

> Rationale: *A better correction for set up errors and organs' motion and a consequent more accurate dose targeting can decrease toxicity and/or increase clinical effectiveness of radiation treatments with radical intent of tumours in proximity of vital organs.*

On the basis of the above rationale the panel outlined the evidence profile of the technology, selecting and agreeing the relevant outcomes for each of the following dimensions of the technology: technical performance, feasibility, safety and clinical efficacy (*Table 3.1*).

The comparator was chosen to be any conformal radiotherapy with bi-dimensional image acquisition.

Table 3.1. Evidence profile: attributes of the technology and outcomes of interest

Attribute	Outcome
Technical performance	Set up error Organ motion
Feasibility	Patients' compliance Learning curve Costs
Safety	Acute adverse effect / toxicity Late adverse effect / toxicity
Clinical efficacy	Surrogate outcomes Tumour response Local control Loco-regional control Secondary outcomes Disease free survival Progression free survival Quality of life Primary outcomes Disease specific survival Overall survival

It should be highlighted that the issue of risk of secondary tumours after IGRT/IMRT in long term survivors was not considered by the panel.

3.2. Clinical indications and research questions

Based on the defined clinical rationale, which considers only radiation treatments with radical intent of tumours in proximity of vital organs, the panel agreed to evaluate the role of IGRT/IMRT only for the following tumours: prostate, head and neck, lung, brain and pancreas.

The specific research questions identified are listed in Table 3.2.

Table 3.2. Research questions

Tumour site	Research questions
Prostate	• Does IGRT/IMRT radical radiation treatment for patients with low or intermediate risk prostate cancer decrease toxicity compared to conformal radiotherapy with bi-dimensional image acquisition? • Does IGRT/IMRT radical radiation treatment, with a higher dose per fraction or hypofractionation, for patients with low or intermediate risk prostate cancer decrease toxicity and increase clinical efficacy compared to conformal radiotherapy with bi-dimensional image acquisition?
Lung	• Does IGRT/IMRT radical radiation treatment with hypofractionation for patients with T1 T2 N0 MO inoperable lung cancer, or patients with stage IIA, IIIA+B lung cancer, or patients with metastatic lung cancer (max 5 cm) increase clinical efficacy without increasing toxicity compared to conformal radiotherapy with bi-dimensional image acquisition?
Head and neck	• Does IGRT/IMRT radiation treatment with radical intent with hypofractionation - exclusive or associated with chemotherapy - in patients with any type of head and neck cancer, excluding those of the larynx, increase clinical efficacy and decrease toxicity compared to conformal radiotherapy with bi-dimensional image acquisition?
Brain	• Does IGRT/IMRT radiation treatment with radical intent with hypofractionation for primary brain tumour decrease toxicity compared to conformal radiotherapy with bi-dimensional image acquisition? • Does IGRT/IMRT radiation treatment with hypofractionation for metastatic brain tumour decrease toxicity compared to conformal radiotherapy with bi-dimensional image acquisition?
Pancreas	• Does IGRT/IMRT pre-operative radiation treatment with hypofractionation for pancreatic tumour increase clinical efficacy and decrease toxicity compared to conformal radiotherapy with bi-dimensional image acquisition? • Does IGRT/IMRT post-operative radiation treatment for pancreatic tumour decrease toxicity compared to conformal radiotherapy with bi-dimensional image acquisition? • Does IGRT/IMRT radiation treatment with hypofractionation for inoperable pancreatic tumour increase clinical efficacy and decrease toxicity compared to conformal radiotherapy with bi-dimensional image acquisition?

For each research question the panel defined the outcomes of interest and the expected benefits compared to the comparator (*Tables 3.3-3.7*). This a priori definition of scenario's specific evidence profile was intended to define clear research questions and ensure that subsequent evaluations and recommendations would be explicit and unbiased by the literature review's results.

A full systematic review on all types of published studies was carried out for the use of IGRT/IMRT in the 5 tumours and the retrieved studies were assessed against the evidence profiles defined for each research question.

Table 3.3. Evidence profile - prostate cancer

Target population

- Radiation treatment with radical intent for patients with low risk prostate cancer (T1-T2 with Gleason score 2-6 or PSA <10 ng/ml)
- Radiation treatment with radical intent for patients with intermediate risk prostate cancer (T2b-T2c with Gleason score 7 or PSA 10-20 ng/ml)

Rationale	Expected benefits	Outcomes	Comparator
Reduction of PTV at same dose and fractions	< toxicity = efficacy	Rectal toxicity grade >2 Erectile dysfunction Genitourinary toxicity Biochemical failure Local recurrence Distant metastasis Overall survival	3D-CRT and/or IMRT with biplanar imaging
Reduction of PTV and dose increase or escalation with conventional fractions	< toxicity > efficacy	Rectal toxicity Genitourinary toxicity Biochemical failure Loco-regional control Overall survival	3D-CRT and/or IMRT with biplanar imaging
Reduction of PTV and hypofractionation (> dose per fraction)	=/< toxicity > efficacy > efficiency	Rectal toxicity Genitourinary toxicity Biochemical failure Loco-regional control Local recurrence Distant metastasis Length of treatment	3D-CRT and/or IMRT with biplanar imaging

Table 3.4. Evidence profile - lung cancer

Target population

- Radiation treatment with radical intent for patients with T1 T2 N0 MO inoperable lung cancer
- Radiation treatment with radical intent (with or without chemotherapy) for stage IIA,IIIA+B lung cancer
- Radiation treatment for metastatic lung cancer max 5 cm

Rationale	Expected benefits	Outcomes	Comparator
Reduction of PTV and hypofractionation (> dose per fraction) (T1-T3)	=/< toxicity > efficacy > efficiency	Acute toxicity (pneumonia, esophagitis) Late toxicity (pulmonary fibrosis, heart disease) Loco-regional control Disease free survival - Quality of Life Distant metastasis Overall survival	3D-CRT and/or IMRT with biplanar imaging with conventional fractions/margins
Reduction of PTV and hypofractionation (> dose per fraction) (IIIA e B)	=/< toxicity > efficacy > efficiency	Acute toxicity (pneumonia, esophagitis) Late toxicity (pulmonary fibrosis, heart disease) Loco-regional control Disease free survival - Quality of Life Distant metastasis Overall survival	3D-CRT and/or IMRT with biplanar imaging with conventional fractions/margins
Reduction of PTV and hypofractionation with Tomotherapy (T1-T3 e IIIA e B)	< toxicity = efficacy > dose homogeneity > efficiency	Acute toxicity (pneumonia, esophagitis) Late toxicity (pulmonary fibrosis, heart disease) Loco-regional control	Other IGRT imaging with hypofractioning

Table 3.5. Evidence profile - head and neck cancer

Target population
• Radiation treatment with radical intent - exclusive or associated with chemotherapy - in patients with any type of head and neck cancer, excluding those of the larynx

Rationale	Expected benefits	Outcomes	Comparator
Reduction of set up error	< toxicity > efficacy	Acute toxicity (mucosytis, esophagitis, function of salivary glands) Late toxicity (xerostomy, spinal cord damages) Loco-regional control Overall survival	3D-CRT and/or IMRT with biplanar imaging
Dose escalation	< toxicity > efficacy	Acute toxicity Late toxicity Loco-regional control Overall survival	3D-CRT and/or IMRT with biplanar imaging
Hypofractionation with Tomotherapy	< toxicity > efficacy > dose homogeneity	Acute toxicity (Mucosytis, esophagitis) Late toxicity (Xerostomy, Cranial nerve deficit) Loco-regional control Disease free survival	Other IGRT imaging with hypofractioning

Table 3.6. Evidence profile - brain cancer

Target population
• Radiation treatment with radical intent for primary brain tumour • Radiation treatment for metastatic brain tumour

Rationale	Expected benefits	Outcomes	Comparator
CTV reduction and hypofractionation	< toxicity	Late cognitive disorders Toxicity Complete response to treatment	SRS + WBRT Customised immobilisation devices
Hypofractionation and SIB	< toxicity = efficacy	Quality of life Loco-regional control Time to disease progression Overall survival	3D-CRT and/or IMRT with biplanar imaging

Table 3.7. Evidence profile - pancreatic cancer

Target population
• Pre-operative radiation treatment for pancreatic tumour • Post-operative radiation treatment for pancreatic tumour • Radiation treatment for inoperable pancreatic tumour

Rationale	Expected benefits	Outcomes	Comparator
PTV reduction and hypofractionation (pre-operative treatment)	< toxicity > efficacy	Acute and late toxicity (enteritis, duodenal stenosis) Cytoreduction Downstaging	3D-CRT and/or IMRT with biplanar imaging
PTV reduction (post-operative treatment)	< toxicity	Acute and late toxicity (enteritis, duodenal stenosis))	3D-CRT and/or IMRT with biplanar imaging
Hypofractionation treatment with chemotherapy (inoperable patients)	< toxicity > efficacy	Acute and late toxicity (gastrointestinal disease) Downstaging Disease specific survival Overall survival	3D-CRT and/or IMRT with biplanar imaging with conventional fractions

3.3. Grading of the evidence and classification of uncertainty

From a quick overview of the published literature it was ascertained that the body of knowledge developed to date is far from robust. The panel therefore agreed on criteria for classification and interpretation of weak evidence. The principle adopted to differentiate levels of uncertainty was the likelihood that further studies of better methodological quality would change the results.

Using this criterion, an uncertainty profile has been outlined that distinguishes results in four categories:

- **Steady results**: results that are highly unlikely to be changed by further studies: results on all outcomes derived from systematic reviews of randomised controlled trials, several randomised controlled trials or quasi randomised trials, or controlled non randomised studies with adequate adjusting for confounding factors, large sample sizes and consistent and statistically significant results.
- **Plausible results**: consistent results on estimate of size and direction of effect, which would probably not change significantly if evaluated through randomised clinical trial:

  - consistent results on clinical efficacy, technical performance and safety derived from high quality observational studies (i.e. prospective comparative cohort studies with adequate adjusting for confounding factors) showing remarkable results for real clinical benefits unlikely to be changed for direction of estimate by further randomised trials;
  - consistent results on technical performance and on safety derived from observational studies or numerous controlled case series.
- **Uncertain results**: results on estimates of size and direction of effect that would most probably change, if evaluated through randomised clinical trials:
  - results on clinical efficacy coming from case series (controlled and uncontrolled) and observational studies;
  - results on technical performance and on safety derived from uncontrolled case series.
- **Unknown results**: results considered as non-existent:
  - results on all outcomes derived from case reports;
  - unreported, non-existent results on outcomes judged to be relevant by the panel.

Table 3.8 shows how different levels of uncertainty have been assigned according to study design and type of outcomes. The purpose of this evidence mapping, was to define the state of knowledge of the technology and to understand how current research is far from, or close to, answering clinically relevant questions. Expected outcome of this appraisal was to chart a future research course of action and define the experimental use of the technology within the health system. For each outcome the number, design and results of the retrieved studies are reported. The level of uncertainty is registered for each outcome evaluated in the studies (or not evaluated but considered relevant by the panel).

Table 3.8. Levels of uncertainty, type of studies and outcomes

Type of studies	Type of outcomes	
	Technical performance and safety	**Clinical efficacy**
SRs of RCTs; RCTs, high quality CCTs with consistent results	STEADY	STEADY
High quality observational studies showing remarkable results for real benefits	PLAUSIBLE	PLAUSIBLE
Observational studies with consistent results	PLAUSIBLE	UNCERTAIN
Numerous controlled case series with consistent results	PLAUSIBLE	UNCERTAIN
Uncontrolled case series	UNCERTAIN	UNKNOWN
Case reports	UNKNOWN	UNKNOWN
No studies	UNKNOWN	UNKNOWN

Following this classification it was agreed that the search in literature would be guided by the following framework (*Table 3.9*), summarising dimensions, outcomes of interest and studies' inclusion criteria.

Table 3.9. Evidence profile of IGRT/IMRT and criteria for the inclusion of studies

Attribute	Outcome	Inclusion criteria
Technical performance	Set up error Organ motion	SR of RCTs or CCTs RCT CCT Controlled case series Uncontrolled case series Studies on treatment planning
Feasibility	Patients' compliance Learning curve Costs	SR of RCTs or CCTs RCT CCT Controlled case series Uncontrolled case series
Safety	Acute adverse effect / toxicity Late adverse effect / toxicity	SR of RCTs or CCTs RCT CCT Controlled case series Uncontrolled case series
Clinical efficacy	Surrogate outcomes Tumour response Local control Loco-regional control Secondary outcomes Disease free survival Progression free survival Quality of life	SR of RCTs or CCTs RCT CCT Controlled case series
	Primary outcomes Disease specific survival Overall survival	SR of RCTs or CCTs RCT CCT

4. Systematic review of literature

The main objective of the review was to assess the technical performance and the clinical efficacy of IGRT/IMRT for lung, head and neck, brain, pancreatic and prostate cancer, which are the clinical indications agreed upon by the panel (*Chapter 3*).

4.1. Methods

Bibliographic search

For primary studies and systematic reviews we searched Medline and the Cochrane Library with no limits for starting date and up to January 2009 using the following key words:

- for IGRT: "image guided"[Title/Abstract]) AND ("radiation therapy"[Title/Abstract] OR "radiotherapy"[Title/Abstract] OR "radiation delivery"[Title/Abstract])) OR (IGRT) OR "Volumetric modulated arc therapy" [Title/Abstract] OR ("volumetric modulated arc" AND "radiotherapy" [Title/Abstract]) OR ("RapidArc" [Title/Abstract])
- for Tomotherapy: tomotherapy [Title/Abstract]

We included studies published in English, Italian, French, Spanish (see *Appendices 1 and 2*).

We also searched main international websites for Health Technology Assessment (HTA) reports. Additional studies were included if identified after the bibliographic search.

Prior to the report's publication an update of literature search was performed in June 2010, to retrieve primary studies on clinical efficacy published between January 2009 and June 2010.

Inclusion/exclusion criteria

To assess technical performance, we included systematic reviews (SR), Health Technology Assessment (HTA) reports, randomized controlled clinical trials (RCTs), controlled clinical trials (CCTs), observational controlled studies, controlled and uncontrolled case series on IGRT/IMRT methods based on volumetric reconstruction employing 3D KV- or MVCT, used in one of the clinical scenarios identified and reporting any of the following outcomes: set up errors and organ motion. We excluded studies on ultrasound systems or IGRT methods based only on systems of 2-D portal imaging or seed markers. No limits for the number of patients included were applied.

In absence of comparative data on set up error and organ motion for bi-dimensional image acquisition, we only report studies' results without advancing any interpretation on their hypothetical clinical relevance.

To assess clinical efficacy we included SRs, HTA reports, RCTs, CCTs, observational controlled studies, controlled and uncontrolled case series on IGRT methods based on volumetric reconstruction employing 3D KV- or MVCT, used in one of the already mentioned clinical scenarios and reporting data on any of the following outcomes: overall and disease specific survival, disease free and progression free survival, local and loco-regional control, acute and late toxicity. Studies recruiting less than 10 patients were excluded.

Quality assessment

Quality of systematic reviews and HTA reports was assessed using the criteria reported in the AMSTAR checklist (1); randomised controlled trials have been assessed using the criteria recommended by the Cochrane Collaboration (2); prospective cohort studies have been assessed using the Newcastle-Ottawa scale (3). Case series were not formally assessed for methodological quality as no standardised criteria are available. Elements considered were: sample size of the series, whether patients were consecutively recruited (yes, no, unclear) and whether the study was prospective (yes, no, unclear).

Data extraction

Data of each study are reported in separate evidence tables (*Appendix 2*) while summary of their results are included in the full document. Information reported in the evidence tables includes: study objective and study design, patients' characteristics, description of the technology, outcome measures, results and conclusions.

4.2. Results

The search resulted in 990 citations, 715 of which were initially excluded for double publication (8), on the basis of language exclusion criteria (9), topic and type of study exclusion criteria (698). We reviewed the full text of 275 articles and excluded 203 studies (6 HTA reports, 23 studies on clinical outcomes and 166 studies on technical performance) because the topic or type of study were not matching our inclusion criteria. Eight further studies on clinical outcomes were excluded as they enrolled less than 10 patients. The full text was not available for another 17 articles.

Fifty-five studies were included: 4 HTA reports, 34 studies on technical performance and 15 studies on clinical outcomes. Following the update of the literature search performed in June 2010 11 further studies were included: 6 on lung cancer, 2 on prostate cancer and 3 on head and neck cancer.

Overall results of the search and selection process are shown below (*Graph 4.1, Tables 4.1 and 4.2*).

Graph 4.1. Flow chart of the search process

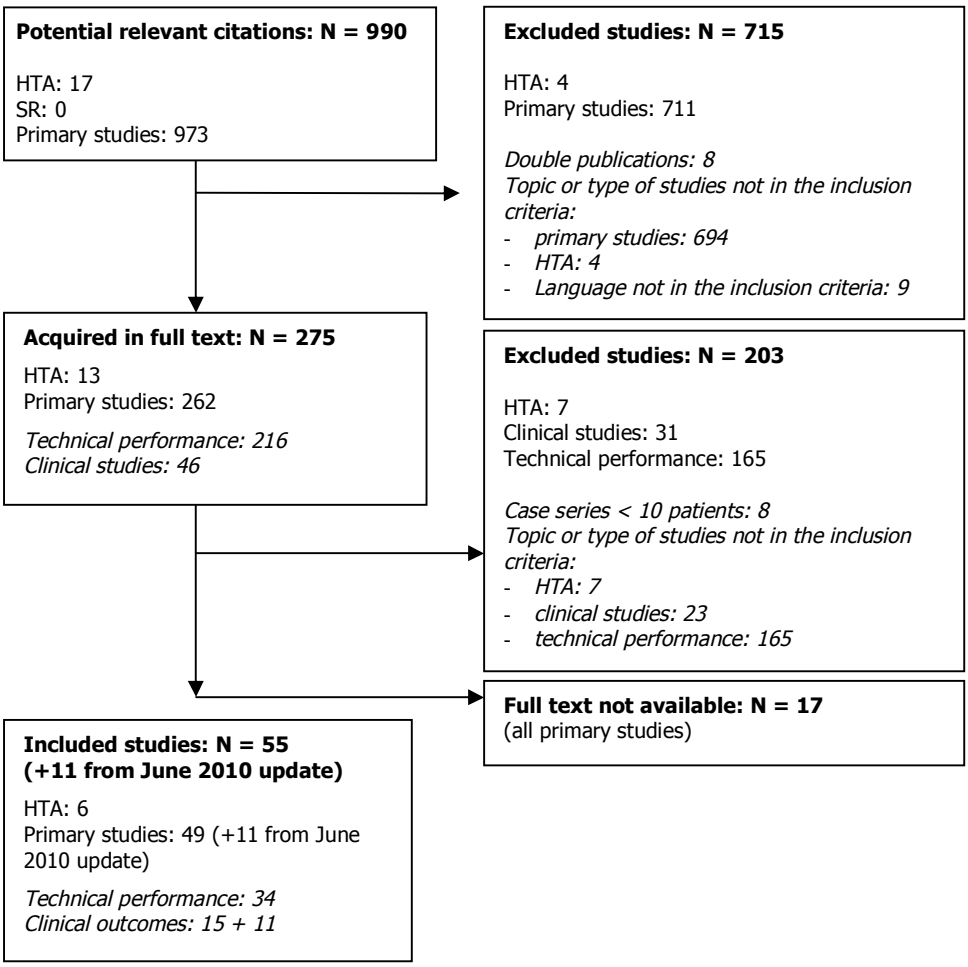


Table 4.1. IGRT/IMRT for lung, brain, head and neck, prostate and pancreatic cancer: number of retrieved publications

Lung cancer	Brain neoplasms	Head and neck cancer	Prostate cancer	Pancreatic cancer
Total number	**Total number**	**Total number**	**Total number**	**Total number**
HTA: 6	HTA: 6	HTA: 5	HTA: 6	HTA: 0
SR: 0	SR:0	SR:0	SR: 0	SR:0
Primary studies on clinical outcomes: 13 case series (7 on IGRT, 6 on Tomotherapy)	Primary studies on clinical outcomes: 2 case series on Tomotherapy	Primary studies on clinical outcomes: 4 case series on Tomotherapy	Primary studies on clinical outcomes: 7 case series (3 on IGRT, 4 on Tomotherapy)	Studies on clinical outcomes: 0
Primary studies on technical performance: 9 case series	Primary studies on technical performance: 4 case series	Primary studies on technical performance: 9 case series	Primary studies on technical performance: 20	Studies on technical performance: 0

Table 4.2. IGRT/IMRT for lung, brain, head and neck, prostate and pancreatic cancer: references of retrieved primary studies

	Lung cancer	Brain neoplasms	Head and neck cancer	Prostate cancer	Pancreatic cancer
IGRT/IMRT technical performance	Oh 2007 (16) Grills 2008 (17) Guckenberger 2007 (18) Harsolia 2008 (19) Purdie 2007 (20) Chang 2007 (21) Bissonnette 2009 (22) Johansen J2008 (23) Guckenberger 2007 (24)	Lawson 2008 (32) Drabik 2007 (33) Masi 2009 (34) Li 2007 (35)	Lawson 2008 (32) Sterzing 2008 (38) Drabik 2007 (33) Johansen 2008 (23) Wang 2008 (39) Zeidan 2007 (40) Sheng 2008 (41) Han 2008 (42) Li 2007 (35)	Lawson 2008 (32) Månsson Haskå 2008 (44) Carl 2008 (45) Oh, 2007 (16) Moseley 2007 (46) Beldjoudi 2008 (47) Kupelian 2008 (48) Fiorino 2008 (49) Langen 2005 (50) Song 2006 (51) Yoo 2009 (52) Nairz 2008 (53) Wertz 2007 (54) Adamson 2008 (55) Gayou 2008 (56) Sterzing 2008 (38) Drabik 2007 (33) Oldham 2005 (57) Smitsmans 2005 (58) Smitsmans 2004 (59)	
Tomo-therapy clinical studies	Siker 2006 (25) Kupelian 2005 (26) Bral 2010 (66) Park 2009 (67) Kim 2009 (68) Song 2010 (69)	Tomita 2008 (36) Do 2009 (37)	Kodaira 2009 (43) Shueng 2010 (72) Chen 2009 (73) Chen 2010 (74)	Keiler 2007 (60) Cozzarini 2007 (61) Cheng 2008 (62) Cozzarini 2008 (63)	
CBCT clinical studies	Franks 2007 (27) Chang 2008 (28) Fukumotu 2002 (29) Guckenberger 2009 (30) Onimaru 2003 (31) Videtic 2010 (70) Grills 2010 (71)			Engels 2009 (64) Pesce 2010 (75) Jereczek-Fossa 2009 (76)	

4.3. HTA Reports

Seventeen HTA reports have been retrieved. Three HTA reports were excluded because considered out of date (published in 2003). One HTA published by the Blue Cross Blue Shield Association in 2006 was excluded because it was a very short policy document with no description of the methodology and no reference for the studies considered. Thirteen HTA reports were included in our analysis for further evaluation (4-15, 65). Seven (4, 8-9, 11-13, 15) were excluded because they did not include any study on CBCT or Tomotherapy. Of the included six HTA reports, five (5-7, 10, 65) were specific on Tomotherapy, the other was on CBCT (14).

In 2008 Avalia (10) published a report on Tomotherapy, including 10 dosimetric/ treatment planning studies and 5 studies evaluating clinical outcomes in head and neck, brain, prostate and lung cancer. All the clinical efficacy studies have been included in our review of primary studies.

The authors do not come to any final conclusion on the technology but highlight the limits of the existing evidence. The little information available on efficacy suggests that the technology is promising, but existing literature consists mainly in studies on treatment simulation or planning. Results on safety of Tomotherapy in the treatment of prostate and lung tumour also seem promising.

In 2006, the NHSC (6) published an horizon scanning technology briefing on Helical Tomotherapy where three studies on treatment planning dosimetry for lung, brain, head and neck tumour are included. In relation to efficacy and safety, the authors highlight that research on the physical and dosimetric aspects suggests that Helical Tomotherapy may be superior to conventional radiotherapy in terms of radiation-dose distribution and dose-rate, but underline that no RCTs have been published. The authors conclude that although the technology is novel, it may not represent a significant breakthrough. Whilst IMRT is likely to prove superior to conventional radiotherapy, the resource implications of evaluating which IMRT system best meets the needs of the NHS will be significant.

In 2005, AHTA (5) published a horizon scanning prioritising summary on Tomotherapy. Two treatment planning studies (one on brain, one on lung tumour) were included. The first showed that the minimum target dose coverage was better with Tomotherapy than other radiotherapy, the second study showed that the quality of planning was slightly improved compared to IMRT planning. The authors conclude that there is limited clinical evidence available on the role of Tomotherapy, but it is currently being investigated in trials worldwide.

In 2006 HAS (7) published an evaluation report on IMRT with or without Tomotherapy. The literature review included 19 studies on IMRT with Tomotherapy, 18 of which were dosimetric studies. As far as head and neck, brain, lung, prostate tumours are concerned, they retrieved 3, 6, 5, 1 studies respectively.

The authors conclude that the benefits of IMRT (with or without Tomotherapy) are sufficient to justify its use in the following conditions: head and neck tumour (when protection of salivary glands is necessary); prostate cancer (radical intent); vertebral tumours (palliation); base of the brain; vault and other irradiation of the cerebral ventricles in children, craniopharyngioma, tumour of the hypophysis excluding high grade glioma (radical intent).

Use of Tomotherapy can also be justified in case of total body irradiation. For other conditions (paediatric tumours, retroperitoneal, muscles, lung tumours, cranio-spinal irradiation, medullar irradiation, multiple bone metastasis) the rationale for its benefit is not sufficiently determined.

In 2007 CHUG - UETMIS (14) published a report on the use of Cone-beam CT to define the clinical indications for the technology. The report includes:

- studies concerning the set up error (4 studies) in treatments for the following tumours: lung, prostate, vessel, head and neck;
- simulation studies (5 studies) on prostate, lung, brain, vertebral metastasis;
- feasibility studies on treatment for prostate, head and neck, lung, vessel, brain and liver (17 studies);
- on-going studies (7 studies);
- studies on the quality of images (14 studies).

The authors stress that:

- the retrieved studies are characterised by various limitations including small size and liaisons with industry;
- the studies highlight that imaging by Cone-beam CT allows the verification of set up errors;
- despite the presence of a greater number of artefacts, CBCT images are of a superior quality than portal images;
- simulation studies suggest the possibility to diminish the irradiation of healthy tissues and increase the target dose;
- there is a great variability among procedures in terms of number of required images and data on learning curves; moreover it is difficult to evaluate length of sessions.

The authors consider that in the absence of clinical studies, it is not possible to evaluate efficacy and safety of CBCT, nor conclude that the technical advantages of the CBCT lead to real clinical benefits. Similarly it is not possible to specify the type of patients that would mostly benefit from this technology. To date the most important application is represented by the set up verification of the patient's positioning. The authors conclude that it is necessary to find a balance between clinical benefits and additional resources and to take into account the potential additional risks associated with an increase in the number of images. Further clinical studies are required to evaluate efficacy and safety.

In 2009, CADTH (65) published a rapid review on the effectiveness and cost-effectiveness of Tomotherapy, cyberknife and gammaknife for the treatment of lung, central nervous system and intra-abdominal tumours. Only HTAs, SRs, RCTs and comparative studies were included.

No clinical or cost-effectiveness studies on Tomotherapy were found by the authors.

The authors conclude that given the current evidence, it is not possible to reliably estimate the comparative clinical effectiveness (benefits and harms) and cost-effectiveness of Tomotherapy, Gammaknife and Cyberknife. They also stress that additional factors. Such as specific patient caseloads and sites requiring radiotherapy, should be considered when buying one of these three technologies.

Summary results of HTA reports and evidence tables are reported in Appendix 2.

4.4. Primary studies

For all clinical conditions the technical outcomes assessed are set up error and organ motion and data on mean 3D vector, set up error and organ motion (V_M), systematic (V_Σ) and random (V_σ) error have been calculated as the square root of the sum of squares.

Summary results of studies and evidence tables of single studies are reported in Appendix 2.

Lung cancer

Studies on technical performance

Nine studies - all case series - assessing technical performance of IGRT/IMRT have been included (16-24). The number of patients enrolled in the studies varied from a minimum of 8 to a maximum of 87.

The technical outcomes assessed are set up error (all 9 studies) and organ motion (3 studies). The average set up error is 3.7 mm, the systematic error 3.5 mm and the random error 3.3 mm. The range of the set up error is 0.4-10.4 mm, 0.4-5.5 mm for the systematic error and 2.7 -3.9 mm for the random error. The average organ motion is 3.4 mm and the systematic error 2.2, with a range of 1.5-5.3 mm and 1.6-2.9 mm respectively.

Studies on clinical efficacy

Sixteen studies have been retrieved which assessed the impact of IGRT/IMRT on clinical outcomes. One study has been excluded because it was a narrative review on 3D-CRT. Another was excluded because it was a systematic review on the association between radiation esophagitis and 3D-CRT. One primary study and one systematic review were not considered because they assessed the efficacy of Cyberknife. One study was excluded because it included patients with tumours in many different sites without giving separate results for each site. Four studies were excluded because they were case series on less than 10 patients.

Seven studies were included, 2 on Tomotherapy (25, 26) and 5 on CBCT Accelerator (27-31).

Seven additional studies have been retrieved with the literature search update carried out in June 2010. Six of these (4 on Tomotherapy and 2 on CBCT Accelerator) met our inclusion criteria (66-71).

CBCT

Five case series were included (27-31). Data collection was retrospective in one study (30) unclear in the remaining studies. All but one (31) studies enrolled consecutively all patients treated during a defined time period. Patients enrolled ranged from 22 to 124. They were patients with T1/T2N0 peripheral lung tumour (27), patients with measurable primary lung cancer 6 cm or less in diameter, for whom surgery was not indicated (31), patients with inoperable stage I NSCLC (Non-Small Cell Lung Cancer) (29), patients with centrally and superiorly located stage 1 (T1/T2N0M0) or isolated lung parenchyma recurrent NSCLC (28), patients with metastases, NSCLC stage 1A, stage 1B, T3N0 (30). Total dose ranged from 40 to 60 Gy in 3-10 fractions. Authors of all studies concluded that treatment delivered with CBCT accelerators seems to be highly effective in achieving local control of the disease with low toxicity, particularly for early stage cancer. The technique could have a significant role in treating inoperable NSCLC and could be an effective alternative to surgery, especially for elderly patients. Prospective randomised trials with longer follow up are necessary to compare CBCT with conventional radiotherapy and/or surgery before any conclusion can be drawn.

From the June 2010 update of the literature search two more studies published in 2010 were included. One case series (70) on 26 patients with inoperable stage I lung cancer, with a mean follow up of 30.9 months, reported a 94.4% for local control at 3 years and an overall survival of 52% at 3 years. The other study (71) is a controlled case series comparing wedge resection (n 69) and SBRT (n 55) in a total of 124 patients with T1-2NO NSCLC. No statistically significant differences were found in regional and loco-regional recurrence and in distant metastases, while patients undergoing wedge resection had a better overall survival (87% versus 72%). The authors conclude that both treatments are reasonable options for inoperable Stage I NSCLC patients.

Tomotherapy

Two case series have been retrieved (25, 26) and neither specify whether data collection was prospective or retrospective. In the first study (25) 32 consecutive patients with any stage NSCLC were enrolled; 7 patients with mediastinal disease or extensive atelectasis had to be excluded because of the considerable difficulty encountered in delineating tumour borders on MVCT. Dosage and fractions varied according to the nature of treatment: 60 Gy in 5 fractions over 2 weeks for definitive radiotherapy with stereotactic radioablation (ESRA) in 4 patients, 57-80 Gy in 25 fractions over 5 weeks for definitive radiotherapy in 17 patients, 22-30 Gy in 8-10 fractions over 2 weeks for palliative therapy in 4 patients. The only outcome assessed was local control at the end of treatment. Authors concluded that tumour regression may be measured during treatment by MVCT.

A substantial reduction in tumour volume, consonant with traditional oncologic definitions of response, occurred only in a minority of patients. Patients treated ablatively or palliatively did not show significant volume decrease in the short interval of two weeks.

In the second study (32) 10 patients were included. Patients were treated with different doses according to different institutional preferences and protocols. The treatment intent was definitive in all cases, with all patients being treated at 2 Gy per fraction. The total doses and treatment fields were implemented at the discretion of the physician. The only outcome measured was tumour regression as documented by the serial MVCT scans. The authors of this study concluded that tumour regression can be documented for patients with non-small-cell lung cancer treated with Helical Tomotherapy. Clinical correlations between the observations made during the course of treatment and ultimate outcomes, e.g. local control, should be investigated.

From the June 2010 update of the literature search 4 additional studies were included (66-69): two retrospective case series and two prospective case series. The number of patients varied from 25 to 40. One study (66) evaluated a moderately hypofractionated treatment on Stage II inoperable locally advanced NSCLC. Outcomes assessed included acute and late toxicity, progression free survival and overall survival. Authors conclude that toxicity is acceptable and results on clinical outcomes are promising. One study (67) evaluated the rate of tomotherapy induced radiation pneumonitis which resulted in 52% of the 25 patients enrolled. The two retrospective case series (68, 69) measured overall survival. The first study reported a 60.5% overall survival at 12 months, while the second one reported a 56% overall survival at 24 months and 4 treatment related deaths. Authors conclude that Tomotherapy is a viable option for selected patients, but draw attention to the rate of fatal pulmonary complications.

Lung cancer - Conclusions

Six case series on Tomotherapy and 7 on CBCT, most of them without comparison with the standard treatment, have been retrieved. Only one controlled case series was found, comparing wedge resection and SBRT in patients with TI-2NO NSCLC and showing no statistically significant differences between the two treatments. The studies provide preliminary information and their methodological quality is generally low: small sample sizes and heterogeneous treatment regimens. Studies of higher methodological quality, i.e. randomised parallel comparisons with the standard treatment with longer follow up, are needed.

No conclusions can be drawn on toxicity, tumour control, relapse free survival and overall survival.

Brain cancer

Studies on technical performance

Four studies - all case series - assessing technical performance of IGRT/IMRT have been included (32-35). The number of patients enrolled in the studies varies from a minimum of 4 to a maximum of 57.

The technical outcome assessed is set up error (all 4 studies). The average set up error is 0.8 mm, the average systematic error 2.5 mm and the average random error 4.4 mm. The range of the set up error is 0.3-1.8 mm and for the systematic error 1.6-3.5 mm.

Studies on clinical efficacy

Eight studies have been retrieved assessing the impact of IGRT/IMRT on clinical outcomes. One study has been excluded because no therapy was given to the patients. Four primary studies and one systematic review were not considered because they assessed the efficacy of Cyberknife, a technique which uses bidimensional radiological and not volumetric imaging system.

Two studies on Tomotherapy were included (36, 37).

No additional studies were retrieve by June 2010 update of the literature search.

CBCT

No studies on safety and efficacy with CBCT were included.

Tomotherapy

Two case series have been included (36, 37) both recruiting patients with brain metastases. One is a retrospective case series on 30 patients (36), the other doesn't specify if the data collection is prospective or retrospective and includes 23 patients (37). Both studies enrolled consecutively all patients treated during a defined time period. In one study SRS (Stereotactic RadioSurgery) or SRT (Stereotactic RadioTherapy) are given as an alternative to whole brain radiotherapy (WBRT, Whole Brain RadioTherapy), in the other the SRS or SRT are given alone or in combination with WBRT depending on the number of metastases (in combination if metastases are more than one); outcomes considered are local recurrence, new recurrence, overall survival, neurologic symptoms, toxicity. Both studies intended to test whether SRS/SRT could be used as an alternative to WBRT to control brain metastases and prolong survival or improve quality of life, as WBRT is highly associated with neurotoxicity. However, without a parallel randomised comparison of SRS/SRT with WBRT on similar patients it is impossible to ascertain if this hypothesis can be confirmed.

Brain cancer - Conclusions

Two case series on Tomotherapy without comparison with the standard treatment have been retrieved. No studies assessing the efficacy of IGRT/IMRT on clinical outcomes were found. The quality of the retrieved studies was low, with small sample sizes and no study compared the safety and efficacy of Tomotherapy with other technologies. No conclusions can be drawn on toxicity, tumour control and overall survival.

Studies of higher methodological quality, i.e. randomised parallel comparisons with the standard treatment and longer follow up, are needed.

Head and neck cancer

Studies on technical performance

Nine studies - all case series - assessing technical performance of IGRT/IMRT have been included (23, 32, 33, 35, 38-42). The number of patients enrolled in the studies varies from a minimum of 4 to a maximum of 37.

The technical outcome assessed is set up error (all 9 studies). The average set up error between studies is 3.9 mm, the average systematic error 2.9 mm and the average random error 2.9 mm. The range of the set up error is 0.7-10.6 mm, for the systematic error 1.6-4.9 mm and for the random error 2.0-3.9 mm.

Studies on clinical efficacy

Six studies have been retrieved which assessed the impact of IGRT/IMRT on clinical outcomes. Two studies have been excluded because they were case series on less than 10 patients, two studies have been excluded because the IGRT was not based on a volumetric system. One was excluded because no clinical outcomes could be retrieved in the full text.

Only one study on Tomotherapy was finally included (43).

Four additional studies have been retrieved with the literature search update carried out in June 2010. Three of these, all on Tomotherapy, met our inclusion criteria (72-74).

CBCT

No studies on safety and efficacy with CBCT were included.

Tomotherapy

One case series on 20 patients with nasopharyngeal carcinoma has been included (43). It is not clear whether the data collection was prospective or retrospective and whether patients' enrolment was consecutive. The patients were at different stages of disease (IIB, III, IVa, IVb, IVc) and almost all (18 out of 20) were treated with chemotherapy with different number of cycles and some with reduced dose because of toxicity. All patients completed the scheduled course of radiotherapy. The planning dose was 70 Gy in 35 fractions, though some patients without chemotherapy were treated by Simultaneous Modulated Accelerated Radiotherapy (SMART) schedules such as 66 Gy for PTV1 in 30 fractions. Both efficacy and safety outcomes were assessed with a minimum follow up period of 3 months after treatment's completion. The authors highlight that all cases achieved clinical disease remission by the end of the treatment, more than half showed at least grade 3 adverse effects, the completion rate of chemo-radiotherapy was sufficient and parotid function recovered among patients with more than 6 months follow up. They conclude that Tomotherapy was effective in terms of IMRT planning and utility for patients with nasopharyngeal cancer.

From the June 2010 update of the literature search 3 additional studies - all case series - were included.

One case series (72) reported clinical outcomes for 10 patients treated for oropharyngeal cancer, which resulted in 67% of overall survival and 70% of disease free survival during a mean follow up of 18 months. Data on 77 patients treated for squamous cell carcinoma of head and neck (73) showed an overall survival and disease free survival of 77% and 71% respectively. One study (74) on re-irradiation of 21 patients with recurrent and second primary cancers of the head and neck reported local control and loco-regional control at 12 months of 72% and 83% respectively, as well as data on acute toxicity (23% of mucositis, 57% of skin desquamation and 23% of odynophagia/dysphagia).

Head and neck cancer - Conclusions

Four case series on Tomotherapy have been included. Sample sizes were small and patients were heterogeneous and at different stages of disease. Only preliminary information on initial clinical experience of very few centres was provided and no definitive conclusions could be drawn on either the safety or the efficacy of this technique. Studies of higher methodological quality, i.e. randomised parallel comparisons with the standard treatment with longer follow up, are needed.

Prostate cancer

Studies on technical performance

Twenty studies - seventeen case series, one simulation and two controlled case series - assessing technical performance of IGRT/IMRT have been included (16, 32, 33, 38, 44-59). The number of patients enrolled in the studies varies from a minimum of 3 to a maximum of 74.

The technical outcomes assessed are set up error (17 studies) and organ motion (4 studies). The average set up error between studies is 3.4 mm, the systematic error 3.4 mm and the random error 4.9 mm. The range of the set up error is 0.1-11.2 mm, for the systematic error 0.3-6.1 mm and for the random error 2.5-7.8 mm.

The average organ motion is 1.1 mm, the average systematic error 1.3 mm and the average random error 1.4 mm. The range of the organ motion is 0-2.8 mm, for systematic error 0.4-2.3 mm and the value of then random error is 1.4 mm.

Studies on clinical efficacy

Sixteen studies have been retrieved which assessed the impact of IGRT/IMRT on clinical outcomes. One study has been excluded because it was a narrative review. Seven have been excluded because the assessment concerned a bidimensional and not a volumetric image-guided system, one has been excluded because the assessment concerned the BAT system (B-mode Acquisition and Targeting System), an ultrasound-based image-guided system. One study was excluded because no clinical outcomes were reported. Two studies were excluded because they were case series on less than 10 patients.

Five studies were finally included, four on Tomotherapy (60-63) and one on CBCT (64).

Nine additional studies have been retrieved with the literature search update carried out in June 2010. Two of these, all on Tomotherapy, met our inclusion criteria (75-76).

CBCT

One case series on 238 patients with prostate cancer was included (64). It is not clear whether, in this study, the data collection was retrospective or prospective and whether patients were enrolled consecutively. Patients were at different levels of risk (from low to very high risk); they received a total dose ranging from 70 to 78 Gy (the number of fraction was not reported) and in some cases (70) a neoadjuvant and/or concurrent hormonal therapy. The authors conclude that the outcome of patients treated with Image-Guided Conformal Arc Radiotherapy is excellent. They underline that they were able to confirm the negative prognostic impact of the distended rectum on the planning computed tomogram described by others, but they highlight the potential pitfalls of image guidance techniques with respect to margin reduction around the clinical target volume.

From the June 2010 update of the literature search 2 additional case series were included.

One study (75) reported the experience of one centre using RapidArc on 45 patients with intermediate risk prostate cancer treated with a range of 76-78 Gy in 2 Gy fractions. Patients were evaluated at the end of treatment for acute rectal toxicity (Grade 0 in 72% and G1 in 28%), acute urinary toxicity (Grade 0 in 19%, Grade 2 in 69% and Grade 2 in 12%), erectile function (no function in 56%) and post-treatment PSA (median 0.4). The authors suggest that treatments resulted in an improvement in all planning objectives but that long term outcome need to be evaluated with adequate follow up. One retrospective case series with historical control (76) of low quality compared acute toxicity events in 179 patients with low and intermediate risk prostate cancer treated with hypofractionated IGRT (7.02 Gy in 26 fractions) with events occurring in an historical cohort of 174 patients with intermediate and high risk prostate cancer treated with non-IGRT (80 Gy in 40 fractions). Results are inconclusive.

Tomotherapy

Four case series have been included (60-63) with a sample size ranging from 35 to 146 patients. In three case series patients were enrolled consecutively while in one case series consecutiveness of the enrolment was not clear. Similarly, in three cases it was not clear whether data collection was prospective or retrospective. In two studies an historical comparison was used (60-63).

In one study radiotherapy was performed exclusively after radical prostatectomy, in three studies radiotherapy was performed in some of the cases with a radical intent. The dose varied from 58 to 84 Gy in 20-46 fractions.

In three studies authors conclude that findings related to toxicity are promising in terms of incidence of toxicity, although one author highlights that acute gastrointestinal toxicity is improved with Tomotherapy at a cost of an increase in genito-urinary toxicity. In one

study post-operative RT resulted in a greater incidence of acute gastrointestinal (GI) toxicity than did definitive RT. For post-operative RT, it would be prudent to use different dose-volume limits.

Prostate cancer - Conclusions

The evidence retrieved is limited: only case series were found and the comparison groups used in three studies were historical cohorts. All studies but one limited their analyses to safety outcome.

The studies only provide preliminary information and no definitive conclusions can be drawn on either safety or efficacy of this technique. Studies of higher methodological quality, i.e. randomised parallel comparisons with the standard treatment with longer follow up are needed.

No conclusions can be drawn on toxicity, tumour control, relapse free survival and overall survival.

Pancreatic cancer

No studies were found on pancreatic cancer.

From the June 2010 update of the literature search only one study on locally advanced pancreatic cancer was found, but excluded because reporting a local experience on two patients.

References

1. Shea B.J., Grimshaw J.M., Wells G.A. *et al*. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology*, 7: 10, 2007.
2. Higgins J.P.T., Altman D.G. Assessing risk of bias in included studies. In Higgins JPT, Green S. *Cochrane handbook for Systematic Reviews of Interventions*. Wiley-Blackwell, UK, 2008.
3. Wells G.A., Shea B., O'Connell D., Peterson J., Welch V., Losos M., Tugwell P. [Newcastle-Ottawa Scale]. http://www.lri.ca/programs/ceu/oxford.htm
4. Maceiras-Rozas C., Garcia-Caeiro A., Rey-Liste T., Castro-Bermudez M. *Intensity modulated radiotherapy*. Santiago de Compostela: Galician Agency for Health Technology Assessment (AVALIA-T), 2005, p. 144.
5. Parrella A., Mundy L., Hiller J. TomoTherapy HI-ART System(R): radiotherapy planning and treatment for cancer patients. *Horizon Scanning Prioritising Summary* - Volume 11. Adelaide: Adelaide Health Technology Assessment (AHTA) on behalf of National Horizon Scanning Unit (HealthPACT and MSAC), 2005.
6. National Horizon Scanning Centre. *Helical tomotherapy Hi-ART system for external cancer radiotherapy.* Birmingham: National Horizon Scanning Centre (NHSC), 2006.

7. Haute Autorité de santé/French National Authority for Health. *Radiothérapie conformationnelle avec modulation d'intensité*. 2006.
8. Van den Steen D., Hulstaert F., Camberlin C. *Radiothérapie conformationelle avec modulation d'intensité (IMRT).* Health Technology Assessment (HTA). Bruxelles: Centre féderal d'expertise des soins de santé (KCE); KCE reports 62B. 2007.
9. Veldeman L., Madani I., Hulstaert F. *et al*. Evidence behind use of intensity modulated radiotherapy: a systematic review of comparative clinical studies. *Lancet Oncol*, 9: 367-375, 2008.
10. Gonzalez M.V., Ravina A.R. *Sistema Hi-Art de tomoterapia helicoidal*. FT2008/02. Avalia, 2008.
11. ETSAD. *Radiothérapie confomrationnelle avec modulation d'intensité*. France, 2009.
12. Cigna. *Intensity modulated radiation therapy (IMRT)*. Coverage Position 0088. 2008.
13. AETS. *Sintesis-nuevas tecnologias. Tomoterapia helicoidal: Tomotherapy Hi-Art System*. 2007.
14. Cantin V., Labadie R., Rhainds M., Simard C. (eds.). *Unité d'évaluation des technologies et des modes d'intervention en santé (UETMIS). L'utilisation de l'accélérateur linéaire avec imagerie embarquée (Cone-beam) en radio-oncologie au CHUQ - Avis préliminaire.* Rapport (UETMIS 07-11). Québec, 2007.
15. Pearson S.D., Ladapo J., Prosse L. *Intensity modulated radiation theraapy (IMRT) for localized prostate cancer. Institute for clinical and economic review*. Final appraisal document 27/11/2007. ICER. 2007.

Lung

16. Oh S., Kim S., Suh T.S. How image quality affects determination of target displacement when using kilovoltage cone-beam computed tomography. *Journal Of Applied Clinical Medical Physics*, 8 (1): 101-107, 2007.
17. Grills I.S., Hugo G., Kestin L.L., Galerani A.P., Chao K.K., Wloch J., Yan D. Image-guided radiotherapy via daily online cone-beam ct substantially reduces margin requirements for stereotactic lung radiotherapy. *Int J Radiation Oncology Biol Phys*, 70 (4): 1045-1056, 2008.
18. Guckenberger M., Baier K., Guenther I., Richter A., Wilbert J., Sauer O., Vordermark D., Flentje M. Reliability of the bony anatomy in image-guided stereotactic radiotherapy of brain metastases. *Int J Radiation Oncology Biol Phys*, 69 (1): 294-301, 2007.
19. Harsolia A., Hugo G.D., Kestin L.L., Grills I.S., Yan D. Dosimetric advantages of four-dimensional adaptive image-guided radiotherapy for lung tumours using online cone-beam computed tomography. *Int J Radiation Oncology Biol Phys*, 70 (2): 582-589, 2008.

20. Purdie T.G., Bissonnette J.P., Franks K., Bezjak A., Payne D., Sie F., Sharpe M.B., Jaffray D.A. Cone-beam computed tomography for on-line image guidance of lung stereotactic radiotherapy: localization,verification, and intrafraction tumour position. *Int J Radiation Oncology Biol Phys*, 68 (1): 243-252, 2007.
21. Chang J., Mageras G.S., Yorke E., De Arruda F., Sillanpaa J., Rosenzweig K.E., Hertanto A., Pham H., Seppi E., Pevsner A., Ling C.C., Amols H. Observation of interfractional variations in lung tumour position using respiratory gated and ungated megavoltage cone-beam computed tomography. *Int J Radiation Oncology Biol Phys*, 67 (5): 1548-1558, 2007.
22. Bissonnette J.P., Purdie T.G., Higgins J.A., Li W., Bezjak A. Cone-Beam Computed Tomographic Image Guidance for Lung Cancer Radiation Therapy. *Int J Radiation Oncology Biol Phys*, 73 (3): 927-934, 2009.
23. Johansen J., Bertelsen A., Hansen C.R., Westberg J., Hansen O., Brink C. Set up errors in patients undergoing image guided radiation treatment.Relationship to body mass index and weight loss. *Acta Oncol*, 47 (7): 1454-1458, 2008.
24. Guckenberger M., Meyer J., Wilbert J., Richter A., Baier K., Mueller G., Flentje M. Intra-fractional uncertainties in cone-beam CT based image-guided radiotherapy (IGRT) of pulmonary tumours. *Radiotherapy and Oncology*, 83: 57-64, 2007.
25. Siker M.L., Tomé W.A., Metha M.P. Tumour volume changes on serial imaging with megavoltage CT for non small cell lung cancer during intensity modulated radiotherapy: how reliable, consistent and meaningful is the effect? *Int J Radiation Oncology Biol Phys*, 66: 135-141, 2006.
26. Kupelian P.A., Ramsey C., Meeks S.L. Serial megavoltage ct imaging during external beam radiotherapy for non-small-cell lung cancer: observations on tumour regression during treatment. *Int J Radiation Oncology Biol Phys*, 63: 1024-1028, 2005.
27. Franks K.N., Bezjak A., Purdie T.G. *et al*. Early results of image guided radiation therapy in lung stereotactic body radiotherapy (SRBT). *Clinical oncology*, 19 (3): S10, 2007.
28. Chang J.Y., Balter P.A., Dong L. *et al*. Stereotactic body radiation therapy in centrally and superiorly located stage 1 or isolated recurrent non small cell lung cancer. *Int J Radiation Oncology*, 72 (4): 967-971, 2008.
29. Fukumotu S., Shirato H., Shimzu S. *et al*. Small volume IGRT using hypofractionated, coplanar and non coplanar multiple fields for patients with inoperable stage I nonsmall cell lung carcinomas *Cancer*, 95: 1546-1553, 2002.
30. Guckenberger M., Wulf J., Mueller G. *et al*. Dose response relationship for image guided stereotactic body radiotherapy of pulmonary tumours: relevance of 4D dose calculation. *Int J Radiation Oncology*, 74 (1): 47-54, 2009.
31. Onimaru R., Shirato H., Shimizu S. *et al*. Tolerance of organs at risk in small-volume, hypofractionated, image-guided radiotherapy for primary and metastatic lung cancers. *Int J Radiation Oncology Biol*, 56: 126-135, 2003.

Brain

32. Lawson J.D., Fox T., Elder E., Nowlan A., Davis L., Keller J., Crocker I. Early clinical experience with kilovoltage image-guided radiation therapy for interfraction motion management. *Med Dosim*, 33 (4): 268-274, 2008.
33. Drabik D.M., MacKenzie M.A., Fallone G.B. Quantifying appropriate PTV set up margins: analysis of patient set up fidelity and intrafraction motion using post-treatment megavoltage computed tomography scans. *Int J Radiation Oncology Biol Phys*, 68 (4): 1222-1228, 2007.
34. Masi L., Casamassima F., Polli C., Menichelli C., Bonucci I., Cavedon C. Cone beam CT image guidance for intracranial stereotactic treatments: comparison with a frame guided set up. *Int J Radiation Oncology Biol Phys*, 71 (3): 926-933, 2008.
35. Li X.A., Qi X.S., Pitterle M., Kalakota K., Mueller K., Erickson B.A., Wang D., Schultz C.J., Firat S.Y., Wilson J.F. Interfractional variations in patient set up and anatomic change assessed by daily computed tomography. *Int J Radiation Oncology Biol Phys*, 68 (2): 581-591, 2007.
36. Tomita N., Kodaira T., Tachibana H. *et al*. Helical tomotherapy for brain metastases: dosimetric evaluation od treatment plans and early clinical results. *Technology in cancer research and treatment*, 7: 417-424, 2008.
37. Do L., Pezner R., Radany E. *et al*. Resection followed by stereotactic radiosurgery to resection cavity for intracranial metastasis. *Int J Radiation Oncology Biol Phys*, 73: 486-491, 2009.

Head and neck

38. Sterzing F., Sroka-Perez G., Schubert K., Munter M.W., Thieke C., Huber P. *et al*. Evaluating target coverage and normal tissue sparing in the adjuvant radiotherapy of malignant pleural mesothelioma: helical tomotherapy compared with step-and-shoot IMRT. *Radiother Oncol*, 86 (2): 251-257, 2008.
39. Wang J., Bai S., Chen N., Xu F., Jiang X., Li Y., Xu Q., Shen Y., Zhang H., Gong Y., Zhong R., Jiang Q. Clinical feasibility and effect of online cone beam computer tomography-guided intensity-modulated radiotherapy for nasopharyngeal cancer. *Radiother Oncol*, 90 (2): 221-227, 2008.
40. Zeidan O.A., Langen K.M., Meeks S.L., Manon R.R., Wagner T.H., Willoughby T.R., Jenkins D.W., Kupelian P.A. Evaluation of image-guidance protocols in the treatment of head and neck cancers. *Int J Radiation Oncology Biol Phys*, 67 (3): 670-677, 2007.
41. Sheng K., Chow M.C., Hunter G., Larner J.M., Read P.W. Is daily CT image guidance necessary for nasal cavity and nasopharyngeal radiotherapy: an investigation based on helical MV CB Tomo. *Appl Clin Med Phys*, 9 (1): 2686, 2008.
42. Han C., Chen Y.J., Liu A., Schultheiss T.E., Wong J.Y. Actual dose variation of parotid glands and spinal cord for nasopharyngeal cancer patients during radiotherapy. *Int J Radiation Oncology Biol Phys*, 70 (4): 1256-1262, 2008.

43. Kodaira T., Tomita N., Tachibana H., Nakamura T., Nakahara T., Nakahara R., Inokuchi H., Fuwa N. Aichi Cancer Center initial experience of intensity modulated radiation therapy for nasopharyngeal cancer using helical tomotherapy. *Int J Radiation Oncology Biol Phys*, 73: 1129-1134, 2009.

Prostate

44. Månsson Haská T., Honore H., Muren L.P., Høyer M., Poulsen P.R. Intrafraction changes of prostate position and geometrical errors studied by continuous electronic portal imaging. *Acta Oncol*, 47 (7): 1351-1357, 2008.

45. Carl J., Nielsen J., Holmberg M., Højkjaer Larsen E., Fabrin K., Fisker R.V. A new fiducial marker for Image-guided radiotherapy of prostate cancer: clinical experience. *Acta Oncol*, 47 (7): 1358-1366, 2008.

46. Moseley D.J., White E.A., Wiltshire K.L., Rosewall T., Sharpe M.B., Siewerdsen J.H., Bissonnette J.P., Gospodarowicz M., Warde P., Catton C.N., Jaffray D.A. Comparison of localization performance with implanted fiducial markers and cone-beam computed tomography for on-line image-guided radiotherapy of the prostate. *Int J Radiation Oncology Biol Phys*, 67 (3): 942-953, 2007.

47. Beldjoudi G., Yartsev S., Battista J.J., Van Dyk J. Optimization of MVCT imaging schedule in prostate cancer treatment using helical tomotherapy. *Cancer Radiother*, 12 (5): 316-322, 2008.

48. Kupelian P.A., Lee C., Langen K.M., Zeidan O.A., Mañon R.R., Willoughby T.R., Meeks S.L. Evaluation of image-guidance strategies in the treatment of localized prostate cancer. *Int J Radiation Oncology Biol Phys*, 70 (4): 1151-1157, 2008.

49. Fiorino C., Di Muzio N., Broggi S., Cozzarini C., Maggiulli E., Alongi F., Valdagni R., Fazio F., Calandrino R. Evidence of Limited Motion of the Prostate by Carefully Emptying the Rectum as Assessed by Daily MVCT Image Guidance with Helical Tomotherapy. *Int J Radiation Oncology Biol Phys*, 71 (2): 611-617, 2008.

50. Langen K.M., Zhang Y., Andrews R.D., Hurley M.E., Meeks S.L., Poole D.O., Willoughby T.R., Kupelian P.A. Initial experience with megavoltage (MV) CT guidance for daily prostate alignments. *Int J Radiation Oncology Biol Phys*, 62: 1517-1524, 2005.

51. Song W.Y., Chiu B., Bauman G.S., Lock M., Rodrigues G., Ash R., Lewis C., Fenster A., Battista J.J., Van Dyk J. Prostate contouring uncertainty in megavoltage computed tomography images acquired with a helical tomotherapy unit during image-guided radiation therapy. *Int J Radiation Oncology Biol Phys*, 65 (2): 595-607, 2006.

52. Yoo S., Wu Q.J., Godfrey D., Yan H., Ren L., Das S., Lee W.R., Yin F.F. Clinical evaluation of positioning verification using digital tomosynthesis and bony anatomy and soft tissues for prostate image-guided radiotherapy. *Int J Radiation Oncology Biol Phys*, 73 (1): 296-305, 2009.

53. Nairz O., Merz F., Deutschmann H., Kopp P., Schöller H., Zehentmayr F., Wurstbauer K., Kametriser G., Sedlmayer F. A strategy for the use of image-guided radiotherapy (IGRT) on linear accelerators and its impact on treatment margins for prostate cancer patients. *Strahlenther Onkol*, 184 (12): 663-667, 2008.
54. Wertz H., Boda-Heggemann J., Walter C., Dobler B., Mai S., Wenz F., Lohr A.F. Image-guided in vivo dosimetry for quality assurance of IMRT treatment for prostate cancer. *Int J Radiation Oncology Biol Phys*, 67 (1): 288-295, 2007.
55. Adamson J., Wua Q. Prostate intrafraction motion evaluation using kV fluoroscopy during treatment delivery: A feasibility and accuracy study. *Med Phys*, 35 (5): 1793-1806, 2008.
56. Gayou O., Miften M. Comparison of mega-voltage cone-beam computed tomography prostate localization with online ultrasound and fiducial markers methods. *Med Phys*, 35 (2): 531-538, 2008.
57. Oldham M., Le'tourneau D., Watt L., Hugo G., Yan D., Lockman D., Kim L.H., Chen P.Y., Martinez A., Wong J.W. Cone-beam-CT guided radiation therapy: A model for on-line application. *Radiotherapy and Oncology*, 75: 271.e1-271.e8, 2005.
58. Smitsmans M.H.P., De Bois J., Sonke J.J., Betgen A., Zijp L.J., Jaffray D.A., Lebesque J.V., Van Herk M. Automatic prostate localization on cone-beam ct scans for high precision image-guided radiotherapy. *Int J Radiation Oncology Biol Phys*, 63 (4): 975-984, 2005.
59. Smitsmans M.H.P., Wolthaus J.W.H., Artignan X., De Bois J., Jaffray D.A., Lebesque J.V., Van Herk M. Automatic localization of the prostate for on-line or off-line image-guided radiotherapy. *Int J Radiation Oncology Biol Phys*, 60 (2): 623-635, 2004.
60. Keiler L., Dobbins D., Kulasekere R., Einsten D. Tomotherapy for prostate adenocarcinoma: A report on acute toxicity. *Radiotherapy and Oncology*, 84 (2): 171-176, 2007.
61. Cozzarini C., Fiorino C., Di Muzio N. *et al*. Significant reduction of acute toxicity following pelvic irradiation with Helical Tomotherapy in patients with localized prostate cancer. *Radiotherapy and Oncology*, 84: 164-170, 2007.
62. Cheng J.C., Schultheiss T.E., Nguyen K.H., Wong J.Y.C. Acute toxicity in definitive versus postprostatectomy image-guided radiotherapy for prostate cancer. *Int J Radiation Oncology Biol Phys*, 71: 351-357, 2008.
63. Cozzarini C., Fiorino C., Di Muzio N., Alonge F., Broggi F., Cattaneo M., Montorsi F., Rigatti P., Calandrino R., Fazio F. Hypofractionated adjuvant radiotherapy with helical. Tomotherapy after radical prostatectomy: Planning data and toxicity results of a Phase I-II study. *N Radiotherapy and Oncology*, 88: 26-33, 2008.
64. Engels B., Soete G., Verellen D., Guy S. Conformal arc radiotherapy for prostate cancer: increased biochemical failure in patients with distended rectum on the planning computed tomogram despite image guidance by implanted markers. *Int J Radiation Oncology Biol Phys*, 74 (2): 388-391, 2009.

65. Boudreau R., Clark M., Nkansah E. *Tomotherapy gammaknife, cyberknife therapies for patients with tumours of the lung, central nervous system or intra abdomen: a systematic review of the clinical effectivenss and cost-effectiveness*. Ottawa: Canadian Agency for Drugs and Technologies in Health, 2009.

June 2010 update

Lung

66. Bral S., Duchateau M., Versmessen H., Engels B., Tournel K., Vinh-Hung V., De Ridder M., Schallier D., Storme G. Toxicity and Outcome Results of a Class Solution with Moderately Hypofractionated Radiotherapy in Inoperable Stage III Non-Small Cell Lung Cancer Using Helical Tomotherapy. *Int J Radiation Oncology Biol Phys*, 77 (5): 1352-1359, 2010.

67. Park H.J., Kim K.J., Park S.H., Kay C.S., Oh J.S. Early CT findings of tomotherapy-induced radiation pneumonitis after treatment of lung malignancy. *AJR Am J Roentgenol*, 193 (3): W209-W213, 2009.

68. Kim J.Y., Kay C.S., Kim Y.S., Jang J.W., Bae S.H., Choi J.Y., Yoon S.K., Kim K.J. Helical tomotherapy for simultaneous multitarget radiotherapy for pulmonary metastasis. *Int J Radiation Oncology Biol Phys*, 75 (3): 703-710, 2009.

69. Song C.H., Pyo H., Moon S.H., Kim T.H., Kim D.W., Cho K.H. Treatment-related Pneumonitis and Acute Esophagitis in Non-small-cell Lung Cancer Patients Treated with Chemotherapy and Helical Tomotherapy. *Int J Radiation Oncology Biol Phys*, 78 (3): 651-658, 2010.

70. Videtic G.M., Stephans K., Reddy C., Gajdos S., Kolar M., Clouser E., Djemil T. Intensity-modulated radiotherapy-based stereotactic body radiotherapy for medically inoperable early-stage lung cancer: excellent local control. *Int J Radiation Oncology Biol Phys*, 77 (2): 344-349, 2010.

71. Grills I.S., Mangona V.S., Welsh R., Chmielewski G., McInerney E., Martin S., Wloch J., Ye H., Kestin L.L. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. *J Clin Oncol*, 28 (6): 928-935, 2010.

Head and neck

72. Shueng P.W., Wu L.J., Chen S.Y., Hsiao C.H., Tien H.J., Cheng P.W., Kuo Y.S., Chen Y.J., Chen C.A., Hsieh P.Y., Hsieh C.H. Concurrent chemoradiotherapy with helical tomotherapy for oropharyngeal cancer: a preliminary result. *Int J Radiation Oncology Biol Phys*, 77 (3): 715-721, 2010.

73. Chen A.M., Jennelle R.L., Sreeraman R., Yang C.C., Liu T., Vijayakumar S., Purdy J.A. Initial clinical experience with helical tomotherapy for head and neck cancer. *Head Neck*, 31 (12): 1571-1578, 2009.

74. Chen A.M., Farwell D.G., Luu Q., Cheng S., Donald P.J., Purdy J.A. Prospective Trial of High-Dose Reirradiation Using Daily Image Guidance with Intensity-Modulated Radiotherapy for Recurrent and Second Primary Head-and-Neck Cancer. *Int J Radiation Oncology Biol Phys*. 2010.

Prostate

75. Pesce G.A., Clivio A., Cozzi L., Nicolini G., Richetti A., Salati E., Valli M., Vanetti E., Fogliata A. Early clinical experience of radiotherapy of prostate cancer with volumetric modulated arc therapy. *Radiat Oncol*, 5 (1): 54, 2010.

76. Jereczek-Fossa B.A., Zerini D., Fodor C., Santoro L., Cambria R., Garibaldi C., Tagaste B., Vavassori A., Cattani F., Alterio D., Gherardi F., Serafini F., Rocco B., Musi G., De Cobelli O., Orecchia R. Acute toxicity of image-guided hypofractionated radiotherapy for prostate cancer: Nonrandomized comparison with conventional fractionation. *Urol Oncol*. [Epub ahead of print]

List of excluded studies

• Adler J.R., Gibbs I.C., Puataweepong P. *et al*. Visual fiels preservation after multisession cynerknife radiosurgery for periotci lesions. *Neurosurgery*, 59: 244-254, 2006.

• Baisden J.M., Romney D.A., Reish A.G. *et al*. Dose as a function of lung volume and planned treatment volume in helical tomotherapy intensity modulated radiation therapy base stereotactic body radiation therapy for small lung tumours. *Int J Radiation Oncology Biol Phys*, 68: 1229-1237, 2007.

• Bayley A., Rosewall T., Craig T., Bristow R., Chung P., Gospodarowicz M., Ménard C., Milosevic M., Warde P., Catton C. Clinical application of high-dose, image-guided intensity-modulated radiotherapy in high-risk prostate cancer. *Int J Radiation Oncology Biol Phys*, 77 (2): 477-483, 2010.

• Bral S., Duchateau M., Versmessen H., Verdries D., Engels B., Ridder M.D., Tournel K., Collen C., Everaert H., Schallier D., De Greve J., Storme G. Toxicity report of a phase 1/2 dose-escalation study in patients with inoperable, locally advanced nonsmall cell lung cancer with helical tomotherapy and concurrent chemotherapy. *Cancer*, 116 (1): 241-250, 2010.

• Brown W.T., Xiadong W., Fowler J.F. *et al*. Lung metastases treated by cyberknife image guided robotic stereotactic radiosurgery at 41 months. *Southern medical Journal*, 101: 376-382, 2008.

• Calcerrada N.D.S., Amaro J.A.B., Cardiel G.A. *et al*. The safety and efficacy of robotic image guided radiosurgery system treatment for intra and extracranial lesions: a systematic review of the literature. *Radiotherapy and Oncology*, 89: 245-253, 2009.

• Chargari C., Campana F., Beuzeboc P., Zefkili S., Kirova Y.M. Preliminary experience of helical tomotherapy for locally advanced pancreatic cancer. *World J Gastroenterol*, 15 (35): 4444-4445, 2009.

• Eisbruch A., Harris J., Garden A.S., Chao C.K., Straube W., Harari P.M., Sanguineti G., Jones C.U., Bosch W.R., Ang K.K. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). *Int J Radiation Oncology Biol Phys*, 76 (5): 1333-1338, 2010.

• Fiorino C., Alongi F., Perna L., Broggi S., Cattaneo G.M., Cozzarini C., Di Muzio N., Fazio F., Calandrino R. Dose-volume relationships for acute bowel toxicity in patients treated with pelvic nodal irradiation for prostate cancer. *Int J Radiation Oncology Biol Phys*, 75 (1): 29-35, 2009.

• Friedland J.L., Freeman D.E., Masterson-McGary M.E., Spellberg D.M. Stereotactic body radiotherapy: an emerging treatment approach for localized prostate cancer. *Technol Cancer Res Treat*, 8 (5): 387-392, 2009.

• Ghia A., Tomé W.A., Thomas S. *et al*. Distribution of brain metastases in relation to the hippocampus: implications for neurocognitive functional preservation. *Int J Radiation Oncology Biol Phys*, 68: 971-977, 2007.

• Hara W., Tran P., Gordon L. *et al*. Cyberknife for brain metastases of malignant melanoma and renal cell carcinoma. *Neurosurgery*, 64: A26-A32, 2009.

• Hodge W., Wolfang A.T., Jaradat H.A. *et al*. Feasibility report of image guided stereotactic body radiotherapy (IG-SBRT) with tomotherapy for early stage medically inoperable lung cancer using extreme hypofractionation. *Acta Oncologica*, 45: 890-896, 2006.

• Jereczek-Fossa B.A., Fariselli L., Beltramo G., Catalano G., Serafini F., Garibaldi C., Cambria R., Brait L., Possanzini M., Bianchi L.C., Vavassori A., Zerini D., Orsi F., de Cobelli O., Orecchia R. Linac-based or robotic image-guided stereotactic radiotherapy for isolated lymph node recurrent prostate cancer. *Radiother Oncol*, 93 (1): 14-17, 2009.

• Joiner M., Salter B.J., Papanikolaou N. *et al*. Stereotactic body radiation therapy for centrally located lung lesions. *Acta Oncologica*, 45: 802-807, 2006.

• Macías V., Biete A. Hypofractionated radiotherapy for localised prostate cancer. Review of clinical trials. *Clin Transl Oncol*, 11 (7): 437-445, 2009.

• Martin J.M., Bayley A., Bristow R., Chung P., Gospodarowicz M., Menard C., Milosevic M., Rosewall T., Warde P.R., Catton C.N. Image guided dose escalated prostate radiotherapy: still room to improve. *Radiat Oncol*, 4: 50, 2009.

• Pervez N., Small C., MacKenzie M., Yee D., Parliament M., Ghosh S., Mihai A., Amanie J., Murtha A., Field C., Murray D., Fallone G., Pearcey R. Acute toxicity in high-risk prostate cancer patients treated with androgen suppression and hypofractionated intensity-modulated radiotherapy. *Int J Radiation Oncology Biol Phys*, 76 (1): 57-64, 2010.

• Pham C.J., Chang S.D., Gibbs I.C. *et al*. Preliminary visual field preservation after staged cyberknife radiosurgery for perioptic lesions. *Neurosurgery*, 54: 799-812, 2004.

• Rose J., Rodrigues G., Yaremko B. *et al*. Systematic review of dose volume parameters in the prediction of esophagitis in thoracic radiotherapy. *Radiotherapy and Oncology*, 91 (3): 282-287, 2009.

• Schirm M., Yartsev S., Bauman G. *et al*. Consistency check of planned adaptive option on helical tomotherapy. *Technology in cancer Research and Treatment*, 7: 425-432, 2008.

• The B.S., Paulino A.C., Lu J.K. *et al*. Versatility of the novalis system to deliver image guided strereotsctic body radiation therapy (SRBT) for various anatomical sites. *Technology in cancer Research and Treatment*, 6: 347-354, 2007.

• Wagner H. Image guided conformal radiation therapy planning and delivery for non small cell lung cancer. *Cancer Control*, 10: 277-288, 2003.

• Yoshikawa K., Saito K., Kajiwara K. *et al*. Cyberknife stereotactic radiotherapy for patients with malignant glioma. *Minim Invas Beurosug*, 49: 110-115, 2006.

5. Classification of uncertainty and identification of research gaps

The results of the literature review have been charted on the evidence profiles defined for each research question, and each dimension and outcome has been classified according to its level of uncertainty (see *Chapter 2*).

A synthesis of results of the evaluation and synthesis of all the evidence retrieved, carried out for each clinical scenario, is given for each tumour (*Tables 5.1-5.6*). Number, design and results of the retrieved studies, together with level of uncertainty, are reported for each outcome.

Available literature has been judged to give sufficient information on technical performance for all research questions, with the exception of those related to the cancer of pancreas. However the information on safety and clinical efficacy was judged to be very scarce. Overall we found:

- some information on safety for use in patients with prostate cancer
- some information on safety and very little on efficacy for use in patients affected by lung, head and neck and metastatic brain cancer.
- no information of any kind on use in patients with pancreatic cancer and with primary brain tumours

Results were presented to and discussed by the panel in order to:

- assess the stage of development of research on the technology and compare stages reached by different clinical indications;
- use the quantity and quality of existing research as criteria for the prioritisation of future clinical research questions;
- have a ready blue print for future clinical trials.

A graphical representation of the exercise of the uncertainty mapping, showing the stage of development of research on each clinical indication, is given in Graphs 5.1. to 5.6. Each graph reports the number, design and dimension of the studies retrieved for each domain of evaluation (technical performance, safety, efficacy on secondary clinical outcomes and efficacy on primary clinical outcomes). The level of uncertainty is shown through the colouring of the grid.

Graph 5.7 shows the studies retrieved for each domain on each clinical indication, allowing a quick comparison between the six scenarios and showing where research has developed and progressed most (or least).

Table 5.1. Prostate cancer: radiation treatment with radical intent for low and intermediate risk prostate cancer

Dimension (study design searched)	Outcome	Studies	Dose + fractions (range)	Results IGRT/IMRT (range)	Level of uncertainty
Technical performance (uncontrolled / controlled case series)	∑ set up error (P point range)	13 case series, 2 controlled case series 1 simulation		0.27 - 6.06 mm	PLAUSIBLE
	∑ organ motion (P point range)	4 case series		0.41 - 2.34 mm	
Safety (RCT, CCT, controlled case series)	Acute gastrointestinal toxicity	3 case series (Tomotherapy) + 1 case series with historical control (Tomo) (mean follow up 10-25 months)	64-84 Gy 28-46 fractions	Grade 0: 11-74% Grade 1: 26-64% Grade 2: 0-25% Grade 3 + 4: 0	UNCERTAIN
		2 case series (IGRT) (follow up 0-53 months) 1 case series with historical control (IGRT	70-78 Gy	Grade 1: 28-29% Grade 2: 0-11%	
	Acute genitourinary toxicity	2 case series (Tomotherapy) + 1 case series with historical control (Tomo) mean follow up 10-25 months)	64-84 Gy 28-46 fractions	Grade 0: 2-26% Grade 1: 45-49% Grade 2: 38-51% Grade 3: 0-4%	UNCERTAIN
		3 case series (IGRT) (follow up 0-53 months) 1 case series with historical control (IGRT)	70-78 Gy	Grade 1: 39-69% Grade 2: 12-39% Grade 3: 0-5%	
	Late gastrointestinal toxicity	1 case series (IGRT) (follow up 53 months)	70-78 Gy	Grade 3+4: 0	UNCERTAIN
	Late genitourinary toxicity	1 case series (IGRT) (follow up 53 months)	70-78 Gy	Grade 3+4: 0.6%	UNCERTAIN

Dimension (study design searched)	Outcome	Studies	Dose + fractions (range)	Results IGRT/IMRT (range)	Level of uncertainty
	Sexual dysfunctions	1 case series (IGRT)	76-78 Gy	No 56%	UNCERTAIN
Efficacy - surrogate outcomes (RCT, CCT, uncontrolled/ controlled case series)	Loco-regional control	No studies			UNKNOWN
Efficacy - secondary outcomes (RCT, CCT, controlled case series)	Local recurrence	No studies			UNKNOWN
	Biochemical failure	1 case series (IGRT) (follow up 53 months)	70-78 Gy	7% (low + intermediate risk)	UNCERTAIN
	Distant metastasis	No studies			UNKNOWN
	Progression free survival	No studies			UNKNOWN
Efficacy - primary outcomes (RCT, CCT)	Disease / relapse free survival	No studies			UNKNOWN
	Overall survival	No studies			UNKNOWN

Table 5.2. Lung cancer: radiation treatment with radical No studies intent for patients with T1+T2, and IIA, IIIA+B lung cancer - radiation treatment in metastatic lung cancer

Dimension (study design searched)	Outcome	Studies	Total mean dose + fractions (range)	Results IGRT/IMRT (range)	Level of uncertainty
Technical performance (uncontrolled / controlled case series)	∑ set up error (P point range)	9 case series		0.45 - 5.5 mm	PLAUSIBLE
	∑ organ motion (P point range)	3 case series		1.6 - 2.9 mm	
Safety (RCT, CCT, controlled case series)	Acute toxicity	4 case series (IGRT) (follow up 8-36 months)	45-60 Gy 3-10 fractions	Grade 0: 0 -45% Grade 1: 0 -50% Grade 2: 0-18% Grade 3: 0-2%	UNCERTAIN
		5 case series (tomotherapy) (follow up 3-24 months	40-70 Gy 20-30 fractions	Grade 0: 8% Grade 1: 32 -42% Grade 2: 51-52% Grade 3: 10-19%	
	Late toxicity	4 case series (IGRT) (mean follow up 8-36 months)	45-60 Gy 3-10 fractions	Grade 1: 0-47% Grade 2: 0-51% Grade 3: 0-11%	UNCERTAIN
		1 case series (Tomotherapy) follow up 24 months	70.5 Gy 30 fractions	Grade 3: 16%	

Dimension (study design searched)	Outcome	Studies	Total mean dose + fractions (range)	Results IGRT/IMRT (range)	Level of uncertainty
Efficacy - surrogate outcomes (RCT, CCT, uncontrolled / controlled case series)	Tumour control	4 case series (IGRT) (follow up 14-36 months)	40-60 Gy 4-8 fractions	29-100% 12 %	UNCERTAIN
		2 case series (Tomotherapy) (follow up 2-5 weeks - 2 months)	60 Gy 5 fractions	average decrease vol. 1.2%	
	Loco-regional control	2 case series (IGRT) (follow up 24-36 months)	48-60 Gy 8 fractions	83-94%	UNCERTAIN
		1 case series (Tomotherapy) (follow up 18 months)	60-70 Gy 30 fractions	63% at 12 months	
Efficacy - secondary outcomes (RCT, CCT, controlled case series)	Recurrence	2 case series (IGRT) (follow up 17-24 months)	40-60 Gy 4-8 fractions	4.5-26% (local) 7.7-18.2% (regional)	UNCERTAIN
		1 controlled case series (SBRT vs wedge resection)	48-60 Gy 4-5 fractions	no difference	
	Quality of life	No studies			UNKNOWN
	Distant metastasis	No studies			UNKNOWN
	Progression free survival	2 case series (IGRT) (mean follow up 18-24 months)	48-60 Gy 8 fractions	45-67% 34% at 36 months	UNCERTAIN
		2 case series (Tomotherapy) (follow up 24 months)	40-70 Gy 10-30 fractions	28-50% at 24 months	

Dimension (study design searched)	Outcome	Studies	Total mean dose + fractions (range)	Results IGRT/IMRT (range)	Level of uncertainty
Efficacy - primary outcomes (RCT, CCT)	Disease / relapse free survival	3 case series (IGRT) (mean follow up 8-36 months)	45-60 Gy 3-10 fractions	60-97% (primary t.) 49% (metastatic)	UNCERTAIN
	Overall survival	5 case series (IGRT) (mean follow up 8-36 months)	45-60 Gy 3-10 fractions	37-87 % (primary t.) 16-49% (metastatic)	UNCERTAIN
		1 controlled case series SBRT (follow up 30 months)			
		3 case series (Tomotherapy) (follow up 18-24)	40-70 Gy 10-30 fractions	27-56% (primary t.) 60% (metastatic)	

Table 5.3. Head and neck: radiation treatment with radical intent- exclusive or associated with chemotherapy - in all types of head and neck cancer, excluding those of the larynx

Dimension (study design searched)	Outcome	Studies	Total mean dose + fractions (range)	Results IGRT/IMRT (range)	Level of uncertainty
Technical performance (uncontrolled / controlled case series)	∑ set up error (P point range)	9 case series		1.58 - 4.75 mm	PLAUSIBLE
Safety (RCT, CCT, controlled case series)	Acute toxicity	1 case series (Tomotherapy)	70 Gy - 35 fractions		UNCERTAIN
	Mucosytis (stomatitis)			100% (G2: 45%; G3: 51%)	
	Skin reactions			100% (G1: 5%; G2: 55%; G3: 40%)	
	Vomiting			95% (G1: 20%; G2: 10%; G3: 65%)	
	Liver function			70% (G1: 45%; G2: 25%)	
	Leukopoenia			100% (G1: 30%; G2: 25%; G3: 35%; G4: 10%)	
	Anemia			90% (G1: 50%; G2: 25%; G3: 10%; G4: 5%)	
	Thrombocytopenia			55% (G1: 40%; G2: 10%; G3: 5%)	
	Renal function			30% (G1: 30%)	
	Late toxicity				UNCERTAIN
	Xerostomia	1 case series (Tomotherapy)	70 Gy - 35 fractions	93.4% (G1: 66.7%; G2: 26.7%)	
	Spinal cord damages	No studies			UNKNOWN
	Cranial nerve deficit	No studies			
Efficacy - surrogate outcomes (RCT, CCT, uncontrolled / controlled case series)	Tumour control	2 case series (Tomotherapy)	60-70 Gy 35 fractions	100% (at 3 months) 65% at 2 yrs	UNCERTAIN
	Loco-regional control	3 case series (tomotherapy)	60-70 Gy	80-83% 12 months	UNCERTAIN

Dimension (study design searched)	Outcome	Studies	Total mean dose + fractions (range)	Results IGRT/IMRT (range)	Level of uncertainty
Efficacy - secondary outcomes (RCT, CCT, controlled case series)	Recurrence	1 case series (Tomotherapy) Nasopharyngeal carcinoma	70 Gy - 35 fractions	10%	UNCERTAIN
	Progression free survival	1 case series (Tomotherapy) Nasopharyngeal carcinoma	70 Gy - 35 fractions	79.7% (95% CI: 40-100%) at 10 months	UNCERTAIN
Efficacy - primary outcomes (RCT, CCT)	Disease / relapse free survival	2 case series	60-70 Gy	70-71%	UNCERTAIN
	Overall survival	3 case series (Tomotherapy) mean follow up 10-18 m	60-70 Gy 35 fractions	67-95%	

Table 5.4. Brain: radiation treatment with radical intent for primary brain tumour

Dimension (study design searched)	Outcome	Studies	Total mean dose + fractions (range)	Results IGRT/IMRT (range)	Level of uncertainty
Technical performance (uncontrolled / controlled case series)	∑ set up error (P point range)	4 case series		1.62 - 3.47 mm	PLAUSIBLE
Safety (RCT, CCT, controlled case series)	Acute toxicity	No studies			UNKNOWN
	Late toxicity	No studies			UNKNOWN
Efficacy - surrogate outcomes (RCT, CCT, uncontrolled / controlled case series)	Tumour control	No studies			UNKNOWN
	Loco-regional control	No studies			
Efficacy - secondary outcomes (RCT, CCT, controlled case series)	Recurrence	No studies			UNKNOWN
	Quality of life	No studies			UNKNOWN
	Distant metastasis	No studies			UNKNOWN
	Progression free survival	No studies			UNKNOWN
Efficacy - primary outcomes (RCT, CCT)	Disease / relapse free survival	No studies			UNKNOWN
	Overall survival	No studies			UNKNOWN

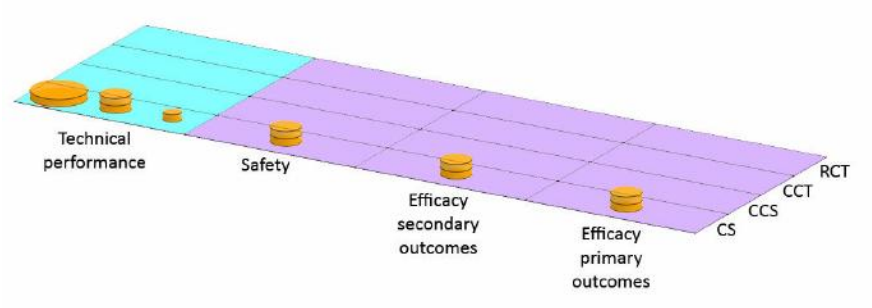
Table 5.5. Brain: radiation treatment for metastatic brain tumour

Dimension (study design searched)	Outcome	Studies	Total mean dose + fractions (range)	Results IGRT/IMRT (range)	Level of uncertainty
Technical performance (uncontrolled / controlled case series)	∑ set up error (P point range)	4 case series		1.62 - 3.47 mm	PLAUSIBLE
Safety (RCT, CCT, controlled case series)	Acute toxicity	1 case series (Tomotherapy)	35-50 Gy - 5-10 fractions	8.7 - 26%	UNCERTAIN
	Late toxicity	No studies			UNKNOWN
Efficacy - surrogate outcomes (RCT, CCT, uncontrolled / controlled case series)	Tumour control	1 case series (Tomotherapy)	35-50 Gy - 5-10 fractions	33% complete 59% partial 7% stable disease	UNCERTAIN
	Loco-regional control	No studies			UNKNOWN
	Symptoms control	1 case series (Tomotherapy)	15-27 Gy - 4-6 fractions	77%	UNCERTAIN
Efficacy - secondary outcomes (RCT, CCT, controlled case series)	Recurrence	1 case series (Tomotherapy)	15-27 Gy - 4-6 fractions	70%	UNCERTAIN
	Quality of life	No studies			UNKNOWN
	Distant metastasis	No studies			UNKNOWN
	Progression free survival	No studies			UNKNOWN
Efficacy - primary outcomes (RCT, CCT)	Disease / relapse free survival	1 case series (Tomotherapy)	15-27 Gy - 4-6 fractions	22% 1 yr	UNCERTAIN
	Overall survival	2 case series (Tomotherapy) (follow up 12 months)	15-50 Gy - 5-10 fractions	51% 4-6 months median surv.	UNCERTAIN

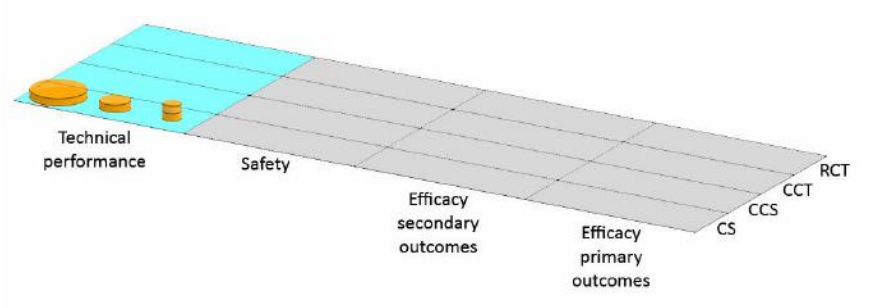
Table 5.6. Pancreas: pre-operative radiation treatment, post-operative radiation treatment and radiation treatment for inoperable pancreatic tumour

Dimension (study design searched)	Outcome	Studies	Dose + fractions (range)	Results IGRT/IMRT (range)	Level of uncertainty
Technical performance (uncontrolled / controlled case series)	∑ set up error (P point range)	No studies			UNKNOWN
	∑ organ motion (P point range)	No studies			
Safety (RCT, CCT, controlled case series)	Acute toxicity	No studies			UNKNOWN
	Late toxicity	No studies			UNKNOWN
Efficacy - surrogate outcomes (RCT, CCT, uncontrolled/controlled case series)	Cytoreduction	No studies			UNKNOWN
Efficacy - secondary outcomes (RCT, CCT, controlled case series)	Downstaging	No studies			UNKNOWN
Efficacy - primary outcomes (RCT, CCT)	Disease / relapse free survival	No studies			UNKNOWN
	Overall survival	No studies			UNKNOWN

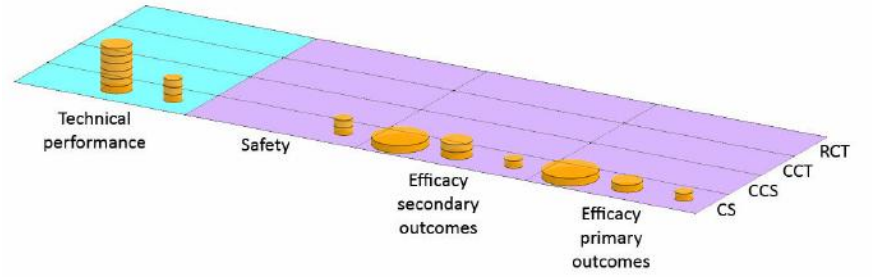
Graph 5.1. Uncertainty mapping - metastatic brain tumour[3]



Graph 5.2. Uncertainty mapping - primary brain tumour

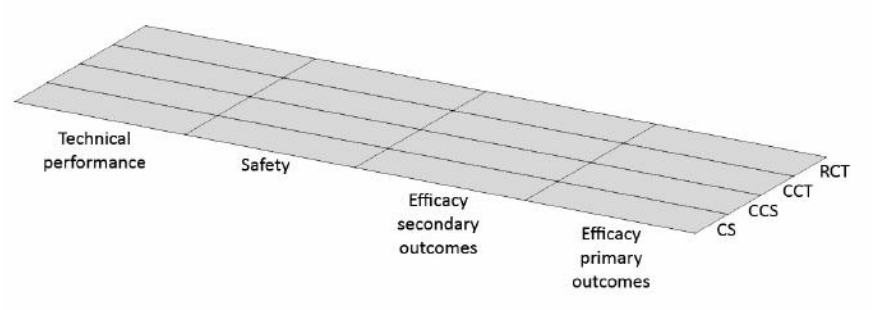


Graph 5.3. Uncertainty mapping - head & neck

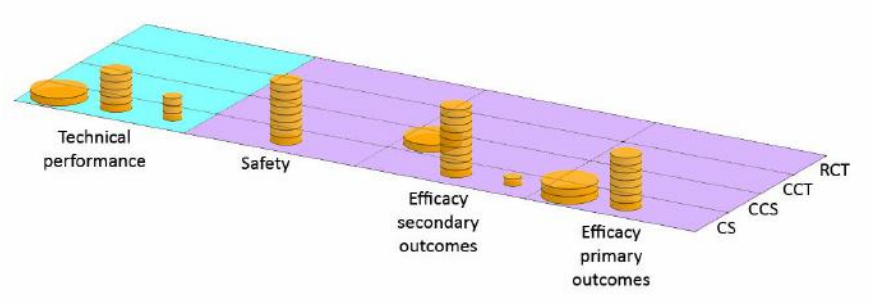


[3] Graphs 5.1 - 5.6 obtained with "5th Dimension" Software developed by A. Milani, S. Accorsi - ASSR Regione Emilia-Romagna.

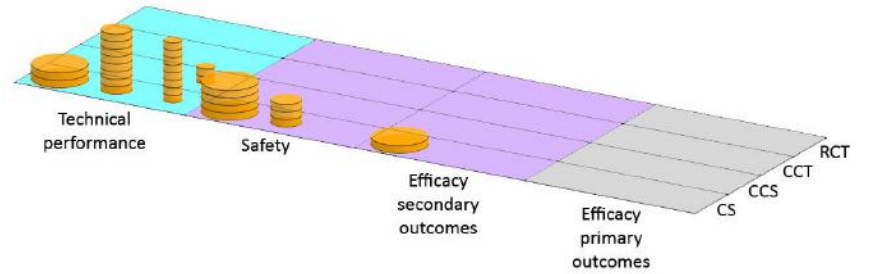
Graph 5.4. Uncertainty mapping - pancreas



Graph 5.5. Uncertainty mapping - Lung cancer

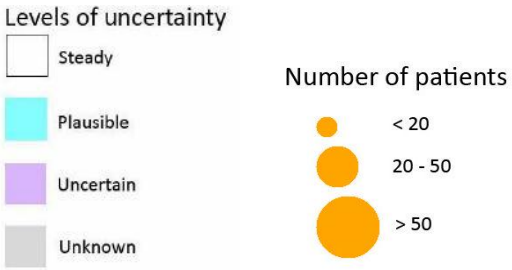


Graph 5.6. Uncertainty mapping - prostate

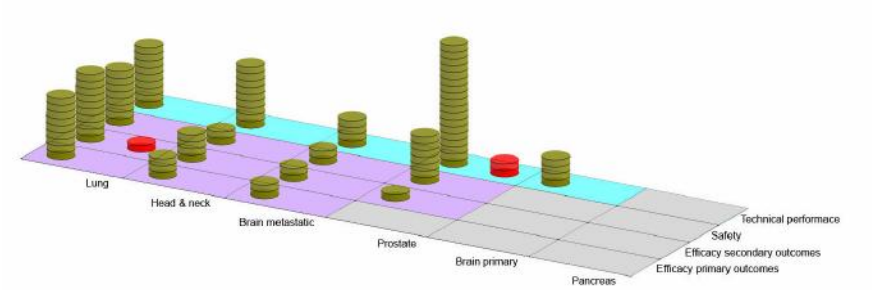


Legend

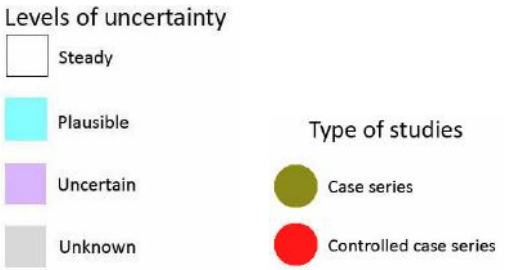
Study design: CS (case series), CCS (controlled case series), CCT (clinical controlled trial), RCT (randomized clinical trial)



Graph 5.7. Uncertainty mapping - all tumours[4]



Legend



[4] Graph 5.7 obtained with "5th Dimension" Software developed by A. Milani, S. Accorsi - ASSR Regione Emilia-Romagna.

6. Analysis of regional context and organisational implications

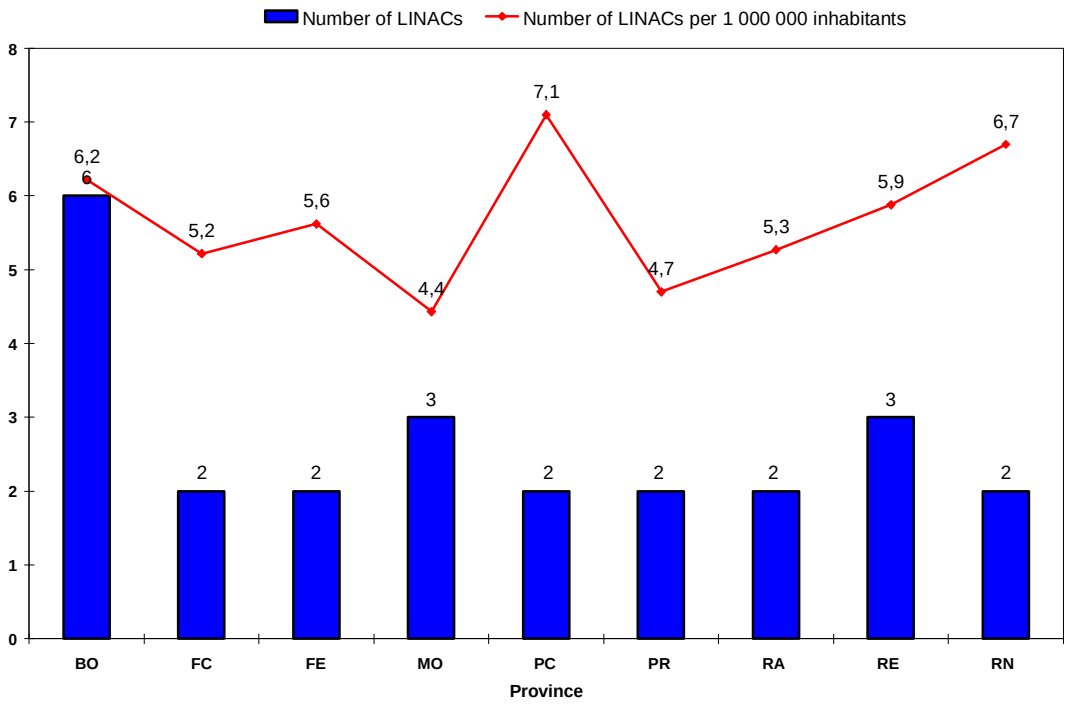
6.1. Radiation therapy infrastructures in the Emilia-Romagna Region

A list of all radiotherapy infrastructures present in our Region on December 2009 is given in Table 6.1. The overall distribution of the Linear Accelerators in the Emilia-Romagna Region per million inhabitants (considering only public Health Care Trusts) is represented in Graph 6.1. In Graph 6.2 the rate per million inhabitants of each province is compared against the regional average of 5.6/million inhabitants.

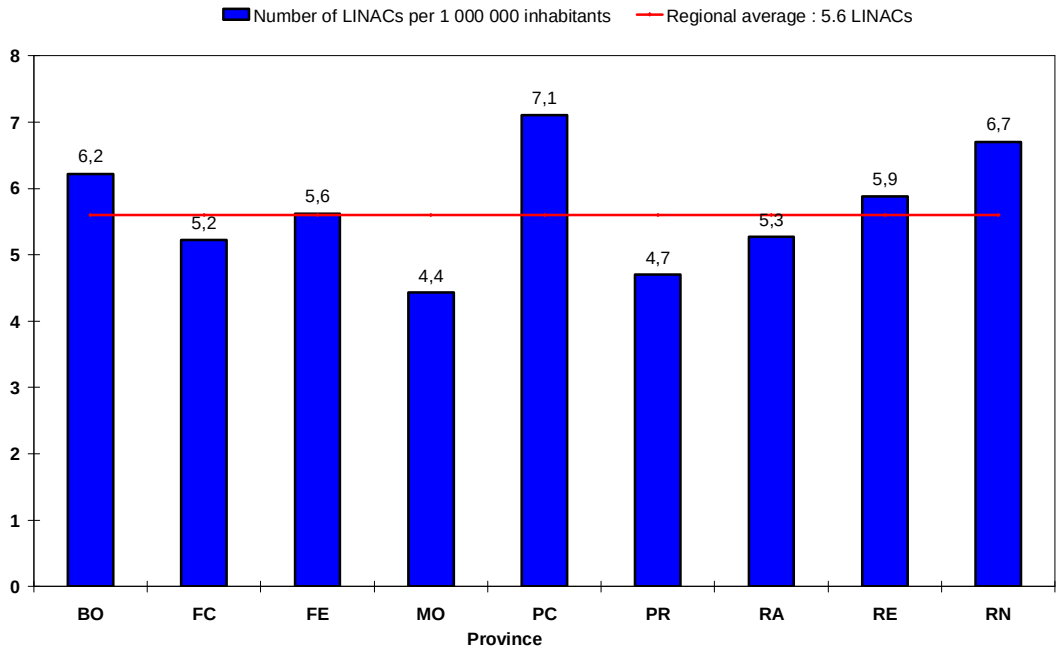
Table 6.1. Linear Accelerators models in the Emilia-Romagna Region (updated to December 2009) *[in grey IGRT/IMRT]*

Location	Manufacturer	Model	Obsolescence (years)
Health Care Trust of Piacenza	VARIAN INC	CLINAC 2300C/D	5
	VARIAN INC	CLINAC DBX	4.4
Health Care Trust of Bologna	ELEKTA AB	PRECISE	6.6
	ELEKTA AB	PRECISE	2.1
	ELEKTA AB	SYNERGY	10.8
Health Care Trust of Ravenna	ELEKTA AB	PRECISE	5
	PHILIPS MEDICAL SYSTEM	SL 75 5	17.1
Health Care Trust of Forlì - Meldola	TOMOTHERAPY	TOMOTHERAPY HI ART	2.5
	ELEKTA AB	SYNERGY	2.3
Health Care Trust of Rimini	SIEMENS AG	PRIMUS	5.1
	SIEMENS AG	ONCOR IMPRESSION IMRT+	2.9
Hospital Trust of Parma	VARIAN INC	CLINAC DHX HP	0.3
	SIEMENS AG	PRIMUS	7.3
Hospital Trust of Reggio Emilia	VARIAN INC	CLINAC 600 C	10.3
	TOMOTHERAPY	TOMOTHERAPY HI ART	1.7
	VARIAN INC	CLINAC 2100C	18.2
Hospital Trust of Modena	ELEKTA AB	SLI	12.5
	SIEMENS AG	PRIMUS	9.2
	TOMOTHERAPY	TOMOTHERAPY HI ART	1.7
Hospital Trust of Bologna	SIEMENS AG	PRIMUS	8.8
	SIEMENS AG	PRIMUS	8
	SIEMENS AG	ONCOR	5.3
Hospital Trust of Ferrara	VARIAN INC	CLINAC DHX	4
	VARIAN INC	CLINAC 2100 C/D	8.6

Graph 6.1. Number of Linear Accelerators (LINACs) in public Health Care Trusts, per province and per 1 000 000 inhabitants

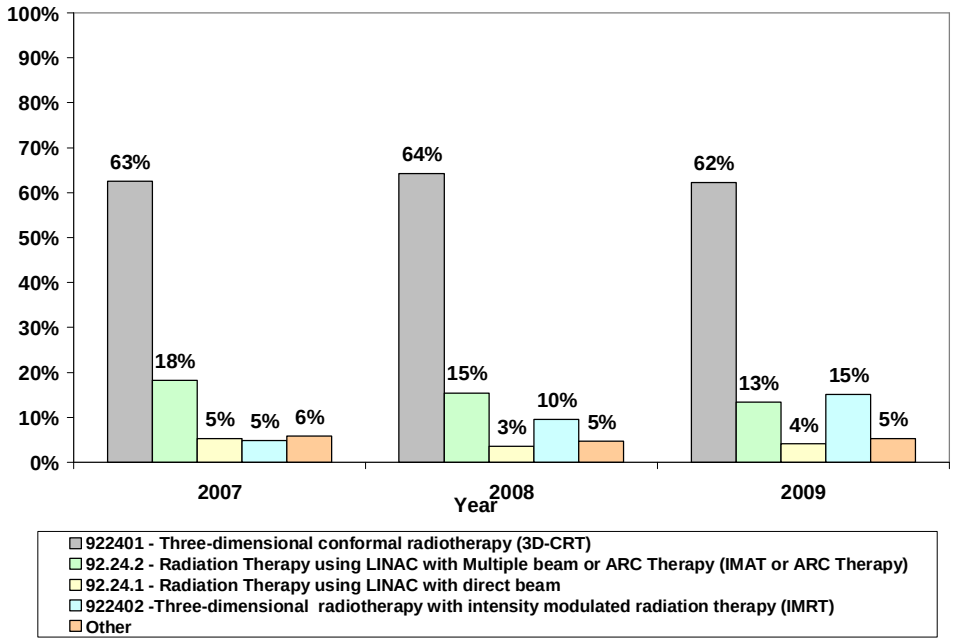


Graph 6.2. Provinces' rates of per 1 000 000 inhabitants



The technological advances offered by innovative systems of IGRT/IMRT have been followed and taken up in the Emilia-Romagna Region. Graph 6.3 shows how radiation treatments are distributed among different types of equipments over several years. The uptake of innovative technology since 2007 is confirmed: more than half of the treatments are delivered through 3D Conformal Radiotherapy but there is an upward trend, from an initial 5% in 2007 to 15% in 2009, of treatments delivered with intensity modulated radiotherapy (IMRT).

Graph 6.3. Distribution of types of radiation treatment



Seven of the eleven regional radiotherapy centres are at the moment equipped with an IGRT/IMRT system, for a total of 8 IGRT/IMRT systems, which is an adequate number for the expected eligible patients, and the geographical distribution of the systems covers most of the region's territory.

6.2. Estimated use of IGRT/IMRT

The analysis of the RER context focused on data relating to tumours identified by the panel as having a clinical indication for IGRT/IMRT (Prostate, Lung, Head & Neck, Brain and Pancreas).

Over a total incidence of 33 679 tumour cases in the Emilia-Romagna Region, the 5 tumours examined add up to 8 659 incident cases, which represent 26% of the total. Graph 6.4 shows the distribution of the 5 tumours by sex.

The 5 types of tumours differ in terms of incidence and mortality, as reported by the RER Tumour Register and shown in Table 6.2.

Graph 6.4. The 5 selected tumours in the RER: distribution over total incident cases by sex

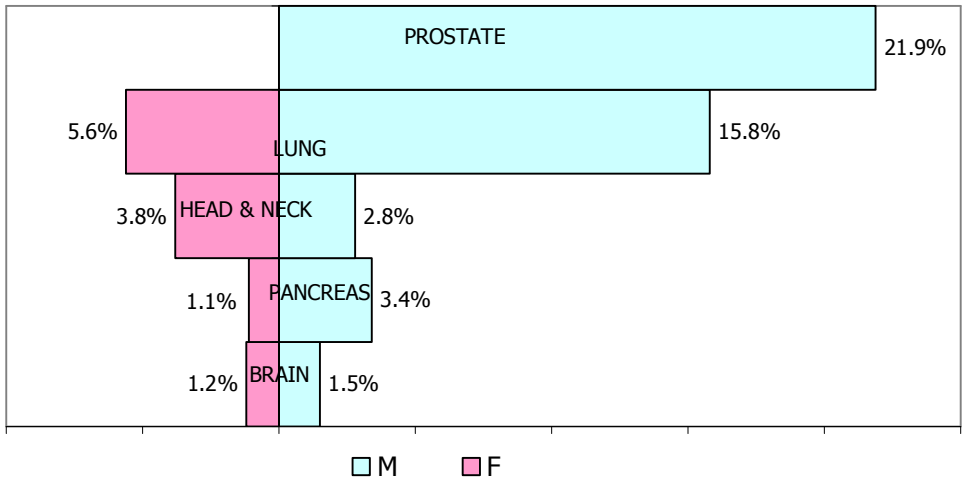


Table 6.2. Standardised rate (*100 000 inhabitants) of incidence and mortality in RER

	INCIDENCE		MORTALITY	
SITE	**Standardised rate (*100 000)**		**Standardised rate (*100 000)**	
	M	**F**	**M**	**F**
Prostate	168.9		32.1	
Lung	120.3	34.1	104.7	30.5
Head & neck	26.7	7.5	12.3	3.2
Pancreas	21.4	22.4	18.5	21.1
Brain	11.4	8.5	8.1	6.6

The estimated volumes for the 5 clinical indications that could potentially benefit from the use of IGRT/IMRT were obtained from a regional survey carried out on all radiotherapy treatments given in a two-month period of 2004. Table 6.3 reports the annual number of expected eligible cases by tumour, with an additional 10% of other possible clinical indications, giving a total of 1 569 eligible patients per year.

This estimate represents 20% of all radiation treatments provided in one year for the 5 tumours. The proportion of patients eligible for IGRT/IMRT for the 5 tumours was obtained dividing incidence by number of cases falling within the clinical indications given by the panel. These proportions resulted to be as follows (*Graph 6.5*): 23% of patients with primary brain cancer; 20% of patients with metastatic brain cancer; 24% of patients with head & neck cancer; 10% of patients with primary lung cancer; 21% of patients with prostate cancer and 18% of patients with pancreatic cancer. The latter proportion was calculated over prevalence rather than incidence, as the indication for IGRT/IMRT in these patients would be for pre and post-operative as well as advanced treatment.

Over the estimated total of 1 569 eligible patients, the proportion of IGRT/IMRT eligible patients for each of the 5 tumours was calculated (*Graph 6.6*). Based on these estimates the activity of an IGRT/IMRT service was hypothetically subdivided in the following proportions: 45% of activity dedicated to patients with prostate cancer, 19% to patients with lung cancer, 11% to patients with head & neck cancer, 6% to patients with primary or metastatic brain cancer, 5 % to patients with pancreatic cancer and the remaining 9% for other clinical indications. If only radical treatments are considered, the total number of eligible patients results in 1 338 per year.

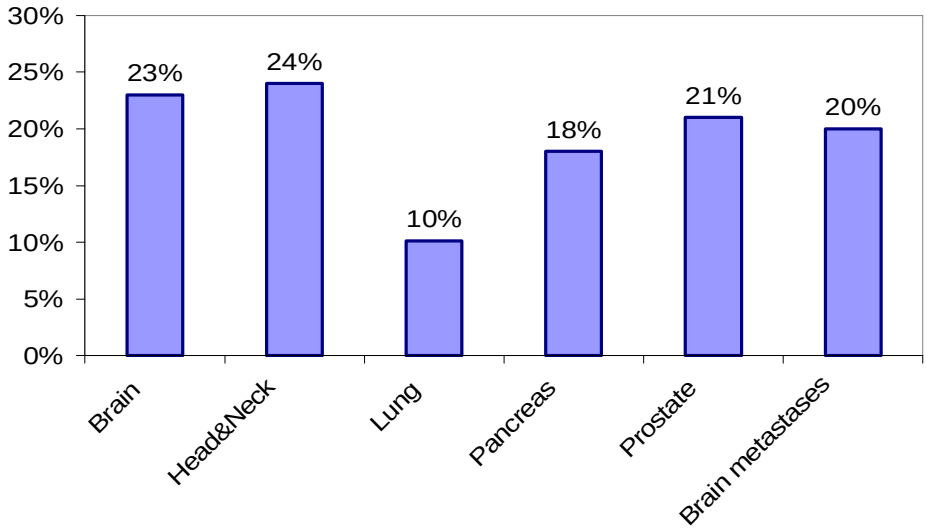
Table 6.3. Cases eligible for IGRT, by tumour site

Tumour site	Total cases*		Incidence[$]	Total cases/incidence*100
	N	%		%
Brain	96	6	411	23
Brain metastases	88	6		20
Head & Neck	168	11	698	24
Lung	294	19	2 899	10
Pancreas (prevalence)	78	5	415	18
Prostate	702	45	3 418	21
SUBTOTAL	1 426			
Other sites	143	9		
Total	***1 569***	***100***		

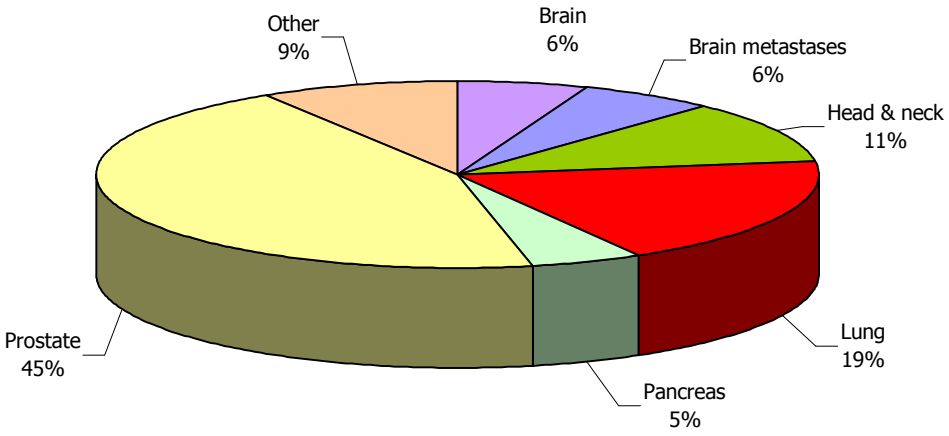
* Data source: survey carried out in the period March-April 2004 on patients treated in the radiotherapy centres of the Emilia-Romagna Region.

[$] Data of incidence are derived from the regional Tumour Register.

Graph 6.5. Percentages of incident cases eligible for IGRT for the 5 tumours



Graph 6.6. Distribution of expected regional IGRT/IMRT activity by tumour



6.3. Organisational implications

The distribution and percentages reported in Graph 6.1 and Graph 6.2 can be used by single radiotherapy centres to asses their use of IGRT/IMRT and estimate their expected volumes. These estimates have been calculated on the basis of current activity of radiation therapy services of Emilia-Romagna.

The distribution over the five tumours of the hospital's IGRT/IMRT activity can be compared to the regional estimated distribution (*Graph 6.2*) and the number of patients eligible for IGRT/IMRT can be worked out by applying the percentages reported in Graph 6.1 to the provincial incident cases.

These considerations can turn out to be of some importance for the organisational implications related to the access to IGRT/IMRT treatment. Patients' pathways leading to radiation therapy treatment, in fact, vary according to whether a multidisciplinary approach for evaluation and therapeutic decision is established and secured to the patient. Should further evaluations of IGRT/IMRT confirm the above clinical indications for this type of treatment, access to the technology would have to be guaranteed for all eligible patients. Given the variability in pathways, it is suggested that referral protocols should be agreed upon by all radiotherapy centres of the RER, requiring that the radiotherapist places an indication for IGRT/IMRT treatment. Single waiting lists for patients eligible for IGRT/IMRT treatments could be set up in each regional sub-area to ensure admittance to the nearest IGRT/IMRT centre within the appropriate time interval.

A close collaboration between centres is recommended ensuring a smooth take over of the patient by the IGRT/IMRT centre, that neither disorients the patient nor undermines the relationship between patients and their local health centre. Such close collaboration, which appears to be long-standing between RER radiotherapy centres, will also guarantee uniform and appropriate waiting times for patients coming from different geographical areas as well as reciprocal support, should system or machines' failures occur.

For a supposed further development of this technology, centres considering acquisition of latest IGRT/IMRT systems should take into account that the system requires dedicated space, consisting in two rooms, one of which acclimatised, often involving the construction of a dedicated bunker. In terms of staff, the technology requires one radiotherapist, one medical physicist and a dosimetrician. A dedicated training programme should also be taken into account, targeted primarily at the medical physicist who needs to become particularly skilful in techniques of invert treatment planning. Such training, which can be offered by any experienced IGRT/IMRT centre, requires a full-time training period of one month, while a 6 month course is necessary to become a trainer.

7. Economic and financial implications

The paucity of available data on clinical effectiveness makes a comprehensive economic evaluation, considering both costs and outcomes, unfeasible at present. An assessment of the main financial and economic implications of acquisition and subsequent utilization of an image-guided approach in radiotherapy, was carried out through the following analyses:

- Estimates, based on current regional tariffs, of a theoretical reimbursement increase and, consequently, of the increase in expenditure for the Regional Health Care Service of Emilia-Romagna.
- Application of the Break Even Analysis model to estimate the minimum number of patients that ensures coverage of total annual costs.

7.1. Treatment reimbursement estimates

The following analysis is based on the regional health reimbursement's scheme for radiation therapy and has the objective of estimating the increase in expenditure due to the use of IGRT/IMRT.

A radiation treatment pathway was mapped out with the contribution of all Emilia-Romagna radiation therapy units. The analysis was limited to radical treatments, ignoring palliative ones. All data (codes, tariffs, etc.) used in calculations are reported below.

A radiation therapy workflow was defined. This can be conceptually divided into two separate phases: the initial planning and the actual delivery of the treatment. In brief, patients' eligibility to treatment is assessed during an initial medical examination. Patients undergo a CT scan, which defines the tumour's characteristics, such as shape, size and location. The CT image is digitally processed to define tumour's position in relation to vital organs. Finally total radiation dosage, the numbers of radiation sessions and single sessions' dose are calculated for the whole treatment. At given intervals (e.g. weekly) or before each radiation session, the target image may be re-acquired in order to adjust for any changes incurred in the meantime, either by the tumour or by the patient (e.g. organ motion and set up error).

To define the "reference-case" scenario, the following were considered:

- A single initial visit for treatment eligibility.
- An initial target acquisition through a single CT scan, without contrast media.
- A single target/vital organs definition.
- A dose study.
- One digital processing.

The workflow was applied to treatments with 3D Conformal Radiotherapy and with IGRT/IMRT, specifying all relevant phases and corresponding current regional tariffs (*Tables 7.1 and 7.2*). When reproducing the analysis a certain degree of variability in actual clinical practice may be observed due to number of visits, need of additional diagnostic/imaging tests (such as PET or MR), number of digital image processings, number of 3D target definition (depending on tumour shape and location) and need for custom shielding/immobilisation/compensators.

The tariff-based remuneration for the phase of "treatment planning" resulted in € 697.55. A value of € 113.60 was computed for "treatment delivery", comprehensive of CT target acquisition, treatment repeatability and radiation delivery. The reimbursement for a complete treatment resulted in € 697.55 + (€ 113.6 * N), where N is the number of sessions required to reach the total planned dose.

Table 7.1. Workflow and tariff breakdown for treatment with 3D Conformal Radiotherapy

Code		Tariff (€)
PHASE 1 - TREATMENT PLANNING		
89.7	General Visit	16.55
92.29.2	Target Acquisition through CT scan	103.00
922903	3D target and vital organs definition	216.00
922950	Dose Study	350.00
92296	In vivo dose-check	12.00
	Subtotal PHASE 1	***697.55***
PHASE 2 - RADIATION THERAPY DELIVERY		
92.29.2	Target Acquisition through CT scan	103/5 = 20.60*
92296	In vivo dose-check	12.00
92.24.01	3D Conformal Radiotherapy	81.00
	Subtotal PHASE 2	***113.60***
(to be repeated N times, according to clinical protocol)		

* CT scan is performed once every 5 treatment sessions.

To estimate the reimbursement for IGRT/IMRT, the same calculations were applied to the IGRT/IMRT workflow resulting in € 922.55 for treatment planning, and € 266 for "treatment delivery" (*Table 7.2*). The main driver for the increase is the dose study (€ 575 vs € 350), followed by type of irradiation (€ 151 vs € 81). Reimbursement for a complete treatment resulted therefore in € 922.55 + (€ 266 * N), where N is the number of sessions required to reach the total planned dose.

Table 7.2. Workflow and tariff breakdown for treatment with IGRT/IMRT

Code		Tariff (€)
PHASE 1 - TREATMENT PLANNING		
89.7	General Visit	16.55
92.29.2	Target Acquisition through CT scan	103.00
922903	3D target and vital organs definition	216.00
922951	Dose Study	575.00
92296	In vivo dose-check	12.00
	Subtotal PHASE 1	***922.55***
PHASE 2 - RADIATION THERAPY DELIVERY		
92.29.2	Target Acquisition through CT scan	103.00
92296	In vivo dose-check	12.00
92.24.02	3D conformal radiotherapy	151.00
	Subtotal PHASE 2	***266.00***
(to be repeated N times, according to clinical protocol)		

To estimate N, radiotherapists were asked to quantify the standard number of sessions needed for each of the five tumours of interest (prostate, head & neck, lung, pancreas, brain) in accordance with clinical protocols. No hypofractionation was applied in order to provide the worst scenario and to represent current clinical practice.

The average number of sessions was 31, range comprised between 27 (pancreas) and 35 (head & neck). Based on this, the overall reimbursement for the two types of treatment for each tumour has been calculated (*Table 7.3*) giving a mean value of € 4 219 for 3D conformal radiotherapy and of € 9 169 for IGRT/IMRT.

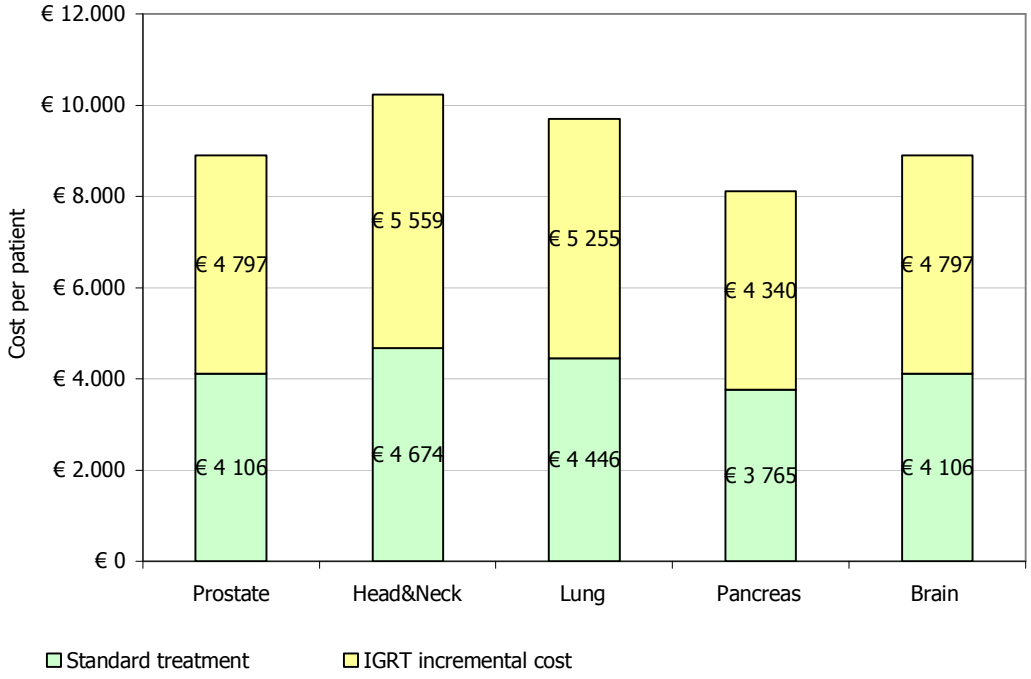
Table 7.3. Reimbursement for Treatments

Tumour	IGRT/IMRT	3D conformal radiotherapy	No. of sessions per treatment
Prostate	€ 8 903	€ 4 106	30
Head and neck	€ 10 233	€ 4 674	35
Lung	€ 9 701	€ 4 446	33
Pancreas	€ 8 105	€ 3 765	27
Brain	€ 8 903	€ 4 106	30
Mean	€ 9 169	€ 4 219	31
Weighted Mean	€ 9 198	€ 4 232	

The incremental expenditure of IGRT/IMRT over 3D conformal radiotherapy for each of the five tumours are represented in Graph 7.3, showing a range of increment between € 4 340 (for treating one patient with pancreatic cancer), to € 5 559 (for treating one patient with head and neck cancer).

Therefore, assuming 1 338 patients/year (702 treated for prostate cancer, 168 for head and neck cancer, 294 for lung cancer, 78 for pancreatic cancer, 96 for brain cancer) undergoing radical treatment with IGRT/IMRT, the additional yearly expenditure for the regional health system would be of approximately 6.6 million Euros.

Graph 7.1. Incremental expenditure of image-guided radiotherapy over standard treatment



7.2. Break Even Analysis

Production cost estimates

Capital cost of the relevant technologies was based on 2008 prices and the annual depreciation cost was estimated assuming the equipment remains in use for 8 years. Set up and training costs were included in the technology capital cost, while annual maintenance was estimated to be 10% of the acquisition cost (considering a "full-risk" contract). Under the term "other materials", we included the costs of dosimeters, masks, drugs (including contrast media) and other consumables. A "top-down" approach was used (1). Indirect costs such as utilities, cleaning and sterilisation were assumed to be 20% of the production cost. Total annual costs for Accelerators with Cone-Beam CT and Tomotherapy are described in detail in Table 7.4.

Table 7.4. Set up and operating costs

	Accelerators with Cone-Beam CT	**Tomotherapy**
Set up costs		
Equipment capital cost	€ 2 200 000	€ 3 500 000
Set up and training	-	-
Direct costs		
Annual depreciation	€ 275 000	€ 437 500
Annual maintenance	€ 220 000	€ 350 000
Indirect costs		
Utilities, cleaning, etc.	€ 484 914.60	€ 581 439.60
Total annual cost	**€ 979 914.60**	**€ 1 368 939.60**

N.B. all costs are comprehensive of VAT

An estimate of full yearly cost and time absorption for all personnel involved in planning and delivery of treatments was obtained from the regional radiotherapy centres. Following this, costs of single sessions and of complete treatments were calculated to build a theoretical scenario (*Tables 7.5 and 7.6*).

For an average number of 31 sessions, the personnel cost of one treatment, was estimated to be € 2 577.78, to which costs for consumable materials and intermediate treatment were added, giving a total of variable cost for one treatment of € 2 624.15 (*Table 7.7*).

Table 7.5. Annual personnel costs - theoretical scenario

Professional	**Annual Cost**
physician	€ 137 000
physicist	€ 93 000
RT technician	€ 57 500
Nurse	€ 41 000

Table 7.6. Time absorption (in minutes) of each relevant phase in the planning and delivery of image-guided radiotherapy - theoretical scenario

Kind of professional expertise	Physician	Physicist	Nurse	Technician
PHASE 1 - TREATMENT PLANNING				
General visit	75		10	
Target acquisition (CT scan)	45			60
Contrast media injection (whenever necessary)			15	
3D target and vital organs definition	120			
Dose study with inverse planning		240		
Digital images processing & definition of functional/radiobiological/ quantitative parameters	15	30		
In vivo dose-check and treatment repeatability	30			5
Subtotal PHASE 1	***285***	***270***	***25***	***65***
PHASE 2 - RADIATION THERAPY DELIVERY				
Weekly visit	15^			
Target acquisition (CT scan)	10			10
Digital images processing & definition of functional/radiobiological/ quantitative parameters	5	25*		5
Treatment repeatability	5	10*		5
Intensity-modulated image guided radiotherapy (IGRT)	5	25*		2x20
Subtotal PHASE 2	***25+15^ (every 5 treatments)***	***60****		***60***

* Only for first treatment (Delivery Quality Assurance)

^ One every 5 treatments

Table 7.7. Variable cost for treatment

Variable costs	
Personnel costs	€ 2 577.78
Consumables	€ 40.82
Intermediate treatments	€ 5.55
Total	***€ 2 624.15***

Break Even Point

The results of the theoretical scenario applied to Accelerator with Cone-Beam CT and Tomotherapy are reported in Table 7.8. The break even points (*Graph 7.2 and Graph 7.3*) have been calculated as the minimum number of patients ensuring revenues (based on the weighted mean treatment cost as shown in Table 7.3 - covering total annual operative costs).

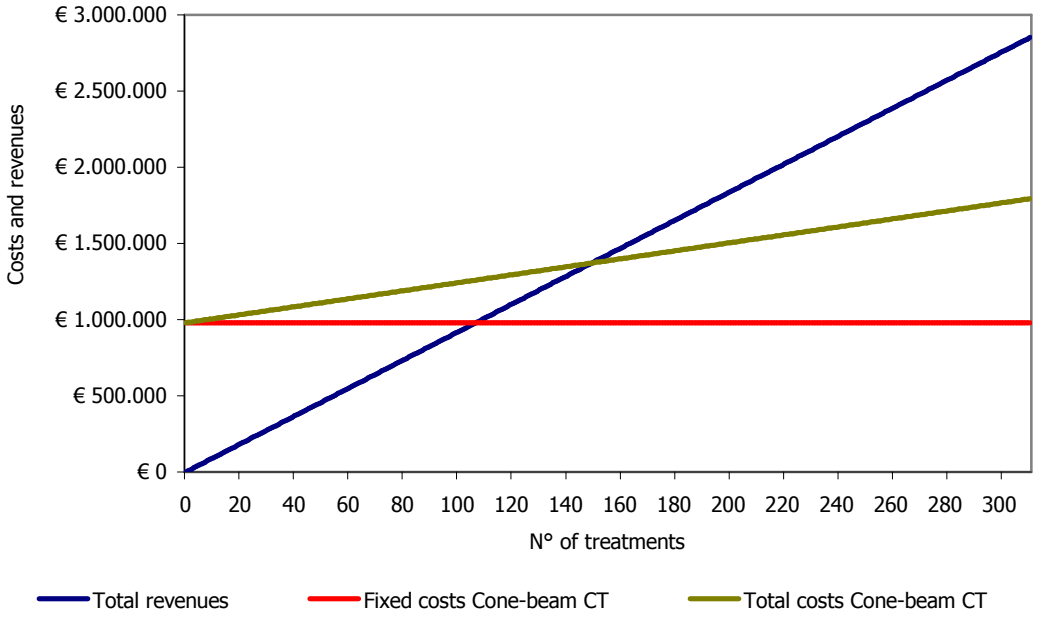
The break even point obtained is significantly different between Accelerators with Cone Beam CT (150 treatments) and Tomotherapy (209 treatments), due to the sizeable difference in the equipment costs.

Based on historical activity of radiation therapy units, the eligible patients for IGRT/IMRT have been estimated to be 1 569 per year. The 8 IGRT/IMRT systems present in our region would be treating around 195 patients each year, which is compatible with both break even points.

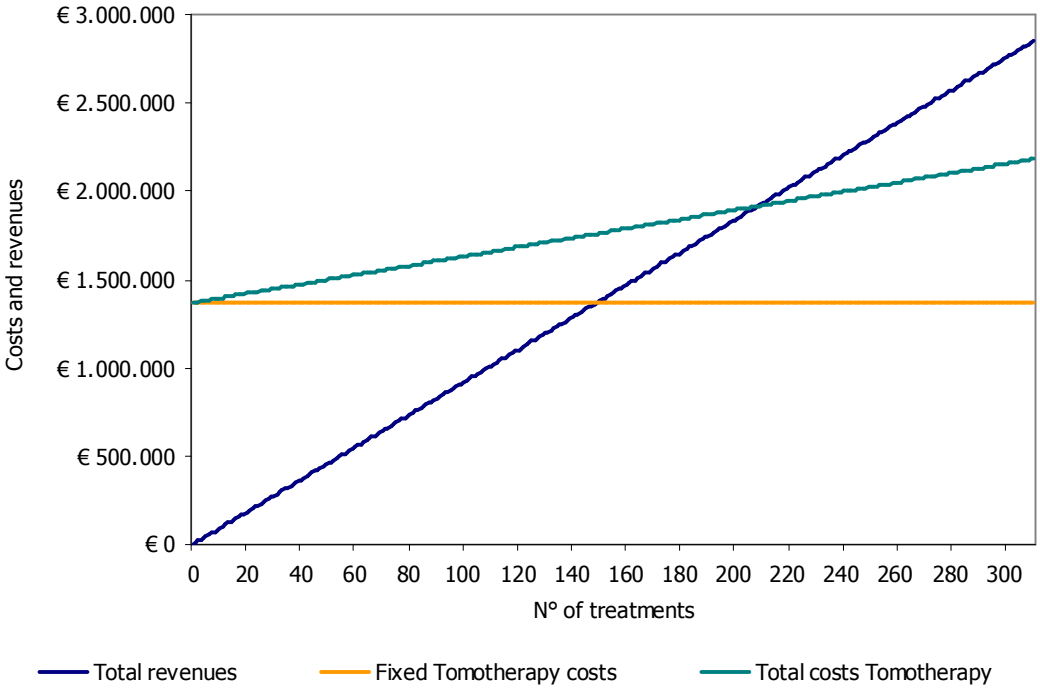
Table 7.8. Break even point: results for the reference case and the two alternative scenarios

	Accelerator with Cone-Beam CT	**Tomotherapy**
Fixed costs	€ 979 914.60	€ 1 368 939.60
Variable costs	€ 2 624.15	€ 2 624.15
Weighted cost	€ 9 198.00	€ 9 198.00
Break even point	***150***	***209***

Graph 7.2. Break even point Cone-Beam CT Accelerator



Graph 7.3. Break even point Tomotherapy



Sensitivity analysis

We performed a one-way sensitivity analysis involving an hypothetical increase/decrease in treatment's payment and in variable costs. As shown in Table 7.9, if payment for treatment decreases, the break even point increases for both CBCT Accelerator and Tomotherapy, but with different impact: a 10% decrement of cost implies a break even point of 173 treatments for Cone-Beam CT Accelerator and a break even point of 242 treatments for tomotherapy, which is close to its production capacity (245 treatments per year).

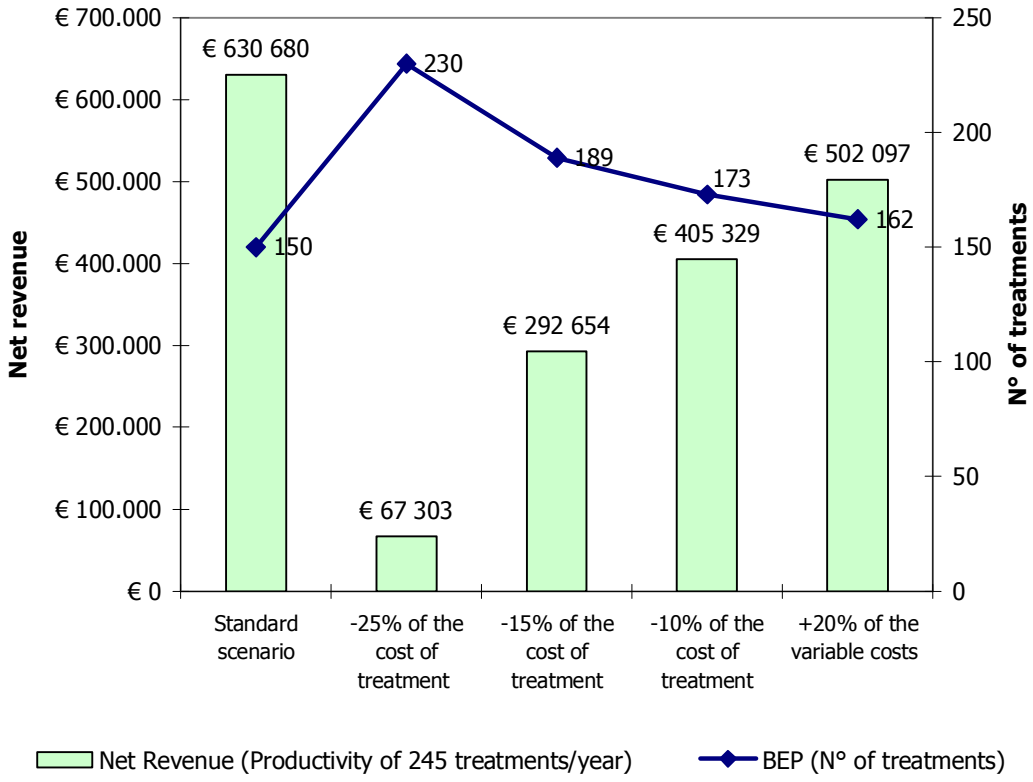
The analysis also shows that the variable costs have a moderate impact on the break even point.

Table 7.9. Sensitivity analysis

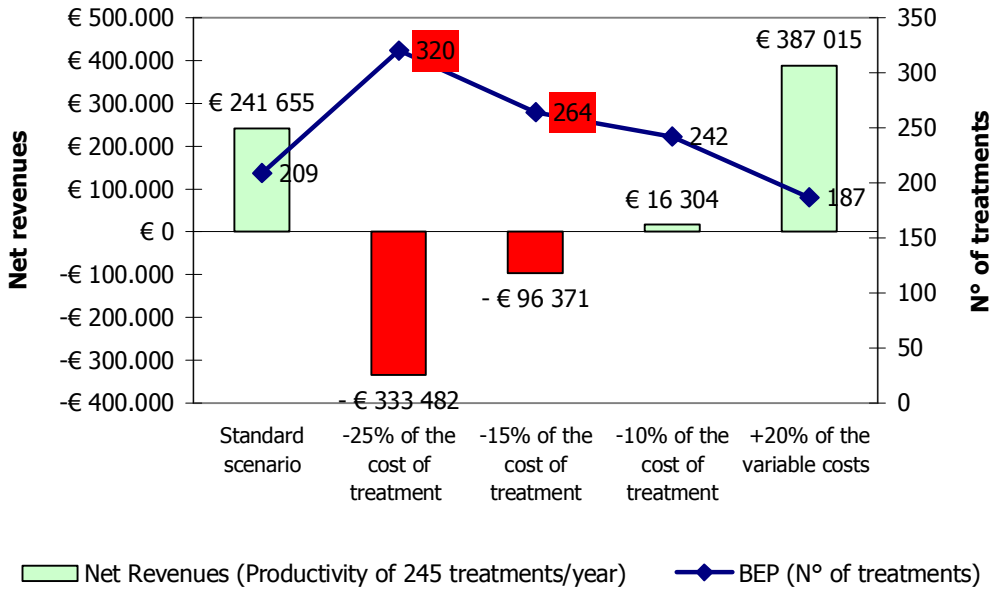
	Change	Cone-Beam CT Accelerator		Tomotherapy	
	%	Cost (€)	BEP	Cost (€)	BEP
Reference case scenario	-	9 198.00	150	9 198.00	209
Cost of treatment	-25	6 898.50	230	6 898.50	320
Cost of treatment	-15	7 818.30	189	7 818.30	264
Cost of treatment	-10	8 278.20	173	8 278.20	242
Variable costs	+20	3 348.97	162	3 148.97	227

Considering a productivity capacity of 245 treatments per year and different scenarios of break even analysis, it is possible to quantify the net revenue for CBCT Accelerator and Tomotherapy (*Graph 7.4, Graph 7.5*). For a decrement of 25% and 15% of the cost of treatment, the net revenue for CBCT Accelerator keeps positive with a break even point within threshold of productivity, while the net revenue turns negative for tomotherapy with a break even point well over the threshold of productivity (*Table 7.9*). A 10% decrease would maintain positive - yet different - net revenues for both CBCT Accelerator and tomotherapy: € 16 304 for Tomotherapy and € 405 329 for CBCT Accelerator.

Graph 7.4. Sensitivity analysis and CBCT net revenue



Graph 7.5. Sensitivity analysis and Tomotherapy net revenue



7.3. Conclusions

Starting from the definition of the treatment pathways for Accelerators with Cone-Beam CT and Tomotherapy, an estimate of the corresponding costs for different types of cancer has been obtained. The estimated additional expenditure for the Regional Health System was calculated to be approximately € 6.6 millions per year.

A break even analysis was performed to estimate the number of treatments per year ensuring financial sustainability for the radiotherapy centres. The central estimate was 150 treatments for Accelerators with Cone-Beam CT and 209 treatments for Tomotherapy, respectively.

The sensitivity analysis showed a different impact of costs variations on CBCT Accelerator and tomotherapy. A decrease of 15% and 25% for CBCT Accelerator would imply a sustainable break even point and a positive net revenue while tomotherapy would work at the limit of its capacity with a negative net revenue. The data gathered can be used to investigate financial impacts in different context, or as a base for future full economic evaluations of these technologies.

Given the lack of data on clinical effectiveness, no cost-effectiveness analyses were undertaken and evaluations of impact of IGRT/IMRT on service's efficiency were not deemed necessary as waiting times for radiation treatment are not an issue at present.

Reference

1. Chapko M.K., Liua C-F., Perkinsa M., Lia Y-F., Fortneyd J., Maciejewskif M.L. Equivalence of two healthcare costing methods: bottom-up and top-down. *Health Econ*, 18: 1188-1201, 2009.

8. Prioritisation of questions for clinical research

Final objective of this report was to develop research recommendations for further evaluation of the role and clinical impact of IGRT/IMRT.

The priority for clinical research topics was defined using a structured process.

The eleven radiotherapy centres' head of department, three oncologists, one radiologist, one nuclear physician and one health director - all members of the panel - were asked to participate in this phase in order to identify clinically relevant research questions on one or more of the following clinical scenarios:

- Prostate cancer - exclusive radiotherapy with radical intent in patient with low and intermediate risk
- Lung cancer - exclusive treatment with radical intent (inoperable T1-T2 and <IIIB)
- Lung cancer - radiant treatment in lung metastasis
- Head and neck cancer - exclusive (or associated with chemotherapy) radiotherapy
- Brain cancer - exclusive radiotherapy in intra- and extra-assial primary tumours
- Brain cancer - radiant treatment of metastatic brain tumours
- Pancreatic cancer - pre-operatory radiotherapy treatment with downstaging and operability goal
- Pancreatic cancer - post-operatory radiotherapy treatment
- Pancreatic cancer - radiotherapy in the advanced disease

Participants were involved in modified Delphi and RAND processes and presented with a voting form (*Appendix 3*) for each clinical scenario, containing the following information:

- estimated target population;
- estimated treatment costs;
- a list of relevant clinical outcomes (suggested by the panel);
- estimates of performance of standard therapy (3D conformal) and of IGRT/IMRT (when available) for each clinical outcome.

Participants were asked to place a vote next to each clinical outcome expressing relevance in both clinical and research terms. They were then asked to rate each research indication in terms of the following dimensions determining priority:

- severity of disease in terms of morbidity and mortality;
- impact of the technology on the morbidity and mortality of the disease;
- feasibility of a clinical trial.

As a final step participants were asked to rate overall priority of each clinical research question.

Three voting categories for relevance were provided: low relevance (score from 1 to 3); moderate relevance (score from 4 to 6); high relevance (score from 7 to 9).

The analysis was carried out as follows: the median of the scores was calculated for each variable (relevance of clinical outcomes and rating of all dimensions contributing to priority). For overall priority, the modified RAND/UCLA method was applied in order to analyse the level of agreement/disagreement among voters.[5]

8.1. Ratings of clinical outcomes

In Table 8.1 the first and second highest rated outcomes in terms of research relevance for each clinical scenario are reported, while full results for the rating of clinical relevance of outcomes are reported in Appendix 3.

Ratings of research and clinical relevance were moderately correlated (r=0.68) with the strength of the correlation varying substantially among clinical conditions (almost null correlation for advanced pancreatic cancer and a very high correlation for primary brain cancer).

[5] Fitch K., Bernstein S.J., Aguilar M.D. et al. *The RAND/UCLA Appropriateness Method User's Manual*. Rand Health. Rand USA 2001.

Table 8.1. First and second highest scoring outcomes for research relevance by clinical scenario

Clinical scenario	Outcomes with first highest median score for research relevance	Outcomes with second highest median score for research relevance
Radical radiation treatment for prostate cancer	Disease specific survival	Local control Recurrence Biochemical recurrence Acute and late genito-urinary toxicity Acute and late gastrointestinal toxicity Sexual problems Metastasis
Radical radiation treatment for primary lung cancer	Local control Loco-regional control	Disease free survival time
Radiation treatment of lung metastasis	Loco-regional control	Disease free survival time Lung fibrosis
Exclusive (or associated with chemotherapy) radiation treatment of head & neck cancer)	Xerostomy	Recurrence Disease free time Overall survival Dysphagia Local control
Radiation treatment of advanced pancreatic cancer	Overall survival Disease specific survival	Enteritis Operability
Pre-operative radiation treatment for pancreatic cancer	Downstaging Cytoreduction	Operability Enteritis
Post-operative radiation treatment for pancreatic cancer	Enteritis	Disease specific survival Overall survival
Radiation treatment for primary brain cancer	Overall survival Recurrence Disease specific survival	Quality of life Chronic toxicity Acute toxicity Local control Symptoms control
Radiation treatment for brain metastasis	Quality of life	Symptoms control Recurrence

8.2. Ratings of priority dimensions and of overall priority

Results on scores for dimensions determining priority are reported in Table 8.2.

Radical treatment for prostate cancer received the highest score for overall priority, followed by treatment for primary lung cancer and for head and neck cancer (*Figure 8.1*). Treatment for primary and metastatic brain cancer and for pancreatic cancer received the lowest median ratings.

Analysis through the RAND method showed that no full agreement among voters was ever registered for any clinical scenario. Most of the clinical scenarios registered a light disagreement with only two scenarios registering a strong disagreement (*Table 8.3*).

In order to investigate possible determinants of ratings given to research priority, correlations with feasibility of the study, size of target population, incremental costs, severity of clinical condition and presumed impact of the technology were analysed.

The variable with the strongest positive correlation with research priority resulted to be feasibility of a regional clinical trial (r=0.85), followed by ratings given to impact of the technology on morbidity of disease (r=0.66) and estimated target population (r=0.55). As expected, feasibility and number of estimated target population were also positively correlated (r=0.62). The correlation between research priority and the remaining variables (burden of disease and impact of technology on mortality) was null or very weak.

In conclusion, in prioritising research topics, feasibility, size of target population and impact of the technology on morbidity were the dimensions most valued by the panel, while impact of the technology on mortality and severity of disease were considered less important. This appears to be in line with the theoretical rationale of the technology which sustains its capacity to reduce adverse effects of radiation treatments, but does not yet claim a major impact on long term clinical outcomes.

Table 8.2. Median of ratings for priority by clinical scenario

Clinical scenario	**Severity of disease**		**Impact of the technology**		**Feasibility** Median (min-max)	**Research priority** Median (min-max)
	Mortality Median (min-max)	**Morbidity** Median (min-max)	**Mortality** Median (min-max)	**Morbidity** Median (min-max)		
Radical radiation treatment for prostate cancer	5 (1-8)	6 (5-9)	5 (1-8)	7.5 (5-9)	7.5 (5-9)	8 (5-9)
Radical radiation treatment for primary lung cancer	7.5 (5-9)	7 (5-9)	6 (5-9)	7 (5-9)	7 (4-9)	7 (6-9)
Exclusive/chemo-assoc. radiation treatment for head & neck cancer	7 (5-9)	7 (4-9)	6 (1-8)	7 (5-9)	7 (3-8)	7 (5-8)
Radiation treatment of lung metastasis	6 (5-9)	6 (3-7)	5 (3-7)	6 (3-7)	5 (2-7)	5 (2-6)
Radiation treatment of advanced pancreatic cancer	8 (6-9)	6 (3-8)	6.5 (3-8)	6 (3-7)	4 (1-7)	5 (1-7)
Radiation treatment for brain metastasis	8 (4-9)	6 (2-8)	5 (2-7)	5 (2-7)	5 (2-7)	4 (1-8)
Pre-operative radiation treatment for pancreatic cancer	8 (5-9)	6 (3-8)	4.5 (2-8)	6 (5-7)	3.5 (1-8)	4 (2-5)
Post-operative radiation treatment for pancreatic cancer	8 (6-9)	7 (3-8)	6 (3-8)	6 (3-8)	3 (1-7)	3 (2-8)
Radiation treatment for primary brain cancer	5 (5-9)	6 (4-8)	5 (3-8)	4 (3-7)	4 (1-7)	3 (1-7)

Figure 8.1. Priority rating by clinical scenario

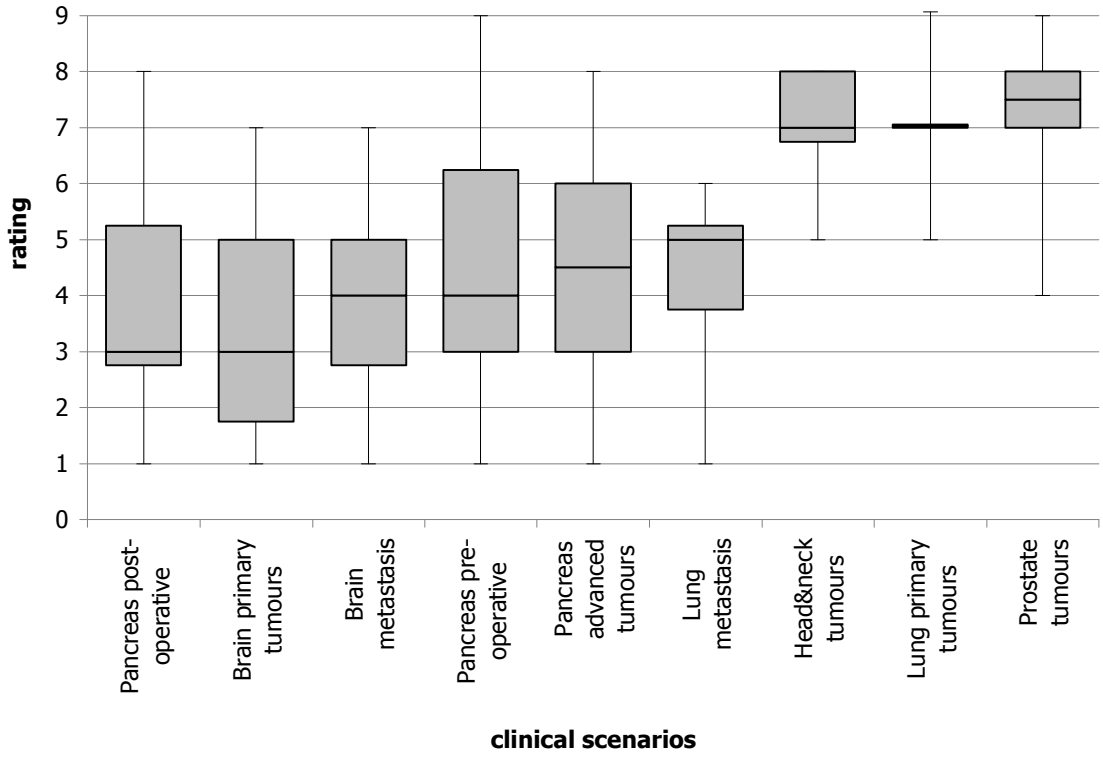


Table 8.3. Priority ratings and level of disagreement by clinical scenarios

Clinical scenario	Median rating (min-max)		Level of agreement/disagreement
Prostate tumours	8	(5-9)	Light disagreement
Lung primary tumours	7	(6-9)	Light disagreement
Head & neck tumours	7	(5-8)	Light disagreement
Lung metastasis	5	(2-6)	Strong disagreement
Pancreas advanced tumours	5	(1-7)	Strong disagreement
Pancreas tumours pre-operative RT	4	(1-8)	Strong disagreement
Brain metastasis	4	(2-5)	Light disagreement
Brain primary tumours	3	(2-8)	Strong disagreement
Pancreas tumours post-operative RT	3	(1-7)	Strong disagreement

8.3. Recommendations for research

As a result of the structured process, the following ranking of topics for research was presented to the panel for discussion:

1. radiation treatment with radical intent in low and intermediate risk prostate cancer
2. radiation treatment with radical intent in inoperable T1-T2, III A and B lung cancer
3. exclusive or associated with chemotherapy radiant treatment of head & neck cancer
4. radiation treatment of lung metastasis
5. radiation treatment of advanced pancreatic cancer
6. radiation treatment of brain metastasis
7. pre-operative radiation treatment of pancreatic cancer
8. radiation post-operative treatment of pancreatic cancer
9. radiation treatment of primary brain cancer

Taking into consideration the quantity and quality of the clinical research published this far, the panel agreed that further research on IGRT/IMRT should not aim at assessing just its impact on adverse effects and toxicity, as the technology is mature enough to undergo evaluation of clinical effectiveness on long-term clinical outcomes. The panel therefore recommended that the role of IGRT/IMRT in treatments with dose escalation and/or hypofractionation should be assessed through randomised controlled clinical trials.

The panel agreed to select the first three most voted research topics and proposed the following research recommendations.

1. To assess whether radical radiation treatment with IGRT/IMRT with a higher biological dose in hypofractionation regimen in patients with low and intermediate risk prostate cancer improves biochemical recurrence and disease specific survival without increasing toxicity, compared to treatment with 3D-CRT/IMRT.
2. To assess whether radical radiation treatment with IGRT/IMRT with a higher biological dose in hypofractionation regimen in patients with primary lung cancer increases local and loco-regional control without increasing toxicity, compared to treatment with 3D-CRT/IMRT.
3. To assess whether radical radiation treatment with IGRT/IMRT with higher dose (not in hypofractionation regimen) in patients with head & neck cancer increase local control without increasing toxicity, compared to treatment with 3D-CRT/IMRT.

9. Conclusions

The main objectives of this report were:

- to evaluate potential clinical benefits of Image Guided Radiotherapy with Intensity Modulated Radiation Therapy;
- to identify in which clinical indications this technology appears to be particularly promising;
- to map a future programme of evaluation suitable to provide robust clinical results.

Image Guided Radiotherapy represents a real breakthrough in radiation treatment for its capacity to delineate the tumour contours, correct for patient positioning and delivery of irradiation beam before and during treatment. The tangible potential benefits of modern IGRT/IMRT are therefore:

- greater precision in irradiating tumour sites with consequential reduction in unwanted irradiation of neighbouring healthy tissues;
- lower incidence of side-effects associated with traditional radiation therapy;
- possibility to use higher dosage with presumed higher efficacy;
- extension of therapeutic use to a larger number of tumours, even as an alternative to surgery.

Despite this convincing theoretical rationale, robust research evidence in support of its promising clinical benefits is still lacking. For the use of IGRT/IMRT in the 5 tumours selected by the panel - lung, head & neck, prostate, brain and pancreatic cancer - there is sufficient evidence on technical performance, some but not yet conclusive information on safety, very scarce information on clinical effectiveness and none on cost-effectiveness.

The proportion of patients with the clinical indications for IGRT/IMRT suggested by the panel was extracted from the RER regional database and resulted in the following estimates: 23% of patients with primary brain cancer; 20% of patients with metastatic brain cancer; 24% of patients with head & neck cancer; 10% of patients with primary lung cancer; 21% of patients with prostate cancer and 18% of patients with pancreatic cancer.

Seven of the eleven regional radiotherapy centres are at the moment equipped with an IGRT/IMRT system, for a total of 8 IGRT/IMRT systems, an adequate number for the expected eligible patients estimated to be below 1 500 per year. The geographical distribution of the systems covers most of the regional territory and strengthening of the existing network of radiotherapy centres is advisable to guarantee an efficient, equal and non-discriminatory access to the technology.

Estimate of treatment costs for the different types of cancer examined suggest that, should IGRT/IMRT be introduced in routine clinical practice, the additional expenditure for the Regional Health System would be of approximately 6.6 million Euros.

Research gaps and research needs to reduce uncertainty on clinical effectiveness of IGRT/IMRT have been identified and the structured process for the prioritisation of research topics, undertaken by the panel, produced a list of research questions, ranked according to priority.

The resulting top three recommendations for research are reported below.

RECOMMENDATIONS FOR FUTURE RESEARCH

1. To assess whether radical radiation treatment with IGRT/IMRT with a higher biological dose in hypofractionation regimen in patients with low and intermediate risk prostate cancer improves biochemical recurrence and disease free survival without increasing toxicity, compared to treatment with 3D-CRT/IMRT.
2. To assess whether radical radiation treatment with IGRT/IMRT with a higher biological dose in hypofractionation regimen in patients with primary lung cancer increases local and loco-regional control without increasing toxicity, compared to treatment with 3D-CRT/IMRT.
3. To assess whether radical radiation treatment with IGRT/IMRT with higher dose (not in hypofractionation regimen) in patients with head & neck cancer increase local control without increasing toxicity, compared to treatment with 3D-CRT/IMRT.

Appendices

Appendix 1.
Comparative tables of linear accelerators and treatment planning systems

Table 1. Comparison between linear accelerators

PRODUCER	ELEKTA	ELEKTA	SIEMENS	SIEMENS	SIEMENS	TOMOTHERAPY	VARIAN	VARIAN	VARIAN	VARIAN	VARIAN
MODEL	**Elekta Synergy**	**Precise Treatment System**	**ONCOR Avant-Garde: ONCOR Expression**	**ONCOR Impression**	**ONCOR Impression Plus**	**Hi-Art Treatment System**	**Clinac 2100C**	**Clinac 2100C/D**	**Clinac 2300C/D**	**Clinac 600C: Clinac 600C/D**	**Clinac 6EX**
Where marketed	Worldwide		Worldwide			Worldwide	Worldwide				
FDA clearance	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CE mark (MDD)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Type	Linear accelerator		Linear accelerator			Linear accelerator, CT design (ring gantry)	Linear accelerator				
Photon energy, MV	4, 6, 10, 15, 18, 25 (select 1 to 3 energies)	4, 6, 8, 10, 15, 25 (select 1 to 3 energies)	4 to 15 (2 energies)		4 to 23 (2 energies)	6	4 to 23 (2 energies), per BJR 17		6, 16, 23, 25 (2 energies), per BJR 17	4 or 6, per BJR 17	
Electron energy, MeV	4, 6, 8, 9, 10, 12, 15, 18, 20, 22 (select 3 to 9 energies)		From 6 to 21 (up to 6 energies)	From 5 to 14 (1 to 6 energies)	From 6 to 21 (up to 6 energies)	NA		NA	NA		
Accelerator type	Travelling wave		Standing wave			Standing wave	Standing wave				
Length, m	2.05	2.05	1.02	1.02	1.02	0.03	Not Specified	Not specified	Not specified	0.03	0.03

PRODUCER	ELEKTA	ELEKTA	SIEMENS	SIEMENS	SIEMENS	TOMOTHERAPY	VARIAN	VARIAN	VARIAN	VARIAN	VARIAN
MODEL	**Elekta Synergy**	**Precise Treatment System**	**ONCOR Avant-Garde: ONCOR Expression**	**ONCOR Impression**	**ONCOR Impression Plus**	**Hi-Art Treatment System**	**Clinac 2100C**	**Clinac 2100C/D**	**Clinac 2300C/D**	**Clinac 600C: Clinac 600C/D**	**Clinac 6EX**
MICROWAVE POWER											
Source	Magnetron	Magnetron	Klystron	Klystron or magnetron	Klystron	Magnetron	Klystron	Klystron	Klystron	Magnetron	Magnetron
Power, MW	5	5	7.05	2.06	7.05	2.06	Not specified	Not specified	Not specified	2.05	3
Beam bending, deg	45, 45, 112 slalom achromatic		270 (achromatic)			NA	270	270	270	0	0
GANTRY											
Rotation range, deg	365		± 185			360, continuous helical delivery	±185				
Position accuracy @ isocenter, ± mm	0.5 degrees		1			0.01	≤0.1 cm radius sphere			Not specified	Not specified
SAD, cm	100		100			85	100				
TREATMENT UNIT											
L x W x H, cm (in)	351 x 390 x 248 (138 x 154 x 98)		313.7 x 143 x 260.4 (123.5 x 56.5 x 102.5)	301 x 132 x 260.4 (120.5 x 53 x 102.5)	313.7 x 143 x 260.4 (213.5 x 56.5 x 102.5)	157 x 271 x 246 (62 x 107 x 97)	322.5 x 124 x 264.2 (127 x 48.8 x 104)			272 x 127 x 269 (107 x 50 x 106)	
Weight, Kg (lb)	6 600 (14 551)	6 200 (13 668)	7 730 (17 000) including counterweight	7 030 (15 466) including counter-weight	7 730 (17 000) including counter-weight	4 500 (10 000)	Not specified	Not specified	Not specified	6 668 (14 700)	

PRODUCER	ELEKTA	ELEKTA	SIEMENS	SIEMENS	SIEMENS	TOMOTHERAPY	VARIAN	VARIAN	VARIAN	VARIAN	VARIAN
MODEL	**Elekta Synergy**	**Precise Treatment System**	**ONCOR Avant-Garde: ONCOR Expression**	**ONCOR Impression**	**ONCOR Impression Plus**	**Hi-Art Treatment System**	**Clinac 2100C**	**Clinac 2100C/D**	**Clinac 2300C/D**	**Clinac 600C: Clinac 600C/D**	**Clinac 6EX**
COLLIMATION											
Rotation range, deg	365	365	360 (270 with MLC)			NA	±95; optional ±165	±165	±165	±95; ±165 option	±165
Field size range at SAD, cm											
X-Ray	0.5 x 0.5 to 40 x 40		40 x 40			0.6 x 1 to 40 x 160	40 x 40				
Electron	6 x 6, 10 x 10, 14 x 14, 20 x 20; optional 25 x 25		Up to 25 x 25			NA	6 x 6 to 25 x 25			NA	NA
Multileaf	Standard	Standard	OPTIFOCUS	OPTIFOCUS	OPTIFOCUS	Yes	Not specified	Not specified	Not specified	Not specified	Not specified
No. of leaves	80	80	OPTIFOCUS, 41@1 cm (measured at isocenter, per side)			64 interdigitating	Optional 52, 80, or 120				
Max field size, mm	400 x 400	400 x 400	40 x 40	40 x 40	40 x 40	Up to 400 x 1 600 treatment volume	26 x 40 cm for 52 leaf, 40 x 40 cm for 80 and 120 leaf				
Leaf size, width @ isocenter, mm	10	10	10	10	10	6.25					
Distance from collimator to isocenter, cm (in)	45	45	43 (17) with accessory holder; 53 (21) without accessory holder			50 (19.7)	Not specified	Not specified	Not specified	Not specified	Not specified
Interleaf leakage, %	Avg 2.5%, <0.5% interleaf (leaves and autotracking backup asymmetric lower jaws)		<1	<1	<1	<0.5%	Not specified	Not specified	Not specified	Not specified	Not specified

PRODUCER	ELEKTA	ELEKTA	SIEMENS	SIEMENS	SIEMENS	TOMOTHERAPY	VARIAN	VARIAN	VARIAN	VARIAN	VARIAN
MODEL	**Elekta Synergy**	**Precise Treatment System**	**ONCOR Avant-Garde: ONCOR Expression**	**ONCOR Impression**	**ONCOR Impression Plus**	**Hi-Art Treatment System**	**Clinac 2100C**	**Clinac 2100C/D**	**Clinac 2300C/D**	**Clinac 600C: Clinac 600C/D**	**Clinac 6EX**
Leaf overtravel, mm	125	125	300	300	300	Leaf state either fully retracted or fully extended across field	Not specified	Not specified	Not specified	Not specified	Not specified
Real-time leaf position monitoring	Yes	Yes	Not specified	Not specified	Not specified	Yes, monitor whether open or closed	Not specified	Not specified	Not specified	Not specified	Not specified
Dynamic leaf	Yes	Yes	Not specified	Not specified	Not specified	Binary leaf states (open or closed), maximum leaf transition time 20 msec	Not specified	Not specified	Not specified	Not specified	Not specified
Positioning, arc therapy	Yes	Yes	Not specified	Not specified	Not specified	Yes	Not specified	Not specified	Not specified	Not specified	Not specified
Virtual wedge	Yes	Yes	Yes	Yes	Yes	NA	Not specified	Not specified	Not specified	Not specified	Not specified
Special features	32.5 cm leaf span with up to 12.5 cm overtravel, autofollowing back jaws minimize leakage to 0.5%, independent asymmetric lower jaws, CID camera for real-time beam's-eye-view display of each leaf position, capable of delivering PreciseBEAM IMRT and VMAT (WIP)		Jaw design allows for tracing divergent beams, even in overtravel; Virtual Wedge; overtravel of 10 cm; double focused, ball bearing technology for optimal reliability; auto-Initialization			Variable-speed ring gantry, special MLC and head design for minimal leakage and scatter, fan beam CT for daily CT guidance, and helical intensity-modulated arc delivery suitable	Not specified	Not specified	Not specified	Extended collimator head rotation and dual independent jaws; enhanced dynamic wedge (600C/D, optional for 600C);	Extended collimator head rotation and dual independent jaws; sliding window, step-and-shoot, and dynamic conformal arc MLC techniques;

PRODUCER	ELEKTA	ELEKTA	SIEMENS	SIEMENS	SIEMENS	TOMOTHERAPY	VARIAN	VARIAN	VARIAN	VARIAN	VARIAN
MODEL	**Elekta Synergy**	**Precise Treatment System**	**ONCOR Avant-Garde: ONCOR Expression**	**ONCOR Impression**	**ONCOR Impression Plus**	**Hi-Art Treatment System**	**Clinac 2100C**	**Clinac 2100C/D**	**Clinac 2300C/D**	**Clinac 600C: Clinac 600C/D**	**Clinac 6EX**
						for advanced treatment of all radiotherapy patients				accessory system; physical wedges; optional sliding window, step-and-shoot, and dynamic conformal arc MLC techniques; optional custom accessory coding	enhanced dynamic wedge; accessory system and physical wedges; optional custom accessory coding
IMAGING											
Megavoltage	iViewGT	iViewGT	Yes	Yes	Yes	3	Optional PortalVision				
Kilovoltage	X-ray volume imager (XVI)	NA	Not specified	Not specified	Not specified	Not specified	Optional on board imaging				
No. of detectors	2	1	1	1	1	540-pixel 1-D array, single-row xenon	One on each system				
Spatial accuracy, mm	1	Not specified	Not specified	Not specified	Not specified	0.74 mm resolution at isocenter, 540 pixels	Not specified	Not specified	Not specified	Not specified	Not specified

PRODUCER	ELEKTA	ELEKTA	SIEMENS	SIEMENS	SIEMENS	TOMOTHERAPY	VARIAN	VARIAN	VARIAN	VARIAN	VARIAN
MODEL	**Elekta Synergy**	**Precise Treatment System**	**ONCOR Avant-Garde: ONCOR Expression**	**ONCOR Impression**	**ONCOR Impression Plus**	**Hi-Art Treatment System**	**Clinac 2100C**	**Clinac 2100C/D**	**Clinac 2300C/D**	**Clinac 600C: Clinac 600C/D**	**Clinac 6EX**
Cone beam CT	X-ray volume imager (XVI)	NA	Yes	Yes	Yes	Fan beam CT with continuous acquisition (like diagnostic CT, not flat panel)	Not specified	Not specified	Not specified	Not specified	Not specified
Ultrasound	NA	NA	Not specified	Not specified	Not specified	NA	Not specified	Not specified	Not specified	Not specified	Not specified
Respiratory gating	Yes	Yes	Yes	Yes	Yes	WIP	Not specified	Not specified	Not specified	Not specified	Not specified
MAXIMUM OUTPUT											
At SAD, rad/min											
X-Ray	600	600	300-500 standard; 1 000 ST mode; 50 low-dose mode	200-300, depends on energy selected; 50 low-dose mode (Magnetron); 300-500 standard; 1 000 ST mode: 50 low-dose mode (Klystron)	300-500 standard; 1 000 ST mode; 50 low-dose mode	850 cGy/min	Not specified	Not specified	Not specified	250 for 4 MV, 400 for 6 MV	400 for 4 MV, 600 for 6 MV
Electron	400	400	300/900	300/900	300/900	NA	Not specified	Not specified	Not specified	NA	NA

PRODUCER	ELEKTA	ELEKTA	SIEMENS	SIEMENS	SIEMENS	TOMOTHERAPY	VARIAN	VARIAN	VARIAN	VARIAN	VARIAN
MODEL	**Elekta Synergy**	**Precise Treatment System**	**ONCOR Avant-Garde: ONCOR Expression**	**ONCOR Impression**	**ONCOR Impression Plus**	**Hi-Art Treatment System**	**Clinac 2100C**	**Clinac 2100C/D**	**Clinac 2300C/D**	**Clinac 600C: Clinac 600C/D**	**Clinac 6EX**
TREATMENT COUCH											
L x W, cm (in)	230 x 50 (90 x 20)		550 TxT, 242.5 x 50 (95.5 x 19.7)			281 x 66 (111 x 26)	236 x 53 (93 x 21) EXACT COUCH: optional 200 x 53 (79 x 21) EXACT IGRT COUCH				
MOVEMENT, CM (IN)											
Vertical range	65-175 (22.6-68.9)		65-170 (25.6-66.9)			57-110 (22.4-43.3) vertical above floor	63-170 (25-67) EXACT COUCH: optional 63-169 (25-67) EXACT IGRT COUCH				
Longitudinal range	100 (39.4)		90 (35.4)			160 (63) treatment range	94-289 (37-114) EXACT COUCH: optional 94-262 (37-103) EXACT IGRT COUCH				
Lateral range	±25 (±9.8)		±25 (±9.8)			±2.5 (±0.98), central, non-isocentric set up	±25 (±10) EXACT COUCH: optional ±25 (±10) EXACT IGRT COUCH				
Base rotation, deg	±95; column rotation, ±180		±180 column, ±120 isocentric			NA	±95 EXACT COUCH: optional ±100 EXACT IGRT COUCH				
Maximum patient weight, Kg (lb)	200 (440)		250 (550)			200 (440)	200 (440) EXACT COUCH: optional 227 (500) EXACT IGRT COUCH				
Remote positioning (from control room)	Yes	Yes	Yes	Yes	Yes	Yes	Not specified EXACT COUCH: optional EXACT IGRT COUCH				

PRODUCER	ELEKTA	ELEKTA	SIEMENS	SIEMENS	SIEMENS	TOMOTHERAPY	VARIAN	VARIAN	VARIAN	VARIAN	VARIAN
MODEL	**Elekta Synergy**	**Precise Treatment System**	**ONCOR Avant-Garde: ONCOR Expression**	**ONCOR Impression**	**ONCOR Impression Plus**	**Hi-Art Treatment System**	**Clinac 2100C**	**Clinac 2100C/D**	**Clinac 2300C/D**	**Clinac 600C: Clinac 600C/D**	**Clinac 6EX**
Treatment couch special features	Silent drive system for all movements, uninterruptible power supply on down drive, optional C-arm tabletop, carbon-fiber tennis racquet, variable speed controls, rotatable couchtop enabling SRS and physics measurements		Available with 4 different carbon-fiber tops; remote control available; repositioning accuracy: ±0.2 mm			CT simulator style, customized for helical delivery, indexing system included, couch positioning accuracy 0.3 mm	Indexed immobilization, carbon-fiber top panels, movable carbon-fiber support rails, local and optional remote couch motion, field and rangefinder lights and laser control, dual control pendants, unipanel couch-top pivot, motion locks for SRS, used with Clinac and Trilogy treatment delivery systems and Acuity standard simulation systems, EXACT COUCH: optional full carbon fibre couch top, indexed immobilization, optional remote couch motion, field and rangefinder lights and laser control, dual control pendants, same couch as used with Acuity standard simulation systems, EXACT IGRT COUCH				
ARC THERAPY											
X-Ray	Yes	Yes	Yes	Yes	Yes	Yes, beam delivery is continuous, unidirectional, helical IMRT	Yes	Yes	Yes	Yes	Yes
Electron	Yes	Yes	Optional	Optional	Optional	NA	Optional	Yes	Yes	NA	NA
RECOMMENDED MINIMUM ROOM SIZE											
L x W x H, m (ft)	6.5 x 6 x 3.2 (21.3 x 19.7 x 10.5)		6.25 x 6.1 x 2.95 (20.5 x 20.0 x 9.7)			6.7 x 5.2 x 2.7 (22 x 17 x 9)	Not specified	Not specified	Not specified	6.7 x 6.1 x 3.2 (22 x 20 x 10.5)	
POWER REQUIREMENTS											
Line voltage, VAC	220/415, 3-phase		480 recommended			480, 3 phase; others may be supported	200-240, 60 Hz; 360-440, 50 Hz				
kVA (beam-on)	30 maximum	30 maximum	42	30	42	NA	45	45	45	15	15

PRODUCER	ELEKTA	ELEKTA	SIEMENS	SIEMENS	SIEMENS	TOMOTHERAPY	VARIAN	VARIAN	VARIAN	VARIAN	VARIAN
MODEL	**Elekta Synergy**	**Precise Treatment System**	**ONCOR Avant-Garde: ONCOR Expression**	**ONCOR Impression**	**ONCOR Impression Plus**	**Hi-Art Treatment System**	**Clinac 2100C**	**Clinac 2100C/D**	**Clinac 2300C/D**	**Clinac 600C: Clinac 600C/D**	**Clinac 6EX**
List price	Not specified	Not Listed	Not specified	Not specified	Not specified	$ 3 500 000	Not specified	Not specified	Not specified	$ 704 600-2 967 100	$1 025 300-3 024 200
Fiscal year	May to April		October to September			January to December	October to September				
Optional accessories	Image-enabled electronic medical record with practice management modules, high-dose-rate electrons, intelligent device management service tools via Internet, service and support agreements, SRT package with fine-resolution add-on mMLC or beam modulator, QA tools, immobilization devices,	Flat-panel (aSi) motorized megavoltage portal imaging system, stereotactic radiosurgery system, image-enabled electronic medical record with practice management modules, networking, electron applicators, intelligent device management	Remote table control, HD 270 MLC, Total Body Irradiation Control (TBIC), MVision (Megavoltage Cone Beam CT) is standard on ONCOR Expression, optional on Avant-Garde; Gated Delivery is standard on ONCOR Avant-Garde, optional on Expression; ModuLeaf mini-MLC for automated SRT and IMRT delivery	SIMTEC option for automatic delivery of a sequence of fields; 2 sec Quick start-up for RAD ON, remote table control, HD 270 MLC, Total Body Irradiation Control (TBIC), IM-MAXX2 for fast IMRT delivery (available with OPTIFOCUS MLC), OPTIVUE aSi flat panel EPID, MVision (Megavoltage Cone Beam CT); Gated Delivery; ModuLeaf mini-MLC for automated SRT and IMRT delivery		Hi-Art planned adaptive, Hi-Art StatRT, additional workstations, DICOM export data services package, Hi-Art Treatment System 1 cm beam slice width commissioning; high-performance couch, Radionics Interfix radiosurgery kit, Hi-Art Treatment System QA options, IBA helical dosimetry package, filmless DQA options from PTW Corp,	PortalVision, Portal Dosimetry, onboard kV imager (radiographic, fluoro, optional cone beam CT) for IGRT, IGRT, high-dose 6 MV SRS energy, optical patient positioning, auto field sequencing, 4-D integrated treatment console, RPM respiratory gating, Argus QA, SonArray ultrasound targeting, retractable beam stopper, M3 micro-MLC (BrainLAB), ARIA radiotherapy information management system, Eclipse and Fast Plan treatment planning		PortalVision, Portal Dosimetry, RPM respiratory gating, Argus QA, optical patient positioning, SonArray ultrasound targeting, 4-D integrated treatment console, retractable beam stopper, M3 micro-MLC (BrainLAB), ARIA radiotherapy information management system, Eclipse treatment planning	

PRODUCER	ELEKTA	ELEKTA	SIEMENS	SIEMENS	SIEMENS	TOMOTHERAPY	VARIAN	VARIAN	VARIAN	VARIAN	VARIAN
MODEL	**Elekta Synergy**	**Precise Treatment System**	**ONCOR Avant-Garde: ONCOR Expression**	**ONCOR Impression**	**ONCOR Impression Plus**	**Hi-Art Treatment System**	**Clinac 2100C**	**Clinac 2100C/D**	**Clinac 2300C/D**	**Clinac 600C: Clinac 600C/D**	**Clinac 6EX**
	respiratory motion management system, stereotactic body frame, IMRT QA tools, range of tabletop inserts, in-room CCTV monitoring system, intercom system, patient-alignment lasers system (green or red), patient-positioning accessories, tabletop accessories, tabletops	service tools via Internet, service and support agreements, QA tools, immobilization devices, respiratory motion management system, IMRT QA tools, range of tabletop inserts, in-room CCTV monitoring system, intercom system, patient-alignment lasers system (green or red), patient-positioning accessories,				TomoPortal remote viewer, BodyFIX immobilization system, Tomotherapy medical physics services					

PRODUCER	ELEKTA	ELEKTA	SIEMENS	SIEMENS	SIEMENS	TOMOTHERAPY	VARIAN	VARIAN	VARIAN	VARIAN	VARIAN
MODEL	**Elekta Synergy**	**Precise Treatment System**	**ONCOR Avant-Garde: ONCOR Expression**	**ONCOR Impression**	**ONCOR Impression Plus**	**Hi-Art Treatment System**	**Clinac 2100C**	**Clinac 2100C/D**	**Clinac 2300C/D**	**Clinac 600C: Clinac 600C/D**	**Clinac 6EX**
		tabletop accessories, tabletops									
Other specifications	Same as Precise Treatment System as well as 4-D Adaptive IGRT from which the best image acquisition method can be chosen; VolumeView and PlanarView correct organ motion/deformation between treatments, MotionView fluoroscopic visualization and tracking of organ motion during treatments, X-ray volume imaging, special	Windows-NT-based GUI; integrated verification; autowedge (0-60°); SliC beam control; open-architecture connectivity via DICOM RT; quick mode for standard therapy for urgent treatments; auto set up designed for dynamic therapy; upper and lower independent collimators;	Fully digital platform; mechanical and radiation isocenters coincide in a sphere with radius of ≤0.5 mm; supports new COHERENCE Suite of Oncology Workspaces (all ONCOR units include COHERENCE Therapist, fully integrated control console); patient clearance of 43 cm from bottom of accessory		Mechanical and radiation isocenters coincide in a sphere with radius of ≤0.5 mm; supports new COHERENCE Suite of Oncology Workspaces; patient clearance of 43 cm from bottom of accessory holder to isocenter; supports respiratory gating; 10-year prorated warranty on waveguide	System designed for CT-guided IMRT treatments delivered helically using a ring gantry with tens of thousands of beamlets delivered in standard treatment times, offering enhanced tumour targeting and normal-tissue sparing; fan beam CT with true Hounsfield units allows dose calculation on the daily image guidance CT for use in treatment	None specified	None specified	None specified	Photon radiotherapy including photon-arc therapy, 3-D CRT, total-body irradiation, IMRT, respiratory-gated treatment delivery, and MV portal imaging. Meets requirements of EN 46001, ETL, and ISO 9001.	Photon radiotherapy including photon-arc therapy, 3-D CRT, total-body irradiation, IMRT, respiratory-gated treatment delivery, and MV portal imaging; fine-beam performance specifications; support for beam matching to Clinac EX, Clinac iX, and Trilogy. Meets requirements

PRODUCER	ELEKTA	ELEKTA	SIEMENS	SIEMENS	SIEMENS	TOMOTHERAPY	VARIAN	VARIAN	VARIAN	VARIAN	VARIAN
MODEL	**Elekta Synergy**	**Precise Treatment System**	**ONCOR Avant-Garde: ONCOR Expression**	**ONCOR Impression**	**ONCOR Impression Plus**	**Hi-Art Treatment System**	**Clinac 2100C**	**Clinac 2100C/D**	**Clinac 2300C/D**	**Clinac 600C: Clinac 600C/D**	**Clinac 6EX**
	robotic gantry drum structure, integrated digital linac with KV and MV imaging, high-precision robotic imaging detector systems, integrated keyboard control for MV and KV imaging, treatment planning image registration software tools	Impac's MOSAIQ electronic medical record; remote service; low (124 cm) isocenter; high-stability drum gantry design; 2 in-room monitors; Arctherapy capability for photons and electrons; mechanical frontpointer; fiberoptic laser backpointer; diagnostic mode for system calibration and onscreen	holder to isocenter; 10-year prorated warranty on waveguide			evaluation and adaptive planning					of EN 46001, ETL, and ISO 9001.

PRODUCER	ELEKTA	ELEKTA	SIEMENS	SIEMENS	SIEMENS	TOMOTHERAPY	VARIAN	VARIAN	VARIAN	VARIAN	VARIAN
MODEL	**Elekta Synergy**	**Precise Treatment System**	**ONCOR Avant-Garde: ONCOR Expression**	**ONCOR Impression**	**ONCOR Impression Plus**	**Hi-Art Treatment System**	**Clinac 2100C**	**Clinac 2100C/D**	**Clinac 2300C/D**	**Clinac 600C: Clinac 600C/D**	**Clinac 6EX**
		fault analysis tools; block tray for shielding blocks; handheld controller; on-site application and follow up training									

Table 2. Comparison of Radiotherapy Treatment Planning Systems

PRODUCER	**BRAINLAB**	**CMS**	**ELEKTA**	**ELEKTA**	**ELEKTA**	**INTEGRA RADIONICS**	**MULTI-DATA**	**MULTI-DATA**	**NUCLETRON**	**NUCLETRON**	**PHILIPS**	**PROWESS SYSTEMS**	**PROWESS SYSTEMS**	**PROWESS SYSTEMS**	**VARIAN**
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
Where marketed	Worldwide	Worldwide	Worldwide			Worldwide	Worldwide		Worldwide		Worldwide	Worldwide			Worldwide
FDA clearance	Yes	Yes	Yes	No (work in progress)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CE mark (MDD)	Yes	Yes	Yes	No (work in progress)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
EXTERNAL BEAM PLANNING															
Photon	Yes	Not specified	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Collapsed cone convolution/superposition	Yes	Yes	Yes	Yes
Electron	No	Electron cutout, 3-D pencil beam with scatter-beam integration	No	No	Yes (applica-tors, inserts)	No	CET and pencil beam		Yes	Generated pencil beam	3-D pencil beam (modified Hog-strom)	Yes	No	No	Generalized Gaussian pencil beam, Monte Carlo

PRODUCER	BRAINLAB	CMS	ELEKTA	ELEKTA	ELEKTA	INTEGRA RADIONICS	MULTI-DATA	MULTI-DATA	NUCLETRON	NUCLETRON	PHILIPS	PROWESS SYSTEMS	PROWESS SYSTEMS	PROWESS SYSTEMS	VARIAN
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
Proton	No	Not specified	No	No	No	No	No	No	Work in progress	No	No	No	No	No	Yes; double scattering, single scattering, modulated scanning
STEREOTACTIC															
Frame	Yes	Not specified	Yes (head/ body; invasive/ relocate-able)	No	Yes (Elekta SBF for SRT)	Yes	Yes	Yes	No	Yes	Yes (BRW, Fisher, Leksell, Compass)	NA	No	No	Yes
Frameless	Yes	Not specified	Yes	No	Yes	Yes	Not specified	Not specified	No	Not specified	No	NA	No	No	Yes
3-D Conformal	Yes	Not specified	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Not specified	Yes
4-D Conformal	Yes, 4-D CT allows target delineation	Not specified	Yes	Yes (4-D data with CBCT for tracking)	No	No	Not specified	Not specified	Yes	Not specified	No	NA	No	No	Yes

PRODUCER	BRAINLAB	CMS	ELEKTA	ELEKTA	ELEKTA	INTEGRA RADIONICS	MULTI-DATA	MULTI-DATA	NUCLETRON	NUCLETRON	PHILIPS	PROWESS SYSTEMS	PROWESS SYSTEMS	PROWESS SYSTEMS	VARIAN
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
IMRT															
Step and Shoot	Yes	Not specified	Yes	No	Yes (aperture-based inverse planning)	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes
Dynamic	Yes	Not specified	Yes (arc modu-lation; AMOA, VMAT)	No	No	Dynamic Arcs	Yes	Yes	No	Yes	Yes	NA	NA	No	Yes
MLC	Yes	Not specified	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes
Solid Block	No	Not specified	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes
Virtual Wedge	No	Not specified	No	No	Yes	Yes	Yes	Yes	Yes	Not specified	Yes	NA	Yes	NA	Yes
IGRT	Yes	Not specified	Yes (with Elekta XVI work-station)	Yes	Yes (with Elekta XVI work-station)	Yes	Not specified	Not specified	No	No	Yes	NA	No	No	Yes
Tomo-therapy	No	Not specified	No	No	No	No	Not specified	Not specified	No	No	No	NA	No	No	Not specified

PRODUCER	BRAINLAB	CMS	ELEKTA	ELEKTA	ELEKTA	INTEGRA RADIONICS	MULTI-DATA	MULTI-DATA	NUCLETRON	NUCLETRON	PHILIPS	PROWESS SYSTEMS	PROWESS SYSTEMS	PROWESS SYSTEMS	VARIAN
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
Adaptive Therapy	NA	Not specified	No	Yes (4-D data with CBCT for tracking)	No	Yes	Not specified	Not specified	Yes	No	No	NA	Work in progress	Work in progress	Yes
BRACHYTHERAPY															
Breast	NA	Not specified	No	No	No	No	Not specified	Not specified	Not specified	Yes	Yes	Yes	NA	NA	Yes
Endo-vascular	NA	Not specified	No	No	No	No	Not specified	Not specified	Not specified	Yes	No	Yes	NA	NA	Yes
Gynaeco-logy	NA	Not specified	No	No	No	No	Not specified	Not specified	Not specified	Yes	Yes	Yes	NA	NA	Yes
Head & neck	NA	Not specified	No	No	No	No	Not specified	Not specified	Not specified	Yes	Yes	Yes	NA	NA	Yes
Intra-operative	NA	Not specified	No	No	No	No	Not specified	Not specified	Not specified	Yes	No	Yes	NA	NA	Yes
Prostate	NA	Not specified	No	No	No	No	Not specified	Not specified	Not specified	Yes	Yes	Yes	NA	NA	Yes

PRODUCER	BRAINLAB	CMS	ELEKTA	ELEKTA	ELEKTA	INTEGRA RADIONICS	MULTI-DATA	MULTI-DATA	NUCLETRON	NUCLETRON	PHILIPS	PROWESS SYSTEMS	PROWESS SYSTEMS	PROWESS SYSTEMS	VARIAN
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
Other		Seed/ linear/ trans-perineal prostate planning, TG-43 and SIEVERT integral formalism with DVH, US image guidance with 3-D stepper system	NA	NA	NA	No	Slice-based support for up to 2,400 seeds, 115 line sources/plan, orthogonal and stereo source entry; prostate, Syed, and other templates	Future development	Multiple data inputs; inter-active 3-D views; multi-ple mixed-source types; DVH; 3-D dose grid; brachy seeds; auto-seed reconstruct-tion on CT; AAPM TG43 implementa-tion; inverse optimization; automatic catheter re-cognition; graphical organization; auto active-tion of Dwell positions; CT reconstruct.	3-D recon-struction, CT-based, digitize sources, TG-43, no limit on modelling source	Orthogonal, US- and CT-based planning support, inverse planning, postplan, and pubic arch study	NA	NA	Brachy Vision: film and image-based, LDR and HDR, all isotopes supported, TG43 compliant, dose shaper interactive optimization

PRODUCER	BRAINLAB	CMS	ELEKTA	ELEKTA	ELEKTA	INTEGRA RADIONICS	MULTI-DATA	MULTI-DATA	NUCLETRON	NUCLETRON	PHILIPS	PROWESS SYSTEMS	PROWESS SYSTEMS	PROWESS SYSTEMS	VARIAN
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
COMPATIBLE TREATMENT DELIVERY															
LINAC	Varian, Siemens, Elekta, BrainLAB, all major Linac models	Not specified	Elekta (All); Varian; Siemens	No	Elekta (all); Varian; Siemens	Siemens, Varian, Elekta	Not specified	Yes	All major Linac vendors	Not specified	Elekta, Varian, Siemens, Mitsubishi	NA	To all LINACs	To all LINACs	Varian, Siemens, Elekta, GE, Mitsubishi
MLC	Novalis Tx (HD 120), BrainLAB m3, Varian MLC-52, Varian MLC-80, Varian MLC-120, Siemens 3-D MLC58, Siemens 3-D MLC82, Siemens Moduleaf, Elekta MLCi, Elekta MLC80, Elekta Beam	Not specified	Elekta; Varian; Siemens; Acces-sory	No	Elekta; Varian; Siemens; Accessory	Siemens, Varian, Elekta (MLCs); XKnife MMLC; Siemens ModuLeaf MMLC	Not specified	Yes	All major Linac vendors	Not specified	Varian (80, 120), Siemens (3-D MLC), Elekta, Radionics (Con-formaxx), Brainlab (M3), 3DLine (DMLC)	NA	To all LINACs	To all LINACs	Varian, Siemens, Elekta, GE, Mitsubishi

PRODUCER	BRAINLAB	CMS	ELEKTA	ELEKTA	ELEKTA	INTEGRA RADIONICS	MULTI-DATA	MULTI-DATA	NUCLETRON	NUCLETRON	PHILIPS	PROWESS SYSTEMS	PROWESS SYSTEMS	PROWESS SYSTEMS	VARIAN
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
	Modulator; all major available avail: Varian, Siemens, Elekta, BrainLAB MLCs														
Stereo-tactic Frames	BrainLAB, Radionics, Leksell	Not specified	SRS/ SRT, invasive/ relo-cateable head, head/ neck and body	No	Elekta stereo-tactic body frame	Radiosurgery (HRAIM), radiotherapy (GTC), paediatric (TLC), head and neck (HNLBSYS), body (BLSYS)	Not specified	Not specified	Not specified	Not specified	Radionics (BRW), Fisher, Elekta (Leksell), Compass	NA	No	No	Varian, BRW
After-loaders	NA	Not specified	NA	NA	NA	No	Not specified	Not specified	Not specified	Yes; classic, HDR, PDR, digital HDR	No	No	NA	NA	Varian/ Varisource, Gamma Med
Other	NA	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Software is capable of configuring to handle any LINAC, MLCs		Proton-IBA, Hitachi, Accel, MPRI

PRODUCER	BRAINLAB	CMS	ELEKTA	ELEKTA	ELEKTA	INTEGRA RADIONICS	MULTI-DATA	MULTI-DATA	NUCLETRON	NUCLETRON	PHILIPS	PROWESS SYSTEMS	PROWESS SYSTEMS	PROWESS SYSTEMS	VARIAN
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
IMAGE DATA															
DICOM 3.0	Yes	Not specified	Yes (CT, MR, PET, SPECT, US)	Yes (CT, MR, PET+CT, US)	Yes (CT, MR, PET through third-party product; outside USA)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Conven-tional Simulator	Yes	Not specified	Yes (angio-graphy)	No	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Digitizer	Yes	Not specified	No	No (WACOM Intuos pen tablet)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Digital Radiograph	Yes	Not specified	Yes (CR, SC)	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes

PRODUCER	BRAINLAB	CMS	ELEKTA	ELEKTA	ELEKTA	INTEGRA RADIONICS	MULTI-DATA	MULTI-DATA	NUCLETRON	NUCLETRON	PHILIPS	PROWESS SYSTEMS	PROWESS SYSTEMS	PROWESS SYSTEMS	VARIAN
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
CT	Yes	DICOM 3.0, optical disk, CD-R, floppy	Yes	Yes	Yes	Yes	CT interface included, virtual simulation support with DRRs, DCRs, and MPRs; beam set up in BEV or room view		Multislice autocontour, image reformatting, multiplanar reconstruction, multiple CT series per case, image registration/ fusion	Yes	Yes	Yes	Yes	Yes	Real-time coronal/ sagittal sections, mean/ media filters, thres-holding, adaptive histogram, nonlinear scaling, multiplanar reconstruc-tion
MR	Yes	Not specified	Yes	Yes	Yes	Yes	Optional	Optional	Yes	Interactive, automated contour creation/edit/ copy, ROI, VOI, volume calculation, 3-D margining	Yes	Yes	Yes	Yes	Yes
PET	Yes	Not specified	Yes	Yes	Yes	Yes	Not specified	Not specified	Yes	Yes	Yes	Yes	Yes	Yes	Yes

PRODUCER	BRAINLAB	CMS	ELEKTA	ELEKTA	ELEKTA	INTEGRA RADIONICS	MULTI-DATA	MULTI-DATA	NUCLETRON	NUCLETRON	PHILIPS	PROWESS SYSTEMS	PROWESS SYSTEMS	PROWESS SYSTEMS	VARIAN
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
SPECT	Not specified	Yes		Not specified	No	No	Not specified	Not specified	No	No	Yes	Yes	Yes	Yes	No
Other	Not specified	Ultrasound		Ultra-sound	NA	None	Not specified	Not specified	Not specified	DICOM ultrasound, DICOM export	Not specified	Incorporates scanned film images		Not specified	Not specified
IMAGE FUSION															
Manual registration	Yes	Not specified	Yes	Yes	Yes (third-party product outside USA)	Yes	Not specified	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fiducial-based Registra-tion	Yes	Not specified	Yes, 2 algo-rithms: stereo-tactic based in localizer fiducials (all SRS/ SRT frames) and marker	No	Yes (Elekta SBF)	Yes	Not specified	Not specified	Yes	Yes	Yes	Yes	Yes	Yes	Yes

PRODUCER	BRAINLAB	CMS	ELEKTA	ELEKTA	ELEKTA	INTEGRA RADIONICS	MULTI-DATA	MULTI-DATA	NUCLETRON	NUCLETRON	PHILIPS	PROWESS SYSTEMS	PROWESS SYSTEMS	PROWESS SYSTEMS	VARIAN
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
			based fusion (anato-mic external markers)												
Anatomy Based Registratio n	Yes	Not specified	Yes, 2 statistica l algo-rithms: frame-less volume-tric chamber match-ing and norma-lized mutual informa-tion	Yes (norma-lized mutual informa-tion)	Yes (third-party product outside USA)	Yes	Not specified	Not specified	Yes	Yes	Yes	No	No	No	Yes
PLANNING METHODOLOGY AND TOOLS															
Module Based Software	Yes (by customer request)	Not specified	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not specified	Yes	Yes	Yes	Yes	Yes

PRODUCER	BRAINLAB	CMS	ELEKTA	ELEKTA	ELEKTA	INTEGRA RADIONICS	MULTI-DATA	MULTI-DATA	NUCLETRON	NUCLETRON	PHILIPS	PROWESS SYSTEMS	PROWESS SYSTEMS	PROWESS SYSTEMS	VARIAN
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
Inverse Planning	Yes	Not specified	Yes	No	Yes	Yes	Not specified	Not specified	Yes	Yes	Yes	Yes	No	Yes	Yes
Dosimetric Algorithms	Pencil Beam, Monte Carlo, measure-ment based for cones	Not specified	Photon pencil beam convo-lution	Monte Carlo	Photon 3-D TAR/ SAR; electron pencil beam	Fast TMR, Primary+ Scatter, pencil beam	Not specified	Not specified	Monte Carlo electron, pencil beam, collapsed cone for photons	Not specified	Collapsed cone convolu-tion/super position, 3-D modified Hogstrom	TG 43	Collapsed cone convolution super-position; Fast Photon	Collapsed cone convolution super-position	Pencil beam convolution, convolution super-position (AAA), generalized Gaussian pencil beam, electron Monte Carlo, dose volume optimizer, beam angle optimizer
Plan Resolution	Freely adjustable (1 mm3)	Not specified	Convolut ion in patient image space	No limit	Dose grid is variable with CT image	1 mm^3	Not specified	Not specified	1 mm3	Not specified	Variable (down to 1 mm3)	<1 mm^3	<1 mm^3	3 mm^3	Convolu-tion superpose-tion (AAA) = 2 mm; electron Monte Carlo = 1 mm

PRODUCER	BRAINLAB	CMS	ELEKTA	ELEKTA	ELEKTA	INTEGRA RADIONICS	MULTI-DATA	MULTI-DATA	NUCLETRON	NUCLETRON	PHILIPS	PROWESS SYSTEMS	PROWESS SYSTEMS	PROWESS SYSTEMS	VARIAN
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
Max Number of Beamlets	Unlimited	Not specified	RAM and disk space	NA	RAM and disk space	Arbitrary, limited only by machine memory	Not specified	Not specified	Unlimited	Not specified	Limited by MLC leaf dimension	NA	NA	No limitations	25 600 beamlets/ field (IMRT)
Max Number of Beam Angles	Unlimited	Not specified	RAM and disk space	NA	RAM and disk space	Arbitrary, limited only by machine memory	Not specified	Not specified	Unlimited	Not specified	No restriction	NA	No limitations	No limitations	25 static fields
Template Library	Yes	Not specified	Yes	No	Yes (and workflow manager via scripts)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Automatic Organ Contouring	Yes	Not specified	Yes (2-D)	Yes (3-D)	Yes (2-D)	No	Not specified	Not specified	Yes	No	Yes (model based segmen-tation)	Yes	Yes	Yes	Yes, Smart segmen-tation
Semi-Automatic Organ Contouring	Yes	Not specified	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

PRODUCER	BRAINLAB	CMS	ELEKTA	ELEKTA	ELEKTA	INTEGRA RADIONICS	MULTI-DATA	MULTI-DATA	NUCLETRON	NUCLETRON	PHILIPS	PROWESS SYSTEMS	PROWESS SYSTEMS	PROWESS SYSTEMS	VARIAN
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
Input Prescription Limitations	Yes	Not specified	Yes	Yes (MOSAIQ diagnoses and inter-ventions)	Yes (and workflow manager)	Yes	Not specified	Not specified	Yes	Yes, IPSA	Yes	No	No	No	Yes
Real-Time Plan Adjustment and Optimiza-tion	Choice of calculation in a single slice or 3-D volume for fast calculation	Not specified	Arc modulati on with inverse planning	No	Anatomic aperture MU optimiza-tion with inter-active DVH feedback real-time	Yes	Not specified	Not specified	User defines desired objectives that can be modified during and after optimization process	No	No	Real-time dose updates, Mixed Integer Program (MIP) based opti-mization	Real-time dose update for any beam/plan changes	Real-time optimization parameter change support; multiple constraints including EUD supported	Yes, interactive IMRT optimization
Composite Modality Planning	Cones + MLC + IMRT; various LINAC included; various energies 4 MV-25 MV	Not specified	Yes (confor-mal and IMRT boost)	No	Photons+ electrons; fraction group support	No	Not specified	Not specified	Work in progress	Yes	Yes	Yes	Yes	Yes	Yes

PRODUCER	BRAINLAB	CMS	ELEKTA	ELEKTA	ELEKTA	INTEGRA RADIONICS	MULTI-DATA	MULTI-DATA	NUCLETRON	NUCLETRON	PHILIPS	PROWESS SYSTEMS	PROWESS SYSTEMS	PROWESS SYSTEMS	VARIAN
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
COMPUTING PLATFORM AND NETWORKING															
Operating System	Windows XP	LINUX	Red Hat Linux	MS-Windows XP	Red Hat Linux	Linux	Windows 2000/XP	Windows 2000/XP/ Vista	Windows XP Pro sp1 or sp2, Windows 2000 Pro sp 4	IRIX (6.5)	Sun Solaris 8.0	Windows XP Pro			Windows XP
Computing Hardware	Intel Dual Quad Core Xeon processors	Not specified	HP xw6400			HP	PC	PCs, server	Pentium 4, 3.6 GHz, 3 GB of RAM	SGI	Philips System 810 (Dual AMD Opteron CPUs, Solaris 10 OS)	PC Platform			PC
Client Server (Remote Access)	Yes, with iPlan Net	Not specified	Yes	Yes	Yes	Yes	Some	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Network Shared Resources	Yes	Not specified	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not specified	Yes	Yes	Yes	Yes
Compatible Oncology Informa-tion System	Yes	Not specified	IMPAC Multi-access/ MOSAIQ; Varian Varis	IMPAC MOSAIQ RTP Suite applica-tions	IMPAC Multi-access/ MOSAIQ; Varian Varis	IMPAC, lantis, Aria, Varis	Most	Most	Impac, Lantis, Aria, others	No	Exporta-tion to IMPAC, Varian, Siemens OIS	DICOM 3.0 compatible			ARIA, IMPAC, Visir, Lantis

PRODUCER	BRAINLAB	CMS	ELEKTA	ELEKTA	ELEKTA	INTEGRA RADIONICS	MULTI-DATA	MULTI-DATA	NUCLETRON	NUCLETRON	PHILIPS	PROWESS SYSTEMS	PROWESS SYSTEMS	PROWESS SYSTEMS	VARIAN
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
DICOM RT	Yes	Not specified	Yes	Yes	Yes (see ATC and IHE-RO com-pliance)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Printer	All Windows compatible	Not specified	Lexmark	Any	Lexmark	Compatible with Post Script Printers	Not specified	Not specified	Text printer: 600 dpi, A4/ Letter; graphics printer (color): 600 dpi, A3/11 x 17 in	HP Business Ink Jet 2800, Lexmark color laser printer	Not specified	HP color laser jet 4700 series			Lexmark 920N (120 V and 230 V)
Warranty	1 year, various service contract options	1 yr, soft-ware and hardware; extensions available	12 months from customer acceptance			1 year, hardware and software	1 year, hardware and software; renewable by support contract		1 year	1 year, parts/labour	1 year	1 year, software; renewable; hardware from original manufacturer			1 year, hardware and software
List price range	Not specified	$ 100 000-230 000	$ 150 000-250 000	NA (work in progress)	$120 000-240 000	Starting at $ 150 000	Starting at $ 50 000	Starting at $ 85 000	$ 150 000-250 000	Not specified	$110 000-200 000 stand-alo-ne server; depends on no. of workstati-ons and options selected	Not specified	Not specified	Not specified	Varies, depending on configure-tion

PRODUCER	BRAINLAB	CMS	ELEKTA	ELEKTA	ELEKTA	INTEGRA RADIONICS	MULTI-DATA	MULTI-DATA	NUCLETRON	NUCLETRON	PHILIPS	PROWESS SYSTEMS	PROWESS SYSTEMS	PROWESS SYSTEMS	VARIAN
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
Number installed	Not specified	1,161 worldwide	150 world-wide	NA (work in progress)	175 USA, 456 worldwide	300+	150 USA, 350 world-wide	Not specified	200	>1,000 worldwide	~950; 300 clinical IMRT installs	Not specified	Not specified	Not specified	>2,500 worldwide
Fiscal year	Not specified	October to Septem-ber	May to April			January to December	July to June		January to December		January to December	January to December			October to September
Other specifica-tions	None specified	Inverse planning optimi-zation; real-time graphics with interactive BEV, DRR, DVH; custom proton planning software; remote time/MU calculator program; factory-	Dedica-ted to SRS, SRT, and arc mo-dulation dynamic IMRT delivery	None specified	Supports Elekta techno-logy and clinical techni-ques	Full support for Radionics stereotactic localizers, immobilizers, patient set up, and QA instrument-tation; interfaces support also includes DICOM RT structure set import, plan export via IMPAC RTP protocol to a number of R	Protocol support with library of treat-ment plans; support for multiple or satellite sites	Protocol support with library of treatment plans	Mutual information image registration; HIPAA ready; data archival in non-proprietary DICOM format; volume rendering	1 computer houses all modules; custom tailored; supports all software; beam data entry service	None specified	Fully modular design; can be upgradeable to 3-D, IMRT	Fully modular design; can include brachy and IMRT modules	Patented DAO and jaws-only IMRT features	Multi-modality image support; plan analyzing tools; plan templates; integrated patient chart; virtual simulation; distributed planning; dynamic/ enhanced dynamic wedge;

PRODUCER	BRAINLAB	CMS	ELEKTA	ELEKTA	ELEKTA	INTEGRA RADIONICS	MULTI-DATA	MULTI-DATA	NUCLETRON	NUCLETRON	PHILIPS	PROWESS SYSTEMS	PROWESS SYSTEMS	PROWESS SYSTEMS	VARIAN
MODEL	**iPlan**	**XiO 2-D, 3-D, and IMRT**	**ERGO++ (3D Line)1**	**IMPAC MOSAIQ RTP Suite**	**Precise PLAN**	**XKnife Radio-surgery System**	**DSS (TPS)**	**RTSuite TPS and Virtual Simula-tion**	**Oncentra MasterPlan**	**PLATO Treatment Planning**	**PINNA-CLE 3**	**Prowess Panther 3D Brachy Pro**	**Prowess Panther 3D External Beam**	**Prowess Panther DAO IMRT**	**Eclipse**
		based formal training. CSA, GS, and UL compliant; ISO 9001/ EN 46001 certified; registered with Japanese Ministry of Health and Welfare				and V systems, and MMLC file export protocol to the Radionics MMLC control system									MLC supported. TG-53 commissio-ning
Last updated	March 2008	October 2004	September 2007			March 2008	September 2007		September 2007		Septem-ber 2007	September 2007			September 2007

Appendix 2. Systematic review of literature: search strategy and tables of primary studies

INTERNATIONAL AGENCIES

Argentina

- Instituto de effectividad cliinica y sanitaria - ICIES

Australia

- Royal Australasian College of Surgeons - ASERNIP
- Centre for Clinical Effectiveness, Monash University
- Medical services advisory committee - MSA
- New Zealand Health Technology Assessment - NZHTA
- The Australia and New Zealand Horizon Scanning Network - ANZHSN
- Adelaide Health Technology Assessment

Austria

- Institute of Technology Assessment
- Department of Public Health, Medical Decision Making and Health Technology Assessment

Belgium

- Belgian Health Care Knowledge Centre

Brasil

- Department of Science and Technology - Brazilian Health Technology Assessment General Coordination, Brasilia (DECIT-CGATS)

Canada

- Agence d'évaluation des technologies et des modes d'intervention en santé - AETMIS
- Alberta Heritage Foundation
- Canadian Agency for Drugs and Technologies in Health - CADTH
- Canadian Coordinating Office for Health Technology Assessment - CCOHTA
- Centre for Health Services and Policy Research, University of British Columbia
- Health Technology Assessment Unit, McGill University
- Institute of Health Economics,- Alberta

- Manitoba Centre for Health Policy
- Ontario Health Technology Advisory Committee - OHTAC
- Ontario Medical Advisory Secretariat
- Program for Assessment of Technology in Health - PAT
- Therapeutics Initiative - Evidence Based Drug Therapy

Denmark

- Danish Centre for Evaluation and Health Technology Assessment

Finland

- Finnish Office for Technology Assessment

France

- HAS Haute autoritè de santè
- Comitè d'evaluation et de diffusion des innovations technologiques - CEDIT
- Catalogue et index des sites médicaux francophones - CISMEF
- REES France Health Evaluation Network

Georgia

- HTA Policy for Georgia

Germany

- Dimdi
- Office of Technology Assessment at the German Parliament (TAB)
- Institute for Quality and Efficiency in Health Care (IQWIG)

Holland

- CEBP Research Department of Medical Technology Assessment
- Health Council of Netherlands
- College voor Zorgverzekeringen/Health Care Insurance
- ZonMw - the Netherlands Organisation for Health Research and Development
- NWO Netherlands Organisation for Scientific Research

Hungary

- Unit of Health Economics and Technology Assessment, Universität Budapest

Norway

- Norwegian Knowledge Centre for the Health Services

Spain

- Agencia d'avaluaciò de tecnologia i ricerca mediques
- Agencia de evaluación de tecnologías sanitarias de Andalucia
- Agencia de evaluación de tecnologías sanitarias - Instituto de Salud Carlos III
- Agencia de evaluación de tecnologías sanitarias del País Vasco
- Axencia de avaliación de tecnoloxias saniatarias de Galicia (AVALIA-t)
- Unidad de evaluación de tecnologías sanitarias de la Comunidad de Madrid
- Asociación española de evaluación de tecnologías sanitarias

Sweden

- Centrum för utvärdering av medicinsk teknologi - CMT
- Swedish Council on Technology Assessment in Health Care - SBU

Switzerland

- Swiss Network For Health Technology Assessment

United Kingdom

- Aberdeen Health Technology Assessment Group
- Aggressive Research Intelligence Facility - ARIF
- Development and Evaluation Committee - DEC
- European Information Network on New and Changing Health Technologies - EUROSCAN
- Health Evidence Bulletins, Wales
- Health Technology Portal (Health Technology Devices Programme)
- Horizon Scanning Centre
- Innovative Health Technologies (Economic and Social Research Council and the Medical Research Council)
- Institute of Applied Health Sciences
- Medicine and Healthcare Products Regulatory Agency - MHRA
- National Coordinating Centre for Health Technology Assessment - NCCHTA
- National Horizon Scanning Centre
- New and Emerging Applications of Technology - NEAT
- NHS Purchasing and Supply Agency - Centre for Evidence-based Purchasing
- NHS Quality Improvement Scotland
- NICE
- Wessex Institute for Health Research and Development at
- West Midlands Health Technology Assessment Collaboration

USA

- Academy for Health Services Research and Health Policy
- Aetna (National provider of health, dental, group, life, disability and long-term care benefits)
- Agency for Healthcare Research and Quality
- Blue Cross Blue Shield Association
- California Health Benefits Review Program
- Center for Medicare and Medical services
- Drug Effectiveness Review Project - DERP
- Drug Effectiveness Review Project, Oregon
- Emergency Care Research Institute - ECRI
- Harvard Centre for Risk Analysis
- Hayes Inc.
- Institute for Clinical System Improvement - ICSI
- Institute for Technology Assessment - Massachusetts General Hospital
- Institute of Medicine of the National Academies
- Medical Technology Practice Patterns Institute - MTPPI
- National Information Center on Health Services Research and Health Care Technology
- Office of Technology Assessment - Congress of United States
- Oregon Evidence-based Practice Centre
- RAND Corporation
- The University Health System Consortium (US)
- The Tufts Medical Center Evidence-based Practice Center, New England
- US Food and Drug Administration
- VA's Technology Assessment Program - VATAP; Department of Veterans Affairs

International

- WHO Health Evidence Network
- PAHO
- HTA South Africa
- Health Technology Assessment International
- EUnetHTA - European Network for Health Technology Assessment -
- EMEA - European Medicines Agency

RESEARCH STRATEGY: SYSTEMATIC REVIEW AND PRIMARY STUDIES ON TOMOTHERAPY SEPTEMBER 2008

Search date

Up to June 2010

COCHRANE LIBRARY

1 intensity modulated radiotherapy *[all fields]*

2 radiotherapy, intensity modulated *[MeSH descriptor]*

3 1 0R 2 34 documents

Results

Systematic reviews Cochrane	7 retrieved / 0 pertinent
Abstracts of Systematic reviews of the Centre for Review Dissemination	1 retrieved / 0 pertinent
Clinical trials	16 retrieved / 0 pertinent
HTA reports from the Center for Review Dissemination database	10 retrieved / 4 pertinent

4 tomotherapy *[all fields]* 2 documents

Results

Systematic reviews Cochrane	0 documents
Abstracts of Systematic reviews of the Center for Review Dissemination	0 documents
Clinical trials	0 documents
HTA reports from the Center for Review Dissemination database	2 retrieved / 2 pertinent

PUBMED*

tomotherapy *[title/abstract]* 303 documents

(*) the term tomotherapy does not exist as a MeSH term

CCT REGISTRIES

Keyword: tomotherapy

ClinicalTrials.gov	17 documents
Cochrane controlled trials	0 documents
MetaRegister of Current Controlled Trials (mRCT)	0 documents

RESEARCH STRATEGY: PRIMARY STUDIES ON IGRT/IMRT SEPTEMBER 2008

1 image guided *[title/abstract]*
2 radiation therapy *[title/abstract]*
3 radiotherapy *[title/abstract]*
4 radiation delivery *[title/abstract]*
5 IGRT
6 2/5 OR
7 6 AND 1
7 AND ("in process" [sb] OR "publisher" [sb])

Limits: humans
Publication date: 2002 - June 2010

1 volumetric modulated arc therapy *[title/abstract]*
2 volumetric modulated arc AND radiotherapy *[title/abstract]*
3 1 OR **2**
no time limits

rapidArc *[title/abstract]*
radiotherapy technology for volumetric arc therapy
tomotherapy *[title/abstract]* May 2008 - January 2009
Cochrane reviews
CRD HTA database

Table 1. Lung cancer. Primary studies on technical performance

Synthesis of primary studies - set up error and organ motion in lung cancer

Ref. No.	Studies	Number of patients	Study design	Type of technology	Set up error (mm)			Organ motion (mm)		
					V_M	V_Σ	V_σ	V_M	V_Σ	V_σ
16	Oh 2007	19	Case series	IGRT CBCT	0.52	0.45				
17	Grills 2008	24	Case series	IGRT CBCT		5.0	3.9		1.6	
18	Guckenberger 2007	24	Case series	IGRT CBCT	0.4	4.6				
19	Harsolia 2008	8	Case series	IGRT CBCT	10.4	5.5				
20	Purdie 2007	28	Case series	IGRT CBCT	6.8	4.9		5.3	2.2	
21	Chang 2007	8	Case series	IGRT CBCT	3.5	4.7				
22	Bissonnette 2009	87	Case series	IGRT CBCT		2.55	2.66			
23	Johansen 2008	20	Case series	IGRT CBCT		2.16				
24	Guckenberger 2007	24	Case series	IGRT CBCT	0.52	2.5		1.46	2.9	
	Overall range				0.4-10.4	0.45-5.5	2.66-3.9	1.46-5.3	1.6-2.9	
	Overall mean				3.7	3.5	3.3	3.4	2.24	

Reference No. 16

Authors: Oh S., Kim S., Suh T.S..

Title: How image quality affects determination of target displacement when using kilovoltage cone-beam computed tomography.

Journal: *Journal of Applied Clinical Medical Physics*, 8 (1): 101-107, 2007.

Study objective: Correct set up error using CBCT by adjusting translational and rotational deviations.

Site: Lung, Prostate

Patients: 19 lung, 20 prostate

Study design: Case series

Set up error (mm)			**Lung**
	M	A-P	0.17
		Left-Right	0.32
		CC	0.37
	Σ	A-P	0.33
		Left-Right	0.17
		CC	0.26
	σ	A-P	
		Left-Right	
		CC	
	Σ + σ	A-P	
		Left-Right	
		CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: In comparing the estimated target displacements obtained using two CBCT image sets (one in high-quality resolution and the other in medium-quality resolution), we found that the translational vector differences between the high-quality resolution and medium-quality resolution were within 1 mm in most cases (53 of 56 cases), and that the rotational differences around each axis were within 1 degree in all but 3 cases.

Reference No. 17

Authors: Grills I.S., Hugo G., Kestin L.L., Galerani A.P., Chao K.K., Wloch J., Yan D.

Title: Image-guided radiotherapy via daily online cone-beam ct substantially reduces margin requirements for stereotactic lung radiotherapy.

Journal: *Int J Radiation Oncology Biol Phys*, 70 (4): 1045-1056, 2008.

Study objective: To determine treatment accuracy and margins for stereotactic lung radiotherapy with and without Cone Beam CT (CBCT) image guidance.

Site: Lung

Patients: 24

Study design: Case series

Type of technology: IGRT CBCT Elekta

			Lung	
			Body frame	**Alpha -cradle**
Set up error (mm)	**M**	A-P		
		Left-Right		
		CC		
	Σ	A-P	2.5	5.8
		Left-Right	2.7	2.0
		CC	3.4	2.9
	σ	A-P	1.7	1.4
		Left-Right	2.3	3.1
		CC	2.7	3.8
	Σ + σ	A-P		
		Left-Right		
		CC		
Organ motion (mm)	**M**	A-P		
		Left-Right		
		CC		
	Σ	A-P	1.0	1.0
		Left-Right	0.8	1.1
		CC	1.0	1.3
	σ	A-P		
		Left-Right		
		CC		
	Σ + σ	A-P		
		Left-Right		
		CC		

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: Set up for stereotactic lung radiotherapy using a SBF or alpha-cradle alone is suboptimal. CBCT image guidance significantly improves target positioning and substantially reduces required target margins and normal tissue irradiation.

Reference No. 18

Authors: Guckenberger M., Baier K., Guenther I., Richter A., Wilbert J., Sauer O., Vordermark D., Flentje M.

Title: Reliability of the bony anatomy in image-guided stereotactic radiotherapy of brain metastases.

Journal: *Int J Radiation Oncology Biol Phys*, 69 (1): 294-301, 2007.

Study objective: To evaluate whether the position of brain metastases remains stable between planning and treatment in cranial stereotactic radiotherapy (SRT).

Site: Lung

Patients: 24

Study design: Case series

Type of technology: IGRT CBCT Elekta

Set up error (mm)		**Lung**	
		Body match	**Tumour match**
M	A-P	-0.3	-0.1
	Left-Right	0.2	0.7
	CC	0.1	0
Σ	A-P	2.1	2.0
	Left-Right	2.9	2.7
	CC	2.9	2.4
σ	A-P		
	Left-Right		
	CC		
Σ + σ	A-P		
	Left-Right		
	CC		

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: With a time interval of approximately 1 week between planning and treatment, the bony anatomy of the skull proved to be an excellent surrogate for the target position in image-guided SRT.

Reference No. 19

Authors: Harsolia A., Hugo G.D., Kestin L.L., Grills I.S., Di Yan.

Title: Dosimetric advantages of four-dimensional adaptive image-guided radiotherapy for lung tumours using online cone-beam computed tomography.

Journal: *Int J Radiation Oncology Biol Phys*, 70 (2): 582-589, 2008.

Study objective: This study compares multiple planning techniques designed to improve accuracy while allowing reduced planning target volume (PTV) margins though image-guided radiotherapy (IGRT) with four-dimensional 4D-Cone-Beam Computed Tomography (CBCT).

Site: Lung

Patients: 8

Study design: Case series

Type of technology: IGRT CBCT Elekta

Set up error (mm): not evaluated

Organ motion (mm)		**Lung**
M	A-P	2.0
	Left-Right	2.0
	CC	10.0
Σ	A-P	2.0
	Left-Right	1.0
	CC	5.0
σ	A-P	
	Left-Right	
	CC	
Σ + σ	A-P	
	Left-Right	
	CC	

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: Adaptive IGRT using CBCT is feasible for the treatment of patients with lung tumours and significantly decreases PTV volume and dose to normal tissues, allowing for the possibility of dose escalation. All analysed 4D planning strategies resulted in improvements over 3D plans, with 4D-online ART appearing optimal.

Reference No. 20

Authors: Purdie T.G., Bissonnette J.P., Franks K., Bezjak A., Payne D., Sie F., Sharpe M.B., Jaffray D.A.

Title: Cone-beam computed tomography for on-line image guidance of lung stereotactic radiotherapy: localization, verification, and intrafraction tumour position.

Journal: *Int J Radiation Oncology Biol Phys*, 68 (1): 243-252, 2007.

Study objective: Cone-beam computed tomography (CBCT) in-room imaging allows accurate inter- and intrafraction target localisation in stereotactic body radiotherapy of lung tumours.

Site: Lung

Patients: 28: T1 T2 stage

Study design: Case series

Type of technology: IGRT CBCT Elekta

			Lung
Set up error (mm)	**M**	A-P	
		Left-Right	
		CC	
		Total	6.8
	Σ	A-P	
		Left-Right	
		CC	
		Total	4.9
	σ	A-P	
		Left-Right	
		CC	
	Σ + σ	A-P	
		Left-Right	
		CC	
Organ motion (mm)	**M**	A-P	
		Left-Right	
		CC	
		Total	5.3
	Σ	A-P	
		Left-Right	
		CC	
		Total	2.2
	σ	A-P	
		Left-Right	
		CC	
	Σ + σ	A-P	
		Left-Right	
		CC	

(to be continued)

Image quality: not evaluated
Additional dose: not evaluated
Acquisition time: not evaluated
Conclusions: In-room volumetric imaging, such as CBCT, is essential for target localization accuracy in lung stereotactic body radiotherapy. Imaging that relies on bony anatomy as a surrogate of the target may provide erroneous results in both localisation and verification.

Reference No. 21

Authors: Chang J., Mageras G.S., Yorke E., De Arruda F., Sillanpaa J., Rosenzweig K.E., Hertanto A., Pham H., Seppi E., Pevsner A., Ling C.C., Amols H.

Title: Observation of interfractional variations in lung tumour position using respiratory gated and ungated megavoltage cone-beam computed tomography.

Journal: *Int J Radiation Oncology Biol Phys*, 67 (5): 1548-1558, 2007.

Study objective: To evaluate the use of megavoltage cone-beam computed tomography (MV CBCT) to measure interfractional variation in lung tumour position.

Site: Lung

Patients: 8

Study design: Case series

Type of technology: IGRT CBCT Varian

Set up error (mm): not evaluated

Organ motion (mm)		**Lung**
M	A-P	-2.0
	Left-Right	2.5
	CC	-1.5
Σ	A-P	2.7
	Left-Right	2.7
	CC	2.7
σ	A-P	
	Left-Right	
	CC	
Σ + σ	A-P	
	Left-Right	
	CC	

Image quality: not evaluated
Additional dose: 12 cGy
Acquisition time: not evaluated
Conclusions: The MV CBCT technique can be used to image lung tumours and may prove valuable for image-guided radiotherapy. Our conclusions must be verified in view of the small patient number.

Reference No. 22

Authors: Bissonnette J.P., Purdie T.G., Higgins J.A., Li W., Bezjak A.

Title: Cone-Beam Computed Tomographic Image Guidance for Lung Cancer Radiation Therapy.

Journal: *Int J Radiat Oncol Biol Phys*, 73 (3): 927-934, 2009.

Study objective: To determine the geometric accuracy of lung cancer radiotherapy using daily volumetric, Cone-Beam CT (CBCT) image guidance and online couch position adjustment.

Site: Lung cancer

Patients: 87

Study design: Case series

Type of technology: IGRT CBCT

Set up error (mm)		**Lung**
M	A-P	
	Left-Right	
	CC	
Σ	A-P	1.2
	Left-Right	1.2
	CC	1.9
σ	A-P	1.4
	Left-Right	1.6
	CC	1.6
Σ + σ	A-P	
	Left-Right	
	CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: Using IGRT, high geometric accuracy is achievable for NSCLC patients, potentially leading to reduced PTV margins, improved outcomes and empowering adaptive radiation therapy for lung cancer.

Reference No. 23

Authors: Johansen J., Bertelsen A., Hansen C.R., Westberg J., Hansen O., Brink C.

Title: Set up errors in patients undergoing image guided radiation treatment. Relationship to body mass index and weight loss.

Journal: *Acta Oncol*, 47 (7): 1454-1458, 2008.

Study objective: The purpose of this study was to quantify the set up errors of patient positioning during IGRT and to correlate set up errors to patient-specific factors such as weight, height, BMI, and weight loss.

Site: Lung, head & neck

Patients: 34 head & neck; 20 lung

Study design: Case series

Type of technology: IGRT CBCT Electa Synergy

Set up error (mm)		**Lung**
M	A-P	
	Left-Right	
	CC	
Σ	A-P	1.1
	Left-Right	1.1
	CC	1.5
σ	A-P	
	Left-Right	
	CC	
Σ + σ	A-P	
	Left-Right	
	CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: This IGRT study did not support the hypothesis that set up errors during radiotherapy are correlated to patient height, weight, BMI, or weight loss.

Reference No. 24

Authors: Guckenberger M., Meyer J., Wilbert J., Richter A., Baier K., Mueller G., Flentje M.

Title: Intra-fractional uncertainties in cone-beam CT based image-guided radiotherapy (IGRT) of pulmonary tumours.

Journal: *Radiotherapy and Oncology*, 83: 57-64, 2007.

Study objective: Intra-fractional variability of tumour position and breathing motion was evaluated in Cone-Beam CT (CBCT) based image-guided radiotherapy (IGRT) of pulmonary tumours).

Site: Lung

Patients: 24

Study design: Case series

Type of technology: IGRT Cone-beam CT Elekta

			Lung
Set up error (mm)	**M**	A-P	-0.5
		Left-Right	-0.1
		CC	-0.1
	Σ	A-P	1.3
		Left-Right	1.7
		CC	1.3
	σ	A-P	
		Left-Right	
		CC	
	Σ + σ	A-P	
		Left-Right	
		CC	
Organ motion (mm)	**M**	A-P	-1.3
		Left-Right	0.3
		CC	0.6
	Σ	A-P	1.9
		Left-Right	1.6
		CC	1.5
	σ	A-P	
		Left-Right	
		CC	
	Σ + σ	A-P	
		Left-Right	
		CC	

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: Intra-fractional tumour position and breathing motion were stable. In IGRT of pulmonary tumours we suggest an ITV-to-PTV margin of 5 mm to compensate intra-fractional changes.

Table 2. Lung cancer - CTCB. Summary table of primary studies

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Efficacy - primary outcomes					
Overall survival	Franks 2007 (27)	Case series T1/T2N0 peripheral lung tumour (n 22)	8 (range 1-25)	45-60 Gy in 3-10 fractions	87%
	Onimaru 2003 (31)	Case series primary lung cancer ≤6 cm diameter for whom surgery was not indicated (n 45)	18 (range 2-44)	48-60 Gy in 8 fractions	Primary: 47.1% (24 months) Metastatic: 48.8%
	Fukumotu 2002 (29)	Case series inoperable stage I NSCLC (n 22)	22-24	48-60 Gy in 8 fractions	45%
	Guckenberger 2009 (30)	Case series 124 patients with 159 pulmonary lesions (metastases: 118, NSCLC: 41, stage 1A:13, stage 1B: 19, T3N0: 9)	14	Dose / fractionation schedules adapted several times	NSCLC: 37% Metastases: 16%
	Videtic 2010 (70)	Case series 26 patients with inoperable Stage I lung cancer	30.9 (range 10.4-51.4)	50 Gy in 5 sequential fractions	52% at 3 yrs
	Grillis 2010 (71)	Controlled case series 124 patients with T1-2N0 NSCLC: 69: wedge resection 58: image-guided lung SBRT	30	wedge resection versus image-guided lung SBRT 48 (T1) or 60 (T2) Gy in 4 to 5 fractions	Wedge resection 87% SBRT 72%

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Disease free survival	Franks 2007 (27)	Case series T1/T2N0 peripheral lung tumour (n 22)	8 (range 1-25)	45-60 Gy in 3-10 fractions	97%
	Onimaru 2003 (31)	Case series primary lung cancer ≤6 cm diameter for whom surgery was not indicated (n 45)	18 (range 2-44)	48-60 Gy in 8 fractions	Primary 60.2% (24 months) Metastatic: 48.8%
	Fukumotu 2002 (29)	Case series inoperable stage I NSCLC (n 22)	22-24	48-60 Gy in 8 fractions	73%
Efficacy - secondary outcomes					
Progression free survival	Fukumotu 2002 (29)	Case series inoperable stage I NSCLC (n 22)	22-24	48-60 Gy in 8 fractions	67%
	Guckenberger 2009 (30)	Case series 124 patients with 159 pulmonary lesions (metastases: 118, NSCLC: 41, stage 1A: 13, stage 1B: 19, T3N0: 9)	14	Dose / fractionation schedules adapted several times	45% at 24 months 34% at 36 months
Symptoms control					
Recurrence	Fukumotu 2002 (29)	Case series inoperable stage I NSCLC (n 22)	22-24	48-60 Gy in 8 fractions	Local: 4.5% Other sites recurrence: 18.2%
	Chang 2008 (28)	Case series centrally and superiorly located stage 1 (T1/T2N0M0) (n 13) or isolated lung parenchyma recurrent NSCLC (n 14)	17 (range 6-40)	40-50 Gy in 4 fractions	Local: 42.8% only in patients treated with 40 Gy Regional: 7.7%

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
	Grillis 2010 (71)	Controlled case series 124 patients with T1-2N0 NSCLC: 69: wedge resection 58: image-guided lung SBRT	30	wedge resection versus image-guided lung SBRT 48 (T1) or 60 (T2) Gy in 4 to 5 fractions	No statistically significant differences
Efficacy - surrogate outcomes					
Tumour control	Onimaru 2003 (31)	Case series primary lung cancer ≤6 cm diameter for whom surgery was not indicated (n 45)	18 (range 2-44)	48-60 Gy in 8 fractions	80.3% (36 months)
	Fukumotu 2002 (29)	Case series inoperable stage I NSCLC (n 22)	22-24	48-60 Gy in 8 fractions	Complete response: 29% Partial response: 65%
	Chang 2008 (28)	Case series centrally and superiorly located stage 1 (T1/T2N0M0) (n 13) or isolated lung parenchyma recurrent NSCLC (n 14)	17 (range 6-40)	40-50 Gy in 4 fractions	100% for patients treated using 50Gy
	Guckenberger 2009 (30)	Case series 124 patients with 159 pulmonary lesions (metastases: 118, NSCLC: 41, stage 1A: 13, stage 1B: 19, T3N0: 9)	14	Dose / fractionation schedules adapted several times	83% (36 months) Dose >100 Gy: 89% Dose <100 Gy: 62%
Loco-regional control	Onimaru 2003 (31)	Case series primary lung cancer ≤6 cm diameter for whom surgery was not indicated (n 45)	18 (range 2-44)	48-60 Gy in 8 fractions	85.2% (24 months)

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
	Videtic 2010 (70)	Case series 26 patients with inoperable Stage I lung cancer	30.9 (range 10.4-51.4)	50 Gy in 5 sequential fractions	94.4% at 3 yrs
Safety					
Acute toxicity	Franks 2007 (27)	Case series T1/T2N0 peripheral lung tumour (n 22)	8 (range 1-25)	45-60 Gy in 3-10 fractions	G0: 45% G1: 55.9%
	Onimaru 2003 (31)	Case series primary lung cancer ≤6 cm diameter for whom surgery was not indicated (n 45)	18 (range 2-44)	48-60 Gy in 8 fractions	1 grade 5 esophagitis (patient died)
	Fukumotu 2002 (29)	Case series inoperable stage I NSCLC (n 22)	22-24	48-60 Gy in 8 fractions	0
	Guckenberger 2009 (30)	Case series 124 patients with 159 pulmonary lesions (metastases: 118, NSCLC: 41, stage 1A: 13, stage 1B: 19, T3N0: 9)	14	Dose / fractionation schedules adapted several times	Grade 2 Penumonitis: 12% Pneumothorax: 1.3% Pleural effusion: 1.3% Dyspnoea: 1.9% Pneumothorax: 1.3% Grade 3 Pneumonitis: 0.6% Esophageal ulceration: 0.6%

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Late toxicity	Franks 2007 (27)	Case series T1/T2N0 peripheral lung tumour (n 22)	8 range 1-25	45-60 Gy in 3-10 fractions	G1: 13.6% G2: 13.6%
	Onimaru 2003 (31)	Case series primary lung cancer ≤6 cm diameter for whom surgery was not indicated (n 45)	18 (range 2-44)	48-60 Gy in 8 fractions	G2: 1
	Fukumotu 2002 (29)	Case series inoperable stage I NSCLC (n 22)	22-24	48-60 Gy in 8 fractions	0
	Chang 2008 (28)	Case series centrally and superiorly located stage 1 (T1/T2N0M0) (n 13) or isolated lung parenchyma recurrent NSCLC (n 14)	17 (range 6-40)	40-50Gy in 4 fractions	Grade 2 pneumonitis: 14.8% Grade 2-3 dermatitis and chest pain: 11.1% Brachial plexus neuropathy: 3.7%
Any toxicity					

Table 3. Lung cancer - Tomotherapy. Summary table of primary studies

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Efficacy - primary outcomes					
Overall survival	Bral 2010 (66)	Case series 40 patients with Stage III, inoperable, locally advanced NSCLC, not eligible for concurrent chemoradiation	24 months	Moderately hypofractionated tomotherapy 70.5 Gy in 30 fractions	65% at 12 months 27% at 24 months (in 30% of patients who had survived)
	Kim 2009 (68)	Retrospective case series 31 patients with pulmonary metastases	24 months	The median doses prescribed were 50 Gy and 40 Gy delivered in 10 fractions over 2 weeks to the 95% isodose volume of the GTV and planning target volume, respectively	60.5% at 12 months
	Song 2010 (69)	Retrospective case series 37 patients with NSCLC	18 (range 6-27 months)	Total dose of 60-70.4 Gy at 2.0-2.4 Gy per fraction to the gross tumour volume and 50-64 Gy at 1.8-2.0 Gy per fraction to the planning target volume	56% at 24 months
Disease free survival/relapse free survival					

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Efficacy - secondary outcomes					
Progression free survival	Bral 2010 (66)	Case series 40 patients with Stage III, inoperable, locally advanced NSCLC, not eligible for concurrent chemoradiation	24 months	Moderately hypofractionated tomotherapy 70.5 Gy in 30 fractions	66% of surviving at 12 months 50% of surviving patients at 24 months
	Kim 2009 (68)	Retrospective case series 31 patients with pulmonary metastases	24 months	The median doses prescribed were 50 Gy and 40 Gy delivered in 10 fractions over 2 weeks to the 95% isodose volume of the GTVand planning target volume, respectively	39.6% at 12 months 27.7% at 24 months
Symptoms control					
Recurrence					

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Efficacy - surrogate outcomes					
Tumour control	Siker 2006 (25)	Case series Any stage NSCLC (32 patients; 7 patients with mediastinal disease or extensive atelectasis had to be excluded because of the considerable difficulty encountered in delineating tumour borders on MVCT)	End of treatment (2-5 weeks)	- Definitive radiotherapy with stereotactic radioablation (ESRA): total dose of 60 Gy in 5 fractions over 2 weeks: 4 patients - Definitive radiotherapy on a dose per fraction escalation protocol; total dose of 57-80 Gy I 25 fraction over 5 weeks: 17 patients - Palliative treatment: total dose of 22-30 Gy in 8-10 fractions over 2 weeks: 4 patients	Complete response: 0 Partial response: 12% Marginal response: 20% Stable disease: 68% Overall response rate (complete+partial): 12% Excluding the 4 patients treated palliatively: 18% None of the 4 patients treated palliatively nor the 5 patients treated ablatively (ESRA) showed meaningful tumour volume change
	Kupelian 2005 (26)	NSCLC (n 10)	2	Patients treated with different doses according to different institutional preferences and protocols	Average decrease in volume. 1.2% per day (range 0.3%-2.3%)

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Loco-regional control	Song 2010 (69)	Retrospective case series 37 patients with NSCLC	18 (range 6-27)	total dose of 60-70.4 Gy at 2.0-2.4 Gy per fraction to the gross tumour volume and 50-64 Gy at 1.8-2.0 Gy per fraction to the planning target volume	63% at 24 months
Safety					
Acute toxicity	Bral 2010 (66)	Case series 40 patients with Stage III, inoperable, locally advanced NSCLC, not eligible for concurrent chemoradiation	24 months	Moderately hypofractionated tomotherapy 70.5 Gy in 30 fractions	Grade 3 Lung toxicity 10%
	Park 2009 (67)	Case series 25 patients with peripheral pulmonary malignancies	3 months	Tomotherapy GTV median dose 50 Gy,(3 fractions) PTV median dose 40 Gy (20 fractions)	Radiation pneumonitis: 52%
	Kim 2009 (68)	Retrospective case series 31 patients with pulmonary metastases	24 months	The median doses prescribed were 50 Gy and 40 Gy delivered in 10 fractions over 2 weeks to the 95% isodose volume of the GTVand planning target volume, respectively	Grade 1: 41.9% Grade 2: 16%

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
	Song 2010 (69)	Retrospective case series 37 patients with NSCLC	18 (range 6-27)	total dose of 60-70.4 Gy at 2.0- 2.4 Gy per fraction to the gross tumour volume and 50-64 Gy at 1.8-2.0 Gy per fraction to the planning target volume	Grade 3 esophagitis: 0 Grade 4 esophagitis: 0 Grade 5 esophagitis: 0 Treatment related pneumonitis Grade 0: 8% Grade 1: 32% Grade 2: 51% Grade 3: 19% There were 4 treatment-related deaths
Late toxicity	Bral 2010 (66)	Case series 40 patients with Stage III, inoperable, locally advanced NSCLC, not eligible for concurrent chemoradiation	24 months	Moderately hypofractionated tomotherapy 70.5 Gy in 30 fractions	Grade 3 Lung toxicity 16%
Any toxicity					

Table 4. Lung cancer. Tables of evidence from primary studies - Clinical outcomes

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Siker M.L., Tomé W.A., Metha M.P. Tumour volume changes on serial imaging with megavoltage CT for non small cell lung cancer during intensity modulated radiotherapy: how reliable, consistent and meaningful is the effect? *Int J Radiation Oncology Biol Phys*, 66: 135-141, 2006	25	To assess volume changes during Tomotherapy. Case series	TOMOTHERAPY Definitive radiotherapy with stereotactic radioablation (ESRA) with a total dose of 60 Gy in 5 fractions over 2 weeks: 4 patients. Definitive radiotherapy on a dose per fraction escalation protocol to a total dose of 57-80 Gy in 25 fractions over 5 weeks: 17 patients. Palliative treatment with a total dose of 22-30 Gy in 8-10 fractions over 2 weeks: 4 patients. Patients underwent daily MVCT before each fraction.	32 consecutive patients with any stage NSCLC	Completion of treatment (2-5 weeks)	Local control	7 (22%) patients with mediastinal disease or extensive atelectasis had to be excluded because of the considerable difficulty encountered in delineating tumour borders on MVCT *Local control:* Complete response: 0 Partial response: 12% Marginal response: 20% Stable disease: 68% Overall response rate (complete+partial):12% Excluding the 4 patients treated palliatively: 18% None of the 4 patients treated palliatively nor the 5 patients treated ablatively (ESRA) showed meaningful tumour volume change	Authors concluded that tumour regression may be measured during treatment by MVCT. A substantial reduction in tumour volume, consonant with traditional oncologic definitions of response, occurred only in a minority of patients. Patients treated ablatively or palliatively did not show significant volume decrease in the short interval of two weeks. Correlating volumetric changes on imaging to clinical outcomes and additional investigation into modifying treatment plans in response to this regression are needed before any recommendation can be made.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Kupelian, P.A., Ramsey C., Meeks S.L. Serial megavoltage ct imaging during external beam radiotherapy for non-small-cell lung cancer: observations on tumour regression during treatment. *Int J Radiation Oncology Biol Phys*, 63: 1024-1028, 2005	26	To assess the rate of regression of NSCLC during the course of external bean radiotherapy by analyzing serial megavoltage CT images. Case series	Tomotherapy Patients were treated to different doses according to different institutional preferences and protocols. The treatment intent was definitive in all cases, with all patients being treated at 2 Gy per fraction. The total doses and treatment fields were implemented at the discretion of the physician.	10 patients with NSCLC, not specified if consecutively recruited.	2 months	Tumour regression as documented by the serial MVCT scans	Average decrease in volume. 1.2% per day (range 0.3%-2.3%)	Authors concluded that the current study demonstrated that tumour regression can be documented for patients with non-small-cell lung cancer treated with Helical Tomotherapy. Clinical correlations between the observations made during the course of treatment and ultimate outcomes, e.g. local control, should be investigated.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Franks K.N., Bezjak A., Purdie T.G. et al. Early results of image guided radiation therapy in lung stereotactic body radiotherapy (SRBT). Conference proceeding. 2007	27	to assess safety and efficacy of stereotactic body radiotherapy (SBRT). Case series	IGRT stereotactic body radiotherapy (SBRT) 4D-CT was used to assess tumour motion. GTV was contoured on the maximum exhale and maximum inhale datasets fused forming an internal target volume. Dose schedules depended on OAR tolerance: 45-60 Gy in 3-10 fractions.	22 consecutive patients with T1/T2N0 peripheral lung tumour	8 months (range 1-25 months)	Acute toxicity Late toxicity Overall survival Disease specific survival	*Acute toxicity*: G0: 45% G1: 50% (skin, cough, esophagitis, fatigue) G2: 5% (fatigue, radiation pneumonitis) *Late toxicity*: G1: 13.6% (pain, skin) G2: 13.6% (pain, bone) No local failure *Disease specific survival*: 97% *Overall survival*: 87%	Authors concluded that these early results indicate high rates of local control with acceptable acute toxicity. However longer follow up is required.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Chang J.Y., Balter P.A., Dong L. et al. Stereotactic body radiation therapy in centrally and superiorly located stage 1 or isolated recurrent non small cell lung cancer. *Int J Radiation Oncology*, 72 (4): 967-971, 2008	28	To assess safety and efficacy of image guided stereotactic body radiotherapy (SBRT). Case series	IGRT stereotactic body radiotherapy (SBRT). Multiple 4DCT datasets at different breath phases used to assess gross tumour volume (GTV) and then modifying these contours by visual verification of the coverage in each phase. Clinical target volume was defined as internal GTV +8 mm margins and 3 mm set up uncertainty margin was added to determine the planning target volume. The first 7 patients received 40Gy PTV in the 75-90% isodose lines. Subsequent patients received 50 Gy. 4 fractions	27 consecutive patients with centrally and superiorly located stage 1 (T1/T2N0M0) (n 13) or isolated lung parenchyma recurrent NSCLC (n 14)	17 months (range 6-40 months)	Local control Chronic toxicity Local recurrence	*Local control*: 100% for patients treated using 50 Gy. *Local recurrence*: 42.8% in 3 out of the 7 patients treated using 40 Gy *Regional recurrence*: 7.7% *Chronic toxicity*: Grade 2 pneumonitis: 14.8% Grade 2-3 dermatitis and chest pain: 11.1% Brachial plexus neuropathy: 3.7%	Authors concluded that their data suggest that 50Gy in four fraction prescribed to the PTV, with the GTV receiving approximately 54-60 Gy, was needed to achieve sufficient local control for centrally and superiorly located lesions in T1 T2 N0M0 disease. 35-40 Gy in four fractions would likely to be a threshold for chronic toxicity with regard to the skin and neuropathy.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Fukumotu S., Shirato H., Shimzu S. et al. Small volume IGRT using hypofractionated, coplanar and non coplanar multiple fields for patients with inoperable stage I non-small cell lung carcinomas. *Cancer*, 95: 1546-1553, 2002	29	To assess safety and efficacy of small volume (IGRT) using hypofractionated, coplanar and non coplanar multiple fields for patients with inoperable stage I NSCLC. Case series	IGRT CT were taken during three respiratory phase and analyzed to define PTV: CT scans data were transferred to 3D radiotherapy planning system. The safety margins for PTV was a combination of the safety margins for daily set up error and that for internal organ motion. Dose: 60 Gy in 8 fractions for 11 patients, 48 Gy for 11 patients.	22 consecutive patients with inoperable stage I NSCLC. Tumour mean size: 26.6 mm	24 (range 2-44 months)	Local control Acute toxicity Overall survival Cancer specific Survival Recurrence free survival Recurrence	*Local control*: complete response: 29% partial response: 65% *Acute toxicity*: 0 *Late toxicity*: 0 *Overall survival*: 45% *Cancer specific survival*: 3% *Recurrence free survival*: 67% *Local recurrence*: 4.5% *Other sites recurrence*: 18.2%	Authors concluded that small-volume IGRT using 60 Gy in 8 fractions is highly effective for curative treatment of stage I NSCLC with low morbidity. This technique has significant role in treating NSCLC and can be an effective alternative to surgery, especially for elderly patients. A prospective randomised trial is necessary to compare IGRT with conventional radiotherapy and/or surgery. In addition it should be determined if patients could benefit from additional prophylactic lymph node irradiation and/or additional radiotherapy for treating potential microscopic metastases.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Guckenberger M., Wulf J., Mueller G. et al. Dose response relationship for image guided stereotactic body radiotherapy of pulmonary tumours: relevance of 4D dose calculation. *Int J Radiation Oncology*, 74 (1): 47-54, 2009	30	To assess safety and efficacy of image guided stereotactic body radiotherapy (SBRT). Retrospective case series	IGRT stereotactic body radiotherapy (SBRT). Treatment planning with multi-sliced CT scanner The GTV was delineated in the CT pulmonary window; the internal target volume is the sum of the CTV position in inhalation and exhalation. The PTV was generated with a 3 dimensional margins of 5 mm. Daily image guidance and online correction of set up errors was used. Dose fractionation schedules were adapted several times during the study because of increasing experience and published results.	124 Consecutive patients with 159 pulmonary lesions (metastases: 118, NSCLC: 41, stage 1A: 13, stage 1B: 19, T3N0: 9)	14 months	Local control Acute toxicity Regional and systemic progression free Overall survival Cancer specific survival	Local control: actuarial control rate: 83% at 36 months. Treatment doses influenced local control significantly: Doses >100 Gy: actuarial control rate at 36 months: 89% Doses <100Gy: actuarial control rate at 36 months: 62% Actuarial rate of regional and systemic *progression free survival*: 45% at 24 months; 34% at 36 months. Actuarial *overall survival* at 36 months: NSCLC: 37% Metastases: 16% *Acute toxicity*: Grade 2: Pneumonitis: 12% Pneumothorax: 1.3% Pleural effusion: 1.3% Dyspnea: 1.9% Pneumothorax: 1.3% Grade 3 Pneumonitis: 0.6% Esophageal ulceration: 0.6%	Authors concluded that their data and data from the published literature suggest that the dose of > 100 Gy to the CTV are necessary to control early stage NSCLC and pulmonary metastases with image guided SBRT.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Onimaru R., Shirato H., Shimizu S. et al. Tolerance of organs at risk in small-volume, hypofractionated, image-guided radiotherapy for primary and metastatic lung cancers. *Int J Radiation Oncology Biol Phys*, 56: 126-135, 2003	31	To assess safety and efficacy of image guided radiotherapy (IGRT) for patients with primary and metastatic lung cancer. Case series	IGRT PTV margins for ITV were 5 mm in the lateral and anteroposterior direction and 10 mm in the craniocaudal direction with the three-phase CT, and an additional 5 mm for patients for whom a three-phase CT was not planned. A 3-dimensional radiation treatment planning (3D-RTP) system was used for treatment planning. Their set up was corrected by comparing two linacographies that were orthogonal at the isocenter with corresponding digitally reconstructed images.	45 Patients with measurable primary lung cancer 6 cm or less in diameter for whom surgery was not indicated. Not specified if consecutively recruited. Patients with small-cell lung cancers or hilar or mediastinum lymph nodes on CT scan were not eligible. Tumour size ranged from 0.6 to 6.0 cm, with a median of 2.6 cm.	18 months (range 2-44)	Local control Acute toxicity Overall survival Cancer specific survival	*Local control*: 80.4 % at 3 years *Regional control*: 85.2% at 2 years *Acute toxicity*: 1 grade 5 esophagitis (patient died) *Late toxicity*: 1 grade 2 chest pain *Overall survival*: Primary tumour: 47.1% at 2 years Metastatic: 48.8% *Cancer specific survival*: Primary tumour: 60.2% at 2 years Metastatic: 48.8%	Authors concluded that small-volume IGRT using 60 Gy in 8 fractions is highly effective for local control of lung tumours, but MTD has not been determined in this study. The prospective study of small-volume, hypofractionated radiotherapy for lung tumours requires dose constraints not only for the spinal cord, large bronchus, esophagus, and brachial plexus, but also for internal chest wall, and probably for other organs with serial structures. Consideration of uncertainty in the contouring of normal structures is critically important in the set up of patients and internal organ in high-dose hypofractionated IGRT. *(to be continued)*

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
			Megavoltage X-rays using noncoplanar multiple static ports or arcs were used to cover the parenchymal tumour mass. Prophylactic nodal irradiation was not performed. The radiation dose was started at 60 Gy in 8 fractions over 2 weeks (60 Gy/8 Fr/2 weeks) for peripheral lesions 3.0 cm or less, and at 48 Gy/8 Fr/2 weeks at the isocenter for central lesions or tumours more than 3.0 cm at their greatest dimension.					

Update January 2009 - June 2010

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Bral S., Duchateau M., Versmessen J. et al. Toxicity and outcome results of a class solution with moderately hypofractionated radiotherapy in inoperable stage III non-small cell lung cancer using helical tomotherapy. *Int J Radiation Oncology Biol Phys*, 77 (5): 1352-1359, 2010	66	To prospectively assess the feasibility, toxicity, and local control of a class solution protocol of moderately hypofractionated tomotherapy in Stage III, inoperable, locally advanced NSCLC patients. Case series	Tomotherapy Moderately hypofractionated tomotherapy 70.5 Gy in 30 fractions	40 consecutive patients with Stage III, inoperable, locally advanced NSCLC, not eligible for concurrent chemoradiation	2 years	Acute lung toxicity Late lung toxicity Survival Progression free survival Overall survival	9 patients died in the first 90 days from start of radiotherapy, two of acute pulmonary toxicity Acute Grade 3 lung toxicity was seen in 10% of patients. Late Grade 3 lung toxicity in 16% of patients Median surviving the 14 surviving patients was 17 months Progression free survival (in 12 surviving patients): 1 year: 66% of surviving patients 2 years: 50% of surviving patients Overall survival: 65% at 12 months 27% at 24 months	Authors concluded that the current class solution using moderately hypofractionated helical tomotherapy in patients with locally advanced NSCLC is feasible. Toxicity was acceptable and in line with other reports on intensity-modulated radiotherapy. The local progression-free survival was encouraging considering the unselected population.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Park H.J., Kim K.J., Park H.P. et al. Early CT Findings of Tomotherapy-Induced Radiation Pneumonitis after Treatment of Lung Malignancy. *AJR*, 193: W209-W213, 2009	67	To evaluate the early CT findings of tomotherapy-induced radiation pneumonitis. Case series	Tomotherapy gross tumour volume (GTV) and planning target volume (PTV = GTV + 0.5-1.5 cm) defined with the CT scan. The median doses (± SD) used were 50.0 ± 5.99 Gy and 40.0 ± 7.03 Gy with 3-20 fractions, respectively. The median treatment duration was 14 days (range, 3-28 days).	25 patients with peripheral pulmonary malignancies	3 months	Acute toxicity	*Acute toxicity*: radiation pneumonitis: 52%	Authors concluded that Radiation pneumonitis commonly developed with minimal clinical findings within 3 months after tomotherapy. The CT findings were non-specific: focal, irregular-shaped ground-glass opacities with minimal fibrosis. However, the location of the radiation pneumonitis tended not to correspond to the planned target volume and had a centrifugal distribution. In addition, the immediate area around the target tended to be spared.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Kim J.Y., Kay C.H., Kim Y.S. et al. Helical tomotherapy for simultaneous multitarget radiotherapy for pulmonary metastasis. *Int J Radiation Oncology*, 75 (3): 703-710, 2009	68	To retrospectively evaluate our experience with tomotherapy for simultaneous multitarget radiotherapy in patients with pulmonary metastasis. Retrospective case series.	TOMOTHERAPY The median doses prescribed were 50 Gy and 40 Gy delivered in 10 fractions over 2 weeks to the 95% isodose volume of the GTV and planning target volume, respectively.	31 patients with pulmonary metastases enrolled retrospectively	24 months	Overall survival at 12 months Progression free survival at 1 and 2 years Median survival time Radiation related acute toxicity	*Overall survival*: 60.5% at 12 months *Median survival time*: 16 months *Progression free survival*: 39.6% at 12 months 27.7% at 24 months *Radiation related toxicity*: Grade 1: 41.9% Grade 2: 16% There were no treatment-related deaths.	Authors concluded that Tomotherapy could be offered to patients as a safe and effective treatment in select patients with lung metastases. However, large-scale, prospective clinical trials should be done to confirm our results.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Song C.H., Pyo H., Moon S.H. et al. Treatment-related pneumonitis and acute esophagitis in NSCLC patients treated with chemotherapy and helical tomotherapy. *Int J Radiation Oncology Biol Phys*, 78 (3): 651-658, 2010	69	To assess clinical outcomes and complications in patients with non-small-cell lung cancer (NSCLC) treated with helical tomotherapy (HT) with or without chemotherapy. Retrospective case series	TOMOTHERAPY Radiotherapy was delivered to a total dose of 60-70.4 Gy at 2.0- 2.4 Gy per fraction to the gross tumour volume and 50-64 Gy at 1.8-2.0 Gy per fraction to the planning target volume.	37 patients with NSCLC (28 at stage III)	18 months (range 6-27 months)	Overall survival at 2 yrs Local control at 2 yrs Acute toxicity	*Overall survival*: 56% at 24 months *Local control*: 63% at 24 months *Acute toxicity*: Grade 3 esophagitis: 0 Grade 4 esophagitis: 0 Grade 5 esophagitis: 0 Treatment related pneumonitis Grade 0: 8% Grade 1: 32% Grade 2: 51% Grade 3: 19% There were 4 treatment-related deaths	Authors concluded that HT with chemotherapy has shown promising clinical outcomes, esophagitis, and TRPs. However, HT has produced a somewhat high rate of fatal pulmonary complications. The data suggest that CLV5 should be considered and kept as low as possible (<60%) in addition to the conventional dosimetric factors.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Videtic C.G., Stephans K., Reddy C. et al. Intensity-modulated radiotherapy-based stereotactic body radiotherapy for medically inoperable early-stage lung cancer: excellent local control. *Int J Radiation Oncology Biol Phys*, 77 (2): 334-349, 2010	70	To validate the use of stereotactic body radiotherapy (SBRT) using intensity-modulated radiotherapy (IMRT) beams for medically inoperable Stage I lung cancer. Case series	IGRT Delivery of 50 Gy in five sequential fractions typically used seven nonopposing, noncoplanar beams. Image-guided target verification was provided by BrainLAB-ExacTrac.	26 patients with inoperable Stage I lung cancer	30.9 months (range 10.4-51.4)	Overall survival Local control	Overall survival 52% at 3 yrs Local control 94.4% at 3 yrs	Authors conclude that Use of IMRT-based delivery of SBRT using restriction of tumour motion in medically inoperable lung cancer demonstrates excellent local control and favourable survival.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Grills I.S., Mangona V.S., Welsh R. et al. Outcomes After Stereotactic Lung Radiotherapy or Wedge Resection for Stage I Non-Small-Cell Lung Cancer. *JCO*, 28 (8): 928-935, 2010	71	To compare outcomes between lung stereotactic radiotherapy (SBRT) and wedge resection for stage I non-small-cell lung cancer (NSCLC). Controlled case series	Wedge resection versus image-guided lung SBRT 48 (T1) or 60 (T2) Gy in four to five fractions	124 patients with T1-2N0 NSCLC: 69: wedge resection 55: image-guided lung SBRT	30 months	Overall survival Regional recurrence Local regional recurrence Distant metastasis	Overall survival Wedge resection 87% SBRT 72% No statistically significant differences in regional recurrence, local regional recurrence, distant metastasis or freedom from any failure.	Both lung SBRT and wedge resection are reasonable treatment options for stage I NSCLC patients ineligible for anatomic lobectomy. SBRT reduced LR, RR, and LRR. In this nonrandomized population of patients selected for surgery versus SBRT (medically inoperable) at physician discretion, OS was higher in surgical patients. SBRT and surgery, however, had identical CSS.

Table 5. Brain cancer. Primary studies on technical performance

Synthesis of primary studies - set up error and organ motion in brain cancer

Ref. No.	Studies	Number of patients	Study design	Type of technology	Set up error (mm)			Organ motion (mm)		
					V_M	V_Σ	V_σ	V_M	V_Σ	V_σ
32	Lawson 2008	25	Case series	IGRT CBCT	1.75	3.47	4.39			
33	Drabik 2007	4	Case series	Tomotherapy	0.28	1.62				
34	Masi 2009	57	Case series	IGRT CBCT	0.54	3.22				
35	Li 2007	19	Case series	Tomotherapy	0.68	1.55				
	Overall range				0.28-1.75	1.62-3.47	4.39			
	Overall mean				0.81	2.47	4.39			

Reference No. 32

Authors: Lawson J.D., Fox T., Elder E., Nowlan A., Davis L., Keller J., Crocker I.

Title: Early clinical experience with kilovoltage image-guided radiation therapy for interfraction motion management.

Journal: *Med Dosim*, 33 (4): 268-274, 2008.

Study objective: Interest in image-guided radiation therapy (IGRT) reflects the desire to minimise interfraction positioning variability. Using a kilovoltage (kV) imaging unit mounted to a traditional LINAC allows daily matching of kV images to planning digitally reconstructed radiographs (DRRs).

Site: Prostate, head & neck, CNS (Central Nervous System)

Patients: 35 prostate, 21 head & neck, 25 CNS

Study design: Case series

Type of technology: IGCT KV CT Varian

Set up error (mm)			**CNS**
	M	A-P	0.4
		Left-Right	1.1
		CC	1.3
	Σ	A-P	1.2
		Left-Right	2.4
		CC	2.2
	σ	A-P	1.8
		Left-Right	2.4
		CC	3.2
	Σ + σ	A-P	
		Left-Right	
		CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: The use of OBI (on-board imaging) effectively corrects set up variability. These shifts are typically small and random. The use of OBI likely can replace weekly port films for isocentre verification; however, OBI does not provide field shape verification.

Reference No. 33

Authors: Drabik D.M., MacKenzie M.A., Fallone G.B.

Title: Quantifying appropriate PTV setup margins: analysis of patient setup fidelity and intrafraction motion using post-treatment megavoltage computed tomography scans.

Journal: *Int J Radiat Oncol Biol Phys*, 68 (4): 1222-1228, 2007.

Study objective: To present a technique that can be implemented in-house to evaluate the efficacy of immobilisation and image-guided set up of patients with different treatment sites on Helical Tomotherapy.

Site: Glioblastoma (Brain), head & neck, prostate cancer

Patients: 12 (4 prostate, 4 brain glioblastoma, 4 head & neck)

Study design: Case series

Type of technology: MV CB Tomo

Set up error (mm)			**Brain**
	M	A-P	0.2
		Left-Right	0
		CC	0.2
	Σ	A-P	0.6
		Left-Right	1.2
		CC	0.9
	σ	A-P	
		Left-Right	
		CC	
	Σ + σ	A-P	
		Left-Right	
		CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: This method could be applied using individual patient post-image scanning and combined with adaptive planning to reduce or increase the margins as appropriate.

Reference No. 34

Authors: Masi L., Casamassima F., Polli C., Menichelli C., Bonucci I., Cavedon C.

Title: Cone beam CT image guidance for intracranial stereotactic treatments: comparison with a frame guided set up.

Journal: *Int J Radiation Oncology Biol Phys*, 71 (3): 926-933, 2008.

Study objective: An analysis is performed of the set up errors measured by a kV Cone Beam Computed Tomography (CBCT) for intracranial stereotactic radiotherapy (SRT) patients immobilised by a thermoplastic mask and a bite-block and positioned using stereotactic coordinates. We evaluated the overall positioning precision and accuracy of the immobilising and localising systems. The potential of image-guided radiotherapy to replace stereotactic methods is discussed.

Site: Brain

Patients: 57

Study design: Case series

Type of technology: IGRT Cone-Beam CT

Set up error (mm)			**Brain**
	M	A-P	0
		Left-Right	0.5
		CC	0.2
	Σ	A-P	1.7
		Left-Right	1.3
		CC	2.4
	σ	A-P	
		Left-Right	
		CC	
	Σ + σ	A-P	
		Left-Right	
		CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: Considering the detected set up errors, daily image guidance is essential for the efficacy of SRT treatments when mask immobilisation is used, and even when a bite-block is used in conjunction. The frame set up is still used as a starting point for the opportunity of rotational corrections. Residual margins after on-line corrections must be evaluated.

Reference No. 35

Authors: Li X.A., Qi X.S., Pitterle M., Kalakota K., Mueller K., Erickson B.A., Wang D., Schultz C.J., Firat S.Y., Wilson J.F.

Title: Interfractional variations in patient setup and anatomic change assessed by daily computed tomography.

Journal: *Int J Radiation Oncology Biol Phys*, 68 (2): 581-591, 2007.

Study objective: To analyse the interfractional variations in patient set up and anatomic changes at seven anatomic sites observed in image-guided radiotherapy.

Site: head & neck; brain

Patients: 37 head & neck; 19 brain

Study design: Case series

Type of technology: MV CB Tomo

Set up error (mm)			**Brain**
	M	A-P	0.62
		Left-Right	0.28
		CC	-0.056
	Σ	A-P	0.75
		Left-Right	0.99
		CC	0.92
	σ	A-P	
		Left-Right	
		CC	
	Σ + σ	A-P	
		Left-Right	
		CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: The interfractional variations in patient set up and in shapes, sizes, and positions of both targets and normal structures are site specific and may be used to determine the site-specific margins. The data presented in this work dealing with seven anatomic sites may be useful in developing adaptive radiotherapy.

Table 6. Brain cancer - Tomotherapy. Summary table of primary studies

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Efficacy - primary outcomes					
Overall survival	Do 2009 (37)	Case series Brain metastases (n 30)	12	Surgery followed by SRS 15-18Gy SRT 24-27 Gy 4-6 fractions	51%
	Tomita 2008 (36)	Case series Brain metastases (n 23)	Not reported	Patients with 1 metastasis treated focally (focal plans); 35Gy, 5 fractions. Patients with 2-4 metastasis treated in combination with WBRT (simultaneous plans); 50 Gy, 10 fractions	Median survival: 4.6 months
Disease free survival/relapse free survival	Do 2009 (37)	Case series Brain metastases (n 30)	12	Surgery followed by SRS 15-18Gy SRT 24-27Gy 4-6 fractions	1 year local relapse free survival: 82% 1 year new metastasis free survival: 31% 1 year overall CNS relapse free survival: 22%

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Efficacy - secondary outcomes					
Progression free survival					
Recurrence	Do 2009 (37)	Case series Brain metastases (n 30)	12	Surgery followed by SRS 15-18Gy SRT 24-27Gy 4-6 fractions	70%
Efficacy - surrogate outcomes					
Tumour control	Tomita 2008 (36)	Case series Brain metastases (n 23)	Not reported	Patients with 1 metastasis treated focally (focal plans); 35 Gy, 5 fractions Patients with 2-4 metastasis treated in combination with WBRT (simultaneous plans); 50 Gy, 10 fractions	Complete response: 33% Partial response: 59% Stable disease: 7% Progressive disease: 0%
Loco-regional control					

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Symptoms control	Do 2009 (37)	Case series Brain metastases (n 30)	12	Surgery followed by SRS 15-18 Gy SRT 24-27Gy 4-6 fractions	77%
Safety					
Acute toxicity	Tomita 2008 (36)	Case series Brain metastases (n 23)	Not reported	Patients with 1 metastasis treated focally (focal plans); 35 Gy, 5 fractions Patients with 2-4 metastasis treated in combination with WBRT (simultaneous plans); 50 Gy, 10 fractions	1 grade 1 nausea and 1 severe headache and nausea
Late toxicity					
Any toxicity	Do 2009 (37)	Case series Brain metastases (n 30)	12	Surgery followed by SRS 15-18 Gy SRT 24-27 Gy 4-6 fractions	Grade 2: 26%

Table 7. Brain neoplasms. Tables of evidence from primary studies - Clinical outcomes

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Tomita N., Kodaira T., Tachibana H. et al. Helical Tomotherapy for brain metastases: dosimetric evaluation of treatment plans and early clinical results. *Technology in cancer research and treatment*, 7: 417-424, 2008	33	To evaluate feasibility of Helical Tomotherapy in patients with brain metastasis. Case series. All patients treated between June 2006 and September 2007 were consecutively enrolled.	TOMOTHERAPY Patients with 1 metastasis were treated focally (focal plans); patients with 2-4 metastasis were treated in combination with WBRT (simultaneous plans), which is considered to have prophylactic effect against new metastasis. 16 patients were treated with focal plans, 7 with simultaneous plans. Clinical target volume (CTV) included the gross tumour volume (GTV) with additional margins of 2mm to create the planning treatment volume (PTV). PTV was delivered with 50 Gy in 10 fractions in simultaneous plans and with 35 Gy in 5 fractions in focal plans.	23 patients with1 to 4 brain metastasis. All patients had active extracranial disease	Not reported	Tumour control Overall survival Toxicity	Follow up imaging only on 57% of patients Tumour control: Complete response: 33% Partial response: 59% Stable disease: 7% Progressive disease: 0% No difference between simultaneous planes and focal plans was seen Overall median survival time: 4.6 months. Toxicity: 2 acute complications: 1 grade 1 nausea and 1 severe headache and nausea	When WBRT is combined with SRS or SRT, the rationale is that WBRT could affect micrometastases no covered by the boost techniques. As a general consensus, WBRT plus SRS or SRT does not improve survival compared with SRS/SRT alone, but intracranial metastases occur more often without WBRT. However prophylactic control of cranial metastases could not be needed in patients short expected survival because of side effect of WBRT and most patients do not live enough to experience new brain metastases. Authors concluded that HT is a feasible technique for brain metastases. COMMENT: no conclusions can be drawn on the possibility to avoid WBRT with similar results because no comparisons have been done.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Do L., Pezner R., Radany E. et al. Resection followed by stereotactic radiosurgery to resection cavity for intracranial metastasis *Int J Radiation Oncology Biol Phys*, 73: 486-491, 2009	34	To assess safety and efficacy of stereotactic radiotherapy(SRT) or stereotactic radiosurgery (SRS) as an alternative to whole brain radiotherapy (WBRT) in patients with resected brain metastasis. Retrospective case series All patients treated between December 1999 and December 2006 were consecutively enrolled.	Tomotherapy SRT with linear accelerator (IMRT 21EX); SRS by Tomotherapy. MRI of the entire brain was obtained before treatment. For lesions <3 cm CTV included the enhancing resection cavity and the PTV was equal to the CTV with 1 mm margins. For lesions >3 mm PTV was equal to CTV with 2-3 mm margins. SRS dose range was 15-18 Gy depending on the size of the metastasis. SRT dose ranges was 24-27 Gy in 4-6 fraction. WBRT administered only as a salvage therapy.	30 patients with brain metastasis who underwent surgical resection followed by SRS/SRT. The most common primary tumour was lung CA, followed by breast and melanoma. 13 had single metastasis. Overall 53 lesions were treated, 33 surgically removed and then treated with SRS/SRT, 20 treated with SRS/SRT alone.	1 year	Local recurrence Neurologic symptoms Relapse free survival Overall survival Toxicity Salvage WBRT	*Local recurrence by lesions*: Surgery + SRS/SRT: 12% SRS/SRT alone: 20% *Overall by patients*: 70% *Recurrence at new site*: 63% *1 year local relapse free survival*: 82% *1 year new metastasis free survival*: 31% *1 year overall CNS relapse free survival*: 22% *Neurologic symptoms*: 23% *Salvage WBRT*: 47% *Toxicity*: 26% experienced grade 2 *1 year overall survival*: 51%	The addiction of SRS/SRT to the resection cavity of brain metastasis might lower the rates of local recurrences. However recurrences in new sites of the brain could be increased. This treatment strategy might prolong the interval to salvage with WBRT and its associated neurotoxicity. COMMENT: the hypothesis is that SRS/SRT could be less dangerous than WBRT but with similar results on tumour control. Without a parallel randomised comparison it is impossible to ascertain.

Table 8. Head and neck cancer - Primary studies on technical performance

Synthesis of primary studies - set up error and organ motion in head and neck cancer

Ref. No.	Studies	Number of patients	Study design	Type of technology	Set up error (mm)			Organ motion (mm)		
					V_M	V_Σ	V_σ	V_M	V_Σ	V_σ
23	Johansen 2008	34	Case series	IGRT CBCT		1.58				
32	Lawson 2008	21	Case series	IGCT KV CT	1.40	3.11	3.82			
33	Drabik 2007	4	Case series	Tomotherapy	0.73	2.68				
35	Li 2007	37	Case series	Tomotherapy	0.34	2.80				
38	Sterzing 2008	28	Case series	Tomotherapy	4.20					
39	Wang 2008	22	Case series	IGRT CBCT	1.03	2.08	2.03			
40	Zeidan 2007	24	Case series	Tomotherapy	9.14	3.76	3.93			
41	Sheng 2008	10	Case series	IGRT CBCT	3.57	2.30				
42	Han 2008	5	Case series	Tomotherapy	10.55	4.85				
	Overall range				0.73-10.55	1.58-4.75	2.03-3.93			
	Overall mean				3.87	2.9	2.9			

Reference No. 23

Authors: Johansen J., Bertelsen A., Hansen C.R., Westberg J., Hansen O., Brink C.

Title: Set up errors in patients undergoing image guided radiation treatment. Relationship to body mass index and weight loss.

Journal: *Acta Oncol*, 47 (7): 1454-1458, 2008.

Study objective: The purpose of this study was to quantify the set up errors of patient positioning during IGRT and to correlate set up errors to patient-specific factors such as weight, height, BMI, and weight loss.

Site: Lung; head & neck

Patients: 34 head & neck; 20 lung

Study design: Case series

Type of technology: IGRT CBCT Electa Synergy

Set up error (mm)		**H&N**
M	A-P	
	Left-Right	
	CC	
Σ	A-P	1.1
	Left-Right	0.9
	CC	0.7
σ	A-P	
	Left-Right	
	CC	
Σ + σ	A-P	
	Left-Right	
	CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: This IGRT study did not support the hypothesis that set up errors during radiotherapy are correlated to patient height, weight, BMI, or weight loss.

Reference No. 32

Authors: Lawson J.D., Fox T., Elder E., Nowlan A., Davis L., Keller J., Crocker I.

Title: Early clinical experience with kilovoltage image-guided radiation therapy for interfraction motion management.

Journal: *Med Dosim*, 33 (4): 268-274, 2008.

Study objective: Interest in image-guided radiation therapy (IGRT) reflects the desire to minimize interfraction positioning variability. Using a kilovoltage (kV) imaging unit mounted to a traditional LINAC allows daily matching of kV images to planning digitally reconstructed radiographs (DRRs).

Site: Prostate, head & neck, CNS (Central Nervous System)

Patients: 35 prostate, 21 head & neck, 25 CNS

Study design: Case series

Type of technology: IGCT KV CT Varian

Set up error (mm)		**H&N**
M	A-P	0.5
	Left-Right	1.1
	CC	0.7
Σ	A-P	1.1
	Left-Right	2.2
	CC	1.9
σ	A-P	1.6
	Left-Right	2.6
	CC	2.3
Σ + σ	A-P	
	Left-Right	
	CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: The use of OBI (on-board imaging) effectively corrects set up variability. These shifts are typically small and random. The use of OBI likely can replace weekly port films for isocenter verification; however, OBI does not provide field shape verification.

Reference No. 33

Authors: Drabik D.M., MacKenzie M.A., Fallone G.B.

Title: Quantifying appropriate PTV setup margins: analysis of patient setup fidelity and intrafraction motion using post-treatment megavoltage computed tomography scans.

Journal: *Int J Radiat Oncol Biol Phys*, 68 (4): 1222-1228, 2007.

Study objective: To present a technique that can be implemented in-house to evaluate the efficacy of immobilisation and image-guided set up of patients with different treatment sites on Helical Tomotherapy.

Site: Glioblastoma (Brain), head & neck, prostate cancer

Patients: 12 patients (4 prostate, 4 brain glioblastoma, 4 head & neck)

Study design: Case series

Type of technology: MV CB Tomo

Set up error (mm)			**H&N**
	M (mm)	A-P	0.7
		Left-Right	0.2
		CC	0.1
	Σ (mm)	A-P	1.4
		Left-Right	1.1
		CC	2.0
	σ (mm)	A-P	
		Left-Right	
		CC	
	Σ + σ (mm)	A-P	
		Left-Right	
		CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: This method could be applied using individual patient post-image scanning and combined with adaptive planning to reduce or increase the margins as appropriate.

Reference No. 35

Authors: Li X.A., Qi X.S., Pitterle M., Kalakota K., Mueller K., Erickson B.A., Wang D., Schultz C.J., Firat S.Y., Wilson J.F.

Title: Interfractional variations in patient setup and anatomic change assessed by daily computed tomography.

Journal: *Int J Radiation Oncology Biol Phys*, 68 (2): 581-591, 2007.

Study objective: To analyse the interfractional variations in patient set up and anatomic changes at seven anatomic sites observed in image-guided radiotherapy.

Site: Head & neck; brain

Patients: 37 head & neck; 19 brain

Study design: Case series

Type of technology: MV CB Tomo

Set up error (mm)			**H&N**
	M	A-P	0.21
		Left-Right	0.26
		CC	0.06
	Σ	A-P	1.32
		Left-Right	1.12
		CC	2.20
	σ	A-P	
		Left-Right	
		CC	
	Σ + σ	A-P	
		Left-Right	
		CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: The interfractional variations in patient set up and in shapes, sizes, and positions of both targets and normal structures are site specific and may be used to determine the site-specific margins. The data presented in this work dealing with seven anatomic sites may be useful in developing adaptive radiotherapy.

Reference No. 38

Authors: Sterzing F., Sroka-Perez G., Schubert K., Münter M.W., Thieke C., Huber P., Debus J., Herfarth KK..

Title: Evaluating target coverage and normal tissue sparing in the adjuvant radiotherapy of malignant pleural mesothelioma: helical tomotherapy compared with step-and-shoot IMRT.

Journal: *Radiother Oncol*, 86 (2): 251-257, 2008.

Study objective: To evaluate the potential of Helical Tomotherapy in the adjuvant treatment of malignant pleural mesothelioma and compare target homogeneity, conformity and normal tissue dose with step-and-shoot intensity-modulated radiotherapy.

Site: Head & neck, prostate

Patients: 28 head & neck, 28 prostate

Study design: Case series

Type of technology: MV CB Tomo

Set up error (mm)		**H&N**
M	A-P	
	Left-Right	
	CC	
	Total	4.2
Σ	A-P	
	Left-Right	
	CC	
σ	A-P	
	Left-Right	
	CC	
Σ + σ	A-P	
	Left-Right	
	CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: Helical Tomotherapy is an excellent option for the adjuvant intensity-modulated radiotherapy of MPM. It is capable of improving target coverage and homogeneity.

Reference No. 39

Authors: Wang J., Bai S., Chen N., Xu F., Jiang X., Li Y., Xu Q., Shen Y., Zhang H., Gong Y., Zhong R., Jiang Q.

Title: The clinical feasibility and effect of online cone beam computer tomography-guided intensity-modulated radiotherapy for nasopharyngeal cancer.

Journal: *Radiother Oncol*, 90 (2): 221-227, 2008.

Study objective: This protocol was designed to evaluate the clinical feasibility and effect of online cone beam computed tomography (CBCT) guidance in IMRT of nasopharyngeal cancer (NPC).

Site: head & neck

Patients: 22

Study design: Case series

Type of technology: IGRT CBCT Elekta Synergy

Set up error (mm)			**H&N**
	M	A-P	-0.3
		Left-Right	-0.7
		CC	-0.7
	Σ	A-P	1.2
		Left-Right	1.1
		CC	1.3
	σ	A-P	1.1
		Left-Right	1.1
		CC	1.3
	Σ + σ	A-P	
		Left-Right	
		CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: CBCT-based online correction increased the accuracy of IMRT for NPC and reduced irradiated margins, by decreasing both the systematic and random errors. Online CBCT correction reduces the radiation dose to normal tissue and creates room for further dose escalation studies.

Reference No. 40

Authors: Zeidan O.A., Langen K.M., Meeks S.L., Manon R.R., Wagner T.H., Willoughby T.R., Jenkins D.W., Kupelian P.A.

Title: Evaluation of image-guidance protocols in the treatment of head and neck cancers.

Journal: *Int J Radiat Oncol Biol Phys*, 67 (3): 670-677, 2007.

Study objective: The aim of this study was to assess the residual set up error of different image-guidance (IG) protocols in the alignment of patients with head and neck cancer.

Site: head & neck

Patients: 24

Study design: Case series

Type of technology: MV CB Tomo

Set up error (mm)		**H&N**
M	A-P	8.7
	Left-Right	0
	CC	-2.8
Σ	A-P	2.2
	Left-Right	1.6
	CC	2.6
σ	A-P	2.3
	Left-Right	2.3
	CC	2.2
Σ + σ	A-P	
	Left-Right	
	CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: Residual set up errors reduce with increasing frequency of IG during the course of external-beam radiotherapy for head-and-neck cancer patients. The inability to reduce random set up errors for fractions that are not image guided results in notable residual set up errors.

Reference No. 41

Authors: Sheng K., Chow M.C., Hunter G., Larner J.M., Read P.W.

Title: Is daily CT image guidance necessary for nasal cavity and nasopharyngeal radiotherapy: an investigation based on helical MV CB Tomo.

Journal: *Appl Clin Med Phys*, 9 (1): 2686, 2008.

Study objective: To analyse the magnitude of set up errors corrected by Helical MV CB Tomo Mega-Voltage CT on a daily or weekly basis and their impact on the delivered dose to the tumour and organs at risk (OAR).

Site: head & neck

Patients: 10 (6 nasal cavity, 4 nasopharyngeal)

Study design: Case series

Type of technology: MV CB Tomo

Set up error (mm)			**H&N**
	M	A-P	1.9
		Left-Right	1.7
		CC	2.5
	Σ	A-P	
		Left-Right	
		CC	
	σ	A-P	
		Left-Right	
		CC	
	Σ + σ	A-P	1.1
		Left-Right	1.1
		CC	1.7

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: Daily image-guided set up corrections can eliminate significant dose variations to critical structures. Constant monitoring of patient anatomic changes and selective replanning should be used during radiotherapy to avoid critical structure complications.

Reference No. 42

Authors: Han C., Chen Y.J., Liu A., Schultheiss T.E., Wong J.Y.

Title: Actual dose variation of parotid glands and spinal cord for nasopharyngeal cancer patients during radiotherapy.

Journal: *Int J Radiat Oncol Biol Phys*, 70 (4): 1256-1262, 2008.

Study objective: This study aimed to evaluate the significance of daily image-guided patient set up corrections and to quantify the parotid gland volume and dose variations for nasopharyngeal cancer patients using Helical MV CB Tomo megavoltage computed tomography (CT).

Site: head & neck

Patients: 5

Study design: Case series

Type of technology: MV CB Tomo

Set up error (mm)		**H&N**
M	A-P	1.0
	Left-Right	10.5
	CC	-0.1
Σ	A-P	2.4
	Left-Right	3.4
	CC	2.5
σ	A-P	
	Left-Right	
	CC	
Σ + σ	A-P	
	Left-Right	
	CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: Daily MVCT is preferred as an important safety measure in the IMRT

Table 9. Head and neck cancer - Tomotherapy - Summary of primary studies

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Efficacy - primary outcomes					
Overall survival	Kodaira 2009 (43)	Nasopharyngeal cancer (n 20): Stage IIB 5 Stage III 8 Stage IVA 4 Stage IVB 2 Stage IVC 1 Case series	10 (range 3-17)	70 Gy (median) 35 fractions	at 10 months: 95% (95% CI 85.2-100%)
	Shueng 2010 (72)	Oropharyngeal cancer (n 10) Case series	18 (range 7-22)	GTV 70 Gy	67%
	Chen 2009 (73)	Squamous cell carcinoma of head and neck (n 77) Case series	Not clear	66 Gy median (range 60 to 72 Gy)	77% (2 yrs)
Disease free survival	Shueng 2010 (72)	Oropharyngeal cancer (n 10) Case series	18 (range 7-22)	GTV 70 Gy	70%
	Chen 2009 (73)	squamous cell carcinoma of head and neck (n 77) Case series	Not clear	66 Gy median (range 60 to 72 Gy)	71%

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Efficacy - secondary outcomes					
Progression free survival	Kodaira 2009 (43)	Nasopharyngeal cancer (n 20): Stage IIB 5 Stage III 8 Stage IVA 4 Stage IVB 2 Stage IVC 1 Case series	10 (range 3-17)	70 Gy (median) 35 fractions	at 10 months: 79.7% (95% CI 40-100%)
Distant metastasis-free survival	Shueng 2010 (72)	Oropharyngeal cancer (n 10) Case series	18 (range 7-22)	GTV 70 Gy	100%
	Chen 2010 (73)	Recurrent and second primary cancers of the head and neck (n 21)	20 (6-33)	66 Gy median (range 60-70)	1 year: 71% 2 yrs: 67%
Symptoms control					
Recurrence					2/20

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Efficacy - surrogate outcomes					
Tumour control	Kodaira 2009 (43)	Nasopharyngeal cancer (n 20) Stage IIB 5 Stage III 8 Stage IVA 4 Stage IVB 2 Stage IVC 1 Case series	10 (range 3-17)	70 Gy (median) 35 fractions	at 3 months: 20/20
	Chen 2010 (74)	Recurrent and second primary cancers of the head and neck (n 21)	20 (6-33)	66 Gy median (range 60-70)	1 year: 72% 2 yrs: 65%
Loco-regional control	Shueng 2010 (72)	Oropharyngeal cancer (n 10) Case series	18 (range 7-22)	GTV 70 Gy	80%
	Chen 2009 (73)	Squamous cell carcinoma of head and neck (n 77) Case series	Not clear	66 Gy median (range 60 to 72 Gy)	82%
	Chen 2010 (74)	Recurrent and second primary cancers of the head and neck (n 21)	20 (6-33)	66 Gy median (range 60-70)	1 year: 83% 2 yrs: 77%

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Safety					
Acute toxicity	Kodaira 2009 (43)	Nasopharyngeal cancer (n 20): Stage IIB 5 Stage III 8 Stage IVA 4 Stage IVB 2 Stage IVC 1 Case series	10 (range 3-17)	70 Gy (median) 35 fractions	Leukopoenia: G1: 6; G2: 5; G3: 7; G4: 2 Anemia: G1: 10; G2: 5; G3: 2; G4: 1 Thrombocytopenia G1: 8; G2: 2; G3: 1; G4: 0 Skin reaction: G1: 1; G2: 11; G3: 8;G4: 0 Vomiting: G1: 4; G2: 2; G3: 13; G4: 0 Liver function: G1: 9; G2: 5; G3 and G4: 0 Stomatitis: G1: 0; G2: 9; G3: 11; G4: 0 Renal function: G1: 6/20 G2, G3 and G4: 0
	Chen 2010 (74)	Recurrent and second primary cancers of the head and neck (n 21)	20 (6-33)	66 Gy median (range 60-70)	Mucositis 23% Skin desquamation 57% Odynophagia/dysphagia: 23%

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Late toxicity	Kodaira 2009 (43)	Nasopharyngeal cancer (n 20): Stage IIB 5 Stage III 8 Stage IVA 4 Stage IVB 2 Stage IVC 1 Case series	10 (range 3-17)	70 Gy (median) 35 fractions	Xerostomia at 9 months: G0: 6.6% G1: 66.7% G2: 26.7%
Any toxicity					

Table 10. Head and neck cancer. Tables of evidence from primary studies - Tomotherapy - Clinical outcomes

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Kodaira T., Tomita N., Tachibana H. et al. Aichi Cancer Center initial experience of intensity modulated radiation therapy for nasopharyngeal cancer using helical Tomotherapy. *Int J Radiation Oncology Biol Phys*, 73: 1129-1134, 2009	43	To assess the feasibility of Helical Tomotherapy for patients with nasopharyngeal carcinoma. Case series	Tomotherapy Hi art system A CT with 2.5 mm slice thickness was taken for treatment planning. The majority of patients were evaluated by PET-CT and these images were used as a guide for contours of the tumour volume. All cases were planned using simultaneous integrated boost method. Planning dose at D95 was prescribed to PTV1 at 70 Gy and PTV2 at 53 Gy in 35 fractions. Dose constraints for organ at risk were as follows: 1 brainstem 54 Gy; spinal cord: 45 Gy; mandible 70	20 Stage IIB: 5; III: 8; IVA: 4; IVB: 2; IVC: 1	10 months (3-17)	Acute and late toxicity Parotid gland function Overall survival Progression rate	Acute toxicity Leukopenia G1: 6; G2: 5; G3: 7; G4: 2 Anemia G1: 10; G2: 5; G3: 2; G4: 1 Thrombocytopenia G1: 8; G2: 2; G3: 1; G4: 0 Stomatitis G1: 0; G2: 9; G3: 11; G4: 0 Skin reaction G1: 1; G2: 11; G3: 8; G4: 0 Vomiting G1: 4; G2: 2; G3: 13; G4: 0 Liver function G1: 9; G2: 5; G3 and G4: 0 Renal function G1: 6/20; G2, G3 and G4: 0 Xerostomia at 9 months: G0: 6.6%; G1: 66.7%; G2: 26.7% Complete response at 3 months: 20/20 Recurrence: 2 at last f up Dead: 1 (other causes)	HT was clinically effective in terms of IMRT planning and utility for patients with nasopharyngeal cancer.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
			Gy, bilateral parotid <30Gy. All patients received daily MVCT for set up verification 2.5 cm for primary collimator width, 0,3 pitch, modulation factor 3-4.0 were used. 18 patients received chemotherapy.				Overall survival rate at 10 months: 95% (95% CI 85.2-100%) Progression free rate at 10 months: 79.7% (95% CI 40-100%)	

Update January 2009 - June 2010

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Shueng P-W., Wu L-J., Chen S-Y. et al. Concurrent chemoradiotherapy with helical tomotherapy for oropharyngeal cancer: a preliminary result. *Int J Radiation Oncology Biol Phys*, 77 (3): 715-721, 2010	72	To review the experience with and evaluate the treatment plan for helical tomotherapy for the treatment of oropharyngeal cancer. Case series	Tomotherapy The prescription dose to the gross tumour planning target volume, the high-risk sub clinical area, and the low-risk sub clinical area was 70Gy, 63Gy, and 56Gy, respectively. During radiotherapy, all patients were treated with cisplatin	10 patients with oropharyngeal cancer	18 months (range 7-22 months)	Overall survival Disease-free survival Loco-regional control Distant metastasis-free rate	Overall survival 67% Disease free survival 70% loco-regional control 80% distant metastasis-free rate 100%	Authors conclude that Helical tomotherapy achieved encouraging clinical outcomes in patients with oropharyngeal carcinoma. Treatment toxicity was acceptable, even in the setting of concurrent chemotherapy. Long-term follow up is needed to confirm these preliminary findings.
Chen A.M., Jennelle R.L.S., Sreeraman R. et al. Initial clinical experience with helical tomotherapy for head and neck cancer. *Head & neck*, 31: 1571-1578, 2009	73	To report a single-institutional experience with the use of helical tomotherapy (HT)-based intensity modulated radiotherapy (IMRT) for head and neck cancer. Case series	Tomotherapy Median dose of 66 Gy (range 60 to 72 Gy)	77 consecutive patients with squamous cell carcinoma of head and neck	(Not clear)	Overall survival Local regional control Disease free survival	The 2-year estimates of overall survival: 77% Local regional control: 82% Disease-free survival: 71%	Authors conclude that HT appears to achieve clinical outcomes comparable to contemporary series reporting on IMRT for head and neck cancer.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Chen A.M., Farwell D.G., Luu Q. et al. Prospective trial of high-dose of re-irradiation using daily image guidance with intensity-modulated radiotherapy for recurrent and second primary head-and-neck cancer. *Int J Radiation Oncology Biol Phys*, 1-8, 2010	74	To report a single-institutional experience using intensity-modulated radiotherapy with daily image-guided radiotherapy for the re-irradiation of recurrent and second cancers of the head and neck	Tomotherapy Median dose of 66Gy (range 60-70)	21 patients undergoing re-irradiations after previous definitive therapy of initial disease (surgical resection and post-operative radiotherapy)	20 months (range 6-33 months) and 27 months (range 6-33 months) among surviving patients	Local control Loco-regional control Distant metastasis-free survival Acute toxicity	<u>Local control</u> 1 year: 72% 2 yrs: 65% <u>Local regional control</u> 1 year: 83% 2 yrs: 77% <u>Distant metastasis-free survival</u> 1 year: 71% 2 yrs: 67% <u>Acute toxicity</u> Mucositis 23% Skin desquamation 57% Odynophagia/dysphagia: 23%	Authors conclude that intensity-modulated radiotherapy with daily image guidance results in effective disease control with relatively low morbidity and should be considered for selected patients with recurrent and second primary cancers of the head and neck.

Table 11. Prostate cancer. Primary studies on technical performance

Synthesis of primary studies - set up error and organ motion in prostate cancer

Ref. No.	Studies	Number of patients	Study design	Type of technology	Set up error (mm)			Organ motion (mm)		
					V_M	V_Σ	V_σ	V_M	V_Σ	V_σ
16	Oh 2007	20	Case series	IGRT CBCT	0.44	0.27				
32	Lawson 2008	35	Case series	IGRT KV	0.83	4.75	7.82			
33	Drabik 2007	4	Case series	Tomotherapy	1.10	3.09				
38	Sterzing 2008	28	Case series	Tomotherapy	11.20					
44	Månsson Haskå 2008	20	Case series	IGRT KV					1.80	
45	Carl 2008	62	Case series	IGRT CBCT				0.45	0.50	
46	Moseley 2007	15	Case series	IGRT CBCT	1.92	2.80	4.30			
47	Beldjoudi 2008	20	Case series	Tomotherapy	1.54					
48	Kupelian 2008	74	Case series	Tomotherapy	8.61	5.76	4.96			
49	Fiorino 2008	21	Case series	Tomotherapy	2.66	3.98	4.52	0	0.41	1.36
50	Langen 2005	3	Case series	Tomotherapy	10.72	5.67				
51	Song 2006	5	Controlled case series	Tomotherapy	4.50	0.79				
52	Yoo 2009	9	Case series	IGRT CBCT	0.95	3.52	5.44			
53	Nairz 2008	27	Case series	IGRT CBCT	0.70	4.46				
54	Wertz 2007	7	Case series	IGRT CBCT				2.76	2.34	
55	Adamson 2008	3	Case series	IGRT CBCT	0.10	0.83				
56	Gayou 2008	17	Controlled case series	IGRT CBCT	2.60	6.06				
57	Oldham 2005	phantom	Simulation	IGRT CBCT		4.49				
58	Smitsmans 2005	32	Case series	IGRT CBCT		1.90				
59	Smitsmans 2004	19	Case series	Tomotherapy	1.00	2.51	2.48			
	Overall range				0.1-11.2	0.27-6.06	2.48-7.82	0-2.76	0.41-2.34	1.36
	Overall mean				3.26	3.40	4.90	1.10	1.30	1.40

Reference No. 16

Authors: Oh S., Kim S., Suh T.S.

Title: How image quality affects determination of target displacement when using kilovoltage cone-beam computed tomography.

Journal: *Journal Of Applied Clinical Medical Physics*, 8 (1): 101-107, 2007.

Study objective: Correct set up error using CBCT by adjusting translational and rotational deviations.

Site: Lung, prostate

Patients: 19 lung, 20 prostate

Study design: Case series

Type of technology: IGRT CBCT Elekta

Set up error (mm)			**Prostate**
	M	A-P	0.27
		Left-Right	0.13
		CC	0.32
	Σ	A-P	0.14
		Left-Right	0.12
		CC	0.20
	σ	A-P	
		Left-Right	
		CC	
	Σ + σ	A-P	
		Left-Right	
		CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: In comparing the estimated target displacements obtained using two CBCT image sets (one in high-quality resolution and the other in medium-quality resolution), we found that the translational vector differences between the high-quality resolution and medium-quality resolution were within 1 mm in most cases (53 of 56 cases), and that the rotational differences around each axis were within 1 degree in all but 3 cases.

Reference No. 32

Authors: Lawson J.D., Fox T., Elder E., Nowlan A., Davis L., Keller J., Crocker I.

Title: Early clinical experience with kilovoltage image-guided radiation therapy for interfraction motion management.

Journal: *Med Dosim*, 33 (4): 268-274, 2008.

Study objective: Interest in image-guided radiation therapy (IGRT) reflects the desire to minimize interfraction positioning variability. Using a kilovoltage (kV) imaging unit mounted to a traditional LINAC allows daily matching of kV images to planning digitally reconstructed radiographs (DRRs).

Site: Prostate, head & neck, CNS (Central Nervous System)

Patients: 35 prostate, head & neck, 25 CNS

Study design: Case series

Type of technology: IGCT KV CT Varian

Set up error (mm)		**Prostate**
M	A-P	0.7
	Left-Right	0.2
	CC	0.4
Σ	A-P	3.4
	Left-Right	2.4
	CC	2.3
σ	A-P	3.5
	Left-Right	5.8
	CC	3.9
Σ + σ	A-P	
	Left-Right	
	CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: The use of OBI (on-board imaging) effectively corrects set up variability. These shifts are typically small and random. The use of OBI likely can replace weekly port films for isocentre verification; however, OBI does not provide field shape verification.

Reference No. 33

Authors: Drabik D.M., MacKenzie M.A., Fallone G.B.

Title: Quantifying appropriate PTV setup margins: analysis of patient setup fidelity and intrafraction motion using post-treatment megavoltage computed tomography scans.

Journal: *Int J Radiat Oncol Biol Phys*, 68 (4): 1222-1228, 2007.

Study objective: To present a technique that can be implemented in-house to evaluate the efficacy of immobilization and image-guided set up of patients with different treatment sites on Helical Tomotherapy.

Site: Glioblastoma (Brain), head & neck, prostate cancer

Patients: 12 (4 prostate, 4 brain glioblastoma, 4 head & neck)

Study design: Case series

Type of technology: MV CB Tomo

Set up error (mm)			**Prostate**
	M	A-P	0.2
		Left-Right	-0.4
		CC	1
	Σ	A-P	1.3
		Left-Right	1.6
		CC	2.3
	σ	A-P	
		Left-Right	
		CC	
	Σ + σ	A-P	
		Left-Right	
		CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: This method could be applied using individual patient post-image scanning and combined with adaptive planning to reduce or increase the margins as appropriate.

Reference No. 38

Authors: Sterzing F., Sroka-Perez G., Schubert K., Münter M.W., Thieke C., Huber P., Debus J., Herfarth K.K.

Title: Evaluating target coverage and normal tissue sparing in the adjuvant radiotherapy of malignant pleural mesothelioma: helical tomotherapy compared with step-and-shoot IMRT.

Journal: *Radiother Oncol*, 86 (2): 251-257, 2008.

Study objective: To evaluate the potential of Helical Tomotherapy in the adjuvant treatment of malignant pleural mesothelioma and compare target homogeneity, conformity and normal tissue dose with step-and-shoot intensity-modulated radiotherapy.

Site: Head & neck, prostate

Patients: 28 head & neck, 28 prostate

Study design: Case series

Type of technology: MV CB Tomo

Set up error (mm)

		Prostate
M	A-P	
	Left-Right	
	CC	
	Total	11.2
Σ	A-P	
	Left-Right	
	CC	
σ	A-P	
	Left-Right	
	CC	
Σ + σ	A-P	
	Left-Right	
	CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: HT is an excellent option for the adjuvant intensity-modulated radiotherapy of MPM. It is capable of improving target coverage and homogeneity.

Reference No. 44

Authors: Månsson Haskå T., Honore H., Muren L.P., Høyer M., Poulsen P.R.

Title: Intrafraction changes of prostate position and geometrical errors studied by continuous electronic portal imaging.

Journal: *Acta Oncol*, 47 (7): 1351-1357, 2008.

Study objective: To evaluate the clinical feasibility and effect of online cone beam computed tomography (CBCT) guidance in IMRT of nasopharyngeal cancer (NPC).

Site: Prostate

Patients: 20

Study design: Case series

Type of technology: IGRT kV CT Varian+OBI

Set up error (mm): not evaluated

Organ motion (mm)			**Prostate**
	M	A-P	
		Left-Right	
		CC	
	Σ	A-P	
		Left-Right	
		CC	
	σ	A-P	
		Left-Right	
		CC	
	Σ + σ	A-P	
		Left-Right	1.0
		CC	1.5

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: Large differences in the intrafraction CC prostate motion patterns were found, however, intrafraction motion only results in a modest additional CC set up margin of around 1mm relative to the margins needed for the residual set up error at treatment start.

Reference No. 45

Authors: Carl J., Nielsen J., Holmberg M., Højkjaer Larsen E., Fabrin K., Fisker R.V.

Title: A new fiducial marker for Image-guided radiotherapy of prostate cancer: clinical experience.

Journal: *Acta Oncol*, 47 (7): 1358-1366, 2008.

Study objective: A new fiducial marker for image guided radiotherapy (IGRT) based on a removable prostate stent made of Ni Ti has been developed during two previous clinical feasibility studies. The marker is currently being evaluated for IGRT treatment in a third clinical study. The use of fiducial marker can lead to reduced margins around the clinical target volume (CTV) which may allow for further dose escalation.

Site: Prostate

Patients: 62

Study design: Case series

Type of technology: IGRT CBCT Varian

			Prostate
Set up error (mm): not evaluated			
Organ motion (mm)	**M**	A-P	0.22
		Left-Right	0.10
		CC	0.38
	Σ	A-P	0.25
		Left-Right	0.30
		CC	0.31
	σ	A-P	
		Left-Right	
		CC	
	Σ + σ	A-P	
		Left-Right	
		CC	

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: The preliminary result of an ongoing clinical study of a Ni Ti prostate stent, potentially a new fiducial marker for image guided radiotherapy, looks promising. The risk of migration appears to be much lower compared to previous designs.

Reference No. 46

Authors: Moseley D.J., White E.A., Wiltshire K.L., Rosewall T., Sharpe M.B., Siewerdsen J.H., Bissonnette J.P., Gospodarowicz M., Warde P., Catton C.N., Jaffray D.A.

Title: Comparison of localization performance with implanted fiducial markers and cone-beam computed tomography for on-line image-guided radiotherapy of the prostate.

Journal: *Int J Radiation Oncology Biol Phys*, 67 (3): 942-953, 2007.

Study objective: The aim of this work was to assess the accuracy of kilovoltage (kV) Cone-Beam Computed Tomography (CBCT)-based set up corrections as compared with orthogonal megavoltage (MV) portal image-based corrections for patients undergoing external-beam radiotherapy of the prostate.

Site: Prostate

Patients: 15

Study design: Case series

Type of technology: IGRT CBCT Elekta

Set up error (mm)		**Prostate**
M	A-P	-0.40
	Left-Right	-1.37
	CC	1.28
Σ	A-P	1.61
	Left-Right	0.60
	CC	2.21
σ	A-P	2.86
	Left-Right	1.50
	CC	2.85
Σ + σ	A-P	
	Left-Right	
	CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: 2.1-3.3 cGy

Acquisition time: 2 min

Conclusions: Cone-beam CT is an accurate and precise tool for image guidance. It provides an equivalent means of patient set up correction for prostate patients with implanted gold fiducial markers. Use of the additional information provided by the visualisation of soft-tissue structures is an active area of research.

Reference No. 47

Authors: Beldjoudi G., Yartsev S., Battista J.J., Van Dyk J.

Title: Optimization of MVCT imaging schedule in prostate cancer treatment using helical tomotherapy.

Journal: *Cancer Radiother*, 12 (5): 316-322, 2008.

Study objective: Megavoltage CT (MVCT) study on Helical Tomotherapy permits to verify and correct the patient set up by coregistration with the planning kVCT. This process is time-consuming and our objective is to investigate a possibility of using a smaller number of imaging studies in the case of patients with prostate cancer.

Site: Prostate

Patients: 20 (9 T1C, 5 T2B, 4 T2A, 2 T3A)

Study design: Case series

Type of technology: IGRT CBCT

Set up error (mm)			**Prostate**
	Σ	A-P	1.12
		Left-Right	0.83
		CC	0.66
	σ	A-P	
		Left-Right	
		CC	
	Σ + σ	A-P	
		Left-Right	
		CC	
	Σ	A-P	
		Left-Right	
		CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: The analysis of the reference position obtained for the set of 20 patients as a function of the number of imaging sessions has shown MVCT studies during first four fractions are sufficient for the majority of patients.

Reference No. 48

Authors: Kupelian P.A., Lee C., Langen K.M., Zeidan O.A., Mañon R.R., Willoughby T.R., Meeks S.L.

Title: Evaluation of image-guidance strategies in the treatment of localized prostate cancer.

Journal: *Int J Radiat Oncol Biol Phys*, 70 (4): 1151-1157, 2008.

Study objective: To compare different image-guidance strategies in the alignment of prostate cancer patients. Using data from patients treated using daily image guidance, the remaining set up errors for several different strategies were retrospectively calculated.

Site: Prostate

Patients: 74

Study design: Case series

Type of technology: MV CB Tomo

Set up error (mm)			**Prostate**
	M	A-P	8.07
		Left-Right	1.6
		CC	-2.53
	Σ	A-P	3.8
		Left-Right	2.8
		CC	3.3
	σ	A-P	3.4
		Left-Right	3.7
		CC	2.4
	Σ + σ	A-P	
		Left-Right	
		CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: Set up errors increased with decreasing frequency of image guidance. However, residual errors were still significant at the 5-mm level, even with imaging was performed every other day. This suggests that localisations must be performed daily in the set up of prostate cancer patients during a course of external beam radiotherapy.

Reference No. 49

Authors: Fiorino C., Di Muzio N., Broggi S., Cozzarini C., Maggiulli E., Alongi F., Valdagni R., Fazio F., Calandrino R.

Title: Evidence of Limited Motion of the Prostate by Carefully Emptying the Rectum as Assessed by Daily MVCT Image Guidance with Helical Tomotherapy.

Journal: *Int J Radiat Oncol Biol Phys*, 71 (2): 611-617, 2008.

Study objective: To assess set up and organ motion error by means of analysis of daily megavoltage computed tomography (MVCT) of patients treated with hypofractionated Helical Tomotherapy (71.4-74.2 Gy in 28 fractions).

Site: Prostate

Patients: 21

Study design: Case series

Type of technology: MV CB Tomo

			Prostate
Set up error (mm)	**M**	A-P	-0.5
		Left-Right	-1.4
		CC	-2.2
	Σ	A-P	3.4
		Left-Right	1.6
		CC	1.3
	σ	A-P	2.3
		Left-Right	3.4
		CC	1.9
	Σ + σ	A-P	
		Left-Right	
		CC	
Organ motion (mm)	**M**	A-P	0
		Left-Right	0
		CC	0
	Σ	A-P	0.3
		Left-Right	0.2
		CC	0.2
	σ	A-P	1.0
		Left-Right	0.6
		CC	0.7
	Σ + σ	A-P	
		Left-Right	
		CC	

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: Daily MVCT-based correction is feasible. The BM + DV matching was found to be consistent between operators. Rectal emptying using a daily enema is an efficient tool to minimize prostate motion, even for centres that have not yet implemented image-guided radiotherapy.

Reference No. 50

Authors: Langen K.M., Zhang Y., Andrews R.D., Hurley M.E., Meeks S.L., Poole D.O., Willoughby T.R., Kupelian P.A.

Title: Initial experience with megavoltage (MV) CT guidance for daily prostate alignments.

Journal: *Int J Radiat Oncol Biol Phys*, 62: 1517-1524, 2005.

Study objective: The on-board megavoltage (MV) computed tomography (CT) capabilities of a Tomotherapy Hi*ART unit were used to obtain daily MVCT images of prostate cancer patients. For patient alignment the daily MVCT image needs to be registered with the planning CT image to calculate couch shifts.

Site: Prostate

Patients: 3

Study design: Case series

Type of technology: MV CB Tomo

Set up error (mm)			**Prostate**
	M(mm)	A-P	9.9
		Left-Right	4.0
		CC	-0.9
	Σ (mm)	A-P	3.6
		Left-Right	3.6
		CC	2.5
	σ (mm)	A-P	
		Left-Right	
		CC	
	Σ + σ (mm)	A-P	
		Left-Right	
		CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: The use of fiducial markers for MVCT image guidance is advantageous to reduce the inter-user variability of the image registration. If fiducial markers are not used, anatomy-based registrations outperform contour-based registrations in terms of (1) agreement with a reference alignment and (2) inter-user variability.

Reference No. 51

Authors: Song W.Y., Chiu B., Bauman G.S., Lock M., Rodrigues G., Ash R., Lewis C., Fenster A., Battista J.J., Van Dyk J.

Title: Prostate contouring uncertainty in megavoltage computed tomography images acquired with a helical tomotherapy unit during image-guided radiation therapy.

Journal: *Int J Radiat Oncol Biol Phys*, 65 (2): 595-607, 2006.

Study objective: To evaluate the image-guidance capabilities of megavoltage computed tomography (MVCT), this article compares the interobserver and intraobserver contouring uncertainty in kilovoltage Computed Tomography (KVCT) used for radiotherapy planning with MVCT acquired with Helical Tomotherapy.

Site: Prostate

Patients: 5; 1 T2b, 3 T1C, 1 T2C

Study design: Controlled case series

Type of technology: MV CB Tomo

Technology comparator: CT

Set up error (mm)			**Prostate**	
			Tomo	**CT**
	M	A-P	2.6	1.2
		Left-Right	0.7	0.5
		CC	3.6	2.0
	Σ	A-P	0.42-0.23	0.17-0.11
		Left-Right	0.39-0.48	0.20-0.32
		CC	0.54-0.29	0.24-0.16
	σ	A-P		
		Left-Right		
		CC		
	Σ + σ	A-P		
		Left-Right		
		CC		

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: Although MVCT was inferior to KVCT for prostate delineation, the application of MVCT in prostate radiotherapy remains useful.

Reference No. 52

Authors: Yoo S., Wu Q.J., Godfrey D., Yan H., Ren L., Das S., Lee W.R., Yin F.F.

Title: Clinical evaluation of positioning verification using digital tomosynthesis and bony anatomy and soft tissues for prostate image-guided radiotherapy.

Journal: *Int J Radiat Oncol Biol Phys*, 73 (1): 296-305, 2009.

Study objective: To evaluate on-board digital tomosynthesis (DTS) for patient positioning vs. two-dimensional (2D) radiography and three-dimensional cone beam (CBCT).

Site: Prostate

Patients: 9

Study design: Case series

Type of technology: IGRT CBCT Varian

Set up error (mm)			**Prostate**	
			Bony anatomy	**Soft tissue**
	M	A-P	-0.8	-0.2
		Left-Right	-0.1	0.2
		CC	-0.5	-0.5
	Σ	A-P	2.1	5.3
		Left-Right	2.0	1.9
		CC	2.0	2.4
	σ	A-P	2.9	3.7
		Left-Right	3.2	3.3
		CC	3.3	3.4
	Σ + σ	A-P		
		Left-Right		
		CC		

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: 3.8 cGy/scan

Acquisition time: not evaluated

Conclusions: DTS could provide equivalent results to CBCT when the bony anatomy is used as landmarks for prostate image-guided radiotherapy. For soft tissue-based positioning verification, coronal DTS produced equivalent results to CBCT, but sagittal DTS alone was insufficient. DTS could allow for comparable soft tissue-based target localisation with faster scanning time and a lower imaging dose compared with CBCT.

Reference No. 53

Authors: Nairz O., Merz F., Deutschmann H., Kopp P., Schöller H., Zehentmayr F., Wurstbauer K., Kametriser G., Sedlmayer F.

Title: A strategy for the use of image-guided radiotherapy (IGRT) on linear accelerators and its impact on treatment margins for prostate cancer patients.

Journal: *Strahlenther Onkol*, 184 (12): 663-667, 2008.

Study objective: To investigated if systematic set up errors can be reduced by a set of initial image-guided radiotherapy (IGRT) sessions.

Site: Prostate

Patients: 27

Study design: Case series

Type of technology: IGRT CBCT Elekta

Set up error (mm)		**Prostate**
M	A-P	0.7
	Left-Right	0
	CC	0
Σ	A-P	3.4
	Left-Right	1.6
	CC	2.4
σ	A-P	
	Left-Right	
	CC	
Σ + σ	A-P	
	Left-Right	
	CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: Only initially performed IGRT might be helpful for eliminating gross systematic errors especially after virtual simulation. However, even with daily IGRT performance, a substantial PTV margin reduction is only achievable by matching internal markers instead of bony anatomical structures.

Reference No. 54

Authors: Wertz H., Boda-Heggemann J., Walter C., Dobler B., Mai S., Wenz F., Lohr A.F.

Title: Image-guided in vivo dosimetry for quality assurance of IMRT treatment for prostate cancer.

Journal: *Int J Radiation Oncology Biol Phys*, 67 (1): 288-295, 2007.

Study objective: In external beam radiotherapy (EBRT) and especially in intensity-modulated radiotherapy (IMRT), the accuracy of the dose distribution in the patient is of utmost importance. It was investigated whether image guided in vivo dosimetry in the rectum is a reliable method for online dose verification.

Site: Prostate

Patients: 7

Study design: Case series

Type of technology: IGRT CBCT Synergy

			Prostate	
Set up error (mm): not evaluated				
Organ motion (mm)			**soft tissue match**	**bone match**
	M	A-P	1.6	0.9
		Left-Right	1.9	1.6
		CC	1.2	0.6
	Σ	A-P	1.3	1.2
		Left-Right	1.1	0.8
		CC	1.6	0.9
	σ	A-P		
		Left-Right		
		CC		
	Σ + σ	A-P		
		Left-Right		
		CC		

Image quality: not evaluated

Additional dose: 10 cGy/scan

Acquisition time: not evaluated

Conclusions: Image-guided dosimetry in the rectum during IMRT of the prostate is a feasible and reliable direct method for dose verification when probe position is effectively controlled.

Reference No. 55

Authors: Adamson J., Wua Q.

Title: Prostate intrafraction motion evaluation using kV fluoroscopy during treatment delivery: A feasibility and accuracy study.

Journal: *Med Phys*, 35 (5): 1793-1806, 2008.

Study objective: Margin reduction for prostate radiotherapy is limited by uncertainty in prostate localization during treatment. The feasibility and accuracy of measuring prostate intrafraction motion using kV fluoroscopy performed simultaneously with radiotherapy was investigated.

Site: Prostate

Patients: 3

Study design: Case series and phantom

Type of technology: IGRT CBCT Elekta Synergy

Set up error (mm)		**Prostate**
M	A-P	0.09
	Left-Right	-0.04
	CC	0.03
Σ	A-P	0.40
	Left-Right	0.30
	CC	0.70
σ	A-P	
	Left-Right	
	CC	
Σ + σ	A-P	
	Left-Right	
	CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: Measuring prostate intrafraction motion using a single kV imager during radiotherapy is feasible and can be performed with acceptable accuracy.

Reference No. 56

Authors: Gayou O., Miften M.

Title: Comparison of mega-voltage cone-beam computed tomography prostate localization with online ultrasound and fiducial markers methods.

Journal: *Med Phys*, 35 (2): 531-538, 2008.

Study objective: To compare Mega-Voltage Cone-Beam computed tomography shift with online ultrasound and fiducial markers methods.

Site: Prostate

Patients: 17 MV-CBCT; 12 SM; 19 US

Study design: Controlled case series

Type of technology: IGRT CBCT Siemens

Technology comparator: Ultrasound (US); Seed markers (SM)

Set up error (mm)

		Prostate		
		MV-CBCT	**SM**	**US**
M	A-P	-0.33	-0.53	-0.95
	Left-Right	0.98	-1.03	-1.18
	CC	-1.27	0.00	-1.73
Σ	A-P	3.93	4.10	5.91
	Left-Right	3.91	3.35	6.75
	CC	2.46	3.35	5.06
σ	A-P			
	Left-Right			
	CC			
Σ + σ	A-P			
	Left-Right			
	CC			

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: 10 cGy

Acquisition time: not evaluated

Conclusions: The online MV-CBCT and SM image-guidance data show that for treatments that do not include daily prostate localisation, one can use a CTV-to-PTV margin that is 4 mm smaller than the one suggested by US data, hence allowing more rectum and bladder sparing and potentially improving the therapeutic ratio.

Reference No. 57

Authors: Oldham M., Le'tourneau D., Watt L., Hugo G., Yan D., Lockman D., Kim L.H., Chen P.Y., Martinez A., Wong J.W.

Title: Cone-beam-CT guided radiation therapy: A model for on-line application.

Journal: *Radiotherapy and Oncology*, 75: 271.e1-271.e8, 2005.

Study objective: This paper presents efficient and generalized processes for the clinical application of on-line X-ray volumetric Cone-Beam CT imaging to improve the accuracy of patient set up in radiation therapy.

Site: Prostate

Patients: Phantom

Study design: Simulation

Type of technology: IGRT CBCT Elekta Synergy

Set up error (mm)		**Prostate**
M	A-P	
	Left-Right	
	CC	
Σ	A-P	
	Left-Right	
	CC	
σ	A-P	
	Left-Right	
	CC	
Σ + σ	A-P	1.2
	Left-Right	-4.3
	CC	-0.5

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: Cone-beam CT imaging has potential to significantly improve the accuracy of radiation treatments. Present image quality is highly encouraging and can enable bony and soft-tissue patient set up error determination and correction. As with all image guided treatment techniques the development of efficient procedures to utilise on-line data are of paramount importance.

Reference No. 58

Authors: Smitsmans M.H.P., De Bois J., Sonke J.J., Betgen A., Zijp L.J., Jaffray D.A., Lebesque J.V., Van Herk M.

Title: Automatic prostate localization on cone-beam ct scans for high precision image-guided radiotherapy.

Journal: *Int J Radiation Oncology Biol Phys*, 63 (4): 975-984, 2005.

Study objective: Previously, we developed an automatic three-dimensional gray-value registration (GR) method for fast prostate localization that could be used during online or offline image-guided radiotherapy. The method was tested on conventional computed tomography (CT) scans. In this study, the performance of the algorithm to localize the prostate on cone-beam CT (CBCT) scans acquired on the treatment machine was evaluated.

Site: Prostate

Patients: 32

Study design: Case series

Type of technology: IGRT CBCT Elekta Synergy

Set up error (mm)		**Prostate**
M	A-P	
	Left-Right	
	CC	
Σ	A-P	
	Left-Right	
	CC	
σ	A-P	
	Left-Right	
	CC	
Σ + σ	A-P	1.2
	Left-Right	1.3
	CC	0.7

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: The feasibility of automatic prostate localization on CBCT scans acquired on the treatment machine using an adaptation of the previously developed three-dimensional gray-value registration algorithm, has been validated in this study. Collimating the FOV during CBCT image acquisition improved the CBCT image quality considerably. Artefacts in the CBCT images caused by large moving gas pockets during CBCT image acquisition were the main cause for unsuccessful registration. From this study, we can conclude that CBCT scans are suitable for online and offline position verification of the prostate, as long as the amount of non-stationary gas is limited.

Reference No. 59

Authors: Smitsmans M.H.P., Wolthaus J.W.H., Artignan X., De Bois J., Jaffray D.A., Lebesque J.V., Van Herk M.

Title: Automatic localization of the prostate for on-line or off-line image-guided radiotherapy.

Journal: *Int J Radiation Oncology Biol Phys*, 60 (2): 623-635, 2004.

Study objective: Knowledge of the precise position of the prostate would allow significant reduction of the treatment field. Better localization of the prostate at the time of treatment is therefore needed, e.g. using a Cone-Beam Computed Tomography (CT) system integrated with the linear accelerator. Therefore, an automatic method to localize the prostate, based on 3D gray value registration, was developed.

Site: Prostate

Patients: 19

Study design: Case series

Type of technology: MV CB Tomo

Set up error (mm)			**Prostate**
	M	A-P	-0.9
		Left-Right	0.4
		CC	0.2
	Σ	A-P	1.8
		Left-Right	1.6
		CC	0.7
	σ	A-P	1.5
		Left-Right	1.8
		CC	0.8
	Σ + σ	A-P	
		Left-Right	
		CC	

Organ motion (mm): not evaluated

Image quality: not evaluated

Additional dose: not evaluated

Acquisition time: not evaluated

Conclusions: This newly developed method localises the prostate quickly, accurately, and with a good success rate, although visual inspection is still needed to detect outliers. With this approach, it will be possible to correct on-line or off-line for prostate movement. Combined with the conformity of intensity-modulated dose distributions, this method might permit dose escalation beyond that of current conformal approaches, because margins can be safely reduced.

Table 12. Prostate cancer - Tomotherapy. Primary studies

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Efficacy - primary outcomes					
Overall survival					
Disease free survival/relapse free survival					
Efficacy - secondary outcomes					
Progression free survival					
Symptoms control					
Biochemical control					
Recurrence					
Efficacy - surrogate outcomes					
Tumour control					

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Safety					
Acute toxicity	Keiler 2007 (60)	Prostate cancer (n 98) T1c-T3b Consecutive case series with a historical comparison group treated with Linac. Tomotherapy: 55 patients with androgen deprivation (32 definite + 23 salvage with hormonal therapy) Versus Linac: 43 patients (32 definite + 11 salvage with hormonal therapy)	25	Definitively treated patients: 81 Gy (range 79.2-82.8) 44-46 fractions Salvage patients: 72 Gy 40 fractions	Gastrointestinal toxicity Grade 0: LINAC 5% vs Tomotherapy: 11% Grade 1: LINAC 56% vs Tomotherapy: 64% Grade 2: LINAC 40% vs Tomotherapy: 25% p = 0.024 Genitourinary toxicity Grade 0: LINAC 2% vs Tomotherapy: 2% Grade 1: LINAC 70% vs Tomotherapy: 47% Grade 2: LINAC 28% vs Tomotherapy: 47% Grade 3: LINAC 0 % vs Tomotherapy: 4% p = 0.001

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
	Cozzarini 2008 (63)	Prostate cancer after radical prostatectomy (n 50) pT2R1/pT3a/pT3b-pN0 Consecutive case series Some outcomes have been compared with a historical case series	25	58 Gy 20 fractions	Gastrointestinal toxicity Grade 1: Tomotherapy 26% vs 3D-CRT: 10% (p =0.05) Grade 2: Tomotherapy 4% vs 3D-CRT: 7% (p = 0.44) Grade 3: 0 Proctitis Grade 1 Tomotherapy 36% vs 3D-CRT: 23% Proctitis Grade 2 Tomotherapy 0% vs 3D-CRT: 9% (p=0.029) Genitourinary toxicity: Grade 1: Tomotherapy 62% vs 3D-CRT: 22% p: <0.0001 Grade 2: Tomotherapy 10% vs 3D-CRT: 13% (NS) Grade 3: Tomotherapy 2% vs 3D-CRT: 2.6% (NS) Prostate problems (IPSS): no significant increases

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
	Cozzarini 2007 (61)	Prostate cancer (n 35) After radical prostatectomy (n 23) With radical intention (n 12) Case series	11.5 months (range 3.5-25.7 months)	With radical intention 71.4-74.2 Gy 28 fractions After prostatectomy 64.4-72 Gy 28-33 fractions	Upper GI part Grade 1: 13/35 (37%) Grade 2: 0 Grade 3: 0 Lower GI part (proctitis) No symptoms: 26 (74%) Grade 1: 23% Grade 2: 1/35 Grade3: 0 Genitourinary toxicity: no sequele: 26% mild: 51% cystitis Grade 2: 2 (6%)

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
	Cheng 2008 (62)	Prostate cancer (n 146) T1-T3 Retrospective consecutive case series Definitive RT: 76 patients Post-operative RT: 70 patients (salvage: 37, adjuvant: 33)	10.65 months (range 3-27.3)	Definite 78.9 (75.3-84.2) Post-operative RT: mean 68.8 (65.1-71.8) 32-46 fractions	Gastrointestinal toxicity: Definitive (n = 76) Grade 0: 49% Grade 1: 26% Grade 2: 25% Grade 3: 0 Grade 4: 0 Post-operative (n = 70) Grade 0: 13% Grade 1: 46% Grade 2: 41% Grade 3: 0 Grade 4: 0 Genitourinary toxicity Definitive (n = 76) Grade 0: 17% Grade 1: 45% Grade 2: 38% Grade 3: 0 Grade 4: 0 Post-operative (n = 70) Grade 0: 16% Grade 1: 49% Grade 2: 36% Grade 3: 0 Grade 4: 0

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Late toxicity	Cozzarini 2008 (63)	Prostate cancer after radical prostatectomy (n 50) pT2R1/pT3a/pT3b-pN0 Consecutive case series Some outcomes have been compared with a historical case series	25	58 Gy 20 fractions	Gastrointestinal toxicity Grade 2 Tomotherapy: 0% vs 3D-CRT: 8.5%. Genitourinary toxicity Grade 2 or more Tomotherapy: 12% vs 3D-CRT: 14% Sexual problems: Sexual potency (IIEF): no significant reductions

Table 13. Prostate cancer CBCT / Rapid Arc - Primary studies on clinical outcomes

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Efficacy - primary outcomes					
Overall survival					
Disease free survival /relapse free survival					
Efficacy - secondary outcomes					
Progression free survival					
Symptoms control					
Biochemical control	Engels 2009 (64)	Prostate cancer (n 238) T1-T3N0M0 Low risk: 97 Intermediate risk: 84 High, very high risk: 57 Case series	53	70 patients received 70 Gy. Low risk: 70 Gy intermediate and high risk: 78 Gy	Biochemical failure at 5 years: 88.4% 70.8% (high / very risk group) 93% (intermediate / low risk group)
Efficacy - surrogate outcomes					
Tumour control					

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
Safety					
Acute toxicity	Engels 2009 (64)	Prostate cancer (n 238) T1-T3N0M0 Low risk: 97 Intermediate risk: 84 High, very high: 57 Case series	53	70 patients received 70 Gy Low risk: 70 Gy intermediate and high risk: 78 Gy	Gastrointestinal toxicity: Grade 3 or 4: 0 Genitourinary toxicity: Grade 3 or 4: 0
	Pesce 2010 (75)	Intermediate risk prostate cancer (Gleason score 6-7) (n 45) Case series	End of treatment	RapidArc Range 76-78 Gy in 2 Gy/fraction	<u>Rectal acute toxicity</u> G0 72% G1 28% G2 0 G3 0 <u>Urinary acute toxicity (dysuria)</u> G0 19% G1 69% G2 12% G3 0

Outcomes	Studies (Ref. No.)	Study design Patients	Follow up, months; median (range)	Total dose Gy (mean); No. fractions	Results
	Jereczek-Fossa 2009 (76)	Low, intermediate and high risk prostate cancer Low and intermediate prostate cancer (n 179) vs intermediate and high prostate cancer (n 174) Retrospective case series with historical cohort control	Not specified	IGRT - 70 Gy 2 Gy /26 fractions vs Non-IGRT 80 Gy/40 fractions	<u>Acute rectal toxicity</u> Hypo-IGRT vs non-IGRT None: 58.7% vs 77.6% G1: 29.1% vs 16.1% G2: 11.2% vs 6.3% G3: 1.1% vs 0 G4: 0 vs 0 <u>Acute urinary toxicity</u> Hypo-IGRT vs non-IGRT None: 22.3% vs 36.2% G1: 33.5% vs 41.4% G2: 39.1% vs 20.7% G3: 5.0% vs 0.6% G4: 0 vs 1.1%
Late gastro-intestinal toxicity	Engels 2009 (64)	Prostate cancer (n 238) T1-T3N0M0 Low risk: 97 Intermediate risk: 84 High, very high: 57 Case series	53	70 patients received 70 Gy Low risk: 70 Gy, intermediate and high risk: 78 Gy	Gastrointestinal toxicity: Grade 3 or 4: 0 Genitourinary toxicity: Grade 3 or 4: 0.6%
Erectile function	Pesce 2010 (75)	Intermediate risk prostate cancer (Gleason score 6-7) (n 45)	End of treatment	RapidArc Range 76-78 Gy in 2 Gy/fraction	<u>Erectile function</u> Yes 34% Yes/no 10% No 56%

Table 14. Prostate cancer. Tables of evidence from primary studies - Clinical outcomes

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Engels B., Soete G., Verellen D., Guy S. Conformal arc radiotherapy for prostate cancer: increased biochemical failure in patients with distended rectum on the planning computed tomogram despite image guidance by implanted markers. *Int J Radiation Oncology Biol Phys*, 74 (2): 388-391, 2009	64	To evaluate the effect of rectal distension on the planning computed tomogram on freedom from biochemical failure (FFBF) of prostate cancer patients treated with image guided conformal arc radiotherapy. Case series	Image guided conformal arc radiotherapy 70 patients received 70 Gy, Low risk: 70 Gy, intermediate and high risk: 78 Whole pelvis irradiation not performed. A margin of CTV to PTV of 6 mm left-right and 10 mm AP an CC was used in 213 without implanted markers. In patients with implanted markers 3 mm LR, 5 mm AP and CC. Radiation is delivered during one gantry rotation with a dynamically shaped 6MV photon beam. 70 patients received neoadjuvant and/or concurrent hormonal treatment.	238 T1-T3N0M0 Low risk: 97 Intermediate risk: 84 High/very high risk: 57	53 months (range 24-93 months)	Toxicity evaluated using RTOG criteria. Biochemical failure using the Phoenix definition.	Acute GI and GU grade 3 and 4: 0 Late GI grade 3 and 4: 0 Late GU grade 3 and 4: 0.6% Biochemical failure at 5 years: 88.4% 70.8% (high / very high risk group) 93% (intermediate / low risk group)	Overall, the outcome of patients treated with image guided conformal arc radiotherapy is excellent. We were able to confirm the negative prognostic impact of the distended rectum on the planning computed tomogram described by others. The study illustrates the potential danger of image guidance techniques as to margin reduction around the clinical target volume.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Keiler L., Dobbins D., Kulasekere R., Einste D. Tomotherapy for prostate adenocarcinoma: A report on acute toxicity. *Radiotherapy and Oncology*, 84 (2): 171-176, 2007	60	To analyze the impact of Tomotherapy (TOMO) intensity modulated radiotherapy (IMRT) on acute gastrointestinal (GI) and genitourinary (GU) toxicity in prostate cancer Consecutive case series with a historical comparison treated with Linac. Clinical characteristics of the two groups of patients at baseline were presented: differences were not statistically significant.	Tomotherapy HI Art system. The definition of the PTV was identical for all groups. PTV1 = (prostate + seminal vesicles) + 0.7 cm margin except at rectal interface where a 0.3 cm margin was utilised. PTV2 = prostate or prostate bed + 0.7 cm margin except at the rectal interface where the margin was reduced to 0.3 cm. For definitively treated patients PTV1 was treated to a minimum of 66 in 1.8 Gy fractions and PTV2 was treated to a total dose of 81 Gy (range 79.2-82.8 Gy) in 44 or 46 1.8 Gy fractions. For salvage patients PTV2 was used and treated to a total dose of 72 Gy in 40 1.8 Gy fractions.	Prostate cancer (n 98) T1c -T3b Tomotherapy: 55 patients with androgen deprivation (32 definite + 23 salvage with hormonal therapy) Versus Linac: 43 patients (32 definite + 11 salvage with hormonal therapy)	25 months	Acute toxicity	Gastrointestinal Grade 0: LINAC 5% vs Tomo: 11% Grade 1: LINAC 56% vs Tomo: 64% Grade 2: LINAC 40% vs Tomo: 25% p = 0.024 Genitourinary Grade 0: LINAC 2% vs Tomo: 2% Grade 1: LINAC 70% vs Tomo: 47% Grade 2: LINAC 28% vs Tomo: 47% Grade 3: LINAC 0 % vs Tomo: 4% p = 0.001	Acute GI toxicity for prostate cancer is improved with Tomotherapy at a cost of increased acute GU toxicity possibly due to differences in bladder and prostate dose distribution.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Cozzarini C., Fiorino C., Di Muzio N. et al. Significant reduction of acute toxicity following pelvic irradiation with Helical Tomotherapy in patients with localized prostate cancer. *Radiotherapy and Oncology*, 84 (2): 164-170, 2007	61	To assess and quantify the possible benefit deriving from IMRT with Helical Tomotherapy (HTT) delivery to the pelvic nodal area in patients with prostate cancer in terms of reduction of acute and late toxicities. Case series	Tomotherapy In this case, a dose of 51.8 Gy in 28 fractions was delivered to the pelvis while concomitantly delivering 56-65.5 Gy to seminal vesicles and 71.4-74.2 Gy to the prostate, excluding the overlap. Patients were CT scanned with a 3 mm slice thickness from L2 to approximately 5 cm below the anus. In patients post-operatively treated, PTV1 was generated by expanding CTV1 by 0.5-0.7 cm isotropically in order to take into account residual set up error after daily correction by bone matching between daily MVCT and planning KVCT, whereas in the case of radical treatments a wider margin (1 cm) was used due to the risk of missing the nodes while tracking the prostate, a relatively large margin was used for PTV1.	35 23 after prostatectomy 12 with a radical intention	11.5 months (range 3.5-25.7)	Acute toxicity	Acute GU toxicities no sequele: 14 (26%) mild: 18 (51%) cystitis Grade 2: 2 (6%) Grade 3: 0 acute upper GI toxicities Grade 1: 13/35 (37%) Grade 2: 0 Grade 3: 0 Acute lower GI (proctitis) No symptoms: 26 (74%) Grade 1: 8 (23%) Grade 2: 1 Grade 3: 0	Whole pelvis radiotherapy with HTT resulted in a very low incidence of acute Grade 2 and in the disappearance of acute Grade 3 toxicities.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Cheng J.C., Schultheiss T.E., Nguyen K.H. et al. Acute toxicity in definitive versus postprostatectomy image-guided radiotherapy for prostate cancer. *Int J Radiation Oncology Biol Phys*, 71: 351-357, 2008	62	To assess the incidence of acute gastrointestinal and genitourinary injury and the dose-volume response in patients with clinically localised prostate cancer treated with image-guided radiotherapy using Helical Tomotherapy. Retrospective consecutive case series	Tomotherapy Hi Art System Definitive RT: mean prescribed dose to PTV: 78.9 (75.3-84.2) Post-operative RT: mean 68.8 (65.1-71.8) The PTV was also 3-6 mm around the respective CTVs in all dimensions, except posteriorly, in which the margin was 3-4 mm. All RT was performed using HT with 6-MV photons in daily fractions of 1.8-2.0 Gy.	146 patients 76 definitive RT and 70 post-operative RT (37 salvage, 33 adjuvant) T1-T3 T1b 0 (0) 1 (2) T1c 49 (64) 42 (66) T2a 10 (13) 6 (10) T2b 6 (8) 8 (13) T2c 8 (11) 4 (7) T3 3 (4) 1 (2)	10.65 months (3-27.3)	Acute GU and GI toxicities	Definitive (n = 76) GI Grade 0: 49% Grade 1: 26% Grade 2: 25% Grade 3: 0 Grade 4: 0 GU Grade 0: 17% Grade 1: 45% Grade 2: 38% Grade 3: 0 Grade 4: 0 Post-operative (n = 70) GI Grade 0: 13% Grade 1: 46% Grade 2: 41% Grade 3: 0 Grade 4: 0 GU Grade 0: 16% Grade 1: 49% Grade 2: 36% Grade 3: 0 Grade 4: 0	The results of our study have shown that acute rectal symptoms are dose-volume related. Postprostatectomy RT resulted in a greater incidence of acute GI toxicity than did definitive RT. For post-operative RT, it would be prudent to use different dose-volume limits.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Cozzarini C., Fiorino C., Di Muzio N. et al. Hypofractionated adjuvant radiotherapy with helical. Tomotherapy after radical prostatectomy: Planning data and toxicity results of a Phase I-II study N. *Radiotherapy and Oncology*, 88: 26-33, 2008	63	To report on planning and toxicity findings of hypofractionated adjuvant radiotherapy with Helical Tomotherapy after radical prostatectomy for prostate carcinoma Consecutive case series. An historical case series have been used to compare Tomotherapy vs 3D-CRT. Authors do not mention about differences or similarities between the two study groups not about any attempt to take account of different risk factors.	Tomotherapy Hi art system 58 Gy in 20 fractions, 2.9 Gy/fractions, 5 fraction/week versus 3D-CRT 68 Gy-72 Gy delivered in fractions of 1.8 Gy. For most patients a field dimension of 2.5 cm, a pitch of 0.3 and a modulation factor of 2-2.5 were used. Location of surgical clips were used to guide the physician in contouring the CTV. It included the tumour bed and was drawn to include the prostatic fossa and the lower bladder neck; inferiorly, the CTV was drawn to about 1-1.5 cm from the caudal limit of the ischiatic tuberosities. Bony structures and the anterior rectal wall were also used to define the edges of CTV. For pT3b patients two different CTVs were drawn.	Tomotherapy: 50 pT2R1/pT3a/pT3b-pN0 3D-CRT: 153 patients	25 months	Acute and late toxicity	Acute genitourinary tract toxicity Grade 1: Tomotherapy 62% vs 3D-CRT: 22% p: <0.0001 Grade 2: Tomotherapy 10% vs 3D-CRT: 13% Grade 3: Tomotherapy 2% vs 3D-CRT: 2.6% Acute gastrointestinal toxicity Grade 1: Tomotherapy 26% vs 3D-CRT: 10% Grade 2: Tomotherapy 4% vs 3D-CRT: 7% Acute proctitis Grade 1 Tomotherapy 36% vs 3D-CRT: 23% Acute proctitis Grade 2 Tomotherapy 0% vs 3D-CRT: 9% Sexual potency (IIEF): no significant reduction Prostatic problems (IPSS) no significant increase.	Acute toxicity and early late toxicity outcomes of a moderately hypofractionated regimen with Tomotherapy post RP are excellent. A longer follow up is needed to fully assess the validity of this approach.

(to be continued)

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
							Late GI Grade 2 Tomotherapy: 0% vs 3D-CRT: 8.5%. Cumulative late GU toxicity Grade 2 or more: Tomotherapy: 12% vs 3D-CRT: 14%	

Update January 2009 - June 2010

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Pesce G.A., Clivio A., Cozzi L. et al. Early experience of radiotherapy of prostate cancer with volumetric modulated arc therapy. *Radiation Oncology*, 5: 54, 2010.	75	To report about initial clinical experience in radiation treatment of carcinoma of prostate with volumetric arcs with the RapidArc (RA) technology Case series	RapidArc Range 76-78 Gy in 2 Gy/fraction	45 patients with intermediate risk prostate cancer (Gleason score 6-7)	Evaluation at end of treatment	Post-treatment PSA Rectal acute toxicity Urinary acute toxicity Erectile function	<u>Post treatment PSA</u> 0.4 median (range 0.0-6.8) <u>Rectal acute toxicity</u> G0 72% G1 28% G2 0 G3 0 <u>Urinary acute toxicity (dysuria)</u> G0 19% G1 69% G2 12% G3 0 <u>Erectile function</u> Yes 34% Yes/no 10% No 56%	Authors conclude that quality of treatments resulted in an improvement of all planning objectives in terms of both target coverage and sparing of organs at risk. Clinical outcomes for early acute toxicity and assessment of biochemical outcome showed encouraging results. Future investigations will aim to appraise treatment of patients with inclusion of pelvic nodes and altered fractionation schemes.

Reference	Ref. No.	Study objective Study design	Technology assessed	Patients	Follow up (median)	Outcome measures	Results	Conclusions
Jereczek-Fossa B.A., Zerini D., Fodor C. et al. Acute toxicity of image-guided hypofractionated radiotherapy for prostate cancer: non randomized comparison with conventional fractionation. *Urologic Oncology*. 2009.	76	To compare acute toxicity of prostate cancer image-guided hypofractionated radiotherapy (hypo-IGRT) with conventional fractionation without image-guidance (non-IGRT). Retrospective case series with historical control	IGRT - 70Gy 2Gy /26 fractions vs Non-IGRT 80Gy/40 fractions	179 patients with low and intermediate risk prostate cancer treated with IGRT vs 174 historical cohort of patients with intermediate and high risk prostate cancer treated with non-IGRT	Not specified	Acute rectal toxicity Acute urinary toxicity	<u>Acute rectal toxicity</u> Hypo-IGRT vs non-IGRT None: 58.7% vs 77.6% G1: 29.1% vs 16.1% G2: 11.2% vs 6.3% G3: 1.1% vs 0 G4: 0 vs 0 <u>Acute urinary toxicity</u> Hypo-IGRT vs non-IGRT None: 22.3% vs 36.2% G1: 33.5% vs 41.4% G2: 39.1% vs 20.7% G3: 5.0% vs 0.6% G4: 0 vs 1.1%	Authors conclude that the acute toxicity rates were low and similar in both study groups with some increase in mild acute urinary injury in the hypo-IGRT patients. Further investigation is warranted in order to exclude the bias due to non randomized character of the study and to test the hypothesis that the potentially injurious effect of hypofractionation can be counterbalanced by the reduced irradiated normal tissue volume using IGRT approach.

Appendix 3. Prioritisation of clinical research questions

1. Voting forms

a. Pancreatic cancer - Pre-operative radiation treatment

AVAILABLE DATA AND INFORMATION			
Estimated annual regional target population (all types of treatment)		78 (18% prevalence)	
Estimated cost of IGRT/IMRT treatment		€ 7 400 - 8 700 [23-30 fractions]	
Estimated cost of 3D-CRT treatment		€ 4 488 [30 fractions]	
Outcome	**Estimate 3D-CRT**	**Expected IGRT/ IMRT**	**Estimate IGRT/ IMRT (from the literature)**
Acute toxicity			
Enteritis	G2: 39% G3: 7.3%	<	No studies
Late toxicity			
Duodenal stenosis	1-2%	<	No studies
Clinical efficacy			
Cytoreduction	?	>	No studies
Downstaging	?	>	No studies
Operability	60%	>	No studies
Disease specific survival	20-25 months (median with surgery) 8-9 months (median without surgery)	>	No studies
Overall survival	20-25 months (median with surgery) 8-9 months (median without surgery)	>	No studies

VOTES	
Outcome's clinical relevance*	**Outcome's relevance in a clinical trial***
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

Prioritarisation of the clinical research question

Severity of disease:	**mortality***	☐
	morbidity*	☐
Expected clinical impact of the technology:	**mortality***	☐
	morbidity*	☐
Feasibility of a regional clinical trial (number of patients, of participating centres, resources availability, etc.)*		☐

** use the following scale to express your vote*

low			*moderate*			*high*		
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

Overall priority score for the clinical research question (please highlight)

low			moderate			high		
1	2	3	4	5	6	7	8	9

b. Pancreatic cancer - Post-operative radiation treatment

AVAILABLE DATA AND INFORMATION				VOTES	
Estimated annual regional target population (all types of treatment)		78 (18% prevalence)			
Estimated cost of IGRT/IMRT treatment		€ 7 400 - 8 700 [23-30 fractions]			
Estimated cost of 3D-CRT treatment		€ 4 488 [30 fractions]			
Outcome	**Estimate 3D-CRT**	**Expected IGRT/ IMRT**	**Clinical relevance of outcome ***	**Outcome's clinical relevance***	**Outcome's relevance in a clinical trial***
Acute toxicity					
Enteritis	G2: 60% G3-4: 15-20%	<	No studies	☐	☐
Late toxicity					
Duodenal stenosis	2-3%	<	No studies	☐	☐
Clinical efficacy					
Disease specific survival at 2 yrs	50-60% (neg. margins) 9% (pos. margins)	≥	No studies	☐	☐
Overall survival at 2 yrs	50-60% (neg. margins) 9% (pos. margins)	≥	No studies	☐	☐

Prioritarisation of the clinical research question

Severity of disease:	**mortality***	☐
	morbidity*	☐
Expected clinical impact of the technology:	**mortality***	☐
	morbidity*	☐
Feasibility of a regional clinical trial (number of patients, of participating centres, resources availability, etc.)*		☐

** use the following scale to express your vote*

low			*moderate*			*high*		
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

Overall priority score for the clinical research question (please highlight)

low			moderate			high		
1	2	3	4	5	6	7	8	9

c. Pancreatic cancer - Radio-chemotherapy treatment - Inoperable advanced disease

AVAILABLE DATA AND INFORMATION			
Estimated annual regional target population (all types of treatment)		78 (18% prevalence)	
Estimated cost of IGRT/IMRT treatment		€ 7 400 - 8 700 [23-30 fractions]	
Estimated cost of 3D-CRT treatment		€ 4 488 [30 fractions]	
Outcome	**Estimate 3D-CRT**	**Expected IGRT/ IMRT**	**Estimate IGRT/ IMRT (from the literature)**
Acute toxicity			
Enteritis	G2: 39% G3: 7.3%	<	No studies
Late toxicity			
Duodenal stenosis	1-2%	<	No studies
Clinical efficacy			
Operability	10-15%	>	No studies
Disease specific survival	20 months (median with surgery)	≥	No studies
Overall survival	20 months (median with surgery)	≥	No studies

VOTES	
Outcome's clinical relevance*	**Outcome's relevance in a clinical trial***
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

Prioritarisation of the clinical research question

Severity of disease:	**mortality***	☐
	morbidity*	☐
Expected clinical impact of the technology:	**mortality***	☐
	morbidity*	☐
Feasibility of a regional clinical trial (number of patients, of participating centres, resources availability, etc.)*		☐

** use the following scale to express your vote*

low			*moderate*			*high*		
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

Overall priority score for the clinical research question (please highlight)

low			moderate			high		
1	2	3	4	5	6	7	8	9

d. Prostate cancer - Exclusive radiant treatment - Radical intent

AVAILABLE DATA AND INFORMATION				VOTES	
Estimated annual regional target population (all types of treatment)		702 (21% incidence)			
Estimated cost of IGRT/IMRT treatment		€ 8 700 - 9 700 [28-34 fractions]			
Estimated cost of 3D-CRT treatment		€ 4 953 [35 fractions]			
Outcome	**Estimate 3D-CRT**	**Expected IGRT/ IMRT**	**Estimate IGRT/ IMRT (from the literature)**	**Outcome's clinical relevance***	**Outcome's relevance in a clinical trial***
Acute toxicity					
Gastrointestinal toxicity	15% proctitis grade >2	<	(all) Grade 0: 11-74% Grade 1: 26-64% Grade 2: 0 - 25% Grade 3 + 4: 0	☐	☐
Genitourinary toxicity	20% (cystitis)	<	(all) Grade 0: 2-26% Grade 1: 45-49% Grade 2: 38-51% Grade 3: 0-4%	☐	☐
Late toxicity					
Genitourinary toxicity	<3% (grade >2)	<	Grade 3 + 4: 0.6%	☐	☐
Gastrointestinal toxicity	<5% (grade >2)	<	Grade 3 + 4: 0	☐	☐
Erectile dysfunction	40 - 50%	<	No studies	☐	☐
Clinical efficacy					
Biochemical failure	15-20% (low risk) 35% (intermediate risk)	<	7% (low + intermediate risk)	☐	☐
Local recurrence	10-15% (low risk) 25% (intermediate risk)	<	No studies	☐	☐
Loco-regional control	80-85% (low risk) 70% (intermediate risk)	>	No studies	☐	☐
Distant metastasis	<10% (low) 30% (intermediate)	<	No studies	☐	☐
Cause specific survival at 10 yrs	80% (low risk) 65% (intermediate)	>	No studies	☐	☐

(to be continued)

Prioritarisation of the clinical research question

Severity of disease:	**mortality***	☐
	morbidity*	☐
Expected clinical impact of the technology:	**mortality***	☐
	morbidity*	☐
Feasibility of a regional clinical trial (number of patients, of participating centres, resources availability, etc.)*		☐

** use the following scale to express your vote*

low			*moderate*			*high*		
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

Overall priority score for the clinical research question (please highlight)

low			moderate			high		
1	2	3	4	5	6	7	8	9

e. Lung cancer - Exclusive radiant treatment in inoperable T1-T2 - <IIIB stages

AVAILABLE DATA AND INFORMATION				VOTES	
Estimated annual regional target population (all types of treatment)		294 (10% incidence)			
Estimated cost of IGRT/IMRT treatment		€ 9 500 - 10 000 [33 fractions]			
Estimated cost of 3D-CRT treatment		€ 5 418 [40 fractions]			
Outcome	**Estimate 3D-CRT**	**Expected IGRT/ IMRT**	**Estimate IGRT/ IMRT (from the literature)**	**Outcome's clinical relevance***	**Outcome's relevance in a clinical trial***
Acute toxicity					
Polmonitis	T1/2 G2: 10-20% T1/2 >G2: 5-28% <IIIB >G2: 25-28%	≤	(all types of acute toxicity) T1/2 + <IIIB Grade 0: 0 -45% Grade 1: 0 -50% Grade 2: 0-18% Grade 3: 0-2%	☐	☐
Esophagitis	T1/2 G3: < 30% <IIIB: 30%	≤		☐	☐
Late toxicity					
Pulmonary fibrosis	T1/2 - G2-3: <20% <IIIB >G2: 10-20%	≤	(all types of late toxicity) T1/2 + <IIIB Grade 1: 0-47% Grade 2: 0-51% Grade 3: 0-11%	☐	☐
Cardiopathies	T1/2: ? <IIIB: 5%	≤		☐	☐
Esophagus	T1/2: <2%	≤		☐	☐
Clinical efficacy					
Local control		>	29-100% (17-36 months) T1/2 + <IIIB	☐	☐
Loco-regional control	T1 80% T2 50% <IIIB 30-40%	>	85% T1/2 + <IIIB	☐	☐
Disease/ progression free time	T1/2 80% at 2 yrs (mean: 18-24 months) <IIIB 20-30% at 2 yrs (12 months)	>	45-67% 2 yrs T1/2 + <IIIB	☐	☐
Recurrence		<	4.5 - 26% (local) T1/2 + <IIIB 7.7 - 31.8% (regional) T1/2 + <IIIB	☐	☐
Quality of life	T1/2 Recovery in 3 months / good <IIIB Moderate	>	Low (T1/2 + <IIIB)	☐	☐
Distant metastasis	T1/2 15-25% <IIIB 30-50%	>	50% T1/2 + <IIIB	☐	☐
Specific survival		>	45-67% T1/2 + <IIIB	☐	☐
Overall survival	T1/2 80-90% at 2 yrs; 50% at 3 yrs <IIIB 15-30% at 2 yrs	>	37-87% (8-24 months) T1/2 + <IIIB	☐	☐

(to be continued)

Prioritarisation of the clinical research question

Severity of disease:	**mortality***	☐
	morbidity*	☐
Expected clinical impact of the technology:	**mortality***	☐
	morbidity*	☐
Feasibility of a regional clinical trial (number of patients, of participating centres, resources availability, etc.)*		☐

** use the following scale to express your vote*

low			*moderate*			*high*		
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

Overall priority score for the clinical research question (please highlight)

low			moderate			high		
1	2	3	4	5	6	7	8	9

f. Lung cancer - Pulmonary metastasis

AVAILABLE DATA AND INFORMATION				VOTES	
Estimated annual regional target population (all types of treatment)		198 (11% prevalence)			
Estimated cost of IGRT/IMRT treatment		€ 9 500 - 10 000 [33 fractions]			
Estimated cost of 3D-CRT treatment		€ 5 418 [40 fractions]			
Outcome	**Estimate 3D-CRT**	**Expected IGRT/ IMRT**	**Estimate IGRT/ IMRT (from the literature)**	**Outcome's clinical relevance***	**Outcome's relevance in a clinical trial***
Acute toxicity					
Polmonitis	negligible - < 10%	≤	(all types of acute toxicity) Grade 2: 18% Grade 3: 1.2%	☐	☐
Esophagitis	negligible - < 10%	≤		☐	☐
Late toxicity					
Pulmonary fibrosis	< 20%	<	No studies	☐	☐
Cardiopathies	?	<		☐	☐
Clinical efficacy					
Loco-regional control	80-90%	=	No studies	☐	☐
Disease/ progression free time	80% at 2 yrs (mean 18-24 months) T1/2 20-30% at 2 yrs (12 months) <IIIB	=	No studies	☐	☐
Specific survival			49%	☐	☐
Overall survival		=	16-49%	☐	☐

Prioritarisation of the clinical research question

Severity of disease:	**mortality***	☐
	morbidity*	☐
Expected clinical impact of the technology:	**mortality***	☐
	morbidity*	☐
Feasibility of a regional clinical trial (number of patients, of participating centres, resources availability, etc.)*		☐

** use the following scale to express your vote*

low			*moderate*			*high*		
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

Overall priority score for the clinical research question (please highlight)

low			moderate			high		
1	2	3	4	5	6	7	8	9

g. Head & neck cancer
Exclusive treatment or with chemotherapy

AVAILABLE DATA AND INFORMATION					
Estimated annual regional target population (all types of treatment)		168 (24% incidence)			
Estimated cost of IGRT/IMRT treatment		€ 9 300 - 9 900 [30-35 fractions]			
Estimated cost of 3D-CRT treatment		€ 5 232 [38 fractions]			
Outcome	**Estimate 3D-CRT**	**Expected IGRT/ IMRT**	**Estimate IGRT/ IMRT (from the literature)**	**Outcome's clinical relevance***	**Outcome's relevance in a clinical trial***
Acute toxicity					
Mucosytis	Nasopharynx: G3: 30%; G4: <2% Oropharynx G3: 40-45%	<	G2: 45%; G.3: 51%	☐	☐
Pharyngitis disphagia	Nasopharynx G3: 30% Oropharynx G3: 35-40%	<	No studies	☐	☐
Cervical-esophagus stenosis	G3: 6-10%	<	No studies	☐	☐
Mandible necrosis	G3: 1-2%		No studies	☐	☐
Gastrostomia feeding	4-5%		No studies	☐	☐
Spinal cord damages	0%		No studies	☐	☐
Cranial Nerve deficit	0%:		No studies	☐	☐
Vomiting			G1: 20%; G2:10%; G3: 65%	☐	☐
Skin reaction			G2: 55%; G3: 40%	☐	☐
Liver function			G1: 45%; G2: 25%	☐	☐
Leukopenia			G1: 30%; G2: 25%; G3: 35%; G4: 10%	☐	☐
Anemia			G1: 50%; G2: 25%; G3: 10%; G4: 5%	☐	☐
Thrombocytopenia			G1: 40%; G2: 10%; G3: 5%	☐	☐
Renal function			G1: 30%	☐	☐

(to be continued)

Late toxicity					
Xerostomy	G2: <40% G3: <20% Nasopharynx G2: 21% G3: 11%	<	G1: 66.7%; G2: 26.7%	☐	☐
Disphagy	Nasopharynx G4: 2% Oropharynx G3: 2% G4: 1%	<	No studies	☐	☐
Esophagus	T1/2: <2%	≤	No studies	☐	☐
Clinical efficacy					
Local control	Nasopharynx: 91-97% at 3 yrs	>	100% at 10 months	☐	☐
Recurrence		<	10%	☐	☐
Loco-regional control	Overall 50-70% Nasopharynx: 93% at 3 yrs Oropharynx: 76-86% at 2 yrs	>	No studies	☐	☐
Disease/progression free time	30-40% at 5 yrs	>	79.7% at 10 months	☐	☐
Overall survival	Nasopharynx: 83-92% at 3 yrs Oropharynx: 63-80% at 2 yrs 50% at 5 yrs	>	95% at 10 months	☐	☐

Prioritarisation of the clinical research question

Severity of disease:	**mortality***	☐
	morbidity*	☐
Expected clinical impact of the technology:	**mortality***	☐
	morbidity*	☐
Feasibility of a regional clinical trial (number of patients, of participating centres, resources availability, etc.)*		☐

** use the following scale to express your vote*

low			*moderate*			*high*		
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

Overall priority score for the clinical research question (please highlight)

low			moderate			high		
1	2	3	4	5	6	7	8	9

h. Brain cancer - Brain metastasis treatment

AVAILABLE DATA AND INFORMATION				VOTES	
Estimated annual regional target population (all types of treatment)		73 (23% incidence)			
Estimated cost of IGRT/IMRT treatment		€ 8 700 - 9 300 [30 fractions]			
Estimated cost of 3D-CRT treatment		€ 5 232 [38 fractions]			
Outcome	**Estimate 3D-CRT**	**Expected IGRT/IMRT**	**Estimate IGRT/IMRT (from the literature)**	**Outcome's clinical relevance***	**Outcome's relevance in a clinical trial***
Acute toxicity					
Non specified acute toxicity		**<**	8.7 - 26%	☐	☐
Late toxicity					
Not available				☐	☐
Clinical efficacy					
Local control		**>**	33% complete 59% partial 7% stable disease	☐	☐
Symptoms control		**>**	77%	☐	☐
Loco-regional control				☐	☐
Quality of life				☐	☐
Recurrence		**=**	70%	☐	☐
Specific survival		**=**	22% at 1 year	☐	☐
Overall survival			51% (median, 4-6 months)	☐	☐

Prioritarisation of the clinical research question

Severity of disease:	**mortality***	☐
	morbidity*	☐
Expected clinical impact of the technology:	**mortality***	☐
	morbidity*	☐
Feasibility of a regional clinical trial (number of patients, of participating centres, resources availability, etc.)*		☐

(to be continued)

** use the following scale to express your vote*

low			*moderate*			*high*		
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

Overall priority score for the clinical research question (please highlight)

low			moderate			high		
1	2	3	4	5	6	7	8	9

i. Brain - Primitive intra- and extra-assial tumours

AVAILABLE DATA AND INFORMATION					
Estimated annual regional target population (all types of treatment)		Not available			
Estimated cost of IGRT/IMRT treatment		€ 8 700 - 9 300 [30 fractions]			
Estimated cost of 3D-CRT treatment		€ 5 232 [38 fractions]			
Outcome	**Estimate 3D-CRT**	**Expected IGRT/ IMRT**	**Estimate IGRT/ IMRT (from the literature)**	**VOTES**	
				Outcome's clinical relevance*	**Outcome's relevance in a clinical trial***
Acute toxicity					
	Not available		No studies	☐	☐
Late toxicity					
	Not available		No studies	☐	☐
Clinical efficacy					
Local control	Not available		No studies	☐	☐
Symptoms control	Not available		No studies	☐	☐
Loco-regional control	Not available		No studies	☐	☐
Quality of life	Not available		No studies	☐	☐
Recurrence	Not available		No studies	☐	☐
Specific survival	Not available		No studies	☐	☐
Overall survival	Not available		No studies	☐	☐

Prioritarisation of the clinical research question

Severity of disease:	**mortality***	☐
	morbidity*	☐
Expected clinical impact of the technology:	**mortality***	☐
	morbidity*	☐
Feasibility of a regional clinical trial (number of patients, of participating centres, resources availability, etc.)*		☐

** use the following scale to express your vote*

low			*moderate*			*high*		
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

Overall priority score for the clinical research question (please highlight)

low			moderate			high		
1	2	3	4	5	6	7	8	9

2. Results - relevance of clinical outcomes

Prostate primary cancer

Ranking	Clinical outcomes	Research relevance			Clinical relevance		
		median	min	max	median	min	max
1	Survival specific	8	4	9	7	4	9
2	Local control	7	4	9	7	5	9
2	Recurrence	7	4	9	7	5	9
2	Biochemical recurrence	7	4	9	7	5	9
2	Late genito-urinary toxicity	7	2	9	7	3	9
2	Late gastrointestinal toxicity	7	2	9	6.5	3	9
2	Acute genito-urinary toxicity	7	2	8	6	2	8
2	Acute gastrointestinal toxicity	7	2	9	6	2	9
2	Sexual problems	7	2	8	6	3	9
2	Metastasis	7	2	8	6	2	8

Lung primary cancer

Ranking	Clinical outcomes	Research relevance			Clinical relevance		
		median	min	max	median	min	max
1	Local control	8	6	9	7	5	9
1	Loco-regional control	8	2	9	7	5	9
2	Disease free time	7.5	5	9	7.5	5	9
3	Polmonitis	7	3	8	7	5	9
3	Esophagitis	7	3	9	7	4	9
3	Lung fibrosis	7	3	8	7	4	8
3	Recurrence	7	5	9	7	5	9
3	Quality of life	7	5	9	7	5	9
3	Disease specific survival	7	4	9	6	3	9
3	Overall survival	7	4	9	6	3	9
4	Cardiopathies	6	1	8	6	2	8
4	Late problems esophagus	6	1	8	6	2	8
4	Metastasis	6	3	8	6	3	8

Lung metastases

Ranking	Clinical outcomes	Research relevance			Clinical relevance		
		median	min	max	median	min	max
1	Loco-regional control	6.5	1	8	7	3	8
2	Free time	6	1	7	6	3	7
2	Lung fibrosis	6	1	8	5	2	8
3	Esophagitis	5	1	9	5	2	7
4	Polmonitis	4	1	8	5	2	7
4	Disease specific survival	4	3	8	5	3	7
4	Overall survival	4	3	8	5	3	8
4	Cardiopathies	4	1	7	3	1	8

Head & neck cancer

Ranking	Clinical outcomes	Research relevance			Clinical relevance		
		median	min	max	median	min	max
1	Xerostomy	8	2	9	8	5	9
2	Local control	7.5	2	9	8	5	9
2	Recurrence	7.5	3	9	8	5	9
2	Free time	7.5	3	9	8	5	9
2	Dysfagia	7.5	2	9	7.5	5	9
2	Overall survival	7.5	3	9	7	6	9
3	Loco-regional control	7	3	9	7.5	4	9
3	Stenosis	7	2	8	7	3	8
4	Mucositis	6.5	3	9	8	6	8
4	Faringitis	6.5	3	9	8	6	9
5	Mandible necrosis	6	1	8	7	3	8
5	Problems at the esophagus	6	1	8	7	3	9
5	Gastrostomia feeding	6	1	7	6	3	8
5	Skin rash	6	1	8	6	3	8
6	Leukopenia	4.5	1	7	5	2	7
6	Renal function	4.5	1	7	5	2	7
6	Hepatic function	4.5	1	7	4.5	2	7
7	Vomit	4	1	7	5	2	8
7	Anemia	4	1	7	4.5	1	7
7	Trombocytopenia	4	1	7	4.5	2	7
8	Marrow damage	3.5	1	8	4	1	9
9	Cranial nerve deficit	3	1	8	4	1	8

Pre-operative treatment for pancreas cancer

Ranking	Clinical outcomes	Research relevance			Clinical relevance		
		median	min	max	median	min	max
1	Downstaging	6.5	3	9	6	5	8
1	Cytoreduction	6.5	3	9	5.5	3	8
2	Operability	6	1	9	7	5	9
2	Enteritis	6	1	7	6	4	8
3	Disease specific survival	5.5	1	8	7	4	8
3	Overall survival	5.5	1	9	7	4	8
4	Stenosis	3	1	8	7	3	9

Pancreas post-operative cancer

Ranking	Clinical outcomes	Research relevance			Clinical relevance		
		median	min	max	median	min	max
1	Enteritis	4.5	1	8	7	3	8
2	Disease specific survival	4	1	8	7	3	8
2	Overall survival	4	1	8	7	3	8
3	Stenosis	3	1	9	7	3	9

Advanced pancreas cancer

Ranking	Clinical outcomes	Research relevance			Clinical relevance		
		median	min	max	median	min	max
1	Overall survival	6.5	1	8	7	3	8
1	Disease specific survival	6.5	1	8	7	3	8
2	Enteritis	5	1	8	6.5	3	8
2	Operability	5	1	9	5.5	3	8
3	Stenosis	3	1	8	6.5	3	9

Brain primary cancer

Ranking	Clinical outcomes	Research relevance			Clinical relevance		
		median	min	max	median	min	max
1	Recurrence	7	2	7	7	2	7
1	Disease specific survival	7	2	8	7	2	8
1	Overall survival	7	3	8	7	2	9
2	Local control	6	2	8	7	2	7
2	Symptoms control	6	2	8	7	2	7
2	Chronic toxicity	6	2	7	6.5	2	8
2	Acute toxicity	6	2	7	6	2	7
2	Quality of life	6	3	7	6	2	8
3	Loco-regional control	5	2	8	6.5	2	8

Brain metastases

Ranking	Clinical outcomes	Research relevance			Clinical relevance		
		median	min	max	median	min	max
1	Quality of life	7	2	7	7	4	8
2	Symptoms control	6	1	8	7	4	8
2	Recurrence	6	1	8	6	1	8
3	Loco-regional control	5	1	8	8	3	7
3	Local control	5	1	7	7	4	7
4	Acute toxicity	4	1	7	5	1	7
4	Disease specific survival	4	3	8	4	3	8
4	Chronic toxicity	4	1	7	4	1	7
5	Overall survival	3	3	8	4	3	8

COLLANA DOSSIER

a cura dell'Agenzia sanitaria e sociale regionale

1990

1. Centrale a carbone "Rete 2": valutazione dei rischi. Bologna. **(*)**
2. Igiene e medicina del lavoro: componente della assistenza sanitaria di base. Servizi di igiene e medicina del lavoro. (Traduzione di rapporti OMS). Bologna. **(*)**
3. Il rumore nella ceramica: prevenzione e bonifica. Bologna. **(*)**
4. Catalogo collettivo dei periodici per la prevenzione. I edizione - 1990. Bologna. **(*)**
5. Catalogo delle biblioteche SEDI - CID - CEDOC e Servizio documentazione e informazione dell'ISPESL. Bologna. **(*)**

1991

6. Lavoratori immigrati e attività dei servizi di medicina preventiva e igiene del lavoro. Bologna. **(*)**
7. Radioattività naturale nelle abitazioni. Bologna. **(*)**
8. Educazione alimentare e tutela del consumatore "Seminario regionale Bologna 1-2 marzo 1990". Bologna. **(*)**

1992

9. Guida alle banche dati per la prevenzione. Bologna.
10. Metodologia, strumenti e protocolli operativi del piano dipartimentale di prevenzione nel comparto rivestimenti superficiali e affini della provincia di Bologna. Bologna. **(*)**
11. I Coordinamenti dei Servizi per l'Educazione sanitaria (CSES): funzioni, risorse e problemi. Sintesi di un'indagine svolta nell'ambito dei programmi di ricerca sanitaria finalizzata (1989 - 1990). Bologna. **(*)**
12. Epi Info versione 5. Un programma di elaborazione testi, archiviazione dati e analisi statistica per praticare l'epidemiologia su personal computer. Programma (dischetto A). Manuale d'uso (dischetto B). Manuale introduttivo. Bologna.
13. Catalogo collettivo dei periodici per la prevenzione in Emilia-Romagna. 2ª edizione. Bologna. **(*)**

1993

14. Amianto 1986-1993. Legislazione, rassegna bibliografica, studi italiani di mortalità, proposte operative. Bologna. **(*)**
15. Rischi ambientali, alimentari e occupazionali, Attività di prevenzione e controllo nelle USL dell'Emilia-Romagna. 1991. Bologna. **(*)**
16. La valutazione della qualità nei Servizi di igiene pubblica delle USL dell'Emilia-Romagna, 1991. Bologna. **(*)**
17. Metodi analitici per lo studio delle matrici alimentari. Bologna. **(*)**

1994

18. Venti anni di cultura per la prevenzione. Bologna.
19. La valutazione della qualità nei Servizi di igiene pubblica dell'Emilia-Romagna 1992. Bologna. **(*)**
20. Rischi ambientali, alimentari e occupazionali, Attività di prevenzione e controllo nelle USL dell'Emilia-Romagna. 1992. Bologna. **(*)**
21. Atlante regionale degli infortuni sul lavoro. 1986-1991. 2 volumi. Bologna. **(*)**

(*) volumi disponibili presso l'Agenzia sanitaria e sociale regionale. Sono anche scaricabili dal sito http://asr.regione.emilia-romagna.it/wcm/asr/collana_dossier/archivio_dossier_1.htm

22. Atlante degli infortuni sul lavoro del distretto di Ravenna. 1989-1992. Ravenna. **(*)**

23. 5ª Conferenza europea sui rischi professionali. Riccione, 7-9 ottobre 1994. Bologna.

1995

24. La valutazione della qualità nei Servizi di igiene pubblica dell'Emilia-Romagna 1993. Bologna. **(*)**

25. Rischi ambientali, alimentari e occupazionali, Attività di prevenzione e controllo nelle USL dell'Emilia-Romagna. 1993. Bologna. **(*)**

1996

26. La valutazione della qualità nei Servizi di igiene pubblica dell'Emilia-Romagna. Sintesi del triennio 1992-1994. Dati relativi al 1994. Bologna. **(*)**

27. Lavoro e salute. Atti della 5a Conferenza europea sui rischi professionali. Riccione, 7-9 ottobre 1994. Bologna. **(*)**

28. Gli scavi in sotterraneo. Analisi dei rischi e normativa in materia di sicurezza. Ravenna. **(*)**

1997

29. La radioattività ambientale nel nuovo assetto istituzionale. Convegno Nazionale AIRP. Ravenna. **(*)**

30. Metodi microbiologici per lo studio delle matrici alimentari. Ravenna. **(*)**

31. Valutazione della qualità dello screening del carcinoma della cervice uterina. Ravenna. **(*)**

32. Valutazione della qualità dello screening mammografico del carcinoma della mammella. Ravenna. **(*)**

33. Processi comunicativi negli screening del tumore del collo dell'utero e della mammella (parte generale). Proposta di linee guida. Ravenna. **(*)**

34. EPI INFO versione 6. Ravenna. **(*)**

1998

35. Come rispondere alle 100 domande più frequenti negli screening del tumore del collo dell'utero. Vademecum per gli operatori di front-office. Ravenna.

36. Come rispondere alle 100 domande più frequenti negli screening del tumore della mammella. Vademecum per gli operatori di front-office. Ravenna. **(*)**

37. Centri di Produzione Pasti. Guida per l'applicazione del sistema HACCP. Ravenna. **(*)**

38. La comunicazione e l'educazione per la prevenzione dell'AIDS. Ravenna. **(*)**

39. Rapporti tecnici della Task Force D.Lgs 626/94 - 1995-1997. Ravenna. **(*)**

1999

40. Progetti di educazione alla salute nelle Aziende sanitarie dell'Emilia Romagna. Catalogo 1995 - 1997. Ravenna. **(*)**

2000

41. Manuale di gestione e codifica delle cause di morte, Ravenna.

42. Rapporti tecnici della Task Force D.Lgs 626/94 - 1998-1999. Ravenna. **(*)**

43. Comparto ceramiche: profilo dei rischi e interventi di prevenzione. Ravenna. **(*)**

44. L'Osservatorio per le dermatiti professionali della provincia di Bologna. Ravenna. **(*)**

45. SIDRIA Studi Italiani sui Disturbi Respiratori nell'Infanzia e l'Ambiente. Ravenna. **(*)**

46. Neoplasie. Rapporto tecnico per la definizione di obiettivi e strategie per la salute. Ravenna.

2001

47. Salute mentale. Rapporto tecnico per la definizione di obiettivi e strategie per la salute. Ravenna.

48. Infortuni e sicurezza sul lavoro. Rapporto tecnico per la definizione di obiettivi e strategie per la salute. Ravenna. **(*)**

49. Salute Donna. Rapporto tecnico per la definizione di obiettivi e strategie per la salute. Ravenna.

50. Primo report semestrale sull'attività di monitoraggio sull'applicazione del D.Lgs 626/94 in Emilia-Romagna. Ravenna. **(*)**

51. Alimentazione. Rapporto tecnico per la definizione di obiettivi e strategie per la salute. Ravenna. **(*)**

52. Dipendenze patologiche. Rapporto tecnico per la definizione di obiettivi e strategie per la salute. Ravenna.

53. Anziani. Rapporto tecnico per la definizione di obiettivi e strategie per la salute. Ravenna. **(*)**

54. La comunicazione con i cittadini per la salute. Rapporto tecnico per la definizione di obiettivi e strategie per la salute. Ravenna. **(*)**

55. Infezioni ospedaliere. Rapporto tecnico per la definizione di obiettivi e strategie per la salute. Ravenna. **(*)**

56. La promozione della salute nell'infanzia e nell'età evolutiva. Rapporto tecnico per la definizione di obiettivi e strategie per la salute. Ravenna. **(*)**

57. Esclusione sociale. Rapporto tecnico per la definizione di obiettivi e strategie per la salute. Ravenna.

58. Incidenti stradali. Proposta di Patto per la sicurezza stradale. Rapporto tecnico per la definizione di obiettivi e strategie per la salute. Ravenna. **(*)**

59. Malattie respiratorie. Rapporto tecnico per la definizione di obiettivi e strategie per la salute. Ravenna. **(*)**

2002

60. AGREE. Uno strumento per la valutazione della qualità delle linee guida cliniche. Bologna.

61. Prevalenza delle lesioni da decubito. Uno studio della Regione Emilia-Romagna. Bologna.

62. Assistenza ai pazienti con tubercolosi polmonare nati all'estero. Risultati di uno studio caso-controllo in Emilia-Romagna. Bologna. **(*)**

63. Infezioni ospedaliere in ambito chirurgico. Studio multicentrico nelle strutture sanitarie dell'Emilia-Romagna. Bologna. **(*)**

64. Indicazioni per l'uso appropriato della chirurgia della cataratta. Bologna. **(*)**

65. Percezione della qualità e del risultato delle cure. Riflessione sugli approcci, i metodi e gli strumenti. Bologna. **(*)**

66. Le Carte di controllo. Strumenti per il governo clinico. Bologna. **(*)**

67. Catalogo dei periodici. Archivio storico 1970-2001. Bologna.

68. Thesaurus per la prevenzione. 2a edizione. Bologna. **(*)**

69. Materiali documentari per l'educazione alla salute. Archivio storico 1970-2000. Bologna. **(*)**

70. I Servizi socio-assistenziali come area di policy. Note per la programmazione sociale regionale. Bologna. **(*)**

71. Farmaci antimicrobici in età pediatrica. Consumi in Emilia-Romagna. Bologna. **(*)**

72. Linee guida per la chemioprofilassi antibiotica in chirurgia. Indagine conoscitiva in Emilia-Romagna. Bologna. **(*)**

73. Liste di attesa per la chirurgia della cataratta: elaborazione di uno score clinico di priorità. Bologna. **(*)**

74. Diagnostica per immagini. Linee guida per la richiesta. Bologna. **(*)**

75. FMEA-FMECA. Analisi dei modi di errore/guasto e dei loro effetti nelle organizzazioni sanitarie. Sussidi per la gestione del rischio 1. Bologna.

2003

76. Infezioni e lesioni da decubito nelle strutture di assistenza per anziani. Studio di prevalenza in tre Aziende USL dell'Emilia-Romagna. Bologna. **(*)**

77. Linee guida per la gestione dei rifiuti prodotti nelle Aziende sanitarie dell'Emilia-Romagna. Bologna. **(*)**

78. Fattibilità di un sistema di sorveglianza dell'antibioticoresistenza basato sui laboratori. Indagine conoscitiva in Emilia-Romagna. Bologna. **(*)**

79. Valutazione dell'appropriatezza delle indicazioni cliniche di utilizzo di MOC ed eco-color-Doppler e impatto sui tempi di attesa. Bologna. **(*)**

80. Promozione dell'attività fisica e sportiva. Bologna. **(*)**

81. Indicazioni all'utilizzo della tomografia ad emissione di positroni (FDG - PET) in oncologia. Bologna. **(*)**

82. Applicazione del DLgs 626/94 in Emilia-Romagna. Report finale sull'attività di monitoraggio. Bologna. **(*)**

83. Organizzazione aziendale della sicurezza e prevenzione. Guida per l'autovalutazione. Bologna.

84. I lavori di Francesca Repetto. Bologna, 2003. **(*)**

85. Servizi sanitari e cittadini: segnali e messaggi. Bologna. **(*)**

86. Il sistema di incident reporting nelle organizzazioni sanitarie. Sussidi per la gestione del rischio 2. Bologna.

87. I Distretti nella Regione Emilia-Romagna. Bologna. **(*)**

88. Misurare la qualità: il questionario. Sussidi per l'autovalutazione e l'accreditamento. Bologna. **(*)**

2004

89. Promozione della salute per i disturbi del comportamento alimentare. Bologna. **(*)**

90. La gestione del paziente con tubercolosi: il punto di vista dei professionisti. Bologna. **(*)**

91. Stent a rilascio di farmaco per gli interventi di angioplastica coronarica. Impatto clinico ed economico. Bologna. **(*)**

92. Educazione continua in medicina in Emilia-Romagna. Rapporto 2003. Bologna. **(*)**

93. Le liste di attesa dal punto di vista del cittadino. Bologna. **(*)**

94. Raccomandazioni per la prevenzione delle lesioni da decubito. Bologna. **(*)**

95. Prevenzione delle infezioni e delle lesioni da decubito. Azioni di miglioramento nelle strutture residenziali per anziani. Bologna. **(*)**

96. Il lavoro a tempo parziale nel Sistema sanitario dell'Emilia-Romagna. Bologna. **(*)**

97. Il sistema qualità per l'accreditamento istituzionale in Emilia-Romagna. Sussidi per l'autovalutazione e l'accreditamento. Bologna.

98. La tubercolosi in Emilia-Romagna. 1992-2002. Bologna. **(*)**

99. La sorveglianza per la sicurezza alimentare in Emilia-Romagna nel 2002. Bologna. **(*)**

100. Dinamiche del personale infermieristico in Emilia-Romagna. Permanenza in servizio e mobilità in uscita. Bologna. **(*)**

101. Rapporto sulla specialistica ambulatoriale 2002 in Emilia-Romagna. Bologna. **(*)**

102. Antibiotici sistemici in età pediatrica. Prescrizioni in Emilia-Romagna 2000-2002. Bologna. **(*)**

103. Assistenza alle persone affette da disturbi dello spettro autistico. Bologna.

104. Sorveglianza e controllo delle infezioni ospedaliere in terapia intensiva. Indagine conoscitiva in Emilia-Romagna. Bologna. **(*)**

2005

105. SapereAscoltare. Il valore del dialogo con i cittadini. Bologna.

106. La sostenibilità del lavoro di cura. Famiglie e anziani non autosufficienti in Emilia-Romagna. Sintesi del progetto. Bologna. **(*)**

107. Il bilancio di missione per il governo della sanità dell'Emilia-Romagna. Bologna. **(*)**

108. Contrastare gli effetti negativi sulla salute di disuguaglianze sociali, economiche o culturali. Premio Alessandro Martignani - III edizione. Catalogo. Bologna.

109. Rischio e sicurezza in sanità. Atti del convegno Bologna, 29 novembre 2004. Sussidi per la gestione del rischio 3. Bologna.

110. Domanda di care domiciliare e donne migranti. Indagine sul fenomeno delle badanti in Emilia-Romagna. Bologna.

111. Le disuguaglianze in ambito sanitario. Quadro normativo ed esperienze europee. Bologna.

112. La tubercolosi in Emilia-Romagna. 2003. Bologna. **(*)**

113. Educazione continua in medicina in Emilia-Romagna. Rapporto 2004. Bologna. **(*)**

114. Le segnalazioni dei cittadini agli URP delle Aziende sanitarie. Report regionale 2004. Bologna. **(*)**

115. Proba Progetto Bambini e antibiotici. I determinanti della prescrizione nelle infezioni delle alte vie respiratorie. Bologna. **(*)**

116. Audit delle misure di controllo delle infezioni post-operatorie in Emilia-Romagna. Bologna. **(*)**

2006

117. Dalla Pediatria di comunità all'Unità pediatrica di Distretto. Bologna. **(*)**

118. Linee guida per l'accesso alle prestazioni di eco-color doppler: impatto sulle liste di attesa. Bologna. **(*)**

119. Prescrizioni pediatriche di antibiotici sistemici nel 2003. Confronto in base alla tipologia di medico curante e medico prescrittore. Bologna. **(*)**

120. Tecnologie informatizzate per la sicurezza nell'uso dei farmaci. Sussidi per la gestione del rischio 4. Bologna.

121. Tomografia computerizzata multistrato per la diagnostica della patologia coronarica. Revisione sistematica della letteratura. Bologna. **(*)**

122. Tecnologie per la sicurezza nell'uso del sangue. Sussidi per la gestione del rischio 5. Bologna. **(*)**

123. Epidemie di infezioni correlate all'assistenza sanitaria. Sorveglianza e controllo. Bologna.

124. Indicazioni per l'uso appropriato della FDG-PET in oncologia. Sintesi. Bologna. **(*)**

125. Il clima organizzativo nelle Aziende sanitarie - ICONAS. Cittadini, Comunità e Servizio sanitario regionale. Metodi e strumenti. Bologna. **(*)**

126. Neuropsichiatria infantile e Pediatria. Il progetto regionale per i primi anni di vita. Bologna. **(*)**

127. La qualità percepita in Emilia-Romagna. Strategie, metodi e strumenti per la valutazione dei servizi. Bologna. **(*)**

128. La guida DISCERNere. Valutare la qualità dell'informazione in ambito sanitario. Bologna. **(*)**

129. Qualità in genetica per una genetica di qualità. Atti del convegno Ferrara, 15 settembre 2005. Bologna. **(*)**

130. La root cause analysis per l'analisi del rischio nelle strutture sanitarie. Sussidi per la gestione del rischio 6. Bologna.

131. La nascita pre-termine in Emilia-Romagna. Rapporto 2004. Bologna. **(*)**

132. Atlante dell'appropriatezza organizzativa. I ricoveri ospedalieri in Emilia-Romagna. Bologna. **(*)**

133. Reprocessing degli endoscopi. Indicazioni operative. Bologna. **(*)**

134. Reprocessing degli endoscopi. Eliminazione dei prodotti di scarto. Bologna. **(*)**

135. Sistemi di identificazione automatica. Applicazioni sanitarie. Sussidi per la gestione del rischio 7. Bologna. **(*)**

136. Uso degli antimicrobici negli animali da produzione. Limiti delle ricette veterinarie per attività di farmacosorveglianza. Bologna. **(*)**

137. Il profilo assistenziale del neonato sano. Bologna. **(*)**

138. Sana o salva? Adesione e non adesione ai programmi di screening femminili in Emilia-Romagna. Bologna. **(*)**

139. La cooperazione internazionale negli Enti locali e nelle Aziende sanitarie. Premio Alessandro Martignani - IV edizione. Catalogo. Bologna.

140. Sistema regionale dell'Emilia-Romagna per la sorveglianza dell'antibioticoresistenza. 2003-2005. Bologna. **(*)**

2007

141. Accreditamento e governo clinico. Esperienze a confronto. Atti del convegno Reggio Emilia, 15 febbraio 2006. Bologna. **(*)**

142. Le segnalazioni dei cittadini agli URP delle Aziende sanitarie. Report regionale 2005. Bologna. **(*)**

143. Progetto LaSER. Lotta alla sepsi in Emilia-Romagna. Razionale, obiettivi, metodi e strumenti. Bologna. **(*)**

144. La ricerca nelle Aziende del Servizio sanitario dell'Emilia-Romagna. Risultati del primo censimento. Bologna. **(*)**

145. Disuguaglianze in cifre. Potenzialità delle banche dati sanitarie. Bologna. **(*)**

146. Gestione del rischio in Emilia-Romagna 1999-2007. Sussidi per la gestione del rischio 8. Bologna. **(*)**

147. Accesso per priorità in chirurgia ortopedica. Elaborazione e validazione di uno strumento. Bologna. **(*)**

148. I Bilanci di missione 2005 delle Aziende USL dell'Emilia-Romagna. Bologna. **(*)**

149. E-learning in sanità. Bologna. **(*)**

150. Educazione continua in medicina in Emilia-Romagna. Rapporto 2002-2006. Bologna. **(*)**

151. "Devo aspettare qui?" Studio etnografico delle traiettorie di accesso ai servizi sanitari a Bologna. Bologna. **(*)**

152. L'abbandono nei Corsi di laurea in infermieristica in Emilia-Romagna: una non scelta? Bologna. **(*)**

153. Faringotonsillite in età pediatrica. Linea guida regionale. Bologna. **(*)**

154. Otite media acuta in età pediatrica. Linea guida regionale. Bologna. **(*)**

155. La formazione e la comunicazione nell'assistenza allo stroke. Bologna. **(*)**

156. Atlante della mortalità in Emilia-Romagna 1998-2004. Bologna. **(*)**

157. FDG-PET in oncologia. Criteri per un uso appropriato. Bologna. **(*)**

158. Mediare i conflitti in sanità. L'approccio dell'Emilia-Romagna. Sussidi per la gestione del rischio 9. Bologna. **(*)**

159. L'audit per il controllo degli operatori del settore alimentare. Indicazioni per l'uso in Emilia-Romagna. Bologna. **(*)**

160. Politiche e piani d'azione per la salute mentale dell'infanzia e dell'adolescenza. Bologna. **(*)**

2008

161. Sorveglianza dell'antibioticoresistenza e uso di antibiotici sistemici in Emilia-Romagna. Rapporto 2006. Bologna. **(*)**

162. Tomografia computerizzata multistrato per la diagnostica della patologia coronarica. Revisione sistematica della letteratura e indicazioni d'uso appropriato. Bologna. **(*)**

163. Le Aziende USL dell'Emilia-Romagna. Una lettura di sintesi dei Bilanci di missione 2005 e 2006. Bologna. **(*)**

164. La rappresentazione del capitale intellettuale nelle organizzazioni sanitarie. Bologna. **(*)**

165. L'accreditamento istituzionale in Emilia-Romagna. Studio pilota sull'impatto del processo di accreditamento presso l'Azienda USL di Ferrara. Bologna. **(*)**

166. Assistenza all'ictus. Modelli organizzativi regionali. Bologna. **(*)**

167. La chirurgia robotica: il robot da Vinci. ORIentamenti 1. Bologna. **(*)**

168. Educazione continua in medicina in Emilia-Romagna. Rapporto 2007. Bologna. **(*)**

169. Le opinioni dei professionisti della sanità sulla formazione continua. Bologna. **(*)**

170. Per un Osservatorio nazionale sulla qualità dell'Educazione continua in medicina. Bologna. **(*)**

171. Le segnalazioni dei cittadini agli URP delle Aziende sanitarie. Report regionale 2007. Bologna. **(*)**

2009

172. La produzione di raccomandazioni cliniche con il metodo GRADE. L'esperienza sui farmaci oncologici. Bologna. **(*)**

173. Sorveglianza dell'antibioticoresistenza e uso di antibiotici sistemici in Emilia-Romagna. Rapporto 2007. Bologna. **(*)**

174. I tutor per la formazione nel Servizio sanitario regionale dell'Emilia-Romagna. Rapporto preliminare. Bologna. **(*)**

175. Percorso nascita e qualità percepita. Analisi bibliografica. Bologna. **(*)**

176. Utilizzo di farmaci antibatterici e antimicotici in ambito ospedaliero in Emilia-Romagna. Rapporto 2007. Bologna. **(*)**

177. Ricerca e innovazione tecnologica in sanità. Opportunità e problemi delle forme di collaborazione tra Aziende sanitarie e imprenditoria biomedicale. Bologna. **(*)**

178. Profili di assistenza degli ospiti delle strutture residenziali per anziani. La sperimentazione del Sistema RUG III in Emilia-Romagna. Bologna. **(*)**

179. Profili di assistenza e costi del diabete in Emilia-Romagna. Analisi empirica attraverso dati amministrativi (2005 - 2007). Bologna. **(*)**

180. La sperimentazione dell'audit civico in Emilia-Romagna: riflessioni e prospettive. Bologna. **(*)**

181. Le segnalazioni dei cittadini agli URP delle Aziende sanitarie. Report regionale 2008. Bologna. **(*)**

182. La ricerca come attività istituzionale del Servizio sanitario regionale. Principi generali e indirizzi operativi per le Aziende sanitarie dell'Emilia-Romagna. Bologna. **(*)**

183. I Comitati etici locali in Emilia-Romagna. Bologna. **(*)**

184. Il Programma di ricerca Regione-Università. 2007-2009. Bologna. **(*)**

185. Il Programma Ricerca e innovazione (PRI E-R) dell'Emilia-Romagna. Report delle attività 2005-2008. Bologna. **(*)**

186. Le medicine non convenzionali e il Servizio sanitario dell'Emilia-Romagna. Un approccio sperimentale. Bologna. **(*)**

187. Studi per l'integrazione delle medicine non convenzionali. 2006-2008. Bologna. **(*)**

2010

188. Misure di prevenzione e controllo di infezioni e lesioni da pressione. Risultati di un progetto di miglioramento nelle strutture residenziali per anziani. Bologna. **(*)**

189. "Cure pulite sono cure più sicure" - Rapporto finale della campagna nazionale OMS. Bologna. **(*)**

190. Infezioni delle vie urinarie nell'adulto. Linea guida regionale. Bologna. **(*)**

191. I contratti di servizio tra Enti locali e ASP in Emilia-Romagna. Linee guida per il governo dei rapporti di committenza. Bologna. **(*)**

192. La *governance* delle politiche per la salute e il benessere sociale in Emilia-Romagna. Opportunità per lo sviluppo e il miglioramento. Bologna. **(*)**

193. Il *mobbing* tra istanze individuali e di gruppo. Analisi di un'organizzazione aziendale attraverso la tecnica del *focus group*. Bologna. **(*)**

194. Linee di indirizzo per trattare il dolore in area medica. Bologna. **(*)**

195. Indagine sul dolore negli ospedali e negli *hospice* dell'Emilia-Romagna. Bologna. **(*)**

196. Evoluzione delle Unità di terapia intensiva coronarica in Emilia-Romagna. Analisi empirica dopo implementazione della rete cardiologica per l'infarto miocardico acuto. Bologna. **(*)**

197. TB FLAG BAG. La borsa degli strumenti per l'assistenza di base ai pazienti con tubercolosi. Percorso formativo per MMG e PLS. Bologna. **(*)**

198. La ricerca sociale e socio-sanitaria a livello locale in Emilia-Romagna. Primo censimento. Bologna. **(*)**

199. Innovative radiation treatment in cancer: IGRT/IMRT. Health Technology Assessment. ORIentamenti 2. Bologna. **(*)**