Real-Time Intrafraction Motion Management During Radiotherapy

Policy Number:
MM.05.011
Line(s) of Business:
HMO; PPO; QUEST Integration
Section:
Radiology
Place(s) of Service:
Outpatient

Original Effective Date:
 02/01/2013
Current Effective Date:
09/01/2018

I. Description

Real-time intra-fraction target tracking is a technique that enables adjustment of the target radiation while it is being delivered (i.e., intra-fraction adjustments) to compensate for movement of the organ inside the body. Real-time tracking, which may or may not use radiographic images, is one of many techniques referred to as "image-guided radiotherapy" (IGRT). For this policy, real-time tracking is defined as frequent or continuous target tracking in the treatment room during radiation therapy, with periodic or continuous adjustment to targeting made on the basis of target motion detected by the tracking system. This policy does not address approaches used to optimize consistency of patient positioning in setting up either the overall treatment plan or individual treatment sessions (i.e., inter-fraction adjustments); instead it deals with approaches to monitor target movement within a single treatment session, which includes technologies using respiratory gating. This policy does not address IGRT used as part of stereotactic (body) radiotherapy.

Real-Time Intrafraction Target Tracking

Evidence for the use of real-time intrafraction target tracking for delivery of radiotherapy comprises studies, mostly in patients with prostate cancer that demonstrate the ability of the technology to track tumor motion. Planning studies indicate that planning target volumes can be reduced with real-time intrafraction target tracking compared with usual set-ups (eg, bony alignment). One study in patients with lung cancer reported difficulties with implantation of radio-emitting transponders, and 1 study in patients with breast cancer indicated little use for real-time intrafraction target tracking because breast tumor motion was small.

There is no data indicating that use of real-time tracking during radiotherapy to adjust the intrafraction dose of radiotherapy or monitor target motion during radiation treatment improves clinical outcomes over existing techniques. Clinical input was mixed, with several reviewers agreeing that head-to-head comparative trials with and without the use of real-time target tracking are necessary to determine whether the use of real-time tracking leads to improved outcomes.

Respiratory Gating

Current non-gated radiotherapy techniques achieve adequate tumor coverage. Therefore, the goal of adding respiratory gating is to reduce irradiation of normal tissue to reduce toxicity and facilitate dose escalation. Increased treatment time and patient inconvenience associated with respiratory gating may be offset if these benefits are realized.

Studies in lung cancer and breast cancer have compared radiation treatment planning with and without respiratory gating using surface markers. Although studies have shown reductions in planning target volume margins, radiation doses to other organs at risk (lungs, heart, esophagus), and local toxicity with respiratory gating, these studies were small and the largest study, in women with breast cancer, was nonrandomized. Increased survival or recurrence outcomes were not shown. Current evidence is therefore considered insufficient to determine whether respiratory gating improves patient outcomes, specifically by reducing toxicity and/or improving survival outcomes. Respiratory gating techniques for the delivery of radiotherapy do not meet payment determination criteria.

Deep Inspiration Breath Hold Technique

Deep Inspiration Breath Hold Technique (DIBH) can be used for breast cancer, as a technique to deliver whole breast irradiation in patients receiving treatment for left-sided breast cancer after breast conserving surgery. The technique can be used when all of the following conditions are met:

1) Significant cardiac radiation exposure is expected to be greater than or equal to 25 Gy to $10cm^3$ or more of the heart (V25 greater than or equal to $10cm^3$) with 3D conformal RT despite the use of a complex positioning device.

2) With the use of DIBH, there is a reduction in the absolute heart volume receiving 25 Gy or higher by at least 20% (e.g., volume predicted to receive 25Gy by 3D RT is $20 \ cm^3$ and the volume predicted by IMRT $\leq 16 \ cm^3$).
3) The other conformal radiation fields results in a lung V 20 that exceeds 35%.

4) Target dose heterogeneity is reduced by an absolute 8% (e.g. hot spot reduced from 118% to 110%).

II. **Policy Statement**

   A. Deep Inspiration Breath Hold Technique is only covered for left breast cancer if the criteria noted above have been met.
   B. Real-time intrafraction target tracking during radiotherapy to adjust radiation doses or monitor target motion during individual radiotherapy treatment sessions is not covered except for DIBH for left breast cancer because current evidence is insufficient to demonstrate that this technique improves health outcomes when compared to existing techniques.
   C. Respiratory gating techniques for the delivery of radiotherapy are not covered because the current evidence is insufficient to determine whether this improves health outcomes.

III. Administrative Guidelines

Precertification is required for DIBH. Complete HMSA's [Precertification Request] and mail or fax the form or use iExchange as indicated. Documentation submitted must include a diagnosis of left breast cancer and medical records indicating the conditions for DIBH are met, as shown under the Deep Inspiration Breath Hold Technique heading above.

Applicable codes:

CPT Code	Description
77387	Guidance for localization of target volume for delivery of radiation treatment delivery, includes intrafraction tracking, when performed
G6017	Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (eg, 3D positional tracking, gating, 3D surface tracking), each fraction of treatment

IV. Scientific Background

In general, intra-fraction adjustments can be grouped into 2 categories: online and off-line. An online correction takes place when corrections or actions occur at the time of radiation delivery on the basis of predefined thresholds. An off-line approach refers to target tracking without immediate intervention.

During radiation therapy, it is important to target the tumor so that radiation treatment is delivered to the tumor, but surrounding tissue is spared. This targeting seems increasingly important as dose-escalation is used in an attempt to improve long-term tumor control and improve patient survival. Over time, a number of approaches have evolved to improve targeting of the radiation dose. Better targeting has been achieved through various approaches to radiation therapy, such as 3-D conformal treatment and intensity-modulated radiation therapy (IMRT). For prostate cancer, use of a rectal balloon has been reported to improve consistent positioning of the prostate and thus reduce rectal tissue irradiation during radiation therapy. In addition, more sophisticated imaging techniques, including use of implanted fiducial markers, have been used to better position the tumor (patient) as part of treatment planning and individual radiation treatment sessions.

Intrafraction target motion can be caused by many things including breathing, cardiac and bowel motion, swallowing or sneezing. Data also suggest that a strong relationship may exist between obesity and organ shift, indicating that without some form of target tracking, the target volume may not receive the intended dose for patients who are moderately to severely obese. Respiration affects the position of all thoracic and abdominal organs, primarily the lungs, liver, and breast. The American Association of Physicists in Medicine Task Group 76 recommends motion management for tumor motion that exceeds 5 mm in any direction or if significant normal tissue-sparing can be gained. Measurement of tumor motion commonly uses fluoroscopy or 4-dimensional computed tomography (4D-CT), a sequence of 3D-CT images over time, with or without fiducial markers.

Five principal respiratory motion management techniques are commonly used: integration of respiratory movements (ie, mean tumor position, range of motion) into treatment planning; abdominal compression plates to force shallow breathing; breath-hold, often using spirometry; respiratory gating; and real-time tumor-tracking. Respiratory gating delivers radiation during a particular portion of the breathing cycle. This "gate" is defined by monitoring respiratory motion with external sensors and selecting a constant cycle amplitude or phase (eg, end-inspiration or end-expiration) for radiation delivery. Respiratory gating assumes a consistent association between the respiratory cycle and tumor position. For patients in whom this association is unreliable, real-time target tracking techniques can be used. These techniques involve fluoroscopic, radiograph, or digital tracking of external respiratory surrogates, eg, an abdominal belt, or, like other real-time tumor-tracking techniques described here, implanted fiducial markers.

As previously noted, the next step in this evolving process of improved targeting is the use of devices to track the target (tumor motion) during radiation treatment sessions and allow adjustment of the radiation dose during a session based on tumor movement. Some of the devices cleared by FDA are referred to as "4-D imaging" (not to be confused with 4D-CT, described earlier). One such device is the Calypso 4D Localization System. This system uses a group of 3 electromagnetic transponders (Beacon) implanted in or near the tumor to allow continuous localization of a treatment isocenter. Beacon transponders are 8.5-mm long with a diameter of 1.85 mm. The 3 transponders have a "field of view" of 14-cm square and a depth of 27 cm.

V. Rationale

Randomized trial data are needed to show the impact on clinical outcomes of real-time tracking devices that allow for adjustments during radiotherapy or monitor the tumor target during individual treatment sessions. The clinical outcomes could be disease control (patient survival) and/or toxicity (eg, less damage to adjacent normal tissue). Because intensity-modulated radiation therapy (IMRT) and IMRT plus real-time tracking are likely to produce equivalent therapeutic results, given the increased cost of real-time tracking, the technique (tracking) needs to demonstrate incremental clinical benefit over IMRT. To date, clinical outcome studies have not been reported for any tumor site but are required to show that target tracking during radiotherapy leads to a clinically meaningful change in outcomes. Most work in this evolving area is in prostate cancer, although there also are studies in other organs such as lung, breast, and bladder.

Studies have focused on movement of the target during radiotherapy sessions. This is considered an initial step in evaluating this technology but not sufficient to determine if patient outcomes are improved. As observed by Dawson and Jaffray in 2007, clinically meaningful thresholds for target tracking and replanning of treatment during a course of radiotherapy are as yet unknown. Even less is known about impacts on outcomes of target tracking within a single treatment session.

These new devices appear to provide accurate localization. In 2008, Santanam et al reported on the localization accuracy of electromagnetic tracking systems and on-board imaging systems. In this study, both the imaging system and the electromagnetic system showed submillimeter accuracy during a study of both a phantom and a canine model. Kindblom et al (2009) similarly showed electromagnetic tracking was feasible with the Micropos transponder system (Micropos Medical; Göteborg, Sweden) and that the accuracy of transponder localization was comparable to radiograph localization of radiopaque markers. Smith et al (2009) successfully coupled an

electromagnetic tracking system with linear accelerator gating for lung cancer. A currently registered trial that was determining movement of the cervix during radiotherapy has been withdrawn (NCT00907634).

Movement

Prostate Cancer

In a 2007 clinical study, Kupelian et al described differences found in radiotherapy sessions performed on 35 patients with prostate cancer. In this article, 6 of the initial 41 patients could not be studied because body habitus (AP dimension) was too large to allow imaging. The results showed good agreement with radiograph localization. Displacements of 3 mm or more and 5 mm or more for cumulative duration of at least 30 seconds were observed during 41% and 15% of radiation sessions, respectively. The clinical sites for the study developed individualized protocols for responding to observed intra-fraction motion. This publication did not report on clinical implications or clinical outcomes, either for control of disease or treatment complications, (eg, proctitis). The clinical impact of these displacements and resultant adjustments in treatments need to be explored in much greater detail.

In a 2008 retrospective analysis of data collected from the treatment of 21 patients with prostate cancer treated with Cyberknife, Xie et al reported on intra-fractional movement of the prostate during hypofractionated radiotherapy. The analysis included 427 datasets comprising movement deviations within an acceptable level (approximately 5 mm). The mean duration of intervals during which the prostate remained within 5 mm of its planned position was approximately 697 seconds. At 30 seconds, motion of more than 2 mm was present in approximately 5% of datasets. The percentage increased to 8%, 11%, and 14% at 60, 90, and 120 seconds, respectively. The authors concluded that these movements could be easily managed with a combination of manual couch movements and adjustment by the robotic arm. As noted earlier, the clinical impact of these displacements and resultant adjustments in treatments needs to be explored in much greater detail.

Langen et al (2008) reported on 17 patients treated at one of the centers in the study noted in the preceding paragraph. In this study, overall, the prostate was displaced by more than 3 mm in 13.6% of treatment time and by more than 5 mm in 3.3% of treatment time. Results for median (instead of mean) treatment time were 10.5% and 2.0%, respectively. Again, the clinical impact of this movement was not determined. The authors commented that potential clinical impact would depend on a number of factors including the clinical target volume. In this small series, intra-fraction movement did not change to a large degree during treatment. However, the likelihood of displacement increased as time elapsed after positioning.

In 2009, Noel et al published data showing that intermittent target tracking is more sensitive than pre- and post-treatment target tracking to assess intra-fraction prostate motion, but to reach sufficient sensitivity, intermittent imaging must be performed at a high sampling rate. They concluded that this supports the value of continuous real-time tracking. While this may be true, there is a major gap in the literature addressing the actual consequences of organ motion during radiotherapy. Li et al (2008) analyzed data from 1267 tracking sessions from 35 patients to look at the dosimetric consequences on intra-fraction organ motion during radiotherapy. Results showed that even for the patients showing the largest overall movement, the prostate uniform equivalent

dose was reduced by only 0.23%, and the minimum prostate dose remained over 95% of the nominal dose. When margins of 2 mm were used, the equivalent uniform dose was reduced by 0.51%, but sparing of the rectum and bladder was significantly reduced using the smaller margins. This study did not report on clinical outcomes, and data from a larger randomized cohort will be needed to verify these results.

Three prospective cohort studies assessed the impact of real-time intra-fraction target tracking on planning target volume (PTV) margins. Tanyi et al (2010) and Curtis et al (2012) both used the Calypso system in men with prostate cancer undergoing IMRT (total N=45). Each patient had 3 transponders implanted in the prostate gland. To deliver 95% of the prescribed dose to 95% of the clinical target volume in 90% of patients, margin requirements with intra-fraction target tracking ranged from 1.4 mm in the lateral direction to 2.3 mm in the vertical direction. Without intra-fraction target tracking, required margins were 2.1 mm and 10.5 mm, respectively, using bony alignment, and 2.8 mm and 3.2 mm, respectively, using image-guided marker alignment. Curtis et al (2013) found that without intra-fraction adjustments, PTV margins of 5 mm were needed to ensure complete geometric coverage. With image-guided adjustments every 4 minutes, margins could be reduced to 3 mm. In the third study, Langsenlehner et al (2013) enrolled 44 men with prostate cancer undergoing 3D conformal radiotherapy (3D-CRT). PTV margins could be reduced from 2.6 mm in the lateral direction and 9.6 mm in the vertical direction using bony alignment, to 2.5 mm and 4.6 mm, respectively, using alignment to 4 implanted gold fiducial markers. None of these studies reported survival or morbidity outcomes associated with margin reductions.

In the 2013 Langsenlehner et al study just described, the authors noted that PTV margins could be reduced even further (to 2.4 mm laterally and 3.9 mm vertically) if treatment time was reduced to 4 minutes or less. This finding was confirmed by Cramer et al in their 2013 study of 143 men with localized prostate cancer who were undergoing conventional IMRT (47%) or faster intensity-modulated arc therapy (IMAT) (53%). Continuous (10 Hz) intra-fraction motion tracking was used in all patients. Positions of implanted electromagnetic transponders were validated at least weekly by volumetric cone-beam computed tomography (CBCT). For each treatment technique evaluated (ie, IMRT vs IMAT and setups based on electromagnetic transponders only vs electromagnetic transponders plus CBCT verification), prostate motion increased progressively as a function of elapsed treatment session duration (IMRT with CBCT verification longest).

Lung Cancer

In 2013, Shah et al reported an observational study of the Calypso system in 7 patients with non-small-cell lung cancer (NSCLC). The purpose of the study was to assess the feasibility of transponder implantation and data acquisition; motion-tracking data were not used to alter radiation treatment. Beacon transponders and fiducial markers (used to fix transponders in place) were placed bronchoscopically in all patients. However, implantation was "difficult and unreliable for routine clinical use," eg, due to pneumothorax in 1 patient and transponder migration during implantation. Similarly, motion tracking was possible but "required additional techniques not practical in a clinical setting," eg, use of surface transponders to bypass limitations of the Calypso system, such as a requirement for at least 2 transponders to initiate tracking.

Breast Cancer

A 2012 systematic review reported on inter- and intra-fraction motion during whole-breast irradiation in the supine position. Literature search was conducted in November 2011, and 18 articles met inclusion criteria. Seven studies (total N=73 patients, >10,000 images) reported on intra-fraction motion. Pooled motion variation was approximately 2 mm in several dimensions (left-right [lateral], anterior-posterior [vertical], cranio-caudal [longitudinal]), indicating that inter-fraction motion may have larger effects on radiation dosing. However, because inter-fraction motion also was small (<5 mm), the authors suggested that PTV margins of 5 mm may be acceptable. A 2012 study of whole-breast irradiation in the supine position (N=23) aligned with this result. Li et al outlined the breast using radio-opaque wires on the skin (optical surface-guided whole-breast irradiation). Mean (SD) intra-fraction motion was 0.1 mm (2.8) in the horizontal and 0.0 mm (2.2) in the longitudinal domain. Given the small amount of intra-fraction motion detected in these studies, real-time intra-fraction tracking may be unnecessary in unselected patients with breast cancer.

Morbidity

Sandler and colleagues reported on 64 patients treated with IMRT for prostate cancer in the Assessing the Impact of Margin Reduction (AIM) study. Patients were implanted with Beacon transponders (Calypso Medical Technologies, Inc., Seattle, WA) and were treated with IMRT to a nominal dose of 81 Gy in 1.8 Gy fractions. Patients in this study were treated with reduced tumor margins, as well as real-time tumor tracking. Patient-reported morbidity associated with radiotherapy was the primary outcome. Study participants were compared to historic controls. Study participants reported fewer treatment-related symptoms and/or worsening of symptoms after treatment than the comparison group. For example, the percentage of patients in the historic comparison group reporting rectal urgency increased from 3% pre-treatment to 22% post-treatment, no increase was observed in the current experimental group.

Disease Control/Patient Survival

Prostate Cancer

A 2013 review of image-guided radiation therapy (IGRT) technologies for prostate cancer acknowledged the lack of clinical trials demonstrating improved clinical outcomes with Calypso 4D.

Bladder Cancer

Nishioka et al (2014) developed a prototype real-time target tracking system in Japan. Using the system, this group conducted a prospective study of 20 patients with clinically inoperable (or surgery refused), stage II/III (node-negative) urothelial bladder carcinoma. All patients had undergone transurethral tumor resection followed by 40 Gy whole-bladder irradiation and implantation of fiducial markers. This was followed by a 25 Gy boost using the prototype target tracking system. Fourteen patients (70%) with adequate renal function (creatinine clearance ≥45 mL/min) received concurrent chemoradiotherapy with nedaplatin, a second-generation platinum complex with reduced gastrointestinal and renal toxicity. Patients were followed every 3 months with cystoscopy and urine cytology; median follow-up was 56 months (range, 9-126). Acute grade 3 toxicities were urinary tract infections in 2 patients and thrombocytopenia in 1 patient; none were attributed to implantation of fiducial markers. Late treatment-related, grade 3 toxicities were hemorrhagic cystitis and intestinal obstruction due to adhesions in 1 patient each. Estimated 5-year

local control rate (defined as absence of pathologically-proven recurrence in the bladder) and overall survival were 64% and 61%, respectively. These results support further investigation in larger controlled studies.

Other Cancers

There are few registered clinical trials of these techniques, and none of a randomized design focused on showing how these additional procedures may improve clinical outcomes, including a decrease in toxicity to surrounding tissue.

<div align="center">

Respiratory Gating

</div>

Because current nongated radiotherapy techniques achieve adequate tumor coverage, the goal of adding respiratory gating is to reduce irradiation of normal tissue to reduce toxicity and facilitate dose escalation.

Lung Cancer

Two small studies compared respiratory-gated and nongated treatment plans in patients with thoracic tumors. Vlachaki et al (2009) evaluated 10 patients (8 with NSCLC, 1 with small cell lung cancer [SCLC], and 1 undetermined due to risk of pneumothorax associated with biopsy) who were treated at several U.S. centers. All patients underwent gated and nongated radiotherapy treatment planning using 4D-conformal treatment (4D-CT). PTV was determined by adding a 1.5 cm or 0.5 cm margin to the clinical target volume in nongated and gated plans, respectively. In each patient, PTVs were smaller in gated compared with nongated plans (mean PTV, 293 mL vs 575 mL, p<0.001), which was attributed to the smaller (0.5 cm) margin used in gated plans. Mean and maximum PTV doses were similar in both plans, but minimum dose was higher in gated plans (53 Gy vs 48 Gy). Mean percentage of total lung volume (outside the PTV) exposed to 20 Gy or more of radiation (lung V20) was 26% in gated and 35% in nongated plans (p<0.001). Mean doses to the heart and esophagus also were lower with gated versus nongated plans (11 Gy and 17 Gy vs 16 Gy and 22 Gy, respectively; p≤0.003).

In 2013, Hau et al evaluated 34 consecutive patients who were treated for thoracic malignancy (23 [68%] NSCLC, 10 [29%] SCLC, and 1 [3%] atypical carcinoid) at a single center in Australia. All patients underwent radiotherapy treatment planning using both a respiratory-gated approach and a free-breathing (nongated) approach. In both plans, a 5.5 mm margin was added to the clinical target volume to derive PTV margins. For respiratory-gated radiotherapy, PTV was selected to cover any tumor motion within the gating window. For the free-breathing approach, PTV was determined to encompass tumor throughout the respiratory cycle. PTV was smaller in respiratory-gated compared with nongated plans (388 cm3 vs 421 cm3, p<0.001), but 95% uniform dose coverage was similar between the 2 plans (94% vs 96%, p=0.028). Bonferroni correction for multiple comparisons yielded a p value less than 0.003 for statistical significance. A priori, a minimum 5% reduction in lung V20 was considered clinically significant. Mean (SD) lung V20 was 23% in gated plans and 25% in nongated plans, for a difference of 2 percentage points (95% confidence interval, 1 to 3; p<0.001). Dosimetric data indicated no statistical difference in radiation doses to the spinal cord, heart, or esophagus. Four patients (12%) had lung V20 reductions of 5% or greater; 75% of these patients had superior-inferior tumor displacement of more than 1 cm compared with 2 (7%) of 30 patients whose lung V20 reduction did not exceed 5% (Fisher exact test, p<0.006). The 4 patients also tended to have gross tumor volumes less than 100 cm3. Based

on these observations, the authors suggested that respiratory gating be applied selectively to patients with gross tumor volumes less than 100 cm3 and superior-inferior tumor displacement of more than 1 cm.

Breast Cancer

A 2011 prospective, nonrandomized study by the French Ministry of Health compared respiratory-gated radiotherapy with standard conformal radiotherapy. Women (N=401) from 20 centers in France who had early stage breast cancer requiring radiotherapy only were enrolled. In the respiratory-gated group (n=218 [54%]), PTV margins were determined by computed tomography (CT) images of radio-opaque surface markers encircling the breast. For most patients in this group (93%), a spirometric breath-holding system was used for gating; 15 patients were gated by a real-time respiratory tracking system that used surface markers. In the standard conformal group (n=183 [46%]), PTV margins were determined by adding 10 mm to the clinical target volume. PTVs were statistically smaller in the respiratory-gated group compared with the standard conformal group (p<0.001). Total radiation dose did not differ statistically between groups. Dosimetric data indicated statistically greater radiation doses to the lungs, heart, and esophagus (organs at risk) in the standard conformal group. This benefit was attributed to the deep inspiration breath-hold respiratory gating technique because these patients had markedly increased total lung volumes, and therefore reduced normal lung tissue irradiated compared with patients treated with real-time tracking. Acute pulmonary toxicity (all grades) occurred in 48% of the standard conformal group and 36% of the respiratory-gated group (p=0.02). This difference persisted until the 12-month assessment. Other acute toxicities did not differ between groups in severity or type (eg, cutaneous, esophageal, cardiac). Late esophageal toxicity (all grades) occurred at 6 months in 6% of the standard conformal group and 3% of the respiratory-gated group, but no longer differed between groups at 12 or 24 months. Other late toxicities did not differ between groups. After a median follow-up of 26 months (range, 1-47), there was no difference between groups in overall survival or disease-free survival.

Ongoing and Unpublished Clinical Trials

A search of the online database, ClinicalTrials.gov, using the search term "calypso" identified 7 active studies of the Calypso 4D Localization System. All were single-arm or observational studies. Two studies involved stereotactic body radiation therapy for prostate cancer and are not listed here.

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Prostate cancer			
NCT00980993	Pilot Study on the Quantification of Respiratory-induced Prostate Motion During Radiation Therapy Using Continuous Real-time Tracking	5	Sep 2010
NCT01588938	External Immobilization Compared to Limited Immobilization Using a Novel Real-time Localization System of the Prostate	20	Sep 2016
NCT01624623	Daily Target Guided Radiation Therapy Using	20	Aug 2016

	the Calypso 4D Localization System in Patients Who Have Had a Prostatectomy for Prostate Cancer		
NCT02033343	Phase I Feasibility Study of Prostate Cancer Radiotherapy Using Realtime Dynamic Multileaf Collimator Adaptation and Radiofrequency Tracking (Calypso)	30	Dec 2018
NCT01589939	Reduced Planning Target Volume (PTV) Margins for the Treatment of Prostate Cancer Using the Calypso 4D Localization System	40	Sep 2016
Lung cancer			
NCT02111681	Calypso-based Deep Inspiration Breath Hold (DIBH) Radiation Treatments of Lung Cancer	30	Apr 2016
NCT01396551	Evaluating an Anchored Transponder in Lung Cancer Patients Receiving Radiation Therapy	70	Dec 2016

Clinical Input Received Through Physician Specialty Society and Academic Medical Centers

In response to requests, input was received through 3 academic medical centers and 1 physician specialty society (3 reviewers) when this policy was under review in 2014. While the various academic medical centers and specialty medical societies may collaborate and make recommendations in this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the academic medical centers or specialty medical societies, unless otherwise noted. Clinical input on the use of real-time intra-fraction target tracking was mixed. Some respondents supported medical necessity for tumors subject to intra-fraction motion, eg, lung and breast; others did not. Three of 5 respondents agreed that head to head trials with and without the use of real-time target tracking are necessary to determine whether the use of real-time tracking leads to improved outcomes.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Prostate Cancer

Current NCCN clinical practice guidelines for prostate Cancer (v.3.2016) state, "The accuracy of treatment should be improved by attention to daily prostate localization with techniques, such as image guided radiation therapy (IGRT) using computed tomography (CT), ultrasound, implanted fiducials, electromagnetic targeting/tracking, or an endorectal balloon to improve oncologic cure rates and reduce side effects." NCCN has replaced **"**daily IGRT with 3D-CRT (conformal radiotherapy)/IMRT" with "highly conformal" or 3D-CRT /IMRT throughout the guidelines. For primary EBRT; IGRT is required if the dose is 78 Gy or more. NCCN is applying a broader definition of IGRT and is addressing interfraction (daily) adjustment rather than intra-fraction adjustments, which are the focus of this policy. Although NCCN states that unless otherwise noted, all recommendations are based on level 2A evidence, no specific citations are provided for basis of their conclusions.

Lung Cancer

Current NCCN guidelines for NSCLC (v.5.2015) and for SCLC (v.1.2015**)** state, "Respiratory motion should be managed when motion is excessive." Recommended approaches include beam- gating with the respiratory cycle and dynamic tumor tracking. When motion is minimal or the internal target volume is small, "motion-encompassing targeting" is appropriate.

Breast Cancer

Current NCCN guidelines for breast cancer (v.2.2015)) state that the goals of radiotherapy are "uniform dose distribution and minimal normal tissue toxicity." Respiratory gating is one of several strategies recommended to accomplish these goals (along with prone positioning and use of wedges, IMRT, and/or forward planning using segments). A recommendation for real-time target tracking is not included.

Bladder Cancer

Current NCCN guidelines for bladder cancer (v.1.2015) do not include a recommendation for real-time intra-fraction target tracking in patients receiving radiotherapy.

American College of Radiology

ACR appropriateness criteria for radiotherapy in prostate cancer, cervical cancer, and non-small-cell lung cancer do not include ratings for real-time intrafraction target tracking.

American Urological Association

A 2013 guideline issued jointly by AUA and the American Society for Radiation Oncology addressed adjuvant and salvage radiotherapy after prostatectomy. This guideline did not include real-time intra-fraction target tracking.

U.K. National Institute for Health and Care Excellence

A 2014 NICE guideline on the diagnosis and treatment of prostate cancer did not include a recommendation for real-time intrafraction target tracking during radiotherapy.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. References

1. Hau E, Rains M, Browne L et al. Minimal benefit of respiratory-gated radiation therapy in the management of thoracic malignancy. J Med Imaging Radiat Oncol 2013; 57(6):704-12
2. Wong JR, Gao Z, Merrick S et al. Potential for higher treatment failure in obese patients: correlation of elevated body mass index and increased daily prostate deviations from the radiation beam isocenters in an analysis of 1,465 computed tomographic images. Int J Radiat Oncol Biol Phys 2009; 75(1):49-55.
3. Cole AJ, Hanna GG, Jain S et al. Motion management for radical radiotherapy in non-small cell lung cancer. Clin Oncol (R Coll Radiol) 2014; 26(2):67-80.
4. Keall PJ, Mageras GS, Balter JM et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76. Med Phys 2006; 33(10):3874-900.
5. Giraud P, Houle A. Respiratory Gating for Radiotherapy: Main Technical Aspects and Clinical Benefits. ISRN Pulmonology 2013; 2013:13.
6. Glide-Hurst CK, Chetty IJ. Improving radiotherapy planning, delivery accuracy, and normal tissue sparing using cutting edge technologies. J Thorac Dis 2014; 6(4):303-18.
7. Dawson LA, Jaffray DA. Advances in image-guided radiation therapy. J Clin Oncol 2007; 25(8):938-46.
8. 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):892-9
9. 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):307-11
10. Smith RL, Lechleiter K, Malinowski K et al. Evaluation of linear accelerator gating with real-time electromagnetic tracking. Int J Radiat Oncol Biol Phys 2009; 74(3):920-7
11. 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):1088-98
12. Xie Y, Djajaputra D, King CR et al. Intrafractional motion of the prostate during hypofractionated radiotherapy. Int J Radiat Oncol Biol Phys 2008; 72(1):236-46.
13. Langen KM, Willoughby TR, Meeks SL et al. Observations on real-time prostate gland motion using electromagnetic tracking. Int J Radiat Oncol Biol Phys 2008; 71(4):1084-90.
14. 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):692-8

15. Li HS, Chetty IJ, Enke CA et al. Dosimetric consequences of intrafraction prostate motion. Int J Radiat Oncol Biol Phys 2008; 71(3):801-12

16. Tanyi JA, He T, Summers PA, et al. Assessment of planning target margins for intensity-modulated radiation therapy of the prostate gland: role of daily inter- and intra-fraction motion. Int J Radiat Oncol Biol Phys. 2010; 1579-1585

17. Curtis W, Khan M, Magnelli A et al. Relationship of imaging frequency and planning margin to account for intrafraction prostate motion: analysis based on real-time monitoring data. Int J Radiat Oncol Biol Phys 2013; 85(3):700-6.

18. Langsenlehner T, Doller C, Winkler P et al. Impact of inter- and intrafraction deviations and residual set-up errors on PTV margins. Different alignment techniques in 3D conformal prostate cancer radiotherapy. Strahlenther Onkol 2013; 189(4):321-8.

19. Cramer AK, Haile AG, Ognjenovic S et al. Real-time prostate motion assessment: image-guidance and the temporal dependence of intra-fraction motion. BMC Med Phys 2013; 13(1):4.

20. Shah AP, Kupelian PA, Waghorn BJ et al. Real-time tumor tracking in the lung using an electromagnetic tracking system. Int J Radiat Oncol Biol Phys 2013; 86(3):477-83.

21. Michalski A, Atyeo J, Cox J et al. Inter- and intra-fraction motion during radiation therapy to the whole breast in the supine position: a systematic review. J Med Imaging Radiat Oncol 2012; 56(5):499-509.

22. Li S, DeWeese T, Movsas B et al. Initial validation and clinical experience with 3D optical-surface-guided whole breast irradiation of breast cancer. Technol Cancer Res Treat 2012; 11(1):57-68.

23. 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):1004-08

24. Das S, Liu T, Jani AB et al. Comparison of Image-guided Radiotherapy Technologies for Prostate Cancer. Am J Clin Oncol 2013.

25. Nishioka K, Shimizu S, Shinohara N et al. Prospective phase II study of image-guided local boost using a real-time tumor-tracking radiotherapy (RTRT) system for locally advanced bladder cancer. Jpn J Clin Oncol 2014; 44(1):28-35.

26. .Vlachaki M, Castellon I, Leite C et al. Impact of respiratory gating using 4-dimensional computed tomography on the dosimetry of tumor and normal tissues in patients with thoracic malignancies. Am J Clin Oncol 2009; 32(3):262-8.

27. Giraud P, Morvan E, Claude L et al. Respiratory gating techniques for optimization of lung cancer radiotherapy. J Thorac Oncol 2011; 6(12):2058-68.

28. Giraud P, Djadi-Prat J, Morelle M et al. Contribution of respiratory gating techniques for optimization of breast cancer radiotherapy. Cancer Invest 2012; 30(4):323-30.

29. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: prostate cancer, version 3.2016.

30. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: non-small cell lung cancer, version. 5.2016

31. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: small cell lung cancer, version 5.2016

32. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: breast cancer, version 2.2016
33. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: bladder cancer, version 1.2016
34. American College of Radiology. Appropriateness criteria - radiation oncology topics: definitive external beam irradiation in stage T1 and T2 prostate cancer, updated November 2013.
35. American College of Radiology. Appropriateness criteria - radiation oncology topics: definitive therapy for early stage cervical cancer, updated November 2013.
36. American College of Radiology. Appropriateness criteria - radiation oncology topics: advanced cervical cancer, updated November 2013.
37. American College of Radiology. Appropriateness criteria - radiation oncology topics: early stage non-small-cell lung cancer, updated November 2013.
38. American College of Radiology. Appropriateness criteria - radiation oncology topics: induction and adjuvant therapy for N2 non-small-cell lung cancer, updated November 2013.
39. American Urological Association. Adjuvant and salvage radiotherapy after prostatectomy: ASTRO/AUA guideline, approved by the AUA Board of Directors April 2013.
40. National Institute for Health and Care Excellence. NICE clinical guidelines (CG175) prostate cancer: diagnosis and treatment, issued January 2014.
41. BCBSA Medical Policy Manual. Real-Time Intrafraction Motion Management During Radiotherapy. Policy # 2.03.10. Archived 05/2015.
42. BCBSA Medical Policy Reference Manual. Intensity Modulated Radiation Therapy (IMRT) of the Breast and Lung. #8.01.46. Reviewed April 2017.