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Image-guided intensity-modulated radiotherapy

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ASERNIP-S

Australian Safety and Efficacy Register of New Interventional Procedures - Surgical

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Executive Summary

Techniques in radiation therapy for the treatment of tumours are undergoing continual refinement. In conventional radiation therapy, a margin of extra tissue around the tumour is irradiated to therapeutic levels, to ensure that the target tumour receives the full dose of radiation. This leads to a higher volume of normal tissue being irradiated, which can cause increased toxicity and can limit the amount of radiation that can be safely delivered. Conversely, insufficient margins during radiation therapy may lead to areas of the tumour not receiving the full dose, due to organ motion or patient positioning errors.

Intensity-modulated radiotherapy aims to improve the accuracy in targeting tumours, while minimising toxicity to surrounding normal tissues by using non-uniform radiation beam intensities to allow modulation of the dose distribution to the target tumour and adjacent normal tissue. Image guidance improves the accuracy and precision of intensity-modulated radiation therapy (as well as other radiotherapy techniques) by allowing clinicians to detect changes in the tumour position, shape, or size, as well as changes in patient anatomy, and organ movement prior to treatment, so that adjustments to the patient's position or treatment beam position can then be made. A variety of image-guidance systems may be employed.

The majority of studies available regarding the use of image-guided intensity-modulated radiation therapy were of low level evidence and reported outcomes for the treatment of prostate tumours. Overall, image-guided intensity-modulated radiation therapy, regardless of the imaging technique applied, was not associated with major toxicity and in one study it was demonstrated that prescription dose was not associated with toxicity outcomes. Control of dose distribution to the tumour appeared to be achieved in many of the included studies and, symptom palliation and disease progression outcomes were found to be favourable. The comparison of different imaging techniques found megavoltage cone beam computer tomography and intra-prostatic seed markers provided better imaging accuracy than ultrasound-based approaches.

Further comparative evidence is required to establish the effectiveness of image-guided intensity-modulated radiation therapy. However, the current evidence available suggests that by reducing treatment related uncertainties, image-guided intensity-modulated radiation therapy may allow the reduction of treatment margins, thus reducing exposure to radiation of normal tissue surrounding the tumour and treatment-related toxicities. This may allow for safe additional dose escalation to the tumour, increasing the likelihood of tumour eradication.

Technological advances in equipment used to plan and deliver therapeutic doses of ionising radiation in the treatment of cancer (radiation therapy or radiotherapy) include the development of technologies that use:

- advanced planning techniques to minimise radiation dose delivered to normal tissues and maximise radiation dose to target tissues (intensity modulated radiation therapy); and/or
- advanced imaging techniques to better target radiation doses delivered to organs or tumours that can move within the body (image guided radiation therapy).

IMRT is a form of "conformal" radiation therapy, which uses computers to create three-dimensional pictures in order to modulate the radiation dose distribution by 'shaping' photon beam intensities to target the tumour and spare adjacent normal tissue. IGRT allows more accurate delivery of the radiation dose by using imaging techniques to track the position of the tumour during treatment.

There has been widespread uptake of these technologies despite the fact that there have been neither randomised trials nor contemporaneous cohort studies comparing the effectiveness and toxicities of intensity-modulated radiation therapy to traditional three-dimensional conformal radiotherapy, let alone an assessment of their comparative cost-effectiveness.

The majority of published research relating to intensity modulated radiation therapy and image guided radiation therapy was of a low level of evidence (mostly case series reports), and mainly related to treatment of prostate cancer. The main research conclusions were that:

- Intensity modulated radiation therapy and image guided radiation therapy appear to be associated with better symptom control due to reduction in radiation of normal tissues;
- The use of cone beam CT scanning and radio-opaque fiducial seed implantation seems to provide better imaging outcomes than the use of ultrasound; and
- Better targeting of tumour tissue may allow for safe and effective dose escalation (such as through hypofractionation), but further research is needed to determine the comparative effectiveness of intensity modulated radiation therapy and image guided radiation therapy with conventional forms of therapy.

Further data are needed to assess patient outcomes and costs (such as the increased time required for treatment planning). To assist in achieving this, the Trans Tasman Radiation Oncology Group (TROG) had received funding from the Commonwealth to develop a clinical register of patients receiving image-guided radiotherapy and intensity-modulated radiotherapy so that more evidence can be collected. These data are expected to form the basis of a submission to the Medical Services Advisory Committee in 2012.

Introduction

The Australian Safety and Efficacy Register of New Interventional Procedures - Surgical, on behalf of the Medical Services Advisory Committee (MSAC), has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play of the introduction and use of image-guided intensity-modulated radiotherapy.

Image-guided intensity-modulated radiotherapy delivers an optimal therapeutic dose of radiation to the target tumour while minimising the dose to the surrounding normal tissue by customising the radiation dose to be consistent with the three dimensional shape of the tumour. This procedure has the potential to improve the quality of radiation therapy delivery, reduce the time in which tumours are treated and destroyed as well as reduce symptoms of toxicity. This technology is currently being used in Australia in a limited capacity.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of image-guided intensity-modulated radiotherapy, its present use, the potential future application of the technology, and its likely impact on the Australian health care system.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with image-guided intensity-modulated radiotherapy.

Description of the technology

Radiation therapy uses ionising radiation to treat cancerous tumours. The radiation damages the DNA in the cancer cells, leaving them unable to divide. Radiation therapy also damages healthy cells, but, unlike cancer cells, they are usually able to recover and regain normal function in time. Not all cancer types are amenable to radiation therapy. Radiation therapy is primarily used to treat localised solid tumours, but it can also be used to treat leukaemia and lymphoma. Certain cancer types that are not suitable for radiation treatment include those that are difficult to detect early enough or those with a high growth rate. Radiation therapy is delivered either as a beam of photons (X-rays and gamma rays) or a beam of subatomic particles. A variety of treatment schedules can be used, ranging from high-dose single fraction (single session) treatment to the more common multi-fraction (multi-session) treatment using lower doses (Yamada et al 2007). Radiation dose is measured in Gray (Gy), with a typical multi-fraction schedule delivering daily fractions of 1.8–2 Gy (compared with $6.5x10^{-4}$ Gy received by the whole body during a typical pelvic x-ray), to achieve an overall dose in the range of 20-80 Gy (Verellen et al 2008).

Techniques in radiation therapy for the treatment of tumours are undergoing continual refinement. In conventional radiation therapy, a margin of extra tissue around the tumour is irradiated to therapeutic levels, corresponding to a 7 – 10mm margin of error (however, a margin greater than 10mm may be used, depending on the tumour being irradiated), to ensure that the target tumour receives the full dose of radiation (Yamada et al 2007). A disadvantage of large margins is that a higher volume of normal tissue is irradiated, which increases toxicity and limits the amount of radiation that can be safely delivered (Yamada et al 2007). Conversely, insufficient margins during radiation therapy may lead to areas of the tumour not receiving the full dose, due to organ motion or patient positioning errors. The only limiting factor to how much radiation can be applied to a tumour is the tolerance and sensitivity of the healthy tissue being irradiated. Newer techniques aim to improve accuracy in targeting tumours with an optimal radiation dosage, while minimising toxicity to surrounding normal tissues (Verellen et al 2008).

Intensity-modulated radiation therapy (IMRT)

One development in radiation oncology is intensity-modulated radiation therapy (IMRT). The goal of IMRT is to deliver a maximal therapeutic dose of radiation to the target tumour while minimising the dose to normal tissue (Yamada et al 2007). IMRT uses non-uniform radiation beam intensities to allow modulation of the dose distribution to the target tumour and adjacent normal tissue (Bentzen 2005). Radiation therapy is usually delivered using a shaped photon beam produced by a linear accelerator, with multiple beams striking the target from different directions (Yamada et al 2007). IMRT uses computer-controlled devices known as multi-leaf collimators (MLCs), or physical compensators, to vary the

intensity of the photon beam. By adjusting the movement of the individual leaves within a MLC, a given point in the body will absorb higher or lower doses of radiation from a given beam angle (Bentzen 2005). The radiation beam can thus be shaped to match the 3-dimensional (3D) shape of the tumor, and the radiation dose intensity raised at the tumor site and lowered near the neighboring normal tissue.

IMRT is generally used in conjunction with a software tool known as inverse treatment planning (Yamada et al 2007). Treatment planning for IMRT is far more complex and time consuming than for most conventional radiation therapy. Treatment planning is concerned with determining how the optimal dose can be delivered to a tumour whilst reducing dose to healthy tissues. It refers to the process of determining the parameters which control the linear accelerator while the patient is being treated, for example multiple positions of MLC leaves for each direction that the x-ray beam is directed toward the patient's tumour, so that optimal dose can be delivered to the tumour whilst reducing the dose to healthy tissues. Treatment planning is accomplished using computer software to produce intensity beam maps for each beam direction. Inverse treatment planning involves a radiation oncology workforce which defines the patient's critical organs and tumours, giving them target doses, along with importance factors. An optimisation program is then run to find a treatment plan which best matches all input criteria. Conversely, forward treatment planning involves the treatment oncologist making decisions in regards to how many radiation beams to use, which angle each will be delivered from, whether attenuated wedges are used, and which MLC configuration be used. Once the treatment oncologist has made the initial plan the treatment planning system determines a predicted dose for the patient. Forward planning is commonly used in conventional radiation therapy and is considered a 'trial and error' approach to treatment planning compared with inverse treatment planning.

A feature of IMRT is that the sharp dose gradients do not allow for misalignment and motion (Verellen et al 2008). Before radiation therapy, pre-treatment imaging is performed to define the treatment volume, organs at risk and the most appropriate way to position the patient, using such technology as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET). The patient can then be positioned to ensure that the appropriate radiation dose is applied to the lesion. However, as the radiation dose is usually delivered in fractions, which correspond to multiple treatment sessions, repeat positioning is required. Organ motion and/or patient positioning errors can lead to areas of the tumour being missed or areas of normal tissue receiving an increased radiation dose. Thus, very precise target localisation is required throughout the treatment period (Verellen et al 2008). To aid in the achievement of this, body immobilisation frames and moulds are often used to hold the patient in the correct position.

Image-guided radiation therapy (IGRT)

Image-guided radiation therapy (IGRT) is used to improve accuracy and precision in targeting the tumour and avoiding healthy tissue (ECRI 2009). IGRT involves

frequent imaging in the treatment room during a course of radiation therapy, in addition to the pre-treatment imaging and planning (Verellen et al 2008). The imaging occurs either daily before a treatment (inter-fractional) or continuously during the treatment (intra-fractional) (ECRI 2009). The imaging performed during pre-treatment planning is used as a reference for the subsequent imaging that takes place during the course of radiation treatment. This enables clinicians to revise the treatment plan according to changes in tumour position, shape, or size, changes in patient anatomy, and organ movement, including that which occurs during breathing (ECRI 2009). On-line or off-line corrections can be made to align the target volume and treatment beam as accurately as possible (Verellen et al 2008). The on-line correction strategy makes use of continuously updated information during the treatment, whereas off-line correction uses data accumulated during previous treatment sessions to determine the best patient position.

A range of imaging technologies can be used with IGRT. There are five basic imaging types used, they include planar x-ray, computed tomography (CT), magnetic resonance imaging (MRI), video based, and ultrasound. Currently in Australia, in-room MRI for IGRT is not yet widely adopted. A commonly used planar image guidance technology is the electronic portal imaging device (EPID) (Verellen et al 2008). The EPID is usually mounted to the treatment delivery system, and uses the actual treatment beam to obtain two dimensional information. Bony landmarks are used to position using two dimensional images, while implanted radio-opaque markers can also be used in some areas of the body to provide surrogates of the target position during two dimensional imaging (Ling et al 2006). To obtain three dimensional information, additional x-ray sources and detector systems are often used, which can be independent of the beam delivery system (Verellen et al 2008). Volumetric image guidance technology can be used to visualise soft tissue, which is not visible using planar technology. This is usually performed through the acquisition of cone beam volumetric CT data (Verellen et al 2008). Other non-radiographic localization tools such as ultrasound may also be used during IGRT (Ling et al 2006). Tomotherapy is a type of CT guided IMRT where radiation is delivered to the tumour slice by slice, compared with conventional external beam radiation therapy which delivers radiation to the entire tumour at once.

Table 1: Summary of IGRT hardware used to achieve 2D/3D x-ray images and 2D non-x-ray images.

2D x-ray planar imaging	Achieved via: 1. Electronic Portal Imaging Device. Where a 2D image is compiled through the activation of a silicon photodiode array after exposure to megavoltage quality x-rays 2. Kilovoltage Images. Created from a typical kilovoltage x-ray tube that can double as a cone beam computed tomography scanner for produce 2D and 3D images
3D x-ray imaging	Achieved primarily by: 1. Cone Beam Computed Tomography which enables 3D image acquisition where the source (kilo-/mega- voltage x-rays) describes a spiral trajectory relative to the object while a 2D array of detectors measures the transmitted radiation on part of a cone of rays emanating from the source
2D non-x-ray imaging	Achieved via: 1. Ultrasound imaging systems 2. Radiofrequency markers 3. External marker tracking (tracking of markers via a video based system)

Commercial devices for IGRT often combine different technologies to improve target localization and to increase versatility, for example, by allowing on-line data acquisition and correction (Ling et al 2006). With any IGRT technology, the reduction of both systematic and random error is important (Ling et al 2006). Systematic error can occur when the image acquired during treatment planning differs from the average target position, while random error occurs as a result of the day-to-day variation in target position. (Ling et al 2006).

Combined IG IMRT

Combining IGRT and IMRT may increase precision and allow for smaller margins around the target tumour, without sacrificing the probability of tumour control (Yamada et al 2007). Image-guided IMRT typically requires a patient table with motorized repositioning capabilities, a linear accelerator with an MLC, one or more imaging methods, a gantry which supports the linear accelerator and imaging components, software for tumour localization, treatment planning, and patient positioning, and hardware such as monitors to view images (ECRI 2009). The patient is required to lie still on the treatment table for the entire treatment session; including the time taken to obtain guidance images, realignment of the treatment table in accordance with these images and treatment planning data, and while the linear accelerator delivers the radiation beam to the tumour. The duration of an IG IMRT treatment session and the number of total fractions delivered varies greatly on the prescribed radiation dose and the treatment site. In hypofractionated IG IMRT the dose delivered to the tumour is elevated so that the number of fractions may be reduced, in some cases as little as one treatment session may be administered. When IG IMRT is used to treat cancer at a site which is prone to movement (such as the prostate) the greater the duration of an individual fraction the more likely movement is to occur; therefore, treatment at these sites usually involves many short fractions.

The combined IG IMRT offers several treatment alternatives. The classic multi-fraction radiation schedule, with its daily treatments lasting for several weeks, can be a burden on patients and hospital resources. However, attempts to reduce the number of treatment sessions by increasing each fraction dose (referred to as hypo-fractionation) have led to unacceptable damage to surrounding healthy tissue. Image-guided IMRT may make hypo-fractionation a more feasible option (Verellen et al 2008).

Intended purpose

The combined IG IMRT is indicated in the treatment of tumours with sensitive organs or structures within the immediate vicinity, or tumours that are prone to shift from locations plotted during the pre-treatment phase (Yamada et al 2008; ECRI 2009). IG IMRT is thus indicated in tumours in the brain, head or neck, spinal column, prostate, lung, liver, and abdomen (ECRI 2009). Spinal tumours, for example, are located close to critical structures such as the spinal cord, kidneys, and gastrointestinal tract (Yamada et al 2008). Prostate tumours are examples of tumours which can shift location, as the prostate is known to have substantial motion independent of the pelvic bony anatomy (Polat 2008), and its

position is affected by changes in bladder and rectal volume (Nijkamp et al 2008). In tumours located in areas of the body that are subject to little or no movement, for example a hip malignancy, the IG component of IG IMRT would be of minimal benefit (ECRI 2009). Expert clinical opinion states that a number of the tumours described here have not previously been treated with standard radiotherapy in large numbers, for example, hepatic tumours have only been successfully treated with radiotherapy since the implementation of IMRT. Therefore, the implementation of IG IMRT might actually open up the ability to treat tumours previously considered untreatable.

Clinical need and burden of disease

Cancer is a major cause of morbidity and mortality worldwide, accounting for 7.1 million deaths annually (12.5% of the global total) (WHO 2009). In Australia, cancers were the leading cause of the burden of disease and injury in 2003 (Begg et al 2007). There were 100,514 new cases of cancer diagnosed in 2005, with prostate cancer the most commonly diagnosed cancer (16,349 cases [16.3% of all cancers, or 29.1% of all male cancers]) (AIHW 2008). Other cancers diagnosed in 2005 of relevance to this review included 9,182 cases of lung cancer (9.1% of all cancers), 2,672 cases of head and neck cancer (2.7% of all cancers), 1,422 cases of brain cancer (1.4% of all cancers), 77 cases of other central nervous system cancers (including spinal cord) (0.1% of all cancers), 2,181 cases of pancreatic cancer (2.2% of all cancers), 1,060 cases of liver cancer (1.1% of all cancers), and 599 cases of gallbladder cancer (0.6% of all cancers) (AIHW 2008). Based on incidence projections to 2010, the number of new cases of cancer in Australia is expected to grow by 3,090 cases per year. The greatest growth is projected for prostate cancer (939 extra cases per year), which is equivalent to a growth of 3.1 cases per 100,000 males per year (AIHW 2008).

In 2005 there were 39,097 deaths from cancer in Australia. Lung cancer accounted for the most cancer deaths (7,427 deaths [19% of all cancer deaths]), while deaths from prostate cancer were also common (2,949 deaths [7.5% of all cancer deaths, or 13.4% of male cancer deaths]) (AIHW 2008). Deaths from other cancers relevant to this review included 889 deaths from head and neck cancer (2.3% of all cancer deaths), 1,050 deaths from brain cancer (2.7% of all cancer deaths), 21 deaths from other central nervous system cancers (including spinal cord) (0.1% of all cancer deaths), 2,026 deaths from pancreatic cancer (5.2% of all cancer deaths), 952 deaths from liver cancer (2.4% of all cancer deaths), and 273 deaths from gallbladder cancer (0.7% of all cancer deaths) (AIHW 2008).

Stage of development

Both IMRT and IG were introduced separately in Australia. IMRT has been in clinical use in Australia since 1999 whilst planar IGRT techniques were commenced clinically in the mid 1990s. Only recently have these two techniques combined as IG IMRT. Ultrasound-based IG IMRT does not appear to be used in Australia (Clinician personal communication 2010), clinical expert opinion states ultrasound-based IG IMRT has been used in Australia but is no longer used due to

its operator dependence and has been superseded by the use of implanted fiducial markers.

Trials of IG IMRT have been conducted in several countries, including the USA, Australia, China, Germany, Italy, Korea, and the Netherlands. Current trials are also being conducted, predominantly in the USA, on IG IMRT in prostate, lung, liver, spine, head and neck, brain, and musculoskeletal cancers (Clinical Trials 2009). As the combined IG IMRT technique is a refinement of conventional radiation therapy, there are multiple devices already on the market that can be utilised to perform IG IMRT, as well as new systems and upgrades (ECRI 2009).

Australian Therapeutic Goods Administration approval

Many systems and components of IG IMRT have received US Food and Drug Administration (FDA) 510(k) marketing clearance, including full IGRT systems, imaging components, linear accelerator systems and MLCs, software applications, and patient positioning tables (US FDA 2009). Components of IG IMRT, including linear accelerators and MLCs to be used with IGRT systems, have also been approved in Australia and are listed on the Australian Register of Therapeutic Goods (ARTG) (TGA 2009).

Existing comparators

Image-guided intensity-modulated radiation therapy is a refinement of an existing technique (IMRT with pre treatment planning); therefore, IMRT with pre treatment planning (with computed tomography) would be considered the comparator of IG IMRT. Previously indirect localisation of the target tumour was achieved using bony landmarks and external skin markings. With IG IMRT these methods are supplemented with direct visualisation of the target and verification of its position prior to fraction delivery.

The aim of this report was to assess the safety and effectiveness of IG IMRT in comparison to IMRT in terms of patient outcomes given the available evidence. Because various imaging techniques are available to facilitate IG IMRT, this report also looked to assessed outcomes according to the imaging technique used.

A total of 14 studies were eligible for inclusion in this report, including four non-randomised comparative studies and ten case series studies. These studies comprise an evidence base of non-randomised controlled trials and case series literature. Clinical outcomes have been separated and reported in groups of the most common cancer types treated with image-guided intensity-modulated radiotherapy; these are prostate cancer, spinal cancer and, head and neck cancer. An additional group has also been included, where less commonly treated cancer types were reported collectively. Due to the variability of the image guidance techniques used and the outcomes reported, it is not possible to combine the results of the studies included. Therefore, studies included for safety and effectiveness have been presented based on the image guidance modality used.

As IG IMRT is a relatively new procedure that is still undergoing refinement, there were a number of papers that only reported technical information. A list of these six studies and their abbreviated results is presented in Appendix C. Only studies that reported patient safety and efficacy outcomes, such as survival rate and treatment toxicity, are analysed in the effectiveness and safety sections of this report.

Prostate cancer

Five studies (three non-randomised comparative and two case series studies) reporting the use of IG IMRT to treat patients with prostate cancer were included in this report. The studies varied widely in the type of image guidance technique used, the IMRT dose (and frequency) delivered, the definition of the clinical target volume (CTV)/planning target volume (PTV) and the correction protocols employed (Table 2).

Helical tomotherapy[1]

Three studies reported the use of helical tomotherapy for the treatment of prostate cancer.

Keiler et al 2007 did not report any effectiveness outcomes. However, this retrospective non-randomised comparative study using a historical control group did report safety outcomes for 55 patients treated using helical tomotherapy. The study compared these with outcomes of 43 matched patients (matched for age, pre-treatment PSA, Gleason score, T stage, pre-treatment urinary function, pre-treatment sexual function) for who underwent treatment with ultrasound-based IG IMRT. Patient characteristics were similar at baseline, however length of follow-up was not reported.

[1] Helical tomotherapy is a volumetric image-guided, fully dynmatic, IMRT delivery system that utilises computer tomotherapy imaging for patient set-up verification (Tome et al 2007).

The prospective case series reported by Di Muzio et al 2009 also reported the use of helical tomotherapy. Sixty consecutively recruited patients, stratified by their respective National Comprehensive Cancer Network (NCCN) risk category were assessed for acute and late toxicities, as well as biochemical free survival and clinical failure. Patients were followed-up for a median of 13 months.

Ultrasound-based

Studies that reported the use of ultrasound-based techniques for the treatment of prostate cancer employed the use of B-mode acquisition and targeting (BAT) systems to attain trans-abdominal images for use in image guidance.

The retrospective non-randomised comparative study by Kupelian et al 2007 compared the biochemical relapse-free survival rate, as well as rectal and urinary toxicities in patients who had undergone US-based IG IMRT. Patients were assessed based on their rectal volumes at the time of treatment planning (< 50 cm^3: n = 108; 50 to < 100 cm^3: n = 113; ≥ 100 cm^3: n = 267). No comparison of patient baseline characteristics was reported. Patients were follow-up for a median period of 60 months.

Martin et al 2007 reports on the use of intra-prostatic seed markers visualised through daily electronic portal imaging for image guidance of IMRT. The prospective case series study presents acute toxicity results, biopsy results, metastatic failure and survival in 92 patients followed up for a median of 38 months.

Definitive versus post-prostatectomy treatment

Cheng et al 2008 carried out a prospective non-randomised comparative study using helical tomotherapy to treat 146 patients with localised prostate cancer. The study assessed a range of toxicity related outcomes in patients undergoing definitive treatment (n = 76) or post-prostatectomy treatment (n = 70). Patient characteristics were generally similar between patient groups, however patients undergoing definitive treatment were generally younger than post-prostatectomy patients (mean age, 65.7 and 70.2 years, respectively), which subsequently led to a slightly lower incidence of medical conditions associated with the elderly. Patients had a median length of follow-up of 10.7 months with no reported losses to follow-up

Table 2 Summary of IG IMRT treatment details for prostate cancer studies

<table>
<tr><th>Study ID</th><th>No. of patients</th><th>Type of IG</th><th>Frequency of IG</th><th>Correction protocol</th><th>Immobilisation</th><th>CTV/PTV</th><th>IMRT dose</th></tr>
<tr><td>Keiler et al (2007)

Level III-2 interventional evidence</td><td>Total: 97
Tomotherapy: 55
BAT US: 43</td><td>Helical Tomo-therapy, BAT US</td><td>Daily</td><td>N/A</td><td>N/A</td><td>For both groups
PTV1: prostate and seminal vesicles plus 0.7 cm margin except in rectal interface where 0.3 cm margin applied

PTV2: prostate or prostate bed plus 0.7 cm margin except in rectal interface where 0.3 cm margin applied</td><td>Patients undergoing definitive treatment
PTV1: minimum 66 Gy in 1.8 Gy fractions
PTV2: total dose 81 Gy (range: 79.2 to 82.8 Gy) in 44 or 46 1.8 Gy fractions

Patients undergoing salvage treatment
PTV2 used and total dosage of 72 Gy in 40 1.8 Gy fractions</td></tr>
<tr><td>Di Muzio et al (2009)

Level IV interventional evidence</td><td>Total: 60</td><td>Helical Tomo-therapy</td><td>Daily MV CT image guidance applied using system integrated in tomotherapy machine</td><td>N/A</td><td>N/A</td><td>CTV1: pelvic nodes
CTV2: upper portion of seminal vesicles
CTV3: lower portion of SVs
CTV4: prostate

PTV: CTV + 8 mm margin, except in cranial-caudal direction (10 mm); for pelvic lymph nodes 10 mm in all directions except the portion close to bony structures where margins decreased to 5 to 7 mm.

At interface between rectum and prostate PTV, an overlap volume define.</td><td>
<table>
<tr><th></th><th colspan="2">Low risk</th><th colspan="2">Intermediate risk</th><th colspan="2">High risk</th></tr>
<tr><th></th><th>Dose per fraction</th><th>Dose</th><th>Dose per fraction</th><th>Dose</th><th>Dose per fraction</th><th>Dose</th></tr>
<tr><td>PTV1 (LN)</td><td>N/A</td><td>N/A</td><td>1.85</td><td>51.8</td><td>1.85</td><td>51.8</td></tr>
<tr><td>PTV2 (SVc)</td><td>2</td><td>56</td><td>2.2</td><td>61.6</td><td>2.34</td><td>65.5</td></tr>
<tr><td>PTV3 (SV1/3)</td><td>2.2</td><td>61.6</td><td>2.34</td><td>65.5</td><td>2.65</td><td>74.2</td></tr>
<tr><td>PTV4 (P)</td><td>2.55</td><td>71.4</td><td>2.65</td><td>74.2</td><td>2.65</td><td>74.2</td></tr>
<tr><td>Overlap</td><td>2.34</td><td>65.5</td><td>2.34</td><td>65.5</td><td>2.34</td><td>65.5</td></tr>
</table>

Varying doses delivered simultaneously to each PTV over 28 fractions</td></tr>
<tr><td>Kupelian et al (2008)

Level III-3 interventional evidence</td><td>Total: 488

Rectal volume groups
< 50 cm^3: 108
50 to < 100 cm^3: 113
≥ 100 cm^3: 267</td><td>BAT US</td><td>Prior to each daily treatment</td><td>N/A</td><td>N/A</td><td>Target was prostate only in patients with stage T1-2, pretreatment PSA ≤ 10 ng/mL and biopsy Gleason score ≤ 6. Target was prostate and seminal vesicles in patients with stage T3 or pretreatment PSA level above 10 ng/mL or biopsy Gleason score ≥ 7.

All cases treated with 4 mm margin posteriorly, 8 mm</td><td>70 Gy at 2.5 Gy per fraction (28 fractions over 5 1/2 weeks)</td></tr>
</table>

Study ID	No. of patients	Type of IG	Frequency of IG	Correction protocol	Immobilisation	CTV/PTV	IMRT dose
						laterally and 5 mm in all other directions	
Martin et al (2007) Level IV interventional evidence	Total: 92	Fiducial markers visualised by electronic portal imaging	Daily	Marker displacements ≥ 3 mm corrected	Patients immobilised using VacLoc cradle extending from waist to mid thigh at time of planning CT. Foam leg stocks abutted inferior edge of VacLoc to immobilise knees and feet	CTV: entire prostate gland and the base of seminal vesicles PTV: CTV plus 10 mm margin except in posterior region of the rectum, where 7 mm margin applied	Minimum dose of 60 Gy in 20 daily fractions
Cheng et al (2008) Level III-2 interventional evidence	Total: 146 Definitive RT: 76 Post-prostatectomy RT: 70	Helical Tomo-therapy	Daily/before each treatment session	N/A	Custom-moulded immobilisation cushion (Vac-Lok, MedTec, Iowa, United States) during kV planning CT scan	*Definitive RT* CTV1: prostate + proximal seminal vesicles CTV2 (patients with risk of seminal vesicle invasion > 15%): prostate + distal portions of seminal vesicles + periprostatic lymph nodes CTV3 (patients with > 15% risk of regional lymph node involvement): prostate + periprostatic and periseminal vesicles and external iliac + obturator + internal iliac lymph nodes PTV: 3 to 6 mm around respective CTVs in all directions, except posteriorly which was 3 to 4 mm *Post-prostatectomy RT* Target volume: prostatic fossa and periprostatic tissues (regional iliac lymphatics	*Definitive RT* Total: 72 to 80 Gy (mean prescribed dose to PTV: 78.9 Gy) PTV1: 75.6 to 80 Gy PTV2: 45 to 54 Gy (initially) followed by 76 o 78 Gy to periprostatic region alone PTV3: external iliac, obturator and internal iliac lymph nodes initially treated with 45 Gy, followed by final reduction to 54 Gy including seminal vesicles, with a final boost to the periprostatic region only. 9% of patients treated to PTV1, 52% to PTV2 and 20% to PTV3 *Post-prostatectomy RT* Total: 63 to 70.2 Gy (mean prescribed dose to PTV: 68.8 Gy) 30% treated to the prostatic bed (including prostatic fossa and periprostatic tissues) with typical prescribed dose of 64 to 66 Gy. 70% treated to the prostatic bed and regional iliac lymphatics (including external iliac, obturator and internal iliac lymph nodes) with prescribed dose of 45 Gy to regional iliac lymphatics, followed by field reduction to the prostatic bed only with a final dose of 66 to 70.2 Gy. All HT RT performed with 6 MV photons in daily fractions of 1.8 to 2.0 Gy.

Study ID	No. of patients	Type of IG	Frequency of IG	Correction protocol	Immobilisation	CTV/PTV	IMRT dose
						included if indicated) PTV: 3 to 6 mm around respective CTVs in all directions, except posteriorly which was 3 to 4 mm	

NOTES: IG = image guidance; CTV = clinical target volume; PTV = planning target volume; IMRT = intensity-modulated radiotherapy; RT = radiotherapy; N/A = not applicable; kV = kilovoltage; CT = computer tomography; MV = megavoltage; SV = seminal vesicle; LN = lymph nodes; SV1/3 = proximal one third of seminal vesicles; SVc = cranial portion of seminal vesicles; P = prostate; US = ultrasound; SM = seed marker; CBCT = cone beam computed tomography; BAT = B-mode acquisition and targeting; PSA = prostate specific antigen; SAL = shrinking-action-level; OAR = organ at risk.

Safety

Five (three non-randomised comparative and two case series) studies reported safety outcomes in relation to the use of IG IMRT in the treatment of prostate cancer, including one study reporting technical effectiveness outcomes. The safety outcomes reported generally related to genitourinary and gastrointestinal toxicities exhibited in treated patients.

Helical tomotherapy

Keiler et al 2007 compared 55 consecutive prostate cancer patients who underwent helical tomotherapy with a matched group of 43 patients who had undergone IG IMRT using the BAT trans-abdominal ultrasound system. Two separate PTVs were calculated each receiving different total IMRT doses (Table 2). Table 3 shows the resultant gastrointestinal and genitourinary acute toxicities based on the Radiation Therapy Oncology Group toxicity scoring system[2]. The data indicate a slightly better outcome in terms of gastrointestinal toxicities with helical tomotherapy. Conversely, the genitourinary toxicity results slightly favour the use of the US-based IG IMRT technique. No patient was reported to experience toxicity ≥ grade 5. Univariate analysis found a significant increase in the occurrence of acute genitourinary toxicity ≥ grade 2 in helical tomotherapy patients versus US-based IG IMRT patients (P = 0.001). On the other hand, the occurrence of acute gastrointestinal toxicity ≥ grade 2 was significantly lower in patients who had undergone helical tomotherapy (P = 0.024). Multivariate analyses revealed that a significant correlation existed between acute genitourinary toxicity and median bladder dose (P = 0.038), bladder dose homogeneity (P = 0.02) and helical tomotherapy use (P = 0.019). No variables were reported to correlate with gastrointestinal toxicity. A subgroup analysis was also performed to determine any difference in toxicity resulting from an intact prostate receiving a higher RT dose. When only definitively treated patients were analysed, the gastrointestinal and genitourinary toxicity patterns remained the same. However, when the analysis of post-prostatectomy patients was performed, no significant difference in gastrointestinal or genitourinary toxicity was seen between the two IG IMRT techniques.

In addition to reporting the acute gastrointestinal and acute genitourinary Radiation Therapy Oncology Group toxicity scores, Di Muzio et al 2009 also reported the acute upper gastrointestinal Radiation Therapy Oncology Group toxicity scores for the sixty patients included (Table 3). Acute genitourinary toxicities were reported more often in these patients. The median time to occurrence of acute genitourinary toxicities was 28 days from the beginning of treatment (range: six to 42 days). The median time to acute gastrointestinal toxicities was 27 days (range: 18 to 72 days). Upper gastrointestinal toxicities were reported in 12 patients (grade 1) with a median time to occurrence of 28 days (range: six to 41 days). Hence, all three types of acute toxicities presented at similar times. Furthermore, when toxicities were stratified according to

[2] Refer to Appendix D for definition of acute/late Radiation Therapy Oncology Group grades

prescription dose (Table 3) it was revealed that prescription dose was not associated with any impact on acute toxicity.

Ultrasound-based

Kupelian et al 2007, which reported technical effectiveness outcomes, was the only study reporting the use of US-based IG IMRT to report safety outcomes.

Kupelian et al 2007 reported both acute and late rectal and urinary toxicity based on the Radiation Therapy Oncology Group scoring system (Table 3). The results demonstrate that for acute toxicity, urinary toxicity (≥ grade 1) occurs more often than acute rectal toxicity. However this pattern is not maintained for late toxicity. The study reports that the actuarial late Radiation Therapy Oncology Group grade ≥ 2 was 6% for urinary and rectal toxicity. When toxicities were analysed in terms of different rectal distension groups, the results demonstrated that both late and acute rectal and urinary toxicity rates did not differ between groups. This finding suggests rectal distension does not impact the occurrence of acute or late rectal and urinary toxicities when an US-based image guidance approach is utilised.

Intra-prostatic seed markers

Martin et al 2007 was the only study utilising intra-prostatic seed markers for image guidance to report safety outcomes. In this study the maximum acute genitourinary and gastrointestinal toxicity based on the Radiation Therapy Oncology Group scoring system were reported. The results were similar to those observed in previous studies using different imaging modalities in that overall there were a greater proportion of patients experiencing ≥ grade 1 acute genitourinary toxicities than acute gastrointestinal toxicities (Table 3). Late toxicity was assessed at the time of last assessment (median last follow-up 38 months) and demonstrated a low incidence of either genitourinary or gastrointestinal toxicities. The actuarial late toxicity results also support this and suggest that late gastrointestinal or genitourinary toxicity is rare.

Definitive versus post-prostatectomy treatment

In the study by Cheng et al 2008, patients receiving definitive treatment (n = 76) had different PTVs (and irradiation doses) depending on the risk of seminal vesicle and regional lymph node involvement (Table 2). Post-prostatectomy patients had a different PTV than patients in the definitive treatment group and also received a lower overall irradiation dose. The acute gastrointestinal and genitourinary toxicities based on Radiation Therapy Oncology Group /European Organisation for Research and Treatment of Cancer scoring are presented in Table 3. The rate of acute gastrointestinal toxicity ≥ grade 2 was significantly ($P < 0.05$) greater in post-prostatectomy patients, despite these patients receiving lower doses. In regards to acute genitourinary toxicities the results were comparable between the two groups. The multivariate analyses showed that radical prostatectomy along with the minimal dose received by the highest 10% of target volume (D10) had the strongest association with gastrointestinal toxicities (Table 3).

Table 3 Prostate radiation therapy safety outcomes

Keiler et al (2007)

GI and GU RTOG scored toxicity

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
GI						
LINC	5%	56%	40%	0%	0%	0%
Tomotherapy	11%	64%	25%	0%	0%	0%
GU						
LINC	2%	70%	28%	0%	0%	0%
Tomotherapy	2%	47%	47%	4%	0%	0%

Di Muzio et al (2009)

RTOG toxicity scores

	Grade 0	Grade 1	Grade 2	Grade 3
Acute GU	25 (42%)	21 (35%)	12 (20%)	2 (3%)
Acute GI	42 (70%)	18 (30%)	0	0
Upper GI	0	12 (20%)*	0	0

* 5 patients received pelvic irradiation

Kupelian et al (2008)

Acute and late toxicity (RTOG score)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Acute rectal toxicity	41%	48%	11%	0%	0%
Acute urinary toxicity	19%	61%	19%	1%	0.2%
Late rectal toxicity	86%	9%	3%	2%	0%
Late urinary toxicity	88%	5%	6%	0.4%	0%

Martin et al (2007)

RTOG acute toxicity

Category	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4+
Gastrointestinal (%)	66	22	11	1	0
Genitourinary (%)	32	43	25	0	0

RTOG late toxicity

Category	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4+
Gastrointestinal (%)	93	2	4	0	0
Genitourinary (%)	90	7	3	0	0

Actuarial late toxicity

Category	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4+
Gastrointestinal (%)	82.7	11.8	5.1	1.2	0
Genitourinary (%)	72.4	17.6	10	0	0

Cheng et al (2008)

Acute GI and GU toxicities with HT using the RTOG and EORTC acute radiation morbidity grading scales

Study ID	Outcomes					
		Acute toxicity grade				
		0	1	2	3	4
	Definitive					
	GI	37 (49%)	20 (26%)	19 (25%)	0 (0%)	0 (0%)
	GU	13 (17%)	34 (45%)	29 (38%)	0 (0%)	0 (0%)
	Post-prostatectomy					
	GI	9 (13%)	32 (46%)	29 (41%)	0 (0%)	0 (0%)
	GU	11 (16%)	34 (49%)	25 (36%)	0 (0%)	0 (0%)

NOTES: GI = gastrointestinal; GU = genitourinary; HT = helical tomotherapy; RTOG = Radiation Therapy Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; RT: radiotherapy; uGI = upper gastrointestinal; NR = not reported; LINC = linear accelerator-based step and shoot intensity modulated radiotherapy; BAT = B-mode acquisition and targeting; US = ultrasound.

Effectiveness

Three (one non-randomised comparative and two case series) studies reported effectiveness outcomes in relation to the use of IG IMRT in the treatment of prostate cancer. The effectiveness outcomes reported varied widely making assessment of effectiveness difficult. Depending on the particular focus of the study different effectiveness outcome measures were reported. Reported outcomes included dose distribution, biochemical response and patient survival.

Helical tomotherapy

Di Muzio et al 2009 was the only helical tomotherapy study to report effectiveness data. A variety of dosimetric parameters, including the mean dose, maximum dose and the mean fraction of structure receiving doses above 20, 40, 50, 55 and 65 Gy were calculated (Table 4). The results show that the volume of both rectum and bladder receiving high doses of radiation were relatively low, an indication of the control of dose distribution with helical tomotherapy. All patients reported biochemical control of disease according to the American Society for Therapeutic Radiology and Oncology definition of biochemical control, complete response at imaging and clinical evaluation at last follow-up (time of last follow-up not reported, median follow-up was 13 months).

Ultrasound-based

Kupelian et al 2008 reported the biochemical relapse free survival rate at five years for all patients was 86%. When the results were split into the three separate rectal distension groups, no statistically significant difference was detected between the groups. The investigators performed a multivariate time-to-failure analysis using the Cox proportional hazards model and found that rectal volume was not an independent predictor of biochemical failure ($P = 0.80$). Furthermore the analysis revealed that rectal distension was not a predictor of either rectal or urinary toxicity. On the other hand, the pretreatment PSA level ($P = 0.01$) and biopsy Gleason score ($P < 0.001$) were both independent predictors of biochemical failure.

Intra-prostatic markers

The study by Martin et al 2007 reported biochemical control according to the Phoenix and American Society for Therapeutic Radiology and Oncology definitions. Phoenix defines biochemical failure as prostate-specific antigen (PSA) nadir + 2 ng/mL and the American Society for Therapeutic Radiology and Oncology group defines biochemical failure as three consecutive rises in PSA. The number of patients at risk of failure at the start of treatment was 92 (100% of sample) according to both definitions. By the Phoenix definition, the number of patients at risk of biochemical failure from the start of treatment to 12 months follow-up decreased by 5%, from 12 to 24 months it decreased by 21%, from 24 to 36 months it decreased by 46%, and from 36 to 48 months it decreased by 89%. For the American Society for Therapeutic Radiation and Oncology definition these decreases were slightly lower at 3%, 17%, 38% and 85%, respectively (Table 4). The authors state that the American Society for Therapeutic radiation

and Oncology definition was associated with increased ‘false calls’ for biochemical failure, as an initial three consecutive rises in PSA was not always followed by a sustained increase in PSA or the development of metastases, explaining why the number of patients at risk of biochemical failure was higher according to the American Society for Therapeutic Radiation and Oncology definition. Consequently, the three year Phoenix biochemical control rate was 97% overall and the 14 month American Society for Therapeutic Radiation and Oncology biochemical control rate was 76%. A significant difference in control rate was seen between patients in the low-, intermediate- and high-risk groups, according to the Phoenix definition ($P = 0.027$); whereas, there were no significant differences seen between the three risk categories according to the American Society for Therapeutic Radiation and Oncology definition ($P = 0.38$) (Table 4). The proportion of positive biopsies taken from the prostate posttreatment was moderately less than the number of negative biopsy results at last follow-up (Table 4). Four patients developed proven metastases in conjunction with rising PSA and no prostate cancer related deaths occurred.

Table 4 Prostate radiation therapy effectiveness outcomes

<table>
<tr><th>Study ID</th><th>Outcomes</th></tr>
<tr><td>Keiler et al (2007)</td><td>NR</td></tr>
<tr><td>Di Muzio et al (2009)</td><td>Dose distribution
<table>
<tr><th></th><th>D_{mean} (median)</th><th>D_{max}</th><th>V20</th><th>V40</th><th>V50</th><th>V55</th><th>V65</th></tr>
<tr><td>Rectum</td><td>36.7 (range: 28.6 to 44.6 Gy)</td><td>-</td><td>-</td><td>43.2% (range: 27.1 to 60%)</td><td>32% (range: 15.9 to 45%)</td><td>-</td><td>10.2% (range: 2 to 19%)</td></tr>
<tr><td>Bladder (for full bladder, > 300 mL)</td><td>40.1 Gy (range: 31.7 to 50 Gy)</td><td>-</td><td>-</td><td>47% (range: 31 to 69%)</td><td>-</td><td>27% (range: 15 to 42%)</td><td>14% (range: 8 to 22%)</td></tr>
<tr><td>Femoral heads/femur</td><td>-</td><td>Range: 22 to 52 Gy</td><td>Range: 0.3 to 40%</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Femoral heads/femur (in cases of nodes irradiation)</td><td>-</td><td>-</td><td>Median: 54% (range: 34 to 92%)</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Intestinal cavity (outside PTV) in case of nodes irradiation</td><td>19.8 Gy (range: 18.8 to 20.8 Gy)</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Penile bulb</td><td>30.5 Gy</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>PTV4 (low risk patients)</td><td>-</td><td>< 76.5 Gy</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>PTV4 (intermediate/high risk patients)</td><td>-</td><td>< 78.5 Gy</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table>
D_{max} = maximum dose; D_{mean} = mean dose; V20, V40, V50, V65 = fraction of rectum receiving above 20, 40, 50, 65 Gy

PTV coverage: V95% (median) for PTV1-4 ranged between 94% and 98%
Overlap region (overlap between rectum and PTV4 for low and intermediate risk and PTV3-PTV4 for high risk) coverage: V95% (median) was 99.7% (range: 96.5 to 100%) with maximum doses between 68 Gy and 73 Gy
All patients reported biochemical control of disease according to ASTRO definition of bNED, complete response at imaging and clinical evaluation at last follow-up
</td></tr>
<tr><td>Kupelian et al (2008)</td><td>Biochemical relapse free survival rate at five years
<table>
<tr><th>All patients</th><th>< 50 cm^3</th><th>50 to < 100 cm^3</th><th>≥ 100 cm^3</th><th>P-value</th></tr>
<tr><td>86%</td><td>90%</td><td>83%</td><td>85%</td><td>0.18</td></tr>
</table></td></tr>
<tr><td>Martin et al (2007)</td><td>Biochemical control according to Phoenix and ASTRO definitions (number of patients at risk at various time points)
<table>
<tr><th></th><th>Start</th><th>12 months</th><th>24 months</th><th>36 months</th><th>48 months</th></tr>
<tr><td>Phoenix definition</td><td>92</td><td>87</td><td>69</td><td>37</td><td>4</td></tr>
<tr><td>ASTRO definition</td><td>92</td><td>89</td><td>74</td><td>46</td><td>7</td></tr>
</table>
3-year biochemical control rates by risk categorisation
<table>
<tr><th></th><th>Low-risk</th><th>Intermediate-risk</th><th>High-risk</th><th>P-value</th></tr>
<tr><td>Phoenix definition</td><td>100%</td><td>85%</td><td>71%</td><td>0.027</td></tr>
<tr><td>ASTRO definition</td><td>84%</td><td>72%</td><td>71%</td><td>0.38</td></tr>
</table></td></tr>
</table>

Study ID	Outcomes
	Biochemical response • In 88 patients (not receiving adjuvant hormones) median PSA nadir was 0.59 ng/mL (range: 0.11 to 3.18 ng/mL) at median 22 months (range: 2 to 44 months) *Posttreatment biopsy results* • At median 34 months (n = 25): negative (n = 13), positive (n = 3), intermediate (n = 4; microfocus of carcinoma in a single core, unable to assign core), results not reported (n = 5) *Metastatic disease* • 4 patients reported proven metastatic disease in conjunction with rising PSA *Survival* • No prostate cancer-related deaths to date • Deaths: 3 from non-prostate cancer-related causes. None had biochemical failure at last follow-up
Cheng et al (2008)	NR

NOTES: NR = not reported; PTV = planning target volume; ASTRO = American Society for Therapeutic Radiology and Oncology; bNED = biochemical control; US = ultrasound; SM = seed markers; mV = megavoltage; SD = standard deviation; LR = left-right; SI = superior/inferior; AP = anterior/posterior; PSA = prostate specific antigen; BAT = B-mode acquisition and targeting; CTV = clinical target volume; CT = computer tomography; BMI = body mass index; CI = confidence interval; SAL = shrinking action level; NAL = no action level.

Spinal cancer

Four case series studies reporting IG IMRT for the treatment of spinal cancers were identified for inclusion (Jin et al 2007; Terezakis et al 2007; Yamada et al 2005; Yamada et al 2008).

Jin et al 2007 reported the outcomes of integrated infrared optical tracking and kV X-ray imaging-based image guided IMRT (single fraction) in the first 49 patients out of 196 consecutive patients to undergo the procedure. In this prospective case series study each of these patients had histological diagnosis of malignant neoplasm and metastasis to a single spinal segment or two contiguous spinal levels, with or without cord compression. Follow-up was conducted at two to three months during the first year following irradiation and every four to six months thereafter.

Terezakis et al 2007 reported IG IMRT using mV electronic portal imaging or kV onboard imaging in 27 consecutive patients with partially resected or unresectable primary or metastatic paraspinal tumours. The majority of tumours were primary (85%). In this retrospective review, patients were followed-up for a median of 17.4 months.

In the study by Yamada et al 2005, 35 patients with primary or metastatic paraspinal solid tumour malignancies that were deemed inoperable, with radiographic evidence of gross disease, underwent image guided and stereotactic IMRT. Patients were immobilised with one of two devices developed by the institution at which they underwent treatment; they were the Memorial stereotactic body frame (MSBF) or the Memorial body cradle (MBC). The image guidance modalities employed by this study were in-room CT scans, electronic portal imaging devices, or both. In this case series patients were followed-up for a median of 11 months and none were lost to follow-up.

The study by Yamada et al 2008 also used digital mV portal imaging or kV imaging to carry out IMRT (single dose). Treatment was delivered to 93 consecutive patients with histologically confirmed solid tumour malignancy, with radiologic evidence of metastasis to the spine. All of the spinal lesions were unresected. Patients were followed-up for a median of 15 months. Three patients were lost to follow-up at 8, 10 and 18 months after treatment.

Patient demographics are given in greater detail in the study profiles table (Table 23). Specific treatment details, including the frequency of image guidance used and radiation dose, can be found in Table 5.

Table 5 Summary of IG IMRT treatment details for spine cancer studies

Study ID	No. of patients	Type of IG	Frequency of IG	Correction protocol	Immobilisation	CTV/PTV	IMRT dose
Jin et al (2007) Level IV intervention evidence	49 patients	Integration of infrared optical tracking component (the ExacTrac system) and kV x-ray imaging component	Before treatment session	N/A	BodyFIX®, (Medical Intelligence,Medizintechnik GmbH, Schwabmuenchen, Germany)	CTV: entire vertebral body of the involved spine PTV: equal to CTV (no extended margin)	Total: mean 14.8 ± 2.3 Gy (gradually escalated from 10-18 Gy in 2 Gy increments; dose total dose ranged from 10 to 16 Gy)) No. of fractions: 1 Dose/fraction: N/A
Terezakis et al (2007) Level IV intervention evidence	27 consecutive	mV electronic portal imaging or kV onboard imaging	Daily	N/A	Immobilisation with Memorial body cradle during CT planning and prior to each treatment session	PTV: gross tumour volume + 10 mm in all directions, except where the margin overlapped either spinal cord or cauda equina	Total (median): 6600 cGy (IQR: 6600 to 7000) No. of fractions (median): 33 (IQR: 32 to 35) Dose/fraction: 180 or 200 cGy V95 (median): 94% (IQR: 92 to 97%) Mean dose to spinal cord (median): 2949 cGy (IQR: 1350 to 3409) Maximal dose to spinal cord (including addition of previous dose to spinal cord for those with previous treatment; median): 5261 cGy (IQR: 3303 to 5383 cGy)
Yamada et al (2005) Level IV intervention evidence	35 patients	In-room computer tomography scan or electronic portal imaging devices, or both	Daily	Patients undergoing standard treatment fractionation who have had no previous radiation to cord, daily positioning accuracy of 2 mm based on the electronic portal imaging device image registration with the planning images to streamline the treatment process was allowed. All	Memorial Sloan-Kettering Cancer Center (Memorial) stereotactic body frame or Memorial body cradle Either used for CT planning	CTV: gross tumour volume PTV: gross tumour volume + 10 mm uniformly, except at the spinal cord interface where the PTV neither includes the spinal cord nor excludes the GTV border (when the distance between PTV and cord < 5 mm)	*Patients with nonmetastatic paraspinal tumours* Total (median): 7000 cGy (range: 5940 to 7020 cGy) No. of fractions: N/A Dose/fraction: N/A %PTV (median): 90% (range: 83 to 100%) Cord maximum (median): 68% (range: 14 to 75%) Cord average (median): 31% (range: 7 to 66%)

Study ID	No. of patients	Type of IG	Frequency of IG	Correction protocol	Immobilisation	CTV/PTV	IMRT dose
				other patients previously treated with conventional or hypofractionated radiation regimens had daily setup corrections based on image guidance results.			*Patients with metastatic lesions (and prior RT)* Prior RT (median): 3000/10 cGy (range: 2000 to 4500 cGy) Total (prescribed) dose (median): 2000 cGy/5 (range: 2000 to 3000 cGy) %PTV (median): 89% (range: 68 to 98%) Cord maximum (median): 34% (range: 13% to 60%) Cord average (median): 14% (range: 4% to 81%)
Yamada et al (2008) Level IV intervention evidence	93 patients	Digital mV portal imaging or kV imaging	Before treatment session	Online. If motion > 2 mm noted, treatment was stopped and positioning verified again with both 2D and 3D imaging	Noninvasive customised cradle developed at the institution	CTV: in case of vertebral body involvement, included entire vertebral body PTV: CTV + ≥ 2 mm in al directions. PTV never allowed to violate spinal cord contour in cases where epidural disease extension present	Total: 18-24 Gy No. of fractions: 1 Dose/fraction: N/A

NOTES: IG: image guidance; CTV: clinical target volume; PTV: planning target volume; IMRT: intensity modulated radiotherapy; CT: computer tomography; GTV: gross tumour volume; RT: radiotherapy; N/A = not applicable; kV: kilovoltage; mV: megavoltage; IQR = interquartile range.

Safety

Jin et al 2007 reported patient tolerance to IG IMRT and found that all patients, regardless of the location of spinal involvement, tolerated treatment without difficulties. There were no incidences of complication related to acute toxicity; only minor transient complications were experienced in some patients. No hospital admissions were required as a direct result of IMRT. Table 6 reports these findings in greater detail.

In the study by Terezakis et al 2007 acute and long-term toxicity grades were also measured using the Radiation Therapy Oncology Group classification score (Table 6). Acute (within eight weeks of treatment completion) toxicity ≥ grade 3 was experienced in two patients only. These patients experienced skin toxicity and consisted of one patient with failure of mechanical hardware (from previous surgery) and another patient who continuously self-excoriated. Grade 1 and 2 toxicity were the most common form of toxicity but was well managed. Skin t oxicity (grade 3 and 4) was the only late toxicity experienced (in 3 patients). Therefore, only mild toxicity was encountered during the immediate posttreatment period, and patients who experienced severe toxicity which continued long-term (beyond eight weeks of treatment completion) were extraordinary cases.

In the study by Yamada et al 2005 toxicity was graded using the Radiation Therapy Oncology Group classification system. Two patients experienced transient grade 2 toxicity in the form of mucositis and in both cases the mucositis resolved within six weeks of radiation therapy. There were no other significant cases of acute or late toxicity (Table 6). The patients enrolled in this study were considered complicated cases as they had either received previous irradiation over the spinal cord (metastatic cancer patients) or required irradiation beyond traditionally tolerated spinal cord doses (4500-5000 cGy in standard fractions) to achieve local control (primary cancer patients). Having only experienced mild and transient toxicity suggests IG IMRT was successful in delivering concentrated radiation to the specific cancer target alone. Overall, there were no significant cases of acute toxicity or late toxicity (including neuropathy or myelopathy) observed.

Yamada et al 2008 reported no acute toxicity ≥ grade 3. Similarly three patients experienced skin reactions of grade 1-2 and another two patients experienced grade 2 acute oesophagitis. Overall the toxicity experienced was minor and no difference in toxicity was noted as a result of the radiation dose received by the spinal cord (12 or 14 Gy).

Table 6 Spine safety outcomes

<table>
<tr><th>Study ID</th><th>Outcomes</th></tr>
<tr><td>Jin et al (2007)</td><td>Patient tolerance
• Procedure time (mean): 50 minutes, including setup, position localisation, verification and delivery.
• Skin reactions were seen in patients with posterior element involvement and when the target was closer to the posterior skin surface.</td></tr>
<tr><td>Terezakis et al (2007)</td><td>Toxicity
<table>
<tr><th>Toxicity</th><th>Skin</th><th>Oesophagitis</th><th>Fatigue</th><th>Nausea</th><th>Pain</th><th>Xerostomia</th></tr>
<tr><td colspan="7">ACUTE (within 8 weeks of treatment completion)</td></tr>
<tr><td>Grade 1</td><td>12</td><td>6</td><td>6</td><td>3</td><td>1</td><td>1</td></tr>
<tr><td>Grade 2</td><td>3</td><td>-</td><td>-</td><td>1</td><td>1</td><td>-</td></tr>
<tr><td>Grade 3</td><td>1</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Grade 4</td><td>1</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td colspan="7">LONG-TERM (beyond eight weeks of treatment completion)</td></tr>
<tr><td>Grade 1</td><td>0</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Grade 2</td><td>0</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Grade 3</td><td>2</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Grade 4</td><td>1</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table>
• No patient experienced radiation-induced myelopathy
• No evidence of radiation toxicity with cord oedema in the absence of local progression on MRI</td></tr>
<tr><td>Yamada et al (2005)</td><td>Toxicity
• Two patients experienced RTOG grade 2 mucositis, both which resolved within 6 weeks of RT completion.
• One patient was diagnosed with idiopathic vasculitis 3 months after RT and had no evidence of active cancer.
• One patient exhibited mild skin hyperpigmentation.</td></tr>
<tr><td>Yamada et al (2008)</td><td>Toxicity
<table>
<tr><th>Outcome</th><th>Number of patients</th></tr>
<tr><td>Myelopathy or radiculopathy</td><td>0</td></tr>
<tr><td>Severe pain following RT</td><td>1*</td></tr>
<tr><td>Radiographic evidence of vertebral body fractures without tumour progression</td><td>2</td></tr>
<tr><td>Acute grade 1-2 skin reactions</td><td>3</td></tr>
<tr><td>Acute esophagitis (grade 2)</td><td>2</td></tr>
<tr><td>Tracheoesophageal fistula†</td><td>1</td></tr>
</table>
* requiring hospitalisation; † an adriamycin recall reaction might have contributed to this</td></tr>
</table>

NOTES: RTOG: Radiation Therapy Oncology Group; RT: radiotherapy; MRI: magnetic resonance imaging.

Effectiveness

In the study by Jin et al 2007 pain relief was experienced in a high proportion of patients by 4 weeks posttreatment, approximately the same percentage of patients experienced complete pain relief as partial pain relief (Table 7). The authors felt delivery of IMRT in a single session was more convenient for patients as it offered rapid pain relief. One patient with epidural spinal cord compression showed neurological improvement and radiographic tumour disappearance after spinal IMRT.

Terezakis et al 2007 reported five deaths during follow-up, all of which were a result of disease progression; the Kaplan-Meier actuarial estimate for 2 year survival was 79%. Recurrence at the IMRT site occurred in 26% of patients and local failure in 11% (Table 7). The Kaplan-Meier actuarial estimate for 2 year local control was 65%. One limitation of this study was the duration of follow-up. Because of the slow growth rate of primary tumours such as chordomas, longer follow-up was necessary to detect actual recurrence and local control rates. However, this study also included patients with metastatic disease; therefore, longer follow-up may not have been achievable as the expected survival of these patients is generally short.

Symptom palliation was reported objectively and subjectively in this study (Table 7). In both cases patient palliation was considered excellent and durable, as it was analysed at each patient's last follow-up or death. The symptoms measured included pain, motor deficit and sensory deficit. Those with reduced motor or sensory function following IMRT also had local or systemic disease progression; the majority of other patients showed improvement in these symptoms. Subjective evaluation of symptoms produced slightly lower palliation rates compared with objective evaluation, except for pain. This is most likely because pain palliation was measured objectively by the cessation of narcotic use. Narcotic addiction as a result of prolonged use may explain why subjective pain palliation was higher than objective pain palliation despite the inverse trend for the other symptoms reported.

In the study by Yamada et al 2005, palliation of symptoms was achieved in a high proportion of patients (Table 7). These symptoms included paresthesia, pain and weakness. Patients graded these symptoms before and after IMRT on a scale of 1 to 10 for pain, where 10 was the worst pain possible, and on a scale of 1 to 5 for paresthesia and weakness, where 5 was no numbness or weakness. Patients considered symptoms of paresthesia, pain and weakness to be significantly improved from pretreatment to posttreatment, with the largest difference seen in the level of pain experienced ($P = 0.02$; $P < 0.0001$; $P = 0.004$, respectively). Median survival from the time of treatment was longer for patients with primary paraspinal disease compared with those with metastatic disease, as expected (statistical significance not reported).

Finally in the study by Yamada et al 2008 local failures occurred in a small proportion of patients, resulting in a Kaplan-Meier actuarial local control rate of 90%. The total death rate in this study was 40%; all of these deaths were attributed to progression of systemic disease. The 45 month actuarial survival rate was 36%. Table 7 describes these results in greater detail. A prescribed dose of <2300-2400 cGy was significantly associated with local failure (2400 cGY versus <2400 cGy, P = 0.03; >2300 cGy versus <2300 cGy, P = 0.04). Oligometastatic progression data can also be seen in Table 7.

Table 7 Spine effectiveness outcomes

<table>
<tr><th>Study ID</th><th>Outcomes</th></tr>
<tr><td>Jin et al (2007)</td><td>Pain at 4 weeks post-RT
<table>
<tr><th>Outcome</th><th>% patients</th></tr>
<tr><td>Overall pain relief</td><td>85%</td></tr>
<tr><td>Complete pain relief</td><td>38%</td></tr>
<tr><td>Partial pain relief *</td><td>47%</td></tr>
</table>
*defined as decrease of ≥3 levels of pain score</td></tr>
<tr><td>Terezakis et al (2007)</td><td>Recurrence/local control
<table>
<tr><th>Outcome</th><th>Number of patients</th><th>Notes</th></tr>
<tr><td>Recurrence at RT site</td><td>7 (26%)</td><td>Median time to recurrence 9.4 months (range: 2.4 to 18.7)</td></tr>
<tr><td>Patients with recurrence with high-grade tumours</td><td>6/7</td><td>Patient without high-grade had metastatic chordoma at treatment</td></tr>
<tr><td>Recurrence in patients with metastatic lesions</td><td>3/4</td><td>1 patient no salvage, 2 received chemotherapy alone, 1 had chemotherapy and surgery</td></tr>
<tr><td>1 additional surgery</td><td>1</td><td>-</td></tr>
<tr><td>2 additional surgeries</td><td>1</td><td>As well as RT for salvage</td></tr>
<tr><td>Successful salvage of local recurrence</td><td>2</td><td>-</td></tr>
<tr><td>Recurrence in patients with metastatic chordoma</td><td>1</td><td>-</td></tr>
<tr><td>Recurrence in patients with paraspinal sarcoma</td><td>6</td><td>-</td></tr>
<tr><td>Recurrence in patients with previous RT</td><td>3</td><td>-</td></tr>
<tr><td>Local failure in patients with chondrosarcoma</td><td>2/6</td><td>-</td></tr>
<tr><td>Local failure in patients with chordoma</td><td>1/7</td><td>-</td></tr>
</table>
The Kaplan-Meier actuarial estimate for 2 years local control was 65%

Death
• Five patients died at a median of 16 months (range, 6.5-40.7 months) after treatment, all had disease progression.
• 4/5 had local failure
• 4 had metastatic disease at the time of their death.
• Kaplan-Meier actuarial estimate for 2 year survival was 79%

Subjective palliative outcomes
<table>
<tr><th>Symptom</th><th>Number of patients</th><th>Palliation (%)</th></tr>
<tr><td>Pain</td><td>25</td><td>N/A</td></tr>
<tr><td>No pain</td><td>8</td><td>N/A</td></tr>
<tr><td>Improved</td><td>13</td><td>84 (21/25)</td></tr>
<tr><td>Worse</td><td>4</td><td>N/A</td></tr>
<tr><td>With stable disease</td><td>0</td><td>N/A</td></tr>
<tr><td>With disease progression</td><td>4</td><td>N/A</td></tr>
<tr><td>Motor deficit</td><td>10</td><td>N/A</td></tr>
</table></td></tr>
</table>

Study ID	Outcomes

Improved	3	N/A
Stable	5	80 (8/10)
Worse	2	N/A
With stable disease	0	N/A
With disease progression	3	N/A
Sensory deficit	12	N/A
Improved	8	N/A
Stable	2	83 (10/12)
Worse	2	N/A
With stable disease	0	N/A
With disease progression	2	N/A

Objective palliative outcomes

Objective assessment	Before RT (n)	After RT (n)	Palliation (%)
Pain (narcotic use)	16	6	62.5 (10/16)
Motor function (ASIA score)	N/A	N/A	89 (24/27)
A	0	2	N/A
B	1	1	N/A
C	5	2	N/A
D	21	22	N/A
ECOG performance status	N/A	N/A	89 (24-27)
0	1	12	N/A
1	23	10	N/A
2	3	3	N/A
3	0	2	N/A

Yamada et al (2005)

- Median survival from the time of treatment for patients with primary and metastatic disease was found to be 15 months and 7 months, respectively.
- One patient died of acute subarachnoid haemorrhage not related to RT, consequently this patient did not complete treatment and was not included in the analysis.

Palliative benefit of IMRT

Symptom	Number of patients pre-treatment	Number of patients post-treatment	% palliation
Paresthesia	12	1/12	92%
Pain	23	2/23	91%
Strength	10	1/10	90%

Patient assessment of palliation

Symptom	Before RT median score	After RT median score	P value
Pain (0-10)* (n=23)	6.6	1.5	<0.0001

<table>
<tr><th>Study ID</th><th>Outcomes</th></tr>
<tr><td></td><td>
<table>
<tr><td>Paresthesia (0-5)‡</td><td>4.5</td><td>4.9</td><td>0.02</td></tr>
</table>
* Where 10 is worst pain possible; † Where 5 is no weakness; ‡ Where 5 is no numbness

• At last follow-up: 90% of patients treated for metastatic disease and 86% of patients treated for primary disease have not exhibited radiographic progression
• Two primary disease patients demonstrated progression at 15 and 22 months
• Two metastatic disease patients demonstrated progression at 3 and 9 months
• Actuarial local control rates: 75% (primary disease patients) and 81% (secondary disease patients)
</td></tr>
<tr><td>Yamada et al (2008)</td><td>
Local control
<table>
<tr><th>Outcome</th><th>Number of patients/percentage of patients</th></tr>
<tr><td>Actuarial local control rate (Kaplan-Meier)</td><td>90%</td></tr>
<tr><td>Local failure</td><td>7 patients</td></tr>
<tr><td>Estimated cumulative incidence of local failure (including death) at 24 months</td><td>7.5%</td></tr>
<tr><td>Died with local recurrence</td><td>3 patients</td></tr>
<tr><td>Failed salvage surgery</td><td>1 patient*</td></tr>
<tr><td>45 month actuarial survival rate</td><td>36%</td></tr>
<tr><td>Total death rate</td><td>37 (40%)†</td></tr>
</table>
*underwent subsequent RT and was without evidence of recurrence; † all deaths attributed to progression of systemic disease, all but 1 death had no evidence of local failure at death

Effect of dose
• Prescribed dose of <2300-2400 cGy (2400 cGY versus <2400 cGy, P=0.03; >2300 cGy versus <2300 cGy, p=0.04) significantly associated with local failure.
• Mean dose of patients with failure after lower dose treatment was 2080 cGy.
• Mean time to failure in low dose patients was 8.2 months (range, 5-13 months).

Oligometastatic status
<table>
<tr><th>Histologic type</th><th>Patients with >3 metastases</th><th>Median time to progression</th><th>Probability of progression</th><th>Median follow-up</th><th>Survival</th></tr>
<tr><td>Head and neck</td><td>1/8</td><td>11.5 months</td><td>20%</td><td>20.7 months</td><td>100%</td></tr>
<tr><td>Breast</td><td>1/3</td><td>12 months</td><td>33%</td><td>12 months</td><td>100%</td></tr>
<tr><td>Prostate</td><td>4/11</td><td>11.2 months</td><td>41%</td><td>18.3 months</td><td>92%</td></tr>
<tr><td>Sarcoma</td><td>2/8</td><td>9.3 months</td><td>35%</td><td>12 months</td><td>66%</td></tr>
<tr><td>Melanoma</td><td>3/8</td><td>6.6 months</td><td>37%</td><td>15.2 months</td><td>60%</td></tr>
<tr><td>Lung</td><td>5/7</td><td>8.8 months</td><td>79%</td><td>15 months</td><td>100%</td></tr>
<tr><td>Renal</td><td>5/10</td><td>7.7 months</td><td>76%</td><td>12 months</td><td>36%</td></tr>
<tr><td>Gastrointestinal</td><td>4/10</td><td>11.3 months</td><td>65%</td><td>16.4 months</td><td>16%</td></tr>
</table>
</td></tr>
</table>

NOTES: RT = radiotherapy; MSBF: Memorial stereotactic body frame; SD: standard deviation; CT = computer tomography; MBC: Memorial body cradle; AP = anterior/posterior; SI = superior/inferior; IMRT = intensity-modulated radiotherapy; DVH: dose volume histogram; N/A = not applicable; ASIA: American Spine Injury Association; ECOG: Eastern Cooperative Oncology Group.

Head and neck cancer

One case series studies reported the use of IG IMRT for the treatment of head and neck cancer (Chen et al 2009). Table 8 describes the specific IG IMRT treatment details for this indication.

Chen et al (2009) evaluated the effectiveness of helical tomotherapy IG IMRT in 77 consecutively recruited patients (46 male). The primary population of this study had histologically proven squamous cell carcinoma of the head and neck (primary site: 39 oropharynx, 13 oral cavity, 6 larynx, 5 hypopharyns, 5 nasopharynx, 5 paranasal sinus, 5 unknown). Median age was 58 years (range: 27-92 years). A total of 42 patients (55%) were treated by helical tomotherapy with definitive intent, while the remaining 35 patients (45%) were treated with helical tomotherapy postoperatively following gross surgical resection. After treatment, patients were evaluated every 2 to 8 weeks for the first 6 months then every 3 months thereafter. Baseline posttreatment CT scan of the head and neck were performed within 2 to 6 months after completion of treatment and yearly thereafter (or when clinically required). Median follow up duration was 21 months (range: 3-29 months) (Chen et al 2009).

Table 8 Summary of IG IMRT treatment details for head and neck cancer study

Study ID	No. of patients	Type of IG	Frequency of IG	Correction protocol	Immobilisation	CTV/PTV	IMRT dose
Chen et al (2009) Level IV interventional evidence	77 patients	Megavoltage computed tomography	Daily	During first week of therapy, physician and radiation therapist reviewed fused image in the sagittal, coronal and axial planes using the fusion split screen display daily. Bony landmarks for confirming alignment and thresholds for positioning correction were established in this initial period. Thereafter, attending physician reviewed the fused images once weekly or when patient position was outside established tolerances. Then patients were automatically repositioned for treatment delivery by the HT system for the calculated superior-inferior and anterior-posterior shorts. The system requires the therapist to move the treatment couch manually for right-left lateral shifts.	Head, neck and shoulders were immobilised in a hyperextended position using a perforated, thermoplastic head mask with the neck supported on a Timo cushion (S-type, med-Tec, Orange City, United States) mounted on carbon fiber board (S-tyoe, Med-Tec, Orange City, United States).	CTV1: GTV plus margin of 1-2cm to account for microscopic disease spread. For patients who received HT postoperatively, this was defined as the surgical tumour bed at risk for harbouring microscopic residual disease. CTV2: included prophylactically treated cervical and supraclavicular nexk (both definitive and postoperative patients) CTV3: used in some cases to designate an area at lowest risk within the prophylactically treated low neck. PTV1/2/3: automated 0.3 to 0.5 expansion of the CTV surgaces to account for patient setup error.	*Definitive therapy* 66 to 70Gy to 95% or more of PTV1 and 60 to 63Gy to 95% or more of the PTV2. *Postoperative therapy* 60 to 66Gy to at least 95% of PTV1. Prescribed dose to PTV3 was 54Gy. Median dose (entire population): 66Gy (range: 60-72Gy)

NOTES: IG = image-guidance; CTV = clinical target volume; PTV = planning target volume; IMRT = intensity-modulated radiotherapy; HT = helical tomotherapy; GTV = gross tumour volume; CBCT = cone beam computer tomography; CT = computer tomography; LR = left/right; SI = superior/inferior; AP = anterior/posterior.

Safety

Chen et al (2009) noted that practically all patients experienced skin erythema, odynophagia, taste alterations and dry mouth in the acute stage (terms 'acute' and 'late' not defined). In a later setting, 74% (57/77) of patients complained of some subjective degree of xerostomia and 13% (10/77) of patients had grade 3 oesophageal toxicity. Of these, seven patients were diagnosed with oesophageal stricture. There were 2 cases of osteonecrosis at 12 and 15 months after definitive radiation therapy where significant sections of the mandible received greater than 70 Gy of radiation. Orocutaneous fistula occurred in 2 patients, both of whom required post-treatment surgical intervention. The investigators reported no cases of neurological or central nervous system toxicity.

Effectiveness

Chen et al (2009) reported that the two-year Kaplan Meier estimates for overall survival, local-regional control and disease-free survival was 82%, 77% and 71%, respectively (Table 9). In the subgroup that received helical tomotherapy as definitive treatment, 19% (8/42) continued to have persistent local-regional disease (all within cervical neck). After neck dissection, four of these had no pathological evidence of residual cancer. The remaining four patients had microscopic foci of malignancy measuring less than 1cm. After salvage surgery, three of these patients developed distant metastasis (lungs) 5 months (median) after completion of HT. An additional five patients who underwent definitive HT had local-regional recurrence at a median of nine months after HT. For the subgroup of patients who received postoperative HT, 26 % (9/35) experienced local-regional recurrence at a median of 10 months. Spatial evaluation of local-regional failures revealed that 89% (16/18) of patients who experienced progression in the primary site or neck failed in the high dose PTV1 (Chen et al 2009).

Table 9 Head and neck effectiveness outcomes

Study ID	Outcomes
Chen et al (2009)	*Survival* • Kaplan-Meier estimate of overall survival at 2 years was 82% • 14 patients died during the evaluation period (7 from progressive disease at local-regional sites, 5 from complications related to metastatic disease, 1 from intercurrent disease, and 1 suicide). *Local-regional control* • Kaplan-Meier estimate of local-regional control at 2 years was 77%. • Total of 18 patients experienced progression or recurrence of local-regional disease. • Spatial evaluation of patients demonstrated 16/18 patients progressed in the primary site or neck failed in the high dose PTV1. • 7/9 of patients with local-regional recurrence treated with definitive intent failed in the high dose (70Gy) PTV1. • Remaining 2/9 patients suffered local-regional failure in the region of the lower dose (60-63Gy) PTV2. *Disease free survival* • Kaplan-Meier estimate of disease free survival at 2 years was 71%. • Total of 15 patients developed distant metastasis at median time of 16 months (range: 6-21 months).

NOTES: PTV = planning target volume margin.

Other cancer types

This section of the report briefly summarises studies reporting the use of IG IMRT for cancers other than prostate, spine, or head and neck. The results related to the use of IG IMRT for prostate, spine or head and neck cancers in these studies have not been reported as results for these indications have been presented in greater detail (and from better quality evidence) in the previous sections. The included studies are grouped below by the image guidance modality employed.

Helical tomotherapy

Two studies reported the use of helical tomotherapy-based IG IMRT to treat various cancers (Jang et al 2009; Adkison et al 2008).

In the study by Jang et al 2009, 42 consecutive patients were treated for hepatocellular carcinoma (HCC) with or without extrahepatic metastases. Each patient underwent two series of CT scans for simulation and computer planning. Before each treatment, an mV CT (MVCT) scan using the tomotherapy Hi-Art system was used to confirm the location of the tumour and surrounding organs at risk. The total radiation dose delivered ranged from 30-57.61 Gy and was delivered in 10 fractions over a two week period. All patients with eligible tumour location underwent adjuvant chemotherapy subsequent to IG IMRT.

Adkison et al 2008 reported the use of helical tomotherapy, delivered using a hypofractionated schedule (five weeks) in 46 patients with inoperable non-small cell lung cancer, to eliminate the effect of accelerated repopulation. Treatment planning imaging included a CT and 4D-CT, which were used to identify the motion-defined envelope of the gross tumour volume, which inturn defined the CTV (motion envelope + 6 mm) and PTV (CTV + 2 mm). All patients were treated over 25 fractions with a dose per fraction of 2.28-3.22 Gy and followed-up for a median of 8.1 months.

Safety

The adverse events experienced by the HCC patients in Jang et al 2009 during the treatment period are listed below (Table 10). Based on these results the authors suggest that IG IMRT is a good method of palliating difficult-to-treat patients. This is due to the reduced toxicity associated with a more direct and accurate delivery of treatment radiation.

Table 10 Adverse events and Radiation Therapy Oncology Group score in Jang et al 2009

Event	Acute (within 1 month) toxicity (n [%])			Subacute or chronic toxicity (n [%])		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Constitutional symptoms	5 (11.9)	0 (0)	0 (0)	8 (19.0)	2 (4.8)	0 (0)
Anorexia	3 (7.1)	0 (0)	0 (0)	6 (14.3)	0 (0)	0 (0)
Neutropenia	1 (2.4)	2 (4.8)	0 (0)	8 (19.0)	6 (14.3)	1 (2.4)
Thrombocytopenia	2 (4.8)	0 (0)	0 (0)	6 (14.3)	4 (9.5)	0 (0)
Hepatitis	4 (9.5)	1 (2.4)	0 (0)	5 (11.9)	8 (19.0)	3 (7.1)
Pneumonitis	0 (0)	0 (0)	0 (0)	4 (9.5)	0 (0)	0 (0)
Ileus	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.4)	0 (0)
Gastric ulcer	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.4)
Gastroenteritis	0 (0)	0 (0)	0 (0)	0 (0)	2 (4.8)	0 (0)

The study by Adkison et al 2008 reported the incidence of adverse events and Radiation Therapy Oncology Group score in the table below (Table 11). Weight loss associated with grade 1 and 2 oesophagitis was minimal (2.3%) and overall weight loss in all patients while under treatment was also minimal (1.6%).

Table 11 Adverse events and Radiation Therapy Oncology Group score in Adkison et al 2008

Adverse event	Percentage of patients		
	Grade 1	Grade 2	≥ Grade 3
Pneumonitis	70%	13%	0%
Oesophagitis	24%	15%	0%

Effectiveness

Jang et al 2009 reported tumour and α-fetoprotein (AFP; a hepatocellular tumour marker) level response for each organ treated with helical tomotherapy (Table 12). Complete response occurred less often than partial response, and the rate of stable disease at each site treated was greater than the incidence of progressive disease. Therefore, although complete tumour eradication often did not occur, disease progression was generally ceased, improving patient survival. The overall survival rate at six, 12, 18 and 24 months was 75.2%, 50.1%, 19.9% and 14.9%, respectively, with a median duration of survival of 12.3 months. Causes of death included tumour progression, hepatic failure without tumour progression, sepsis and pneumonia.

Table 12 Tumour, AFP and disease response to treatment in Jang et al 2009

RT site	Number of patients (%)				
	Intrahepatic HCC	Pulmonary metastasis	Lymph node/adrenal metastasis	Soft-tissue metastasis	AFP response
Complete response	0/31 (0)	5/19 (26.3)	1/20 (5.0)	0/6 (0)	4/33 (12.1)
Partial response	14/31 (45.2)	8/19 (42.1)	11/20 (55.0)	4/6 (66.7)	20/33 (60.6)
Stable disease	15/31 (48.4)	6/19 (31.6)	7/20 (35.0)	2/6 (33.3)	5/33 (15.2)
Progressive disease	2/31 (6.5)	0/19 (0)	1/20 (5.0)	0/6 (0)	4/33 (12.1)

This study found helical tomotherapy to be safe and feasible, as it is associated with high local control and improved survival in patients with HCC with extrahepatic metastases who would normally have a poor prognosis.

In the study by Adkison et al 2008 complete or partial response to treatment was achieved in 17% and 43% of patients, respectively. Stable disease was the best response for 26% of patients, compared with 6.5% of patients who developed

immediate progressive disease. Local failure occurred in six patients (13%), four of whom had disease progression. Thirteen patients (28%) developed distant metastases. The actuarial 2-year overall survival rate was 46.8% ± 9.7%, with a median survival of 18 months. Overall, the authors demonstrated that higher doses of radiation (hypofractionated radiotherapy) may be delivered to patients safely, with lower than expected toxicities (< grade 3).

Ultrasound

Two studies report the use of US-based IG IMRT to treat abdominal, biliary tract, and pancreatic malignancies (Fuller et al 2009; Fuss et al 2007).

Fuller et al 2009 conducted a retrospective non-randomised comparative study with a historical comparison group. The study used US-based IG to deliver IMRT to patients with malignancies of the biliary tract (gallbladder and extrahepatic bile ducts) and compared IG- and non-IG IMRT in 24 patients each. Patient characteristics were similar between both patient groups. In the majority of patients, similar treatment planning and delivery methodology was employed as in the previous study by Choi et al 2009. The prescribed dose to the PTV (in patients receiving IG IMRT) ranged from 46-56 Gy in daily fractions of 1.8-2 Gy (median 50 Gy), while the median total prescribed dose in patients undergoing conventional RT was 48 Gy (range: 46 to 50.4 Gy).

Fuss et al 2007 reported a retrospective case series in which US-based IG IMRT was used to treat pancreatic cancer in 41 patients. The PTV was defined as the CTV plus 6-10 mm. CT-delineated target and guidance structure outcomes were superimposed onto real-time transabdominal US images, the required correctional shifts were made and a second US image for verification of alignment was acquired. The total prescribed dose for these patients ranged from 45-64 Gy (median 54 Gy, mean 55 Gy). Patients were followed-up for a median of 12.8 months.

Safety

Acute (term ‘acute’ not defined) toxicity reported in the study by Fuller et al 2009 are presented in Table 13. Minimal treatment interruptions occurred for most patients, none of which were due to acute radiation toxicity. There were also no treatment related deaths, or hospital readmissions for symptoms relating to treatment. Chi-square analysis with Fisher’s exact test were used to compare the ratio of patients with Radiation Therapy Oncology Group ≤ grade 2 versus grade 3, and found there was no significant difference (P = 0.067). There was a significant difference between the proportion of patients with Radiation Therapy Oncology Group ≤ grade 2 in the conventional RT group and the IG IMRT group (P = 0.0465).

Table 13 Radiation Therapy Oncology Group acute toxicity grade in Fuller et al 2009

Acute toxicity	Number of patients (%)				
	All patients	IG IMRT	Conventional RT	Bile duct	Gallbladder
Upper gastrointestinal (%)					
0	15 (31)	7 (29)	8 (33)	7 (37)	8 (28)
1	11 (23)	4 (17)	7 (29)	3 (16)	8 (28)
2	20 (42)	11 (46)	9 (38)	8 (42)	12 (41)
3	2 (4)	2 (8)	-	1 (5)	1 (4)
Lower gastrointestinal (%)					
0	30 (63)	10 (42)	18 (62)	18 (62)	12 (63)
1	12 (25)	8 (33)	7 (24)	7 (24)	5 (26)
2	6 (12)	6 (25)	4 (14)	4 (14)	2 (10)
Maximum (%)					
0	13 (27)	5 (21)	6 (31)	6 (31)	7 (24)
1	11 (23)	4 (17)	4 (21)	4 (21)	7 (24)
2	22 (46)	13 (54)	8 (42)	8 (42)	14 (48)
3	2 (4)	2 (8)	1 (4)	1 (4)	1 (3)

In the study by Fuss et al 2007 a total of four patients (9.7%) were unable to complete their prescribed course due to treatment-related toxicity, and five other patients had treatment interruptions as a result of toxicity (however, they were able to complete the prescribed course).

Table 14 Acute treatment-related toxicity according to Radiation Therapy Oncology Group grading in Fuss et al 2007

Toxicity (RTOG criteria)	Grade	Number of patients	%
Upper gastrointestinal	0	12	23.9
	1	10	24.4
	2	16	39.0
	3	3	7.3
	4	0	0.0
Lower gastrointestinal	0	24	58.5
	1	8	19.5
	2	7	17.1
	3	0	0.0
	4	2	4.9
Maximum observed	0	9	22.0
	1	11	26.8
	2	17	41.5
	3	2	4.9
	4	2	4.9

Effectiveness

Fuller et al 2009 reported a statistically significant difference in the mean delivered dose of radiation between the IG and conventional treatment groups (P = 0.0001). Patterns of local failure, distant metastases and disease progression are summarised below (Table 15).

Table 15 Patterns of failure (n=37) in Fuller et al 2009

	N_{events}	$N_{censored}$	Median (months)
Local failure			
Conventional RT	6	11	12.0[a]
IG IMRT	9	11	9.6
Gallbladder	7	13	7.8[a]
Bile duct	8	9	7.5
Distant metastasis			
Conventional RT	7	10	21.00
IG IMRT	6	14	26.4
Gallbladder	4	16	22.0[a]
Bile duct	9	8	17.7
Recorded disease progression (any)			
Conventional RT	12	5	5.2
IG IMRT	13	7	7.5
Gallbladder	11	9	6.5
Bile duct	14	3	7.8

[a] Biased estimate on product-limit analysis
* Survival data collected and examined using Kaplan-Meier method

At last follow-up, 16% (8/48) of patients were alive. The table below (Table 16) lists the median survival outcomes for patients completing radiation prescription (confidence intervals in brackets). Overall, in comparison with conventional radiation techniques, IG IMRT was feasible for biliary tumours (Fuller et al 2009).

Table 16 Survival in Fuller et al 2009

Cohort	Series	Bile duct	Gallbladder
All patients	13.9 (9.0-17.6)	11.1 (6.6-17.6)	14.7 (9.0-31.2)
Radiotherapy			
IMRT	17.6 (10.3-32.3)	15.0 (7.6-22.3)	23.0 (9.8-36.5)
Conventional RT	9.0 (6.6-17.3)	6.9 (1.7-11.2)	13.3 (5.9-31.4)
Surgery			
Unresectable	6.6 (3.2-8.9)	7.6 (1.7-11.1)	3.2 (9.8-36.5)
Resectable	17.3 (13.0-31.4)	17.6 (5.7-*)	17.2 (12.4-34.1)
R0	16.9 (9.8-24.2)	*	17.3 (9.0-*)
R1/R2	14.7 (8.22-22.1)	15.0 (5.7-21.1)	14.7 (8.1-36.5)
Chemotherapy			
None	11.1 (4.9-17.3)	8.7 (4.9-14.2)	17.3 (6.5-36.5)
Chemoradiation	14.7 (9.0-23.0)	17.8 (6.6-*)	13.0 (9.8-31.7)

Fuss et al 2007 also reported median overall survival rate in patients with adenocarcinoma to be 10.3 months (Kaplan-Meier estimate). The median estimated survival in patients with inoperable tumours was 10.0 months (range: 3.4 to 28.0 months) and the median estimated survival in patients treated in the postoperative adjuvant setting (salvage RT) was 10.8 months (range: 6.2 to 55.1 months). The actuarial survival at 1- and 2-years for all patients diagnosed with adenocarcinoma was 38% and 25%. Overall, daily IG IMRT for pancreatic carcinoma is clinically feasible. The outcomes of this study supported the conclusion that margin reduction and moderate dose escalation made possible by IG IMRT techniques, yields positive preliminary outcomes.

Cost Analysis*

A cost-outcome analysis of IG IMRT for the treatment of prostate cancer was reported by Ploquin et al 2009. The study used activity based costing to determine the incremental cost of adding image-guided patient repositioning (a significant component of IG IMRT) to IMRT and 3D-conformal radiation therapy (3D-CRT). A metric developed by the authors, based on the Equivalent Uniform Dose was used. The analysis modelled three approaches to image guidance acquisition (MV, KV and cone beam CT) with the assumption that the inherent accuracy of the three techniques is identical. The analysis estimated the dosimetric outcome benefit resulting from the implementation of image guided patient repositioning (IGPR) from the study by van der Heide et al 2007 (included for safety and effectiveness) in which the setup accuracy of using each of four correction protocols was reported. The results demonstrated that based on the calculated metric, the daily shrinking action level protocol was the protocol which would provide the greatest dose gradient between target and surrounding healthy tissue. Furthermore, when 3D-CRT and IG IMRT were compared, IG IMRT demonstrated superior cost-outcome ratio. The incremental cost (2005 Euros) and cost outcome (2005 Euros/Gy) for a course of 3D-CRT and IMRT with 21 or 35 fractions with each of the four correction protocols described by van der Heide et al 2007 were calculated. These demonstrated that regardless of the correction protocol applied, imaging modality utilised or the number of fractions delivered, the cost-outcome was lower for IMRT.

The analysis did not consider image-guided corrective translations of the patient and did not address margin reduction, rotations, organ deformation or major equipment failure modes. Therefore the authors claim that additional clinical benefit, without additional cost, would result when these variables were factored in.

Knight et al (2009) reported the purchase costs of installing a linear accelerator with in-room CT capabilities. The Siemens PRIMATOM™ (Siemens Medical Systems, Muenchen, Germany), consisting of a PRIMUS™ linear accelerator (Siemens Medical Systems, Muenchen,Germany) and a Somatom Balance CT scanner (Siemens Medical Systems, Muenchen,Germany) mounted on rails was the system used to enable image guidance. At the time of purchase, 2002, the Somatom Balance CT scanner cost an additional $A563,000 (2002) in order to transform the Primus to a Primatom. One additional week was required to commission the machine, including verification of the geometry. Furthermore the machine requires an additional 30 minutes each day quality assurance time to maintain the CT scanner. While additional data storage was not purchased (because of sufficient space on the CT hardware), the authors state that backup tapes have been used to transfer data no longer required.

Newer linear accelerators have IG IMRT capabilities integrated into each system. At the time of writing no cost data based on these newer linear accelerators was available.

Ethical Considerations

Informed Consent

Practice guidelines for image guided radiation therapy state it is the role of the radiation oncologist to have ample and clear discussion with patients regarding the impact of image guided treatment, including the potential benefits and harms of the procedure (ACT Practice Guideline 2009).

Access Issues

In order to perform IG IMRT the treating centre must have access to a linear accelerator, multi-leaf collimator and inverse treatment planning software. Linear accelerators are used to deliver conventional radiotherapy; therefore, many hospitals may already have access to one. A linear accelerator can be retrofitted with the appropriate equipment to perform IG IMRT.

Rural hospitals may not have access to a linear accelerator or the associated IMRT equipment; therefore, patients from rural areas may need to travel to receive treatment. Because IG IMRT allows the direct treatment of tumours with higher dose radiation compared with conventional radiation treatment, the time in which it takes to complete IMRT may be reduced, making IG IMRT more convenient for these patients. Several studies also report single-dose IG IMRT, which, where appropriate, could offer an even more convenient treatment option for patients from rural areas.

Because different image guidance modalities can be used to deliver IMRT, centres need not invest in new equipment. Hospitals equipped with BAT ultrasound, low- or high-energy (kV or mV) cone beam CT, or portal imaging facilities that can be coupled with IMRT equipment can carry out IG IMRT.

It is also important the patient is able to receive IG IMRT whilst immobilised on the treatment couch so that alignment data are not lost once the patient is moved or whilst they wait for imaging or irradiation equipment to be transported to them. Position verification should be carried out and corrected in the same room as each treatment fraction is delivered.

A team of radiation oncology personnel is required to carry out IG IMRT, they include a radiation oncologist, a medical physicist, and a radiation therapist. These personnel are responsible for managing the overall disease-specific treatment regimen for patients undergoing IG IMRT including proper patient positioning, the recommendation of procedures to account for inherent organ motion (such as breathing), deciding the acceptable day-to-day set-up variations allowed, and implementing and managing a quality assurance programme.

Ethical and social issues

There were no cultural or religious considerations identified from the literature in regards to the use of this technology.

Training

There is little literature available regarding the training that is required to carry out IG IMRT. As previously stated, a radiation oncologist, a qualified medical physicist and a radiation therapist are needed to perform image guided radiation therapy (ACR Clinical Guideline 2009).

As with any procedure, a learning curve would be expected when IG IMRT is first introduced within a hospital. In some of the included studies, IG-based position verification was assessed by two independent radiologists until a consented agreement was reached regarding the repositioning of the patient.

Expert clinical opinion states that there is in fact a significant learning curve associated with the use of IG IMRT and that difficulties lay in commissioning expertise amongst medical physicists and radiation therapists with regards to the assessment of treatment setup variability. Historically, adequate training in the delivery of IG IMRT is received by 1-2 key people per hospital/department and if these people move the process stops; therefore, efforts in training entire teams of radiation oncology personnel is necessary to make IG IMRT use sustainable.

Due to the wide range of IG techniques available training is likely to be conducted per centre, as each centres facilities for IG IMRT would vary slightly from the next.

Clinical Guidelines

Recent practice guidelines were identified for image-guided radiation therapy. These guidelines were developed collaboratively by the American College of Radiology (ACR) and the American Society for Therapeutic Radiology and Oncology (ASTRO) with the aim of assisting practitioners in providing appropriate radiologic care for patients. Specifically, the guidelines address the clinical implementation of image guided radiation therapy, including personnel qualifications, quality assurance standards, and suggested documentation.

Several of the included prostate cancer studies outlined the importance of consistent bladder and bowel preparation protocol. The general consensus was that an empty bowel and full bladder were ideal for improving image quality and minimising movement of the target organ.

There does not appear to be any Australian clinical guidelines available for IG IMRT. For reasons mentioned previously, clinical guidelines should cover all of the imaging techniques that can be used in conjunction with IMRT, so that

depending on the facilities of each centre IG IMRT can be performed in a uniform manner across Australia.

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

An Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, an Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of image-guided intensity-modulated radiotherapy, its present and potential use in the Australian public health system, and future implications for the use of this technology.

Search Strategy used for the Report

The sources utilised in this assessment are listed in Table 17. The medical literature was searched with the search terms outlined in Table 18 to identify relevant studies up to August 2009 in English only. In addition to this, major international health technology assessment databases and clinical trial registers were searched.

Table 17 Literature sources utilised in assessment

Source	Location
Electronic databases	
AustHealth	University of Adelaide library
Australian Medical Index	University of Adelaide library
CINAHL	University of Adelaide library
Cochrane Library – including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	University of Adelaide library
Current Contents	University of Adelaide library
Embase	Personal subscription
Pre-Medline and Medline	University of Adelaide library
PyscINFO	Personal subscription
RACS electronic library	Personal subscription
Internet	
Blue Cross and Blue Shield Association's Technology Evaluation Center	http://www.bcbs.com/tec/
Canadian Agency for Drugs and Technologies in Health	http://www.cadth.ca
Current Controlled Trials metaRegister	http://www.controlled-trials.com/
EuroScan	http://www.euroscan.bham.ac.uk/
Health Technology Assessment International	http://www.htai.org/
International Network for agencies for Health Technology Assessment	http://www.inahta.org
Medicines and Healthcare products Regulatory Agency (UK)	http://www.mhra.gov.uk/
US Food and Drug Administration, Center for Devices and Radiological Health	http://www.fda.gov/cdrh/index.html
US Food and Drug Administration, Manufacturer and User Facility Device Experience Database	http://www.fda.gov/cdrh/maude.html
UK National Research Register	http://www.nrr.nhs.uk/
Websites of specialty organisations	http://www.anzdata.org.au

Table 18 Search terms utilised

Search terms
MeSH
N/A
Text words
Image guid*, IG, intensity modulat*, radiotherapy*, radio therap*
Limits
English

Availability and Level of Evidence

The medical literature (Table 17) was searched utilising the search terms outlined in Table 18 to identify relevant studies and reviews, until August 2009. In addition, major international health assessment databases were searched.

A total of 20 studies were retrieved for inclusion in this horizon scanning report. Fourteen studies were included for safety and effectiveness while an additional six studies presenting technical outcomes were presented in Appendix C. Of the studies included in the safety and effectiveness section, four were non-randomised comparative studies (Level III-2 evidence n = 2; Level III-3 evidence n = 2), and ten were case series studies (Level IV evidence). The profiles of the included studies are summarised in Appendix B.

Sources of Further Information

Searches of clinical trial registers revealed several clinical trials currently being implemented for the use of IG IMRT to treat various cancer types. All of these trials are currently recruiting patients. The list below summarises the number of patients looking to be recruited in each trial, along with the location at which the trial is being conducted and its approximate conclusion date.

- Study using high-dose single fraction image-guided radiotherapy for metastatic lesions to soft tissue masses, lymph node, or bone. n=290, Memorial Sloan-Kettering Cancer Center, May 2010.

- Image guided intensity modulated reirradiation (IG IMRT) with Cetuximab for locoregionally confined recurrent head and neck squamous cell carcinoma. n=30, Penn State University, July 2016.

- Dose escalation study using ultra-hypofractionated, image-guided, intensity-modulated radiotherapy in prostate cancer. n=200, Memorial Sloan-Kettering Cancer Center, May 2013.

- Evaluation of Image Guided Radiotherapy Techniques for Prostate Radiotherapy. n=48, Clatterbridge Centre for Oncology, December 2009.

Other pertinent studies reporting the use of IG IMRT, which were excluded from the current review due to insufficient patient numbers (< 30 patients) or study design (case reports) are listed below.

- Polat B, Guenther I, Wilbert J, Goebel J, Sweeney RA, Flentje M, Guckenberger M. Intra-fracrtional uncertainties in image-guided intensity-modulated radiotherapy (IMRT) of prostate cancer. *Strahlentherapie und Onkologie* 2008; **184** (12): 668-673.

- Soete G, Arcangeli S, De Meerleer G, Landoni V, Fonteyne V, Arcangeli G, De Neve W, Storme G. Phase II study of a four-week hypofractionated external beam radiotherapy regimen for prostate cancer: report on acute toxicity. *Radiotherapy and Oncology* 2006; **80** (1): 78-81.

- Sandhu A, Sethi R, Rice R, Wang J, Marcus L, Salem C, Downs T, Kellogg Parsons J, Millard F, Pawlicki T, Mundt A. Prostate bed localisation with image-guided approach using on-board imaging: reporting acute toxicity and implications for radiation therapy planning following prostatectomy. *Radiotherapy and Oncology* 2008; **88** (1): 20-25.

- Wong JR, Grimm L, Uematsu M, Oren R, Cheng CW, Merrick S, Schiff P. Image-guided radiotherapy for prostate cancer by CT-linear accelerator

combination: prostate movements and dosimetric considerations. *International Journal of Radiation, Oncology, Biology, Physics* 2005; **62** (2): 561-569.

- Wright JL, Lovelock M, Bilsky MH, Toner S, Zatcky J, Yamada Y. Clinical outcomes after reirradiation of paraspinal tumours. *American Journal of Clinical Oncology* 2006; **29** (5): 495-502.

- Sterzing F, Schubert K, Sroka-Perez G, Kalz J, Debus J, Herfarth K. Helical tomotherapy: experiences of the first 150 patients in Heidelberg. *Strahlentherapie und Onkologie* 2008; **184** (1): 8-14.

Studies that appeared to be eligible for inclusion from their abstracts, but did not yet have published full text, therefore were excluded from the report, include the following.

- 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. *International Journal of Radiation, Oncology, Biology, Physics* 2009 Apr 21 [Epub ahead of print].

- Stoiber EM, Lechsel G, Giske K, Muenter MW, Hoess A, Bendl R, Debus J, Huber PE, Thieke C. Quantitative assessment of image-guided radiotherapy for paraspinal tumors. *International Journal of Radiation, Oncology, Biology, Physics* 2009 Jul 11 [Epub ahead of print].

- Eisbruch A, Harris J, Garden AS, Chao CK, Straube W, Harari PM, Sanguineti G, Jones CU, Bosch WR, Ang KK. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer. *International Journal of Radiation, Oncology, Biology, Physics* 2009 Jun 17 [Epub ahead of print].

- Den RB, Doemer A, Kubicek G, Bednarz G, Galvin JM, Keane WM, Xiao Y, Machtay M. Daily image guidance with cone-beam computer tomography for head-and-neck cancer intensity-modulated radiotherapy: a prospective study. *International Journal of Radiation, Oncology, Biology, Physics* 2009 Jun 17 [Epub ahead of print].

Conclusions

Intensity-modulated radiotherapy is now established as a method of delivering highly conformal radiation to tumours. The use of IMRT allows the sparing of high radiation doses to sensitive structures in close proximity to the tumour. Image guidance through various techniques and its combination with IMRT has further improved the ability to deliver highly conformal and accurate radiation delivery.

The majority of evidence available regarding the use of IG IMRT to treat tumours came from case series studies. Furthermore, the majority of evidence available reported the use of IG IMRT to treat tumours of the prostate.

The evidence available suggests that IG IMRT, regardless of the imaging technique applied, was not directly associated with major adverse events, and that of the adverse events that did occur toxicity (both acute and long term) was the most common. The results indicate that patients treated with IG IMRT generally report mild and transient toxicity. More specifically, patients with prostate cancer treated with IG IMRT generally exhibited genitourinary toxicities more often than gastrointestinal toxicities. Importantly, in one study it was demonstrated that prescription dose was not associated with toxicity outcomes, indicating the ability of IG IMRT to provide adequate tumour dose coverage whilst minimising exposure to surrounding healthy tissue.

In terms of effectiveness outcomes the results indicate that IG IMRT enables control of dose distribution by sparing critical structures from receiving high doses of radiation. Where reported, the use of IG IMRT led to substantial improvements in patient symptoms and the technique was associated with a reduction in disease progression.

High quality comparative evidence is required to establish the effectiveness of IG IMRT in regards to IMRT. However, the current evidence available suggests that by reducing treatment related uncertainties, IG IMRT may allow the reduction of treatment margins, thus reducing exposure to radiation of normal tissue surrounding the tumour and treatment-related toxicities. This may allow for safe additional dose escalation to the tumour, increasing the likelihood of tumour eradication.

Further cost analysis data, preferably comparing IG IMRT with IMRT, is also needed so that cost implications in terms of patient outcomes and the increased time required for treatment planning can be determined.

Appendix A: Levels of Evidence

Table 19 Designation of levels of evidence according to type of research question

Level	Intervention [§]	Diagnosis [**]	Prognosis	Aetiology [†††]	Screening
I [*]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, [§§] among consecutive patients with a defined clinical presentation [††]	A prospective cohort study [***]	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, [§§] among non-consecutive patients with a defined clinical presentation[††]	All or none [§§§]	All or none [§§§]	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial [†] Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study [‡] Interrupted time series without a parallel control group	Diagnostic case-control study [††]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) [‡‡]	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Tablenotes

* A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

§ Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

† This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C).

‡ Comparing single arm studies ie. case series from two studies.

** The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See *MSAC (2004) Guidelines for the assessment of diagnostic technologies*. Available at: www.msac.gov.au .

§§ The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology*, 2003, 3: 25.

†† Well-designed population based case-control studies (eg population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. These types of studies should be considered as Level II evidence. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

‡‡ Studies of diagnostic yield provide the yield of diseased patients, as determined by an index test, without confirmation of accuracy by a reference standard. These may be the only alternative when there is no reliable reference standard.

*** At study inception the cohort is either non-diseased or all at the same stage of the disease.

§§§ All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

††† If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence etc.

Hierarchies adapted and modified from: NHMRC 1999; Lijmer et al 1999; Phillips et al 2001; Bandolier editorial 1999)

Table 20 Prostate study profiles

Study ID	Study design	Study population	Outcomes assessed	Length of follow-up	Concurrent treatments
Cheng JC et al (2008) California, United States	Non-randomised comparative study Level III-2 Interventional evidence IG: Helical Tomotherapy	146 patients with localised prostate cancer Definitive RT: n = 76 Post-prostatectomy RT: n = 70 Mean age (definitive RT): 70.2 years (range: 50 to 85 years) Mean age (post-prostatectomy RT): 65.7 years (range: 43 to 80 years) T stage (definitive RT): T1c 49 (64%), T2a 10 (13%), T2b 6 (8%), T2c 8 (11%), T3 3 (4%) T stage (post-prostatectomy RT): T1b 1 (2%), T1c 42 (66%), T2a 6 (10%), T2b 8 (13%), T2c 4 (7%), T3 1 (2%)	Acute rectal and bladder toxicity, comparisons in prescribed dose, mean dose and rectum and bladder volume, significance of dosimetric variables and dose-response function	Median: 10.65 months (range: 3 to 27.3 months)	*Hormonal therapy* Definitive RT: neoadjuvant 18 (24%), adjuvant 23 (30%), none 35 (46%). Post-prostatectomy: neoadjuvant 15 (21%), adjuvant 18 (26%), none 37 (53%)
Di Muzio N et al (2009) Milan, Italy	Case series Level IV interventional evidence IG: Helical Tomotherapy (Hi ART 2, Tomotherapy ® Hi-Art® treatment system, TomoTherapy Incorporated®, Wisconsin, United States)	60 patients with localised prostate cancer Median age: 75 years (range: 60 to 79 years) T stage: 38 T1, 20 T2, 2 T3 Gleason score (median): 6 (range: 2+2 to 5+5) Initial PSA (median): 7 ng/mL (range: 1.2 to 24.0 ng/mL) NCCN risk groups: low risk (n = 31; clinical stage T1-T2, Gleason score ≤ 6, PSA ≤ 10), intermediate risk (n = 20; clinical stage T1-T2, Gleason score ≤ 6, PSA > 10; clinical stage T1-T2, Gleason score > 6, PSA ≤ 10; or clinical stage T3, Gleason score < 6, PSA < 10), high risk (n = 9; clinical stage T1-T3, Gleason score ≥ 7, PSA > 10)	Acute GU or gastrointestinal GI toxicity within 3 months of radiotherapy, late GU and GI toxicity, biochemical-free survival, clinical failure	Median: 13 months (range: 6 to 28 months)	Previous or concomitant hormonal therapy for local disease allowed. Hormonal therapy (neoadjuvant or adjuvant): 40 (hormonal therapy prescribed when PSA >c10, Gleason score > 7 or if prostate gland volume was > 50 cc prior to treatment)
Keiler L et al (2007) Ohio, United States	Non-randomised comparative study Level III-2 interventional evidence	97 patients (55 consecutive for tomotherapy group and 43 matched patients for US group) Mean age (tomotherapy group): 66 years Mean age (US group): 64 years	Acute GI toxicity, acute GU toxicity, univariate and multivariate analysis of toxicity	N/A	N/A

Study ID	Study design	Study population	Outcomes assessed	Length of follow-up	Concurrent treatments
	IG: Tomotherapy (Tomotherapy Hi Art) or BAT ultrasound	Stage of cancer (tomotherapy group): T1c (n = 27), T2a (n= 8), T2b (n = 2), T2c (n = 2), T3a (n = 3), T3b (n = 2) Stage of cancer (US group): T1c (n = 21), T2a (n = 4), T2b (n = 4), T2c (n = 0), T3a (n = 5), T3b (n = 0)			
Kupelian PA et al (2008) Florida, United States	Non-randomised comparative study Level III-3 interventional evidence IG: ultrasound using the BAT trans-abdominal ultrasound system (NOMOS, Pennsylvania, United States)	488 patients with localised prostate cancer *Rectal volume groups* < 50 cm^3: 108 50 to < 100 cm^3 : 113 ≥ 100 cm^3: 267 Mean age: 67 years (range: 44 to 87 years) African American proportion: 27% Clinical stage: T1-T2A (86%), T2B/C (9%), T3 (5%) Median PSA: 8.5 ng/mL(range: 1.1 to 111.1 ng/mL) Biopsy Gleason score distribution: ≤ 6 (54%), ≥ 46%	Biochemical relapse-free survival rate, rectal toxicity, urinary toxicity	Median: 60 months (range: 24 to 96 months)	Neoadjuvant or adjuvant androgen deprivation: 57% of patients Median duration of hormonal therapy: 6 months (range: 2 to 6 months) Only patients receiving ≤ 6 months of hormonal therapy included
Martin JM et al (2007) Toronto, Canada and Toowoomba, Australia	Case series Level IV interventional evidence IG: intraprostatic fiducial markers (3 subcapsular gold seeds) visualised by means of daily electronic portal imaging	92 patients with histologically confirmed prostate adenocarcinoma Median age: 71 years (range: 50 to 82 years) Clinical stage: T1c (n = 39), T2a (n = 43), T2b (n = 8), T2c (n = 2) Gleason score: 6 (n = 35), 7 (n = 54), 8-10 (n = 3) Initial median PSA: 7.06 ng/mL (range: 2 to 25.38 ng/mL) Risk stratification: low (n = 29), intermediate (n = 56), high (n = 7)	Acute bowel and bladder toxicities, biopsy results at last follow-up, metastatic failure, survival	Median: 38 months (range: 17 to 58 months)	Hormonal therapy: 8 (3 neoadjuvant, 5 adjuvant, all LHRH agonists except for 1 neoadjuvant patient who received flutamide)

NOTES: IG = image guidance; RT = radiotherapy; PSA = prostate specific antigen; NCCN = National Comprehensive Cancer Network; GU = genitourinary; GI = gastrointestinal; BAT = B-mode acquisition and targeting; mV = megavoltage; CBCT = cone beam computed tomography; IMRT = intensity-modulate radiotherapy; SM = seed marker; CTV = clinical target volume; PTV = planning target volume; N/A = not applicable; US = ultrasound; LHRH = luteinizing hormone-releasing hormone.

Table 21 Spine study profiles

Study ID	Study design	Study population	Outcomes assessed	Length of follow-up	Concurrent treatments
Jin JY et al (2007) Michigan, United Stated	Case series Level IV intervention evidence IG: Integration of infrared optical tracking component (the ExacTrac system) and kV x-ray imaging component	The first 49 patients out of 196 consecutive patients with histological diagnosis of malignant neoplasm and metastasis to a single spinal segment or two contiguous spinal levels, with or without cord compression undergoing radiosurgery. Age: N/A Number and site of spine lesions: cervical 30 lesions (11%), thoracic 142 lesions (53%), lumbar 82 lesions (30%), sacrum 16 lesions (6%) *total for 196 patients Lesion type: metastatic	Pain control, performance status, neurological examination, tumour control.	2-3 months for first year following RT and every 4-6 months thereafter	Chemotherapy: 0 patients
Terezakis SA et al (2007) New York, United States	Case series Level IV intervention evidence IG: mV electronic portal imaging or kV onboard imaging on Varian accelerators (Varian Medical Systems, Palo Alto, California)	27 consecutive patients with partially resected or unrespectable paraspinal tumours. Age: median 51 years (range: 22 to 74 years) Histologic type: sarcoma 18 patients, chordoma 7 patients, ependymoma 2 patients Lesion type: primary 23 patients, metastatic 4 patients Tumour grade: high/intermediate 12 patients, low 4 patients, not specified 11 patients	Local control, survival, subjective and objective quality of life outcomes, subjective and objective pain outcomes, subjective and objective motor and sensory function, acute toxicity, late toxicity	Median 17.4 months (range: 2.1 to 47.3 months)	Previous surgery: 22 patients Previous chemotherapy: 4 patients Previous radiotherapy: 5 patients
Yamada Y et al (2005) New York, United States	Case series Level IV intervention evidence IG: In-room computer tomography scan or electronic portal imaging devices, or both	35 patients with primary or metastatic paraspinal solid tumour malignancies deemed to be inoperable with radiographic evidence of gross disease. Age: mean 56.26 years (range: 29 to 79 years) Histologic diagnosis: renal cell carcinoma 7 patients, chondrosarcoma 6 patients, non-small cell lung cancer 3 patients, chordoma 3 patients, thyroid cancer 2 patients, gastrinoma, cervical cancer, osteogenic sarcoma, solitary fibrous tumour, malignant fibrous histiocytoma, hemagiopericytoma, herthle cell carcinoma, endometrial cancer, bladder carcinoma, melanoma, leiomyosarcoma, cholangiocarcinoma, breast cancer, high-grade sarcomatoid neoplasm 1 patient each Lesion type: primary 14 patients, metastatic 21 patients	Set-up variation for each immobilisation device in the lateral, AP and SI planes, local control, survival, palliation of symptoms (pain, motor strength and paresthesia), acute toxicity, late toxicity	Median 11 months (range: 1 to 42 months) Patients with primary lesions (median): 15 months (range: 2 to 30 months) Patients with metastatic disease (median): 7 months (range: 1 to 24 months)	Prior surgery: 32 (91%) (range: 1 to 9 operations) Previous RT: 4 patients with primary cancer, 20 patients with metastatic cancer
Yamada Y et	Case series	93 patients with histologically confirmed diagnosis of solid tumour malignancy,	Local control, effort of	Median 15 months	Systemic therapy

al (2008) New York, United States	Level IV intervention evidence IG: Digital mV portal imaging or kV imaging	with radiologic evidence of metastasis to the spine. All lesions of interest were unresected. Age: median 62 years (range: 38 to 91 years) Histologic type: breast 6 patients, cholangiocarcinoma 6 patients, colon cancer 11 patients, hemangiopericytoma 2 patients, hepatocellular cancer 4 patients, sarcoma 10 patients, melanoma 15 patients, non-small cell lung cancer 5 patients, paraganglioma 1 patient, prostate cancer 13 patients, renal cell cancer 21 patients, salivary gland cancer 2 patients, thyroid cancer 5 patients, squamous cell cancer 1 patient, bladder 1 patient	RT dose, ogliometastatic status, dosimetry, toxicity	(range: 2 to 45 months)	

NOTES: IG: image guidance; AP: anterior/posterior; SI: superior/inferior; RT: radiotherapy; kV: kilovoltage; N/A: not applicable; mV: megavoltage.

Table 22 Head and neck study profiles

Study ID	Study design	Study population	Outcomes assessed	Length of follow-up	Concurrent treatments
Chen AM et al (2009) California, United States	Case series Level IV intervention evidence IG: Megavoltage computed tomography	77 consecutive patients with squamous cell carcinoma of the head and neck. Age: median 58 years (range: 27-92 years) Primary sites: 39 oropharynx, 13 oral cavity, 6 larynx, 5 hypopharynx, 5 nasopharynx, 5 paranasal sinus, 4 unknown.	Overall survival, local-regional control, disease-free survival. Acute and late toxicity.	21 months (mean/median not stated)	Prior surgery: 35 patients (45%) Chemotherapy: 48 patients (62%), 32 from definitive therapy group, 16 from postoperative therapy group.

NOTES: IG = image guidance; CBCT = cone beam computer tomography; PTV = planning target volume; RT = radiotherapy; IMRT = intensity-modulated radiotherapy.

Appendix C: IG IMRT Technical studies

Table 23 IG IMRT Technical studies

Study ID	Location	Study design	Study population	Outcomes assessed	Outcomes
Gayou and Miften (2008)	Pennsylvania, United States	Comparative Level III-2 interventional evidence IG: BAT ultrasound system (NOMOS, Pennsylvania, United States), MV portal imaging of implanted seed markers, MV-CBCT	48 patients undergoing IMRT of the prostate Ultrasound imaging: n = 19 MV portal imaging of SMs: n = 12 MV CBCT imaging: n = 17	Couch shifts, 3D shift vector, estimated CTV-to-PTV expansion margins	Of the three techniques assessed, image guidance with MV CBCT results in the smallest systematic and random errors as well as the smallest recommended margins, although imaging using seed markers reported similar results.
Little et al (2003)	Texas, United States	Case series Level IV intervention evidence IG: Orthogonal portal images and BAT ultrasound images	35 patients with clinically localised prostate cancer	Image quality and accuracy, correlation of BAT and portal shifts, organ motion, comparison of setup error and organ motion, geographic misses of CTV, treatment margins	The percentage of cases in which prostate motion or setup error would result in the CTV falling outside the PTV margins if no guidance used is between 26.1% and 47.3%. Misses of the CTV owing to prostate motion alone, assuming perfect daily setup (i.e. eliminating setup error) yielded no significant decrease in percentage of geographic misses of the CTV.
Melancon et al (2007)	Texas, United States	Case series Level IV interventional evidence IG: ultrasound (BAT™, North American Scientific, California, United States)	46 patients with prostate cancer	Prostate and seminal vesicle dose coverage	Prostate coverage lost was minimal and not clinically significant in most patients. Seminal vesicle coverage loss was similar. Minimal dose delivered to 0.1 cm^3 of prostate reduced by 0.5 Gy (median) and 1.5 Gy (median) for seminal vesicles. Bladder volume variation correlated with prostate dosimetric changes ($P \leq 0.006$). Rectum volume variation correlated with seminal vesicle dose metrics ($P \leq 0.004$).
Pinkawa et al (2008)	Aachen, Germany	Case series Level IV interventional evidence IG: ultrasound-	32 patients with localised prostate cancer	Inter- and intrafraction organ motion, image quality, predictors to poor image quality	It is possible to predict poor image quality during the planning CT stage through various parameters. In patients likely to have poor image quality larger margins

		based using the BAT SXi system			extending the CTV may be needed.
van der Heide et al (2007)	Utrecht, The Netherlands	Case series Level IV interventional evidence IG: Portal images using iView-GT amorphous silicon flat-panel detector (Elekta Ltd., Crawley, UK) with fiducial gold markers	453 patients with prostate cancer	Distance between gold markers, position verification results without correction, comparison of off-line correction protocols	Fiducial markers are reliable to be used for IG IMRT, Possible reasons for variation in alignment include rectal filling.
Wang et al (2009)	Chengdu, China	Case series Level IV interventional evidence IG: Cone beam computed tomography	22 patients with nasopharyngeal cancer	Systematic and random setup errors, PTV margin at different correction threshold levels	CBCT using online correction protocol increased IMRT accuracy, decreasing random and systematic setup errors.

NOTES: IG = image guidance; BAT = B-mode acquisition and targeting; mV = megavoltage; CBCT = cone beam computed tomography; IMRT = intensity-modulate radiotherapy; SM = seed marker; CTV = clinical target volume; PTV = planning target volume.

Appendix D: Toxicity scoring systems

Table 24 **Radiation toxicity oncology group criteria for acute* morbidity**

	0	1	2	3	4
Lower gastrointestinal	No change	Increased frequency or change in quality of bowel habits not requiring medication/ rectal discomfort not requiring analgesics	Diarrhoea requiring parasympatholytic drugs (e.g., Lomotil)/ mucous discharge not necessitating sanitary pads/ rectal or abdominal pain requiring analgesics	Diarrhoea requiring parenteral support/ severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
Upper gastrointestinal	No change	Anorexia with <=5% weight loss from pretreatment baseline/ nausea not requiring antiemetics/ abdominal discomfort not requiring parasympatholytic drugs or analgesics	Anorexia with <=15% weight loss from pretreatment baseline/nausea &/ or vomiting requiring antiemetics/ abdominal pain requiring analgesics	Anorexia with >15% weight loss from pretreatment baseline or requiring N-G tube or parenteral support. Nausea &/or vomiting requiring tube or parenteral support/abdominal pain, severe despite medication/hematemesis or melena/ abdominal distention (flat plate radiograph demonstrates distended bowel loops	Ileus, subacute or acute obstruction, performation, GI bleeding requiring transfusion/abdominal pain requiring tube decompression or bowel diversion
Genitourinary	No change	Frequency of urination or nocturia twice pretreatment habit/ dysuria, urgency not requiring medication	Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium)	Frequency with urgency and nocturia hourly or more frequently/ dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/ without clot passage	Hematuria requiring transfusion/ acute bladder obstruction not secondary to clot passage, ulceration or necrosis

Source: http://www.rtog.org/members/toxicity/acute.html

*Acute morbidity criteria relevant from the commencement of radiation therapy (day 1) to day 90. Late effects criteria, using RTOG/ European organisation for research and treatment of cancer (EORTC) scoring system, relevant from 90 days postoperative.

Table 25 **RTOG/ European organisation for research and treatment of cancer (EORTC) criteria for late effects***

	0	1	2	3	4
Small/large intestine	None	Mild diarrhea, Mild cramping, Bowel movement 5 times daily, Slight rectal discharge or bleeding	Moderate diarrhea and colic, Bowel movement >5 times daily, Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/ Perforation, Fistula

Source: http://www.rtog.org/members/toxicity/late.html

*There were no criteria available for upper/lower gastrointestinal or genitourinary toxicities specifically.

Appendix E: HTA Internet Sites

AUSTRALIA

- Centre for Clinical Effectiveness, Monash University
  http://www.med.monash.edu.au/healthservices/cce/evidence/

- Health Economics Unit, Monash University
  http://chpe.buseco.monash.edu.au

AUSTRIA

- Institute of Technology Assessment / HTA unit
  http://www.oeaw.ac.at/ita/welcome.htm

CANADA

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/en/

- Alberta Heritage Foundation for Medical Research (AHFMR)
  http://www.ahfmr.ab.ca/publications.html

- Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
  http://www.cadth.ca/index.php/en/

- Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database http://www.mycabot.ca

- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org

- Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca

- Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm

- Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca

DENMARK

- Danish Institute for Health Technology Assessment (DIHTA)
  http://www.dihta.dk/publikationer/index_uk.asp

- Danish Institute for Health Services Research (DSI)
  http://www.dsi.dk/engelsk.html

FINLAND

- Finnish Office for Health Technology Assessment (FINOHTA)
  http://finohta.stakes.fi/FI/index.htm

FRANCE

- L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)

  http://www.anaes.fr/

GERMANY

- German Institute for Medical Documentation and Information (DIMDI) / HTA

  http://www.dimdi.de/dynamic/en/

THE NETHERLANDS

- Health Council of the Netherlands Gezondheidsraad
  http://www.gr.nl/adviezen.php

NEW ZEALAND

- New Zealand Health Technology Assessment (NZHTA)
  http://nzhta.chmeds.ac.nz/

NORWAY

- Norwegian Centre for Health Technology Assessment (SMM)

  http://www.kunnskapssenteret.no/

SPAIN

- Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III" / Health Technology Assessment Agency (AETS)

  http://www.isciii.es/htdocs/investigacion/Agencia_quees.jsp

- Catalan Agency for Health Technology Assessment (CAHTA)
  http://www.aatrm.net/html/en/dir394/index.html

SWEDEN

- Swedish Council on Technology Assessment in Health Care (SBU)

  http://www.sbu.se/www/index.asp

- Center for Medical Health Technology Assessment

  http://www.cmt.liu.se/

SWITZERLAND

- Swiss Network on Health Technology Assessment (SNHTA)

  http://www.snhta.ch/

UNITED KINGDOM

- NHS Quality Improvement Scotland

  http://www.nhshealthquality.org

- National Health Service Health Technology Assessment (UK) / National Coordinating Centre for health Technology Assessment (NCCHTA)

  http://www.hta.nhsweb.nhs.uk/

- University of York NHS Centre for Reviews and Dissemination (NHS CRD)

  http://www.your.ac.uk/inst/crd/

- National Institute for Clinical Excellence (NICE)

  http://www.nice.org.uk/

UNITED STATES

- Agency for Healthcare Research and Quality (AHRQ)
  http://www.ahrq.gov/clinic/techix.htm

- Harvard School of Public Health – Cost-Utility Analysis Registry
  http://www.tufts-nemc.org/cearegistry/index.html

- U.S. Blue Cross / Blue Shield Association Technology Evaluation Center (TEC)
  http://www.bcbs.com/tec/index.html

References

American College of Radiology and American Society of Therapeutic Radiology and Oncology. Practice guideline for image-guided radiation therapy (IGRT). October 1st 2009 (Resolution 2): 1-9.

Australian Institute of Health and Welfare (AIHW) & Australasian Association of Cancer Registries (AACR). Cancer in Australia: an overview, 2008. Cancer series no. 46. Cat. no. CAN 42. Canberra: AIHW 2008.

Begg S, Vos T, Barker B, Stevenson C, Stanley L, Lopez AD. The burden of disease and injury in Australia 2003. PHE 82. Canberra: AIHW 2007.

Bentzen SM. Radiation therapy: Intensity modulated, image guided, biologically optimized and evidence based. *Radiation and Oncology* 2005; **77**(3): 227-230.

Clinical Trials. Last Updated 2009. http://clinicaltrials.gov/ [Accessed September 2009].

ECRI Institute 2009. Image-guided radiation therapy (overview). www.ecri.org [Accessed September 2009].

Ling CC, Yorke E, Fuks Z. From IMRT to IGRT: Frontierland or Neverland? *Radiotherapy and Oncology* 2006; **78**(2): 119-122.

Nijkamp J, Pos FJ, Nuver TT, De Jong R, Remeijer P, Sonke J-J, Lebesque JV. Adaptive radiotherapy for prostate cancer using kilovoltage cone-beam computed tomography: First clinical results. *International Journal of Radiation Oncology* 2008; **70**(1): 75-82.

Polat B, Guenther I, Wilbert J, Goebel J, Sweeney RA, Flentje M, Guckenberger M. Intra-fractional uncertainties in image-guided intensity-modulated radiotherapy (IMRT) of prostate cancer. *Strahlentherapie und Onkologie* 2008; **184**(12): 668-73.

Therapeutic Goods Administration (TGA). Last updated 2009. eBS Australian Register of Therapeutic Goods – Devices. https://www.ebs.tga.gov.au/ebs/ANZTPAR/PublicWeb.nsf/cuDevices?OpenView [Accessed September 2009].

Tome WA, Jaradat HA, Nelson IA, Ritter MA, Mehta MP. Helical tomotherapy: image guidance and adaptive dose guidance. *Front Radiat Ther Oncol* 2007; **40**: 162-178.

US Food and Drug Administration (FDA). Last updated 2009. 510(k) Premarket Notification. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm [Accessed September 2009].

Verellen D, De Ridder M, Storme G. A (short) history of image-guided radiotherapy. *Radiotherapy and Oncology* 2008; **86**(1): 4-13.

World Health Organisation (WHO). Last updated 2009. Cancer: diet and physical activity's impact. http://www.who.int/dietphysicalactivity/publications/facts/cancer/en/print.html [Accessed September 2009].

Yamada Y, Lovelock DM, Bilsky MH. A review of image-guided intensity-modulated radiotherapy for spinal tumors. *Neurosurgery* 2007; **61**(2): 226-235.

Included studies

Prostate cancer

Cheng JC, Schultheiss TE, Nguyen KH, Wong JYC. Acute toxicity in definitive versus postprostatectomy image-guided radiotherapy for prostate cancer. *International Journal of Radiation Oncology, Biology, Physics* 2008; **71**(2): 351 – 357.

Di Muzio N, Fiorino C, Cozzarini C, Alongi F, Broggi S, Mangili P, Guazzoni G, Valdagni R, Calandrino R, Fazio F. Phase I-II study of hypofractionated simultaneous integrated boost with tomotherapy for prostate cancer. *International Journal of Radiation Oncology, Biology, Physics* 2009; **74**(2): 392 – 398.

Gayou O, Miften M. Comparison of mega-voltage cone-beam computed tomography prostate localization with online ultrasound and fiducial markers methods. *Medical Physics* 2008; **35**(2): 531 – 538.

Keiler L, Dobbins D, Kulasekere R, Einstein D. Tomotherapy for prostate adenocarcinoma: a report on acute toxicity. *Radiotherapy and Oncology* 2007; **84**(2): 171 – 176.

Kupelian PA, Willoughby TR, Reddy CA, Klein EA, Mahadevan A. Impact of image guidance on outcomes after external beam radiotherapy for localized prostate cancer. *International Journal of Radiation Oncology, Biology, Physics* 2008; **70**(4): 1146 – 1150.

Little DJ, Dong L, Levy LB, Chandra A, Kuban DA. Use of portal images and BAT ultrasonography to measure setup error and organ motion for prostate IMRT: implications for treatment margins. *International Journal of Radiation Oncology, Biology, Physics* 2003; **56**(5): 1218 – 1224.

Martin JM, Rosewall T, Bayley A, Bristow R, Chung P, Crook J, Gospodarowicz M, McLean M, Menard C, Milosevic M, Warde P, Catton C. Phase II trial of hypofractionated image-guided intensity-modulated radiotherapy for localized prostate adenocarcinoma. *International Journal of Radiation Oncology, Biology, Physics* 2007; **69**(4): 1084 – 1089.

Melancon AD, O'Daniel JC, Zhang L, Kudchadker RJ, Kuban DA, Lee AK, Cheung RM, de Crovoisier R, Tucker SL, Newhauser WD, Mohan R, Dong L. Is a 3-mm intrafractional margin sufficient for daily image-guided intensity-modulated radiation therapy of prostate cancer? *Radiotherapy and Oncology* 2007; **85**(2): 251 – 259.

Pinkawa M, Pursch-Lee M, Asadpour B, Gagel B, Piroth MD, Klotz J, Nussen S, Eble MJ. Image-guided radiotherapy for prostate cancer. Implementation of ultrasound-based prostate localization for the analysis of inter- and intrafraction organ motion. *Strahlentherapie und Onkologie* 2008; **184**(12): 679 – 685.

van der Heide UA, Kotte AN, Dehnad H, Hofman P, Lagenijk JJ, van Vulpen M. Analysis of fiducial marker-based position verification in the external beam radiotherapy of patients with prostate cancer. *Radiotherapy and Oncology* 2007; **82**(1): 38 – 45.

Spinal cancer

Jin JY, Chen Q, Jin R, Rock J, Anderson J, Li S, Movsas B, Ryu S. Technical and clinical experience with spine radiosurgery: a new technology for management of localized spine metastases. *Technology in Cancer Research and Treatment* 2007; **6**(2): 127 – 133.

Terezakis SA, Lovelock DM, Bilsky MH, Hunt MA, Zatcky J, Yamada Y. Image guided intensity-modulated photon radiotherapy using multifractionated regimen to paraspinal chordomas and rare sarcomas. *International Journal of Radiation Oncology, Biology, Physics* 2007; **69**(5): 1502 – 1508.

Yamada Y, Bilsky MH, Lovelock DM, Venkatraman ES, Toner S, Johnson J, Zatcky J, Zelefsky MJ, Fuks Z. High-dose single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions. *International Journal of Radiation Oncology, Biology, Physics* 2008; **71**(2): 484 – 490.

Yamada Y, Lovelock DM, Yenice KM, Bilsky MH, Hunt MA, Zatcky J, Leibel SA. Multifractionated image-guided and stereotactic intensity-modulated radiotherapy of paraspinal tumors: a preliminary report. *International Journal of Oncology, Biology, Physics* 2005; **62**(1): 53 – 61.

Head and neck cancer
Chen AM, Jennelle RL, Sreeraman R, Yang CC, Liu T, Vijayakumar S, Purdy JA. Initial clinical experience with helical tomotherapy for head and neck cancer. *Head & Neck* 2009 [Epub ahead of print].

Wang J, Bai S, Chen N, Xu F, Jiang X, Li, Xu Q, Shen Y, Zhang H, Gong Y, Zhong R, Jiang Q. The clinical feasibility and effect of online cone beam computer tomography-guided intensity-modulated radiotherapy for nasopharyngeal cancer. *Radiotherapy and Oncology* 2009; 90**(2)**: 221 – 227.

Other cancer types
Adkinson JB, Khuntia D, Bentzen SM, Cannon GM, Tome WA, Jaradat H, Walker W, Traynor AM, Weigl T, Mehta MP. Dose escalated, hypofractionated radiotherapy using helical tomotherapy for inoperable non-small cell lung cancer: preliminary results of arisk-stratified phase I dose escalation study. *Technology in Cancer Research and Treatment* 2008; 7**(6)**: 441 – 447.

Choi M, Fuller CD, Wang SJ, Siddiqi A, Wong A, Thomas CR, Fuss M. Effect of body mass index on shifts in ultrasound-based image-guided intensity-modulated radiation therapy for abdominal malignancies. *Radiotherapy and Oncology* 2009; 91**(1)**: 114 – 119.

Fuller CD, Dang ND, Wang SJ, Desai P, Choi M, Thomas CR, Fuss M. Image-guided intensity-modulated radiotherapy (IG IMRT) for biliary adenocarcinomas: initial clinical results. *Radiotherapy and Oncology* 2009; 92**(2)**: 249 – 254.

Fuss M, Wong A, Fuller CD, Salter BJ, Fuss C, Thomas CR. Image-guided intensity-modulated radiotherapy for pancreatic carcinoma. *Gastrointestinal Cancer Research* 2007; 1**(1)**: 2 – 11.

Jang JW, Kay CS, You CR, Kim CW, Bae SH, Choi JY, Yoon SK, Han CW, Jung HS, Choi IB. Simultaneous multitarget irradiation using helical tomotherapy for advanced hepatocellular carcinoma with multiple extrahepatic metastases. *International Journal of Radiation Oncology, Biology, Physics* 2009; 74**(2)**: 412 – 418.

Schubert LK, Westerly DC, Tomé WA, Mehta MP, Soisson ET, Mackie TR, Ritter MA, Khuntia D, Harari PM, Paliwal BR. A comprehensive assessment by tumor site of patient setup using daily MVCT imaging from more than 3,800 helical tomotherapy treatments. *International Journal of Radiation Oncology, Biology, Physics* 2009; **73**(4): 1260 – 1269.

Sterzig F, Schubert K, Sroka-Perez G, Kalz J, Debus J, Herfarth K. Helical tomotherapy. Experiences of the first 150 patients in Heidelberg. *Strahlentherapie und Onkologie* 2008; 184**(1)**: 8 – 14.

Cost
Knight K, Touma N, Zhu L, Duchesne GM, Cox J. Implementation of daily image-guided radiation therapy using an in-room CT scanner for prostate cancer isocentre localization. *Journal of Medical Imaging and Radiation Oncology* 2009; 53**(1)**: 132 – 138.

Ploquin N, Dunscombe P. A cost-outcome analysis of image-guided patient repositioning in the radiation treatment of cancer of the prostate. *Radiotherapy and Oncology* 2009; 93**(1)**: 25 – 31.