2

STAT RAD: A Potential Real-Time Radiation Therapy Workflow

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1. Introduction

1.1 Epidemiology and cost of metastatic disease

The American Cancer Society estimates that approximately 1.5 million people in the United States will be diagnosed with cancer, and 560,000 will die of cancer in 2010 (Jemal et al., 2010). These numbers are projected to increase rapidly in the near future due to national demographics with a large number of Americans reaching retirement age over the next 15-20 years, resulting in a doubling of projected new cancer diagnoses in 2050 to 3 million (Hayat et al., 2007). Most cancer deaths involve extensive locoregional tumors or metastatic disease to brain, lung, liver, or bone causing pain, disability, and decreased quality of life. As treatments for cancer improve, patients are living longer with advanced cancer than ever before, and the management of metastatic disease is becoming increasingly more multi-disciplinary and complex with patients treated simultaneously with systemic therapy, surgery, and radiation. It is well documented that cancer-related pain is often inadequately controlled in the palliative care setting, and both the pain and opioid medication interfere with patient function and quality of life (Bruera & Kim, 2003; Cleeland et al., 1994; McGuire, 2004). Radiotherapy is an important treatment for the alleviation of pain and suffering for cancer patients. It prevents pathologic bone fractures, and palliates tumor-induced obstruction, bleeding, and pain that is not well palliated with pharmacologic treatment (Halperin et al., 2008).

The skeleton is one of the most common sites of metastatic disease and is often the first site affected by metastases and the most common origin of cancer-related pain (Schulman & Kohles, 2007; Coleman, 2006). It was estimated that in 2004, 250,000 cancer patients were afflicted with metastatic bone disease (Schulman & Kohles, 2007). Bone metastases are most common in patients with multiple myeloma, of whom 90% develop bone metastases (Lipton, 2010). Approximately 70% of patients dying of breast and prostate cancer have evidence of metastatic bone disease, and bone metastases are also common in thyroid, kidney, and lung cancers, occurring in 30-40% of these cancers (Coleman, 2006). Metastatic bone disease causes considerable morbidity in patients with cancer, resulting in pain, hypercalcemia, pathologic fractures, compression of the spinal cord or cauda equina, and spinal instability (Coleman, 2006).

The treatment of metastatic bone disease is financially costly. Schulman and Kohles estimated that the mean per patient direct cost for cancer patients after diagnoses with metastatic bone disease was $75,329 compared to $31,455 for cancer-matched controls without metastatic bone disease (Schulman & Kohles, 2007). Using this data, the authors estimated that the national cost burden for patients with metastatic bone disease was $12.6 billion in 2004, which was 17% of the NIH-reported $74 billion direct medical costs for cancer (Schulman & Kohles, 2007). These costs will clearly increase with our aging population and associated increase in cancer prevalence (Hayat et al., 2007). From a societal standpoint, looming Medicare financial constraints will likely result in reduced reimbursement for palliative services, driving the economic incentive to develop the next generation of more clinically efficient palliative radiotherapy workflows.

2. Standard palliative radiotherapy techniques

2.1 Lack of dose conformality

For 30-40 years, standard palliative radiotherapy treatment techniques have utilized simple opposed beam arrangements such as treating a patient with parallel opposed anterior and posterior beams. Although simple to plan and deliver, such techniques provide poor conformality, and large volumes of organs at risk (OARs) may receive the full prescribed dose depending on the area treated. See Figure 1. Radiation to these OARs (skin, lung, esophagus, trachea, stomach, small bowel, rectum, bladder, or genitals) may result in cough, dysphagia, odynophagia, nausea, vomiting, weight loss, fatigue, diarrhea, dysuria, erythema, and pruritus of the skin and genitals (Gaze et al., 1997; Langendijk et al., 2000). Despite being planned and delivered on sophisticated systems, these treatments are frequently only moderately effective, and cause significant toxicity to an already ill patient population with a limited life expectancy (Gaze et al., 1997).

2.2 Slow treatment planning and quality assurance workflow

Conventional simulation and treatment planning is performed over a several day process prior to the first delivered treatment. The patient is first seen in consultation and scheduled for a CT simulation on a subsequent day. During the CT simulation the patient is placed in the position in which they will ultimately be treated on a treatment unit, and immobilization and support devices are fabricated, after which they undergo a CT scan in the treatment position. He or she must then wait, sometimes several days, for the contouring of the CT simulation images, a process by which the radiation oncologist specifies the planning target volume (PTV) of the tumor to be treated and the regional OARs or adjacent tissues that may receive radiation resulting in toxicity. Following the contouring of the CT images, radiation treatment planning is performed, during which time medical dosimetrists and physicians determine the beam angles and treatment techniques to deliver the prescribed dose to the PTV while attempting to minimize dose to OARs if possible. Following treatment planning, quality assurance calculations and/or measurements are performed by medical physicists before delivery of the first treatment to ensure accuracy of delivering the planned dose and ensure patient safety. Finally, the first treatment is then delivered 3-7 working days after the initial consultation.

2.3 Inconvenient, modestly effective treatments

Although fractionation schedules in Europe are trending toward hypofractionation (fewer treatments), the most common palliative dose fractionation schedules in the United States vary between 20 and 30 gray (Gy) in 5 -10 fractions delivered over 1 -2 weeks (Fairchild et al., 2009). Adding the one week pre-treatment work process to the 1-2 weeks of treatment delivery results in an overall duration of 2-3 weeks for completion of palliative treatment. Conventional radiotherapy, regardless of fractionation schedule, has been found to be modestly effective in treatment of bone metastases, resulting in an improvement in pain in only about 60% of patients (Wu et al., 2003; Chow et al., 2007). In a retrospective study of end stage cancer patients receiving palliative radiotherapy, Gripp et al found that half of the patients received treatment for >60% of their final days of life (Gripp et al., 2010). Thus, these often modestly effective treatments subject the patients to repeated visits to the treatment center and consume precious time and energy for ill patients and their families. Clearly it is important that we design more effective palliative treatments that are more efficient to plan and deliver, minimize acute toxicity, and require fewer total treatments and time.

2.4 Mark-and-start radiation therapy workflows

Traditional emergent radiation therapy workflows referred to as "mark and start" protocols were developed to rapidly treat patients with severe pain, spinal cord compression, superior vena cava syndrome, and life-threatening obstruction of major organs. They generally rely on a good understanding of surface anatomy to direct placement of square or rectangular treatment fields on the patient with the patient on the treatment couch. A port film is obtained to confirm that the target is being treated and to document the treatment volume. The treatment field is then marked on the patient and documentation photos are obtained. Following anatomic volume determination and verification, the prescription dose is converted to treatment unit monitor units which are calculated using the field size, treatment distance, treatment depth, and machine-specific output factors for a given photon energy. The best quality assurance practices are to have two people calculate the monitor units independently and to have at least one person perform the calculation by hand if a computer calculation program is used. Once the monitor units are calculated, the patient can be treated. Emergent treatments generally use one or two parallel opposed beams to deliver non-conformal dose with large volumes of non-target tissue being irradiated to the prescribed dose.

Since most patients treated with radiation therapy on an emergent basis are symptomatic with pain, bleeding, or obstruction, it can be difficult for them to lie still on a flat treatment table for prolonged periods of time. Therefore, the faster the clinical workflow, the better the patient will tolerate the process. Most new linear accelerators (LINACs) are equipped with kilovoltage imaging capabilities on the treatment unit which can make the initial field placement easier by functioning similar to a CT or fluoroscopic simulator. This can increase the efficiency of the process since accurate field placement is the most time consuming part of the "mark and start" workflow. Once the field is accurately marked, the monitor unit calculations take only a few minutes, and the patient can rapidly be treated.

Clearly, for emergency situations, a simple treatment option is highly desirable for any treatment system, especially for a system in a one-unit radiation oncology clinic. Some

complex treatment systems have no easy methodology or workflow to treat patients emergently with simple fields if the patient has not undergone a separate CT simulation. This is due to the fact that they have no way to calculate a treatment plan without a contoured CT image dataset. In addition, some intensity modulated radiation therapy (IMRT) dedicated systems with their own CT treatment planning algorithms do not have an easy way to perform an independent calculation to verify the accuracy of the planned dose calculation. Due to these limitations, the treatment of the emergency patient on these systems generally requires performance of the standard workflow of CT simulation, CT contouring, dose calculation, dose verification with unit measurements, and then image guided treatment delivery to the patient. The development of novel and greatly expedited workflows for these systems that utilize conformal dose delivery would provide an improved method to treat emergency patients that could also be used to treat non-emergent palliative patients more rapidly. In this chapter, we propose the development of one potential rapid clinic workflow utilizing the TomoTherapy system called STAT RAD.

3. Stereotactic Body Radiotherapy (SBRT): A more effective, highly conformal hypofractionated palliative radiation technique

In the search for more effective and less toxic radiotherapy techniques, much attention has been focused on stereotactic body radiotherapy (SBRT). SBRT utilizes hypofractionated, highly conformal, high dose radiation delivery that has been modeled after intracranial stereotactic radiosurgery (SRS). Like SRS, SBRT uses multiple beams that converge on the target volume. This minimizes the volume of tissue receiving high dose to where the beams intersect, reducing dose to normal tissue. This allows for the delivery of ablative doses of radiation in a few fractions with acceptable toxicity (Read, 2007; Timmerman et al., 2010). SBRT is a proven method for treating lung cancer, yielding excellent rates of local control for non-small-cell lung cancer and resulting in 5-year survival rates potentially comparable to that of surgery (Timmerman et al., 2010; Onishi et al., 2010). In addition, the treatment of liver metastases with SBRT has yielded promising results, achieving local control rates at 2 years of approximately 70–90% (Dawood, Mahadevan, & Goodman 2009; Rusthoven et al., 2009).

SBRT has also been used in the palliative treatment of bone metastases to the spine with remarkable success. Multiple studies have used SBRT to safely deliver high doses of radiation to spinal metastases while significantly limiting dose to the spinal cord and achieving local control rates of >80% at one year (Gerszten et al., 2007; Nelson et al., 2009; Gibbs et al., 2007). Fractionations in these studies have ranged from 1 to 5 fractions delivering 4 – 24 Gy per individual fraction, with total doses between 10 to 30 Gy (Gerszten et al., 2007; Nelson et al., 2009; Gibbs et al., 2007). In the largest prospective study of spine SBRT by Gerszten, 336 cases were treated primarily to relieve pain, and they achieved significant pain improvement in 290 patients (86%). Nelson, Gibbs, and Ryu, have also reported pain reduction in greater than 80% of patients in their studies (Gerszten et al. 2007; Nelson et al., 2009; Gibbs et al., 2007; Ryu et al., 2008), much improved over the 60% in conventional radiotherapy (Wu et al., 2003; Chow et al., 2007). Not only do more people experience pain relief with SBRT, but the pain relief is reported to be more durable. Gagnon demonstrated statistically significant improvement in pain scores lasting throughout 4 years of follow-up (Gagnon et al., 2009). Ryu found the median duration of pain relief to be 13.6 months with SBRT (Ryu et al., 2008), which is a dramatic improvement compared to the

average 3 to 6 months of palliation with conventional therapy (Gaze et al., 1997; Foro Arnalot et al., 2008). Additionally, spinal SBRT treatments have been effective in achieving local control in tumors typically resistant to radiotherapy, such as renal cell carcinoma and melanoma, reportedly due in part to radiation injury to the tumor vasculature (Gerszten et al., 2007; Gibbs et al., 2007; Ryu et al., 2008; Gagnon et al., 2009).

3.1 Adverse events with SBRT: Minimal toxicity

Though great success is seen in high dose, hypofractionated therapy, care must be taken to avoid incorrectly delivering the high dose radiation to normal tissue. Prevention of damage to normal tissue is ensured through careful patient immobilization, co-registration of multiple diagnostic imaging modalities (MRI, PET CT, contrast enhanced CT) to the kVCT simulation to accurately define the target and OARs, inverse treatment planning with the use of intensity modulated radiation therapy, patient-specific quality assurance, and CT image guidance at the time of treatment delivery. Nevertheless, common side effects of radiotherapy can occur with SBRT. However, the advantage of conformal radiation is that it spares high radiation dose to normal tissue with the relatively small target volumes employed in this technique compared to parallel opposed techniques in which prescription doses are delivered to all tissues, target and OARs, in the beam path through the patient. This advantage of SBRT has been demonstrated in many trials by reports of little to no toxicity (Gerszten et al., 2007; Gagnon et al., 2009), and is reinforced by the findings of McIntosh et al, who compared conformal TomoTherapy to conventional 3D conformal treatment techniques on an anthropomorphic phantom and showed that TomoTherapy plans significantly improved conformality and reduced dose to regional critical structures (McIntosh et al., 2010).

Most significant adverse events in spinal SBRT have occurred with treatments that used extremely high-doses (>20 Gy) in a single fraction. Gomez et al reported odynophagia and dysphagia in 1 patient who had received 22 Gy to the esophagus in a single dose, and another patient developed an esophageal ulcer and necrosis after receiving 24 Gy to his esophagus in one fraction (Gomez et al., 2009). Another patient developed bronchial stenosis after receiving 11 Gy to a bronchus in a single fraction. In another study with similarly high dose fractionation schedules, 39% of patients treated with 18 to 24 Gy in a single dose developed new or progressive vertebral fractures (Rose et al., 2009). However, their patient selection did not utilize a scoring system to identify patients at high risk for pathologic fracture, such as the Mirels scoring system (Cumming et al., 2009). In contrast, Gagnon et al, using mean doses of 26 Gy in 3 fractions in 200 patients, only had 2 patients (1%) develop vertebral fractures (Gagnon et al., 2009). Sahgal et al reported 5 cases of radiation myelopathy and concluded that for single fraction SBRT, up to 10 Gy to a maximum point to the thecal sac is safe (Sahgal et al., 2010).

3.2 Extrapolation of spinal SBRT-like dose distributions to non-spine metastases

Given the advances in radiation delivery with SBRT and its success in palliation of spine metastases, it is logical to apply these advancements in technology to extra-axial bone metastases; however, no trials have been published to date. This is due to the fact that SBRT is only reimbursed for limited indications such as spinal metastases. It is fair to hypothesize that the extrapolation of SBRT-like dose distributions to extra-axial bone metastases will

improve pain control and that rapid institution of radiation will minimize the time patients are in pain and on high dose opioids that place them at risk for iatrogenic medical complications. By applying the concepts of spinal SBRT, highly conformal hypofractionated radiation therapy plans could be used to treat non-spinal metastases. This allows for increased dose per fraction and fewer total fractions with less toxicity compared to standard non-conformal palliative regimens. See Figures 1-2.

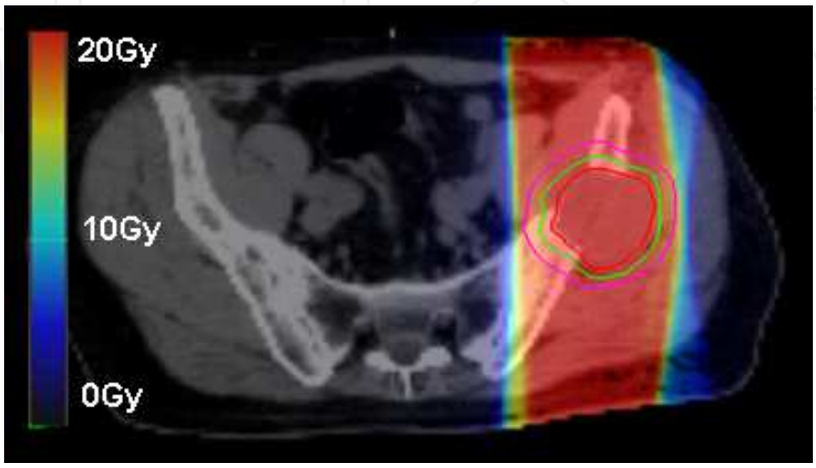

Fig. 1. Nonconformal Technique

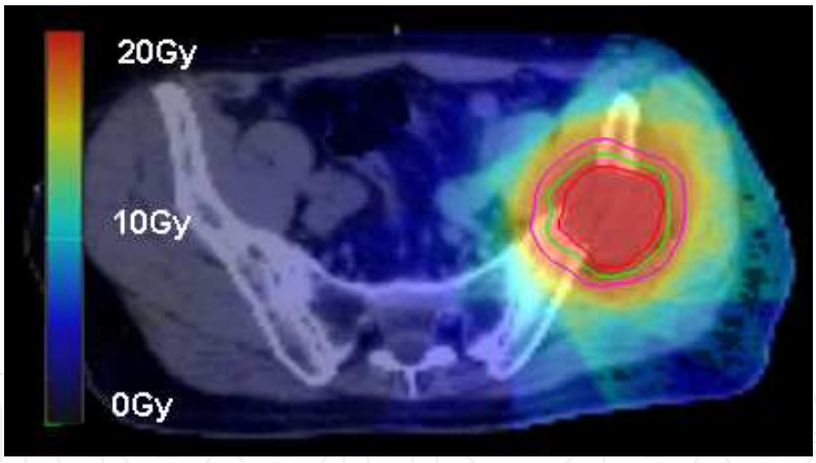

Fig. 2. Conformal Technique

3.3 Relative Biologic Effective Dose: A method to compare different dose fractionation schedules

Based on the linear-quadratic equation, one can calculate the biologic effective dose (BED) to compare dose delivery of different fractionation schedules using the equation:

$$BED = nd\ [1+d(alpha/beta)] \quad (1)$$

n = number of fractions, d = dose per fraction, alpha/beta = the ratio of intrinsic radiosensitivity to repair capacity

As seen in Table 1, when compared with conventional fractionation schedules for palliative osseous metastases, such as 30 Gy in 10 fractions or 20 Gy in 5 fractions, high dose per fraction regimens deliver very similar BED to early responding tissues and slightly higher BED to late responding tissues. We believe that for reasonable rates of symptom relief and duration of palliation that palliative regimens should deliver a minimum BED of 25 Gy to most treatment targets. Twenty-four Gy in 3 fractions (8 Gy x 3 fractions) is an attractive palliative regimen that balances a high radiobiologic dose with the convenience of a highly hypofractioned regimen. This daily dose can generally be delivered in 10 minutes or less depending on target size and modulation allowing patients in pain to tolerate the treatment without moving. Finally, doses of 8 Gy or higher may be more effective against tumor histologies thought to be more radioresistant such as melanoma or renal cell carcinoma due to cytotoxic effects to the tumor vasculature. However, the dose per treatment, number of treatments, and total dose will depend on the patient's overall condition and tumor-specific factors including histology, location, proximity to critical OARs, and size. Relative BED provides a method to compare different dose fractionation schedules that can be used to correlate the treatment with patient outcomes.

	Total dose	# of fractions	Dose per fraction (Gy)	Alpha/beta	BED
Early Responding Tissues	30	10	3	10	39
	20	5	4	10	28
	24	3	8	10	43
Late Responding Tissues	30	10	3	3	60
	20	5	4	3	47
	24	3	8	3	88

Table 1. Comparison of BED in Different Palliative Fractionation Schedules

4. STAT RAD: A rapid palliative radiotherapy workflow in clinic development

Clearly a faster, more efficient workflow to treat metastatic disease is needed. Patients with widespread metastases frequently have short life expectancies and need treatments that minimize their time in clinic while providing rapid and durable pain relief for the remainder of their lives. Additionally, this need for efficiency will further rise with the increasing cancer burden and health care costs due to the aging baby-boom population.

Thus, at the University of Virginia we are piloting a new workflow called "STAT RAD" to rapidly deliver advanced radiotherapy to patients with metastatic disease on an internal review board approved clinical trial. This STAT RAD workflow offers same-day palliation in an approximately 6-hour time frame similar to a standard GammaKnife ® (Elekta, Stockholm, Sweden) workflow. STAT RAD is a highly coordinated conventional workflow that includes kVCT simulation, treatment planning, treatment plan quality assurance, and delivery of conformal hypofractionated radiotherapy in a single day. All treatments are planned and delivered on FDA-approved systems including the TomoTherapy treatment machine. This workflow allows patients to receive an entire course of palliative treatment from start to finish in a few days, a process that conventionally takes 2-3 weeks. Since patients are billed for each individual treatment, requiring fewer treatments reduces health care costs in addition to being more convenient. With the STAT RAD program we are now

able to offer a unique workflow that delivers rapid, effective, and efficient palliative radiotherapy that is cost effective, less toxic, and more convenient for cancer patients and their families.

We have treated approximately 50 cancer patients with the conformal hypofractionated STAT RAD treatment regimen for a variety of palliative indications. We have treated patients with IMRT and 3D delivery using TomoHelical and TomoDirect planning modes. Retrospective review of these patients shows that the majority of these patients experienced rapid and durable palliation of symptoms with minimal toxicity (unpublished data). In general, patients are extremely satisfied with the speed at which their treatment is initiated and the convenience of the hypofractionated regimens.

In our current trial we are quantifying patient outcomes following treatment with the current STAT RAD workflow in an effort to determine its benefits and risks to patients. In addition, we are systematically evaluating and optimizing software and hardware necessary to make the STAT RAD workflow even more efficient.

4.1 Technologic rationale for the choice of the TomoTherapy platform

The TomoTherapy platform has been chosen for the STAT RAD workflow for a variety of reasons. TomoTherapy delivers highly conformal and homogenous dose distributions through modulation of dose from a bank of 64 binary 6.25-mm-wide collimator leaves capable of pneumatic opening or closing 51 times per revolution as the gantry revolves around the patient. The system can also treat patients with discreet beam angles (i.e. the radiation beam not rotating) in a mode called TomoDirect. Although all TomoTherapy treatment delivery is technically IMRT, the treatment planning can be done in either a 3D or IMRT mode allowing highly conformal treatments to be billed as 3D and thus used in the treatment of all patients with bone metastases. While the 3D planning mode limits the planning options for dose constraints on OARs, partial and complete blocking can be assigned to non-target structures. Partial blocking allows beams to exit through the structure after treating the PTV but not to enter through the structure prior to treating the PTV, and complete blocking restricts beams from entering or exiting through a structure. In addition, good preliminary data exists to support the use of the fan beam MVCT as a CT simulation image set for treatment planning and the use of CT detector-based exit dose methodology for quality assurance, making this system an excellent platform to pilot and optimize this workflow.

5. Scan-plan-verify-treat STAT RAD workflow: A novel and more efficient STAT RAD workflow

With recent advances in software and technology, we plan to further condense the STAT RAD workflow into the Scan-Plan-Verify-Treat workflow, a 30-minute process in which all steps (MVCT simulation, diagnostic image co-registration, treatment planning, and treatment delivery with real time quality assurance) are performed on the TomoTherapy unit. This advanced workflow will eliminate the need for the patients to undergo a kVCT simulation on a separate unit as well as make it unnecessary for the patient to leave the treatment table between the simulation and treatment.

Requirements for the clinical implementation of the Scan-Plan-Verify-Treat STAT RAD workflow are envisioned as follows:

1. **Scan:** MVCT simulation image acquisition (10 minutes) then rigid or deformable image co-registration of existing diagnostic image sets with pre-contoured target and OAR volumes to the MVCT simulation scan for contour transfer (3-5 minutes).
2. **Plan:** Rapid inverse treatment planning (3-5 minutes).
3. **Verify:** Real-time patient-specific quality assurance using CT detectors prior to or during treatment delivery (10 minutes).
4. **Treat:** Simple real-time patient motion tracking to monitor patient position real-time during the Scan-Plan-Verify-Treat process to ensure accurate delivery.

5.1 New image co-registration workflow

In the conventional workflow, target volumes and OARs are contoured on recent diagnostic images (MRI, PET-CT, or diagnostic CT that are already available in the patient's electronic radiology chart). After the patient undergoes a kVCT simulation, the contoured diagnostic images are rigidly or deformably co-registered to the kVCT simulation images, and the contours are transferred. This allows for high resolution diagnostic images to be used for tumor and normal tissue identification, which are not always possible to differentiate on CT simulation scans due to the resolution of standard wide bore CT simulation scanners and images that are frequently obtained without intravenous contrast. Multiple commercial image processing systems are available for this image processing, and we are currently using Velocity® (Atlanta, GA) image processing software. Following treatment planning, the patient then undergoes image guided treatment delivery, a process in which a daily MVCT scan is obtained on the TomoTherapy unit and co-registered to the planning kVCT scan. Patient setup shifts can then be made to ensure accurate patient setup, and the patient is treated. Therefore, this is a two image co-registration workflow. See Figure 3.

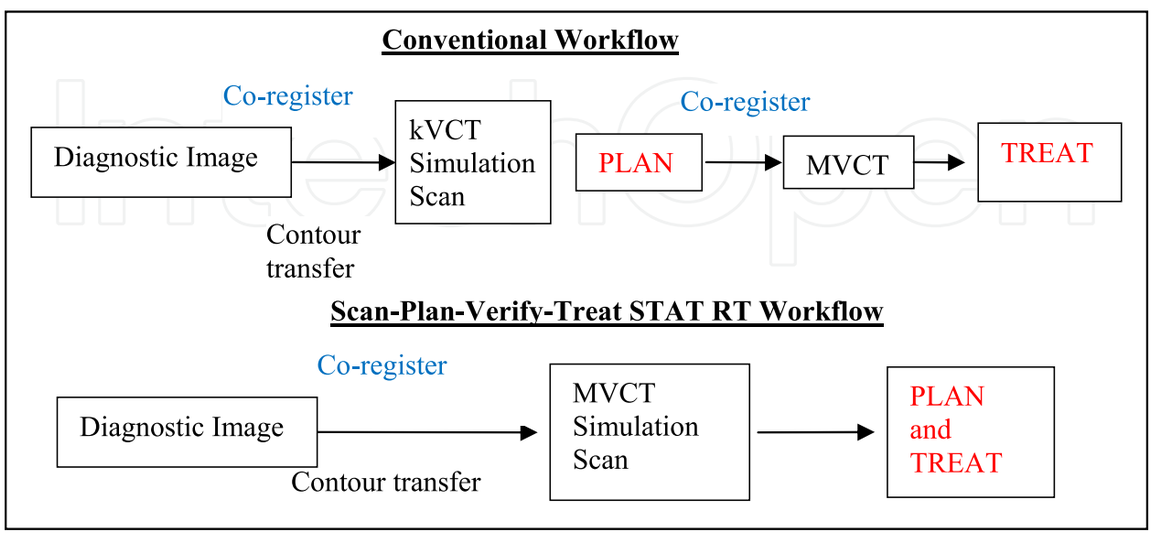

Fig. 3. Comparison of Image Co-Registration Workflows

A kVCT simulation scan has historically been used for simulation in the conventional workflow for both palliative and curative radiation planning. Compared to MVCT scans, it has higher resolution and allows the possibility for administration of iodinated IV and/or GI contrast, which makes it easier to identify soft tissues and bony anatomy for treatment planning. However, contrast agents are not generally given for kVCT simulations of patients for palliative treatment of metastases since the soft tissue and bone windows are adequate. Soft tissue and bone windows of MVCT scans have quite reasonable resolution and can easily be co-registered to higher resolution diagnostic studies for contour transfer. Software has been used clinically since 2004 to automatically co-register kVCT simulation images and daily MVCT scans for image guidance on a daily basis.

Our preliminary unpublished data confirms that the MVCT scan has sufficient resolution, particularly of bone anatomy, for accurate co-registration to contoured diagnostic images and that this one step co-registration process yields comparable agreement to the conventional two step image co-registration workflow with +/- 2-3 mm differences. See Figure 3. This level of agreement is consistent with results reported from image co-registration studies performed on a multi-institutional pediatric clinical trial with co-registration data of 51 patients from 45 institutions using 11 different image software systems. They reported an inherent uncertainty of 2 mm for MRI to CT co-registration (Ulin, Urie, & Cherlow 2010). Thus, preliminary data suggests that the optimization of this one step image co-registration workflow of diagnostic image sets to a MVCT simulation scan will be clinically similar to the conventional two image co-registration workflow. MVCT image guidance scans and kVCT simulation co-registration occurs routinely in the clinic and only takes a few seconds, therefore, we do not believe that this will be a rate-limiting step in the clinical implementation of the Scan-Plan-Verify-Treat STAT RAD workflow. Further optimization of the image co-registration workflow will make the 30-minute Scan-Plan-Verify-Treat STAT RAD workflow feasible.

5.2 Rapid inverse treatment planning on MVCT scans

CT image sets are used for radiation treatment planning because the electron density of tissues, which is required for calculating dose, is easily determined based on the Hounsfield units. The tissue electron density determination is essentially the same for MVCT and kVCT scans. It has previously been reported that as far as the dose calculations are concerned, treatment planning on either a kVCT simulation image set or a MVCT simulation image set yields treatment plans that are within 1% of each other (Langen et al., 2005).

We have recently published that the TomoTherapy STAT RT treatment planning module can calculate SBRT plans in just a few minutes (Dunlap et al., 2010). The computing speed of radiation treatment planning systems is about to take a quantum leap forward with the incorporation of new algorithms that will take advantage of the processing power of graphics processing units (GPU) whose more rapid and parallel calculating potential can improve treatment planning speed by 10-20 times (Hissoiny, Ozell, & Despres, 2010; Hissoiny, Ozell, and Despres, 2009). Same-day inverse treatment planning of IMRT or 3D TomoTherapy plans has not been a problem for patients treated with STAT RAD to date. We are comparing planning times for current FDA-approved treatment planning systems to those of newer, in-development GPU-based algorithms. In general, highly conformal 3D or IMRT plans can be generated in 2-3 minutes with GPU-based algorithms.

We have shown that accelerated treatment planning software for Helical TomoTherapy provides clinically acceptable dosimetry, with conformality and homogeneity that is superior to standard LINAC-based 3D conformal planning and is only slightly inferior to standard Helical TomoTherapy dosimetry (McIntosh et al., 2010). We have also shown that, with planning times of 2-5 minutes, this accelerated treatment planning software provides levels of dosimetric conformality, heterogeneity, and avoidance of organs at risk for simple SBRT treatments that are clinically equivalent to those generated with conventional Helical TomoTherapy treatment planning (Dunlap et al., 2010). This preliminary data supports that treatment planning speed is not likely to be rate limiting in the ultimate clinical implementation of the Scan-Plan-Verify-Treat STAT RAD workflow.

5.3 Novel CT-detector-based quality assurance methodology

Current standard of care TomoTherapy quality assurance methodology requires that each patient-specific treatment plan be delivered to a cylindrical plastic phantom with ion chamber and film measurement to ensure geometric and planar dose distribution accuracy using gamma criteria of 3%/3mm. However, this method does not measure the dose that the patient is receiving during treatment or provide full 3D dose verification. It causes another delay in delivering the first treatment to the patient as it requires approximately 30 minutes to complete, and is generally done by a medical physicist after daily clinic patient treatment is finished. A methodology to monitor the patient exit dose in real time would increase patient safety through verification of daily treatment accuracy as well as expedite the treatment workflow. Clearly, a real-time quality assurance methodology that does not require moving the patient off the TomoTherapy treatment couch for phantom measurements is essential for the development of a 30-minute Scan-Plan-Verify-Treat workflow. Current dose verification methodologies measuring dose at the time of patient treatment are limited to point measurements on the patient surface (Essers & Mijnheer, 1999), which is rarely in the target volume or a critical OAR, or through expensive implanted dosimeters (Beyer et al., 2007; Scarantino et al., 2004), which are not practical for most palliative patients. Since there is no method to directly measure the three dimensional dose in the patient, alternative approaches are being developed and tested in academic clinical settings. These alternative approaches reconstruct the delivered three dimensional dose distribution based on the measurement of either entrance or exit dose and back-projecting the measurements onto simulation or image guidance CT image sets.

The opportunity to reconstruct dose from information collected during treatment became available with the incorporation of radiation imaging detectors, such as electronic portal imaging devices (EPID) on linear-accelerators and CT detector arrays on TomoTherapy. Dose reconstruction using in-line EPID was first described by McNutt et al (McNutt, Mackie, & Paliwal 1997; McNutt et al., 1996). The EPID, when deployed during treatment, collects exit fluence from the patient and then back-projects this to X-ray fluence before entering the patient; then, the dose in the patient is re-computed using this entrance fluence and the planning CT images. However, there are many limitations to EPID-based dose verification. For example, the EPID was originally designed for semi-quantitative portal imaging; and for the purpose of dose reconstruction, it suffers from a narrow dynamic range, short life span, non-linearity in the dose response, ghost artifacts from low temporal resolution, and cross-plane scatter photon contribution to the measured fluence (Mijnheer, 2008). Investigators are currently working on methods to overcome these challenges.

The TomoTherapy unit has an in-line source-patient-detector geometry with CT ion chamber detectors that are used for daily MVCT scan image guidance for accurate patient positioning that remain in place during both imaging and treatment. These CT detectors can also be used to measure the patient exit dose fluence and back-project this onto a planning CT scan for volumetric or 3D dose reconstruction. Dose verification on TomoTherapy was first studied by Kapatoes et al., who calculated the entrance fluence from the exit dose using a transfer matrix, which is calculated based on the radiological path length from the source to the detector (Kapatoes et al., 2001; Kapatoes et al., 2001). The use of a CT ion chamber array has multiple advantages over EPID for exit fluence measurement. It is more durable, and has a much longer life span. It has a wider dynamic range and doesn't limit treatment positions. Finally, it is less sensitive to the noise from cross-plane scatter photons that complicate EPID-based dose reconstruction (Siewerdsen & Jaffray 2001).

Our pre-clinical evaluation of the CT detector-based exit radiation dose verification algorithm has been retrospectively studied by Sheng et al. using in-development software (Sheng et al., 2011). We compared planned and delivered doses with the conventional phantom quality assurance measurements for 24 patients and 347 treatment fractions. The concordance of planned to delivered dose calculated by the in-development software was shown to be +/- 5% (Sheng et al., 2011). This tolerance is within the standard of care of other current clinically available quality assurance methods. Further refinements are expected to improve dose monitoring accuracy for this or other algorithms.

5.4 Optical tracking methods for patient intra-fractional motion monitoring

Consistent patient positioning during CT image acquisition and treatment is critical to ensure accurate dose delivery. Physical immobilization devices such as external body frames, aquaplast masks and other body molds, and vac-lock vacuum bags are commonly used to ensure patient positioning reproducibility. X-ray or CT image guidance prior to radiation delivery on the treatment unit is routinely employed in the clinic. Methods for optical tracking of markers on the patient surface or tracking of the patient's skin surface itself are available to ensure consistent patient positioning after image guidance and during treatment, known as intra-fractional motion (Wagner et al., 2007; Wiersma et al., 2010). This provides a method without ionizing radiation for confirming patient position that can be used real-time during treatment delivery. With this information, if the patient's position moves outside of acceptable limits in any direction, treatment could be paused. A mechanism to ensure that the patient's position doesn't change between MVCT simulation and treatment delivery would obviate the need for a repeat image guidance MVCT scan just prior to delivery in the Scan-Plan-Verify-Treat workflow.

We have recently developed an in-house optical tracking system using multiple OptiTrack FLEX:V100 cameras (Natural Point, Corvallis, OR). The camera utilizes 26 infrared light-emitting diodes and a charge coupled device to capture the reflective light from markers with special coating. By using multiple cameras, the 3D position of each reflective marker can be determined precisely. Multiple markers can be placed on a patient and monitored simultaneously. In the lab, localization precision of 0.1 mm was achieved (unpublished data). Through strategic positioning of the markers, movements of the head, neck, and extracranial locations can be closely monitored.

6. Clinical benefits and future directions of STAT RAD implementation

6.1 Additional benefits to patients with metastatic disease

Several advantages of this streamlined workflow are envisioned that will improve the care of patients with metastatic disease. The most obvious is that patients who live far from treatment centers can be offered palliative radiation therapy as an option. Take for example the case of a patient who lives 50 miles from a radiation oncology center. If they are seen in consultation, undergo a CT simulation on a second visit, and then are treated with 30 Gy in 10 fractions, they will have to drive 1200 miles for this treatment course. Clearly this is not practical for many ill patients in the last few months of life. If they can receive a conformal high dose palliative treatment in one day, it is much more likely that they will receive this treatment. We have been coordinating STAT RAD treatments on days that patients have appointments with other oncologists or specialists. Patients come to the radiation oncology clinic and undergo a consultation and CT simulation and then go to their other appointments while planning and quality assurance measurements are performed, and then they return to the radiation oncology clinic later that same day for treatment. Once the Scan-Plan-Verify-Treat STAT RAD workflow is available, we envision treating patients at the end of the scheduled workday on a same-day physician request basis. This service holds high utilization potential because many times physicians do not know if a patient is in significant need of palliation until they examine the patient at the time of a scheduled appointment.

Frequently patients are admitted to the hospital for management of cancer-related symptoms such as intractable pain, spinal cord compression, profuse tumor bleeding, or tumor related acute obstruction. These patients are frequently treated with palliative radiation therapy. The STAT RAD workflow enables patients to receive high dose and conformal treatments that start faster than conventional kVCT simulation workflows and can shorten the length of hospitalization to complete treatment.

Finally, this workflow makes the treatment of patients with oligometastatic disease more streamlined and practical because it enables SBRT-like dose distributions to be delivered to multiple lesions that currently cannot be treated with SBRT, such as nodal disease or non-spinal bone metastases.

6.2 Incorporation of translational technology development into routine clinic care for all patients

Several aspects of the Scan-Plan-Verify-Treat STAT RAD clinical development can be incorporated into the routine care of patients undergoing curative radiation therapy. Specifically, CT detector-based quality assurance of all treatments could be automated and performed daily. Such quality assurance could provide a warning if the delivered dose is greater than a threshold such as +/- 5% for a patient and trigger an investigation into the cause of this deviation. Quality assurance of each fraction of treatment would be a major advancement compared to current quality assurance methods of checking each plan prior to treatment. Using daily quality assurance to monitor changes in patient status such as significant weight loss in a head and neck cancer patient could trigger re-planning that could be done on an adaptive basis.

A simple system to monitor patient motion following image guidance could reduce the risk of geometric misses due to intra-fractional patient motion. If it were determined that a specific patient had more or less intra-fractional motion than accounted for in their PTV expansion, then their treatment plan could be adaptively re-planned to mirror their specific expansion requirements.

6.3 Future directions for spinal SBRT

The Scan-Plan-Verify-Treat STAT RAD workflow could easily be incorporated into the treatment of spinal SBRT patients. We have previously reported that treatment planning algorithms currently exist that can create highly conformal spinal SBRT plans in just a few minutes (Dunlap et al., 2010) and that the CT detector-based quality assurance algorithms can measure exit dose to within +/- 5% (Sheng et al., 2011). Real-time spinal SBRT simulation, planning, and delivery would eliminate the need for patients to be accurately re-set up and positioned between simulation and treatment to within two millimeters of accuracy which is the current accuracy of most co-registration-based image guided systems. In addition, differences in pitch, yaw, or roll of the patient between simulation and treatment delivery setups cannot be routinely corrected by most CT-based image guidance systems, requiring the patient to be re-positioned and re-imaged prior to treatment if they are out of tolerance. With this proposed workflow, the patient could be treated in the planning position, which could potentially eliminate these re-positioning error issues.

7. Conclusion

As the cancer burden in the population increases and heath care costs continue to rise, a faster, more efficient workflow is needed to treat patients with metastatic disease. Conformal hypofractionated treatment has demonstrated promising results for the palliation of bone metastases, and its incorporation into a workflow such as the STAT RAD workflow also improves patient convenience. In the near future, we believe the optimization of new software and hardware will enable a 30-minute Scan-Plan-Verify-Treat STAT RAD workflow to further maximize patient convenience and efficiency. This more efficient and cost effective workflow may result in more widespread incorporation of palliative radiation for cancer patients failing systemic therapy earlier in their disease process, reducing pain and functional loss and improving quality of life.

8. Abbreviations

3D - 3-dimensional
BED - biologic effective dose
CT – computed tomography
CTV – clinical target volume
EPID - electronic portal imaging device
FDA – Food and Drug Administration
GI - gastrointestinal
GPU - graphics processing unit
Gy - gray
IMRT- intensity modulated radiation therapy

IV - intravenous
kVCT – kilovoltage CT
LINAC - linear accelerator
MRI – magnetic resonance imaging
MVCT – megavoltage CT
OAR - organ at risk
PET CT – positron emission tomography CT
PTV - planning target volume
SBRT - stereotactic body radiotherapy
SRS - stereotactic radiosurgery
STAT RAD - urgent and rapid radiation treatment

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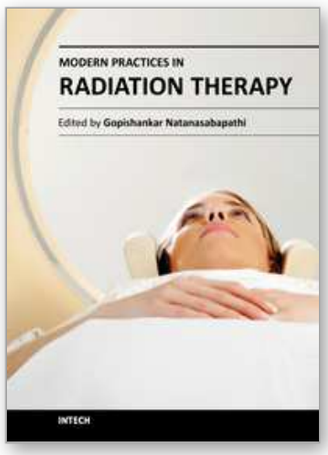

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Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries. It is an enormous global health encumbrance, growing at an alarming pace. Global statistics show that in 2030 alone, about 21.4 million new cancer cases and 13.2 million cancer deaths are expected to occur, simply due to the growth, aging of the population, adoption of new lifestyles and behaviors. Amongst the several modes of treatment for cancer available, Radiation treatment has a major impact due to technological advancement in recent times. This book discusses the pros and cons of this treatment modality. This book "Modern Practices in Radiation Therapy" has collaged topics contributed by top notch professionals and researchers all around the world.

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