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Lung cancer SBRT

Local control dependence on consecutive vs. nonconsecutive fractionation in lung stereotactic body radiation therapy

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ABSTRACT

Background: Recent reports demonstrate impaired tumor re-oxygenation 24–48 h after stereotactic body radiation therapy (SBRT), suggesting that non-consecutive treatment delivery may be advantageous. To test this hypothesis clinically, we compared local control in patients treated in consecutive daily fractions vs. nonconsecutive fractions.

Methods: We retrospectively reviewed 107 lung SBRT patients (117 tumors) treated for T1–T2N0 NSCLC with LINAC based SBRT (50 or 60 Gy/5 fractions). Patients were characterized as having been treated in consecutive daily fractions vs. in non-consecutive fractions. Local control, survival and toxicity end points (CTCAE V4.0) were compared. Propensity score matching and Cox regression analyses were performed in order to determine the effect of fractionation on local control.

Results: With a median follow up of 23.7 months, 3-year local control was superior at 93.3% vs. 63.6% in the non-consecutive and consecutive group, respectively ($p = 0.001$). Multivariate analysis and propensity score matching showed that consecutive fractionation was an independent predictor of local failure. Overall survival trended toward improvement in the non-consecutive group, but this was not statistically significant ($p = 0.188$). Development of any grade 2 toxicity was not significantly different between the two groups ($p = 0.75$).

Conclusion: Five-fraction SBRT delivered over non-consecutive days imparts superior LC and similar toxicity compared to consecutive fractionation. These results should be validated in independent datasets and in a prospective fashion.

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Stereotactic body radiation therapy (SBRT) utilizing high doses per fraction, often in 5 or fewer treatments, is being increasingly employed in the setting of early stage non-small cell lung cancer as well as oligometastatic disease [1,2]. Published guidelines recommend doses ranging from 48 to 60 Gy in 3–8 fractions [3]. Improved target visualization, treatment delivery and image guidance have allowed for significantly higher doses to be delivered, which has translated in the clinic to a ⩾90% local control (LC) rate at 3 years [4–7].

The biology underpinning the impressive effects of SBRT has not been clearly elucidated, and debate over the mechanisms of cell kill in SBRT is approaching a critical junction [8–12]. Classical radiation biology principles introduce an important concern when employing fewer delivered fractions since it allows for less opportunity for tumor reoxygenation. Radiobiological modeling has shown that radiation delivery with fewer than 10 fractions results in a significant decrease in tumor cell killing compared to standard fractionation as a result of tumor hypoxia [13]. Several reports have detailed that the linear quadratic formalism adequately models clinical tumor control probability in multifraction SBRT, but also have shown that single fraction regimens impart inferior local control compared to multifraction regimens irrespective of dose escalation within the reported range, with the most likely explanation being presence of radio-resistant subpopulation of hypoxic cells [9,14–17]. In addition, tumor hypoxia-induced radioresistance has been postulated as a plausible explanation between discrepant results from radiobiological modeling and clinical results, since biological effective doses (BEDs) of ⩾100 Gy, much higher than would be predicted by standard modeling for fully oxygenated cells, are needed to achieve ⩾90% LC [18]. This suggests that an inherent radio-resistant cell population exists [18,19]. Standard fractionation in radiotherapy functions to inhibit this effect by exploiting reoxygenation, allowing for the hypoxic component of

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cells to become oxygenated over multiple fractions, likely from transient and non-uniform changes in blood flow. Therefore, tumor hypoxia may be a more important determinant of tumor response in hypofractionated regimens. Alternatively, new biology particularly functioning through vascular and immunogenic effects has been espoused by some groups to account for the clinical effects of SBRT [21,20,22,23].

The timing of reoxygenation after radiation delivery can vary, and reports utilizing preclinical models and one clinical report using noninvasive molecular imaging via [^{18}F]-fluoromisonidazole positron emission tomography ([^{18}F]-FMISO PET) imaging have demonstrated detectable hypoxia in lung tumors 24–48 h after a single fraction of SBRT to the lung [24–27]. Therefore, nonconsecutive treatment delivery with a significant interval of time between fractions may be advantageous in order to exploit reoxygenation kinetics. One published trial randomized 54 patients between a 4 fraction consecutive daily scheme and a 4 fraction course delivered over 11 days and reported a trend toward increased toxicity in the consecutively treated group, but did not report on LC or survival [28]. As of yet, no trial has investigated LC effects from consecutive vs. nonconsecutive treatment delivery schedule. The purpose of the study is to compare LC of lung SBRT in patients treated in consecutive daily fractions vs. treatment on nonconsecutive days.

Methods

We analyzed our database of 193 SBRT patients treated at one institution from 2006 to 2014 with linear accelerator (LINAC)-based lung SBRT to identify patients. Study design and development were approved by institutional review and privacy boards (IRB Number LU205020).

Patients treated with curative intent for T1–T2N0 NSCLC were included in the analysis. A total of 107 patients (117 individual tumors) having at least 6 months follow up were identified. Patients were treated with 50 Gy or 60 Gy in 5 fractions, prescribed to the 70–100% isodose line. Patients who received treatment for metastatic tumors, patients who received dose fractionation other than five fraction 50 Gy or 60 Gy, and patients not completing course of SBRT were excluded. Patients were simulated with helical 4-dimensional (4D) computed tomography (CT) scan utilizing respiratory imaging and synchronization via Real-time Position Management System (Varian Oncology, Palo Alto, California). An internal target volume (ITV) was delineated incorporating maximum inspiratory, maximum expiratory, as well as maximum intensity projection of the CT data. A uniform 5 mm planning target margin (PTV) was placed around the ITV. Respiratory-gated treatment was reserved for tumors with motion of greater than 1 cm. Three-dimensional conformal technique, static intensity modulated radiation therapy, or volumetric modulated arc therapy were employed for treatment delivery.

Based on treatment duration determined from the record, patients were characterized as having been treated in consecutive days ($\leqslant$7 days) vs. non-consecutive days (>7 days). Seven days was chosen because a 5 fraction course that was started mid-week would conclude the following week for a total duration of 7 days. The most common delivery schedule employed in the consecutively treated group included patients treated daily Monday–Friday in one week. The most common non-consecutive delivery schedule employed treatment with at least one day between SBRT fractions, treating two fractions per week as shown in Fig. 1.

Local control was classified by the Radiation Therapy Oncology Group (RTOG) 0236 criteria, and defined as the absence of local failure. Local failure was defined as at least 20% increase in the largest dimension of treated tumor measurable by CT and positron emission tomography (PET) imaging with uptake of a similar intensity as the pretreatment staging PET, or the measurable tumor should be biopsied confirming viable carcinoma. Marginal failures defined as failure within 1 cm of the treated tumor were considered local failures [3,29].

Clinicopathologic characteristics were collected including age, Karnofsky performance status (KPS), clinical stage, tumor histology, and central vs. peripheral tumor location. On-treatment and post treatment toxicity graded by Common Toxicity Criteria for Adverse Events, Version 4.0, on multiple domains of pulmonary, cardiac, upper gastrointestinal, esophagus, chest wall, and rib fracture was also obtained and compared between groups [30].

Statistics

Kaplan–Meier method was used to calculate time to local failure and overall survival. Log-rank test was used to compare treatment groups. A propensity score analysis was performed to generate a matched cohort using nearest-neighbor methodology on the following criteria: tumor size, dose, age, KPS, follow up time, and tumor pathology. Fisher's exact test and chi square analysis were used for categorical variable analysis, student's *T*-test was used for continuous variables. Adjusted logistic regression model was used to calculate odds ratios for a categorical comparison with correction applied to resolve zero cell observations [31]. To evaluate the effects of treatment and patient factors affecting LC simultaneously, hazard ratios for time to local failure were estimated by Cox regression survival model. Propensity score was performed in R Version 3.2.2 (Vienna, Austria) and other analyses were conducted using SAS version 9.4 (Cary, NC).

Results

With a median follow up of 23.7 months, we identified 43 cases that were treated consecutively and 74 cases that were treated non-consecutively. The majority (78.7%) of cases were T1 and most patients were treated with 50 Gy in 5 fractions (88.0%) (see Table 1).

Of the entire cohort, 18 (15.4%) local failures were recorded, with 14 (32.6%) failures in the group treated consecutively and 4 (5.4%) failures in the non-consecutive group. Three-year local control was significantly superior at 93.3% in the non-consecutive treated group vs. 63.6% in the consecutive group ($p = 0.001$) (see Fig. 2a). After propensity score matching with 1:1 ratio adjusting for variations in dose, tumor size, patient age, KPS, follow up time, and tumor pathology, 41 consecutively treated and 41 nonconsecutively treated cases were successfully matched. Three-year LC rates remained significantly superior at 97.5% in the non-consecutive vs. 63.6% in the consecutively treated group ($p = 0.003$) (see Supplementary Fig. 1a).

On univariate analysis, LC did not vary depending on age, KPS, median follow up, tumor stage, tumor size, and radiation dose (50 Gy vs. 60 Gy) (see Supplementary Table 1). There was a significant difference in the frequency of patients who experienced local failure between treatment eras ($p = .0497$). The majority of the patients (91.3%) in the 2006–2008 era were treated consecutively, but 22.6% continued to be treated consecutively in 2009–2014 era (see Supplementary Table 2). In order to elucidate the interaction of fractionation schedule and treatment era, adjusted logistic regression was performed and determined the effect of treatment on local failure did not vary as a function of era ($p = .65$).

Multivariate Cox regression survival analysis determined patients treated consecutively were 4.83 (95% CI 1.56–14.98) at any given time to experience local failure ($p = 0.006$) (Table 2). This effect of treatment on LC continued to be significant when