ORIGINAL ARTICLE

A Competing Risk Model of First Failure Site after Definitive Chemoradiation Therapy for Locally Advanced Non-Small Cell Lung Cancer

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ABSTRACT

Introduction: The aim of the study was to build a model of first failure site– and lesion-specific failure probability after definitive chemoradiotherapy for inoperable NSCLC.

Methods: We retrospectively analyzed 251 patients receiving definitive chemoradiotherapy for NSCLC at a single institution between 2009 and 2015. All patients were scanned by fludeoxyglucose positron emission tomography/computed tomography for radiotherapy planning. Clinical patient data and fludeoxyglucose positron emission tomography standardized uptake values from primary tumor and nodal lesions were analyzed by using multivariate cause-specific Cox regression. In patients experiencing locoregional failure, multivariable logistic regression was applied to assess risk of each lesion being the first site of failure. The two models were used in combination to predict probability of lesion failure accounting for competing events.

Results: Adenocarcinoma had a lower hazard ratio (HR) of locoregional failure than squamous cell carcinoma (HR = 0.45, 95% confidence interval [CI]: 0.26–0.76, $p = 0.003$). Distant failures were more common in the adenocarcinoma group (HR = 2.21, 95% CI: 1.41–3.48, $p < 0.001$). Multivariable logistic regression of individual lesions at the time of first failure showed that primary tumors were more likely to fail than lymph nodes (OR = 12.8, 95% CI: 5.10–32.17, $p < 0.001$). Increasing peak standardized uptake value was significantly associated with lesion failure (OR = 1.26 per unit increase, 95% CI: 1.12–1.40, $p < 0.001$). The electronic model is available at http://bit.ly/LungModelFDG.

Conclusions: We developed a failure site–specific competing risk model based on patient- and lesion-level characteristics. Failure patterns differed between adenocarcinoma and squamous cell carcinoma, illustrating the limitation of aggregating them into NSCLC. Failure site–specific models add complementary information to conventional prognostic models.

Keywords: Locally advanced non–small cell lung cancer; Chemoradiotherapy; Competing risk; Patient and lesion failure probability; FDG PET

Introduction

Curative-intent chemoradiotherapy has long been the standard of care for patients with inoperable NSCLC.[1] Local or distant progression is frequently seen after therapy, but death due to competing events is also relatively frequent. Despite advances in targeted therapy for a subset of patients with relatively rare genetic mutations, 5-year overall survival (OS) rates remain

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unsatisfactory at around 15%.[2,3] The natural course of disease depends on histologic type, with adenocarcinoma (AC) metastasizing to the brain more often than squamous cell carcinoma (SCC).[4–7] Nevertheless, AC and SCC are often lumped together as NSCLC in clinical trials or treatment guidelines.

The Union for International Cancer Control TNM classifications[8,9] provide important prognostic information. However, when deciding on a combination of systemic and local therapies, estimating the risk of locoregional versus distant recurrence separately would be of obvious clinical interest. Other factors such as tumor volume and number of fludeoxyglucose positron emission tomography (FDG-PET)-positive lymph nodes have been proposed to improve the pretreatment prognostic assessment.[10,11]

Clinical radiotherapy (RT) trials have tested dose escalation to the primary lung tumor in an attempt to improve local control and, in turn, OS. However, the large RTOG 0617 randomized trial[12] found no clinical benefit in the dose escalation arm, emphasizing that local intensification may not be a viable strategy for all patients with NSCLC. Improved knowledge of the most likely failure sites within a patient may be of relevance for further individualization of treatment options in the future.

The aim of the current study was to establish a model of the failure patterns on a patient and lesion level by using baseline clinical data and FDG-PET/computed tomography (CT) scans.

Materials and Methods

Patients

Data were retrospectively retrieved from medical records and archived scans from consecutive patients who received a diagnosis of inoperable, locally advanced NSCLC and were treated at Rigshospitalet, Copenhagen University Hospital from January 2009 to February 2015. In this period, operability was determined according to clinical stage below IIIAN2, comorbidity of the patient, and lung function by a multidisciplinary tumor board consisting of pulmonologists, thoracic surgeons, and medical/radiation oncologists. Patients received definitive chemoradiotherapy or RT alone. Chemotherapy was given either sequentially before radiation or concomitantly with the first cycle of chemotherapy before the PET/CT planning scan. Chemotherapy regimens consisted of either cisplatin/vinorelbin or carboplatin/vinorelbin in a 3-week schedule, given three to six times. Patients who had prior early-stage lung cancer treated with surgery but were now candidates for concomitant chemotherapy and radiotherapy were also included in the study. This could, for example, be due to relapse in a lymph node station or a new primary tumor. These patients were restaged according to the seventh TNM classification from the Union for International Cancer Control.[8]

FDG-PET

In preparation for RT planning, an FDG-PET/CT scan was performed on a Siemens Biograph mCT (Siemens Healthineers, Erlangen, Germany) on a flat table top in treatment position approximately 60 minutes after FDG injection (4 MBq/kg). An iodine-based contrast medium was injected intravenously during the CT scan according to departmental guidelines. Details on PET and CT data acquisition from our institution have been published previously.[13] A maximum of five lesions per patient were evaluated (two tumor sites [T sites]/three lymph node sites [N sites]). If a patient had multiple FDG-avid lesions, the five lesions with the highest FDG uptake and the largest diameter were chosen. FDG-avid lesions were contoured with region of interest (ROI) drawn semi-automatically by using a threshold of 50% of the maximum standardized uptake value (SUV_{max}). SUV_{max}, SUV_{peak}, mean SUV, and volume (in cm^3) were calculated for all individual FDG-positive lesions. SUV_{peak} was defined according to the Positron Emission Tomography Response Criteria in Solid Tumors criteria[14] as a sphere of 1 cm^3 centering on the hottest point in the lesion. The total lesion glycolysis was defined as volume times mean SUV. If a primary tumor (T site) could not be separated from affected lymph nodes (N site), the lesion was analyzed as a T-site lesion. Data from the PET scan were analyzed on a Mirada XD workstation, version 1.1.0.31 (Mirada Medical, Oxford, UK).

RT

RT was given in 2-Gy fractions at five fractions per week for a total of 60 to 66 Gy. Three-dimensional conformal (until January 2014) or volumetric modulated arc therapy planning techniques were applied and based on the midventilation phase of a four-dimensional CT scan.[15] Cone beam CT with tumor match were used for daily image guidance.

The study was approved by the Danish Health and Medicines Authority (case No. 3-3013-569/1/), and it complied with national data protection regulations. According to Danish law, no research ethics approval was necessary because of the retrospective nature of the study.

Statistics and Data Analysis

Wilcoxon-Mann-Whitney *U* tests were used for comparison of ordinal or continuous baseline clinical data in patients with AC versus in those with SCC. The