Close

aetna

(https://www.aetna.com/)

Intensity Modulated Radiation Therapy

Number: 0590

Policy History

Last Review 09/14/2016
Effective: 02/12/2002
Next Review: 06/22/2017

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes

Policy

Aetna considers intensity modulated radiation therapy (IMRT) medically necessary where critical structures cannot be adequately protected with standard 3-dimensional (3D) conformal radiotherapy (see appendix).

Aetna considers placement of fiducial markers medically necessary if the above criteria are met, and the radiation target is not clearly visible, and bony anatomy is not sufficient for adequate target alignment.

Aetna considers interfraction image guidance (i.e., image guidance between fractions) or intrafraction image guidance systems (i.e., real-time within fraction image guidance) (e.g., Calypso 4D Localization System, the RayPilot System) medically necessary for delivering IMRT and other conformal radiotherapy.

Background

Note on Definition of Intensity Modulated Radiation Therapy

(IMRT): For purposes of this policy, to qualify as IMRT, radiation therapy requires highly sophisticated treatment planning utilizing numerous beamlets to generate dosimtery in accordance with assigned dose requirements to the tumor and organs at risk.

Note: For purposes of this policy, critical structures can not be adequately protected with standard three-dimensional (3D) conformal radiotherapy if IMRT would decrease the probability of grade 2 or grade 3 radiation toxicity, as compared to conventional 3D conformal radiation therapy, in greater than 15 % of irradiated similar cases.

Intensity-modulated radiation therapy, also known as tomotherapy, is a type of stereotactic radiosurgery that delivers a highly conformal, 3D distribution of radiation doses. IMRT uses computer-controlled linear accelerators to deliver precise radiation doses to specific areas within a tumor. This therapy allows for increased precision by the conforming of the radiation to the planned target site while significantly reducing the amount of radiation to surrounding healthy tissues. Image-guided radiation therapy (IGRT) may be performed in conjunction with IMRT and includes, but may not be limited to, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound or X-ray. IGRT is utilized to direct and guide the delivery of radiation to maximize accuracy and precision throughout treatment.

Different techniques are utilized to control the radiation amount given during IMRT. The most common approach is the use of multileaf collimators (MLCs). These devices are attached to the linear accelerator. The MLCs are composed of computer controlled tungsten “leaves” or panels that move while the radiation beam is directed toward the target. The leaves act as filters that block out certain areas. This modifies the beam’s intensity so that the radiation is distributed according to the treatment plan.

Another delivery approach is compensator-based IMRT. This

approach utilizes custom made (based on the 3D images and the treatment plan) high density blocks to control the administration of the radiation. The blocks are put into place, the patient is positioned and the radiation is delivered.

Fiducial markers are gold seeds or stainless steel screws that are implanted in and/or around a soft tissue tumor or within the bony spine, to act as a radiologic landmark, to more precisely define the target lesion's position. Fiducial markers may be placed using CT, endoscopic or surgical guidance.

The PEACOCK (CORVUS) system, the Varian system, and the Elekta system are some of the currently available IMRT systems. In contrast to conventional trial-and-error approach, IMRT uses inverse planning (automated optimization), computer-controlled radiation deposition, and normal tissue avoidance. In the PEACOCK system, IMRT is delivered through a treatment planning and delivery system called PEACOCK, which shapes or conforms a radiation dose to the contour of the tumor while minimizing the impact on surrounding healthy tissue or organs. The delivery system combines 2 components: (i) the multileaf intensity-modulating collimator (MIMiC) that modulates the intensity of thin beams of radiation, and (ii) the CORVUS planning system, a planning computer that inversely plans the dose of radiation based on the tumor size, shape and location. When IMRT is used for head and neck tumors, it allows for the treatment of multiple targets with different doses, while simultaneously minimizing radiation to uninvolved critical structures such as the major salivary glands (e.g., the parotid glands), optic chiasm, and mandible.

Collimator-based IMRT uses computers to modify the intensity of the beam across each individual field with the use of moving collimators. Conventional treatment with multi-leaf collimation (MLC) uses static positions of the collimator leaves whereas IMRT allows the dynamic motion of the various collimator leaves during each session of therapy.

With compensator-based IMRT, a pre-shaped piece of material

(the compensator or modulator) is used to modulate the beam. The amount of modulation of the beam is based on the thickness of material through which the beam is attenuated. This modulation requires the fabrication and the manual insertion of the modulator into the tray mount of a linear accelerator.

Intensity-modulated radiation therapy typically involves inverse treatment planning, although forward treatment planning has been used. Forward treatment planning involves estimating the radiation delivery profile based on the number, directions and shape of the beams. In inverse treatment planning, the radiation oncologist and physicist determine the treatment target, the normal structures that should be protected, the required radiation dose for the tumor and the tolerated doses for the surrounding normal tissues; the computer then computes the beam profiles needed to yield those results.

The outlined objectives for radiation dose distribution are in prescribed dose volume histograms. The histograms are translated into beam configurations that will deliver tumor and normal tissue doses prescribed. Intensity-modulated radiation therapy optimizes the treatment plan based on the physician's dose instructions, the specific dose constraints for planned treatment volume (PTV) and information about tumor size, shape and location in the body. A medical linear accelerator equipped with a dynamic MLC shapes the radiation beams wrapping around the tumor, conforming to its shape and delivers the radiation.

Intensity-modulated radiation therapy involves at least 5 separate ports. The beam angle or gantry position is what determines a port or entry point of the beam. Segments are part of the individual beam profile and there may be many per port or beam angle. If the segment is truly an independent port within a port (often called "en field") and can be demonstrated to provide sufficient beam profiling, then it may be considered a separate port within the same beam angle and be considered a port for purposed of defining IMRT.

An evidence review by ANAES (2003) noted that, although the clinical indications for IMRT remain to be established, clinical interest in IMRT is greatest for cancers of the head and neck and for prostate cancer. In addition, ANAES found that there is some emerging interest in use of IMRT for cancers of the lung and central nervous system (CNS).

An assessment by the Belgian Health Care Knowledge Centre (KCE) (Van den Steen et al, 2007) concluded that weak-to-moderate quality evidence is available demonstrating a reduction in toxicity after IMRT compared with 2D RT or 3D CRT for head and neck cancer, prostate cancer and breast cancer. The assessment found that current reports do no allow for a good comparison of relapse or survival data between IMRT and conventional techniques.

On the topic of patient safety, the assessment observed that total body irradiation is higher using IMRT and, in theory, may overall double the incidence of fatal secondary malignancies compared with standard external radiotherapy techniques. The assessment noted that younger patients are especially at risk. The report also noted that large variations exist in total body irradiation between various IMRT techniques. Also use of daily radiation-based imaging for treatment set-up verification adds to the overall radiation exposure.

CNS and Head and Neck Tumors

Intensity-modulated radiation therapy may be indicated in CNS and head and neck tumors, due to the close proximity of critical structures in these anatomic regions.

A study by Claus and associates (2001) examined the use of IMRT for the treatment of patients with ethmoid sinus tumors. The authors suggested that IMRT has the potential to save binocular vision because the dose to the optic pathway structures can be reduced selectively by this procedure. Nutting and colleagues (2001) compared conventional, 3D conformal, and IMRT for the treatment of parotid gland

tumors. The researchers found that compared to conventional radiotherapy, IMRT not only reduced radiation dose to critical normal tissues, but also produced a further reduction in the dose to the cochlea and oral cavity. These encouraging findings are corroborated by more recent studies.

Nutting et al (2001) reported that IMRT improved the planning target volume coverage and reduced the spinal cord dose, and concluded that IMRT should reduce the risk of myelopathy or may allow dose escalation in patients with thyroid cancer. Adams and co-workers (2001) stated that IMRT offers significant advantages over conventional radiotherapy and 3D-conformal RT techniques for treatment of maxillary sinus tumors.

Chao et al (2001) reported that the dosimetric advantage of IMRT, when compared with conventional techniques, did translate into a significant reduction of late salivary toxicity in patients with oropharyngeal carcinoma (n = 430). There was no adverse impact on tumor control and disease-free survival in patients treated with IMRT. Huang and colleagues (2002) observed that for pediatric patients with medulloblastoma (n = 26), the conformal technique of IMRT delivered much lower doses of radiation to the auditory apparatus, while still delivering full doses to the desired target volume. These findings suggest that, despite higher doses of cisplatin, and despite RT before cisplatin therapy, treatment with IMRT can achieve a lower rate of hearing loss.

Dogan and associates (2002) noted their improvement of IMRT treatment plans for patients with concave-shaped head and neck tumors. They stated that IMRT showed better target coverage and sparing of critical structures than that of 3D conformal RT and 2D RT.

Lee et al (2002) reported their experience with IMRT in the treatment of patients with nasopharyngeal carcinoma (n = 67). These investigators found excellent local-regional control for nasopharyngeal carcinoma with IMRT. This technique provided

excellent tumor target coverage and allowed the delivery of a high dose to the target with significant sparing of the salivary glands and other nearby critical normal tissues.

An assessment by the Belgian Health Care Knowledge Center (KCE) (Van den Steen et al, 2007) concluded that, as IMRT for head and neck cancer is more difficult to plan and deliver, and still an area of investigation, for the time being its use in these patients should be restricted to centers with the necessary expertise and preferentially those that are performing research in this area. The assessment (Van den Steen et al, 2007) identified a total of 9 comparative trial reports, including 1 randomized controlled clinical trial (RCT), concerning head and neck cancer (9 reports, including 1 RCT). The reported stated that head and neck cancer constitutes an appropriate candidate indication for the highly accurate irradiation achievable using IMRT as organ motion is practically absent. The report found that the benefit of IMRT has been documented compared with 3D CRT for the sparing of organs at risk, mainly the salivary glands, and in 1 study also the optic nerve. From the trials published it can be concluded that well-performed IMRT can improve quality of life (e.g., less xerostomy) in head and neck cancer patients. There are, however, no robust data comparing IMRT with 3D CRT with regard to relapse or survival. As head and neck cancer radiation treatment is reportedly not being performed optimally by many radiation oncologists and as IMRT remains difficult to plan and deliver, it has been suggested to restrict such IMRT treatments to centers with the necessary expertise (e.g., IMRT research activities, patient outcome follow-up).

The assessment identified 1 non-randomized trial concerning medulloblastoma (Van den Steen et al, 2007), a small retrospective comparison in cisplatin treated children with medulloblastoma, which suggests IMRT can reduce ototoxicity compared with 3D conformal RT.

Prostate Cancer

Guidelines on prostate cancer from the National Comprehensive Cancer Network (NCCN, 2003) indicate that IMRT is an alternative to 3D conformal RT for ultra-high dose (dosage of 75 Gy or more) radiation treatment of prostate cancer. NCCN guidelines state that "3D conformal or IMRT (intensity modulated radiation therapy) techniques should be employed in preference to conventional techniques" in the treatment of prostate cancer. "The standard dose has been 70 Gy in 35-38 fractions to the prostate ± seminal vesicles, which appears to be appropriate for patients with low risk cancers. For patients with intermediate or high risk cancers, doses between 75-80 Gy are better …. If target (PTV) margins are reduced, such as for doses above 75 Gy, extra attention to daily prostate localization with ultrasound or implanted fiducials is indicated."

A coding guide from the American Society for Therapeutic Radiation and Oncology (ASTRO, 2007) explains that IMRT has several advantages for use in prostate cancer, where dose escalation is planned to delivery radiation doses in excess of those commonly utilized with conventional treatments. In prostate cancer, the target volume is in close proximity to critical structures (rectum, bladder, femoral head, and penile bulb) and must be covered with narrow margins to adequately protect immediately adjacent structures to reduce the probability of radiation toxicity. The coding guide explains that IMRT is the only treatment modality that can achieve this, rather than conventional 3D treatment planning.

Zelefsky and colleagues (2001) presented the long-term outcome and tolerance of 3D CRT and IMRT for localized prostate cancer. Patients (n = 1,100) were categorized into prognostic risk groups based on pre-treatment prostate specific antigen (PSA), Gleason score and clinical stage. At 5 years the PSA relapse-free (RF) survival rates in patients at favorable, intermediate and unfavorable risk were 85 %, 58 %, and 3 %, respectively. Radiation dose was the most powerful variable impacting PSA RF survival in each prognostic risk group. The 5-year actuarial PSA RF survival rate for patients at favorable

risk who received 64.8 to 70.2 Gy was 77 % compared to 90 % for those treated with 75.6 to 86.4 Gy. The corresponding rates were 50 % versus 70 % in intermediate risk cases, and 21 % versus 47 % in unfavorable risk cases. Only 4 of 41 patients (10 %) who received 81 Gy had a positive biopsy 2.5 years or greater after treatment compared with 27 of 119 (23 %) after 75.6 Gy, 23 of 68 (34 %) after 70.2 Gy and 13 of 24 (54 %) after 64.8 Gy. The incidence of toxicity after 3D conformal CRT was dose-dependent. The 5-year actuarial rate of grade 2 rectal toxicity in patients who received 75.6 Gy or greater was 14 % compared with 5 % in those treated at lower dose levels. Treatment with IMRT significantly decreased the incidence of late grade 2 rectal toxicity since the 3-year actuarial incidence in 189 cases managed by 81 Gy was 2 % compared with 14 % in 61 cases managed by the same dose of 3D CRT. The 5-year actuarial rate of grade 2 urinary toxicity in patients who received 75.6 Gy or greater 3D CRT was 13 % compared with 4 % in those treated up to lower doses. Intensity modulated radiation therapy did not affect the incidence of urinary toxicity. Sophisticated CRT techniques with high dose 3D CRT and IMRT improve the biochemical outcome in patients with favorable, intermediate and unfavorable risk prostate cancer. Intensity modulated radiation therapy is associated with minimal rectal and bladder toxicity, and, hence, represents the treatment delivery approach with the most favorable risk-to-benefit ratio.

An assessment by the Belgian Health Care Knowledge Center (KCE) (Van den Steen, 2007) concluded that IMRT or 3D CRT is recommended for high dose external radiotherapy in prostate cancer. The report identified a total of 6 comparative trial reports (no RCTs) of IMRT for prostate cancer. The report noted that the standard curative treatments for prostate cancer are radical prostatectomy and radiotherapy (external beam or brachytherapy). The report found fairly strong evidence that patients with localized, intermediate risk, and high risk disease, i.e., patients normally not suited for surgery, benefit from a higher than conventional total radiation dose as can be achieved using 3D CRT or IMRT. No additional overall survival

benefit has been shown. The report explained that IMRT plans can provide a steep high to low-dose gradient at the edge of the target volume for improved avoidance of adjacent normal structures, such as the rectum, bowel and bladder. For this reason IMRT was used first for prostate cancer treatment in many centers. Most comparative studies report less rectal toxicity after IMRT compared with 3D CRT, also at high doses. The challenge is to precisely target the prostate (and sometimes the lymph nodes) each session. Frequent image-based adjustments can help to achieve this.

Canter and colleagues (2011) stated that surgical treatment for men with localized prostate cancer -- open, laparoscopic, or robotically-assisted -- remains one of the therapeutic mainstays for this group of patients. Despite the stage migration witnessed in patients with prostate cancer since the introduction of PSA screening, detection of extra-prostatic disease at the time of surgery and biochemical recurrence following prostatectomy pose significant therapeutic challenges. Radiation therapy after radical prostatectomy (RP) has been associated with a survival benefit in both the adjuvant and salvage setting. Nevertheless, optimal targeting of the prostate bed following surgery remains challenging. The Calypso 4D Localization System (Calypso Medical Technologies, Seattle, WA) is a target positioning device that continuously monitors the location of 3 implantable electromagnetic transponders. These transponders can be placed into the empty prostatic bed after prostatectomy to facilitate the delivery of RT in the post-surgical setting. The authors detailed their technique for transrectal placement of electromagnetic transponders into the post-prostatectomy bed for the delivery of adjuvant or salvage IMRT. They prefer this technique of post-surgical RT because it allows for improved localization of the target area allowing for the maximal delivery of the radiation dose while minimizing exposure of surrounding normal tissues. The authors noted that although emerging, their initial oncologic and functional outcomes have been promising.

Sheets et al (2012) examined the comparative morbidity and disease control of IMRT, proton therapy, and conformal RT for primary prostate cancer treatment. Main outcome emasures were rates of gastro-intestinal (GI) and urinary morbidity, erectile dysfunction, hip fractures, and additional cancer therapy. Use of IMRT versus conformal RT increased from 0.15 % in 2000 to 95.9 % in 2008. In propensity score-adjusted analyses (n = 12,976), men who received IMRT versus conformal RT were less likely to receive a diagnosis of GI morbidities (absolute risk, 13.4 versus 14.7 per 100 person-years; relative risk [RR], 0.91; 95 % confidence interval (CI): 0.86 to 0.96) and hip fractures (absolute risk, 0.8 versus 1.0 per 100 person-years; RR, 0.78; 95 % CI: 0.65 to 0.93) but more likely to receive a diagnosis of erectile dysfunction (absolute risk, 5.9 versus 5.3 per 100 person-years; RR, 1.12; 95 % CI: 1.03 to 1.20). Intensity-modulated radiation therapy patients were less likely to receive additional cancer therapy (absolute risk, 2.5 versus 3.1 per 100 person-years; RR, 0.81; 95 % CI: 0.73 to 0.89). In a propensity score-matched comparison between IMRT and proton therapy (n = 1,368), IMRT patients had a lower rate of GI morbidity (absolute risk, 12.2 versus 17.8 per 100 person-years; RR, 0.66; 95 % CI: 0.55 to 0.79). There were no significant differences in rates of other morbidities or additional therapies between IMRT and proton therapy. The authors concluded that among patients with non-metastatic prostate cancer, the use of IMRT compared with conformal RT was associated with less GI morbidity and fewer hip fractures but more erectile dysfunction; IMRT compared with proton therapy was associated with less GI morbidity.

Breast Cancer

According to an ASTRO coding guide, IMRT is not routinely indicated in breast cancer, but may be indicated in selected cases of breast cancers with close proximity to critical structures (ASTRO, 2007).

There are no evidence-based guidelines from leading national medical organizations or Federal public health agencies that

conclude that IMRT is routinely indicated for breast cancer. An assessment from the BlueCross BlueShield Association Technology Evaluation Center (BCBSA, 2006) concluded that available data are insufficient to determine whether IMRT is superior to 3D CRT for improving health outcomes of patients with breast cancer. The assessment identified no studies (randomized or non-randomized; prospective or retrospective) that directly compared health outcomes of IMRT with health outcomes of 3D CRT (using concurrent or historical controls). The TEC assessment noted that follow-up was short (less than 1 year) in the 2 available single-arm (non-comparative) studies on IMRT for breast cancer, and that acute skin toxicity and cosmesis were the only outcomes reported in these studies.

Since publication of the TEC assessment, Pignol et al (2008) reported on a RCT that found that breast IMRT (BIMRT) reduced acute skin toxity compared to standard adjuvant breast irradiation using wedge compensation (WC). The investigators explained that standard adjuvant breast irradiation using wedge compensation is associated with a high rate of acute skin reactions including moist desquamation. These side effects are more likely to occur in the breast crease and for women with large breasts. In this study, 358 patients receiving breast irradiation were randomized to receive either BIMRT or WC up to 50 Gy, with or without a boost of 16 Gy. Study subjects were assessed for skin toxicity weekly during the treatment and until 6 weeks post-treatment by a masked clinical research assistant. The investigators found that BIMRT compared to WC reduced moist desquamation in all breast quadrants (31 % versus 48 %), p = 0.0019) and in the infra-mammary fold (26 % versus 43 %, p = 0.0012). The investigators reported that BIMRT did not significantly reduce the maximum toxicity grade 3 to 4 in all breast quadrants compared to WC (p = 0.20). The use of IMRT significantly reduced infra-mammary fold skin toxicity grade 3 to 4 (odds ratio [OR] = 2.62, 95 % CI: 0.136 to 0.603). The investigators reported that breast volume was the most significant patient related factor associated with increased acute skin toxicity. The authors concluded that, compared to the standard WC radiation treatments, BIMRT significantly

reduced the development of severe moist desquamation.

Donovan et al (2007) reported on the results of a RCT that found that BIMRT was associated with fewer late adverse effects compared to WC. In this study, 306 women were prescribed whole breast radiation therapy after tumour excision for early stage cancer were randomized to BIMRT or 2D RT delivered using standard WC. All patients were treated to a dose of 50 Gy in 25 fractions over 5 weeks followed by an electron boost to the tumor bed of 11.1 Gy in 5 fractions. The primary endpoint was change in breast appearance scored from serial photographs taken before radiotherapy and at 1, 2 and 5 years follow-up. Secondary endpoints included patient self-assessments of breast discomfort, breast hardness, quality of life and physician assessments of breast induration. Two hundred forty (79 %) patients with 5-year photographs were available for analysis. Change in breast appearance was identified in 71 of 122 (58 %) subjects assigned to WC compared to 47 of 118 (40 %) subjects assigned to BIMRT. The investigators reported that the subjects assigned to WC were 1.7 times more likely to have a change in breast appearance than subjects assigned to IMRT after adjustment for year of photographic assessment (95 % CI: 1.2 to 2.5, p = 0.008). Significantly fewer subjects assigned to BIMRT developed palpable induration assessed clinically in the center of the breast, pectoral fold, infra-mammary fold and at the boost site. The investigators stated that no significant differences between treatment groups were found in patient reported breast discomfort, breast hardness or quality of life. The authors concluded that this analysis suggests that minimization of unwanted radiation dose inhomogeneity in the breast reduces late adverse effects. Incidence of change in breast appearance was statistically significantly higher in subjects in the WC group compared with the BIMRT group. The investigators noted that a beneficial effect on quality of life remains to be demonstrated.

In an editorial that accompanied the paper by Pignol et al (2008), Haffy and colleagues (2008) stated that it is clear from

the phase III clinical trials by Pignol et al (2008) as well as Donovan et al (2007) that there are both dosimetric and clinical advantages to improved homogeneity achieved with IMRT to the whole breast.

An assessment by the Belgian Health Care Knowledge Center (KCE) (Van den Steen et al, 2007) concluded that use of IMRT may reduce skin complications in breast cancer radiotherapy, primarily in heavy breasted women. The assessment identified a total of 3 comparative trial reports, including 2 RCTs, of IMRT in breast cancer. The assessment found that, in large breasted patients treatment to the whole breast with standard tangential fields may produce rather inhomogeneous dose distributions. This may lead to increased late skin toxicity (poor cosmesis, fibrosis, pain). Two RCTs (1 reported as abstract only) and 1 retrospective comparison of IMRT with conventional external radiotherapy confirm that IMRT reduces the frequency of skin complications. No improvement in overall quality of life could be demonstrated using standard techniques. The assessment stated that long term studies are required to assess the risk of induction of a secondary tumor in the contralateral breast after IMRT before introduction into common practice.

Lung Cancer

An assessment from the BlueCross BlueShield Association Technology Evaluation Center (BCBSA, 2006) concluded that available data are insufficient to determine whether IMRT is superior to 3D CRT for improving health outcomes of patients with lung cancer. The assessment identified no studies that directly compared health outcomes of IMRT with health outcomes of 3D CRT for lung cancer, using concurrent or historical controls. The report noted that the only available single-arm study of IMRT for lung cancer, a dose-escalation trial, closed for excessive toxicity after 5 patients received 84 Gray.

Other Indications

Many of the technical advances associated with the delivery of

external-beam radiotherapy, including IMRT, have been accepted without formal evaluation of their impact on patient-related outcomes, largely because the evolution of radiotherapy has been on empirical grounds wherein an improvement in the distribution of radiation dose is seen as necessarily beneficial. It is not as clear, however, that increased prescribed doses of radiation are necessarily beneficial. A key question of debate is whether indications for IMRT are established based solely upon results of dosimetric planning studies, or whether well-designed clinical outcome studies are necessary to prove the benefits of IMRT over standard 3D CRT for each of IMRT's potential applications.

The benefit of IMRT in rests in its potential to increase the therapeutic ratio by allowing, in theory, the delivery of higher doses of radiation with little or no increase in normal tissue complications. These goals are achieved by more accurately targeting the radiation, and by reducing the irradiated volume to vital structures. The potential risks of IMRT lie in these reduced margins (given the uncertainties associated with tumor delineation, organ movement, patient set-up variation) and in the tolerance of small volumes of normal tissue to high-dose treatment. Briefly stated, should the treatment volumes be conformed too tightly to the contour, uncertainties in treatment reproducibility may lead to geographic "misses" of the target. In addition, dose escalation beyond the tolerance of normal tissues may increase late complications and reduce the therapeutic ratio, and exposure of more normal tissue to modest doses peripheral to the target volume may increase treatment-induced oncogenesis.

Guerro-Urbano et al (2004) systematically reviewed the evidence of the effectiveness of IMRT in cancer. The investigators found that dosimetric planning studies have demonstrated which tumor types have the largest potential gains, and small clinical studies are beginning to report short-term outcome data from patients. “Most of these reports are small Phase I or Phase II trials where there has been no true comparison of IMRT with conventional radiotherapy

technique." The investigators note that, because "a better dose distribution does not necessarily correlate with better clinical outcome or improved sparing associated with improved side effect profile and/or improvements in quality of life", IMRT "should be tested head to head with conventional radiotherapy techniques where possible."

A structured review of current evidence for IMRT (Maceiras-Rozas et al, 2005) prepared for the Galician Agency for Health Technology Assessment concluded that the scientific evidence on the effectiveness and security of IMRT in comparison with CRT is scarce and of low quality, which limits establishment of rigorous conclusions. The evidence review identified studies comparing IMRT to CRT that met their predetermined quality criteria. The evidence review summarized the results of studies of IMRT for prostate cancer and head and neck cancer that met these predetermine criteria. There were no studies of IMRT for other indications that met their previously established criteria. The evidence review concluded that prospective comparative studies are necessary to evaluate the effectiveness and cost-effectiveness of IMRT in comparison with CRT.

Guidelines from the National Cancer Institute (2005) on the use of IMRT in clinical trials summarize the current state of the evidence supporting IMRT. The guidelines state that "IMRT is still a nascent technology." The guidelines state: "Currently, most published reports on the clinical use of IMRT are single institution studies, and are either treatment planning studies for a limited number of cases showing the improvement in dose distributions generated by IMRT, or dosimetric studies confirming IMRT treatment. There are no published reports at present of prospective randomized clinical studies involving IMRT, and this lack of information clearly limits our knowledge of the effect of the use of IMRT on clinical outcomes." The guidelines state that, although IMRT has potential advantages in physical dose distribution with IMRT, and therefore the potential for improvement in patient outcomes, there exists concern for actual IMRT treatment execution. The guidelines

discussed a number of specific concerns, including the potential to miss a tumor (or at least underdose a portion of the tumor) and/or to have significant high dose volumes in the normal tissues. Another specific concern is that the widespread use of IMRT could lead to an increased incidence of RT associated carcinomas due to the larger volume of normal tissue exposed to low doses and the increase in whole body doses as a result of the increased doses of radiation required for delivery of IMRT (NCI, 2005).

An assessment of IMRT by the Belgian Health Care Knowledge Center (KCE) (Van den Steen et al, 2007) found that, in general, more long-term data are needed for IMRT treated patients, to confirm any survival advantage and to assess the increased risk of secondary malignancies in comparison with standard external radiotherapy techniques. Manufacturers and users of IMRT hardware and software should be made more aware of this risk of induction of secondary malignancies, and product improvement is to be stimulated.

Over the next decade, prospective, RCTs will clarify the role of IMRT in radiation oncology (ACCC, 2003). The issues explored will include which tumor sites are appropriate for IMRT treatment and the total maximum body dose to the patient for specific beam plans.

A number of groups have been created to help foster successful IMRT clinical trials. In 1999, the National Cancer Institute funded the Advanced Technology Radiation Therapy Quality Assurance Review Consortium. This group will develop guidelines for using IMRT techniques in national clinical trials. Protocol requirements for IMRT treatment delivery were agreed upon by the committee chairs of the NCI-funded clinical trial groups at a meeting held in Bethesda, MD, on June 20, 2002, and the required nomenclature has been published in the NCI IMRT Working Group Report (2001).

In a phase II clinical study, Rochet and colleagues (2011) will evaluate the toxicity of whole abdominal IMRT in patients with

advanced ovarian cancer. The OVAR-IMRT-02 study is a single-center one-arm trial. A total of 37 patients with optimally debulked ovarian cancer stage FIGO III (International Federation of Gynecology and Obstetrics) having a complete remission after chemotherapy will be treated with intensity-modulated whole abdominal radiotherapy (WAR) as a consolidation therapy. A total dose of 30 Gy in 20 fractions of 1.5 Gy will be applied to the entire peritoneal cavity including the liver surface and the pelvic and para-aortic node regions. Organ at risk are kidneys, liver (except the 1 cm-outer border), heart, vertebral bodies and pelvic bones. Primary endpoint is tolerability; secondary objectives are toxicity, quality of life, progression-free and overall survival. Intensity-modulated WAR provides a new promising option in the consolidation treatment of ovarian carcinoma in patients with a complete pathologic remission after adjuvant chemotherapy. Further consequent studies will be needed to enable firm conclusions regarding the value of consolidation radiotherapy within the multi-modal treatment of advanced ovarian cancer.

Image-Guided Radiotherapy

An assessment by the Belgian Health Care Knowledge Centre (KCE) (Van den Steen et al, 2007) concluded that more frequent imaging for guidance of IMRT is expected to further improve the efficacy and safety of IMRT, particularly in targets showing internal movement, e.g., in case of prostate cancer. The assessment noted that the high degree of dose conformality achievable with IMRT creates a challenge for the radiotherapist to accurately delineate the target and the organs at risk (Van den Steen et al, 2007). It is also a challenge to reduce the variation between clinicians. Another challenge is the accuracy and precision with which the target volume and critical structures can be localized day to day, especially for indications other than head and neck. The assessment noted that image guided corrections for day to day set up errors or for internal organ motion have become important issues. The report also stated that intrafraction organ motion has become the limiting factor for margin reduction around the clinical target volume.

Image-guided radiotherapy (IGRT) is therefore a growth area. The report noted that recent reviews on the subject have been published (citing Balter and Kessler, 2007; Dawson and Jaffray, 2007).

In some cases, a treatment preparation session may be necessary to mold a special device that will help the patient maintain an exact treatment position (Van den Steen et al, 2007). Prior to treatment, the patient's skin may be marked or tattooed with colored ink to help align and target the equipment. Radio-opaque markers may also be use (e.g., gold marker seeds in case of prostate treatment).

The report observed that, in IMRT, images are acquired for 3 reasons (Van den Steen et al, 2007):

1. Treatment planning, i.e., delineation of target and normal structures, typically created once prior to treatment. The report stated that IMRT planning may include positron emission tomography (PET) and magnetic resonance imaging (MRI). Typically, IMRT sessions begin about 1 week after simulation. The report noted that it is expected this model will become outdated and be replaced by image-guided IMRT.
2. Image guidance and/or treatment verification, for setup verification and correction. The report stated that some treatment machines already have an integrated scanner integrated. The report stated that the frequency of imaging (CT or other) will vary based on characteristics of the tumor dose gradient and the patient, e.g., daily (often on-line) imaging can be required for a pelvic irradiation of an obese patient.
3. Follow-up of treatment response, CT, MRI and PET scans are often used for this purpose.

A report on image-guided intensity modulated radiation therapy Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S) (Zamora, et al. (2010) concluded: "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."

The Calypso 4D Localization System (Calypso Medical Technologies, Seattle, WA) is an example of a device for intrafraction image guidance. The system is intended to improve the accuracy of radiotherapy by tracking the exact position and motion of target organs during daily treatments (CMS, 2008). Beacon electromagnetic transponders are implanted passive resonant circuits, encapsulated in a hermetically sealed, medical grade biocompatible glass capsule. These miniature electrical circuits are comprised of a copper coil, ferrite rod and capacitor. Each electromagnetic transponder is approximately the size of a small grain of rice. Beacon transponders are activated by the Calypso 4D Localization System when the transponders are positioned directly under the system's electromagnetic array. The Calypso System is an electromagnetic tumor target positioning technology used in radiation therapy delivery. The electromagnetic transponders emit an electromagnetic signal which is detected, measured, and used by the Calypso System to determine the location of the tumor target relative to the linear accelerator beam. Electromagnetic transponders are implanted into the tumor target tissue prior to the delivery of radiation therapy. This technology is intended to provide clinicians with continuous position information of a tumor target during external beam radiation therapy with sub-millimeter accuracy.

Kupelian and colleagues (2007) reported the technical ability of the Calypso system to track the movement of the prostate. The system was used at 5 centers to position 41 patients over a full

course of therapy. Electromagnetic positioning was compared to set-up using skin marks and to stereoscopic X-ray localization of the transponders. Continuous monitoring was performed in 35 patients. The authors concluded that the Calypso System is a clinically efficient and objective localization method for positioning prostate patients undergoing radiotherapy.

Proponents of the Calypso 4D Localization System argue that use of this tumor target position information can improve radiation treatment accuracy, thereby reducing the likelihood of radiation induced complications and improving the effectiveness of radiation therapy. The Calypso system was cleared for marketing by the FDA based on a 510(k) application for use in prostate cancer. Thus, the manufacturer was not required to provide the evidence of efficacy necessary to support a premarket approval application. There are no published clinical trials demonstrating that the use of the Calypso system improves clinical outcomes of radiation therapy. This technology is relatively new, and clinical studies are currently ongoing (Aral et al, 2010).

Sandler et al (2010) examined if patient-reported quality of life after high-dose external beam IMRT for prostate cancer can be improved by decreasing PTV margins while using real-time tumor tracking. Study patients underwent radiotherapy with nominal 3-mm margins and electromagnetic real-time tracking. Morbidity was assessed before and at the end of radiotherapy using Expanded Prostate Cancer Index Composite (EPIC) questionnaires. Changes in scores were compared between the Assessing Impact of Margin Reduction (AIM) study cohort and the comparator Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment (PROST-QA) cohort, treated with conventional margins. The 64 patients in the prospective AIM study had generally less favorable clinical characteristics than the 153 comparator patients. Study patients had similar or slightly poorer pre-treatment EPIC scores than comparator patients in bowel, urinary, and sexual domains. AIM patients receiving radiotherapy had less bowel morbidity than the comparator group as measured by changes in mean bowel

and/or rectal domain EPIC scores from pre-treatment to 2 months after start of treatment (-1.5 versus -16.0, p = 0.001). Using a change in EPIC score greater than 0.5 baseline standard deviation as the measure of clinical relevance, AIM study patients experienced meaningful decline in only 1 health-related quality of life domain (urinary) whereas decline in 3 health-related quality of life domains (urinary, sexual, and bowel/rectal) was observed in the PROST-QA comparator cohort. The authors concluded that prostate cancer patients treated with reduced margins and tumor tracking had less radiotherapy-related morbidity than their counterparts treated with conventional margins. They stated that highly contoured IMRT shows promise as a successful strategy for reducing morbidity in prostate cancer treatment.

Helical tomotherapy is a novel 360-degree radiation treatment modality that combines a helical computed tomography (CT) scanner for online imaging with a linear accelerator that delivers IMRT. It is available by means of the TomoTherapy Hi-ART System. The on-board CT scanner provides image guidance and dose verification, allowing adjustments for slight, but critical, changes in the shape and position of the tumor. It is intended to be a substitute for the curative or palliative treatment of specific cancers using conventional methods. The novel features of the Hi-ART system supposedly offer the following advantages over conventional radiotherapy:

- Faster operating times.
- Lower doses to adjacent critical structures, and therefore fewer adverse effects.
- More accurate pre-treatment localization of the target on a daily basis (the mega-voltage CT images provide greater anatomical detail).
- More precise conformal dose coverage of the tumor, and hence the possibility of higher doses per session and shorter courses of treatment.

Helical tomotherapy is one form of IMRT. However, the function of IGRT, i.e., the capability for 3D cross-sectional

imaging available on a linear accelerator, may also be combined with other IMRT systems; currently available products are the Elekta Synergy system and the Varian On-Board imager system. The Hi-ART system offers a fully integrated IMRT/IGRT package with CT imaging.

Research on the physical and dosimetric aspects suggests that helical tomotherapy may be superior to conventional radiotherapy in terms of radiation-dose distribution (including avoidance of sensitive structures) and dose-rate. However, no full RCTs have yet been published. A United Kingdom assessment concluded that "[a]lthough the Hi-ART system is novel it may not represent a significant breakthrough and the case for the Hi-ART system versus other IMRT systems (e.g., Elekta and Varian) has not yet been made" (National Horizon Scanning Centre, 2006).

The RayPilot System (formerly known as the Micropos 4DRT System) is another 4D intra-fraction image guidance system that has not yet received FDA approval. Similar to the Calypso 4D Localization System, the RayPilot System entails the implantation of markers into the tumor, i.e., the prostate gland. Continuous monitoring of the markers is then used for intra-fraction guidance.

Kindblom et al (2009) noted that the Micropos 4DRT system is being developed to provide accurate, precise, objective, and continuous target localization during radiotherapy. This study involved the first in-vivo use of the system, aiming to evaluate the localization accuracy of this electromagnetic positioning technique compared with radiographic localization and to assess its real-time tracking ability. An active positioning marker was inserted in the prostatic urethra of 10 patients scheduled to receive radiotherapy for localized prostate cancer. A receiving sensor plate (antennae system) was placed at a known position in the treatment table-top. Initial in-vivo system calibrations were performed in 3 subjects. Ten additional patients were then enrolled in a study arm that compared radiographic transponder location to radio-

transponder location simultaneously acquired by the Micropos 4DRT system. Frontal and side radiographs were taken with the radiopaque transponder located at 3 different positions within the prostatic urethra. The transponder insertions were all successful and without complications. Comparison of the transponder location as per the Micropos 4DRT system with the radiographic transponder localization showed an average (+/-SD) absolute and relative 3D difference of 2.7 +/- 1.2 and 1.7 +/- 1.0mm, respectively. Continuous transponder tracking capability was also demonstrated. The authors concluded that electromagnetic positioning using the Micropos transponder system is feasible in-vivo. Evaluation of this novel non-ionizing localization system, in this study using a transponder positioned in the prostatic urethra, indicated transponder localization accuracy to isocenter comparable with X-ray localization of a radiopaque marker. This was a feasibility study. The clinical value of this novel electromagnetic positioning system needs to be validated by well-designed studies.

Shah et al (2011) stated that in the past decade, techniques to improve radiotherapy delivery, such as IMRT, IGRT for both inter- and intra-fraction tumor localization, and hypo-fractionated delivery techniques such as stereotactic body radiation therapy, have evolved tremendously. This review article focused on electromagnetic tracking in radiation therapy. Electromagnetic tracking is still a growing technology in radiation oncology and, as such, the clinical applications are limited, the expense is high, and the reimbursement is insufficient to cover these costs. At the same time, current experience with electromagnetic tracking applied to various clinical tumor sites indicates that the potential benefits of electromagnetic tracking could be significant for patients receiving radiation therapy. Daily use of these tracking systems is minimally invasive and delivers no additional ionizing radiation to the patient, and these systems can provide explicit tumor motion data. Currently, work is being done to incorporate electromagnetic tracking in several sites (e.g., breast, central nervous system, cervix, liver, lung, and pancreas) outside of the prostate (The Calypso 4D Localization System is

approved by the FDA for use in prostate and post-prostatectomy prostate bed radiation therapy). Hopefully, while these preliminary investigations are not yet FDA-approved, viable options to treat these sites will become clinically available within the next several years based on this early work. The authors concluded that although there are a number of technical and fiscal issues that need to be addressed, electromagnetic tracking systems are expected to play a continued role in improving the precision of radiation delivery. There are a number of technical and fiscal issues that need to be addressed in the near term, however, to ensure the success of these technologies in improving patient care over the next 10 years and beyond.

According to a coding guide from the American Society for Therapeutic Radiation and Oncology (ASTRO, 2007), IMRT is clinically indicated when highly conformal dose planning is required. IMRT planning may be clinically indicated when one or more of the following conditions are present:

- An immediately adjacent area has been previously irradiated and abutting portals must be established with high precision.
- Dose escalation is planned to deliver radiation doses in excess of those commonly utilized for similar tumors with convetional treatment.
- The target volume is concave or convex, and the critical normal tissues are within or around that convexity or concavity.
- The target volume is in close proximity to critical structures that must be protected.
- The volume of interest must be covered with narrow margins to adequately protect immediately adjacent structures.

According to the coding guide (ASTRO, 2007), the most common sites that currently support the use of IMRT include:

- Carcinoma of the prostate

- Primary, metastatic or benign tumors of the central nervous system, including the brain, brain stem, and spinal cord.
- Primary, metastatic tumors of the spine where spinal cord tolerance may be exceeded by conventional treatment.
- Primary, metastatic or benign lesions to the head and neck area, including:

    - Aerodigestive tract
    - Orbits
    - Salivary glands
    - Sinuses
    - Skull base

- Re-irradiation that meets the requirements for medical necessity (as noted above).
- Selected cases of thoracic and abdominal malignancies
- Selected cases (i.e., not routine) of breast cancers with close proximity to critical structures
- Other pelvic and retroperitoneal tumors that meet requirements for medical necessity (as noted above).

IMRT may be necessary in lung cancer cases involving bilateral mediastinal involvement, extension to the midline of the mediastinum, cardiac involvement, or tumor abutting or involving vertebrae or brachial plexus, or great vessels.

Although not routinely indicated in breast cancer, IMRT may be necessary when more than 2 gantry angles are required to meet dose constraints or when internal mammary nodes must be treated.

IMRT is also indicated in pancreatic cancer, anal cancer and for postoperative use in endometrial, cervical and advanced rectal cancer.

Appendix

Aetna considers IMRT medically necessary for the following indications when there is a concern about damage to

surrounding critical structures with the use of external beam or 3D conformal radiation therapy:

- Anal cancer; *or*
- Anaplastic thyroid cancer; *or*
- Brain tumors in close proximity to critical structures; *or*
- Esophageal cancer where dose exceeds 50 Gy; *or*
- Gallbladder cancer where dose exceeds 50 Gy; *or*
- Head and neck cancer excluding T1 and T2 glottic cancer; *or*
- Left breast cancer if the lesion is in close proximity to the heart or other cardiovascular structures; *or*
- Lung cancer if the lesion is in close proximity to the heart or other critical structures; *or*
- Pancreatic cancer where dose exceeds 50 Gy; *or*
- Postoperative radiation to pelvis for endometrial cancer; *or*
- Prostate cancer.

Aetna considers IMRT experimental not medically necessary for right breast cancer. Aetna considers IMRT experimental and investigational for all other indications.

CPT Codes / HCPCS Codes / ICD-10 Codes	
Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":	
CPT codes covered if selection criteria are met:	
32553	Placement of interstitial device(s) for radiation therapy guidance (eg, fiducial markers, dosimeter), percutaneous, intra-thoracic, single or multiple
49327	Laparoscopy, surgical; with placement of interstitial device(s) for radiation therapy guidance (eg, fiducial markers, dosimeter), intra-abdominal, intrapelvic, and/or retroperitoneum, including imaging guidance, if performed, single or multiple (List separately in addition to code for primary procedure)

49411	Placement of interstitial device(s) for radiation therapy guidance (eg, fiducial markers, dosimeter), percutaneous, intra-abdominal, intra-pelvic (except prostate), and/or retroperitoneum, single or multiple
49412	Placement of interstitial device(s) for radiation therapy guidance (eg, fiducial markers, dosimeter), open, intra-abdominal, intrapelvic, and/or retroperitoneum, including image guidance, if performed, single or multiple (List separately in addition to code for primary procedure)
77301	Intensity modulated radiotherapy planning, including dose-volume histograms for target and critical structure partial tolerance specifications
77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (MRT), design and construction per IMRT plan
77385 - 77386	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed
77387	Guidance for localization of target volume for delivery of radiation treatment delivery, includes intrafraction tracking, when performed
HCPCS codes covered if selection criteria are met:	
A4648	Tissue marker, implantable, any type, each
C9728	Placement of interstitial device(s) for radiation therapy/surgery guidance (eg, fiducial markers, dosimeter), for other than the following sites (any approach): abdomen, pelvis, prostate, retroperitoneum, thorax, single or multiple
G6015	Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session

G6016	Compensator-based beam modulation treatment delivery of inverse planned treatment using 3 or more high resolution (milled or cast) compensator, convergent beam modulated fields, per treatment session
G6017	Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment
ICD-10 codes covered if selection criteria are met:	
C00.0 - D49.9	Neoplasms
Z51.0	Encounter for antineoplastic radiation therapy

The above policy is based on the following references:

1. Claus F, De Gersem W, De Wagter C, et al. An implementation strategy for IMRT of ethmoid sinus cancer with bilateral sparing of the optic pathways. Int J Radiat Oncol Biol Phys. 2001;51(2):318-331.
2. Alberta Heritage Foundation for Medical Research (AHFMR). Intensity-modulated radiation therapy. Edmonton, AB: AHFMR; 2000.
3. Nutting CM, Rowbottom CG, Cosgrove VP, et al. Optimisation of radiotherapy for carcinoma of the parotid gland: A comparison of conventional, three-dimensional conformal, and intensity-modulated techniques. Radiother Oncol. 2001;60(2):163-172.
4. Nutting CM, Convery DJ, Cosgrove VP, et al. Improvements in target coverage and reduced spinal cord irradiation using intensity-modulated radiotherapy (IMRT) in patients with carcinoma of the thyroid gland. Radiother Oncol. 2001;60(2):173-180.
5. Adams EJ, Nutting CM, Convery DJ, et al. Potential role of intensity-modulated radiotherapy in the treatment of tumors of the maxillary sinus. Int J Radiat Oncol Biol Phys.

2001;51(3):579-588.

6. Eisbruch A, Kim HM, Terrell JE, et al. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2001;50(3):695-704.
7. Chao KS, Deasy JO, Markman J, et al. A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: Initial results. Int J Radiat Oncol Biol Phys. 2001;49(4):907-916.
8. Chao KS, Majhail N, Huang CJ, et al. Intensity-modulated radiation therapy reduces late salivary toxicity without compromising tumor control in patients with oropharyngeal carcinoma: A comparison with conventional techniques. Radiother Oncol. 2001;61(3):275-280.
9. Shu HK, Lee TT, Vigneauly E, et al. Toxicity following high-dose three-dimensional conformal and intensity-modulated radiation therapy for clinically localized prostate cancer. Urology. 2001;57(1):102-107.
10. Huang E, Teh BS, Strother DR, et al. Intensity-modulated radiation therapy for pediatric medulloblastoma: Early report on the reduction of ototoxicity. Int J Radiat Oncol Biol Phys. 2002;52(3):599-605.
11. Bragg CM, Conway J, Robinson MH. The role of intensity-modulated radiotherapy in the treatment of parotid tumors. Int J Radiat Oncol Biol Phys. 2002;52(3):729-738.
12. Dogan N, Leybovich LB, King S, et al. Improvement of treatment plans developed with intensity-modulated radiation therapy for concave-shaped head and neck tumors. Radiology. 2002;223(1):57-64.
13. Vineberg KA, Eisbruch A, Coselmon MM, et al. Is uniform target dose possible in IMRT plans in the head and neck? Int J Radiat Oncol Biol Phys. 2002;52(5):1159-1172.
14. Lee N, Xia P, Quivey JM, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: An update of the UCSF experience. Int J Radiat Oncol Biol Phys. 2002;53(1):12-22.
15. Price RA, Hanks GE, McNeeley SW, et al. Advantages of

using noncoplanar vs. axial beam arrangements when treating prostate cancer with intensity-modulated radiation therapy and the step-and-shoot delivery method. Int J Radiat Oncol Biol Phys. 2002;53(1):236-243.

16. Chao KS. Protection of salivary function by intensity-modulated radiation therapy in patients with head and neck cancer. Semin Radiat Oncol. 2002;12(1 Suppl 1):20-25.
17. Teh BS, Mai WY, Grant WH 3rd, et al. Intensity modulated radiotherapy (IMRT) decreases treatment-related morbidity and potentially enhances tumor control. Cancer Invest. 2002;20(4):437-451.
18. Zelefsky MJ, Fuks Z, Hunt M, et al. High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. J Urol. 2001;166(3):876-881.
19. Zietman AL. Editorial comment. J Urol. 2001;166(3):881.
20. Walsh PC. Letter to the editor. Re: High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized cancer. J Urol. 2001;166(6): 2321-2322.
21. Nutting CM, Corbishley CM, Sanchez-Nieto B, et al. Potential improvements in the therapeutic ratio of prostate cancer irradiation: Dose escalation of pathologically identified tumour nodules using intensity modulated radiotherapy. Br J Radiol. 2002;75(890):151-161.
22. National Comprehensive Cancer Network (NCCN). Prostate cancer. Clinical Practice Guidelines in Oncology - v.1.2004. Rockledge, PA: NCCN; 2004.
23. National Comprehensive Cancer Network (NCCN). Breast cancer. Clinical Practice Guidelines in Oncology - v.2.2003. Rockledge, PA: NCCN; 2003.
24. American College of Radiology (ACR). ACR Practice Guideline for Intensity Modulated Radiation Therapy. 2002 (Res. 17). ACR Practice Guideline. Reston, VA: ACR; effective January 1, 2003:561-566. Available at: http://www.acr.org/departments/stand_accred /standards/pdf/

imrt.pdf. Accessed February 16, 2004.

25. Medical Services Advisory Committee (MSAC). Conformal radiotherapy. Assessment Report No. 107. Canberra, Australia: MSAC; 2002.
26. Association of Community Cancer Centers (ACCC). Intensity modulated radiation therapy (IMRT). Practical know-how for community cancer centers. Oncology Issues. 2003;18(3 Supp).
27. Intensity Modulated Radiation Therapy Collaborative Working Group. Intensity modulated radiotherapy: Current status and issues of interest. Int J Radiat Onc Biol Physics. 2001;51(4):880-914.
28. Cancer Care Ontario Practice Guideline Initiative (CCOPGI), Genitourinary Cancer Disease Site Group. Brundage M, Lukka H, Crook J, Warde P, Bauman G, Catton C, Markman BR, Charette M. The use of conformal radiotherapy and the selection of radiation dose in T1 or T2 prostate cancer [full report]. Practice Guideline; no. 3-11. Toronto, ON: Cancer Care Ontario (CCO); October 2002.
29. Hummel S, Paisley S, Morgan A, et al. Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: A systematic review. Health Technol Assess. 2003;7(3). Available at: **http://www.hta.ac.uk/ (http://www.hta.ac.uk/)**. Accessed December 3, 2003.
30. Heron DE, Gerszten K, Selvaraj RN, et al. Conventional 3D conformal versus intensity-modulated radiotherapy for the adjuvant treatment of gynecologic malignancies: A comparative dosimetric study of dose-volume histograms small star, filled. Gynecol Oncol. 2003;91(1):39-45.
31. Lin A, Kim HM, Terrell JE, et al. Quality of life after parotid-sparing IMRT for head-and-neck cancer: A prospective longitudinal study. Int J Radiat Oncol Biol Phys. 2003;57(1):61-70.
32. Lee N, Xia P, Fischbein NJ, et al. Intensity-modulated radiation therapy for head-and-neck cancer: The UCSF experience focusing on target volume delineation. Int J Radiat Oncol Biol Phys. 2003;57(1):49-60.

33. L'Agence Nationale d'Accreditation d'Evaluation en Sante (ANAES). Intensity modulation radiotherapy. Technology Evaluation Service. Paris, France: ANAES; May 2003.
34. Haute Autorite de Sante (HAS)/French National Authority for Health. Assessment of intensity-modulated radiotherapy. Paris, France: Haute Autorite de Sante/French National Authority for Health (HAS); 2003.
35. Adams EJ, Convery DJ, Cosgrove VP, et al. Clinical implementation of dynamic and step-and-shoot IMRT to treat prostate cancer with high risk of pelvic lymph node involvement. Radiother Oncol. 2004;70(1):1-10.
36. Parliament MB, Scrimger RA, Anderson SG, et al. Preservation of oral health-related quality of life and salivary flow rates after inverse-planned intensity-modulated radiotherapy (IMRT) for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2004;58(3):663-673.
37. Chao KS, Ozyigit G, Thorsdad WL. Toxicity profile of intensity-modulated radiation therapy for head and neck carcinoma and potential role of amifostine. Semin Oncol. 2003;30(6 Suppl 18):101-108.
38. Bai YR, Wu GH, Guo WJ, et al. Intensity modulated radiation therapy and chemotherapy for locally advanced pancreatic cancer: Results of feasibility study. World J Gastroenterol. 2003;9(11):2561-2564.
39. George R, Keall PJ, Kini VR, et al. Quantifying the effect of intrafraction motion during breast IMRT planning and dose delivery. Med Phys. 2003;30(4):552-562.
40. Crane CH, Antolak JA, Rosen II, et al. Phase I study of concomitant gemcitabine and IMRT for patients with unresectable adenocarcinoma of the pancreatic head. Int J Gastrointest Cancer. 2001;30(3):123-132.
41. Donovan EM, Bleackley NJ, Evans PM, et al. Dose-position and dose-volume histogram analysis of standard wedged and intensity modulated treatments in breast radiotherapy. Br J Radiol. 2002;75(900):967-973.
42. Wang L, Yorke E, Chui CS. Monte Carlo evaluation of 6 MV intensity modulated radiotherapy plans for head and neck and lung treatments. Med Phys. 2002;29(11):2705-2717.

43. Evans PM, Donovan EM, Partridge M, et al. The delivery of intensity modulated radiotherapy to the breast using multiple static fields. Radiother Oncol. 2000;57(1):79-89.
44. Kwong DL, Pow EH, Sham JS, et al. Intensity-modulated radiotherapy for early-stage nasopharyngeal carcinoma. Cancer.2004;101(7):1584-1593.
45. Goodman KA, Hong L, Wagman R, et al. Dosimetric analysis of a simplified intensity modulation technique for prone breast radiotherapy. Int J Radiat Oncol Biol Phys. 2004;60(1):95-102.
46. Xiao Y, Werner-Wasik M, Michalski D, et al. Comparison of three IMRT inverse planning techniques that allow for partial esophagus sparing in patients receiving thoracic radiation therapy for lung cancer. Med Dosim. 2004;29(3):210-216.
47. Guerrero M, Li XA, Earl MA, et al. Simultaneous integrated boost for breast cancer using IMRT: A radiobiological and treatment planning study. Int J Radiat Oncol Biol Phys. 2004;59(5):1513-1522.
48. Wu VW, Sham JS, Kwong DL. Inverse planning in three-dimensional conformal and intensity-modulated radiotherapy of mid-thoracic oesophageal cancer. Br J Radiol. 2004;77(919):568-572.
49. Li JS, Freedman GM, Price R, et al. Clinical implementation of intensity-modulated tangential beam irradiation for breast cancer. Med Phys. 2004;31(5):1023-1031.
50. Ben-Josef E, Shields AF, Vaishampayan U, et al. Intensity-modulated radiotherapy (IMRT) and concurrent capecitabine for pancreatic cancer. Int J Radiat Oncol Biol Phys. 2004;59(2):454-459.
51. Milano MT, Chmura SJ, Garofalo MC, et al. Intensity-modulated radiotherapy in treatment of pancreatic and bile duct malignancies: Toxicity and clinical outcome. Int J Radiat Oncol Biol Phys. 2004;59(2):445-453.
52. Nioutsikou E, Bedford JL, Christian JA, et al. Segmentation of IMRT plans for radical lung radiotherapy delivery with the step-and-shoot technique. Med Phys. 2004;31(4):892-901.

53. Bilsky MH, Yamada Y, Yenice KM, et al. Intensity-modulated stereotactic radiotherapy of paraspinal tumors: A preliminary report. Neurosurgery. 2004;54(4):823-831.
54. Jani AB, Roeske JC, Rash C. Intensity-modulated radiation therapy for prostate cancer. Clin Prostate Cancer. 2003;2(2):98-105.
55. Liu HH, Wang X, Dong L, et al. Feasibility of sparing lung and other thoracic structures with intensity-modulated radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2004;58(4):1268-1279.
56. Murshed H, Liu HH, Liao Z, et al. Dose and volume reduction for normal lung using intensity-modulated radiotherapy for advanced-stage non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2004;58(4):1258-1267.
57. Frazier RC, Vicini FA, Sharpe MB, et al. Impact of breathing motion on whole breast radiotherapy: A dosimetric analysis using active breathing control. Int J Radiat Oncol Biol Phys. 2004;58(4):1041-1047.
58. Cozzi L, Fogliata A, Bolsi A, et al. Three-dimensional conformal vs. intensity-modulated radiotherapy in head-and-neck cancer patients: Comparative analysis of dosimetric and technical parameters. Int J Radiat Oncol Biol Phys. 2004;58(2):617-624.
59. Thilmann C, Sroka-Perez G, Krempien R, et al. Inversely planned intensity modulated radiotherapy of the breast including the internal mammary chain: A plan comparison study. Technol Cancer Res Treat. 2004;3(1):69-75.
60. Mock U, Georg D, Bogner J, et al. Treatment planning comparison of conventional, 3D conformal, and intensity-modulated photon (IMRT) and proton therapy for paranasal sinus carcinoma. Int J Radiat Oncol Biol Phys. 2004;58(1):147-154.
61. Ozyigit G, Yang T, Chao KS. Intensity-modulated radiation therapy for head and neck cancer. Curr Treat Options Oncol. 2004;5(1):3-9..
62. Huh SJ, Kang MK, Han Y. Small bowel displacement

system-assisted intensity-modulated radiotherapy for cervical cancer. Gynecol Oncol. 2004;93(2):400-406.

63. Fu WH, Wang LH, Zhou ZM, et al. Comparison of conformal and intensity-modulated techniques for simultaneous integrated boost radiotherapy of upper esophageal carcinoma. World J Gastroenterol. 2004;10(8):1098-1102.
64. American Society for Therapeutic Radiology and Oncology (ASTRO). Reimbursement of intensity modulated radiation therapy. Policy and Practice. Fairfax, VA: ASTRO; 2002. Available at: **http://www.astro.org/publications/astronews/2002/Apr/PolicyPractice.htm (http://www.astro.org/publications/astronews/2002/Apr/PolicyPractice.htm)**. Accessed September 27, 2004.
65. Partridge M, Aldridge S, Donovan E, Evans PM. An intercomparison of IMRT delivery techniques: A case study for breast treatment. Phys Med Biol. 2001;46(7):N175-N185.
66. Jiang SB, Ayyangar KM. On compensator design for photon beam intensity-modulated conformal therapy. Med Phys. 1998;25(5):668-675.
67. Dimitriadis DM, Fallone BG. Compensators for intensity-modulated beams. Med Dosim. 2002;27(3):215-220.
68. Bakal A, Laub WU, Nusslin F. Compensators for IMRT--an investigation in quality assurance. Z Med Phys. 2001;11(1):15-22.
69. Lohr F, Dobler B, Mai S, et al. Optimization of dose distributions for adjuvant locoregional radiotherapy of gastric cancer by IMRT. Strahlenther-Onkol. 2003;179(8):557-563.
70. Bos LJ, Damen EM, de Boer RW, et al. Reduction of rectal dose by integration of the boost in the large-field treatment plan for prostate irradiation. Int J Rad Biol Phys. 2002;52(1):254-265.
71. Braaksma M, Levendag P. Tools for optimal tissue sparing in concomitant chemoradiation of advanced head and neck cancer: Subcutaneous amifostine and computed tomography-based target delineation. Semin Oncol.

2002;29(6 Suppl 19):63-70.

72. Eisbruch A, Schwartz M, Rasch C, et al. Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: Which anatomic structures are affected and can they be spared by IMRT? Int J Radiat Oncol Biol Phys. 2004;60(5):1425-1439.
73. De Salles AA, Pedroso AG, Medin P, et al. Spinal lesions treated with Novalis shaped beam intensity-modulated radiosurgery and stereotactic radiotherapy. J Neurosurg. 2004;101 Suppl 3:435-440.
74. Lauve A, Morris M, Schmidt-Ullrich R, et al. Simultaneous integrated boost intensity-modulated radiotherapy for locally advanced head-and-neck squamous cell carcinomas: II--clinical results. Int J Radiat Oncol Biol Phys. 2004;60(2):374-387.
75. Chang EL, Shiu AS, Lii MF, et al. Phase I clinical evaluation of near-simultaneous computed tomographic image-guided stereotactic body radiotherapy for spinal metastases. Int J Radiat Oncol Biol Phys. 2004;59(5):1288-1294.
76. Cuzick J. Radiotherapy for breast cancer. J Natl Cancer Inst. 2005;97:406-407.
77. Giordano SH, Kuo Y, Freeman JL, et al. Risk of cardiac death after adjuvant radiotherapy for breast cancer. J Natl Cancer Inst. 2005; 97: 419-424.
78. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med. 1997;337:949-955.
79. Hojris I, Overgaard M, Christensen JJ, Overgaard J. Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: Analysis of DBCG 82b and 82c randomised trials. Radiotherapy Committee of the Danish Breast Cancer Cooperative Group. Lancet. 1999;354:1425-1430.
80. Royal College of Radiologists, The Society and The College of Radiographers, and Institute of Physics and

Engineering in Medicine. Development and implementation of conformal radiotherapy in the United Kingdom. London, UK: Royal College of Radiologists; June 2002.

81. Chang SX, Deschesne KM, Cullip TJ, et al. A comparison of different intensity modulation treatment techniques for tangential breast irradiation. Int J Rad Oncol Biol Phys. 1999;45(5):1305-1314.
82. Chang SX, Cullip TJ, Deschesne KM. Intensity modulation delivery techniques: 'Step & shoot' MLC auto-sequence versus the use of a modulator. Med Phys. 2000;27(5):948-959.
83. Chang SX, Cullip TJ, Deschesne KM, et al. Compensators: An alternative IMRT delivery technique. J Appl Clin Med Phys. 2004;5(3):15-36.
84. Coles CE, Moody AM, Wilson CB, Burnet NG. Reduction of radiotherapy-induced late complications in early breast cancer: The role of intensity-modulated radiation therapy and partial breast irradiation. Part II--Radiotherapy strategies to reduce radiation-induced late effects. Clin Oncol (R Coll Radiol). 2005;17(2):98-110.
85. Chang JY, Liu HH, Komaki R. Intensity modulated radiation therapy and proton radiotherapy for non-small cell lung cancer. Curr Oncol Rep. 2005;7(4):255-259.
86. Bogardus CR. A User's Guide for Radiation Oncology Management & Billing Procedures. 7th ed. Oklahoma City, OK: Cancer Care Network; 2005.
87. Horton JK, Halle JS, Chang SX, Sartor CI. Comparison of three concomitant boost techniques for early stage breast cancer. Int J Radiation Oncol Biol Phys. 2005 [in press].
88. Pichon Riviere A, Augustovski F, Ferrante D, et al. Intensity modulated radiotherapy (IMRT) for prostate cancer [summary]. Rapid Report No. 31. Buenos Aires, Argentina: Institute for Clinical Effectiveness and Health Policy; 2004. Available at: **http://www.iecs.org.ar/iecs-visor-publicaciones.php (http://www.iecs.org.ar/iecs-visor-publicaciones.php)**. Accessed October 4, 2005.
89. Maceiras-Rozas C, Garcia-Caeiro A, Rey-Liste T, Castro-

Bermudez M. Intensity modulated radiotherapy. Santiago de Compostela, Spain: Galician Agency for Health Technology Assessment (AVALIA-T); 2005:1-144.

90. National Cancer Institute (NCI). The National Cancer Institute Guidelines for the Use of Intensity-Modulated Radiation Therapy in Clinical Trials. Bethesda, MD: NCI; January 14, 2005.
91. National Comprehensive Cancer Network (NCCN). Breast cancer. Clinical Practice Guidelines in Oncology Version 2.2005. Jenkintown, PA: NCCN; 2005.
92. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Special Report: Intensity Modulation Radiation Therapy for Cancer of the Breast or Lung. TEC Assessment in Press. Chicago, IL: BCBSA; November 2005. Available at: **http://www.bcbs.com /tec/tecinpress/07.html (http://www.bcbs.com /tec/tecinpress/07.html)**. Accessed January 5, 2006.
93. Ben-Josef E, Shields AF, Vaishampayan U, et al. Intensity-modulated radiotherapy (IMRT) and concurrent capecitabine for pancreatic cancer. Int J Radiat Oncol Biol Phys. 2004;59(2):454-459.
94. Fuss M, Salter BJ, Cavanaugh SX, et al. Daily ultrasound-based image-guided targeting for radiotherapy of upper abdominal malignancies. Int J Radiat Oncol Biol Phys. 2004;59(4):1245-1256.
95. Wilkowski R, Thoma M, Weingandt H, et al. Chemoradiation for ductal pancreatic carcinoma: Principles of combining chemotherapy with radiation, definition of target volume and radiation dose. JOP. 2005;6(3):216-230.
96. Paulino AC, Ferenci MS, Chiang KY, et al. Comparison of conventional to intensity modulated radiation therapy for abdominal neuroblastoma. Pediatr Blood Cancer. 2006;46(7):739-744.
97. Pisansky TM. External-beam radiotherapy for localized prostate cancer. N Engl J Med. 2006;355(15):1583-1591.
98. Pignol J, Olivotto I, Rakovich E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. J Clin Oncol.

2008;26(13):2085-2092.

99. Donovan E, Bleakley N, Denholm E, et al.; Breast Technology Group. Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. Radiother Oncol. 2007;82(3):254-264.
100. American Society for Therapeutic Radiation and Oncology (ASTRO). The ASTRO/ACR Guide to Radiation Oncology Coding 2007. Fairfax, VA: ASTRO; 2007.
101. Balter JM, Kessler ML. Imaging and alignment for image-guided radiation therapy. J Clin Oncol. 2007;25(8):931-937.
102. Dawson LA, Jaffray DA. Advances in image-guided radiation therapy. J Clin Oncol. 2007;25(8):938-946.
103. Haffty BG, Buchholz TA, McCormick B. Should intensity-modulated radiation therapy be the standard of care in the conservatively managed breast cancer patient? J Clin Oncol. 2008;26(13):2072-2074.
104. Lu H, Yao M. The current status of intensity-modulated radiation therapy in the treatment of nasopharyngeal carcinoma. Cancer Treat Rev. 2008;34(1):27-36.
105. Small W Jr, Mell LK, Anderson P, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int J Radiat Oncol Biol Phys. 2008;71(2):428-434.
106. Veldeman L, Madani I, Hulstaert F, et al. Evidence behind use of intensity-modulated radiotherapy: A systematic review of comparative clinical studies. Lancet Oncol. 2008;9(4):367-375.
107. Van den Steen D, Hulstaert F, Camberlin C. Intensity-modulated radiotherapy. KCE Reports 62. Brussels, Belgium: Belgian Health Care Knowledge Centre (KCE); 2007.
108. Centers for Medicare & Medicaid Services (CMS). Centers for Medicare & Medicaid Services (CMS) Healthcare Common Procedure Coding System (HCPCS) Public Meeting Summary Report. Supplies & Other – Day 1. Baltmore, MD: CMS; April 22, 2008.

109. Sullivan T, Merlin T. Dose Verification System for the measurement of radiation dose in patients undergoing radiotherapy for breast and prostate cancer. National Horizon Scanning Unit, Horizon Scanning Prioritising Summary. Adelaide, SA: Adelaide Health Technology Assessment, Discipline of Public Health, University of Adelaide; September 2006;14(2).
110. National Horizon Scanning Centre. Helical Tomotherapy Hi-ART System for external cancer radiotherapy. Horizon Scanning Technology Briefing. Birmingham, UK: National Horizon Scanning Centre, Department of Public Health and Epidemiology, University of Birmingham; August 2006.
111. U.S. Food and Drug Administration (FDA), Center for Devices and Radiologic Health (CDRH). Calypso 4D Localization System. Summary of Safety and Effectivness. 510(k) No. K060906. Rockville, MD: FDA; July 28, 2006.
112. U.S. Food and Drug Administration (FDA), Center for Devices and Radiologic Health (CDRH). Calypso 4D Localization System. Summary of Safety and Effectivness. 510(k) No. K080726. Rockville, MD: FDA; May 14, 2008.
113. Zhu X, Bourland JD, Yuan Y, et al. Tradeoffs of integrating real-time tracking into IGRT for prostate cancer treatment. Phys Med Biol. 2009;54(17):N393-N401.
114. Rajendran RR, Plastaras JP, Mick R, et al. Daily isocenter correction with electromagnetic-based localization improves target coverage and rectal sparing during prostate radiotherapy. Int J Radiat Oncol Biol Phys. 2010;76(4):1092-1099.
115. Smith RL, Sawant A, Santanam L, et al. Integration of real-time internal electromagnetic position monitoring coupled with dynamic multileaf collimator tracking: An intensity-modulated radiation therapy feasibility study. Int J Radiat Oncol Biol Phys. 2009;74(3):868-875.
116. Ogunleye T, Rossi PJ, Jani AB, Fox T, Elder E. Performance evaluation of Calypso 4D localization and kilovoltage image guidance systems for interfraction motion management of prostate patients. ScientificWorldJournal. 2009;9:449-458.

117. Sawant A, Smith RL, Venkat RB, et al. Toward submillimeter accuracy in the management of intrafraction motion: The integration of real-time internal position monitoring and multileaf collimator target tracking. Int J Radiat Oncol Biol Phys. 2009;74(2):575-582.
118. Noel C, Parikh PJ, Roy M, et al. Prediction of intrafraction prostate motion: accuracy of pre- and post-treatment imaging and intermittent imaging. Int J Radiat Oncol Biol Phys. 2009;73(3):692-698.
119. Murphy MJ, Eidens R, Vertatschitsch E, Wright JN. The effect of transponder motion on the accuracy of the Calypso Electromagnetic localization system. Int J Radiat Oncol Biol Phys. 2008;72(1):295-299.
120. Quigley MM, Mate TP, Sylvester JE. Prostate tumor alignment and continuous, real-time adaptive radiation therapy using electromagnetic fiducials: Clinical and cost-utility analyses. Urol Oncol. 2009;27(5):473-482.
121. Li HS, Chetty IJ, Enke CA, et al. Dosimetric consequences of intrafraction prostate motion. Int J Radiat Oncol Biol Phys. 2008;71(3):801-812.
122. Santanam L, Malinowski K, Hubenshmidt J, et al. Fiducial-based translational localization accuracy of electromagnetic tracking system and on-board kilovoltage imaging system. Int J Radiat Oncol Biol Phys. 2008;70(3):892-899.
123. Kupelian P, Willoughby T, Mahadevan A, et al. Multi-institutional clinical experience with the Calypso System in localization and continuous, real-time monitoring of the prostate gland during external radiotherapy. Int J Radiat Oncol Biol Phys. 2007;67(4):1088-1098.
124. Willoughby TR, Kupelian PA, Pouliot J, et al. Target localization and real-time tracking using the Calypso 4D localization system in patients with localized prostate cancer. Int J Radiat Oncol Biol Phys. 2006;65(2):528-534.
125. Pearson SD, Ladapo J, Prosser L. Intensity modulated radiation therapy (IMRT) for localized prostate cancer. Final Appraisal Document. Boston, MA: Institute for Clinical and Economic Review (ICER); November 23, 2007.
126. Wilt T J, Shamliyan T, Taylor B, et al. Comparative

effectiveness of therapies for clinically localized prostate cancer. Comparative Effectiveness Review No. 13. Rockville, MD: Agency for Healthcare Research and Quality; 2008.

127. Pichon-Riviere A, Augustovski F, Garcia Marti S, et al. Intensity modulated radiotherapy (IMRT) for prostate cancer [summary]. IRR No. 165. Buenos Aires, Argentina: Institute for Clinical Effectiveness and Health Policy (IECS); 2009.
128. Nachtnebel A, Mathis S, Geiger-Gritsch S, Mittermayr T. [Image guided radiotherapy using cone-beam computed tomography. Systematic Review.] [summary]. Decision Support Document 26. Vienna, Austria: Ludwig Boltzmann Institut fuer Health Technology Assessment (LBI-HTA); 2009.
129. Purins A, Mundy L, Hiller J. TomoTherapy HI-ART System Radiotherapy planning and treatment for cancer patients. Horizon Scanning Technology Prioritising Summary. Adelaide, SA: Adelaide Health Technology Assessment; November 2009.
130. Small W Jr, Mell LK, Anderson P, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int J Radiat Oncol Biol Phys. 2008;71(2):428-434.
131. Chung HT, Xia P, Chan LW, et al. Does image-guided radiotherapy improve toxicity profile in whole pelvic-treated high-risk prostate cancer? Comparison between IG-IMRT and IMRT. Int J Radiat Oncol Biol Phys. 2009;73(1):53-60.
132. Curtis AE, Okcu MF, Chintagumpala M, et al. Local control after intensity-modulated radiotherapy for head-and-neck rhabdomyosarcoma. Int J Radiat Oncol Biol Phys. 2009;73(1):173-177.
133. Catton C, Rumble RB, Warde P, et al.; IMRT Indications Expert Panel. The role of IMRT in soft-tissue sarcomas. Evidence-Based Series #21-3-6. Toronto, ON: Cancer Care Ontario; October 29, 2010.
134. Bezjak A, Rumble RB, Rodrigues G, et al.; IMRT Indications

Expert Panel. The role of IMRT in lung cancer. Evidence-Based Series #21-3-5. Toronto, ON: Cancer Care Ontario; November 22, 2010.

135. Bauman G, Rumble RB, Chen J, et al. The role of IMRT in prostate cancer. Evidence-Based Series #21-3-1. Toronto, ON: Cancer Care Ontario; October 27, 2010.
136. Aral IA, Hussain F, Aziz H, Godec C. Prostate cancer - external beam radiotherapy. eMedicine Urology. New York, NY: Medscape; updated March 26, 2010.
137. Hartford AC, Palisca MG, Eichler TJ, et al; American Society for Therapeutic Radiology and Oncology; American College of Radiology. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) Practice Guidelines for Intensity-Modulated Radiation Therapy (IMRT). Int J Radiat Oncol Biol Phys. 2009;73(1):9-14.
138. Potters L, Gaspar LE, Kavanagh B, et al; American Society for Therapeutic Radiology and Oncology; American College of Radiology. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guidelines for image-guided radiation therapy (IGRT). Int J Radiat Oncol Biol Phys. 2010;76(2):319-325.
139. Zamora L, Leopardi D, Lee I, Humphreys K. Image-guided intensity-modulated radiotherapy. Horizon Scanning Technology Horizon Scanning Report. Stepney, SA: Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S); November 2010.
140. Hummel S, Simpson EL, Hemingway P, et al. Intensity-modulated radiotherapy for the treatment of prostate cancer: A systematic review and economic evaluation. Health Technol Assess. 2010;14(47):1-108.
141. Sandler HM, Liu PY, Dunn RL, et al. Reduction in patient-reported acute morbidity in prostate cancer patients treated with 81-Gy Intensity-modulated radiotherapy using reduced planning target volume margins and electromagnetic tracking: Assessing the impact of margin reduction study. Urology. 2010;75(5):1004-1008.

142. McCormick B, Hunt M. Intensity-modulated radiation therapy for breast: Is it for everyone? Semin Radiat Oncol. 2011;21(1):51-54.
143. Lim K, Small W Jr, Portelance L, et al; Gyn IMRT Consortium. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer. Int J Radiat Oncol Biol Phys. 2011;79(2):348-355.
144. Rochet N, Kieser M, Sterzing F, et al. Phase II study evaluating consolidation whole abdominal intensity-modulated radiotherapy (IMRT) in patients with advanced ovarian cancer stage FIGO III--the OVAR-IMRT-02 Study. BMC Cancer. 2011;11:41.
145. Bayouth J, Chetty I, Correa C, et al. Continuous localization technologies for radiotherapy delivery. American Society for Radiation Oncology (ASTRO) Emerging Technology Committee Report. Fairfax, VA: ASTRO; January 7, 2010.
146. Canter D, Kutikov A, Horwitz EM, Greenberg RE. Transrectal implantation of electromagnetic transponders following radical prostatectomy for delivery of IMRT. Can J Urol. 2011;18(4):5844-5848.
147. Sheets NC, Goldin GH, Meyer AM, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. JAMA. 2012;307(15):1611-1620.
148. Clark EE, Thielke A, Kriz H, et al. Intensity modulated radiation therapy. Draft Evidence Report. Prepared by the Oregon Health & Science University, Center for Evidence-based Policy for the Washington State Health Care Authority, Health Technology Assessment Program. Olympia, WA: Washington State Health Care Authority, Health Technology Assessment Program; July 5, 2012.
149. Kindblom J, Ekelund-Olvenmark AM, Syren H, et al. High precision transponder localization using a novel electromagnetic positioning system in patients with localized prostate cancer. Radiother Oncol. 2009;90(3):307-311.

150. Shah AP, Kupelian PA, Willoughby TR, Meeks SL. Expanding the use of real-time electromagnetic tracking in radiation oncology. J Appl Clin Med Phys. 2011;12(4):3590.
151. Zhang B, Mo Z, Du W, et al. Intensity-modulated radiation therapy versus 2D-RT or 3D-CRT for the treatment of nasopharyngeal carcinoma: A systematic review and meta-analysis. Oral Oncol. 2015;51(11):1041-1046.
152. Yu T, Zhang Q, Zheng T, et al. The effectiveness of intensity modulated radiation therapy versus three-dimensional radiation therapy in prostate cancer: A meta-analysis of the literatures. PLoS One. 2016;11(5):e0154499.
153. Liu X, Fang H, Tian Y, et al. Intensity modulated radiation therapy for early-stage primary gastric diffuse large B-cell lymphoma: Dosimetric analysis, clinical outcome, and quality of life. Int J Radiat Oncol Biol Phys. 2016;95(2):712-720.