

HyTEC Organ-Specific Paper: Lung

Local Control After Stereotactic Body Radiation Therapy for Stage I Non-Small Cell Lung Cancer

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Summary

Stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR) is an effective treatment for medically inoperable early stage NSCLC. The authors quantitatively

Purpose: Numerous dose and fractionation schedules have been used to treat medically inoperable stage I non-small cell lung cancer (NSCLC) with stereotactic body radiation therapy (SBRT) or stereotactic ablative radiation therapy. We evaluated published experiences with SBRT to determine local control (LC) rates as a function of SBRT dose.

Methods and Materials: One hundred sixty published articles reporting LC rates after SBRT for stage I NSCLC were identified. Quality of the series was assessed by evaluating the number of patients in the study, homogeneity of the dose regimen, length of

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evaluated published experience with thoracic SBRT for early NSCLC and modeled local control rates as a function of SBRT dose. Early stage NSCLC is radio-responsive when treated with SBRT/SABR. A steep dose-response relationship exists with high rates of durable LC when physical doses of 43-50 Gy are delivered in 3-5 fractions.

follow-up time, and reporting of LC. Clinical data including 1, 2, 3, and 5-year tumor control probabilities for stages T1, T2, and combined T1 and T2 as a function of the biological effective dose were fitted to the linear quadratic, universal survival curve, and regrowth models.

Results: Forty-six studies met inclusion criteria. As measured by the goodness of fit χ^2/ndf , with ndf as the number of degrees of freedom, none of the models were ideal fits for the data. Of the 3 models, the regrowth model provides the best fit to the clinical data. For the regrowth model, the fitting yielded an α -to- β ratio of approximately 25 Gy for T1 tumors, 19 Gy for T2 tumors, and 21 Gy for T1 and T2 combined. To achieve the maximal LC rate, the predicted physical dose schemes when prescribed at the periphery of the planning target volume are 43 ± 1 Gy in 3 fractions, 47 ± 1 Gy in 4 fractions, and 50 ± 1 Gy in 5 fractions for combined T1 and T2 tumors.

Conclusions: Early-stage NSCLC is radioresponsive when treated with SBRT or stereotactic ablative radiation therapy. A steep dose-response relationship exists with high rates of durable LC when physical doses of 43-50 Gy are delivered in 3 to 5 fractions. © 2019 Elsevier Inc. All rights reserved.

1. Clinical Significance

Non-small cell lung cancer (NSCLC) is the second most common cancer overall (228,190 cases per year in the US) and the leading cause of cancer-related death (159,480 deaths) in both men and women.¹ Stage I disease represents approximately a quarter of the patients receiving diagnoses of NSCLC and accounts for the most curable cohort of the population.^{2,3} The standard treatment for medically operable stage I NSCLC has historically been an anatomical resection with lobectomy as well as hilar and mediastinal lymph node dissection.⁴⁻⁷ However, the majority of patients with NSCLC have a history of chronic tobacco use and a median age of diagnosis of 65-74 years and often have cardiopulmonary comorbidities (eg, cardiac and pulmonary) that make them at high risk for resection.^{2,3} Some patients are deemed to be medically inoperable.^{8,9} The increasing use of screening for lung cancer based on the National Lung Screening Trial may increase the number of patients with early-stage NSCLC appropriate for nonsurgical treatments.¹⁰

The historical standard therapy for patients with unresectable early-stage NSCLC was conventionally fractionated radiation therapy (eg, 2-3 Gy per fraction to a dose of ≈ 54 -60 Gy). However, the reported long-term local control (LC; $\approx 30\%$ -70%) and overall survival ($\approx 15\%$ -30%) rates with this approach are suboptimal.¹¹⁻¹³ Advances in imaging and radiation treatment planning and delivery (eg, with image guidance and motion management) enable the delivery of “ablative doses” of radiation (eg, 18-20 Gy x 3 fractions) to very small targets, often termed stereotactic body radiation therapy (SBRT) or stereotactic ablative radiation therapy (SABR). This method appears to yield better outcomes for early-stage NSCLC.¹⁴⁻¹⁹

In most of the reports using this approach, typical patient selection criteria include comorbid conditions that preclude a safe oncologic resection, such as poor pulmonary function tests (forced expiratory volume in

1 second < 1.2 liters; diffusing capacity of the lungs for carbon monoxide $< 50\%$).^{17,20,21} Most patients are staged with a whole-body computed tomography (CT) or positron emission tomography-computed tomography (PET-CT) scan. Patients suspected of having lymph node involvement (interlobar, hilar, or mediastinal) are not candidates for SBRT. More often than not, pathological staging of the mediastinal nodes is not done because of the risk of invasive procedures in this patient population.^{22,23} However, tissue diagnosis of the NSCLC subtype using CT guided or endobronchial ultrasound guided needle biopsy is recommended.^{22,24} Of note, endobronchial ultrasound directed biopsy is usually only appropriate for centrally located primary tumors. Ideally, primary tumor size is restricted to ≤ 5 cm (eg, T1a-T2a), and thus the optimal patients for SBRT include those with clinically staged IA and IB medically inoperable NSCLC. Of note, recent American Society for Radiation Oncology guidelines conditionally recommend SBRT for tumors larger than 5 cm that are not suitable for surgical resection with appropriate counseling of patients regarding the higher risk of locoregional and distant failures.²⁵ Nevertheless, the majority of patients in the available literature were treated for lesions ≤ 5 cm and in noncentral locations as tumors in central locations have less favorable outcomes with SBRT (see section “Special Situations”).

2. Endpoints

The primary endpoint reported in the literature was local tumor control at the primary site of SBRT. When reported, the actuarial rates of LC, defined as no local progression at the primary tumor site as assessed by CT or PET-CT imaging, at 1, 2, 3, and 5 years were recorded; however the majority of the studies only reported outcomes up to 3 years. Overall survival data are often reported in the literature and were collected in this review. However, these

data were not used in the final analysis or modeling owing to the lack of consistent reporting of this endpoint in the reviewed literature. Distant failure was not recorded in our review owing to minimal observed correlations to models assessing local tumor control probabilities (TCP).

Comparisons with surgical series are challenging because most surgical series define local failure to include failure within the lobe of the lung (in cases of sublobar resection) in addition to locoregional or regional failures (failures within hilar and mediastinal lymph nodes). These metrics are not routinely reported in the SBRT literature. Further, patients undergoing SBRT for early-stage NSCLC generally have greater competing risks for death from causes other than their lung cancer compared with patients undergoing surgery because the latter have fewer competing comorbidities.^{26,27} Thus, it is possible that reported actuarial LC rates at 1 to 3 years after SBRT overestimate the true LC. Patients that die of intercurrent deaths (deaths not owing to lung cancer during the follow-up period for lung cancer after treatment) are censored, perhaps leaving an “enriched, healthier” subset of evaluable patients, whereas those that died of intercurrent illnesses may have had occult local progression before death. Indeed, most matched-pair comparisons between SBRT and surgery report an inferior overall survival with SBRT despite comparable cause-specific survival.^{28,29}

In most SBRT series, LC was assessed using CT and PET-CT–based imaging and applying the Response Evaluation Criteria in Solid Tumors and changes in PET-fluorodeoxyglucose (FDG) activity. Some studies reported pathological confirmation of tumor recurrence in a subset of the patients. Nevertheless, given that the majority of the recurrences were assessed radiographically, there is some uncertainty in the reported LC rates. SBRT can cause scarring or inflammatory changes that result in tissue distortion, making radiographic interpretations difficult.³⁰⁻³² These changes can mask, and thus delay, the diagnosis of tumor recurrence. Similarly, local inflammation soon (within 1 year) after SBRT often causes an increase in FDG uptake, which can make response assessment unreliable and can lead to false positives.^{33,34} Thus, data from studies with longer follow-up are likely more accurate in their assessment of LC.

3. Challenges defining and segmenting anatomic volumes

Respiration-induced tumor motion is a challenge for target definition. Older series often used breath-hold (both deep exhalation and deep inhalation) CTs or fluoroscopy as a surrogate to define extreme borders of the target’s motion envelope. Most of the modern studies use 4-dimensional CT (4DCT) scans to define the target volume, where the images acquired in the same respiratory phase or amplitude are grouped together to reconstruct multiple 3DCTs. The amplitude-based 4DCT reconstruction is preferred because

it generates fewer image motion artifacts. A separate free-breathing scan, with or without contrast, is often also obtained. Intravenous contrast may be useful in settings where the target lesion abuts a large vessel or the mediastinal structures.³⁵⁻³⁷

Some studies have used methods to control the amplitude of tidal volume and thus tumor excursion by simulating the patient with a 4DCT or fluoroscopy while also using abdominal compression devices.³⁸ The degree of abdominal compression can be determined by using fluoroscopy or imaging implanted radio-opaque fiducial markers within or near the tumor such that the excursion of the marker and tumor is within an acceptable range.^{39,40} It is of note that the use of implanted fiducial markers is optional for all respiratory management tools during CT simulation. These motion-management strategies at the time of CT simulation are also used to characterize respiratory motion of organs at risk. Fusion of a PET and a CT scan can help define the tumor borders and is especially helpful when the tumor is adjacent to lung atelectasis, the mediastinum, diaphragm, stomach, liver, etc.^{41,42} Ideally, the PET-CT fusion should be performed in the same respiratory phase (amplitude).

During treatment planning, the contrast-enhanced CT and the 4DCT can be used to segment an internal target volume (ITV) using a Boolean operation to account for the motion envelope.^{37,43} Various methods, including using only the end-expiratory and end-inspiratory phases, segmenting the tumor in all respiratory phases and using a Boolean operation to combine the contours, and generating maximal intensity projection images and segmenting the target, have been used to define the ITV. In addition, based on the ICRU-62 definition, clinical target volume = gross tumor volume (GTV) with no margin.^{44,45} Further, owing to the high doses per fraction, the doses to the “nontarget” tissues immediately adjacent to the planning target volume (PTV) receive a relatively high, and likely “therapeutic,” dose for potential microscopic disease. Thus, the favorable outcomes reported without a formal clinical target volume expansion should not be taken as proof that there is no microscopic spread. Typical expansions from ITV to PTV are in the range of 3-8 mm in the axial dimensions and 5-10 mm in the craniocaudal dimensions with or without respiratory gating or tracking. If respiratory gating is utilized, then the ITV is defined based on the phases selected for treatment. Commonly, near end-expiratory phases (gating phase 30%-70%) are used owing to maximal tumor stability and minimal tumor motion in these phases. Alternatively, some studies choose near-inspiratory phases (gating phase 90%-10% or inspiration breath-hold) because the total lung volume is larger and the percent of lung irradiated to any given dose is likely lowest in these phases.

Various techniques to control, monitor, or limit respiratory motion can be used, including passive breath-hold with visual or audio feedback to the patient, active breath control where air movement is restricted by a device, tracking of external (eg, surface markers) or internal (eg, implanted

markers, diaphragm, or the tumor itself) respiratory motion, and abdominal compression.^{46,47} Each of these approaches has its own benefits and limitations. Typically, gating and tracking to improve normal tissue sparing are most useful for tumors with relatively large respiratory excursions,^{48,49} but these approaches typically increase treatment times. Tumors in the middle and lower lobes are generally more mobile than those in the upper lobes. Caveats in characterizing tumor and organ motion using a 4DCT include artifacts induced due to patients' irregular breathing patterns and reproducibility of the breathing patterns at CT simulation compared with treatment days.

Adjusting the window and level on the CT scan will affect target definition.⁵⁰ Typically, a "lung window" is best to define a parenchymal tumor because irregular spiculations can be better appreciated. When a tumor abuts another organ composed mostly of soft tissue (heart, mediastinum, diaphragm, liver, or chest wall), assessing the boundaries of the target at the interface is best done using a mediastinal or soft-tissue window.⁵¹

4. Review of outcomes Data

A keyword search for "SBRT and lung" and "stereotactic ablative radiotherapy (SABR) and lung" using PubMed identified 160 studies reporting clinical outcomes from thoracic SBRT for early-stage NSCLC published through May 2014. These studies were systematically reviewed. Articles relating to the treatment of oligometastatic disease to the lung were specifically excluded. Each publication was assessed to determine whether the data were collected prospectively or retrospectively, the number of patients, homogeneity of dose prescriptions, the length of follow-up, and whether LC was reported. Studies with fewer than 10 patients or tumor stage higher than T2 were excluded. Three of the included studies that met the above publication selection criteria had doses in the 3 to 4 Gy per fraction range (211 patients). Owing to the paucity of data in the intermediate dose per fraction range, these studies were included to improve model fitting in the shoulder region. The rest of the included studies had dose per fraction ≥ 6 Gy per fraction (3268 patients). Based on this metric for "quality," 46 studies were identified and included for data collection and modeling of outcomes.^{17,52-96} Of note, a retrospective series was included if it met all the other criteria for "quality" listed earlier as long as it had included ≥ 10 patients (see [Supplementary Material](#) for all included studies and input from each study, available at <https://doi.org/10.1016/j.ijrobp.2019.03.045>).

Extracting and comparing dose information

The reported dose was prescribed to the isocenter in 17 studies (36%) or to an isodose surface that covered a certain percent of the PTV in 30 studies (64%). To facilitate the pooling of data from multiple studies for analysis, in the

latter studies, reported doses were converted to presumed isocenter doses by dividing the reported dose by the reported percent of isodose coverage. In the 10 cases where the percent of isodose coverage was not given, authors were contacted directly for this information (3 cases) or 80% isodose coverage was assumed (7 cases). Thus, from each study, we extracted an estimate of the isocenter dose and the dose per fraction, the number of fractions, and an estimate of the total elapsed days of treatment.

In all analyzed studies, treatment plans were based on multiple noncoplanar or coplanar fields delivered with conformal fields, dynamic conformal arcs, volumetric modulated arc therapy, or with multifield intensity modulated radiation therapy (IMRT).

Notably, a variety of tissue inhomogeneity algorithms were used, which confounds the estimation of the dose at the isocenter. Among the various sources of uncertainty, these algorithms may be inaccurate in estimating the PTV dose and distort the dose distribution in a patient-specific manner. Although most protocols recommend prescriptions to the PTV margin,^{97,98} the dose calculation introduces more uncertainty in this region than at the isocenter or at a suitable calculation point within the tumor for IMRT.^{74,99-101} In particular, the dosimetric uncertainty at lung-tissue interfaces,⁹⁹ at the periphery of a PTV,⁷⁴ and at shallow depths near the skin or surface of a lung tumor can be large, up to 120%,^{100,101} with the less-accurate dose calculation methods. In contrast, even for small fields in a heterogeneous environment, dose measurements and Monte Carlo calculations can match within 3% at the isocenter.¹⁰¹ To resolve the dilemma, the HyTEC dose-response model was constructed using isocenter dose, and for clinical conclusions based on the analysis (section 8), the results were converted to a PTV margin equivalent using a generic 80% isodose line; the interested reader can convert the results using an applicable isodose line for individual situations.

Most of the studies used linear accelerator-based radiosurgical delivery systems including CyberKnife (Accuray, Sunnyvale, CA) and other more traditional linear accelerator-based delivery systems (TrueBeam, Triology, Novalis, Artiste, etc). A few studies utilized either helical tomotherapy or proton beam therapy. Several conventional linac studies noted that only a limited number of noncoplanar beams could be used owing to issues relating to patient or couch collision.

Immobilization devices included stereotactic body frames, customized cradles, and evacuated vacuum cushions; a few studies used no special immobilization. Respiratory motion management strategies varied and included free-breathing techniques with a 4DCT from simulation defining an ITV with or without tracking of implanted metallic fiducials, abdominal compression with fluoroscopic assessment of diaphragmatic motion as surrogate for tumor motion, and no (or unreported) motion management. There were too many permutations related to patient set-up, immobilization, respiratory motion management strategies, and target definition to conduct a meaningful analysis relating outcomes to any of

these variables. Thus, data were pooled from studies independent of how these issues were addressed, which leads to further uncertainty. Similarly, there was not enough specificity in the available reports to consider factors such as histology, absolute tumor volume (although T1 vs T2 tumors were evaluated as variables for the regrowth model), total treatment duration, minimum PTV dose, dose heterogeneity within the tumor, fraction number, tumor location, and irradiation technique (eg, margin, immobilization, set-up considerations, delivery method, etc). Additional factors that were not addressed that may affect outcome include molecular mutation status, invasive versus in situ disease, and staging work-up requirements (invasive or noninvasive mediastinal nodal staging).

Extracting and comparing outcome information

From each study, the reported LC rates at 1, 2, 3, and 5 years were extracted (as able). For the studies where results were presented in Kaplan–Meier and actuarial figures, the corresponding data were extracted from the figures.

Owing to the heterogeneity of data reporting and insufficient reporting of outcomes other than LC (ie, overall survival), outcome modeling was limited to the effect of tumor size (T1 vs T2 disease for regrowth model), total dose prescribed to the isocenter, and number of fractions on LC (Table 1).

Pooled crude data

Figure 1 presents TCP of 3-, 4-, and 5-fraction SBRT for combined T1- and T2-stage NSCLC as a function of estimated physical isocenter dose.

Table 1 Required physical doses (Gy) at isocenter and covering PTV with the 80% isodose line to reach the maximum TCP, calculated from the 3 models with the parameters determined in section “Mathematical and Biological Models.”

Isocenter dose (Gy)		3 fractions	4 fractions	5 fractions
Regrowth	T1	52 ± 1	57 ± 1	60 ± 1
	T2	56 ± 1	62 ± 1	66 ± 1
	T1 + T2	54 ± 1	59 ± 1	63 ± 1
LQ	T1 + T2	55 ± 1	59 ± 1	63 ± 1
	USC	T1 + T2	55 ± 1	59 ± 1
PTV dose (Gy)		3 fractions	4 fractions	5 fractions
Regrowth	T1	42 ± 1	46 ± 1	48 ± 1
	T2	45 ± 1	50 ± 1	53 ± 1
	T1 + T2	43 ± 1	47 ± 1	50 ± 1
LQ	T1 + T2	44 ± 1	47 ± 1	50 ± 1
	USC	T1 + T2	44 ± 1	47 ± 1

Abbreviations: LQ = linear quadratic; PTV = planning target volume; TCP = tumor control probabilities; USC = universal survival curve.

Factors affecting outcomes

Using data from the reviewed literature, we studied the dependence of LC on total isocenter dose and number of fractions. We converted dose to biological effective doses using the 3 models described below. The available large pool of clinical data shows a steep dose-response for LC for SBRT for early-stage lung cancer (Fig. 1). An additional factor that affects LC is tumor size based on T stage. To achieve a maximum TCP, T2 lesions consistently required a higher physical dose at the isocenter than T1 lesions (approximately 1.3 Gy per fraction higher based on the regrowth model; Table 1).

Mathematical and biological models

Three biophysical models were considered and fit to the collected clinical data: the linear-quadratic (LQ) model, the universal survival curve (USC) model,¹⁰² and the regrowth model.¹⁰³ These were chosen owing to either common usage (LQ and USC) or having the best fit to the data (regrowth). For the LQ model, biologically effective dose (BED) is expressed:

$$BED^{LQ} = D \left(1 + \frac{d}{\alpha/\beta} \right), \text{ where } \alpha \text{ and } \beta \text{ characterize the intrinsic radiosensitivity of cells, and } D \text{ and } d \text{ are the total and fractional doses, respectively. For the USC model,}$$

$$BED^{USC} = \begin{cases} D \left(1 + \frac{d}{\alpha/\beta} \right), & d < d_T \\ \frac{1}{\alpha D_0} (D - nD_q), & d \geq d_T \end{cases}$$

where $-1/D_0$ and D_q are the slope and x intercept of the logarithm survival curve, n is the number of fractions, and d_T is the transition dose where the LQ model smoothly transitions to the terminal asymptote of the multitarget model. For these 2 models, TCP can be expressed as $= e^{-K_0 * e^{-\alpha * BED}}$, where K_0 is the number of clonogenic cells at the beginning of radiation therapy.

The regrowth model links the population-averaged

TCP and BED as $TCP = 1 - \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-\frac{x^2}{2}} dx$, where

$$t = \frac{K - K_{cr}}{\sigma_k}, K = K_0 e^{-\left[\alpha BED - \left(\frac{\ln 2}{T_d} (\tau - T) \right)^{\delta} \right]}, \text{ and}$$

$BED = D \left(1 + \frac{d}{\alpha/\beta} \right) - \frac{\ln 2}{T_d} \frac{T}{\alpha}$; α and β are radiobiological parameters¹⁰⁴; τ is follow-up time starting from the beginning of radiation treatment; T is the elapsed treatment time for the SBRT treatment course; T_d is the potential tumor doubling time; δ is a fitting parameter characterizing the speed of tumor cell regrowth after SBRT; D and d are the total and fractional doses, respectively; K_0 is the number of clonogenic cells at the beginning of radiation; K_{cr} is the critical clonogenic cell number that defines control of an individual tumor; and σ_k is the Gaussian width of the distribution of tumor cell numbers. The

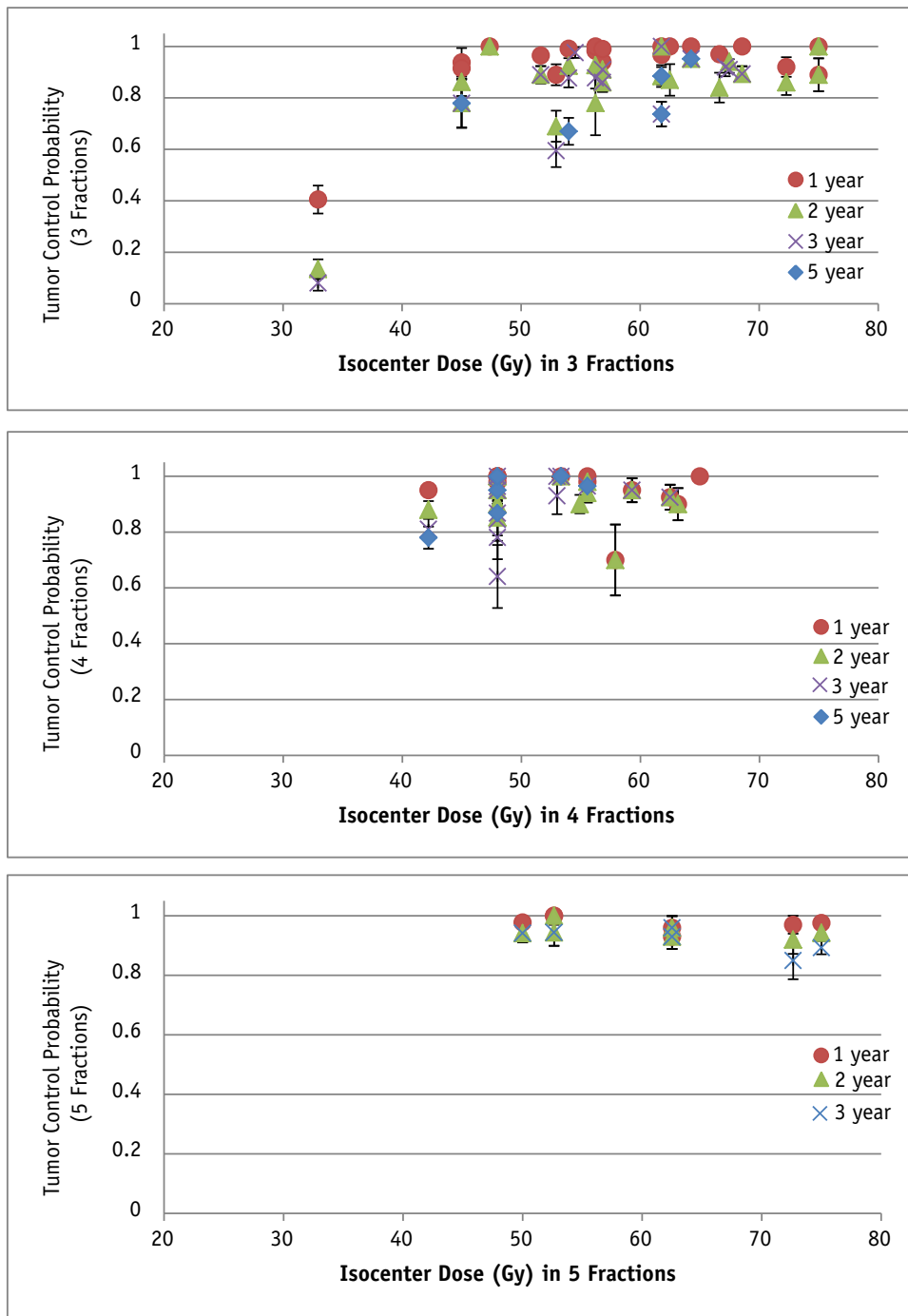


Fig. 1. Tumor control probability of 3- (top), 4- (middle) and 5- (bottom) fraction SBRT for T1- and T2-stage NSCLC as a function of physical dose at isocenter. A large error bar for a data point represents a small number of patients associated with that data point.

independent model parameters (α , α/β , T_d , K_{cr}/K_o , σ_k/K_o , and δ) were determined from a simultaneous fit to the 1-, 2-, 3-, and 5-year actuarial or Kaplan–Meier TCP data.

Clinical data including 1-, 2-, 3-, and 5-year TCP for T1, T2, and combined T1 and T2 stage as a function of the BED to isocenter were fitted to each of the above models, allowing all model parameters to freely float to achieve the best fit. The studies with fractional doses of greater than 3 Gy were considered.^{17,52-96} The TCP data were separated

for stage T1 and T2 tumors if data were available; otherwise, analysis was performed for mixed stages. The elapsed treatment time of seven-fifth times the number of fractions was used if not reported. The least chi-squared (χ^2) method was used to fit the data with a single set of parameters for all data and 2 sets for T1 and T2 separately. The goodness of fit was measured by χ^2/ndf , where ndf is the number of degrees of freedom, defined as the total number of data points minus the number of free parameters in the fit. [Table 2](#)

Table 2 The goodness of fit (χ^2/ndf) and model parameters determined from simultaneous fits to 1-, 2-, 3-, and 5-year TCP data for stage T1 and T2 lung tumors using the regrowth model and from the fits to the 3-year TCP data for combined stages T1 and T2 tumors using the LQ and USC models

Parameters		χ^2/ndf	α (Gy ⁻¹)	$\alpha:\beta$ (Gy)	Various parameters
Regrowth	T1	3.8	0.129 ± 0.004	24.8 ± 1.9	$T_d = 47.1 \pm 16.2$ days, $\delta = 0.267 \pm 0.041$, $K_{cr}/K_0 = 0.010 \pm 0.002$ $\sigma_K/K_0 = 0.005 \pm 0.001$
	T2	3.8	0.110 ± 0.004	19.3 ± 2.3	$T_d = 95.1 \pm 31.0$ days $\delta = 0.278 \pm 0.035$ $K_{cr}/K_0 = 0.012 \pm 0.001$ $\sigma_K/K_0 = 0.007 \pm 0.001$
	T1 + T2	3.8	0.123 ± 0.007	20.7 ± 1.0	$T_d = 63.8 \pm 5.8$ days $\delta = 0.253 \pm 0.025$ $K_{cr}/K_0 = 0.008 \pm 0.003$ $\sigma_K/K_0 = 0.004 \pm 0.002$
LQ	T1 + T2	7.1	0.163 ± 0.010	32.5 ± 3.5	$K_0 = (1.07 \pm 0.07) \times 10^4$
USC	T1 + T2	7.2	0.163 ± 0.005		$D_0 = 1.7 \pm 0.1$ Gy $D_q = 16.1 \pm 1.2$ Gy $K_0 = (1.06 \pm 0.07) \times 10^4$

Abbreviations: LQ = linear quadratic; TCP = tumor control probabilities; USC = universal survival curve.

The α -to- β value in the USC model equals to 34.1, which was calculated by $\alpha/\beta = \frac{4\alpha D_0 D_q}{(1 - \alpha D_0)^2}$.

presents the goodness fit and the model parameters determined from the data fitting. Notice that the regrowth model leads to a lower χ^2/ndf value compared with the LQ and USC models. The fitting with the regrowth model extracted the model parameters separately for T1 and T2. This is because the regrowth model considers the tumor regrowth after the treatment, allowing fitting of all the TCP data collected at different follow-up times. In contrast, the simpler versions of the LQ and USC models that are more often used clinically do not account for posttreatment regrowth and can only be used to fit the TCP data for a given follow-up time, which could not lead to a convergent fitting for T1 and T2 separately.

Figure 2 presents examples of fitting the TCP data with the regrowth, LQ, and USC models. The fittings of combined T1 and T2 data yield large α -to- β values (>20 Gy) based on the regrowth and LQ models (Table 2). The results indicate that TCP has a steep dose-response, reaching the maximum TCP at BED \geq 90 and 110 for T1 and T2 tumors, respectively. As indicated by the value of χ^2/ndf in Figure 2, the regrowth model yields slightly better fitting than the LQ and USC models (4.9 vs 7.1 and 7.2, respectively) to the TCP data. Details on the methods and results for the TCP modeling have been reported separately.¹⁰⁵

Special Situations

The summarized data and model-based results are derived entirely from patients with T1 and T2 medically inoperable early-stage NSCLC treated with 3 to 5 fractions of SBRT without prior radiation. The degree to which these data are

applicable to operable patients, those with metastatic disease to the lung from other primary sites (eg, breast, colorectal, sarcoma), those with previous lung radiation therapy, or those treated with hypofractionation schedules <3 or >5 fractions is not well known. For example, data from patients with lung metastases from primary colorectal tumors suggest an inferior LC.¹⁰⁶ There may be meaningful clinical endpoints beyond LC that were not addressed (eg, recurrence rate in the same lobe, hilar or mediastinal lymph nodes, distant metastases and overall survival). The heterogeneity of the published data and lack of consistent reporting for these endpoints precludes a rigorous assessment of this relationship at present. Currently, there are few studies reporting LC for large tumors (eg, >5 cm). Additional analyses will be necessary to characterize the relationship between LC as a function of tumor size while accounting for the BED.

Data suggest that the therapeutic ratio is likely different for centrally located tumors,^{58,107} and thus the selection of optimal dose, schedule, technique, and treatment volume might differ in this setting. For example, in a study that included the risks of late toxicity and complications from SBRT in early-stage NSCLC by tumor location, there appeared to be an 8-fold increase in grade 3 or higher complications (bacterial pneumonia, radiation pneumonitis, trachealbronchial fistula formation, etc) when the tumor was within or touched a volume within 2 cm of the tracheal-bronchial tree treated in a dose-escalated manner in 3 fractions.⁸⁹ This study set the current definition for a centrally located tumor. The finding of unacceptable toxicity for central tumors has been further investigated, including in a cooperative group setting such as RTOG 0813, a phase I/II study

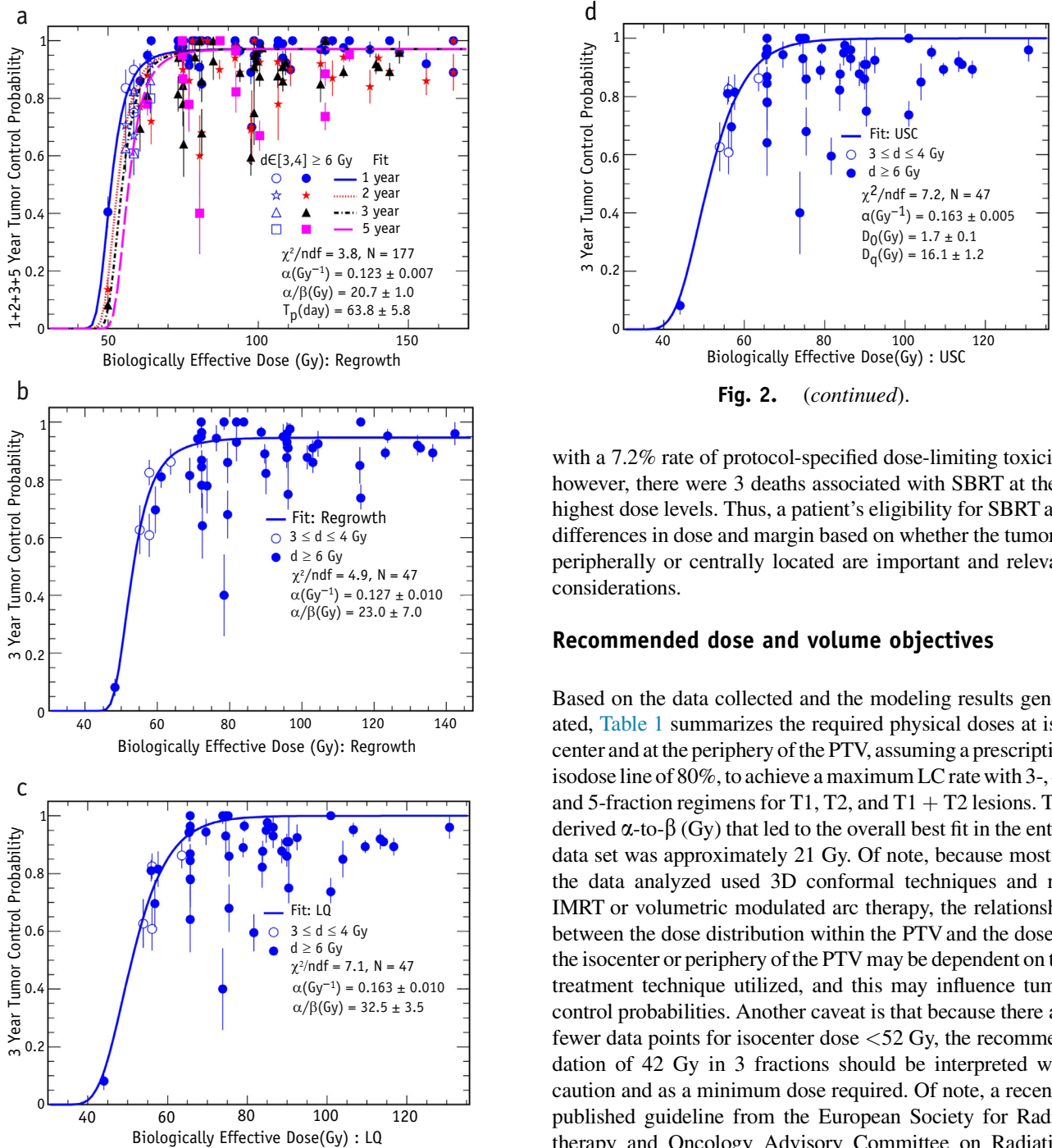


Fig. 2. (continued).

with a 7.2% rate of protocol-specified dose-limiting toxicity; however, there were 3 deaths associated with SBRT at the 2 highest dose levels. Thus, a patient’s eligibility for SBRT and differences in dose and margin based on whether the tumor is peripherally or centrally located are important and relevant considerations.

Recommended dose and volume objectives

Based on the data collected and the modeling results generated, Table 1 summarizes the required physical doses at isocenter and at the periphery of the PTV, assuming a prescription isodose line of 80%, to achieve a maximum LC rate with 3-, 4-, and 5-fraction regimens for T1, T2, and T1 + T2 lesions. The derived α -to- β (Gy) that led to the overall best fit in the entire data set was approximately 21 Gy. Of note, because most of the data analyzed used 3D conformal techniques and not IMRT or volumetric modulated arc therapy, the relationship between the dose distribution within the PTV and the dose at the isocenter or periphery of the PTV may be dependent on the treatment technique utilized, and this may influence tumor control probabilities. Another caveat is that because there are fewer data points for isocenter dose <52 Gy, the recommendation of 42 Gy in 3 fractions should be interpreted with caution and as a minimum dose required. Of note, a recently published guideline from the European Society for Radiotherapy and Oncology Advisory Committee on Radiation Oncology Practice reached a consensus that “risk-adapted” SBRT fractionation was achieved with 3 × 15 Gy for peripherally located lesions. For patients free from severe comorbidities and with favorable long-term OS expectancy, use of the maximum tolerated dose of 3 × 18 Gy should be considered.¹⁰⁸

5. Future Studies

Maturation of reported studies with updated outcomes would benefit the robustness of our tumor control models in early-stage NSCLC treated with SBRT. Consistent reporting

Fig. 2. Fitting tumor control probability data of SBRT for T1- and T2-stage NSCLC with the regrowth, USC, and LQ models: (a) fitting 1-, 2-, 3-, and 5-year TCP data simultaneously using the regrowth model; fitting 3-year TCP data with the (b) regrowth model, (c) - LQ model, and (d) USC model.

designed to determine the maximal tolerated dose and efficacy of SBRT in a dose-escalated, 5-fraction regimen from 10 to 12 Gy per fraction.⁹⁷ Early reported results showed reasonable overall rates of toxicity even at the highest dose level allowed by the protocol (60 Gy in 5 fractions), which was associated

of 5-year outcomes is needed to compare to the surgical outcomes, which is often considered the standard of care. For example, the early reports from RTOG 0236 noted a 3-year LC rate of 97.6% and a nodal control rate of 87.2%. A subsequent report with more mature follow-up data noted a 5-year LC rate of 93% and a nodal control rate of 62%.⁹⁸ It is reassuring that only 3 additional local recurrences occurred with longer follow-up compared with the 3-year outcomes.

Reporting standards for outcomes

More rigorous and consistent reporting of clinical outcomes together with the doses delivered is needed to improve the accuracy of TCP models for early-stage NSCLC treated with SBRT (see Table 3 for summary). For example, as mentioned previously, consistent reporting of long-term outcomes of at least 5 years differentiating LC, interlobar control, local regional control (hilar and mediastinal recurrences) and incidence of distant metastases and overall survival are needed. In addition, reporting of details regarding the histology of treated tumors, the medical operability status of these patients, and tumor location will help refine TCP models for specific circumstances. Finally, standard dose-reporting metrics are needed. For example, reports should describe how the GTV is defined, how respiratory motion is accounted for at simulation and treatment, and the extent of expansion for the PTV. Doses to the GTV can vary by up to 20% to 30%, depending on whether the dose is prescribed to the isocenter, prescribed to cover a certain percentage of the PTV or prescribed to a specific isodose line (eg, 80%). Such dramatic differences in the actual dose delivered may obscure any real dose response when they are incorrectly represented. Regarding dose calculations, we recommend that modern algorithms be used for future published studies, tissue heterogeneity corrections should be accounted for using modern calculation algorithms.

Perhaps new dose metrics are needed because current prescription methods were designed for conventionally fractionated 3D conformal radiation therapy designed to deliver more homogenous dose distributions within the PTV. Owing to increase heterogeneity of doses delivered with IMRT, the observed dose-response (Fig. 1) may be related to the GTV minimal dose, mean dose, maximal dose, or possibly to an equivalent uniform dose (with the model parameter “a” to be determined). Other important metrics to report may include the percent of GTV receiving >110% of the prescribed dose, the GTV D95%, or the percentage of microscopic disease coverage achieved by a particular treatment technique and dose fractionation schedule. In fact, treatment technique and dose fractionation schedule cannot be decoupled from each other but must be considered in combination. For instance, in a planning and modeling study, Arvidson et al found that dose fractionation schedules and treatment techniques that varied by up to 174 Gy in the LQ model with 2 Gy fraction equivalents at the edge of the PTV yielding a similar predicted LC did cover more than 80% of possible microscopic disease extensions to a dose of 55 Gy or higher in 2-Gy fraction equivalents.¹⁰⁹ They concluded that the high dose per fraction is necessary for some SBRT treatment regimens to obtain adequate microscopic extension coverage, whereas in other regimens yielding similar LC rates, lower prescribed doses per fraction can be employed because adequate microscopic extension coverage is obtained through added treatment margins. Therefore, a detailed description of target volume definition, treatment margins, and treatment technique is necessary in addition to dose parameters. Further support to reporting the percentage of microscopic disease coverage as a metric for a given dose fractionation schedule and treatment technique is provided by the systematic review of van Baardwijk et al, who found no significant relationship between the dose at the edge of the PTV and freedom of local progression.¹¹⁰ More recently, Shaverdian et al reported a clinical series

Table 3 Recommendations for reporting standards

	Reporting recommendations
Clinical	Up to 5 years of outcome, including LC, interlobar control, local regional control (hilar/mediastinal recurrences), rates of distant metastases, overall survival, histology, tumor molecular makeup, medical operability status, tumor location, tumor size, and treatment related toxicities
Treatment simulation	Type of images, treatment immobilization, motion management strategies (breath-hold, gating, tracking, ITV, etc.)
Target volume definitions	Definition of GTV, ITV, CTV (if added), PTV margins
Dose calculation	Dose calculation algorithm used, heterogeneity correction, prescription parameters (isocenter, % of PTV, or specific isodose line), minimal GTV, ITV, or PTV coverage, mean doses, maximum doses, and equivalent uniform dose. Percent of GTV receiving >110% of prescribed dose, the GTV D95%, total dose, dose per fraction, total number of fractions, number of elapsed days during treatment
Dose delivery	Dose delivery machine, type of image guidance (4D, 3D, 2D, gated), frequency of image guidance, motion management strategies (breath-hold, gating, tracking, compression), motion monitoring

Abbreviations: 2D = 2-dimensional; 3D = 3-dimensional; 4D = 4-dimensional; CTV = clinical target volume; GTV = gross tumor volume; ITV = internal target volume; LC = local control; PTV = planning target volume.

of 120 consecutive stage I NSCLC patients treated with a physical dose regimen of 54 Gy in 3 fractions prescribed to either the PTV (ITV + 3-6 mm) or to the ITV alone.¹¹¹ The LC was 100% at 3 years in both clinical scenarios, confirming the hypothesis that doses to adjacent nontarget tissue are likely sufficient to sterilize the microscopic disease near the GTV.

These metrics should be consistently reported in all future publications. Moreover, it is essential when different dose schemes are used in a single publication that a breakdown of the patients, tumor characteristics, and LC outcomes be reported for each prescription scheme used. Ideally, a prospective web-based dosimetric and outcomes registry that is updated and curated in real time for the entire country would facilitate future endeavors in analyzing radiation outcomes as a function of treatment parameters.

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