Stereotactic Body Radiotherapy (SBRT) For Lung Cancer

Report of the ASTRO Emerging Technology Committee (ETC)

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INTENDED USE OF TECHNOLOGY

This report will evaluate stereotactic body radiotherapy (SBRT) in the treatment of lung cancer. Stereotactic refers to precise positioning of the target volume in three-dimensional space. The target volume is usually localized in space using some external frame of reference, which can be related to the treatment delivery system. The term 'body' is used to distinguish the technique from treatments performed in the brain and skull base called intracranial stereotactic radiosurgery (SRS) or intracranial stereotactic radiotherapy (SRT) where the treatment accuracy can be related to positioning of the rigid skull with high reliability. In contrast to SRS and SRT, SBRT performed outside the brain and skull base requires special evaluation and accounting of target motion in the absence of a reliable bony surrogate such as the skull. Stereotactic positioning can be precise and as a result, SRS and SBRT commonly employ much higher doses per fraction and fewer fractions than with conventional radiation. Based on the definition as approved by the Common Procedural Terminology (CPT®) Editorial Panel, SBRT consists of a full course of treatment administered in five or fewer fractions. Because SBRT concentrates therapeutic doses of radiotherapy into a few, high-dose, highly-conformal, precisely-targeted treatments, it is a highly specialized technology that requires a significant quality assurance program in order to be effectively used to benefit patients. Given the scope of quality issues involved, the quality assurance program would need to address set up, testing, maintenance and interoperability of equipment, treatment planning, patient positioning, and process of care, as well as staffing, education, training, and appropriate supervision. While important, these aspects of SBRT are outside the scope of this paper.

DESCRIPTION OF TECHNOLOGY

<u>Introduction</u>

A basic, longstanding principle of radiotherapy is to maximize the dose of radiation delivered to a tumor while sparing normal tissue to the greatest extent possible. This will increase the tumor control probability (TCP) and decrease the normal tissue complication probability (NTCP). Any inaccuracy in patient setup can have serious consequences both in terms of expected TCP and induced normal tissue complications. In the case of hypofractionation for lung cancer, this maxim becomes ever more important since the geometry of the beams, rather than differential radio-sensitivity of normal and target tissue, is the predominate factor in sparing normal tissues.

Conformal radiation therapy, delivered by three-dimensional (3D) conformal (3D-CRT) or intensity-modulated radiotherapy (IMRT) techniques, allows the delivery of a high dose to the tumor with a high graduation of dose between the tumor and normal tissue. Therefore, an exact knowledge of the position of the tumor is necessary to fully benefit from hypofractionation. This is further complicated in thoracic and abdominal tumors due to respiratory induced intra-fraction motion (Cox, Schechter et al. 2003)`.

Tumors in the thorax can move up to 3-5 cm and commonly 1.5-2.5 cm with respiration (Shirato, Seppenwoolde et al. 2004; Shirato, Suzuki et al. 2006; Hugo, Yan et al. 2007; Liu, Balter et al. 2007). This motion must be first quantified and subsequently can be accounted for by various methods. These methods include measuring and treating the entire track of tumor motion using four-dimensional computed tomography (4DCT) for targeting (Underberg, Lagerwaard et al. 2004; Rietzel, Pan et al. 2005; Chang, Balter et al. 2006), applying abdominal compression to reduce motion (Murray, Forster et al. 2007), gating the treatment to a specific portion of the respiratory cycle (Shirato, Shimizu et al. 2000; Nelson, Starkschall et al. 2005; D'Souza, Nazareth et al. 2007), active breathing control (Wong, Sharpe et al. 1999), or tracking

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the tumor with the radiation beam (Neicu, Shirato et al. 2003; Keall, Joshi et al. 2005; Kamino, Takayama et al. 2006; Nuyttens, Prevost et al. 2006)

Target localization and motion management

Unlike intracranial SRS, SBRT lung 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, Debus et al. 1999; Hadinger, Thiele et al. 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, Shimizu et al. 2000; Starkschall, Forster et al. 2004; Nelson, Starkschall et al. 2005; Underberg, Lagerwaard et al. 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, Keller et al. 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, Shimizu et al. 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, Zhu et al. 2002) and Cyberknife® (Accuray, Sunnyvale, CA) (Adler, Chang et al. 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, Wright et al. 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.

Respiratory correlated 4DCT was developed over the past several years to address the issues of respiratory motion in radiotherapy targeting (Rietzel, Pan et al. 2005). 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. This is feasible, but somewhat unnatural when not under physical exertion. To help 'remind' the patient to use primarily chest wall breathing, a firm but tolerable pressure plate is applied to the upper abdomen to inhibit abdominal diaphragmatic motion. Numerous reports show that this technique can reliably dampen target motion, even for targets close to the diaphragm, to under 1 cm (Hadinger, Thiele et al. 2002; Lax, Panettieri et al. 2006).

Treatment Planning

A significant requirement of SBRT is tight conformality of the prescription isodose shell to the tumor volume with sharp dose fall-off. Kavanagh et al. (Kavanagh, Timmerman et al. 2003) suggest that this may be accomplished by implementing multiple, non-opposing, and often non-coplanar beams or arcs, spread in a large solid angle with fairly equal weighting to minimize the entrance dose and ultimately the volume of the irradiated normal tissue. Using this technique, the proportion of scatter contribution will also be reduced.

Chang et al. (Chang and Timmerman 2007) in a review on this subject suggest that a clinical factor in deciding the number of beam directions and the relative beam weights is the entrance dose and that should be kept to a modest level to prevent potential severe skin or chest wall toxicity while keeping a uniform isotropic dose fall-off. The beam's eye-view for each

beam coincides with the planning target volume (PTV) outline leading to a lower prescription isodose line of 60% to 80% providing 95% PTV coverage, rather than what is typically seen with more homogeneous target dose distributions associated with conventionally fractionated radiotherapy. In assessment and evaluation of dosimetric properties of the SBRT plans, three major criteria are considered: conformity index, high-dose spillage, and intermediate-dose spillage. The conformity index is defined as the ratio of the volume of the isodose shell that provides 95% PTV coverage to the PTV volume. It is recommended that this ratio be kept to less than 1.2 to minimize the volume of tissue receiving an ablative dose. Any areas receiving greater than 105% of the prescription dose, commonly referred to as high-dose spillage, are generally confined to the PTV. Intermediate-dose spillage, which is responsible for most of the toxicity associated with SBRT, is evaluated using one or both the following methods: 1) to keep dose to any point 2 cm away from the PTV surface below a limit that is a function of PTV volume, and 2) the region of intermediate-dose spillage is defined as the ratio of 50% isodose coverage to the PTV volume. These concepts have been used in all of the RTOG multicenter lung studies to date, and constraints as a function of target volume can be viewed in the radiotherapy sections of these protocols (RTOG 0236, 0618, 0813 and 0915).

An additional challenge in treatment planning for small lesions in the lung parenchyma is lack of electronic equilibrium. Many methods of determining dose distributions assume that each dose calculation point is in an area of electronic equilibrium (e.g. that a similar amount of scatter is entering as is leaving this area). This is, in general, not true when irradiating small lesions surrounded by air space in the lung. Various treatment planning systems have been compared to Monte Carlo calculations (Lax, Panettieri et al. 2006; Panettieri, Wennberg et al. 2007; Morgan, Knoos et al. 2008) and measurements (Davidson, Ibbott et al. 2007). Only

convolution superposition algorithms were found to have good agreement for these types of tumors. These algorithyms are commercially available from at least two manufactures (Pinnacle™, Philips Medical Systems, Madison, WI, Eclipse™ AAA, Varian Medical Systems, Palo Alto, CA). In the past the high doses and high dose gradients associated with SBRT have made them somewhat insensitive to these dosimetric uncertainties but as doses are lowered to reduce toxicity and to allow the treatment of centrally located lesions, accurate dosimetry is becoming more important. Manufacturers have responded to this need and one now has direct Monte Carlo based planning (MultiPlan®, Accuray, Sunnyvale, Ca) and one has improved their photon pencil beam algorithm (Eclipse™, Varian Medical Systems, Palo Alto, CA) to better account for areas of electronic disequilibrium (Gagne and Zavgorodni 2007).

Treatment Delivery

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. The treatment units we are aware of that provide this treatment are the Novalis® (Brain LAB, Inc.), the Tomotherapy® HiArt® System (Tomotherapy, Madison, WI), the Varian Trilogy™ (Varian, Inc., Milpitas, CA), the Elekta Synergy-S® (Elekta, Inc., England), the Siemens Primatom™ System, and the Cyberknife® (Accuray, Sunnyvale, CA).

The Novalis® system uses a 6 MV linear accelerator with micro-multileaf collimators ranging in leaf thickness from 3 to 5.5 mm. Two orthogonal keV X-ray systems are mounted in

the room to track bony landmarks or implanted fiducial markers in relation to the digital radiographs (DRR's) generated from CT simulation. Alternatively, cone-beam CT for in room volumetric imaging is available with a 2.5 mm leaf width (Novalis® Tx). The patient is then aligned in the treatment position in accordance with identified positions of markers. This alignment can be evaluated by imaging throughout the treatment. This system also has a respiratory gating system that uses infrared cameras in the room to track reflective markers placed on the patient's abdomen. Prior to treatment a relationship is developed between these external markers and the radiographically determined tumor position. This relationship can be verified by imaging throughout the treatment.

The Tomotherapy® system employs a 6 MV linear accelerator mounted on a CT-type slip ring gantry. Like a CT scanner the field width is very narrow and the patient is treated by moving the treatment couch through the beam aperture while the linear accelerator is rotating around the patient. The megavoltage beam from the accelerator can be used both to image and treat the patient. A binary collimator system is mounted in front of the accelerator to allow the delivery of various intensity distributions for intensity-modulated radiotherapy (IMRT). Generally this system images the patient with a very low dose and uses these data for precise alignment. This alignment can be verified during treatment by using the portion of the treatment beam not absorbed in the patient for imaging. This system does not allow for respiratory gating but research has been reported to demonstrate techniques to use this device in the presence of respiratory motion (Hodge, Tome et al. 2006; Sheng, Cai et al. 2006; Smeenk, Gaede et al. 2007; Luan, Wang et al. 2008).

The Varian Trilogy™ and Elekta Synergy® devices both have kVp x-ray systems mounted on the treatment gantry at 90 degrees from the treatment head. These kVp-imaging

systems can be used for projection x-ray-based setup or can be used to generate cone-beam CTs. The Varian system has integrated respiratory gating based on a reflective marker placed on the patient's abdomen. This gating system can be used to gate the treatment beam as well as the kVp and MV X-ray imagers. The ability to gate the setup beams combined with implanted fiducial markers allows the simultaneous verification of the patient positioning and the gating threshold level. The cone-beam CT cannot be dynamically gated but can be acquired over a series of breath holds to obtain a breath-hold CT. Several researchers have demonstrated the ability to obtain 4D cone-beam CTs on both the Varian and the Elekta units. Elekta also has a gating system that is based on spirometry combined with visual feedback that enables the patient to be treated with voluntary reproducible breath-hold (active breathing coordinator). The system is composed of a micro-MLC system with leaf thicknesses of 3 mm, 5 mm, or 7 mm, head and body frames for positioning and localization (CT/MR & angiography), dynamic patient support assembly with all translational, rotational, pitch, yaw, & roll movement, and an integrated optical tracking system for positioning. Additionally, an inverse treatment-planning package with intensity-modulated arc therapy (IMAT) capability, unique to 3D Line with optimization routines for stereotactic radiotherapy techniques, is included

Siemens has two potential products with in-room guidance, a CT-on-rails system and a megavoltage cone-beam system. The CT-on-rails employs a diagnostic CT scanner that has been modified to move over a stationary patient rather that the patient moving through the CT. The CT unit is linked to the accelerator via a shared tabletop enabling the patient to be imaged in the treatment position and then treated on the same treatment table. Once CT imaging is completed the tabletop rotates to the linear accelerator for treatment delivery, thereby providing a near real-time localization for treatment delivery. The megavoltage cone-beam CT system is similar to the

Varian and Elekta systems except that instead of using a separate kVp imaging system the linear accelerators treatment beam is used in a low dose mode to provide the imaging beam.

The Cyberknife® uses an imaging system similar to the Novalis® system but is unique in that it does not use an isocentrically-mounted linear accelerator. The linac is mounted to a robotic arm allowing a large number of degrees of freedom in delivering the dose to the patient. Since the accelerator is very light and the system has few restrictions in range of motion it has been adapted to tumor tracking and is the only commercial system with this capability (Nuyttens, Prevost et al. 2006). Implanted fiducial markers or reliable bony landmarks are used to localize the tumor in real-time for treatment delivery. For tumor tracking or gating operations the patient wears a vest containing a number of light-emitting markers which are tracked by a camera system to determine a respiratory pattern and its relationship to the motion of the tumor. These external markers are then used to gate or track the tumor during delivery, if the system detects a change in respiration the treatment is stopped and a new relationship is established.

Summary

Lung SBRT requires the ability to precisely determine the location and extent of motion of tumors, to be able to develop complicated 3D treatment plans in non-equilibrium conditions, and to deliver the high dose with great geometric precision. This can be done effectively with some existing CT simulators, treatment planning systems and linear accelerators, but requires a great deal of care on the part of the treatment team. New delivery systems have been developed specifically to facilitate SBRT and may offer some benefit due to their greater imaging abilities and flexibility in delivering the treatments.

DESCRIPTION OF PATIENTS POTENTIALLY BENEFITING FROM USE OF TECHNOLOGY

Rationale for Lung Stereotactic Body Radiotherapy

Medically Inoperable Lung Cancer

Historically, early stage (Stage I/II) non-small cell lung cancer (NSCLC) has been managed with definitive surgical resection, however many patients are unfit for surgery due to underlying medical co-morbidities, such as cardiopulmonary disease related to chronic smoking. Medical inoperability is defined as the presence of co-morbid illnesses that renders the patient at higher than acceptable risk of surgical morbidity and mortality (Colice, Shafazand et al. 2007). Often this results in a competing risk scenario where risk of death from medical illnesses is balanced by the risk of death from lung cancer.

Medical inoperability is generally regarded as either poor pulmonary function based on objective criteria (baseline FEV1 $\leq$ 40% predicted, post-operative predicted FEV1 $\leq$ 30% predicted, diffusion capacity $\leq$ 40% predicted, baseline hypoxemia ($\leq$ 70 mmHg) and/or hypercapnia ($\geq$ 50 mmHg) or exercise oxygen consumption $\leq$ 50% predicted) or as specified by a thoracic surgical oncologist.(Timmerman, Michalski et al. 2009) Contraindications to surgery may include severe pulmonary hypertension, diabetes mellitus with severe end-organ damage, severe cerebral, cardiac, or peripheral vascular disease, or severe chronic heart disease. Any one of these criteria may preclude surgery.

Despite often severe competing risk of death from other causes in these patients, McGarry et al. (McGarry, Song et al. 2002) have shown that the risk of dying from lung cancer can still exceed 50%, favoring aggressive treatment. Historically, conventional radiotherapy consisting of 6 to 7 weeks of daily treatment has been considered the standard of care for this

group. (Scott, Howington et al. 2007) A large systematic review of an estimated 2,003 medically inoperable patients with stage I/II NSCLC receiving radiotherapy alone showed complete response rates ranging between 33-61% and local failure rates between 6-70%. (Rowell and Williams 2001) Better response rates and survival were seen in those with smaller tumors and in those receiving higher doses. Lung SBRT has the potential to deliver higher radiation doses to these patients while minimizing exposure to surrounding normal tissues and significantly reducing overall treatment time.

Operable Lung Cancer

For patients with early stage NSCLC who are surgical candidates but refuse surgery, lung SBRT is also an alternative. Radiation dose escalation is a method that has been proposed to improve outcome (Narayan, Henning et al. 2004; Bradley, Graham et al. 2005; Belderbos, Heemsbergen et al. 2006) and can be achieved easily with SBRT. SBRT provides a very high degree of dose conformality to target volume that spares normal tissue, requires five or fewer patient and target positionings reducing the risk for errors compared to conventional fractionation, and dose fractionation schedules can be modified for various levels of dose escalation. Lung SBRT may be an alternative to surgery for small volume, early stage disease if local control proves durable.

DESCRIPTION OF PATIENT RISKS FROM TECHNOLOGY

Higher doses in fewer fractions using SBRT may result in less of the sparing of normal tissue that conventional fractionation allows and therefore greater toxicity. The much smaller treatment volume used with SBRT, that therefore places less normal tissue at risk, may offset these concerns. However, smaller volumes could compromise local control if tumors are not selected carefully. Clinical experience as well as basic radiotherapy and radiobiology principles

help to better understand the balance between toxicity and local control. For example, clinical experience indicates that local control of primary lung tumors treated with radiotherapy is proportional to the total radiotherapy dose delivered. Based on studies using radiotherapy dose escalation at the University of Michigan, the dose required with conventional radiotherapy to locally control primary lung tumors $\geq$ 50% of the time at 30 months after treatment is approximately 84 Gy when delivered in 2.0 Gy daily fractions (Martel, Ten Haken et al. 1999). However, conventional radiotherapy treatments typically only deliver doses in the range of 60 to 70 Gy because of increased risks of toxicity in normal tissues surrounding the target, such as the lung, heart, and esophagus.

The efficacy of radiotherapy in killing tumor cells is proportional not only to the total dose delivered in the course of treatment, but also in relation to the size of the radiotherapy fractions delivered daily. Tumor cells may be able to repair a proportion of radiation injury after each fraction, depending on the size of the shoulder of the survival curve, and this effect could be less marked if a high dose per fraction and fewer fractions are used. The biological equivalent dose (BED) delivered by any given radiotherapy treatment schedule can be calculated using the following formula, which describes how different tissues respond to dose fractionation:

$$BED = n * d \left[1 + \left(d / \{\alpha/\beta\}\right)\right]$$

where n equals the number of radiotherapy fractions, d equals the dose per fraction, and α/β equals a variable dependent on the sensitivity of the tissue to changing size of dose per fraction.(Hall 1994) The α/β for lung cancer has been estimated to be as high as 50 to 90 Gy (Cox, Byhardt et al. 1980) however, traditionally 10 Gy is used for a typical tumor. Normal lung tissue α/β has been estimated to be much lower, in the 2 to 4 Gy range.(Travis, Thames et al. 1987) BED calculations can be used to compare the relative effective dose delivered to a tissue when differing dose-fractionation schedules are being compared and show the significant

increase in effective dose when daily doses increase into the range typically delivered during stereotactic therapy. A conventionally fractionated course of radiotherapy for lung cancer, 60 Gy in 30 fractions of 2 Gy per day, has a BED of 72 Gy_{10}, when calculated for a lung tumor with an estimated α/β ratio of 10 Gy. For comparison, a course of 84 Gy in 2 Gy fractions has a BED of 100 Gy_{10}, so an effective course of treatment for lung cancer is likely to require greater than this for long-term tumor control (Martel, Ten Haken et al. 1999), which is typically difficult to achieve with conventional radiotherapy techniques.

Stereotactic radiotherapy is potentially more effective in tumor killing by delivering a few very large doses of daily radiotherapy from which cells will have limited ability to recover. Indeed, for a course of SBRT, where an equivalent total dose of 60 Gy is delivered in 3 fractions of 20 Gy per day, calculation from standard principles provides us with a BED of 180 Gy_{10}. However, it is critical to note that caution should be exercised in making such extrapolations since the linear-quadratic equation was chosen for its ability to model effects of dose fractionation only within the conventional treatment range; no additional compensation is made for the fact that large dose fractions in this range may lead not only to enhanced tumor cell killing, but also to ablation of the underlying microvasculature and other factors supporting tumor growth, further enhancing radiotherapy efficacy. (Hall 1994; Fowler, Tomé et al. 2004; Onishi, Araki et al. 2004; Fuks and Kolesnick 2005; Cesaretti, Pennathur et al. 2008)

A radiobiological principle that favors the fewer larger factions used with SRBT over protracted courses of conventional radiotherapy is that of tumor repopulation. In response to cell death following conventional fractionation, the effective tumor cell re-growth rate can increase starting perhaps two to four weeks after initiation of treatment. (Mehta, Scrimger et al. 2001; Saunders 2001) Therefore, a typical course of SBRT delivered in two weeks would conclude before the onset of accelerated repopulation.

In summary, an expected increase in tumor response using SBRT for primary non-small carcinomas of the lung is supported radiobiologically with the important caveat that changes to the efficacy of reoxygenation are not addressed using the BED model. It is assumed that the

very large increase in BED overcomes this issue and that the smaller field size offsets normal tissue toxicity concerns.

EVALUATION/SUMMARY OF RESULTS OF EXISTING STUDIES

Single Institutional Experiences

North America

A phase I trial from Indiana University of medically inoperable T1-2 patients escalated dose from 24 Gy in 3 fractions with an increase in 6 Gy total at each incremental cohort group of three patients. (McGarry, Papiez et al. 2005) The stereotactic body frame and abdominal compression were used for immobilization. Forty-seven patients in total were accrued. Maximum tolerated dose was not reached in T1 patients, but was 66 Gy in three fractions for T2 patients. At 72 Gy there was Grade 3 or higher toxicity in 3/5 patients. There were four other grade 3 toxicities, and four grade 2 toxicities. Local failures occurred in 10 of the 47 patients, nine of which occurred at doses ≤ 16 Gy per fraction. There were three regional only recurrences, four distant only recurrences, and seven both regional and distant recurrences.

This was followed by a phase II trial of seventy patients reported in 2006. (Timmerman, McGarry et al. 2006) The patient population (T1-2 < 7cm, medically inoperable) and SBRT technique (stereotactic body frame with abdominal compression for immobilization) were similar to the Indiana report. Stage T1 lesions were treated to a dose of 60 Gy delivered in three fractions, while T2 lesions were treated to 66 Gy in three fractions. The two-year local control was 95%. The median overall survival was 33 months. Eight of the 70 patients developed a grade 3-4 toxicity including pneumonia, pleural effusion, apnea, skin reaction and decline in pulmonary function tests. Six patients died as a result of toxicity. High-grade toxicity (≥ 3) was

predicted by location on both univariate and multivariate analysis, with hilar/pericentral having higher rates of toxicity as compared to peripheral.

Staten Island University Hospital published the results of 75 patients treated over five years for NSCLC. (Beitler, Badine et al. 2006) Patients were either medically inoperable or refused surgery. Immobilization was accomplished with a custom fiducial box with foaming material. Twenty three percent did not have a biopsy prior to treatment and the remaining patients had NSCLC. Five patients had mediastinal invasion, one had chest wall invasion. Twenty patients had lymph node positive disease. Sixty-seven patients received stereotactic radiation alone; the remaining 8 received conventional dose radiation prior to a stereotactic radiotherapy boost (which would not actually qualify as SBRT based on the CPT® definition). With a median follow-up of 17 months, 2-year overall survival was 45%. The median total radiation dose was 40 Gy (range 30-90), median fraction size was 8 Gy (1.8-9) and total treatment duration was 7-83 days. Post-treatment imaging was used to characterize outcome. Complete response occurred in seven patients, decreased disease in 25 patients, no change in 22, and progressive disease in 9. There was no documentation data on 12 patients. The authors reported that "numerous" patients developed metastases within the lung and outside the chest. Toxicities reported were radiation pneumonitis in two patients, acute nausea and vomiting in one patient, pleural effusion in two and one case of pneumothorax.

M.D. Anderson Cancer Center reported preliminary data on both stage I (n = 37) and isolated peripheral recurrent (n = 22) NSCLC. (Chang, Balter et al. 2006) Four-dimensional CT scanning was used for target delineation and the prescription dose was 50 Gy delivered in four fractions. The median follow-up was 10 months. Control rates were not reported, however all patients treated had a complete response, partial response or stable disease. There were no cases

of grade 2 or higher radiation pneumonitis in the stage I patients. Ten percent had grade 2 dermatitis.

Fox Chase Cancer Center conducted a Phase I dose escalation trial of SBRT for lung tumors. (Feigenberg 2008; Sharma 2008) Total doses were escalated in 8 Gy (i.e., 2 Gy per fraction) increments from 40 Gy to 56 Gy, delivered in 4 equal fractions administered 2 to 3 times per week. The highest dose level was predetermined to be biologically equivalent to 114 Gy. Dose-limiting toxicity was defined as any grade 3 or higher toxicity using the RTOG Common Toxicity Criteria. Accrual was completed between April 2004 and February 2008, with 18 patients receiving the prescribed treatment (40 Gy n = 6, 48 Gy n = 7, 56 Gy n = 5). Seventeen of 18 patients had non-small cell lung cancer (1 with metastatic rectal cancer), 4 of whom were treated for an oligometastasis. The mean tumor size was 2.6 cm (range, 0.9-4.5 cm). Three patients developed symptoms from therapy; with only 1 (48 Gy) that was grade 3. This patient developed a bacterial pneumonia 2 days after treatment that was assumed to be radiation related. Serial CT and PET scans were used to assess local control. With a mean follow-up of 17 months, the one-year local control rate was 97% and 18 month local control was 93%. No late pulmonary complications have occurred. No patient had a decrease in FEV1 or DLCO by 1 month after treatment. The maximum tolerated dose was not reached during this study.

Asia

Yoon et al. reported on 91 patients in Korea. (Yoon, Choi et al. 2006) Thirty-eight patients had primary lung lesions; the remaining patients had metastatic disease. The primary lung cases were T1-2N0 NSCLC, < 5 cm. Of the 38 primary lung lesions, 21 were treated definitively and 17 were attempts at salvage after local recurrences. Patients were immobilized with stereotactic body frame and abdominal compression. In addition some patients used an

active breathing control mechanism to further reduce tumor motion. Initially the dose used was 30 Gy in 3 fractions; this was then increased to 40 Gy in 4 fractions and ultimately to 48 Gy in 4 fractions. With a median follow up of 14 months the 2-year progression free survival was 81%. Thirty percent of the patients treated to 30 Gy developed a local recurrence as compared to 23% of the patients treated to 40 Gy. There were no local recurrences in the 48 Gy group, though median follow-up was 10 months. The two-year overall survival rate was 51%. There were no RTOG grade 3 or greater pulmonary complications and acute treatment related toxicity was deemed "negligible."

The Kyoto University published the results of a phase I/II trial in 2005. (Nagata, Takayama et al. 2005) Forty-five patients with T1-2N0 NSCLC were treated with 48 Gy in 4 fractions prescribed to the isocenter. Patients were treated in the Elekta stereotactic body frame and used a diaphragm control device to limit respiratory motion. Twenty-seven patients were medically inoperable, the remainder refused surgery. Median follow-up was 30 months for stage IA patients, and 22 months for stage IB patients. There was a 4% rate of symptomatic pneumonitis requiring steroids. Twenty two percent experienced a mild cough, malaise or slight fever without need for intervention. Outcome was divided by stage. For the stage IA patients, the five-year local relapse-free survival was 95%, disease-free survival was 72% and overall-survival was 83%. For the stage IB patients, there were no local failures in the follow-up period of the study. The five-year disease-free survival was 71% and overall-survival was 72%.

Europe

In Sweden, forty-five medically inoperable patients with NSCLC, tumors < 5 cm were treated to a dose of 45 Gy in 3 fractions at Sahlgrenska University Hospital. (Nyman, Johansson et al. 2006) Patients with tumors proximal to the trachea, mainstem bronchus or esophagus were

not treated. Immobilization was accomplished with a stereotactic body frame and abdominal compression. Nine patients (20%) had acute skin reactions ranging from slight erythema to moist desquamation (n = 2). Four patients (9%) had grade 1 esophagitis and four had transient chest pain. Another four had infections, bronchitis or pneumonia, and three had increased cough. Fifty-one percent had no acute side effects. Late toxicity developed in two patients who had rib fracture and three patients who developed significant atelectasis. There was no reported symptomatic pneumonitis. With a median follow-up of 43 months, nine patients (20%) developed a local recurrence or had local persistence of disease. Three-year overall survival was 55%, with a median survival of 39 months. The three-year lung cancer-specific mortality was 67%.

Forty patients with stage I NSCLC were treated to a dose of 45 Gy in 3 fractions on a phase II study from Denmark. (Baumann, Nyman et al. 2006) Patients were medically inoperable, with tumors < 6 cm and at least 1 cm away from the bronchi or esophagus. A stereotactic body frame was used in 32 patients, and a custom made vacuum pillow in the remainder. Actuarial 2-year progression-free survival was 54%, cancer-specific survival was 62% and overall-survival was 48%. There was only 1 isolated local failure. Toxicity was graded using the WHO scale. There were four grade 3-4 dyspnea, and two patients with grade 3 chest pain.

Zimmermann et al. from Munich, Germany treated thirty medically inoperable patients with stage I NSCLC. (Zimmermann, Geinitz et al. 2005) The median radiation dose was 37.5 Gy (24-37.5) in 3-5 fractions, delivered using a vacuum fixation device and abdominal belt for respiratory limitation. Most patients (69%) received 37.5 Gy in 3 fractions. Patients were also given oxygen by mask at a rate of 6 L/min to reduce respiratory motion.

Immediate acute toxicity, defined as those occurring during the course of RT, was observed in nine patients. The most frequent finding was fatigue, occurring in 6 patients (grade 1, n = 5; grade 2, n = 1), while slight pain, fever and pneumonia (questionably related to the treatment) occurred in one patient, each. Acute toxicity, occurring up to 3 months post RT occurred in 19 patients. It consisted of pneumonitis grade 1 in 8 (26%) and grade 2 in 5 (17%) patients, while only one (3%) patient had pneumonitis grade 3. Nausea grade 1 occurred in 2 (7%) patients, while dermatitis, fatigue, and dysphagia (all grade 1) occurred in 1 patient, each. With short follow up (20% < 6 months), only one long-term side effect was noted (e.g. a rib fracture). Two-year local control was 87%. Two-year disease- free survival was 72%. There were two regional failures (7%) and five distant failures (17%). Overall-survival at two years was 75%.

Pulmonary Toxicity

The most common cause of inoperability among patients with non-small cell lung cancer is chronic obstructive pulmonary disease (emphysema or chronic bronchitis), typically associated with many years of exposure to tobacco smoke. Several groups have attempted to define the safe limits of dose-volume exposure in SBRT, and whether SBRT causes worsening dyspnea or lung function tests in these already compromised patients. The main limitation of these studies is their small size, but Ohashi et al. (Ohashi, Takeda et al. 2005) studied 15 patients with 17 lesions representing either primary lung cancer (T1-2,N0,M0, twelve patients) or metastases from colon cancer (two patients) or from oropharyngeal cancer (one patient). Pulmonary function testing was performed prospectively prior to SBRT and at one year following treatment. In general, radiation doses of 50 Gy were delivered in 5 fractions over 5 to 7 days. Two patients also received conventional radiation therapy (30–40 Gy given in 15–20 fractions over 2–4 weeks)

before SRT. An 8-mm margin was placed on the GTV, and this PTV was covered with the prescription dose, typically resulting in a 125 % hot spot within the tumor. Local-control rates were excellent, with only one recurrence during the study follow-up. These authors found no significant declines in total lung capacity, vital capacity, or forced expiratory volume in 1.0 second. However, there was a significant increase in diffusion capacity of lung for carbon monoxide among all patients, especially those with a heavy smoking history. This is more likely due to the fact that none of the smokers returned to smoking after SBRT.

Similarly, Paludan et al. (Paludan, Hansen et al. 2006) studied 28 medically inoperable stage I NSCLC patients receiving SBRT at a single institution in Denmark in the years 2000-2003. World Health Organization (WHO) toxicity scoring was performed at baseline and at 6-month follow-up after SBRT. All patients received 45 Gy in 3 fractions (BED 112.5 Gy) over 5-8 days prescribed to the isocenter in the tumor. There were an equal number of T1 and T2 lesions in the population, tumors were more typically apical or middle lobe (79 %), and a roughly equal number of patients had baseline dyspnea of 0, 1, and 2, respectively. The authors reported that aggravated dyspnea was seen in 11 patients (40 %), but these seemed to share no time-relationship to the SBRT, and the aggravations of dyspnea seemed most closely associated with the presence of underlying chronic obstructive pulmonary disease (COPD). The authors concluded that the aggravations seen were COPD exacerbations rather than toxicity from SBRT.

In a phase II trial at Indiana University, Henderson et al. (Henderson, McGarry et al. 2008) studied 70 medically inoperable patients with stage I NSCLC, treated with 60 Gy (for T1 lesions) or 66 Gy (T2) in three equal fractions, typically separated by 2-3 days. Baseline and serial pulmonary function testing was performed. Median follow-up was 26 months. Patients were compared by quartile in pretreatment FEV1.0 and DLCO with endpoints of survival,

FEV1.0 and DLCO. Patients in the lowest quartile or lowest two quartiles of pulmonary function had equivalent overall-survival to the patients above those respective cutoffs. Curiously, the patients in the highest quartile of FEV1.0, consisting mainly of patients deemed inoperable because of cardiac morbidity, had a statistically significant decrease in overall-survival (p = 0.049), although interpretation is debatable since no Bonferroni correction for type I error was used for the many comparisons in the paper. The authors note a statistically significant decrease in DLCO of 1.11 ml/min/mm Hg/year (p < 0.001), and that in Cox multivariate analysis of survival, increasing baseline FEV1.0 correlated with decreased survival, as already mentioned (p = 0.014). The authors concluded that they had found no justification for restricting access to SBRT for the patients lowest in pulmonary function.

Follow-up evaluations

The natural history of radiographic findings after SBRT for lung cancers remains an area of active investigation as suggested in a review by Bradley (Bradley 2007)). The Hiroshima group (Kimura, Matsuura et al. 2006) recently published on CT findings after SBRT for primary or metastatic lung tumors, finding 5 patterns of radiographic change in the acute phase (< 6 months) and 3 patterns of longer-term change. The acute changes were termed: 1) diffuse consolidation (appearing in 38.5 % of patients), 2) patchy consolidation and ground-glass opacities (GGO) in 15.4 %, 3) diffuse GGO, 11.5 %, patchy GGO, 2.0 %, and 5) no evidence of increasing density, 32.6 %. The longer-term changes were termed: 1) modified conventional pattern, 61.5 %, 2) mass-like pattern, 17.3 %, and 3) scar-like pattern, 21.2 %. Many comparisons were made in this manuscript, although it appears that "diffuse consolidation" seems to correlate well with grade 2 acute radiation pneumonitis, and CT-identified pulmonary emphysema seems to protect against pneumonitis and radiation-induced fibrosis. Unfortunately,

no assessment of inter-observer variability (kappa) was yet made, limiting the application of this system to a greater audience.

In abstracts, Matsuo et al. (Matsuo, Nakamoto et al. 2006) confirmed that FDG avidity is expected to decline over time, and Hoopes et al. (Hoopes, Fletcher et al. 2006) successfully fit declining SUV values to an exponential curve. Significantly, the one patient with local failure, of 14 patients on the prospective study, had an initial decrease in FDG avidity at 2-weeks post-SBRT, followed by monotonically increasing avidity over time, and 6 of 13 patients without evidence of local failure at longer follow-up nonetheless continued to have elevated SUV > 3.5 at twelve months post-procedure. In an earlier abstract, Hoopes et al. (Hoopes, Tann et al. 2005) found that while 24% of T1-2N0 patients treated with 60 - 66 Gy in three fractions ultimately failed in nodal regions, isolated nodal failure occurred in only 10% of the 57 patients. Furthermore, the authors found 4 patients for whom FDG avidity was elevated (SUV 2.5-5.1) between 12 - 24 months, but without evidence of local recurrence with continued follow-up in the next 8 - 22 months. Together, these preliminary data indicate that computed-tomography and PET surveillance of patients after SBRT may be fairly sensitive but not entirely specific.

Multi-institutional Trials of SBRT for Lung Cancer

In the medically inoperable setting, the RTOG has investigated SBRT for medically inoperable lung cancer in a multi-center cooperative group trial (RTOG 0236: A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I/II Non-Small Cell Lung Cancer) where the primary objective of the study was to determine if radiotherapy involving high biological dose with limited treatment volume (using SBRT techniques) achieves acceptable local control. Patients with T1, T2 ($\leq$ 5 cm), T3 ($\leq$ 5 cm), N0, M0 medically inoperable non-small cell lung cancer; patients with T3 chest wall primary

tumors only; no patients with tumors of any T-stage in the zone of the proximal bronchial tree. Patients with T3 tumors based on mediastinal invasion or < 2 cm toward carina invasion are not eligible. Patients received 20 Gy per fraction for 3 fractions over 1.5 - 2 weeks, for a total of 60 Gy. W With median follow-up of 24.8 months, 3 patients (5%) have been scored with a local failure giving an estimated 2-year local control rate of 93.7% (95% CI: 81.5%, 98.0%). No patients have experienced regional failure while eight patients (15%) experienced distant failure. Two year estimates of disease free and overall survival are 66.6% (95% CI: 52.2%, 77.5%) and 72.0% (95% CI: 57.9%, 82.1%), respectively.(Timmerman, Paulus et al. 2009)

The role for SBRT in early-stage lung cancer patients who are medically fit for surgery is evolving. While investigators from Japan (Nagata, Takayama et al. 2005) have reported similar local control results to surgery, approximately 50 percent of patients in the Japanese trial were medically operable but refused surgery, thus representing a more favorable group in terms of survival. Late failures and toxicity may be more evident in the operable group with additional follow-up. The RTOG is also investigating SBRT in the operable setting in RTOG 0618, a phase II trial of SBRT for medically operable patients with clinical stage I/II non-small cell lung cancer. Medical operability in this trial is strictly defined. A qualified thoracic surgeon must determine that there would be a high likelihood of obtaining negative surgical margins and the patient must have good pulmonary reserve (FEV1 > 40% predicted, estimated post operative FEV1 > 30% predicted, diffusion capacity > 40 % predicted, absent hypoxemia and or hypercapnia, exercise oxygen consumption > 50 % predicted) and no major co-morbid illnesses. Adjuvant chemotherapy is recommended. Early stopping rules and frequent evaluation with opportunity for salvage surgery have been incorporated. Results of this trial are also eagerly awaited.

Single-Fraction Stereotactic Radiotherapy to Lung Tumors

The overwhelming majority of clinical studies have utilized fractionated radiotherapy for stereotactic treatment of lung tumors. However, some studies are emerging which have utilized single-fraction treatment.

Stanford has published a phase I dose escalation trial in which patients were treated with doses ranging from 15 Gy to 30 Gy in a single fraction. (Le, Loo et al. 2006) The treatments were delivered using the Cyberknife® Stereotactic Radiotherapy System (Accuray, Sunnyvale, CA). Three to five fiducial markers were implanted into the tumors under CT guidance. The first 30 patients were simulated using a breath-hold technique, while the last three were simulated using a 4D-CT scanner. The first 23 patients were treated using a breath-hold technique; treatment times ranged from 2-6 hours. (Murphy, Martin et al. 2002) The last ten patients were treated using the Synchrony® Respiratory Tracking System (Accuray, Sunnyvale, CA). This software/hardware package utilizes an infrared camera to continuously track light-emitting diodes placed on the patient's chest wall, which allows adjustment of the linear accelerator treatment head in real-time to track the patient's breathing.

Treatment was delivered to NSCLC and tumors metastatic to lung measuring up to 5 cm in maximum dimension. Twenty-six patients (81%) had previously undergone radiotherapy. Nine patients were treated with 15 Gy, one with 20 Gy, twenty with 25 Gy, and two with 30 Gy. Dose was prescribed to the isodose line encompassing the tumor (60-80% in all cases), which corresponded to a biologic effective dose (BED) to the isocenter which was >100 Gy in 23/32 cases. In contrast, the BED to the periphery of the tumor was >50 Gy in 23 (62%), but lower in the remaining patients. A median of 117 beams (range, 81 – 225) was used in the treatment plans. Both peripheral and central lesions were treated.

At the 25 Gy dose level, three grade 5 toxicities were noted. Two were described as pneumonitis, and the third as a tracheoesophageal fistula. These patients were all treated with chemotherapy before or after stereotactic treatment (two with gemcitabine). Two of these patients had also previously received external beam radiotherapy to the chest. Two other patients with central lesions experienced grade 2 (symptomatic) pneumonitis. Two patients with peripheral lesions experienced grade 2 - 3 pneumonitis, and another a grade 2 pleural effusion. Based upon this experience, the trial continued to the 30 Gy dose escalation, but only for patients without prior chemotherapy and tumors < 50 cc. The one year freedom from local progression was 91% for patients who received > 20 Gy and 54% for those who received less (p = 0.03).

During the course of the Stanford trial, Timmerman et al. from Indiana published data regarding fatal toxicity in patients treated with high dose-per-fraction radiotherapy to central lesions. (Timmerman, McGarry et al. 2006) As a consequence, the Stanford group concluded that they were considering more conventional fractionated therapy for central lesions in future patients.

A German series was published in 2006, describing treatment to 58 patients with single-fraction stereotactic radiotherapy for NSCLC or metastases. (Fritz, Kraus et al. 2006) Lesions were described as peripheral, but ranging in size up to 10 cm in maximum diameter. Dose to the isocenter was 30 Gy and the prescription mandated that > 90% of the GTV receive that dose. The GTV was expanded by 10 - 15 millimeters to PTV, at least 80% of which was required to receive the prescribed dose. With a minimum of one year of follow-up, 94% of primary lung tumors were controlled locally. Toxicity was very limited. There were four cases of grade I radiation dermatitis (WHO-Toxicity Criteria) in patients with disease near the thoracic call. The

authors report no additional side effects and specifically note there were no cases of pneumonitis or death due to respiratory insufficiency.

Hara et al. have published the Japanese experience. (Hara, Itami et al. 2006) Fifty-nine lung tumors (48 representing metastases), all measuring < 4 cm in greatest dimension, were treated with single-fraction treatment. Tumors were quite small (largest 19 cc) and all were peripherally-located. Nine received a prescribed dose of 20 or 25 Gy, with the remainder receiving 30-34 Gy. Dose was prescribed to the periphery of the CTV. Treatment was gated to the respiratory cycle in approximately half of the cases. Two-year local control was 83% for tumors treated to at least 30 Gy, and 52% for those prescribed a lower dose. A single patient, with active tuberculosis and lung fibrosis, experienced grade 3 "respiratory morbidity."

In 2007, the University of Pittsburgh published their experience. (Pennathur, Luketich et al. 2007) Patients were treated with a single fraction of 20 Gy using a Cyberknife® system. A median dose of 20 Gy, prescribed to the 80% isodose line, was delivered in a single fraction. Local control data are not specifically reported, though 22% had an initial complete response and an additional 31% had a partial response, with 28% demonstrating stable disease. Median follow-up was nine months. Toxicity data are not specifically recorded.

The University of Miami published its findings in treating inoperable early-stage NSCLC patients with a Cyberknife® system. (Brown, Wu et al. 2007) Fifty-nine patients were treated to 61 isocenters. The prescription dose varied from 15 - 67.5 Gy in 1-5 fractions. A (non-quantified) number of the stage 1A (but not 1B) patients were treated with single-fraction radiotherapy. Treatment was typically prescribed to the 60-80% isodose line. Patients were treated over a three-year span, though median follow-up is not mentioned. Local failure was

15.6% for the stage 1A lesions. The paper does not specify whether these patients were treated with single-fraction radiotherapy.

Overall, published clinical experience with single-fraction stereotactic radiotherapy for lung tumors is limited. Fractionated treatment has been shown to be safe and effective in a number of studies. A single fraction of 20 Gy is likely not sufficient, given that Timmerman et al. describe a dose response with three fractions of 20 Gy. The Stanford data demonstrate dose-limiting toxicity at 25 - 30 Gy in a single fraction. Based on the research to date, single fraction SBRT would likely be conducted only in the setting of a clinical trial.

FUTURE PREDICTION BASED ON TECHNOLOGY DEVELOPMENT

With the continuing development of tumor tracking technologies it may be possible to further reduce the target size through margin reduction. This could have the potential to reduce both early and late unwanted side effects by reducing the amount of normal tissues irradiated to high dose. As criteria mature for tumor size, total dose, fractional dose, and normal tissue dose limits, SBRT for NSCLC may become a routinely viable option for these patients. ASTRO supports ongoing clinical trials such as those being conducted by the RTOG to further define efficacy and toxicity of fractionated and single fraction SBRT for lung cancer.

ANAYLYSIS AND TECHNOLOGY ASSESSMENT FINDINGS

Technological advancements such as the development of a body frame with external fiducal markers, respiratory gating and breath holding techniques, cone beam, 4D-CT, and robotically-assisted linear accelerators, allow for increasingly smaller treatment volumes through the implementation of stereotactic lung radiotherapy. Careful selection for small inherently

demarcated tumors, typically located in the periphery of the lung away from sensitive normal structures such as the heart and proximal tracheobronchial tree permits the use of multiple, non-coplanar beams and allows for a rapid reduction in dose beyond a few millimeters outside the tumor target volume. Multiple clinical trials throughout the world have shown successful escalation of BED while limiting normal tissue toxicity with doses in the range of 48 Gy in 4 fractions to 60-66 Gy in 3 fractions. Tolerability of treatment and local-control has been excellent in single institutional reports in both the medically inoperable and operable settings. In the medically inoperable setting, we conclude that SBRT is an accepted treatment option for Stage I-II NSCLC. In the operable setting, we conclude more study and longer follow-up is necessary to ensure that results are equivalent to those of surgery. Ideally, medically operable patients with Stage I lung cancer would likely receive SBRT on a structured investigative protocol. By and large, tumor location has been a concern since Timmerman et al. have demonstrated an increased risk of mortality with centrally located tumors. However, others have successfully treated central tumors, albeit with a more fractionated approach. Based on the research to date, single fraction SBRT would likely be conducted only in the setting of a clinical trial.

Emerging Technology Committee Note

"Assignment of this project to the Task Group was made on April 20, 2008 and data collection for preparation of the full report available on the ASTRO website and this condensed version was closed on May 29, 2008. Clinical, physics or biology data and regulatory revisions available after that date are not included in this review."

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