Radiotherapy and Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Patterns and correlates of treatment failure in relation to isodose distribution in non-small cell lung cancer: An analysis of 1522 patients in the modern era

Todd A. Pezzi [a], Chad Tang [a], Cameron W. Swanick [a], Penny Fang [a], Kenneth Hess [b], Ting Xu [a], Stephen M. Hahn [a], Joe Y. Chang [a], Zhongxing Liao [a], Daniel Gomez [a,*]

[a] Department of Radiation Oncology; and [b] Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, United States

ARTICLE INFO

Article history:
Received 17 January 2017
Received in revised form 9 September 2017
Accepted 16 September 2017
Available online xxxx

Keywords:
NSCLC
Dose–response
BED
Radiation therapy

ABSTRACT

Background and purpose: To examine the relationship between radiation dose and tumor control in limited stage non-small cell lung cancer (NSCLC).

Materials and methods: We searched a database of 1552 patients who received radiation therapy for non-metastatic NSCLC between 2000 and 2016. The primary endpoint was freedom from in-field failure.

Results: Increasing BED correlated with decreasing estimated gross tumor volume–planning target volume expansion, and on multivariable analysis increasing BED was associated with an increased chance of field-edge failures (hazard ratio [HR] 1.032, 95% confidence interval [CI] 1.004–1.062, $P = 0.027$). Increasing BED also correlated with improved freedom from in-field failure on multivariable analysis (HR 0.978, 95% CI 0.964–0.993, $P = 0.003$), with the dose–response curve showing a sigmoidal relationship between increasing BED and freedom from in-field failure.

Conclusion: In this large study of patients treated in the modern era with varying dose fractionation regimens, higher BED was associated with improved freedom from in-field failure, and that this relationship appeared to be consistent with the classically described sigmoid shape. We also found that increased BED was associated with higher field-edge failures, implying that margin size may need to be further studied in patients receiving ablative regimens of radiation.

Introduction

Lung cancer is the leading cause of cancer death in the United States, with more than 200,000 new diagnoses expected in 2016 [1]. Outcomes of patients with non-small cell lung cancer (NSCLC) are generally poor, with overall 5-year survival rates of about 15% across all stages of disease. The putative dose–response relationship between radiation dose and tumor control probability has been studied extensively in both in vitro and in vivo models. Although this relationship probably varies on the basis of individual tumor biology, it has been reported most often as variations on the classically described sigmoidal curve [2–6].

Dose-escalation trials in patients with NSCLC have shown mixed outcomes [7–9]. The rapid technologic advances in radiation therapy (RT) planning and delivery have led to pressure to conduct additional dose-escalation trials using modern RT techniques [10–13]. Although the benefit of high-dose radiation has been shown for patients with early-stage disease, its broader application was challenged by the findings of RTOG 0617, a phase III trial that showed inferior overall survival, along with a detriment in quality of life, at a dose of 74 Gy as compared with 60 Gy for patients with locally advanced NSCLC who receive concurrent chemotherapy [14–18].

To our knowledge, no large clinical series has reported rates of *in-field* failure of limited stage NSCLC across a variety of biological effective doses (BED). The purpose of this study was to (1) provide such a report for a large number of patients across various dose and fractionation regimens, (2) assess relationships between failures to dose-fractionation regimens to identify potential patterns based on dose threshold, and (3) determine the form of the relationship between BED and the probability of in-field tumor control, assuming a clear relationship exists.

* Corresponding author at: Department of Radiation Oncology, Unit 1422, The University of Texas MD Anderson Cancer Center, 1400 Pressler St., Houston, TX 77030-4008, United States.

E-mail address: Dgomez@mdanderson.org (D. Gomez).

https://doi.org/10.1016/j.radonc.2017.09.018
0167-8140/

Materials and methods

Patient selection

We retrospectively reviewed charts from 2042 patients diagnosed with NSCLC who received RT at MD Anderson Cancer Center in Houston, TX from 2000 through 2016. The following data were extracted from the charts: age, histology, disease stage per the 6th or 7th edition of the American Joint Committee on Cancer staging system, gross tumor volume (GTV), planning tumor volume (PTV), Eastern Cooperative Oncology Group (ECOG) functional status, chemotherapy, total radiation dose, number of fractions, and the date and location of first failure. We did not consider induction and concurrent chemotherapy categories to be mutually exclusive. BED was calculated from the prescribed dose to standardize the various fractionation schemes using the linear quadratic equation. An alpha/beta ratio of 10 Gy was used [19]. Alternative BEDs were also calculated to correct for repopulation in treatment schedules longer than 21 days [20]. Patients with T3 or T4 disease (AJCC 6th or 7th edition) were combined for analysis. A total of 490 patients were excluded from analysis because of presentation with recurrent disease, metastasis, missing follow-up data, or unknown or T0T status. The final study group comprised 1552 patients.

Definition of endpoints

The primary endpoint was freedom from in-field failure, which was defined as any evidence of tumor progression or recurrence within the 90% isodose line on the patient's radiation treatment plan when subsequently captured by surveillance imaging. The epicenter of grossly visible tumor was used as the point of reference. Secondary endpoints were freedom from field-edge recurrence and freedom from out-of-field failure, defined as between the 50% and 90% isodose lines, and outside the 50% isodose line, respectively. Out-of-field failure was considered equivalent to distant progression.

Treatment failure was determined from diagnostic images obtained during follow-up. The location of the recurrent site in relationship to the treatment site was estimated by superimposing patient imaging with the radiation treatment plan. Diagnostic images were generally obtained every 3 months after treatment for the first year, every 4 months for the second to third year, and annually thereafter. Patients were censored at time of last available imaging. The imaging modality of choice was positron emission tomography–computed tomography (PET-CT) or CT alone. Fibrosis was differentiated from recurrence with physician judgement, and biopsy was performed when feasible and deemed clinically necessary to confirm failure, but also at the discretion of the treating physician.

BED analysis

Patients were separated into 5 mutually exclusive groups based on BED as follows: 70–75 Gy_{10}, 75–80 Gy_{10}, 80–85 Gy_{10}, 85–90 Gy_{10}, and 90–120 Gy_{10}. There were no patients falling on the lines of divisions between BED groups. The Kaplan–Meier curves were generated for freedom from in-field failure, field-edge failure, and out-of-field failure. All endpoints were calculated independently from one another, even in the event of simultaneous distant metastasis and local progression. Times to events were indexed to the date of radiation completion. Outcomes were compared using the log-rank test. One-dimensional, linear estimates of the estimated GTV–PTV expansion were calculated under the assumption that the GTV and PTV were represented by spherical volumes. Cases diagnosed before 2009 were excluded from the GTV–PTV expansion calculation due to limitations of data availability. Cox proportional hazard models were generated to identify correlates of treatment failure. A correlation matrix and variance inflation factors were used to confirm the absence of significant multicollinearity.

To explore the functional form of the relationship between BED and in-field control, a plot of in-field control as a function of BED was created using the Kaplan–Meier–based moving averages and visualized with a lowess (local regression) smoother. A multivariable Cox proportional hazard model was also generated. All analyses were 2-sided when appropriate, with $\alpha < 0.05$ considered statistically significant. Statistical analyses were done with SAS v. 9.4, JMP Pro v. 10 (Cary, NC), and IBM SPSS v. 24 (Armonk, NJ).

Results

Patient characteristics, stratified by the 5 BED groups, are presented in Table 1. The BED distribution is shown in Fig. 1. Of the 1552 patients in the final study group, the median age at diagnosis was 67 years (interquartile range [IQR] 15). In terms of tumor histology, 662 patients (42.7%) had adenocarcinoma, 562 (36.2%) had squamous cell carcinoma, and 328 (21.1%) had miscellaneous or unspecified NSCLC. As for performance status, 454 patients (29.3%) had an ECOG score of 0, 957 (61.7%) had ECOG 1, 115 (7.4%) had ECOG 2, and 16 (1.0%) had ECOG $\geq$ 3. The tumor category distribution was 378 patients (24.4%) with T1, 593 (38.2%) with T2, and 581 (37.4%) with either T3 or T4 tumors. Mean GTV was 162.3 cm^3 (IQR 138.8 cm^3). Most patients had N2 disease: 389 (25.1%) had N0 (or NX), 156 (10.1%) N1, 694 (44.7%) N2, and 313 (20.1%) N3. A total of 495 patients (31.9%) received induction chemotherapy, 1045 (67.3%) received concurrent chemoradiation therapy, and 261 (16.8%) received adjuvant chemotherapy.

Of the 701 cases diagnosed in 2009–2016, 489 (70.0%) had data available on both GTV and PTV. The distance of the estimated GTV–PTV expansion was noted to decrease with increasing BED (Fig. 2A), and the rate of field-edge failure (total of 41 events) increased with decreasing length of estimated GTV–PTV expansion (Fig. 2B) The estimated GTV–PTV expansion was a significant predictor of field-edge failure on univariate Cox proportional hazard analysis (hazard ratio [HR] 0.269, 95% confidence interval [CI] 0.112–0.647, $P = 0.003$); however, this factor lost its significance in the multivariable model (not shown).

According to the reverse Kaplan–Meier method, the median follow-up time was 45.6 months. The Kaplan–Meier estimates (±standard error [SE]) of the 12-month and 24-month rates of in-field freedom from failure were 86.7% (±1.1%) and 79.5% (±1.2%), respectively. When the patients were stratified into the 5 BED groups, rates of in-field freedom from failure at 12 months were similar between the 4 lower-BED groups (82.9% ± 1.9%–87.6% ± 2.4%), but the in-field rate for the highest-BED group was significantly improved (95.8% ± 2.2%) ($P < 0.001$, Fig. 3A). On multivariable analysis, squamous histology (HR 1.435, 95% CI 1.043–1.974, $P = 0.026$), T2 status (HR 1.620, 95% CI 1.138–2.305, $P = 0.007$), and increasing BED (HR 0.978, 95% CI 0.964–0.993, $P = 0.003$) were significant predictors of in-field failure (Table 2).

The 12- and 24-month rates of freedom from field-edge failure were 98.6% ± 0.4% and 95.7% ± 0.8%, respectively. The rates of freedom from field-edge failure at 12 months were again similar between the 4 lower-BED groups (98.0% ± 1.6%–98.6% ± 1.1%), but the field-edge rates were significantly inferior for the highest-BED group (93.7% ± 2.2%) ($P = 0.003$, Fig. 3B). On multivariable analysis, only increasing BED (HR 1.032, 95% CI 1.004–1.063, $P = 0.027$) remained a statistically significant correlate of field-edge failure (Table 2).

The 12- and 24-month rates of freedom from out-of-field failure were considerably lower than those for in-field and field-edge

Please cite this article in press as: Pezzi TA et al. Patterns and correlates of treatment failure in relation to isodose distribution in non-small cell lung cancer: An analysis of 1522 patients in the modern era. Radiother Oncol (2017), https://doi.org/10.1016/j.radonc.2017.09.018