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Chapter 7

Curative Radiotherapy in Metastatic Disease: How to Develop the Role of Radiotherapy from Local to Metastases

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Additional information is available at the end of the chapter

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1. Introduction

Metastasis is the leading cause of cancer death and in patients with proven distant metastases from solid tumors, it has been a notion that the condition is incurable and the treatment is usually conducted with palliative intent, with rare exceptions. Treatment predominantly involves the use of systemic chemotherapy, targeted radiotherapy or local measures typically reserved for symptom relief (Argiris, 2004; Escudier, 2007; Hurwits, 2004). Chemotherapy is delivered without expectation of long term survival, except for highly chemosensitive malignancies, such as leukemia, lymphoma, and germ cell tumors. According to the conventional treatment strategy for solid tumors, the presence of metastatic disease is a contraindication for local therapy because it is believed that these tumor cells have already spread systemically. However, from the viewpoint of reducing tumor burden, local therapy may be an adequate strategy when the target lesions account for the major portion of the total tumor volume. The local therapies are metastasectomy, heating or cooling, and radiotherapy.

In a subset of patients with a limited number of metastases or oligometastases, local ablative therapy, such as surgical resection, can potentially yields favorable outcomes. For instance, in surgical literature, it has been demonstrated that surgical resection of limited lung and liver metastases has results in prolonged survival and possibly cure in a significant proportion of patients with oligometastases (Fong, 1999; Friedel, 1994). International registry of lung metastases reported that lung metastasectomy is a safe and curative procedure in selected patients with disease free interval (DFI) ≥ 3 years, single lesion and germ cell tumor (Pastorino, 1997). And the lung and liver metastasectomy is a surgical approach used in colon and breast cancers, with upto 22% of colon cancer patients surviving 10 years and 35-46% of breast cancer patients surviving upto 5 years (Fong et al, 1999; Friedel et al, 1994; Pocard et al, 2001).

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However, resection may not be feasible in patients of extremely advanced age or with poor cardiopulmonary function or multiple comorbidities because of the risk of significant morbidity and mortality in these settings. In such patients, external radiotherapy is often the treatment of choice. However, this treatment also has its drawbacks, including the potential to damage adjacent or nearby structures and its association with a local failure rate that is higher than that was seen in resection. To minimize collateral injury to normal tissues, adequate fractionation (e.g. 1.8-2.0 Gy/fraction) over 6 to 7 weeks is commonly used. The use of radioablative treatment such as using stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) to overcome problems with normal tissue injury in patients with medically inoperable metastatic tumor has now been actively studied at many institutions.

2. Oliogmetastases

2.1. Definition

In 1889, Paget's "seed and soil" hypothesis stated that the development of a metastasis depends on cross talk between selected cancer cells (the seed) and a specific organ microenvironment (the soil) (Paget, 1889). This means that successfully establishing a distant metastasis depends on certain properties of the host organ as well as those of tumor cells. Dissemination of tumor cells in general circulation does not necessarily mean that wide spread metastatic disease will always develop. This hypothesis is still widely accepted. Observing the natural history of breast cancer, Hellmann and Weichselbaum hypothesized the existence of an intermediate state between widespread metastatic disease and locally confined disease and coined the term "oligometastases" (Hellman & Weichselbaum, 1995). Thus, local control of oligometastatic disease may allow better systemic control. In addition, thanks to the evolution of radiologic imaging technique, detection of metastasis at a size previously impossible to be detected may result in under treatment and an effective chemotherapy may downstage these metastatic diseases to oligometastases.

2.2. Clinical significance

Clinically, there are two types of oligometastases. The De novo type is the tumor early in the evolution of metastatic progression producing metastasis that are limited in number and location, and the induced type is generated when effective systemic chemotherapy eradicates the majority of metastatic deposits in a patients with wide spread metastatic disease (MacDermed, 2008).

In a retrospective study, Mehta et al tracked the number of individual metastatic sites and the number of organs involved using serial computerized tomography of the body in 38 patients with stage IIIb or IV non small cell lung cancer treated with chemotherapy. Seventy four percent of patients (n=28) had a metastatic disease limited to 1-2 organs and 50% (n=29) had a disease limited to the primary tumor and three or less metastatic lesions at presentation. Fifty percent (n=19) had stable (n=12) or progressive (n=7) disease in initially involved site without development of new metastatic lesion. Among the 17 patients with four or fewer metastatic sites with no pleural effusions, 65% (n=11) had stable or progressive

disease in initially involved sites without development of new metastatic lesions (Mehta, 2004). The results of this study suggest that a subset of patients with oligometastases from lung cancer may benefit from a combination of systemic chemotherapy and local aggressive therapy. In another study, records of 387 patients with advanced non small cell lung cancer were reviewed and 64 patients with measurable advanced stage non small cell lung cancer who received first line systemic chemotherapy and follow up were identified. Thirty four patients were deemed theoretically SBRT eligible. Disease in the lung and liver was limited to ≤ 3 sites each. Among the 34 SBRT eligible patients, the pattern of failure were local only in 68%, distant only in 14%, and mixed in 18%. The time to first progression was 3.0 months in those with local only failure (Rusthoven, 2009). The results of this study suggest that SBRT may improve the time to first progression in a significant proportion of patients with metastatic non small cell lung cancer. After all, because any patient with oligometastatses may exist in a spectrum between orderly metastatic progressions and wide spread occult disease, the role of the local modality to ablate oligometastases need to be determined.

3. Stereotactic Body Radiation Therapy (SBRT)

3.1. Definition and characteristics

The scientific study and clinical practice of oncology have progressed remarkably in recent years. Insights into molecular interactions occurring within a cancer cell have been translated into novel medical treatments, and a variety of technological advances have allowed new surgical and radiotherapeutic techniques. Within the discipline of radiation oncology in particular, the fusion of state-of the-art tumor imaging with precision radiation treatment delivery systems has created an opportunity to shift from the classic radiation therapy paradigm of administering thirty or more individual allow-dose treatments toward briefer, more intense, and more potent regimens in which a much higher dose per treatment is used for greater clinical effect. Stereotactic body radiation therapy (SBRT) refers to an emerging radiotherapy procedure that is highly effective in controlling early stage primary and oligometastatic cancers at locations throughout the abdominopelvic and thoracic cavities, and at spinal and paraspinal sites. The major feature that separates SBRT from conventional radiation treatment is the delivery of large doses in a few fractions, which results in a high biological effective dose (BED). In order to minimize the normal tissue toxicity, conformation of high doses to the target and rapid fall-off doses away from the target is critical. The practice of SBRT therefore requires a high level of confidence in the accuracy of the entire treatment delivery process.

In SBRT, radiation is targeted almost exclusively to the tumor, while tissues not grossly involved with the tumor are spared. However, unique radiobiology of SBRT that ensures maximal tumor control but minimal normal tissue complication is what really sets SBRT apart from other radiotherapy techniques. Additional defining characteristics of SBRT include the abilities to securely immobilize the patient for the typically long treatment sessions; to accurately duplicate patient position between simulation and treatment; to minimize normal tissue exposure through the use of multiple- or large angle, arcing, small-

aperture fields; to rigoursly account for organ motion; to stereoctactically register tumor target and normal tissue structures; and to deliver ablative dose fractions with subcentimeter accuracy to the patient (Timmerman, 2007).

Immobilization and repositioning devices include the Elekta Stereotactic Body Frame™ (Elekta, Norcross, Ga., USA), the Leibinger stereotactic body fixation system (Stryker, Kalamazoo, Mich., USA), and the Medical Intelligence Bodyfix™ system (Medical Intelligence, Schwabmuenchen, Germany).

Several systems provide one or another solution to the problem of respiratory motion. A breath-hold device is the Active Breathing Coordinator™ (Elekta), which allows coordination of beam-on time during a fixed level of inspiration; a respiratory gating system is the RPMTM (Varian, Palo Alto, USA) which tracks inspiration and expiration and turns the accelerator off when indicators predict that the tumor position is outside of an acceptable range of distance from baseline; a another gating system is the ANZAI (Anzai, Japan).

(a) Siemens (CT on Rail) (b) Tomotherapy (c) Elekta

(d) Cyberknife (e) VERO (f) Varian

(g) Novalis

Figure 1. Various system of Stereotactic Body Radiation Therapy (SBRT)

Also now available for purchase are specialized SBRT-ready linear accelerators that combine capacity for image-guided radiotherapy with compatibility with modern immobilization and respiratory motion solution technology. The Novalis™ (BrainLAB, Inc.), Elekta Synergy™, Varian Trilogy™, Siemens Atiste™ System, Tomotherapy HiArt™ System (TomoTherapy, Madison, Wisc., USA), and Cyberknife™ (Accuray, Sunnyvale, Calif., USA) are linear accelerators for SBRT (Fig. 1).

3.2. Radiobiologic aspect of Hypofractionated SBRT

The most prevalent method of radiotherapy in the past 100 years of radiation oncology has been a strategy known as protracted fractionation in which daily small doses of radiation (e.g. 1.8~4 Gy) are delivered repeatedly over many days. The basis of this method of radiotherapy was that normal tissue repairs sublethal injury between fractions better than does tumor tissue. With the advent of SRS to treat intracranial tumors, an alternatively strategy of giving an ablative dose (e.g. 12~30 Gy) was born. A SBRT is an extension of this technique to deliver ablative radiotherapy (8~30 Gy) to extracranial sites. When alternate fractionation schemes are considered, we need some model for calculating isoeffect doses and a linear quadratic (LQ) formalism is most commonly used for quantitative prediction of dose/fractionation dependencies. The LQ model approximates clonogenic survival data with a truncated power series (second order polynomial) expansion of natural log of S (surviving proportion) as follows (see Equation 1).

$$\ln S = -\alpha * d - \beta * d^2 \quad (1)$$

The d is daily dose and α & β are expansion parameters: α is the slope of the survival curve at the limit $d \rightarrow 0$, and β is the parameter determining the relative contribution from the quadratic component (Fig. 2A). This model was initially derived to fit experimental observation of the effects of dose and fractionation on cell survival, chromosomal damage, and acute radiation effects. Later, some ascribed underlying biological mechanism to the mathematical terms, primarily the formation of single- and double-strand break in DNA. The LQ model has been useful for predicting and understanding the effects of conventional fractionated radiotherapy. The biological effective dose (BED) is a characteristic dose value that facilitated comparisons between the effects of different dose fractionation schemes. The BED is defined as the total dose delivered in an infinite number of infinitesimally small dose fractions that has the same biologic effect as the dose fractionation scheme in question and described as $BED=D*[1+d/(\alpha/\beta)]$.

This BED based on LQ model is known reasonably predictive of dose response relation, both in vivo and vitro, in the dose per fractions range of 2 to 15 Gy (Brenner, 2008), however, the LQ model predicts a continuously bending curve in the high dose range and experimentally measured data have decidedly shown a linear relationship between the dose and log of the proportion of surviving clonogen. In addition, in the early phase of its development, one of the developers of the LQ model stated that "LQ is not intended for doses higher than 8-10 Gy. In any case, LQ is simply a loose dose approximation to equation

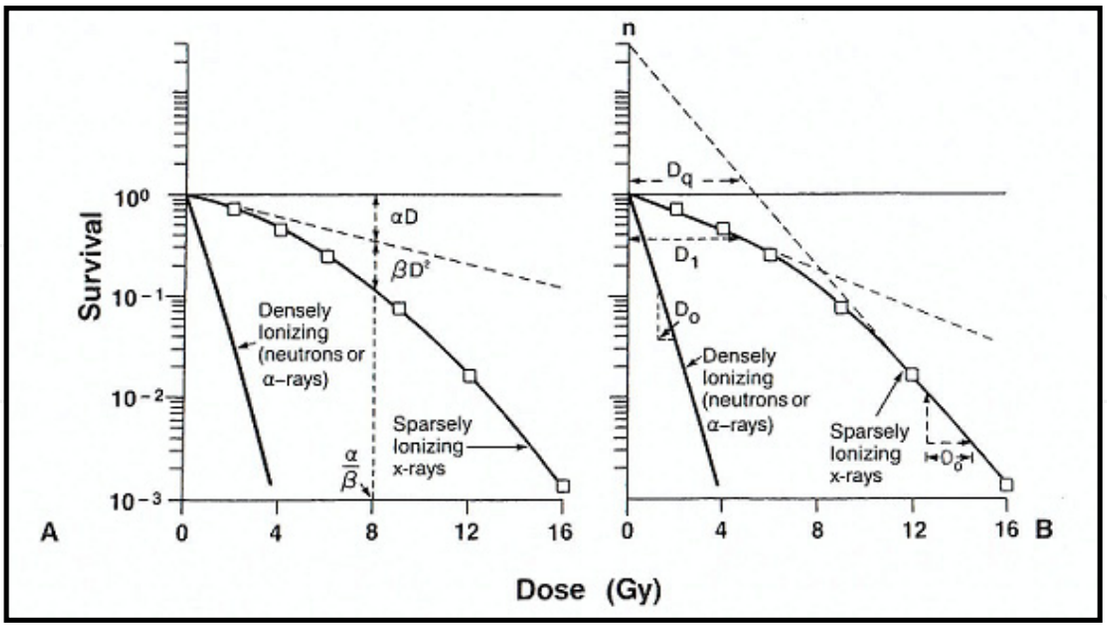

Figure 2. Shape of survival curve for mammalian cells exposed to radiation. The fraction of cells surviving is plotted on a logarithmic scale against on a linear scale. For α-particles or low energy neutrons (said to be densly ionizing), the dose-response curve is a straight line from the origin (i.e., survival is an exponential function of dose). The survival curve can be described by just one parameter, the slope. For X- or γ-rays (said to be sparsely ionizing), the dose-response curve has an initial slope, followed by a shoulder; at higher dose, the curve tends to become straight again. A: The linear quadratic model. The experimental data are fitted to a linear quadratic function. There are two components of cell killing: One is proportional to dose (αD); the other is proportional to the square of the dose (βD^2). The dose at which the linear and quadratic components are equal is the ratio α/β. The linear quadratic curve bends continuously but is a good fit to experimental data for the first few decades of survival. B: The multitarget model. The curve is described by the initial slope (D_1), the final slope (D_0), and a parameter that represents the width of the shoulder, either n or D_q (Hall, 2006).

that do become straight exponential at higher dose" (Hall, 1993). Thus, LQ model overestimates the effect of radiation on clonogenicity in the high dose commonly used in SBRT and inappropriate to apply at the high doses per fraction encountered in radiosurgery because it (1) does not accurately explain the observed (in vivo) data; (2) was derived largely from, in vitro, rather than in vivo, observations and, thus, does not consider the impact of ionizing radiation on the supporting tissues; (3) does not consider the impact of subpopulation of radioresistant clonogens (ie, the "cancer stem cell" response); and (4) creates a "false belief" that this simplified model represent an absolute truth (Kirkpatrick, 2008). Substantial modifications are needed to apply the LQ model to the SBRT regimen; at which point the model loses its simplicity and natural appeal (Guerrero & Li, 2004). The multitarget model (Fig. 2B) provides an alternative description of the clonogenic survival as a function of radiation dose and is still valuable because it fits the empirical data well, especially in the high dose range. In a study of University of Texas, Park et al proposed a new model, universal survival curve (USC), to reconcile the strengths of these LQ model and multitarget model into single, unifying model and stressed that the proposed survival curve model (Fig. 3) (Park, 2008).

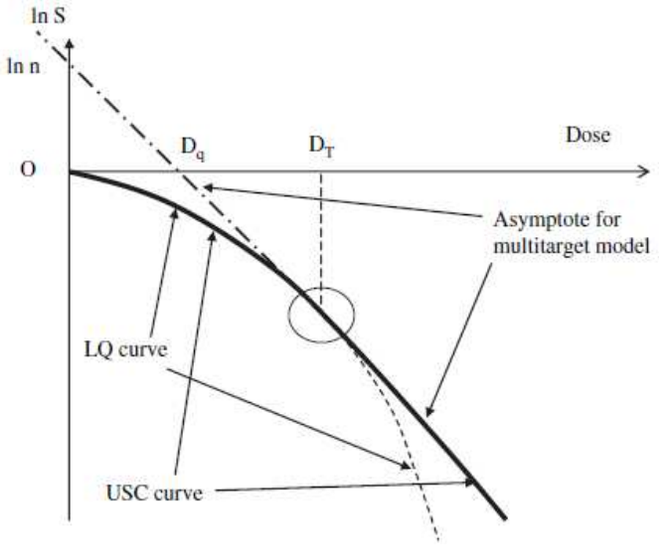

Figure 3. Universal survival curve (USC) and transition between dose range at which linear quadratic (LQ) model is valid and dose range at which multitarget model is valid. Below transition dose D_T, USC curve is identical with LQ model curve and above D_T, USC curve is identical with terminal linear portion of multitarget model curve.

The USC model can be used to derive isoeffective relations (equivalent dose function) of any arbitrarily fractionated RT. For SBRT, a novel concept of the single fraction equivalent dose (SFED) can serve as an alternative and more intuitive way to compare different dose fractionation schemes. SFED was defiend as the dose delivered in a single fraction that would have the same biologic effects as the dose fractionation scheme in question. For total dose D given in n fractions, each fraction with the dose, d, SFED is determined by the intersection line crossing the effective survival curve at D=d*n (Fig. 4) (Park, 2008).

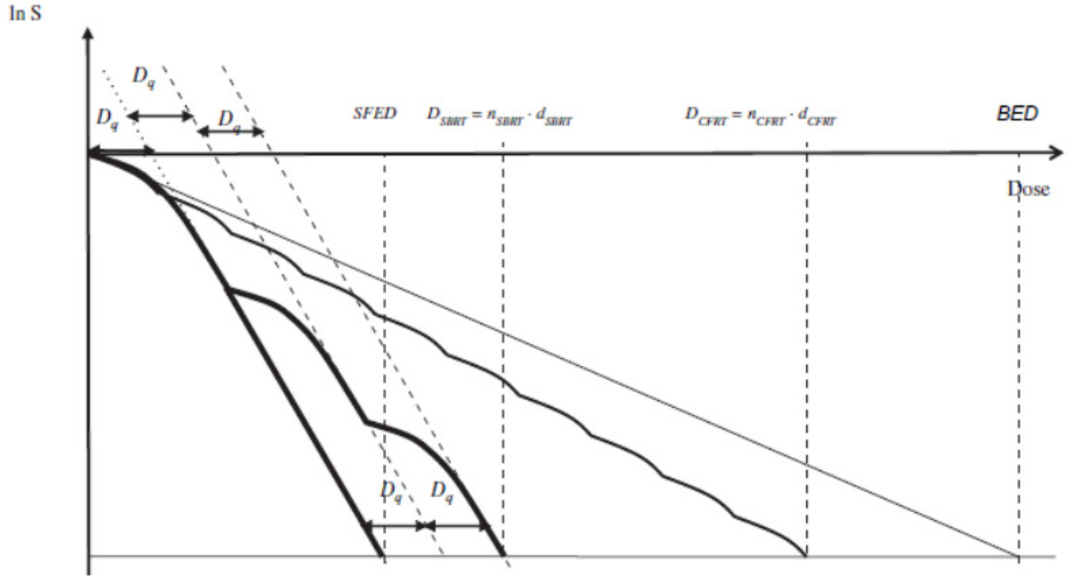

Figure 4. Graphic representation of stereotactic body radiotherapy (SBRT) and conventionally fractionated radiotherapy (CFRT) effective survival curves compared with single fraction equivalent dose (SFED) and biological effective dose (BED). Note, $D_{CFRT}$and D_{SBRT} are always situated between biologically equivalent dose parameters of SFED and BED.

The definition of BED and SFED using the USC curve remain applicable for any fractionation regimen. The ln S in fractionated conventional fractionated radiation therapy (CFRT) and SBRT is calculated (see Equation 2A and 2B).

$$\begin{aligned} \ln S &= -n*\left(\alpha*d+\beta*d^2\right) \text{ if } d \le D_T \quad \text{(A)} \\ &= -n*\left(1/D_0*d - D_q/D_0\right) \text{ if } d \ge D_T \quad \text{(B)} \end{aligned} \tag{2}$$

Thus, Equations. 2A and 2B are arranged to reflect the common clinical practice in designing dose fraction scheme in which d_{CFRT} and n_{CFRT} is varied for CFRT, and n_{SBRT} is fixed and d_{SBRT} is varied for SBRT. By letting d_{CFRT}=2 Gy, the equation for D_{CFRT} can be used to calculated the standard effective dose (SED), total dose in 2 Gy fractions with equivalent effect (see Equation 3A and 3B).

$$\begin{aligned} D_{SBRT} &= \alpha*D_0*D_{CFRT}*\left[1+d_{CFRT}/\left(\alpha/\beta\right)\right]+n_{SBRT}*D_q \quad \text{(A)} \\ D_{CFRT} &= 1/\alpha*D_0\left\{\left[D_{SBRT}-\left(n_{SBRT}*D_q\right)\right]/\left[1+d_{CFRT}/\left(\alpha/\beta\right)\right]\right\} \quad \text{(B)} \end{aligned} \tag{3}$$

From the report of 12 non small cell lung cancer cell lines from National Cancer Institute, the value for α, D_0 or D_q was obtained by determining the arithmetic mean values of each parameter. The range of D_q was wide, between 1.5 Gy and 2.5 Gy. The mean value for α, D_0, and D_q was 0.33 Gy^{-1}, 1.25 Gy and 1.8 Gy, respectively (Carmichael, 1989; Morstyn, 1984). The transition dose, D_T was calculated to be 6.2 Gy, reassuring results, because the dose per fraction used in CFRT is < 6.2 Gy and SBRT regimens commonly use a dose per fraction > 6.2 Gy. This USC is a new model that may offer a superior description of the mammalian cell survival curve in the ablative dose range beyond the shoulder, on the same time, preserving all the strengths of the LQ model in the low dose range (around the shoulder). However, the true survival of in vivo tumors depends on multiple factors that cannot possibly be contained in simplified mathematical formulas. The only way to truly know the tumor control rates or the tolerance of different fractionation schemes is through performing prospectively designed trial.

3.3. Variable imaging technique to guarantee high accuracy radiotherapy

In delivering SBRT, many commercially available units can be utilized. Sophisticated image guidance is a common feature to these treatment units. Units equipped with online image-guided radiation therapy (IGRT) capability minimize the uncertainty associated with tumor localization. In-house developed systems such as RT-RT and CT-on-rails were employed prior to the widespread availability of in-treatment-room imaging. Recent developments have spread the availability of in-treatment-room imaging to many facilities.

3.3.1. Cone beam CT Linear accelerator IGRT

The first commercially available cone beam CT (CBCT) IGRT system was the Elekta Synergy™ (Elekta, Crawley, UK), the other medical linear accelerator (linac) manufacturers

have also now embraced the IGRT concept and have either produced their own version of an IGRT linac, Varian Trilogy™ (Varian Medical Systems, Palo Alto, Calif., USA), or are in the process of such developments, Siemens ARTÍSTE™ (Siemens Medical Solutions USA, Inc., Malvern, Pa.,USA). The Synergy and Trilogy consists of a retractable kV X-ray source, an amorphous silicon flat panel imager mounted on the linear accelerator perpendicular to the radiation beam direction, and a software module (referred to as the XVI system). The system provides planar, motion, and volumetric images.

For CBCT image acquisitions, the gantry is rotated around the patient for a preset angle (between 180° and 360° to allow sufficient data acquisition) and images are acquired via an amorphous silicon panel. Volumetric image reconstruction is performed simultaneously with the acquisition to expedite the process. The reconstructed three-dimensional geometry is subsequently registered with the reference geometry planning image, either manually or automatically (using either soft tissue or bone mode). For some disease sites, such as prostate cancer, the soft tissue mode is conceptually ideally suited, since the prostate often moves relative to the bones. However, at present, it is difficult to visualize the prostate in all cases, and thus implanted radiopaque seeds are used to make the registration process more efficient. Based on the registration, the difference between the data sets is calculated and displayed as translation along and rotation about the three axes. Subsequent treatment table adjustments are made and the patient treated. One can clearly appreciate that CBCT-based IGRT shows great potential for objective, precise positioning of patients for treatment, matching the treatment setup image model to that of the planning image model. It remains to be determined exactly which imaging features on the integrated CBCT linacs (i.e., kVp CBCT, planar, motion, and MV electronic portal imaging device) are best suited for a particular disease site.

3.3.2. Helical tomotherapy IGRT

Helical tomotherapy was first proposed by Mackie et al. in 1993 and is now commercially available as the TomoTherapy HI -ART system (TomoTherapy, Inc., Madison, Wisc., USA). A short in-line 6-MV linac (Siemens Oncology Systems, Concord, Calif., USA) rotates on a ring gantry at a source-axis distance of 85 cm. The IMRT treatment is delivered while the patient support couch is translated in the y-direction (toward the gantry) through the gantry bore, in the same way as a helical CT study is conducted. In the patíent's reference frame, the treatment beam is angled inwards along a helix with the midpoint of fan beam passing through the center of the bore. Similar to helical CT, the treatment beam pitch is defined as the distance traveled by the couch per gantry rotation, divided by the field width in the y-direction. The width of the beam in the y-direction is defined by a pair of jaws that is fixed, for any particular patient treatment, to one of three selectable values (1, 2.5 or 5 cm). Laterally, the treatment beam is modulated by a 64 leaf binary multileaf collimator, whose leaves transition rapidly between open and closed states providing a maximum possible open lateral field length of 40 cm at the bore center. Highly modulated treatments can achieve great conformality, though they inevitably take longer to deliver. A helical MV CT image is acquired prior to treatment each day using the on-board xenon CT detector system

and the 6-MV linac (detuned to 3.6 MV). Registration software is provided to compare the daily patient setup image with the stored prescription CT planning image. After image registration, table adjustments are then automatically made and the patient is then treated.

3.3.3. Megavoltage Cone Beam CT Linear Accelerator IGRT

The only MV Cone Beam CT (CBCT) system currently available is the most recent addition to the family of in-room 3D systems designed for IGRT. The MV CBCT imaging system consists of a 6-MV x-ray beam produced by a conventional linear accelerator (Oncor, Siemens AG, Erlangen, Germany) equipped with an amorphous-silicon EPID (AG9-ES, PerkinElmer Optoelectronics, Waltham, MA., USA) flat panel detector. The system is controlled by a computer workstation (Syngo Coherence RTT, Siemens AG, Erlangen, Germany) that is responsible for all tasks related to portal or MV CBCT imaging, including calibration of the system, quality assurance, image acquisition, and image registration (2D or 3D) for patient alignment. The use of MV photons for imaging is a departure from conventional preferences of using kilovoltage (kV) photons, which have resulted in superior image quality for diagnostic purposes. The MV CBCT system is capable of measuring setup errors of fiducials in an anthropomorphic head phantom with submillimeter accuracy and reproducibility. The gantry rotates in a continuous 200° arc (270° to 110°) while acquiring one low-dose portal image per degree. The 200 projection images acquired are then used for MV CBCT reconstruction, which is completed approximately 2 minutes after the starts with an automatic registration, based on a maximization of mutual information algorithm, which utilizes all information in both 3D images to maximize the alignment of similar structures.

Routine quality assurance on the system has also demonstrated that the calibrated MV CBCT imaging isocenter remained within 1 mm to the machine treatment isocenter over a period of 1 year. As for the field-of-view, anatomical information situated in a 27 X 27 X 27 cm^3 volume centered at isocenter is reconstructed in the MV CBCT system with a half-beam acquisition mode should increase the reconstruction size in the axial plane by up to 40 cm.

3.3.4. Vero IGRT

Vero SBRT is specifically designed for IGRT and a new type of 6 MV linac with attached MLC is mounted on an O-ring gantry. The MLC consists of sixty 5-mm-leaves and produces a maximum field size of 150 x 150 mm^2. The gantry rotates 360 degree and the horizontal axis, similar to a C-arm linac platform, but additionally allows rotation about the vertical axis. The system incorporates the MHI-TM2000 linear accelerator and sophisticated software to deliver radiation therapy. The system is equipped with a dual orthogonal kV imaging systems attached to the O-ring at 45 from the MV beam. This imaging system allows simultaneous acquisition of orthogonal X-rays images and fluoroscopy. Also kV CBCT imaging is available. Vero SBRT dynamically contours the treatment beam exactly to the tumor from every angle as the machine moves around the patient. Furthermore, Vero's technology allows clinicians to dynamically treat with a moving beam in order to spare surrounding healthy tissue and organs while maximizing such as x-ray, CT and

fluoroscopy, so that clinicians can modify their plans during treatment as needed. The targeted beam adapts to breathing and other body movements to maintain safe, complete and accurate dose delivery.

3.3.5. Electromagnetic tracking

One of the earliest applications of electromagnetic tracking in RT was for the nonradiographic localication of interstitial abdominal implants for intraoperative high-dose-rate (HDR). In this application a then-commercially available 3SPACE-FASTRAK system (Polhemus Inc, Colchester, VT., USA) was configured to fit in the lumen of a catheter. The system was then used to measure the spatial path of all catheters by inserting the wired sensor sequentially into each catheter. This information was then used by the planning system to accurately determine and calculate dwell positions and times. The stated accuracy of the system was a root mean square (RMS) of 0.8 mm, but measurements in the operating environment found the RMS accuracy to be 0.38 mm in the absence of metallic surgical retractors and 0.70 mm in the presence of three retractors, with maximum absolute errors of 2.1 mm or less.

In 2000, the Paul Scherrer Institute reported on an electromagnetic tracking system they had developed for real-time (50 Hz) target volume tracking during proton therapy with continuous spot scanning delivery. This system consisted of an external magnetic field generator, a wired implantable sensor, and the associated signal processing electronics. When compared with an optical tracking device with 30 μm accuracy, the RMS spatial accuracy was reported to be 1 mm to 2 mm, whereas the RMS angular accuracy of determining the orientation of the dipole was 0.5 to 1 degree. The system's ability to track and gate was tested in a moving phantom and qualitatively shown to very nearly restore the dose distribution to the planned static distribution when a 3-mm gating window was implemented. The technology for this system was developed by a spin-off company from the Paul Scherrer Institute called Mednetix AG, which was acquired by Northern Digital Inc (Waterloo, ON, Canada). Further development efforts have focused on a wired electromagnetic tracking system for guidance of medical instruments, which is commercially available in the Aurora system.

3.3.6. Cyberknife IGRT

The use of a small X-band linear accelerator mounted on an industrial robot was first developed for radiosurgery. The robot provides the capability of aiming beamlets with any orientation relative to the target volume. The system uses two ceiling-mounted diagnostic X-ray sources, and amorphous silicon image detectors mounted flush to the floor. The treatment is specified by the trajectory of the robot and by the number of monitor units delivered at each robotic orientation. During the patient's treatment, the Cyberknife System correlates live radiographic images with preoperative CT or MRI scans in real time to determine patient and tumor position repeatedly over the course of treatment. More details are provided by users of this system in subsequent articles in this volume.

3.4. Compensation of respiratory motion of the tumor and internal organ

SBRT requires precise delineation of patient anatomy, targets for planning, and clear visualization for localization during treatment delivery. Three-dimensional data sets assembled from CT or 4DCT for visualizations and dose calculation and/or MRI and positron emission tomography (PET) images assist in target and visualization for SBRT.

3.4.1. Four-Dimensional CT scanning

Respiratory correlated 4DCT was developed over the past several years to address the issues of respiratory motion in radiotherapy targeting (Rietzel, 2005). Respiration-correlated CT uses a surrogate signal, such as the abdominal surface, respiratory air flow, or internal anatomy to provide a signal that permits resorting of the reconstructed image data, resulting in multiple coherent spatiotemporal data sets at different respiratory phases. The scan time for 4DCT with multi-slice scanners is on the order of a few minutes, and post-processing takes an additional 30 min if manual phase selection is required. The output of this process is typically 10 CT volumes, each with a temporal resolution of approx. 1/10 of the respiratory period. 4DCT uses multi-slice CT scanners combined with a respiratory surrogate to develop a series of 3DCT scans each representing the patient in a different respiratory phase. The entire 4DCT dataset can be used to determine an envelope of tumor motion which can be expanded to include areas of subclinical disease resulting in an internal target volume (ITV) (ICRU 1999) which can be used as the treatment target. Alternatively, select phases from the 4DCT can be used to determine an ITV that only covers a select range of respiratory phases (i.e. 40%-60% corresponding to a ± 10% window around end exhalation) that would be the target for gated treatments. The most common form of motion management used in RTOG studies to date and also at many experienced centers using SBRT across the world has been chest wall breathing with abdominal compression. Chest wall breathing exerts forces on the intrathoracic tissues in multiple opposing directions in contrast to the mostly craniocaudal force vectors associated with diaphragmatic breathing. As a result, the amplitude of tumor motion with chest wall breathing can be significantly decreased. With this technique, the patient is first coached to expand the lungs using their upper chest wall rather than by moving their diaphragm toward their abdomen.

The 4DCT implementation relies on sensing the respiratory phase by using the Varian RPM system or Anzai system. 4DCT provides an imaging tool to quantify and characterize tumor and normal tissue shape and motion as a function of time. This provides the radiation oncologist and treatment planner with information essential in the design of an aperture that more adequately covers the internal target volume (assuming respiration during treatment is reproducible to that during CT simulation). 4DCT data can also be used as input in making treatment decisions on when to intervene with gating or other motion management strategies. In addition, the 4DCT data can be used as direct input into four-dimensional treatment planning, and to generate time-varying dose-volume histograms or

isodose distributions. An effective method of conveying the utility of 4DCT is through computer animation. Dr. Choi et al. [pers. commun., 2005] have found that approximately one half of patients with early-stage disease have motion of less than 10 mm during quiet breathing (in approx. 100 cases). Seppen woolde et al. reported on the motion of 21 lesions in 20 patients and found a mean motion of 5.5 mm in the craniocaudal direction (data ranged from 0 to 2.5 cm). Average periodicity was observed to be 3.5 s, and ranged from 2.8 to over 6 s. The clinical importance of 4DCT is that it provides insight into patient-specific organ motion.

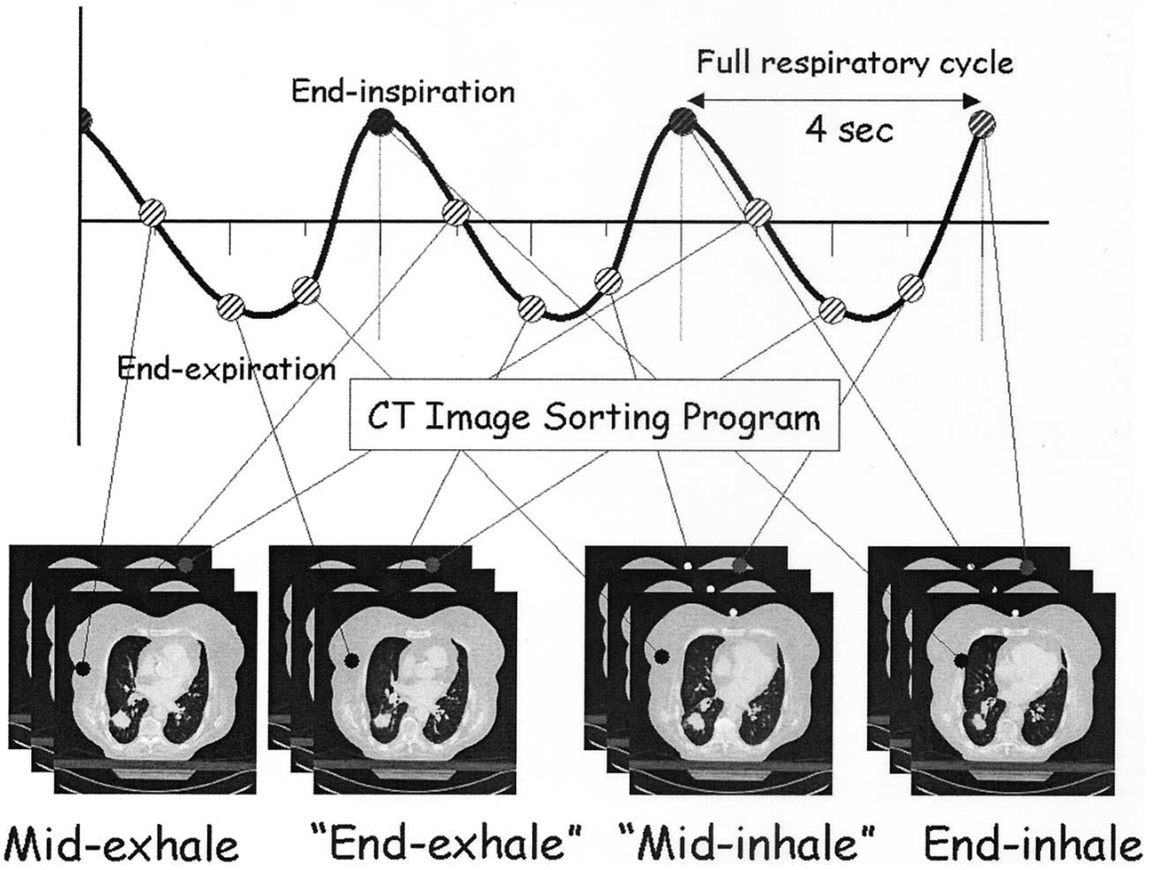

Figure 5. Overview of respiratory phase "bin" generation from four-dimensional computed tomography data.

3.4.2. Image registration & Motion management

SBRT treatments do not use invasive external frames. A body frame system has been developed that incorporates several features to ensure reproducible setup, including a vacuum bag that is fit to the patient at the time of simulation, a scale that facilitates reproducible positioning of the patient in the frame, an abdominal compression paddle to restrict abdominal motion, and external fiducial markers to improve setup accuracy (Lohr, 1999; Hadinger, 2002). This system is particularly useful when the patient is to be imaged in one room and the entire patient/body frame system is moved to the treatment room. Without a body frame, either implanted fiducial markers or in-room volumetric imaging is required for accurate internal soft tissue-based setup.

One technique for minimizing the effects of respiratory motion is to activate the radiation beam only when the tumor is at a predetermined location in the respiratory cycle. This is referred to as respiratory gating (Shirato, 2000; Starkschall, 2004; Nelson, 2005; Underberg, 2005). The use of gating requires some measure of the tumor location within the respiratory cycle, which can be done directly but is more often done through some respiratory surrogate such as abdominal height or diameter. Spirometry has also been used to gate based on tidal volume (Zhang, 2003).

Alternative motion management techniques include dynamic gating and breath-hold techniques. During dynamic gating the patient is allowed to breath normally with or without audio or visual coaching and the radiation beam is activated only when the patient reaches the planned points in their respiratory cycle. Breath-hold gating requires the patient to hold their breath at a given abdominal height or tidal volume generally with the aid of visual feedback and the radiation beam is activated only when the patient is holding their breath in this target position. The breath-hold can either be voluntary or assisted with an occlusion valve. Breath-hold has several benefits over dynamic gating including the ability to do volumetric imaging over a series of breath holds, longer irradiation times to allow radiotherapy beams to stabilize, and the ability to expand the lungs and give more fall-off distance between the target and nearby critical structures.

Gating is performed with real time or near time verification of the target position in the gate with in-treatment-room imaging. An early example of in-treatment-room imaging was developed by Shirato et al. (Shirato, 1999) who developed a real-time tumor tracking method in which four sets of x-ray tubes and fluoroscopic imagers are used to measure the position of four implanted radiopaque markers relative to the isocenter. The linear accelerator was configured so that it irradiated the tumor only when the markers were within certain coordinates. This system is effective for the treatment of lung tumors but requires the invasive implantation of fiducial markers. In addition this system has not become commercially available. A similar method is used by two commercially available stereotactic systems, Novalis®/Exactrac® (BrainLAB, Feldkirchen, Germany) (Yin, 2002) and Cyberknife® (Accuray, Sunnyvale, CA) (Adler, 1997). These systems both have room mounted orthogonal x-ray systems that can observe the patient's anatomy in the treatment

position. Implanted fiducial markers are required for all lung tumors on the Novalis® system but the Cyberknife® can use either fiducial markers or direct imaging depending on the tumor location. The Novalis® system does not employ real-time tumor tracking but rather relies on a relationship between external surrogates and the tumor position developed immediately prior to treatment. Cyberknife® can either confirm the position of the target at regular intervals during treatment or utilize a respiratory tracking system that continuously synchronizes beam delivery to the motion of the target.

Non-radiographic localization was investigated by Balter et al. (Balter, 2005) who studied the use of the Calypso™ 4D system for patient positioning based on real-time localization of implanted electromagnetic transponders (beacons). This study demonstrated the accuracy of the system before clinical trials were conducted. The system consists of 5 major components: wireless transponders, a console, a detector array, a tracking station and infrared cameras. The array emits electromagnetic radiation that excites the implanted transponders. Due to the resonance response the array can locate the 3D coordinates of the wireless transponders. The infrared cameras allow the registration of the position of the array relative to the isocenter of the linear accelerator. This system offers the potential for real-time tracking and is commercially available for prostate but not yet for other body sites including the lungs.

3.5. Quality Assurance of SBRT

An important goal of a quality assurance (QA) program is to instill confidence that patients are receiving their prescribed treatments accurately. The goal should not be simply getting through some mandatory tests as quickly and painlessly as possible. Unfortunately, many catastrophic events are produced by failures happening at a moment that cannot be predicted or caught by routine quality control (QC) procedures. As there are built-in interlocks in treatment devices, most failures occur in human processes rather than in equipment. Finding the proper balance between effort spent on specific QC procedures and effort spent on an overall quality management program is major challenge at most institutions.

The QA program for an SBRT process based on IGRT system must evaluate the entire treatment process, including patient immobilization, setup, simulation imaging, treatment planning (including the production of reference images to guide corrections), verification imaging, image registration, patient position correction, and treatment. Tests that assess the entire process from beginning to end inspire confidence that the overall process is accurate and robust. In such as study, planning images of a phantom are acquired and transferred to the treatment planning system. A treatment plan is designed and reference images are produced. The phantom is then taken to the treatment unit and positioned for treatment. A verification images is acquired and registered to the reference image. Any necessary corrections to the position are made. Treatment is then delivered and measured by using an ion chamber and/or film. The dosimeter readings are compared with the expected values from the treatment plan. The frequency of such tests should be based upon an analysis of

system stability during the initial operation of the SBRT system. Also, the image-guidance procedures should be reviewed on a regular basis to ensure that the procedures are consistent with the initial design and to initiate appropriate changes if necessary. The review results and any new changes must be communicated among staff. The review of the guidance elements of a patient's treatment can be integrated into the institutional chart rounds and quality control programs to verify that the image guidance procedure is operating correctly.

Conventional linear accelerator-based IGRT consists of imaging in the treatment room during a course of radiotherapy. Planar (two-dimensional [2D]) and volumetric (three-dimensional [3D]) imaging are used for repositioning the patient immediately prior to treatment. The common elements of a QA program include: (1) safety and functionality, (2) geometric accuracy (agreement of MV and kV beam isocenters), (3) image quality, (4) registration and correction accuracy, and (5) dose to patient and doseimetric stability.

Helical Tomotherapy requires synchrony of gantry rotation, couch translation, linear accelerator pulsing, and opening and closing of the binary MLC leaves used to modulate the radiation beam. The accuracy of this highly dynamic treatment process depends on the correct performance of the radiation source, MLC, gantry, and couch table. The dose delivered to the patient depends on the static beam dosimetry, system geometry, system dynamics, and system synchrony. Systematic QA of the system dynamics and synchrony has been suggested, which includes jaw width constancy, actual fraction of time leaves are open, couch drive distance, speed and uniformity, linear accelerator pulsing and gantry synchrony, leaf opening and gantry synchrony, and couch drive and gantry synchrony.

Quality assurance programs for IGRT are not easy to implement. Rapid development of new IGRT techniques and devices is quickly making traditional QA guidelines outdated. Because of the diversity of IGRT, it is extremely difficult to develop industry-wide specific QA guidelines, forcing a conversion to process-centered quality management guidelines, which each institution can tailor to its individual needs. An optimal QA program is always a balance between available resources, manpower, and time to perform the work.

Patient-specific QA procedures for SRS/SBRT should be developed as an integrated part of a comprehensive ongoing QA program in the clinic. Therefore, before implementing an SBRT program, the clinic first needs to determine which system(s) will be used and develop QA procedures to match. SBRT-enabled systems often have specialized equipment such as immobilization systems, localization systems, and on-board imaging systems which are not always found in the clinic. In other cases, the entire system is specialized for SBRT (e.g. the Accuray Cyberknife). For example, Table 1 summarizes the stereotactic localization and image guidance strategies used by commercially-available systems. These specialized components require detailed and specialized QA procedures, over and beyond the general guidelines for external beam radiotherapy as specified in the AAPM Reports of TG 40, 142, and 45.

Author	Site	Immobilization/repositioning	Reported accuracy
Lax, 1994	Abdomen	Wood frame/stereotactic coordinates on box to skin marks	3.7 mm Lat. 5.7 mm Long
Hamilion, 1995	Spine	Screw fixation of spinous processes to box	2 mm
Murphy, 1997	Spine	Frameless/implanted fiducial markers with real-time imaging and tracking	1.6 mm radial
Lohr, 1999	Spine	Body cast with stereotactic coordinate	≤ 3.6 mm mean vector
Yenice, 2003	Spine	Custom stereotactic frame and in-room CT guidance	1.5 mm system accuracy, 2-3 mm positioning accuracy
Chang, 2004	Spine	MI™ BodyFix with stereotactic frame/linac/CT on rails with 6D robotic couch	1 mm system accuracy
Tokuuye, 1997	Liver	Prone position jaw and arm straps	5 mm
Nakagawa, 2000	Thoracic	MVCT on linac	Not reported
Wulf, 2000	Lung, liver	Elekta™ body frame	3.3 mm Lat. 4.4 mm long
Fuss, 2004	Lung, liver	MI™ Body Fix	Bony anatomy translation 0.4, 0.1, 1.6 mm (mean X, Y, Z); tumor translation before image guidance 2.9, 2.5, 3.2 mm (mean X, Y, Z)
Herfarth 2001	Liver	Leiginger body frame	1.8 – 4.4 mm
Nagata, 2002	Lung	Elekta™ body frame	2 mm
Fukumoto, 2002	Lung	Elekta™ body frame	Not reported
Hara, 2002	Lung	Custom bed transferred to treatment unit after confirmatory scan	2 mm
Hof, 2003	Lung	Leibinger body frame	1.8 – 4 mm
Timmerman, 2003	Lung	Elekta™ body frame	Approx. 5 mm
Wang, 2006	Lung	Medical Intelligence body frame stereotactic coordinates/CT on rails	0.3±1.8 mm AP. -1.8±3.2 mm Lat. 1.5±3.7 mm SI

Table 1. Achievable accuracies reported in the literature categorized by body site and immobilization/repositioning device.(AAPM TG101)

Source	Purpose	Proposed test	Reported achievable	Proposed frequency
Ryu et al., 2001	End-to-end localization accuracy	Stereo x ray/DRR fusion	1.0 to 1.2 mm root mean square	Initial commissioning and annually thereafter
Ryu et al., 2001	Intrafraction targeting variability	Stereo x ray/DRR fusion	0.2 mm average, 1.5 mm maximum	Daily (during treatment)
Verellen et al., 2003	End-to-end localization accuracy	Hidden target (using stereo x ray/DRR fusion)	0.41 ± 0.92 mm	Initial commissioning and annually thereafter
Verellen et al., 2003	End-to-end localization accuracy	Hidden target (using implanted fiducials)	0.28 ± 0.36 mm	Initial commissioning and annually thereafter
Yu et al., 2004	End-to-end localization accuracy	Dosimetric assessment of hidden target (using implanted fiducials)	0.68 ± 0.29 mm	Initial commissioning and annually thereafter
Sharpe et al., 2006	CBCT mechanical stability	Constancy comparison to MV imaging isocenter (using hidden targets)	0.50 ± 0.5 mm	Baseline at commissioning and monthly thereafter
Galvin et al., 2008	Overall positioning accuracy, including image registration (frame-based systems)	Wiston-Lutz test modified to make use of the in-room imaging system	≤ 2 mm for multiple couch angles	Initial commissioning and monthly thereafter
Palta et al., 2008	MLC accuracy	Light field, radiographic film or EPID	< 0.5 mm (especially for IMRT delivery)	Annually
Solberg et al., 2008	End-to-end localization accuracy	Hidden target in anthropomorphic phantom	1.0 ± 0.42 mm	Initial commissioning and annually thereafter
Jiang et al., 2008	Respiratory motion tracking and gating in 4D CT	Phantoms with cyclical motion	N/A	N/A
Bissonnette et al., 2008	CBCT geometric accuracy	Portal image vs CBCT image isocenter coincidence	2 mm	daily

Table 2. Summary of published QA recommendations for SBRT and SBRT-related techniques. .(AAPM TG101)

4. Clinical aspect

4.1. Proper selection of patients

The most important goal of SBRT in oligometastases is to achieve local control, however, whether obtaining local control of the metastasis would translate into clinical or survival benefit of the patients is dependent on multiple factors, including age, performance status, medical comorbidities and histology of malignancies. Therefore, the patients' whole condition should be fully considered. In general, patients with younger age, high performance status, controlled primary sites, limited number of metastases from three to five or fewer, metachronous occurrence of primary disease and metastatic disease, histologies, such as colorectal carcinoma, breast cancer and radioresistant cancer including renal cell ca, melanoma and sarcoma, are most likely to benefit from SBRT of their oligometastases (Carey-Sampson et al, 2006). In addition, SBRT delivers the individual ablative radiation doses to a planning target volume with a steep dose gradient outside the lesion treated and it is crucial that the lesions to be treated must be easily delineated on diagnostic imaging.

4.2. Lung metastases

	type	No of pts /targets	Dose(Gy/fx)	FU (mo)	LC (%)	Survival
Blomgren et al, 1995a	retrospective	10/14	7.7-45Gy/1-4fx	8	92	Med.S 11.3mo
Uematsu et al, 1995b	retrospective	22/43	33-71Gy/5-15fx	9	98	
Nakagawa et al, 2000	retrospective	14/21	16-24Gy/1fx	10	95	2YOS 35%
Wulf et al, 2001	retrospective	41/51	30-37.5 Gy/3fx ; 26 Gy/1fx	14	80%	2YOS 33%
Hara et al, 2002	retrospective	14/18	20-30Gy/1fx	12	78	
Lee et al, 2003	retrospective	19/25	30-40 Gy/3-4fx	18	88	Med.LPFS 18mo
Hof et al, 2007	retrospective	61/71	12-30 Gy/1fx	14	88.6 (1YR)	3YOS 47.8%
Okunieff et al, 2006	retrospective	42/125	50 Gy/10fx	18.7	94	Med.S 23.4mo
Norihisa et al, 2008	retrospective	34/43	48-60 Gy/4-5fx	27	90	2YOS 84.3%
Kim et al, 2009	retrospective	31/134	50 Gy/10fx	16	87.1	Med.S 16mo
Ernst-Stecken et al, 2006	prospective	21/39	35-40 Gy/5fx	NA	CR:51 PR:33 SD:3	Med.LPFS 6.4mo
Rusthoven et al, 2009	prospective	38/63	48-60 Gy/3fx	15.4	96	Med.S 19mo

Table 3. Results of SBRT in lung metastases

There are numerous retrospective studies on the use of SBRT for the treatment of lung oligometastases from North America, Europe and East Asia (Table 3). Early results from Blomgren's and Uematsu's studies showed excellent local control rates of 92% and 98%, respectively although the follow up periods were short (Blomgren et al, 1995; Uematsu et al, 1995). Subsequently, Nakagawa treated 14 patients with 21 tumors with SBRT to a single dose of 16 to 24 Gy. The local control rate and 2 year overall survival rate were 95% and 35%, respectively (Nakagawa et al, 2000). In a report of Wulf et al, the 41 patients with 51 metastatic lung tumors were treated with SBRT of 30 to 37.5 Gy in 3 fractions or 26 Gy of a single dose. The crude local control rate was 80% at a median follow up 14 months and 2 years overall survival rate was 33% (Wulf et al, 2001). And Hof et al also treated 61 patients with 71 lung metastases with SBRT to a single dose of 12 Gy to 30 Gy. The actuarial local progression free rate was 79% at 1 year and overall survival rate was 47.8% on 3 years (Hof et al, 2007). In a report of Okunieff et al, they treated 50 patients with five or fewer lung metastases with SBRT. At a median follow up of 18.7 months, 94% local control rate and 50% of 2 years overall survival rate were yielded (Okunieff et al, 2006). Kim et al also treated the patients with multiple lung metastases with SBRT to a dose of 50 Gy in 10 fractions during 2 weeks. The local control rate was 87.1% and median survival time was 16.0 months (Kim et al, 2009). Two prospective studies' outcomes were also shown in table 3. In a report from Germany, Ernst-Stecken et al reported the results of dose escalating phase I/II trial of SBRT for lung tumors, Overall, 21 patients (three with primary lung tumors) with 39 tumors were treated with SBRT starting at dose level of 35 Gy (7 Gy x 5) and the dose was then escalated to 40 Gy (8 Gy x 5). In total, 21 and 18 tumors were treated to 35 Gy and 40 Gy, respectively. Rates of complete response, partial response, stable disease and progressive disease were 51%, 33%, 3% and 13%, respectively (Ernst-Stecken et al, 2006). In 2009, in a multi-institutional phase I/II trial of SBRT for patients with 1 to 3 lung metastatic tumors less than 7 cm diameter, the total radiation dose was safely escalated from 48 Gy to 60 Gy in 3 fractions. The 2 year actuarial local control rate was 96% and median survival time was 19 months (Rusthoven et al, 2009).

4.3. Liver metastases

	type	No of pts /targets	Dose(Gy/fx)	FU (mo)	LC(%)	Survival
Blomgren et al, 1998	retrospective	17/21	20-40 Gy/1-2fx	9.6	95	
Katz et al, 2007	retrospective	69/174	30-55Gy/2-6fx	14.5	76-57	Med.S 14.5mo
Wulf et al, 2001	retrospective	23/23	28-30Gy/2-4fx	9	76-61	
Herfarth et al, 2001	prospective	33/56	14-26Gy/1fx	18	67	1YSR 72%
Kanavagh et al, 2006	prospective	21/28	36-60Gy/3fx	18	93	
Mendez-Romero et al, 2006	prospective	17/34	37.5Gy/3fx	12.9	100-86	

Table 4. Results of SBRT in liver metastases

Blomgren's early data on SBRT for liver metastases showed promising results of 95% local control rate on 9.6 months follow up (Blomgren et al, 1998). In the study of University of Rochester, which represents the largest study in SBRT for liver metastases, Katz et al treated 69 patients with 174 liver metastases with SBRT to a median dose of 48 Gy(range, 30-55Gy) in 2 to 6 fractions. The mean number of lesions was 2.5 (range, 1-6). The most common primary sites were colorectal (n=20) and breast (n=16). The median follow up was 14.5 months. The local control rates were 76% and 57% at 10 and 20 months, respectively. The median overall survival time was 14.5 months (Katz et al, 2007). Wulf et al reported their experience on 23 patients treated with SBRT for liver metastases. The prescribed dose was 30 Gy in three fractions. The actuarial local control rates on one and two year after treatment were 76 and 61%, respectively (Wulf et al, 2001). Herfarth et al performed a dose escalation study utilizing single dose SBRT from 14 Gy to 26 Gy. Fifty six liver metastases of 33 patients were treated and their local control rate was 67% on 18 months after treatment. Local failures were observed mainly in patients treated to a lower dose. For patients treated to higher dose (>20 Gy), the actuarial local control rate was 81% (Herfarth et al, 2001). In a study of Colorado University, Kavanagh et al reported 93% of actuarial local control rate on 18 months and indicated that a very high rate of durable in-filed tumor control can be safely achieved with SBRT to one to three liver lesions to a prescription dose of 60 Gy in 3 fractions (Kanavagh et al, 2006). Mendez-Romero et al reported the results of 17 patients with 34 metastatic liver tumors treated in phase I/II study of SBRT. The prescribed dose was 37.5 Gy in 3 fractions. The actuarial one and two year local control rates were 100% and 86%, respectively and the actuarial overall survival rate at one and two years were 85% and 62%, respectively (Mendez-Romero et al, 2006).

4.4. Spine metastases

SBRT has emerged as a novel treatment modality in the multidisciplinary management of spinal metastasis. Compared with conventional radiotherapy, SBRT can deliver a much higher biologic equivalent dose to the spinal tumor while respecting the dose constraints of the spinal cord or cauda equine, which are usually the dose limiting structures. The inclusion criteria for spinal SBRT are solitary or oligometastatic disease or bone only disease in otherwise high performance status patients, maximum of two consecutive or non contiguous spinal segments involved by tumor, failure of prior XRT (upto one course and 45 Gy maximum) or surgery, non myeloma tumor type, gross residual disease or deemed to high risk for recurrence postsurgery, patients refusal or medical comorbidities precluding surgery, gross tumor optimally more than 5 mm from the spinal cord, Karnofsky performance status > 40-50, MRI- or CT documented spinal tumor, histologic confirmation of neoplastic disease and Age > 18. These are yielded from reports by various authors for spine SBRT. And these criteria are based on relevant studies, which include those reporting both the dose/fractionation used and duration of follow up for patients treated for metastatic spinal tumors. However, the final treatment recommendation should involve ideally a multidisciplinary tumor board composed of surgeons, radiation oncologists, medical oncologists, and medical physicists.

	Number of Tumor/pts	Target volume/image	Dose/fx	Re-RTx	FU (mo)	LC/criteria
Ryu et al, 2004	61/49	Involved spinal segment/CT or MR	10-16 Gy/1fx	ERT 25 Gy/10 plus SBRS boost 6-8 Gy/1	6-24	93%/imaging and clinical
Milker-Zabel et al, 2003	19/18	PTV=GTV plus entire VB/CT-MRI fusion	24-45 Gy, Median 2 Gy fraction	19/18 Median 39.6 Gy, 2 Gy fraction	12	95%/clinical
Gerszten et al, 2005	26/26	Postkypoplasty VB+extension/ CT	16-20 Gy/1fx		4-36	92%/imaging or clinical
Gerszten et al, 2007	500/393	GTV=PTV/CT	12.5-25 Gy/1	7 patients combined EBRT plus SBRT boost	3-53	88%/imaging
Sahgal et al, 2007	60/38	GTV=PTV/CT	8-30 Gy/1-5	37/26 tumors had previous irradiated	1-48	87%/imaging and clinical
Chang et al, 2007	74/63	GTV + potential extension of structure /CT	30 Gy/5fx or 27 Gy/ 3fx	35/63 (55.6%) patients of previous spinal RT (median 33 Gy; range 30-54 Gy)was allowed	1-50	77%/imaging

Table 5. Clinical Results of SBRT in spinal metastasis

In a report from Henry Ford Hospital, Ryu et al treated 61 spinal tumors in 49 patients with single dose of SBRT alone to a dose of 10 to 16 Gy. With follow up time ranging from 6 to 24 months, the local control rate was 93% on imaging and clinical response including complete or partial pain control was achieved in 52 of 61 tumors (85%) (Ryu et al, 2004). In a report of SBRT as reirradiation, Milker-Zable treated 19 tumors from 18 patients with a dose range from 24 to 45 Gy in 2 Gy fractions. Their previous median dose was 39.6 Gy in 2 Gy fractions. With a median follow up time 12 months, the clinical response rate was 95%. They defined PTV as a gross tumor volume plus entire vertebral body through CT with MRI fusion and defined spinal cord as spinal cord from MRI plus safety margin of 2 to 3 mm. Dose constraints of spinal cord on SBRT as reirradiation was maximal dose to spinal cord less than 20 Gy in 10 fractions to a median percent of spinal cord (Milker-Zabel et al, 2003). In a postoperative SBRT series from Pittsburg Medical center, Gerszten et al reported the results of SBRT using Cyberkinife from 26 tumors in 26 patients. The prescribed dose was 16 to 20 Gy at the 80% isodose line with a median follow up of 16 months, the local control rate

was 92%. Pain control was evaluated using a ten point verbal visual analog scale and was improved in 24 out of 26 patients (Gerszten et al, 2005). And in the largest report from same group, Gerszten et al treated a total of 393 patients with 500 spinal metastases with Cyberknife based single dose SBRT to doses ranging from 12.5 to 25 Gy. Seven patients also received external radiation therapy. With a median follow up of 21 months, the local control rate was 88%. Among the 336 evaluable patients, 290 (86%) achieved improvement in pain based on a ten point visual analog scale (Gerszten et al, 2007). Sahgal et al reported the treatment results of Cyberknife based SBRT for spinal metastases from University of California SanFrancisco in abstract form. They treated 60 spinal metaststases in 38 patients with a dose ranging from 8 to 30 Gy in one to five fractions (median 24 Gy in three fractions). With a median follow up of 8.5 months, the local control rate was 87% and the pain improvement was achieved in 31 out of 46 tumor sites (67%) (Sahgal et al, 2007). In a phase I/II trial from MD Anderson Cancer Center, Chang et al reported the results of 63 patients with 74 tumors treated with SBRT to a dose of 30 Gy in five fractions or 27 Gy in three fractions. Thirty five patients had prior external radiotherapy. With a median follow up of 21.3 months, the local control rate was 77% and the one year progression free rate was 84% (Chang et al, 2007).

4.5. Multiple organ oligometastases

Authors	No of pts/tumors	Sum of GTV	Dose/fx	FU (mo)	Outcome
Milano et al, 2008	121 /293	0.3-422 ml Med. 28 ml	50Gy/10 (SRS 10-20Gy/1)		2 year OS/PFS/LC/DC, 50%/26%/67%/34%; 4 year OS/PFS/LC/DC, 28%/20%/60%/25%
Salama et al, 2008	29/56	Max. dimension of volume ≤ 10cm or < 500cm^3	24-36 Gy/3	5.3-27 (med. 14.9)	Response rate 59%; PFSR 21%; LC 57%
Salama et al, 2011	61/113	Max. dimension of volume ≤ 10cm or < 500cm^3	24-48 Gy/3	Med. 20.9	1 year OS/PFS 81.5%/33.3%; 2 year OS/PFS 56.7%/22.0%

Table 6. Clinical results of 5 or fewer oligometastases

There are fewer reports about SBRT in multisite oliogometastases (Table 6). Among them the largest trial was performed in Rochester University hospital. Milano et al reported that the 4 year overall survival, progression free survival, local control and distant control were 28%, 20%, 60% and 25%, respectively after SBRT for multiple sites oligometastases from 121 patients. And they showed that number of metastases (range, 1~5) was not correlated with

treatment outcomes. Salama et al firstly performed dose escalation study of SBRT in patients with oligometastases involving multiple organs (Milano et al, 2008). In phase I/II trial, they treated 56 tumors in 29 patients with a dose to 24 to 36 Gy in 3 fractions. With a median follow up 14.9 months, local control and progression free survival rate were, 57% and 21%, respectively (Salama et al, 2008). In a final report from same group, Salama et al could escalate the dose from 24 Gy to 48 Gy in 3 fractions. Fifty six tumors in 29 patients were treated and their 1 and 2 year overall survival rate was 81.5% and 56.7%, respectively. And they showed superior outcome in the patient with one to three metastases to the others with four or five metastases (2 year overall survival; 60.3% vs 21.9%) but there was not statistical significance (p=0.22) (Salama et al, 2011).

4.6. Dose constraints to prevent normal tissue toxicity

SBRT has been defined as hypofractionated (1-5 fractions) extracranial stereotactic radiation delivery, thus when selecting the fractional and total dose, several clinical considerations are important, including; (1) predicted risks of late normal tissue complications; (2) predicted tumor control; (3) financial costs and time expenditure for treatment planning and delivery. Among these, the long term effect of hypofractionated dose delivery to small volumes of normal tissues is not well understood, and certainly more clinical studies with longer follow up are needed to better define the variable associated with risks of late toxicity. Table 7 shows the normal tissue dose volume constraints to prevent late radiation complication in NCCN guidleline version 2.2012.

OAR	1 fraction	3 fractions	4 fractions	5 fractions
Spinal cord	14 Gy	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	30 Gy (6 Gy/fx)
Esophagus	15.4 Gy	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Brachial plexus	17.5 Gy	21 Gy (7 Gy/fx)	27.2 Gy (6.8 Gy/fx)	30 Gy (6 Gy/fx)
Heart/pericardium	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	35 Gy (7 Gy/fx)
Great vessels	37 Gy	39 Gy (13 Gy/fx)	49 Gy (12.25 Gy/fx)	55 Gy (11 Gy/fx)
Trachea & proximal bronchi	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy.fx)	32.5 Gy (6.5 Gy/fx)
Rib	30 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy.fx)	32.5 Gy (6.5 Gy/fx)
Skin	26 Gy	30 Gy (10 Gy/fx)	36 Gy (9 Gy/fx)	40 Gy (8 Gy/fx)
Stomach	12.4 Gy	27 Gy (9 Gy/fx)	30 Gy (7.5 Gy)	35 Gy (7 Gy/fx)

Table 7. Normal tissue dose volume constraints for SBRT from NCCN guidelines

The recommendation from Table 7 is frequently referenced in SBRT for non small cell lung cancer (Ettinger et al, 2012) and so, there is no information about intra abdominal organ including small intestine, liver and kidney. Radiobiologically, normal tissues can be categorized into two groups of serially arranged tissues and parallel arranged tissues. In a review article from Rochester University in New York, Milano et al recommended the fractional dose limitations to small volume of normal tissue which were expected to be safe with respect to risk of radiation necrosis in serially arranged tissues and they also noted the dose constraints of parallel arranged normal tissues such as lung, liver and kidney for safe SBRT in same article (table 8 and 9) (Milano, 2008).

Number of fractions					
Normal tissue	1	3	5	8	10
Spinal cord	8-10 Gy	5-6 Gy	4-5 Gy	3-4 Gy	3 Gy
Trachea & bronchi	-	-	7-9 Gy	6-7 Gy	4-5 Gy
Brachial plexus	-	-	8-10 Gy	6-7 Gy	5-6 Gy
esophagus	-	-	6-8 Gy	4-5 Gy	3-4 Gy
Chest wall/ribs	-	10-15 Gy	6-8 Gy	6-7 Gy	5-6 Gy
Small bowel	10-12 Gy	10-12 Gy	6-8 Gy	5-6 Gy	4-5 Gy
Lung	20 Gy	20 Gy	8-10 Gy	7-8 Gy	5-7 Gy
Liver	25 Gy	20 Gy	8-10 Gy	7-8 Gy	5-6 Gy

Table 8. Recommendation for safe hypofractionated SBRT fractional dose to small volume of serially arranged tissues.

Lung	700-1000 ml of lung not involved with gross disease or planning target volume V20 of 25-30%
Liver	700-1000 ml of liver not involved with gross disease or planning target volume Two thirds of normal liver < 30 Gy
Kidney	Minimize dose receiving > 20 Gy Two thirds of one kidney < 15 Gy (with another functional kidney)

Table 9. Recommendation for safe hypofractionated SBRT dose volume metrics for parallel arranged normal tissues

Deriving standard acceptable maximally effective and minimally toxic dose fractionation schemes presents a challenge, even with available outcome data. In fact, this complexity arises from not only the different dose-fractionation schemes used, but also in differences in how the dose is prescribed. Further study and longer follow up are needed to ascertain the dose fractionation schedule that optimizes tumor control while minimizing toxicity and to better understand the optimal normal tissue dose volume constraints.

4.7. Patterns of failure

A subset of patients with oligometastases have been alive a prolonged disease free state, some > 7 years, most eventually succumbed to further metastatic progression. There are

several studies which have examined the pattern of recurrence after resection, radiofrequency ablation, or cryosurgery and SBRT of oligometastases. Table 10 shows the literature summary of the pattern of recurrence after treatment of limited liver metastases.

First author	Sugihara et al, 1993	Aloia et al, 2006	Kosari et al, 2002	Ravikumar et al, 1991	Milano et al, 2010
Primary cancer	colorectal	colorectal	various	colorectal	various
Treatment modality	resection	resection	radio-frequency	cryosurgery	SBRT
Number of recur/total	64/107 (60%)	71/150 (57%)	23/45 (51%)	17/24 (71%)	37/42 (88%)
Follow up(mo)	6-164 Median 35	4-138 Median 31	6-34 Median 19.5	5-60 Median 24	6-67 Median 21
Recurrence in					
Liver only	-	18%	52%	35%	22%
Extrahepatic only	-	62%	4%	6%	5%
Liver+extrahepatic	-	20%	43%	59%	73%
Liver	53%	38%	96%	94%	95%
Lung	31%	58%	-	-	32%
CNS	-	1%	-	-	8%
Bone	-	6%	-	-	19%
other	28%	17%	-	-	32%

Table 10. The pattern of recurrence after local treatment of limited liver metastases

All authors reported that the first new recurrence or metastases occurred quite commonly in the same organ, although metastases to other organs are common as well. New metastases occurring shortly after completion of treatment including SBRT presumably represents the growth of initially occult metastatic disease versus rapid metastatic progression, whereas new metastases that occurs after a longer time interval represents more indolent growth of initially occult metastatic disease versus a more remote occurrence of distant spread. However, a few present studies can determine a mechanism to account for new metastases. Some variables are thought important in predicting where subsequent metastases are likely to occur. The initial organ involvement, use of chemotherapy, type of local therapy, primary cancer type, histology and grade are expected to be important which can impact the pattern of subsequent recurrence. In addition, genotypic and phenotypic changes which lead to metastatic potential must exist and should be explained in the future.

5. Conclusion and future aspect

In its current form, stereotactic hypofractionated radiotherapy is still in its infancy as an experimental treatment for oligometastases. At this point, a recommendation cannot be made for a fractionation scheme, which suggests the need for prospective investigation. There are multiple ongoing clinical trials on the use of SBRT for oligometastases in various body sites and the results of those trials are eagerly awaited. Given the high propensity for distant progression, the combination of novel systemic therapy and SBRT is to be explored. Interested readers can visit the web site (www.clinicaltrials.gov) to a full list of clinical trials of SBRT for various metastatic sites.

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