IGRT and Hypofractionation for Primary Tumors

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Abstract

Advancements in radiation planning and delivery have resulted in the ability to safely deliver higher doses per fraction to the tumor while also sparing normal tissue. Known as hypofractionated radiation therapy (HRT), or stereotactic ablative radiation therapy (SABR), this technique has been developed in multiple sites outside the brain, including lung, prostate, and pancreas. Accompanying such treatment is some form of image guided radiation therapy (IGRT). Localization of these tumors requires high quality soft tissue imaging, in addition to the ability to ascertain tumor location *during* radiation delivery. This chapter will outline the role of IGRT as it pertains to HRT treatment schemes for various malignancies.

Keywords

Hypofractionation · Image guided · Radiotherapy · Stereotactic

List of Abbreviations

HRT	Hypofractionated radiation therapy
SABR	Stereotactic ablative radiation therapy
IGRT	Image guided radiation therapy
NSCLC	Non-small cell lung cancer
CT	Computed tomography
PTV	Planning target volume
CBCT	Cone beam computed tomography
4DCT	Four-dimensional computed tomography

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AVB	Audio-visual feedback
kV	Kilovoltage
IMRT	Intensity modulated radiation therapy
RTOG	Radiation therapy oncology group
KIM	Kilovoltage intrafraction monitoring
MV	Megavoltage
ERB	Endo-rectal balloon
Gy	Gray
XRT	External beam radiotherapy
SBRT	Stereotactic body radiation therapy
LED	Light emitting diode
ITV	Internal target volume

1 Introduction

Hypofractionated radiation therapy (HRT) when given with definitive intent is defined as delivering doses per fraction that are higher than conventional radiation, typically greater than 4 Gy. These higher doses have clinically demonstrated superior benefit to conventional 2 Gy/day treatment in specific disease sites, such as stage I NSCLC. In order to safely administer such higher doses, understanding the position of the tumor during simulation and treatment is essential. Advances in linear-accelerator-based imaging, placement of fiducial markers, and patient-assisted devices, have enabled the clinician to deliver HRT with higher levels of certainty, facilitating narrower treatment margins around the tumor. This chapter will describe examples of these advances, as it pertains to specific solid tumor types, including lung, prostate, and pancreatic cancers.

2 Non-small Cell Lung Cancer (NSCLC)

Treatment planning. Stereotactic ablative radiation therapy (SABR) is considered a standard-of-care treatment option for patients with medically inoperable stage 1 NSCLC. One major challenge with treatment delivery is the ability to account and manage motion of the lung tumor. During the treatment planning, one option is to obtain a computed tomography (CT) scan at 3 timepoints: end-expiration, end-inspiration, and free breathing. A more sophisticated approach is to use a four-dimensional CT scan, which provides additional detail regarding the tumor trajectory between the peak and nadir. This approach can facilitate the use of

narrow planning target volume (PTV) margins, thereby reducing normal tissue dose (Wang et al. 2009).

Image guidance. Cone-beam CT (CBCT) is now a standard imaging modality available on most linear accelerators, and is critical for verification of tumor position prior to treatment. Studies have shown that aligning to bony anatomy is not a substitute for aligning to the tumor soft tissue, as the first method can still result in significant shifts to match the tumor position (Corradetti et al. 2013). However, intra-fraction motion, or tumor motion that occurs during radiation delivery, is another important issue that can impact the accuracy of treatment. With 4D CT planning, recommended PTV margins around the gross tumor and motion are 5 mm (Corradetti et al. 2013). The purpose of this margin is to encompass tumor motion or migration during each treatment, in addition to daily setup differences between each treatment fraction. Corradetti et al. examined CBCT scans in 87 patients that were taken before and after each fraction (Corradetti et al. 2013). The mean shifts ranged from 1.1 to 1.6 mm, with 27 and 10% of shifts exceeding 3 and 5 mm, respectively.

Intra-fraction motion. Multiple strategies have been used to address the quandary of lung tumor motion during the time of the radiation delivery. These approaches include limiting the tumor motion itself, with external compression devices, or employing bio-feedback so that patient restricts their breathing on their own within a pre-specified window. Tumors are generally treated throughout the entire trajectory, under the presumption that the trajectory itself is being restricted. An alternative approach, known as *gating*, is to turn on the beam only during a specific range of the tumor's trajectory. More complex are tumor-tracking techniques. These various options are outlined below.

External compression was one of the first techniques used to address tumor motion in lung SBRT. The compression paddle is applied below the xiphoid in order to restrict tumor motion (Fig. 1: http://qfix.com/qfix-products/sbrt.asp). The goal was to limit the motion to less than 1 cm, using fluoroscopic guidance. Another option is to use a vacuum chamber around the patient, which restricts the amplitude of respiratory excursion (Fig. 2: http://ecatalog.elekta.com/oncology/oncology/breast-_-thorax-positioning-and-immobilization/products/0/22325/22341/20231/breast-_-thorax-positioning-and-immobilization.aspx). Li et al. examined positioning data from over 2000 CBCT scans from patients receiving lung SBRT (Li et al. 2011). There were no significant differences in the intra-fraction motion between an evacuated cushion with, or without abdominal compression. Image guidance with CBCT prior to delivery was sufficient to provide treatment that allowed for a 5 mm PTV margin. They concluded that performance status (ECOG 2 vs. 0-1) was a significant factor for cranial-caudal drift.

Audiovisual biofeedback (AVB) allows for patients to be an active participant in managing their tumor motion. Specialized eyewear can display a particular breathing pattern that is customized to the patient, which the patient can then follow during simulation, pre-treatment image guidance, and therapy. Lee et al. compared the consistency of displacement (or amplitude), and periodicity of breathing patterns as seen on MRI, in patients receiving AVB versus free breathing (Lee et al. 2016). They showed a significantly higher level of consistency in the AVB cohort,

Fig. 1 External compression was one of the first techniques used to address tumor motion in lung SBRT

Fig. 2 Image guidance with CBCT prior to delivery was sufficient to provide treatment that allowed for a 5 mm PTV margin

for both inter-fraction and intra-fraction breathing. AVB had the strongest benefit with periodicity (70% improvement compared to free-breathing) compared to displacement. These results have spawned the development of a phase II multi-institutional randomized trial in Australia comparing AVB versus the free-breathing approach (Pollock et al. 2015).

Even when controlling or restricting the motion trajectory, it is still quite common for tumors to have displacements of more than 1 cm, especially those located in the lower lobes. In these cases, delivering dose during a limited range in the trajectory, or *gating*, can facilitate using narrower PTV margins and also expose less normal lung tissue (Jang et al. 2014). In addition, the process of gating itself has not been shown to impact tumor motion variability, highlighting the reproducibility of this approach (Saito et al. 2014). Advances have been made to use fiducial marker motion data generated from on-board kilo-voltage (kV) imaging (Ali et al. 2011; Wan et al. 2016). This has led to development of emerging technologies such as gated-CBCT and tumor-tracking treatment delivery.

The implantation of small inert metal markers near or within a tumor target to guide setup accuracy is not a novel concept. Before the advent of CBCT, this was the main approach for localizing the prostate gland and helped foster the coupling of dose-escalation with narrower PTV margins. Techniques of Implanting such markers in the lung have dramatically improved over the past 10 years, with advances in electromagnetic navigational bronchoscopy. A recent report by Minnich et al. indicated marker retention rates exceeding 90% (Minnich et al. 2015). Others have shown similar outcomes, with very low rates of complications and minimal intra-fraction migration (Nabavizadeh et al. 2014; Rong et al. 2015). These markers can be used for localization on the CBCT, and are also seen on intra-fraction kV images during arc-IMRT delivery. This allows for opportunity to correct for shifts that can occur during longer treatment delivery sessions.

One limitation of inert markers is the reliance of obtaining serial imaging repeatedly during the delivery fraction, and the inevitable inherent time lag in receiving the marker positional data and the ability for the therapist to intervene if necessary. With this mind, the feasibility of placing electro-magnetic transponder fiducials (Calypso Inc, Seattle, WA) in the lung were first reported in a pilot study of 7 patients (Shah et al. 2013). Two markers were placed per patient using bronchoscopic guidance. Placement into the lung itself was difficult, and therefore markers were placed into the most distal bronchus that was closest to the tumor. Thirteen of the 14 markers remained stable and were able to be tracked by the system. Based on this data, the Calypso system is now approved for intra-fraction motion monitoring and gating in lung cancer patients.

Active tumor tracking is the ability of the linear accelerator to shape the radiation beam to match the contour of the lung tumor, but treating it during the entire trajectory. The benefit to this approach is a shorter treatment time compared to gating, which can minimize risk for intra-fraction positional changes in the tumor and/or patient. One phantom study has demonstrated feasibility to reconstruct motion of the fiducial marker data to improve imaging artifact of CBCT due to patient breathing (Ali et al. 2011). This is an important development that can provide real-time motion data to the linear accelerator to assist with tracking. A new linear accelerator platform has been developed with a gimble-pivoting mechanism to permit simultaneous tracking and treatment of the lung tumor throughout the respiratory cycle (Vero Inc) The commissioning and quality assurance report is presented by Solberg et al. (2014). Clinical outcome data in the United States are still pending.

3 Prostate Cancer—Intact Gland

There have been remarkable advances in the technology of radiation treatment delivery for prostate cancer over the past 20 years. The advent of intensity modulated radiation therapy (IMRT), with more conformal dose distributions and steeper dose gradients next to normal tissue, enabled clinicians to employ narrower

PTV margins. This also enabled the ability to increase the potency of treatment by increasing the prescription dose. Doses as high as 86 Gy are now used in the definitive setting with conventional fractionation, with excellent outcomes and acceptable toxicity (Spratt et al. 2013). Hypofractionated dosing schedules have also been studied to increase patient convenience. The Radiation Therapy Oncology Group (RTOG) protocol 0415 was recently published by Lee et al., indicating that 70 Gy in 28 fractions is not inferior to conventionally fractionated treatment (73.8 Gy in 41 fractions) (Lee et al. 2016). SBRT has also been studied for low-risk and intermediate-risk prostate cancer, with greater than five year follow-up (Hannan et al. 2016; Katz et al. 2013). With dose escalation to 50 Gy in 5 fractions, Hannan et al. report biochemical control rates of 100% at five years (Hannan et al. 2016). As clinical outcomes from more potent dose schedules continue to emerge, there have also been a parallel of advancements in image-guidance to monitor and limit intra-fraction motion.

The only commercially available wireless radiotransponder fiducial system (Calypso Inc, Seattle, WA) was originally pioneered in patients with prostate cancer (Willoughby et al. 2006). Kupelian et al. reported multi-insitutional intra-fraction motion data on 35 patients (Kupelian et al. 2007). They found that displacement of the beacons exceeded 3 mm in more than 40% of treatment sessions. Motion trajectory was unpredictable in majority of cases. Radiotransponder beacons were used in the SBRT trial by Hannan et al., although intra-fraction motion data have not been reported. The majority of the clinical experience comes from patients treated using the Cyberknife platform, which uses orthogonal kV images to assess implanted marker motion at multiple time-points during delivery. A report of pooled outcomes using the Cyberknife system has been recently published by King et al. (2013).

Alternatives to wireless transponders are also being explored, given several limitations with this system, most notably imaging artifact on MRI. Keal et al. report on a novel approach known as kilovoltage intrafraction monitoring (KIM), using inert metal fiducial markers (Keall et al. 2016). A major advantage with KIM is it uses the standard kV-imager already built into the standard modern linear accelerator without necessity to purchase any additional hardware. In a preliminary study of 6 patients, they assessed the impact of KIM as a method for reducing gating events using a 3 mm/5 s action threshold, compared to patients without KIM. Out of 200 delivered fractions, 15% had a gating event. Percentage of beam-on time with the prostate being >3 mm away from isocenter was reduced in patients who had KIM (24% vs. 73%). The accuracy of KIM was also measured as <0.3 mm in all 3 dimensions by comparing it to simultaneously acquired kv/MV triangulation data. Given that the majority of published prostate SBRT studies did not use Calypso, this approach to intra-fraction motion management may have far-reaching clinical impact.

The use of an endo-rectal balloon (ERB) may overcome daily variation in rectal distention and peristalsis. This physiologic motion is the dominating contributor to intra-fraction motion of the prostate gland. Langen et al. demonstrated that the magnitude of intra-fraction motion using Calypso was largest in the

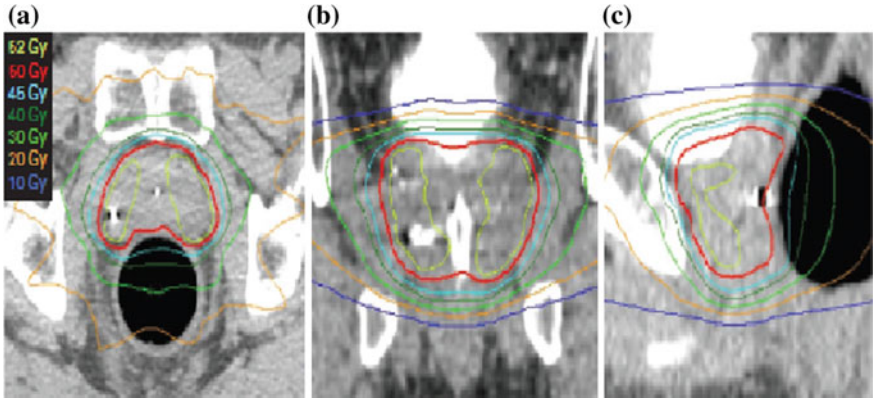

Fig. 3 Rectal balloon placement for prostate SBRT (Boike et al., Journal of Clinical Oncology © 2011). Reprinted with permission

anterior-posterior direction, with both positional drift and transient pulsatile motion (Langen et al. 2008). The total elapsed treatment time also had a significant impact on the motion, with larger movements seen with longer treatment times. In the setting of SBRT, such displacement of the target organ can result in under-dosing the PTV. To assess the potential benefit of ERB, Wang et al. compared the motion between 30 patients who were treated with and without ERB (Wang et al. 2012). They report that the ERB group had significant decreases in the motion in all dimensions, especially the anterior-posterior direction. In the University of Texas phase I prostate SBRT trial, daily endorectal balloon was used for simulation and treatment (Hannan et al. 2016). The rectal catheter was filled a pre-determined quantity of air, thereby fixing the interface between the anterior rectal wall and the prostate itself (Fig. 3). Another purpose of the ERB is to also *displace* the lateral and posterior rectal wall away from the PTV, facilitating lower doses received to these areas. The lack of any grade 2 or higher late gastro-intestinal toxicities in the 45 Gy arm, with a median follow-up of 74 months, illustrates the benefit with this technique (Hannan et al. 2016). The 45 Gy starting dose was the highest 5-fraction dose reported in the literature to date. Intra-fraction motion data has not been reported for this trial.

4 Prostate Cancer Following Prostatectomy

Salvage XRT is a standard treatment recommendation to treat biochemical recurrence of prostate cancer following radical prostatectomy. IMRT is now considered the preferred technique to optimize sparing of adjacent rectal tissues. Given the lack of a solid tumor target, radiation delivery in this setting presents multiple challenges. As IMRT inherently results in sharper dose gradients away from the target

volume, intra-fraction data on the location of the tumor bed is critical. The definition of the CTV itself is fundamentally based on the relationship between the bladder and rectum. After multiple reports of successful implantation of fiducial markers in the intact-gland, a similar approach was started in the prostate bed.

Inter- and Intra-fraction motion data from 20 patients who received Calypso implantation was presented by Klayton et al. (2012). Prostate bed displacement was measured after aligning to bony landmarks. The shift in the superior-inferior direction exceeded 5 mm in more than 21% of delivered fractions. During delivery, motion was predominant in the posterior direction toward the rectum. Approximately 15% of all treatments were interrupted due to motion threshold being exceeded. It is possible that ERB may be useful to minimize motion of the prostate bed. In the absence of markers, soft tissue imaging with CBCT is essential to visualize the rectal wall. Besides traditional x, y, and z translation movements, yaw, pitch, and roll changes have also been shown to be contributors to intra-fractional target changes using Calypso (Zhu et al. 2013). Real-time adaptive planning strategies may be important in order maximize target coverage. It is proposed by Zhu et al. that intra-fraction data obtained early in the treatment course can be helpful in the decision making process to modify the existing treatment plan (Zhu et al. 2013).

To date, there are no published 5-fraction SBRT studies in the treatment of the prostate bed, analogous to the approach in the intact-gland setting. Hypofractionation schedules over 4-5 weeks have been explored. There is a clinical trial studying a 5-fraction technique which is actively accruing patients (clinicaltrials.gov), employing fiducial marker placement, CBCT, and ERB. Both intra- and inter-fraction motion will need to be considered for the successful implementation of this technique.

5 Pancreatic Cancer

Given that local failure was observed in 30-50% of patients with unresectable pancreatic cancer with conventional fractionation, the intention of SBRT in this setting was to develop a more potent local therapy (Willett et al. 2005). Colleagues from Stanford recently published their long-term experience, including patients receiving single-fraction and multi-fraction SBRT. They reported a 12-month crude local failure rate of approximately 10%, and 12-month survival of 30–35% (Pollom et al. 2014). Herman et al. reported a median survival of 13 months in 49 patients using a 5-fraction scheme (Herman et al. 2015).

In an earlier publication, Chang et al. outlined their treatment planning and simulation techniques (Chang et al. 2009). Patients were treated using a robotic radiosurgery system (Cyberknife, Accuray Inc, Sunnyvale, CA). Placement of fiducial markers into or around the pancreas has been shown to be safe using an endoscopic ultrasound (EUS) technique, although a traditional CT-guided percutaneous approach is the most common (Park et al. 2010). Approximately 1–2 weeks

later, patients received a 4D-CT simulation with contrast (after 2004) and a PET/CT scan. GTV was delineated on the various phases of the 4D-CT and constituted a combined internal target volume. A 2–3 mm margin was then added to create the PTV.

6 Image-Guided Therapy

Chang et al. describe their approach to image guidance and respiratory management using the Cyberknife platform (Chang et al. 2009). The Cyberknife imaging system consists of 2 diagnostic orthogonal X-ray sources in the ceiling paired with detectors on the ground, enabling real-time images to verify bony anatomy and fiducial marker location during treatment. Outlining the fiducial markers on the 4D-CT is thus crucial to creating an internal motion trajectory, which is then paired with external motion trajectory data. The Synchrony respiratory tracking system uses motion data from LEDs placed on the chest wall of the patient. A model is generated from the LED and fiducial marker data to enable the linear accelerator to monitor the tumor motion during beam-on delivery, and make adjustments to the beam based on change changes in motion.

Such real-time tracking of tumor motion is critical, since it has been demonstrated that range of tumor trajectory at the time of 4D-CT simulation may not replicable at time of treatment (Minn et al. 2009). Minn et al. indicate that in the superior-inferior direction, the range of the centroid motion during simulation was 0.9–28.8 mm, compared to 0.5–12.7 mm during treatment. This suggests that the amplitude of the tumor motion can sometimes *decrease* compared to simulation, and therefore careful intra-fraction monitoring of tumor fiducials is essential to avoid missing the target. In patients receiving a 3–5 week fractionation regimen Len et al. describe differences in cranial-caudal motion magnitude between 4DCT and tumor motion seen on CBCT (Lens et al. 2014). Differences exceed 5 mm in 17% of the fractions delivered. The authors suggested employing breath-hold treatment techniques to address this issue.

Relying on external motion data alone during treatment may also be inadequate, as highlighted by Li et al. They performed the first clinical study assessing the geometric accuracy of gated Rapidarc treatment. Patients had fiducial marker placement in or near the tumor, and location of these markers were identified on the kV image portal prior to each beam-on delivery during the gating process. The distance between the ITV and the markers on the kV images were very small. The largest difference was in the cranial caudal direction, where a 1.5 mm margin was calculated. However, there were cases where the difference exceeded 2 mm, which approaches the uncertainty margin used in SBRT planning.

The Calypso marker system has also been used to monitor inter- and intra-fraction motion in pancreatic cancer. In their initial experience, Shinohara et al. demonstrated feasibility of marker implantation (Shinohara et al. 2012). They also report novel intra-fraction motion that was higher than anticipated, with a mean

shift of 7 and 12 mm in the superior and inferior dimensions, respectively. They also suggested that implementing a breath-hold gating technique may be prudent.

7 Conclusions

With the advent of SBRT and shorter radiation treatment schedules, it is now of paramount importance that accurate and reproducible localization of the target be achieved. Both inter- and intra-fraction verification of target localization are necessary in order to ensure optimal outcomes, given the sharper dose gradients seen in SBRT planning. This is accomplished with highly complex imaging technology, that is becoming increasingly integrated with the treatment delivery platform. Each solid tumor type presents a unique set of treatment delivery challenges which require an individualized approach. Several strategies to account for intra-fraction tumor motion and deformation based on tumor type have been presented in this chapter. Future advancements are anticipated in the area of adaptive radiation planning and delivery based on real-time inter- and intra-fraction imaging data.

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