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Histology significantly affects recurrence and survival following SBRT for early stage non-small cell lung cancer

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ABSTRACT

Background: Contrary to prevailing notions of uniform efficacy regarding stereotactic body radiation therapy (SBRT) for early-stage non-small cell lung cancer (NSCLC), a recent report has indicated increased risk of local failure for squamous cell carcinoma (SCC). As those data have not been corroborated by other studies, we performed a multi-institutional analysis to evaluate the influence of histology on post-SBRT outcomes.

Materials and methods: Records from 152 consecutive patients who received SBRT for primary early-stage NSCLC at two academic medical centers were retrospectively assessed. Primary comparison was between SCC and adenocarcinoma. Patient outcomes including actuarial recurrences and overall survival were calculated using the Kaplan-Meier method. Univariable and multivariable logistic regression analyses addressed associated factors.

Results: At a median follow-up of 44 months, patients with SCC had an increased risk of local, (hazard ratio (HR) (95% confidence interval (CI)): 1.69 (1.05–2.73), p = 0.032), regional (HR (95% CI): 2.03 (1.24–3.33), p = 0.005), and distant failure (HR (95% CI): 1.71 (1.06–2.77), p = 0.036). Median times to local (32 m vs 50m, p = 0.023), regional (26 m vs 50 m, p = 0.011), and distant (26 m vs 50 m, p = 0.024) failure were all significantly reduced in SCC histology. SCC histology was also independently associated with an increased risk for death (HR: 1.80 (1.10–2.94), p = 0.019) and had a 5-yr overall survival of 26%, versus 41% for adenocarcinoma (p = 0.016).

Conclusions: This multi-institutional analysis corroborates that SCC histology is independently predictive for local, regional, and distant recurrence and worse overall survival. Future data are needed to determine if treatment paradigms should differ by histology for early stage NSCLC.

1. Introduction

Stereotactic body radiation therapy (SBRT) has gained momentum in recent years for the treatment of early stage non-small cell lung cancer (NSCLC) [1–5]. To date, multiple clinical trials have demonstrated a local control rate of greater than 90% with SBRT with minimal associated morbidity [6–9]. While current evidence for this treatment modality resides primarily in the setting of patients deemed medically inoperable or who refused surgical resection, its use is increasingly being considered in operable patients as well [10,11]. A pooled analysis from two randomized controlled trials comparing SBRT to surgical resection, both of which closed early due to poor accrual, demonstrated that SBRT provided disease control rates equivalent to that of surgery but with higher overall survival, potentially owing to surgery-associated morbidity/mortality [12].

Previous reports have consistently demonstrated that multiple factors including patient age, tumor size, tumor grade, and radiation dose and fractionation regimen significantly affect local control and, in some reports, overall survival [4,13–16]. To this extent, a recent novel retrospective analysis comprising 740 patients who underwent SBRT at Cleveland Clinic reported that histology may play an important role in outcomes following SBRT [17]. Specifically, squamous cell histology was the greatest predictor of local failure following SBRT on multivariable analysis with a respective 3-year actuarial local failure rate of 18.9% versus 8.7% and 4.1% for patients with adenocarcinoma or NSCLC not otherwise specified, respectively. While the rate of either regional or distant failure was greater in patients who failed locally (54.2% vs 21.1%), histology in itself did not predict for other

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recurrences, nor was it significantly associated with overall survival. However, it was noteworthy that patients with squamous cell histology were significantly more likely to have higher T- and overall stage; these factors were not directly analyzed on multivariable analysis, indicating potential confounding variables therein [17]. This association of histology with local control following SBRT was further confirmed in a German patient cohort but, again, no association with development of distant recurrence or overall survival was revealed [18]. Notably, this more recent study from the University of Heidelberg did not assess for the impact of histology on nodal recurrence specifically but rather combined regional and distant failure together, potentially blinding the reader to associations between histology and site of non-local recurrence.

As the results of these previous studies are potentially of high clinical significance, validation of these findings across other patient populations with more focused assessment on region of failure is necessary. This is important in light of an expected rise in screen-detected early stage NSCLC cases, many of which will be treated with SBRT [19–21]. In this current study, we attempted to address these concerns using a multi-institutional patient cohort to assess outcomes following SBRT according to histology for early stage NSCLC.

2. Materials and methods

Data were retrospectively collected for consecutive patients treated with SBRT for primary NSCLC ≤5 cm between 2006 and 2015 at both the University of Pennsylvania and University of Nebraska Medical Centers. All patients were required to have undergone positron emission tomography-computed tomography (PET/CT) either with or without invasive mediastinal nodal staging prior to treatment without evidence of regional or distant metastatic disease [22]. Only patients with histologic diagnosis of adenocarcinoma or squamous cell carcinoma were included herein, and patients with NSCLC not otherwise specified or unbiopsied cases were both excluded. This was done in an attempt minimize confounders and provide a patient population that was unambiguous for analysis. Collected patient data included patient, disease, and treatment characteristics, along with parameters related to recurrence and survival or last follow-up. This study was approved by the respective institutional review boards of the University of Nebraska Medical Center and University of Pennsylvania prior to initiation (IRB# 398-17-EP and 826881, respectively).

For all patients, four-dimensional simulation CT was performed using a custom-made immobilization device. The gross tumor volume was contoured using the free-breathing scan, with images from eight breathing phases utilized to create a respective internal target volume. The planning target volume was produced via the addition of a 5 mm isotropic margin to the internal target volume. Treatment planning utilized various techniques, including fixed-beam and arc techniques, as well as both forward and inverse planning. Dose constraints to organs-at-risk were per the protocols of Radiation Therapy Oncology Group (RTOG) 0236, 0813, and 0915. All treatments were performed with daily image guidance. Following treatment, surveillance imaging was performed using either CT thorax or PET/CT every 3–4 months for post-treatment years 1–2, every 4–6 months for post-treatment years 3–5, and then annually thereafter.

Recurrences were classified as local, regional (ipsilateral hilar or mediastinal lymph nodes), or distant (all other locations). Local failure referred specifically to recurrence within 1 cm of the PTV and was defined as 1) progression on two consecutive post-treatment scans or 2) histologic confirmation of tumor recurrence with time to failure backdated as the date of the first respective scan to indicate recurrent disease. If a potential local recurrence remained unclear on follow-up CT scans, further confirmation was obtained via PET/CT or biopsy. Any new lesion occurring with-in the lung but outside of the region defined as local failure (PTV + 1 cm) was defined as a distant metastasis. Recurrence-free survivals were classified as time from SBRT to the respective recurrence or death. Overall survival was classified as time from start of SBRT to any-cause death or censored at last patient contact.

All data were analyzed using SAS software (version 9.4; SAS Institute Inc, Cary, NC). The limit for statistical significance was set at $p < 0.05$, and all analyses were two-sided. Survival analysis was conducted through Kaplan-Meier methodology. The log-rank test was used to evaluate population distributions for equality. The effects of demographic and clinical factors on survival endpoints in both univariable and multivariable analyses were assessed through Cox proportional hazards modeling. Specific covariates included tumor histology, demographic features such as age at diagnosis, race, gender, smoking history and ECOG performance status, patient factors such as medical operability, tumor location, tumor size, and radiation dose and number of fractions used. For patients in whom multiple lesions were treated, each lesion was counted individually for local failure analyses while each patient was singularly counted for regional and distant failure and overall survival.

3. Results

3.1. Patient population

In total, 152 patients met the inclusion criteria, with SBRT delivered to a total of 164 lesions. Median follow-up was 44 months (range: 1–81 months). The majority of patients were Caucasian (73.0%), had an ECOG status if 0–1 (62.5%), and were medically inoperable (84.2%). Pertinent demographic information can be found in Table 1. No statistically significant differences were observed in any patient, tumor, or treatment parameter between squamous cell versus adenocarcinoma histology. There was a non-significant trend toward squamous cell lesions being of greater size at diagnosis ($p = 0.059$) on univariable analysis, although this was less apparent on multivariable assessment ($p = 0.094$). Following treatment, 9 (5.5%) treated tumors suffered local failure, 21 (13.8%) patients failed regionally, and 9 (7.2%) patients failed distantly.

3.2. Local failure

Both univariable and multivariable analyses were performed to assess for risk of local failure, as described in Table 2. Local failure-free survival was found to be significantly longer in lesions with adenocarcinoma vs squamous cell histology, with median times to failure of 50 months vs. 32 months ($p = 0.023$) (Fig. 1a). When accounting for potential confounding variables on multivariable analysis, squamous cell histology remained independently associated with local failure (hazard ratio (HR) (95% confidence interval (CI)): 1.69 (1.05–2.73), $p = 0.032$). Additionally, advancing age (HR (95% CI): 1.04 (1.01–1.08), $p = 0.010$) and medical inoperability (HR (95% CI): 2.63 (1.14–6.25), $p = 0.025$) also significantly decreased local failure-free survival.

3.3. Regional and distant failure

Similar to local failure patterns, regional and distant failure-free survivals were also significantly increased in lesions with adenocarcinoma histology, with median times to failure of 50 months vs 26 months for each ($p = 0.011$ and 0.024, respectively) (Fig. 1b and c). On multivariable analysis, squamous cell histology was independently associated with both regional (HR (95% CI): 2.03 (1.24–3.33), $p = 0.005$) and distant (HR (95% CI): 1.71 (1.06–2.77), $p = 0.036$) relapse-free survivals as well (Table 3).

3.4. Overall survival

Median and 5-year overall survivals were also greater in patients