Original Report

Stereotactic body radiation therapy and 3-dimensional conformal radiotherapy for stage I non-small cell lung cancer: A pooled analysis of biological equivalent dose and local control

Niraj Mehta MD, Christopher R. King MD, PhD, Nzhde Agazaryan PhD, Michael Steinberg MD, Amanda Hua BA, Percy Lee MD*

Department of Radiation Oncology, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California

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Abstract

Purpose: To determine the relationship between tumor control probability (TCP) and biological effective dose (BED) for radiation therapy in medically inoperable stage I non-small cell lung cancer (NSCLC).

Methods and Materials: Forty-two studies on 3-dimensional conformal radiation therapy (3D-CRT) and SBRT for stage I NSCLC were reviewed for tumor control (TC), defined as crude local control \( \geq \) 2 years, as a function of BED. For each dose-fractionation schedule, BED was calculated at isocenter using the linear quadratic (LQ) and universal survival curve (USC) models. A scatter plot of TC versus BED was generated and fitted to the standard TCP equation for both models.

Results: A total of 2696 patients were included in this study (SBRT: 1640; 3D-CRT: 1056). Daily fraction size was 1.2-4 Gy (total dose: 48-102.9) with 3D-CRT and 6-26 (total dose: 20-66) with SBRT. Median BED was 118.6 Gy (range, 68.5-320.3) and 95.6 Gy (range, 46.1-178.1) for the LQ and USC models, respectively. According to the LQ model, BED to achieve 50% TC (TCD50) was 61 Gy (95% confidence interval, 50.2-71.1). TCP as a function of BED was sigmoidal, with TCP \( \geq \) 90% achieved with BED \( \geq \) 159 Gy and 124 Gy for the LQ and USC models, respectively.

Conclusions: Dose-escalation beyond a BED 159 by LQ model likely translates into clinically insignificant gain in TCP but may result in clinically significant toxicity. When delivered with SBRT, BED of 159 Gy corresponds to a total dose of 53 Gy in 3 fractions at the isocenter.

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* Corresponding author. Department of Radiation Oncology, UCLA Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at UCLA, 200 UCLA Medical Plaza, Suite B265, Los Angeles, CA 90025.

E-mail address: percylee@mednet.ucla.edu (P. Lee).

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Introduction

Non-small cell lung cancer (NSCLC) still remains the leading cause of cancer-related mortality. Although early-stage disease represents a minority of NSCLC cases, an increasing number of patients are now presenting with stage I disease, likely paralleling the aging population and increasing use of computed tomography (CT).

The conventional oncologic procedure of choice to treat stage I NSCLC is lobectomy with hilar and mediastinal lymph node removal, resulting in 5-year overall survival rates of 50%-70% and greater than 80% local control rates. Nevertheless, one-third of patients with potentially curable disease do not undergo surgery because of age and various other medical comorbidities such as chronic obstructive pulmonary disease, cardiac disease, and vascular disease. Historically, for patients not eligible for lobectomy, the options were limited to observation, minimally invasive wedge resection (video-assisted thoracic surgery), and local conventional radiotherapy. However, long-term local control and survival rates have historically been poor, with conventional radiation ranging from 30% to 70% and 15% to 30%, respectively.

Even though dose escalation had been shown to improve local control, efforts to maximize the therapeutic ratio of thoracic radiotherapy were limited largely by normal tissue toxicity. Based on a dose escalation analysis at the University of Michigan, TC was correlated with dose: the D50, or total dose required to achieve 50% local control, at 30 months was reported at 84.5 Gy. Similarly, an analysis by Fowler et al predicted that 70 Gy would achieve local progression-free survival of only 24%, whereas > 100 Gy would be required to achieve a local progression-free survival > 80%.

In order to safely deliver high doses to the tumor and avoid prolonged treatment periods, hypofractionated high-dose stereotactic body radiation therapy (SBRT) has emerged to treat early-stage NSCLC. Because of the relatively high cumulative BED and short treatment time course, SBRT has yielded durable local control results comparable to surgery, with excellent overall survival outcomes, highlighted in medically inoperable patients.

Among the technical considerations in delivering SBRT, issues concerning dose and fractionation have been studied. Dose escalation results and dose-dependent toxicities were described in the RTOG (Radiation Therapy Oncology Group) phase I study of medically inoperable stage I NSCLC. Onishi et al demonstrated in a large multi-institutional retrospective review that a BED of 100 Gy or more produced local control and survival rates that were superior to BED less than 100 Gy.

Fowler et al proposed a radiobiologic rationale using the linear-quadratic (LQ) model to compare the relative biologic effectiveness of various SBRT regimens with typical conventional fractionated regimens for NSCLC. However, Park et al demonstrated that the high doses per fraction used in SBRT may overestimate BED. Although not yet validated, the group proposes a universal survival curve (USC) that models both the LQ and multitarget models based on their experience with NSCLC cell lines.

We sought to investigate the issue of dose by analyzing BED and TC based on the available clinical data. Given the variation in dose-fractionation, we revisited the issue of BED with respect to both the LQ and USC models. Comparing BEDs between the LQ and USC models is important because of the criticism that the LQ model does not apply for higher doses per fraction. Using both the traditional and universal survival curve models, can we delineate an approximate dose range above which little clinical benefit is to be gained with respect to complications?

Methods and materials

Patients

Between 1998 and 2010, 2696 patients with stage IA/IB NSCLC, as defined by the 7th edition of the American Joint Committee on Cancer staging system, underwent definitive thoracic radiation as single modality treatment with either 3-dimensional conformal radiation therapy (3D-CRT) or SBRT as reported in 42 original prospective or retrospective studies. Tables 1 and 2 summarize the dose-fractionation schemes documented in these studies. Pretreatment evaluation always consisted of a history and physical examination and computed tomography, and usually [18F] fluorodeoxyglucose positron emission tomography scan and pulmonary function tests. The diagnosis of NSCLC was either confirmed by biopsy, cytology, or evidence of growth by imaging. Biopsy was usually performed unless medically contraindicated. No patient was staged with mediastinoscopy. Most patients were deemed medically inoperable, although some also refused surgery. Treatment outcomes were reviewed in the context of crude local control as a function of BED.

Radiation therapy technique

Three-dimensional conformal therapy and various techniques for SBRT were utilized, including cyberknife or linear-accelerator based techniques. All patients were simulated via CT scan with standard computer-based planning. Various techniques were used for target volume delineation, dose algorithm calculation, and tumor localization. For the purpose of this analysis, the treatment was categorized as SBRT for fraction sizes greater than or equal to 6 Gy, and as 3D-CRT for fraction sizes less than 5 Gy.
<table>
<thead>
<tr>
<th>Series</th>
<th>Dose per fraction</th>
<th>No. of fractions</th>
<th>Prescription point</th>
<th>Dose per fraction (corrected to isocenter)</th>
<th>BED LQ</th>
<th>BED USC</th>
<th>No. of patients</th>
<th>Tumor control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baumann 2009</td>
<td>15 15</td>
<td>3</td>
<td>67% isodose at PTV periphery</td>
<td>22 15-22.5</td>
<td>234.7</td>
<td>146.9</td>
<td>57</td>
<td>93.0%</td>
</tr>
<tr>
<td>Baumann 2006</td>
<td>10-15 10</td>
<td>3-4</td>
<td>100% isodose at PTV periphery; thus 140%-150% at the isocenter; we used 150%</td>
<td>15-22.5 202.7</td>
<td>133.7</td>
<td>138</td>
<td>88.0%</td>
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</tr>
<tr>
<td>Ricardi 2010</td>
<td>15 15</td>
<td>3 3</td>
<td>80% isodose-encompassing PTV, with normalization to 100% at isocenter</td>
<td>18.75 178.8</td>
<td>123.3</td>
<td>62</td>
<td>92.7%</td>
<td></td>
</tr>
<tr>
<td>Fakiris 2009</td>
<td>20-22 20</td>
<td>3 3</td>
<td>80% isodose includes &gt;95% PTV</td>
<td>25-27.5 320.3</td>
<td>178.1</td>
<td>70</td>
<td>94.3%</td>
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<tr>
<td>Kopek 2008</td>
<td>15-22.5 15-22.5</td>
<td>3</td>
<td>Isocenter</td>
<td>15-22.5 158.7</td>
<td>111.9</td>
<td>89</td>
<td>94.4%</td>
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<tr>
<td>Koto 2005</td>
<td>7.5-15 21</td>
<td>3-8</td>
<td>Isocenter</td>
<td>7.5-15 119.5</td>
<td>101.2</td>
<td>31</td>
<td>71.0%</td>
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<tr>
<td>Takeda 2009</td>
<td>10 10</td>
<td>5 5</td>
<td>80% isodose at PTV periphery</td>
<td>12.5 12.5</td>
<td>153.3</td>
<td>129.7</td>
<td>63</td>
<td>95.2%</td>
</tr>
<tr>
<td>Onimaru 2008</td>
<td>10-12 10</td>
<td>4</td>
<td>Isocenter</td>
<td>10-12 95.5</td>
<td>85.7</td>
<td>41</td>
<td>57.0%</td>
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<tr>
<td>Nagata 2005</td>
<td>12 12</td>
<td>4 4</td>
<td>Isocenter</td>
<td>12 114.9</td>
<td>98.9</td>
<td>45</td>
<td>98.0%</td>
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<tr>
<td>Salazar 2008</td>
<td>10 10</td>
<td>4</td>
<td>70% isodose at PTV periphery</td>
<td>13 130.6</td>
<td>108.6</td>
<td>60</td>
<td>98.0%</td>
<td></td>
</tr>
<tr>
<td>Chang 2008</td>
<td>10 10</td>
<td>4-5</td>
<td>75%-90% isodose at PTV periphery</td>
<td>11.9 114.6-143.2 98.7-123.3 13 13 57.1%/100%</td>
<td>57.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hof 2007</td>
<td>19-30 19-30</td>
<td>1 1</td>
<td>85% isodose dose calculated at 80% isodose</td>
<td>19-30 85.4-116.6 51.6-62.6 42 42 60.0%/94.0%</td>
<td>60.0%</td>
<td></td>
<td></td>
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<tr>
<td>Hoyer 2005</td>
<td>15 15</td>
<td>3 3</td>
<td>Isocenter</td>
<td>15 143.2</td>
<td>96.0</td>
<td>40</td>
<td>85.0%</td>
<td></td>
</tr>
<tr>
<td>Lagerwaard 2008</td>
<td>7.5-20 7.5-20</td>
<td>3-8</td>
<td>80% isodose at PTV periphery</td>
<td>9.4-25 236.7 162.1 96.0 206 206 97.0%</td>
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<td></td>
</tr>
<tr>
<td>Le 2006</td>
<td>15-30 15</td>
<td>1 1</td>
<td>Median IDL 72% 85%-90% isodose includes &gt;95% PTV</td>
<td>20.8-41.7 71.3-185.4 13.7-20.6 91.1 130.7 20 95.0% 93.0%</td>
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<tr>
<td>Ng 2008</td>
<td>12-18 12</td>
<td>3-4</td>
<td>50% isodose includes &gt;95% PTV</td>
<td>10 216.2</td>
<td>99.4</td>
<td>43</td>
<td>95.0%</td>
<td></td>
</tr>
<tr>
<td>Xia 2006</td>
<td>5 5</td>
<td>5</td>
<td>90% isodose at PTV periphery</td>
<td>11.1-13.3 149.3</td>
<td>95.3</td>
<td>21</td>
<td>81.0%</td>
<td></td>
</tr>
<tr>
<td>Yoon 2006</td>
<td>10-12 10</td>
<td>3-4</td>
<td>60% isodose at PTV periphery</td>
<td>11.7-20.8 183.5 130.9 68 94.1%</td>
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<tr>
<td>Zimmerman 2006</td>
<td>7-12.5 7-12.5</td>
<td>3-5</td>
<td>75%-80% isodose at PTV periphery</td>
<td>15.5-25.8 309.6 174.6 70 96.0%</td>
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<td></td>
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<tr>
<td>van der Voort 2009</td>
<td>12-20 12-20</td>
<td>3 3</td>
<td>85% isodose covering 95% PTV</td>
<td>11.8-23.5 149.3 115.7 32 87.5%</td>
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<td></td>
<td></td>
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<tr>
<td>Song 2009</td>
<td>10-20 10-20</td>
<td>3-4</td>
<td>90% isodose covering 95% PTV</td>
<td>11.8-23.5 149.3 115.7 32 87.5%</td>
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<td></td>
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</tr>
<tr>
<td>Fritz 2008</td>
<td>30 30</td>
<td>1</td>
<td>95% PTV covered</td>
<td>30 134.6 68.4 40 92.5%</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Timmerman 2010</td>
<td>20 20</td>
<td>3</td>
<td>80% PTV isodose</td>
<td>20 199.5 132.4 55 97.6%</td>
<td></td>
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</tr>
<tr>
<td>Haasbeek 2010</td>
<td>7.5-20 7.5-20</td>
<td>3-8</td>
<td>80% isodose line</td>
<td>9.4-25 227.4 160.8 193 97.6%</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Pennathur 2007</td>
<td>20 20</td>
<td>1</td>
<td>65%-80% isodose at PTV periphery</td>
<td>25 97.6</td>
<td>56.2</td>
<td>16</td>
<td>46.8%</td>
<td></td>
</tr>
<tr>
<td>Guckenberger 2009</td>
<td>6-26 6-26</td>
<td>1-8</td>
<td>65%-80% isodose at PTV periphery</td>
<td>9.2-32.5 175.5 120.8 41 92.7%</td>
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</tbody>
</table>

BED, biological effective dose; LQ, linear quadratic; NSCLC, non-small cell lung cancer; PTV, planning target volume; SBRT, stereotactic body radiation therapy; USC, universal survival curve.
Study design and statistical analysis

Only studies with at least 2-year crude tumor control (TC) data were included (Tables 1 and 2). Some studies reported distinct results for patients treated with different doses and were therefore included as separate data points in this analysis. For a given dose-fractionation schedule, some institutions prescribed to the planning target volume (PTV) periphery and others to the isocenter. These differences were accounted for by scaling the isocenter dose ($d_{\text{iso}}$) using the following calculation: $d_{\text{iso}} = \frac{d_{\text{reported}}}{\% \text{ isodose at PTV periphery}}$.

The USC-predicted BED ($\text{BED}_{\text{USC}}$) and standard effective dose (SED), which is the USC-predicted equivalent dose in 2 Gy, were calculated from the model described by Park et al.\(^{15}\) According to the USC model, $D_T$ is the transition dose from the linear-quadratic to the multi-target model, $D_0$ is the parameter that determines the final slope of the survival curve, and $D_q$ is the x-intercept or quasi-threshold dose. To calculate $\text{BED}_{\text{USC}}$, $\text{BED} = d \left[1+(d/n)/(\alpha/\beta)\right]$ (Equation 1, LQ model) was used, assuming an $\alpha/\beta$ ratio of 8.6 for tumor ($n$ = number of fractions, $d$ = total dose) for $d < D_T$, and the following equation was used for $D_T \geq 6$: $\text{BED} = \left(\frac{1}{\alpha*\text{D}_0}\right) \times \left[D - n \times \text{D}_q\right] - \left(\frac{1}{\alpha/\beta}\right)$, where $d_{\text{CRT}} = 2$ (to obtain USC-predicted dose at 2 Gy per fraction) and $\alpha/\beta = 8.6$ (derived from formulas in Park et al.\(^{15}\)). We use an $\alpha/\beta$ ratio of 8.6 to be consistent because the USC model derived their values for $\alpha$, $D_0$, and $D_q$ from reports of 12 NSCLC cell lines from the National Cancer Institute.

The $\text{BED}_{\text{LQ}}$ was then calculated at the isocenter using the LQ formula, Equation 1, assuming an $\alpha/\beta$ ratio of 8.6 for tumor based on data of Park et al.\(^{15}\) to achieve a direct comparison with $\text{BED}_{\text{USC}}$. The equivalent dose in 2 Gy (EQD2) was calculated using the LQ model using the following equation:

$$\text{EQD2} = \frac{d(\alpha/\beta + d/n)}{(\alpha/\beta + 2)}.$$

Scatter plots of TC as a function of $\text{BED}_{\text{LQ}}$, $\text{BED}_{\text{USC}}$, EQD2, and SED were then created. The scatter plots were fitted to the standard tumor control probability (TCP) equation by the least-squares method: TCP = $\exp\left(\frac{d - \text{TCD}_{50}}{k}\right)$, where TCD$_{50}$ is the dose to attain 50% local control, and $k$ is a fitting parameter corresponding to the slope at the TCD$_{50}$ dose point. The proportional increase in TCP per additional Gray in the steep part of the curve is given by parameter Slope$_{50} = 25/k$.

Results

Patient, disease, and treatment factors

Of 2696 total patients described in the range of studies, 61% were treated using SBRT and 39% were treated using various 3D-CRT techniques (Table 3). The most commonly reported histology was squamous cell carcinoma. Stage I tumors were treated, including T1 and T2 lesions, although there was insufficient information to analyze outcomes stratified by size or volume. The upper limits
of the prescription doses were 66 Gy and 102 Gy for the SBRT and 3D-CRT cohorts, respectively.

The TCP curves fitted to the 3D-CRT and SBRT series are shown in Figs 1 and 2 for equivalent dose representing the standard LQ and USC models, respectively. Because of the relatively narrow range of BEDs (68.5-120.9 Gy) employed via 3D-CRT, a separate least-squares analysis for the 3D-CRT data points alone was not possible.

Table 4 describes the predicted local control rates over various specified ranges of $BED_{LQ}$ and $BED_{USC}$. The observed TCP is $\geq 90\%$ for $BED_{LQ} \geq 159$ Gy and $EQD2 \geq 125$ Gy. Using the USC model, the predicted TCP is $\geq 90\%$ for $BED_{USC} \geq 124$ Gy and $SED \geq 128$ Gy, respectively. The fitted values for $TCD_{50}$, $k$, and $R^2$ are given in Table 5 for $BED_{LQ}$, $BED_{USC}$, $EQD2$ and $SED$ plotted against local control.

Qualitatively, the differences between the 2 models are most significant within the intermediate dose range between 75 and 175 Gy, beyond which the TCP is approximately the same for the LQ and USC models. For instance, to achieve 75%-80% TCP, the LQ model corresponds to 111-125 Gy, whereas the USC model corresponds to 87-97 Gy. At the 90%-95% TCP, the magnitude of variability is still prominent at 161-196 Gy and 126-153 Gy for the LQ and USC models, respectively. With BEDs above 200 Gy, both models predict for $N95\%$ TCP.

### Discussion

We have analyzed the relationship between TCP and BED based on a systematic review of patients treated definitively with radiation therapy via both SBRT and conventional therapy. A $BED_{LQ}$ of 159 Gy and $BED_{USC}$ of 124 Gy predicts $90\%$ local control, which corresponds to a prescription isocenter dose of 53 Gy, 59 Gy, and 64 Gy for the LQ model and 57 Gy, 59 Gy, and 60 Gy for the USC model in 3, 4, and 5 fractions, respectively, assuming standard BED calculations with an $\alpha/\beta = 8.6$. As expected, the LQ model estimates a higher dose requirement for equivalent tumor control compared with the USC model. However, at therapeutic doses in an SBRT regimen, the clinical significance between the 2 models is minimal, as highlighted above.

As more research in the United States continues to develop in evaluating the benefits of screening high-risk patients, a significantly greater proportion of cancers will be diagnosed at an early stage. In parallel, efforts to improve quality control of imaging analysis, identify clinical clues, and order key diagnostics will be pivotal in potentially increasing the overall cure rate. But as SBRT continues to play an expanded role in managing these early-stage patients, key issues regarding dose-fractionation and BED will become important.

Our conclusions are consistent with the Indiana phase I dose escalation study, which reported 9 of 10 local failures at doses below a BED of 125 Gy, corresponding to $\leq 48$ Gy at 16 Gy per fraction. Also, in a large single-institution study from Japan, using total doses 18-75 Gy in 1-22 fractions, Onishi et al noted that local recurrence rates were 8.4% and 26.4% for BEDs $\geq 100$ and BEDs < 100, respectively. In contrast, our pooled analysis...
incorporates various fractionation regimens for SBRT as well as conventional 3D-CRT techniques to demonstrate the relationship between BED and tumor control on a continuous scale. The given variation of local control for a given dose range between this analysis and prior single-institution cohorts can be partly attributed to our adoption of an $\alpha/\beta$ ratio = 8.6, which was used to compare the LQ and USC models. Also, the heterogeneity in treatment planning techniques, tumor size, tumor volume, image guidance, and the incorporation of substantially lower 3D-CRT doses may contribute to the disparity. Nevertheless, our results also confirm that achieving an acceptable local control $\geq 90\%$ would require BEDs substantially above 100 Gy for both models.

Our analyses also suggest that there exists a range of BEDs ($\geq 200$ Gy) for both models beyond which an insignificant benefit would be gained, suggesting that lower BEDs can still successfully eradicate disease, regardless of what model is used. This is supported by the experience at various institutions where single fraction stereotactic regimens successfully eradicated stage I tumors. The rationale for accepting a slightly lower BED to achieve maximal tumor control is twofold: to avoid unnecessary complications and to successfully treat tumors in central locations where excess toxicities have been reported in the literature. Our model can be used when creating dose prescriptions, where issues of normal tissue constraints come into effect specified by RTOG guidelines by delivering an acceptable BED$_{LQ}$ without significantly exceeding normal tissue constraints.

There were several limitations to this study, including different planning techniques, radiation delivery systems, tumor repopulation in non-SBRT cohorts, and its retrospective nature, which may account for the inherent degree of differences in tumor control for a given dose utilized. Our model represents the dose-response curve for a heterogeneous biologic population, and not for the individual patient, as every point on the graph represents a specific cohort of patients in a study. In addition, we reported crude, not actuarial, local control because many deaths in the medically inoperable population occur unrelated to lung cancer.

Aside from dose, there are other variables such as biologic and geographic misses, tumor size, and location that impact TC that could not be integrated into the analysis. Tumor burden measured in volume plays an integral role in determining outcome with SBRT, as demonstrated by several studies showing trends for decreased local control for stage IB versus IA patients. Due to the lack of information, correlating dose and tumor volume with local control was not possible. Lesions in the proximal bronchial tree are often managed differently than more peripheral neoplasms. Because of reported complications such as bronchitis, tracheal necrosis, bleeding, and fistula, patients with central tumors may have received lower doses, thus impacting the local control rate.

Neither BED model adjusted for potential accelerated repopulation seen in an extended 3D-CRT treatment regimen as opposed to a substantially shorter SBRT course. There was also no uniform quality control for issues pertaining to PTV coverage, geographic misses, and dose calculation algorithms. Pencil beam convolution-based algorithms have shown deficiency in managing the presence of heterogeneous tissues. Another inconsistent variable was the use of inhomogeneity corrections to

<table>
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<th>Table 4</th>
<th>Biological equivalent dose versus tumor control for LQ and USC models</th>
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<tr>
<td>BED–Gy</td>
<td>Projected tumor control: LQ</td>
</tr>
<tr>
<td>50-75 Gy</td>
<td>44%-58%</td>
</tr>
<tr>
<td>76-100 Gy</td>
<td>58%-70%</td>
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<tr>
<td>101-125 Gy</td>
<td>70%-80%</td>
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<tr>
<td>126-150 Gy</td>
<td>80%-88%</td>
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<tr>
<td>151-175 Gy</td>
<td>86%-92%</td>
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<tr>
<td>176-200 Gy</td>
<td>92%-95%</td>
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<tr>
<td>200-225 Gy</td>
<td>95%-97%</td>
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<tr>
<td>225-250 Gy</td>
<td>97%-98%</td>
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<tr>
<td>$\geq 250$ Gy</td>
<td>$\geq 98%$</td>
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</table>

BED, biological effective dose; LQ, linear quadratic; USC, universal survival curve.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Fitting parameters for dose-response curves</th>
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<tbody>
<tr>
<td>$TCD_{50}$ (Gy)</td>
<td>Slope$_{50}$ (%/Gy)</td>
</tr>
<tr>
<td>BED$_{LQ}$</td>
<td>61.04</td>
</tr>
<tr>
<td>BED$_{USC}$</td>
<td>46.83</td>
</tr>
<tr>
<td>EQD$_2$</td>
<td>50.01</td>
</tr>
<tr>
<td>SED</td>
<td>34.96</td>
</tr>
</tbody>
</table>

BED, biological effective dose. $^a$ Corresponds to fit $P$ value $<$ .0001.
compute dose and actual prescription points to the PTV periphery or the isocenter.

In summary, this analysis presents dose-response curves using both the standard LQ model and the universal survival curve for patients with early stage NSCLC being treated with definitive radiotherapy. These curves may be useful for treating physicians, especially with respect to choosing a particular dose per fraction and overall BED\textsubscript{LQ}. The USC model differs from the LQ model in predicting BED, but its clinical significance is questionable at higher therapeutic doses required to obtain >90% TC. Our results lend further support to the previous data reported on the minimal BED necessary to achieve TC in early stage NSCLC. Future efforts need to examine the actual effect of the dose per fraction in addition to the impact of tumor volume such that dose may be tailored to the individual patient.

References

30. Lagerwaard FJ, Haasbeek CJ, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for...


