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<th>Manuscript Number:</th>
<th>JTO-D-17-01410R1</th>
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<td>Article Type:</td>
<td>Original Article</td>
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<td>Keywords:</td>
<td>Locally advanced non-small cell lung cancer; chemo/radiotherapy; competing risk; patient and lesion failure probability; FDG PET</td>
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| Abstract:         | Introduction 
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We retrospectively analyzed 251 patients receiving definitive chemo/radiotherapy for NSCLC at a single institution between 2009-2015. All patients were FDG PET/CT scanned for radiotherapy planning. Clinical patient data and FDG PET standardized uptake values from primary tumor and nodal lesions were analyzed using multivariate cause-specific Cox regression. In patients experiencing loco-regional failure, multivariable logistic regression was applied to assess risk of each lesion being first site of failure. The two models were used in combination to predict lesion failure probability accounting for competing events. Results 
Adenocarcinoma had a lower hazard ratio (HR) of loco-regional (LR) failure than squamous cell carcinoma, HR 0.45, 95% 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 primary tumors were more likely to fail than lymph nodes, OR 12.8, 95% CI |
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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 'non-small-cell lung cancer'. Failure site specific models add complementary information to conventional prognostic models.
Dear Editor

Attached, please find our manuscript “A competing risk model of first failure site after definitive (chemo) radiation therapy for locally advanced non-small cell lung cancer”

We hereby present to you our study on 251 lung cancer patients with PET/CT workup and treated with radiotherapy between 2009-2015. We have performed competing risk analysis on a patient and lesion level using the clinical data and FDG PET/CT uptake metrics. Failure patterns differed between adenocarcinoma and squamous cell carcinoma, illustrating the limitation of aggregating them into 'non-small-cell lung cancer'. We were able to provide a - to our knowledge - first example of individual risk prediction of first failure site, also within the treated volume. We propose that such failure site specific models add complementary information to conventional prognostic models. Further to the paper description of the models, we publish electronic web applications as supplements, see http://bit.ly/LungModelFDG.

We trust you will find this paper of interest for the readership of Journal of Thoracic Oncology and we hope you will consider our research article for publication.

All authors of this paper have directly participated in the planning, execution, and analysis of the study. The corresponding author confirms that she had full access to all the data and takes final responsibility for the submission of this manuscript.

As stated in the manuscript, the study was approved by the Danish Health and Medicines Authority, case no 3-3013-569/1/ and complied with national data protection regulations. According to Danish law, no research ethics approval was necessary due to the retrospective nature of the study.

There have not been any prior interactions with JTO regarding this manuscript and it will not be copyrighted, submitted, or published elsewhere while acceptance by your journal is under consideration.

On behalf of all authors,

Yours sincerely,

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A competing risk model of first failure site after definitive (chemo) radiation therapy for locally advanced non-small cell lung cancer

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The aim of the study was to build a model of first failure site and lesion specific failure probability after definitive chemo-radiotherapy for inoperable non-small cell lung cancer (NSCLC).

**Methods**

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

**Results**

Adenocarcinoma had a lower hazard ratio (HR) of loco-regional (LR) failure than squamous cell carcinoma, HR 0.45, 95% 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 primary tumors were more likely to fail than lymph nodes, OR 12.8, 95% CI [5.10; 32.17], p<0.001. Increasing SUVpeak was significantly associated with lesion failure, OR 1.26 per unit increase, 95% CI [1.12; 1.40], p<0.001. Electronic model: 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 'non-small-cell lung cancer'. Failure site specific models add complementary information to conventional prognostic models.
Keywords

Locally advanced non-small cell lung cancer; chemo/radiotherapy; competing risk; patient and lesion failure probability; FDG PET
1. INTRODUCTION

Curative intended chemo-radiotherapy has long been standard of care for inoperable non-small cell lung cancer patients\(^1\). Local or distant progression is frequently seen after therapy, but also death due to competing events is relatively frequent. Despite advances in targeted therapy for a subset of patients with relatively rare genetic mutations, five-year overall survival rates remain unsatisfactory, around 15\% \(^2,3\). The natural course of disease depends on histology, with adenocarcinoma (AC) metastasizing to the brain more often than squamous cell carcinoma (SCC) \(^4,5,6,7\). Nevertheless, adenocarcinoma and squamous cell carcinoma are often lumped together as 'non-small-cell lung cancer' in clinical trials or treatment guidelines.

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

Clinical radiotherapy trials have tested dose escalation to the primary lung tumor in an attempt to improve local control and in turn overall survival. 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 NSCLC patients. 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 using baseline clinical data and FDG-PET/ computed tomography (CT) scans.

2. MATERIALS AND METHODS

Patients

Data were retrospectively retrieved from medical records and archived scans from consecutive patients diagnosed with inoperable, locally advanced NSCLC and treated at Rigshospitalet, Copenhagen University Hospital from January 2009 to February 2015. In this time period, operability was determined according to clinical stage below IIIAN2, co-morbidity of the patient and lung function by a multidisciplinary tumor board consisting of pulmonologists, thoracic surgeons and medical/radiation oncologists. Patients received definitive chemo/radiotherapy or radiotherapy alone. Chemotherapy was either given sequentially prior to radiation or concomitantly with the first cycle of chemotherapy prior to the PET/CT planning scan. Chemotherapy regimens consisted of either cisplatin/vinorelbin or carboplatin/vinorelbin in a three-week schedule, given three to six times. Patients with prior early-stage lung cancer treated with surgery but now candidates for concomitant chemo/radiotherapy (cCRT) 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 7th TNM classification from UICC8.

FDG-PET

In preparation for radiotherapy planning, an FDG-PET/CT scan was performed on a Siemens Biograph mCT (Siemens Healthineers, Erlangen), on a flat table top in treatment position approximately 60 min after FDG injection (4MBq/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 is previously published\textsuperscript{13}. A maximum of five lesions per patient were evaluated (Two T-sites/three 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)s drawn semi-automatically using a threshold of 50\% of the maximum standardized uptake value (SUV\textsubscript{max}). SUV\textsubscript{max}, SUV\textsubscript{peak}, SUV\textsubscript{mean} and volume (cm\textsuperscript{3}) were calculated for all individual FDG positive lesions. SUV\textsubscript{peak} is defined according to the PERCIST criteria\textsuperscript{14} as a sphere of 1 cm\textsuperscript{3} centering the hottest point in the lesion. The total lesion glycolysis (TLG) is defined as volume x SUV\textsubscript{mean}. 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 was analyzed on a Mirada XD\textsuperscript{®} workstation (version 1.1.0.31).

Radiotherapy

Radiotherapy was given in 2 Gy fractions, five fractions per week to a total of 60-66 Gy. 3D conformal (until January 2014) or volumetric modulated arc therapy (VMAT) planning techniques were applied and based on the midventilation phase of a 4D CT\textsuperscript{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 complied with national data protection regulations. According to Danish law, no research ethics approval was necessary due to 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 AC versus SCC patients. The chi square test was used to test for associations between two categorical variables, Table 1.
Date of histology-confirmed diagnosis was used as the start date, and the date of imaging (CT, FDG PET or MR scans) confirming a relapse/progression, was used as failure dates. The time interval between the start date and the earliest radiologically confirmed treatment failure was defined as *time to first failure* (TFF). Patients alive with no evidence of disease (NED) were censored at the last follow-up in the clinic. Overall survival (OS) and TFF data was analyzed using Kaplan Meier plots\textsuperscript{16} and univariate Cox regression. IBM\textsuperscript{®} SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp) was used for these analyses.

First site of failure was specified as Tumor-site (T-site) local failure (LF), lymph node (N-site) regional failure (RF), distant metastases, either extra-cranial (ECDM) or intra-cranial (ICDM). Failure within the thorax but outside the radiotherapy planning target volume (PTV) was scored as ECDM. In case of synchronous local and distant failure, the patient was scored as failing distantly (ECDM or ICDM). Patients with loco-regional failure were scored on a lesion level regarding T versus N site lesions and the lesion SUV\textsubscript{peak} value from the radiotherapy planning scan was calculated for subsequent statistical analysis.

Failure sites in adenocarcinoma and squamous cell carcinoma were compared in univariate competing risk modeling. The cuminc function of the CMPRSK package (version 2.2.7) was used to compare the groups with Fine and Gray’s test.

A statistical plan was made prior to the multivariate cox regression analysis. Coding and variables are listed in Table 2. The variables were preselected to reflect a parsimonious list of clinical prognosticators. Subsequent to data collection changes were made by excluding TLG measures due to strong correlation with GTV and SUV\textsubscript{peak} yielding unstable models, supplementary Figure 1.

SUV\textsubscript{peak} was chosen prior to seeing the data due to its use in the PERCIST guidelines\textsuperscript{14}. Also, smoking status in pack-years was excluded as there was no sign of prognostic value (log rank test).
p=0.43 for trend between tertiles) in the current data set. The exclusion of smoking status avoided
the complication of imputing six cases with missing data on smoking history.

In all cases the model was stratified for the use of concomitant platinum based chemotherapy. In
multivariate modeling, ECDM and ICDM were combined to "DM" for power and interpretability of
the electronic nomogram. Cause specific Cox multivariate regression was performed using the CSC
function of the RiskRegression package, version 1.4.3 in R\textsuperscript{17}.

\textit{Lesion level analysis}

Multivariable logistic regression analysis was applied to all lesions in patients with known loco-
regional failure. Two variables on lesion specific outcome were included in the analysis: SUV\textsubscript{peak}
and tumor versus node (TvsN) (categorical variable T=1, N=0).

\[ P = \frac{\exp(b_0 + b_1 \times TvsN + b_2 \times SUVpeak)}{1 + \exp(b_0 + b_1 \times TvsN + b_2 \times SUVpeak)} \]

where \( P \) is the probability of being first site of failure in the group of patients with known LRF. We
interpret \( P \) as the conditional failure probability of a lesion, given loco-regional failure. This
conditional failure probability, \( P \), is subsequently multiplied by the absolute risk of loco-regional
failure from the competing risk analysis to yield individual lesion failure risk at RT planning
PET/CT. Thus, the probability of lesion failure, predicted at the time of RT planning, is calculated
by multiplying \( P \) with the risk of loco-regional failure after 24 months according to the competing
risk model.

Model calibration was assessed by plotting the lesion predicted probability against observed
probability in 8 quantiles.
The risk models were published as web applications\textsuperscript{18} at \url{http://bit.ly/LungModel}, \url{http://bit.ly/LungModelGTV} and \url{http://bit.ly/LungModelFDG} using the R statistical software package "shiny". We used logistic regression of observed failures vs. predicted risk of lesion failure to estimate the uncertainty of predictions and provide +/- 1.96 times the standard error of the logistic fit as estimate of the uncertainty of the lesion failure probability in the web applications.

\section*{RESULTS}

\textit{Treatment response and follow-up}

In this retrospective study 251 patients, of 376 patients screened, were included. The eligibility criteria were: retrievable radiotherapy planning PET/CT scans (5 patients excluded); receiving curative intent radiotherapy (39 patients excluded); available medical records (15 patients excluded); histology of AC or SCC (49 patients excluded), and with FDG PET positive lesions to analyze (17 patients excluded). Patient characteristics are shown in Table 1.

Missing data were handled as follows. Performance status (PS) was missing in seven patients but could be retrospectively assessed from electronic file information. Gross tumor volume (GTV) was missing in two patients. A specialist in lung cancer radiology contoured these GTVs retrospectively. Eighteen patients had initial stage IV disease, eleven of which had M1a disease. These lesions received curative intended radiotherapy. Five patients had brain metastases that were either surgically removed or had stereotactic radiotherapy prior to curative intended therapy of the lung lesions. Two patients had M1b disease due to metastases to 1) the adrenal gland and 2) a target in the left breast region. These targets were treated with a stereotactic dose and up to 34 Gy, respectively. Outliers in patient characteristics were age with AC having a larger fraction of
younger patients than SCC. T-stage also showed a slight imbalance between the groups, supplementary Figures 2 and 3.

Three patients relapsed in new lymph nodes inside the thorax but outside the PTV. Six patients failed loco-regionally with LN failure outside the thorax (neck, axilla, below the diaphragm). These nine patients were coded with ECDM as first site of failure.

Seven patients relapsed inside the thorax but outside the PTV, e.g. contralateral lung (M1a disease) and were coded ECDM. Two of them had other distant metastases (bone and pleura). Seven T-site failures and four N-site failures also failed in distant sites and were scored as distant metastases. See supplementary Table 1 for distribution of first failure sites in AC versus SCC.

Median time from diagnosis to first relapse was 10.5 months and median time from first relapse to death was 6 months. Overall survival was median 18 months for the whole group of 251 patients with no difference in the two histology groups, HR 0.84, 95% CI [0.62; 1.15]. TFF in the two histology groups were equal, median time 12 months, HR 1.23, 95% CI [0.90; 1.67]. Patients receiving cCRT versus sequential therapy did not have significantly longer OS, HR 1.11, 95% CI [0.81; 1.52].

**Competing risk analysis**

Competing risk analysis found a strong association between relapse patterns and histology. AC had lower risk of failing LRF compared to SCC, HR 0.45, 95% CI [0.26; 0.76], p= 0.003. The risk of
failing distantly was twice as high in the AC group, HR 2.21, 95% CI [1.41; 3.48], p< 0.001. See Table 2.

Figure 1 shows the risk of various first-failure types from the competing risk model. The risk of an event increases with time but no major change in risk from two to three years since most failures occur within the first 24 months.

Stacked patient level outcome shows by Fine and Grey test, AC to have a higher rate of ICDM, p=0.00014 and ECDM, p= 0.04 compared to SCC. SCC tend to fail loco-regionally more often than AC, p=0.0002. There was no difference in Death, NED, p=0.18, see Figure 2.

Lesion risk assessment

Among the 251 patients, 517 lesions were registered with FDG PET uptake from the radiotherapy planning PET/CT scan. Seventy-six lesions (15%) failed in local or regional sites with 60 T-site failures and 16 N-site failures. Logistic regression showed SUVpeak and TvsN to be predictors of lesion failure. T-site lesions were >12 times more likely to fail than N-site lesions, OR 12.8; 95% CI [5.10; 32.17], p= <0.0001. Increasing SUVpeak was associated with an increased likelihood of lesion failure, OR 1.26; 95% CI [1.12; 1.40], p<0.0001.

We found and analyzed 245 FDG avid lymph nodes, up to three lymph nodes per patient. Of these FDG avid N-site lesions 168 lesions (68.6%) were biopsy proven malignant. Lymph node stations 4, 7 and 10 were predominantly represented. Twenty N-site lesions with corresponding positive biopsies relapsed. 238 patients with a total of 493 lesions were included in the overall predicted lesion failure probability analysis. Thirteen patients with no T-site but with 24 nodal lesions were excluded from this analysis. Figure 3 illustrates two patients with different histology and thus difference in lesion failure assessment based on the combined lesion failure probability analysis.
The lesion model check was performed and showed agreement between calculated risk and actual failure on a lesion level, Figure 4.

3. DISCUSSION

We developed a competing risk model able to estimate the patient level risk of LRF, DM and death NED. Further, the radiation target was subdivided in individual lesions and the model could predict the lesion level risk of failure in the current dataset. Competing risk analysis showed that histology was the strongest predictor for LRF versus DM failure. We found T- versus N-site and SUV$_{\text{peak}}$ to be predictive of lesion specific outcome in addition to the patient level prognostics. Internal consistency of the model was examined and we found reasonable agreement between predicted lesion failure probability and actual lesion failure in calibration plots.

It is of importance that the model is only used for decision support and should be read with caution. Results from the model are generated under the assumption that all clinical targets, T- and N-sites, are given a homogeneous normo fractionation scheme of 2 Gy times 30-33 times, 5F/W to a total of 60 to 66 Gy. It should be stressed that an estimate of low risk of lesion failure does not indicate that it is safe to reduce the dose or otherwise compromise radiation delivery to that lesion.

Nevertheless, our results illustrate the importance of differentiating AC and SCC patients since they have different relapse patterns. The aggregate term non-small cell lung cancer may not be helpful in advancing the field.

There are numerous reports of the prognostic value of SUV$_{\text{max}}$ of the primary lesion and overall cut-off values have been suggested to define good versus poor prognosis$^{19,20,21,22}$. The lack of external validation should be acknowledged as a limitation of the current study. A number of externally validated prognostic models for overall survival have been published, see for example
predictcancer.org. Failure site prognostication as in the current study potentially has, if externally validated, additional clinical interest.

We have previously found support for early lesion-specific PET response ($\Delta$SUV$_{\text{peak}}$) after one series of chemotherapy to be predictive of failure site in tumor versus nodal sites$^{13}$. A decrease in FDG uptake in both tumor and lymph nodes after radiotherapy was also found to be a prognostic factor for survival and recurrence$^{23}$. Looking at subvolumes within the original T-site, other authors have found that high SUV values could identify areas of high local failure risk$^{24,25}$. This led to studies investigating dose-escalation to these areas hoping to achieve a better local tumor control$^{26,27}$.

When analyzing FDG uptake in lymph nodes$^{28}$, a risk of false positive findings must be taken into consideration. The rate of false positive lymph node lesions cannot be extracted from our data. SUV measurements varies by glucose blood levels, acquisition modes and reconstruction algorithms of the PET scans which makes data hard to reproduce and define a definitive cut-off value that is prognostic of outcome in a cancer population. An external validation of our findings should be conducted to confirm the rationale in differentiating between histology groups and lesion characteristics and a prospective study could ideally validate our findings of lesion specific risk prediction.

Improved estimates of the probability of these competing risks will allow individual treatment approaches that would target the patient’s most likely failure type if managed with current standard therapy. The need for such personalized patient selection is particularly evident after the impairment in survival observed for patients in the experimental RT arm of RTOG0617$^{12}$, possibly due to excess mortality as a result of the aggressive local treatment intensification. Future randomized
trials of local radiotherapy intensification are encouraged to distinguish upon histology and risks of competing events upon inclusion.

In conclusion, adenocarcinoma and squamous cell carcinoma of the lung differ in patterns of first failure site after definitive chemo-radiotherapy. Competing risk estimates of DM, LRF and death NED were generated. Moreover, it was possible to estimate risk of failure in sub-lesions of the radiation target based on lesion site, SUV_{peak} and patient level clinical variables.
REFERENCES


doi:10.1097/JTO.0000000000000185.


SUPPLEMENTAL DATA

Supplemental Figure 1.eps
Supplemental Figure 2.eps
Supplemental Figure 3.eps
Supplemental Table 1.word
A competing risk model of first failure site after definitive (chemo) radiation therapy for locally advanced non-small cell lung cancer

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Introduction

The aim of the study was to build a model of first failure site and lesion specific failure probability after definitive chemo-radiotherapy for inoperable non-small cell lung cancer (NSCLC).

Methods

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

Results

Adenocarcinoma had a lower hazard ratio (HR) of loco-regional (LR) failure than squamous cell carcinoma, HR 0.45, 95% 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 primary tumors were more likely to fail than lymph nodes, OR 12.8, 95% CI [5.10; 32.17], p<0.001. Increasing SUVpeak was significantly associated with lesion failure, OR 1.26 per unit increase, 95% CI [1.12; 1.40], p<0.001. Electronic model: 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 'non-small-cell lung cancer'. Failure site specific models add complementary information to conventional prognostic models.
Keywords

Locally advanced non-small cell lung cancer; chemo/radiotherapy; competing risk; patient and lesion failure probability; FDG PET
1. INTRODUCTION

Curative intended chemo-radiotherapy has long been standard of care for inoperable non-small cell lung cancer patients\(^1\). Local or distant progression is frequently seen after therapy, but also death due to competing events is relatively frequent. Despite advances in targeted therapy for a subset of patients with relatively rare genetic mutations, five-year overall survival rates remain unsatisfactory, around 15% \(^2,3\). The natural course of disease depends on histology, with adenocarcinoma (AC) metastasizing to the brain more often than squamous cell carcinoma (SCC) \(^4,5,6,7\). Nevertheless, adenocarcinoma and squamous cell carcinoma are often lumped together as 'non-small-cell lung cancer' in clinical trials or treatment guidelines.

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

Clinical radiotherapy trials have tested dose escalation to the primary lung tumor in an attempt to improve local control and in turn overall survival. 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 NSCLC patients. 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 using baseline clinical data and FDG-PET/computed tomography (CT) scans.

2. MATERIALS AND METHODS

Patients

Data were retrospectively retrieved from medical records and archived scans from consecutive patients diagnosed with inoperable, locally advanced NSCLC and treated at Rigshospitalet, Copenhagen University Hospital from January 2009 to February 2015. In this time period, operability was determined according to clinical stage below IIIAN2, co-morbidity of the patient and lung function by a multidisciplinary tumor board consisting of pulmonologists, thoracic surgeons and medical/radiation oncologists. Patients received definitive chemo/radiotherapy or radiotherapy alone. Chemotherapy was either given sequentially prior to radiation or concomitantly with the first cycle of chemotherapy prior to the PET/CT planning scan. Chemotherapy regimens consisted of either cisplatin/vinorelbin or carboplatin/vinorelbin in a three-week schedule, given three to six times. Patients with prior early-stage lung cancer treated with surgery but now candidates for concomitant chemo/radiotherapy (cCRT) 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 7th TNM classification from UICC.

FDG-PET

In preparation for radiotherapy planning, an FDG-PET/CT scan was performed on a Siemens Biograph mCT (Siemens Healthineers, Erlangen), on a flat table top in treatment position approximately 60 min after FDG injection (4MBq/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 is previously published\textsuperscript{13}. A maximum of five lesions per patient were evaluated (Two T-sites/three 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)s drawn semi-automatically using a threshold of 50% of the maximum standardized uptake value (SUV\textsubscript{max}). SUV\textsubscript{max}, SUV\textsubscript{peak}, SUV\textsubscript{mean} and volume (cm\textsuperscript{3}) were calculated for all individual FDG positive lesions. SUV\textsubscript{peak} is defined according to the PERCIST criteria\textsuperscript{14} as a sphere of 1 cm\textsuperscript{3} centering the hottest point in the lesion. The total lesion glycolysis (TLG) is defined as volume x SUV\textsubscript{mean}. 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 was analyzed on a Mirada XD\textsuperscript{®} workstation (version 1.1.0.31).

*Radiotherapy*

Radiotherapy was given in 2 Gy fractions, five fractions per week to a total of 60-66 Gy. 3D conformal (until January 2014) or volumetric modulated arc therapy (VMAT) planning techniques were applied and based on the midventilation phase of a 4D CT\textsuperscript{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 complied with national data protection regulations. According to Danish law, no research ethics approval was necessary due to 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 AC versus SCC patients. The chi square test was used to test for associations between two categorical variables, Table 1.
Date of histology-confirmed diagnosis was used as the start date, and the date of imaging (CT, FDG PET or MR scans) confirming a relapse/progression, was used as failure dates. The time interval between the start date and the earliest radiologically confirmed treatment failure was defined as *time to first failure* (TFF). Patients alive with no evidence of disease (NED) were censored at the last follow-up in the clinic. Overall survival (OS) and TFF data was analyzed using Kaplan Meier plots\(^1\) and univariate Cox regression. IBM® SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp) was used for these analyses.

First site of failure was specified as Tumor-site (T-site) local failure (LF), lymph node (N-site) regional failure (RF), distant metastases, either extra-cranial (ECDM) or intra-cranial (ICDM). Failure within the thorax but outside the radiotherapy planning target volume (PTV) was scored as ECDM. In case of synchronous local and distant failure, the patient was scored as failing distantly (ECDM or ICDM). Patients with loco-regional failure were scored on a lesion level regarding T versus N site lesions and the lesion SUV\(_{\text{peak}}\) value from the radiotherapy planning scan was calculated for subsequent statistical analysis.

Failure sites in adenocarcinoma and squamous cell carcinoma were compared in univariate competing risk modeling. The cuminc function of the CMPRSK package (version 2.2.7) was used to compare the groups with Fine and Gray’s test.

A statistical plan was made prior to the multivariate cox regression analysis. Coding and variables are listed in Table 2. The variables were preselected to reflect a parsimonious list of clinical prognosticators. Subsequent to data collection changes were made by excluding TLG measures due to strong correlation with GTV and SUV\(_{\text{peak}}\) yielding unstable models, supplementary Figure 1. SUV\(_{\text{peak}}\) was chosen prior to seeing the data due to its use in the PERCIST guidelines\(^{14}\). Also, smoking status in pack-years was excluded as there was no sign of prognostic value (log rank...
p=0.43 for trend between tertiles) in the current data set. The exclusion of smoking status avoided the complication of imputing six cases with missing data on smoking history.

In all cases the model was stratified for the use of concomitant platinum based chemotherapy. In **multivariate** modeling, ECDM and ICDM were combined to "DM" for power and interpretability of the electronic nomogram. Cause specific Cox multivariate regression was performed using the CSC function of the RiskRegression package, version 1.4.3 in R.**

**Lesion level analysis**

Multivariable logistic regression analysis was applied to all lesions in patients with known loco-regional failure. Two variables on lesion specific outcome were included in the analysis: SUV peak and tumor versus node (TvsN) (categorical variable T=1, N=0).

\[
P = \frac{\exp(b_0 + b_1 \times TvsN + b_2 \times SUVpeak)}{1 + \exp(b_0 + b_1 \times TvsN + b_2 \times SUVpeak)}
\]

where \(P\) is the probability of being first site of failure in the group of patients with known LRF. We interpret \(P\) as the conditional failure probability of a lesion, given loco-regional failure. This conditional failure probability, \(P\), is subsequently multiplied by the absolute risk of loco-regional failure from the competing risk analysis to yield individual lesion failure risk at RT planning PET/CT. Thus, the probability of lesion failure, predicted at the time of RT planning, is calculated by multiplying \(P\) with the risk of loco-regional failure after 24 months according to the competing risk model.

Model calibration was assessed by plotting the lesion predicted probability against observed probability in 8 quantiles.
The risk models were published as web applications\textsuperscript{18} at http://bit.ly/LungModel, http://bit.ly/LungModelGTV and http://bit.ly/LungModelFDG using the R statistical software package "shiny". We used logistic regression of observed failures vs. predicted risk of lesion failure to estimate the uncertainty of predictions and provide +/- 1.96 times the standard error of the logistic fit as estimate of the uncertainty of the lesion failure probability in the web applications.

RESULTS

Treatment response and follow-up

In this retrospective study 251 patients, of 376 patients screened, were included. The eligibility criteria were: retrievable radiotherapy planning PET/CT scans (5 patients excluded); receiving curative intent radiotherapy (39 patients excluded); available medical records (15 patients excluded); histology of AC or SCC (49 patients excluded), and with FDG PET positive lesions to analyze (17 patients excluded). Patient characteristics are shown in Table 1.

Missing data were handled as follows. Performance status (PS) was missing in seven patients but could be retrospectively assessed from electronic file information. Gross tumor volume (GTV) was missing in two patients. A specialist in lung cancer radiology contoured these GTVs retrospectively.

Eighteen patients had initial stage IV disease, eleven of which had M1a disease. These lesions received curative intended radiotherapy. Five patients had brain metastases that were either surgically removed or had stereotactic radiotherapy prior to curative intended therapy of the lung lesions. Two patients had M1b disease due to metastases to 1) the adrenal gland and 2) a target in the left breast region. These targets were treated with a stereotactic dose and up to 34 Gy, respectively. Outliers in patient characteristics were age with AC having a larger fraction of
younger patients than SCC. T-stage also showed a slight imbalance between the groups, supplementary Figures 2 and 3.

Three patients relapsed in new lymph nodes inside the thorax but outside the PTV. Six patients failed loco-regionally with LN failure outside the thorax (neck, axilla, below the diaphragm). These nine patients were coded with ECDM as first site of failure.

Seven patients relapsed inside the thorax but outside the PTV, e.g. contralateral lung (M1a disease) and were coded ECDM. Two of them had other distant metastases (bone and pleura). Seven T-site failures and four N-site failures also failed in distant sites and were scored as distant metastases. See supplementary Table 1 for distribution of first failure sites in AC versus SCC.

Median time from diagnosis to first relapse was 10.5 months and median time from first relapse to death was 6 months. Overall survival was median 18 months for the whole group of 251 patients with no difference in the two histology groups, HR 0.84, 95% CI [0.62; 1.15]. TFF in the two histology groups were equal, median time 12 months, HR 1.23, 95% CI [0.90; 1.67]. Patients receiving cCRT versus sequential therapy did not have significantly longer OS, HR 1.11, 95% CI [0.81; 1.52].

Competing risk analysis

Competing risk analysis found a strong association between relapse patterns and histology. AC had lower risk of failing LRF compared to SCC, HR 0.45, 95% CI [0.26; 0.76], p= 0.003. The risk of
failing distantly was twice as high in the AC group, HR 2.21, 95% CI [1.41; 3.48], p< 0.001. See Table 2.

Figure 1 shows the risk of various first-failure types from the competing risk model. The risk of an event increases with time but no major change in risk from two to three years since most failures occur within the first 24 months.

Stacked patient level outcome shows by Fine and Grey test, AC to have a higher rate of ICDM, p=0.00014 and ECDM, p= 0.04 compared to SCC. SCC tend to fail loco-regionally more often than AC, p=0.0002. There was no difference in Death, NED, p=0.18, see Figure 2.

Lesion risk assessment

Among the 251 patients, 517 lesions were registered with FDG PET uptake from the radiotherapy planning PET/CT scan. Seventy-six lesions (15%) failed in local or regional sites with 60 T-site failures and 16 N-site failures. Logistic regression showed SUVpeak and TvsN to be predictors of lesion failure. T-site lesions were >12 times more likely to fail than N-site lesions, OR 12.8; 95% CI [5.10; 32.17], p= <0.0001. Increasing SUVpeak was associated with an increased likelihood of lesion failure, OR 1.26; 95% CI [1.12; 1.40], p<0.0001.

We found and analyzed 245 FDG avid lymph nodes, up to three lymph nodes per patient. Of these FDG avid N-site lesions 168 lesions (68.6%) were biopsy proven malignant. Lymph node stations 4, 7 and 10 were predominantly represented. Twenty N-site lesions with corresponding positive biopsies relapsed. 238 patients with a total of 493 lesions were included in the overall predicted lesion failure probability analysis. Thirteen patients with no T-site but with 24 nodal lesions were excluded from this analysis. Figure 3 illustrates two patients with different histology and thus difference in lesion failure assessment based on the combined lesion failure probability analysis.
The lesion model check was performed and showed agreement between calculated risk and actual failure on a lesion level, Figure 4.

### 3. DISCUSSION

We developed a competing risk model able to estimate the patient level risk of LRF, DM and death NED. Further, the radiation target was subdivided in individual lesions and the model could predict the lesion level risk of failure in the current dataset. Competing risk analysis showed that histology was the strongest predictor for LRF versus DM failure. We found T- versus N-site and SUV_{peak} to be predictive of lesion specific outcome in addition to the patient level prognostics. Internal consistency of the model was examined and we found reasonable agreement between predicted lesion failure probability and actual lesion failure in calibration plots.

It is of importance that the model is only used for decision support and should be read with caution. Results from the model are generated under the assumption that all clinical targets, T-and N-sites, are given a homogeneous normo fractionation scheme of 2 Gy times 30-33 times, 5F/W to a total of 60 to 66 Gy. It should be stressed that an estimate of low risk of lesion failure does not indicate that it is safe to reduce the dose or otherwise compromise radiation delivery to that lesion.

Nevertheless, our results illustrate the importance of differentiating AC and SCC patients since they have different relapse patterns. The aggregate term non-small cell lung cancer may not be helpful in advancing the field.

There are numerous reports of the prognostic value of SUV_{max} of the primary lesion and overall cut-off values have been suggested to define good versus poor prognosis^{19,20,21,22}. The lack of external validation should be acknowledged as a limitation of the current study. A number of externally validated prognostic models for overall survival have been published, see for example
predictcancer.org. Failure site prognostication as in the current study potentially has, if externally validated, additional clinical interest.

We have previously found support for early lesion-specific PET response ($\Delta \text{SUV}_{\text{peak}}$) after one series of chemotherapy to be predictive of failure site in tumor versus nodal sites. A decrease in FDG uptake in both tumor and lymph nodes after radiotherapy was also found to be a prognostic factor for survival and recurrence. Looking at subvolumes within the original T-site, other authors have found that high SUV values could identify areas of high local failure risk. This led to studies investigating dose-escalation to these areas hoping to achieve a better local tumor control.

When analyzing FDG uptake in lymph nodes, a risk of false positive findings must be taken into consideration. The rate of false positive lymph node lesions cannot be extracted from our data. SUV measurements vary by glucose blood levels, acquisition modes and reconstruction algorithms of the PET scans which makes data hard to reproduce and define a definitive cut-off value that is prognostic of outcome in a cancer population. An external validation of our findings should be conducted to confirm the rationale in differentiating between histology groups and lesion characteristics and a prospective study could ideally validate our findings of lesion specific risk prediction.

Improved estimates of the probability of these competing risks will allow individual treatment approaches that would target the patient’s most likely failure type if managed with current standard therapy. The need for such personalized patient selection is particularly evident after the impairment in survival observed for patients in the experimental RT arm of RTOG0617, possibly due to excess mortality as a result of the aggressive local treatment intensification. Future randomized
trials of local radiotherapy intensification are encouraged to distinguish upon histology and risks of competing events upon inclusion.

In conclusion, adenocarcinoma and squamous cell carcinoma of the lung differ in patterns of first failure site after definitive chemo-radiotherapy. Competing risk estimates of DM, LRF and death NED were generated. Moreover, it was possible to estimate risk of failure in sub-lesions of the radiation target based on lesion site, SUV$_{\text{peak}}$ and patient level clinical variables.


Nygård L, Vogelius IR, Fischer BM, et al. Early lesion-specific 18F-FDG PET response to...


**SUPPLEMENTAL DATA**

Supplemental Figure 1.eps

Supplemental Figure 2.eps
RE: JTO-D-17-01410, entitled "A competing risk model of first failure site after definitive (chemo) radiation therapy for locally advanced non-small cell lung cancer"

Dear Mrs Nygård,

I am pleased to inform you that your paper has been found acceptable for publication pending minor revision. I anticipate that you will easily be able to answer the criticisms of the reviewers in a satisfactory manner. I will verify that this has been done upon receipt of the revised manuscript. Please find the comments of the reviewers listed below.

Please include the following materials when you submit your revision:

Completed ICMJE forms for each co-author.

An itemized, point-by-point response to the comments of the reviewers. (Label file "Response to Reviewers")

One version of the revised manuscript that includes continuous line and page numbers; these numbers should be used in the "Response to Reviewers" to indicate where specific changes have been made in response to the editorial feedback and reviews. This version should also include "highlighting" in the manuscript to highlight new material. This feature can be found on the formatting toolbar in Microsoft under highlight. (Label file "Highlighted Version")

Finally, please include a version of the manuscript without highlighting and line numbers. (Label file "Revised Version")

Color figures will be published online at no charge. Color figures will be published in print at the discretion of the Editor. The publisher will convert color figures to grayscale figures for print publication. Therefore, you should submit the color version of your figures as you would like it to appear online. We offer the option to use the VIRTUAL MICROSCOPE, a feature that enables authors to add detailed microscopic images to their papers and enables users to view the images at their highest resolution. For more information about this feature, please see: http://www.elsevier.com/about/content-innovation/virtual-microscope. In case your article contains microscopic images, you are invited to use this Virtual Microscope feature for your paper. For use of the Virtual Microscope or any related questions, please contact virtualmicroscope@elsevier.com. In your email, please include Ms.Ref.No JTO-D-17-01410.

The revisions should be completed within four weeks to avoid being considered as a new
To submit a revision, go to http://jto.edmgr.com/ and log in as an Author. You will see a menu item called "Submission Needing Revision." Please click on this item to obtain your submission record and begin the revision process.

Your username is: Lotte Nygaard
click here to reset your password

With Kind Regards,

Dirk De Ruysscher
Associate Editor
Journal of Thoracic Oncology

Reviewer Comments:

Reviewer #1: The authors have presented a well written and original manuscript building a model of first failure site and lesion specific probability after definitive chemo-radiotherapy for inoperable NSCLC. The discussion and interpretations is careful performed and contains the limitations of the study. I enjoyed the assessment of each separate lesion within one patient and the conclusion that adenocarcinoma’s and SCC should not be dealt with as the same disease.

Comments:
1) 251 patients were included, a minority (n=10) had a local recurrence after VATS surgery. Would it not be better to exclude these patients to form a more homogenous group of ‘first treatment’?

This is something we discussed extensively in our group when planning the data analysis. Patients treated at our clinic present with diverse histories, as is customary for NSCLC, and we decided to prioritize an unselected ‘real life’ cohort of SCC and AC rather than excluding more patients.

2) Patients were all diagnosed with inoperable NSCLC. How many medical inoperable (WHO score was 0 in 61%), how many oncological inoperable? What is considered as oncological inoperable in your centre? IIIAN2 in general, single level disease, multilevel disease?
Patient cases are presented at multidisciplinary tumor boards which consist of pulmonologists, thoracic surgeons, medical/radiation oncologists and pathologists. Here it is decided which treatment the patient is offered taking histology, performance status, co-morbidity, UICC stage and lung function into consideration. In general, IIIAN2 was considered a multilevel disease and oncologically inoperable during the time period covered by our study. Recently, however, it is becoming increasingly common to consider operation on these patients. We have modified the manuscript to make our practice clearer as follows.....

page 5: “In this time period, operability was determined according to clinical stage below IIIAN2, co-morbidity of the patient and lung function by a multidisciplinary board consisting of pulmonologists, thoracic surgeons and medical/radiation oncologists.

3) Some abbreviations are not explained to the reader: ROIs , TvsN

Thank you. This is corrected in the manuscript: page 6: ROIs (region of interest), page 8: TvsN (tumor versus node)

4) A maximum of five lesions per patient were evaluated (2 T, 3 N sites) Where patients with more lesions excused? If not, how did you select the lesions?

Patients with multiple lesions, the five lesions were selected as follows:

T1 and T2 (primary tumor and a potential satellite tumor). If more than 1 satellite tumor, the lesion with the highest FDG uptake and the largest diameter was chosen.

The same principle for Nodal disease. If more than 3 N-sites, then the three with the largest diameter and highest FDG uptake were selected.

The following sentence has been added on page 6:

"If a patient had multiple FDG avid lesions, the five lesions with the highest FDG uptake and the largest diameter were chosen."

5) Page 6There is a " , " missing between SUV peak and SUV mean

Thank you, this is corrected
6) Page 7 In general, I have a problem with the fact that “failure within the thorax but outside the radiotherapy PTV is considered a distant metastasis. Ipsilateral recurrence in pleura and lymph nodes or same lobe as primary tumor should be considered as local recurrence even if not in the PTV. I understand that only 7 patients had recurrence in the thorax outside PTV.

We are very well aware that the definition of failure within the thorax but outside the PTV is debatable. We cannot include a third type of failure (regional failure) in the model as there are only 7 of these events. In this study we focus on lesion failure probability prediction and classifying failures outside PTV as ‘local’ is problematic for the following reasons; these lesions were obviously subclinical (and in particular FDG PET negative) when planning radiotherapy and it is thus not meaningful to include them in an analysis of lesion-specific failure probability. If the model should work in future studies where one wishes to treat the lesion at highest risk with e.g. dose-escalation and the low risk lesions with e.g. normo-fractionation or standard dose, this is not feasible for lesions that aren’t visible from the beginning and therefore not meaningful to “treat in advance”. We have therefore chosen to retain the definition in this study. In future studies with more power, it should ideally be separated as a distinct mode of failure.

7) Page 8: Lesion level analysis. Can you comment why multivariate (multivariable is preferred over multivariate if there is a single outcome variable) logistic regression analysis is only applied to the lesions in patients with known locoregional failure? In comparison, when performing a multivariable regression for death, you would not exclude the survivors?

1: We changed ‘multivariate to multivariable’ in the logistic regression analysis.

2: The reason for applying the logistic regression analysis in all lesions within patients failing locoregionally is to derive the _conditional_ probability of lesion failure given locoregional failure. This is multiplied with the probability of failing locoregionally from the competing risk analysis to yield the baseline probability of lesion failure. In other words we apply the law of total probability \( p(A) = p(A \text{ given } B) \cdot p(B) \) with the approximation that most locoregional failures are seen within 24 months. We have modified the methods section to clarify as follows: …..

Page 8: “This conditional failure probability, \( P \), is subsequently multiplied by the absolute risk of locoregional failure from the competing risk analysis to yield individual lesion failure risk at RT planning PET/CT. Thus, the probability of lesion failure, predicted at the time of RT planning, is calculated by multiplying \( P \) with the risk of loco-regional failure after 24 months according to the competing risk model.”
8) Page 11 and figure 4: Lesion model check: Can you comment why there are only 8 points in this chart?

A rule of thumb is to use $\sqrt{\text{number of lesion failures}}$ as the number of groups in such plots. From experience we rounded down from $\sqrt{76}=8.7$. This decision on grouping was made prior to making the calibration plot.

In general, when making a prediction model, one should keep a cohort out of the model building to perform a internal validation. Is it correct to state that the same patients were used for the model building and model check? If so, this should be in the limitations.

We agree with the reviewer that sample splitting techniques can be potentially attractive as a method for validation, but we consider it as an in-between level; between internal validation and external validation if sufficient power is present. In our case, we needed all data in the model building to make the prediction model and therefore used the pure internal validation of the calibration plot, demonstrating that the model provides a good description on the data, but acknowledging the need for (full) external validation as stated in the discussion. We are in the process of finding collaborators for external validation of the model.

9) References: typo's in ref 18 (specific) and 19 (European Lu...), ref 29 Name missing of VJ

Thank you. All three references have been corrected.

10) Figure 1: black arrow is missing

We apologize for the missing arrow. The black arrow is added in the triangle at 3 years (Figure 1).

11) Table 1: The total of nodal stage is different from the rest of the manuscript: 56+20+131+54 equals 261 instead of 251; TX abbreviation unclear in context.

Thank you for your careful revision. There must have been a typo error in N2. We reviewed the data and the correct number is 121. This is corrected in Table 1.

Nstadie
Furthermore, a careful revision of Table 1 showed another error: T1: AC 25 and T1: SCC 8. This is wrong. It should be T1: AC 26 and T1 SCC 7. This is corrected with added % as suggested by reviewer 2. We apologize for this.

Table 1. In legends is added: **TX: no primary tumor.**

Reviewer #2: This is a retrospective study on 251 patients receiving definitive chemoradiation for locally advanced non-small cell lung cancer. The aim of this report was to build a model of first failure site and the Authors reached the goal finding an useful model for daily practice. Even if the argument is not so original because a lot of researchers' group are working on predictive model, the solution proposed is rapid and simple and can give some suggestion for daily activity.

Two minor suggestions can be done:
- In Materials and Method Patients, FDG-PET, Radiotherapy and Statistics are well described. Probably could be added a small addendum for chemotherapy regimen (which is however described in table 1)

Thank you for that comment. The data is available in Table 1 and to maintain readability, we did not repeat this data in the text.

- Table 1 could be ameliorated adding the percentage values also for AC and SCC

This is true, thank you. Percentage values for AC and SCC are added to Table 1.

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<td>P-value</td>
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<td>0.27</td>
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Table 1. Patient characteristics divided by histology. Categorical variables (Clinical stage, T-stage, N-stage, gender, performance status, chemotherapy regime, and radiation dose) were tested by Chi-square method (p-values in cursive). Non parametric variables (Age, pack year, and target characteristics) were tested by Mann Whitney U test. Significant p-values (p<0.05) are highlighted. UICC: The Union for International Cancer Control. AC: Adenocarcinoma. SCC: Squamous cell carcinoma. Gy: Gray. GTV: Gross tumor volume. PTV: Planning target volume. MLD: Mean lung dose. SUV: Standardized uptake value. TLG: Total lesion glycolysis. * 13 patients without SUV uptake in T-site (10 VATS) and 3 TX. TX: no primary tumor. Patients with VATS surgery before definitive radiotherapy with no SUVpeak values in their T-sites are listed with their T-stage prior to surgery. * In case of multiple T-site or N-site lesions, the highest value of SUVpeak was chosen.
Figure 1. Predicted outcome one, two and three years after diagnosis for 251 patients with adenocarcinoma (grey dots) - or squamous cell carcinoma (black dots) of the lung treated at Rigshospitalet from January 2009 to February 2015. Each side of the plot corresponds to the probability of a given endpoint. The black arrow points to the intersection of lines corresponding to 70% probability of no evidence of disease (Alive or dead, NED) – 10% probability of distant metastases (DM), and 20% probability of loco-regional failure (LRF).
Figure 2. Competing risk analysis of first failure site depending on histology. NED: no evidence of disease. ECDM: extra cranial distant metastases. ICDM: intracranial distant metastases. LRF: loco-regional failure.
Figure 3. Illustration of two patients and their lesion failure probabilities.

Adenocarcinoma: Primary tumor in right lung. Predicted failure probability=20% [9 to 31%]

Lymph node metastasis in mediastinum. PFP=2% [0 to 5%]

Squamous cell carcinoma: Primary tumor in left lung. Predicted failure probability=42% [28 to 56%]

Lymph node metastasis in mediastinum. PFP=12% [9 to 15%]
Figure 4. Binominal calibration plot of predicted failure probability on a lesion level and observed lesion failure divided into 8 quantiles including 95% confidence intervals.
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Figure 1

1 year

2 years

3 years
Figure 2

Adenocarcinoma

Squamous cell carcinoma

Cumulative incidence [%]

Time since diagnosis [years]

No at risk:

Adenocarcinoma:
- 144
- 117
- 76
- 44

Squamous cell carcinoma:
- 23
- 107
- 98
- 58
- 33
- 26

Alive, NED □
Dead, NED □
ECDM
ICDM
LRF
Figure 3

AC

20%  2%

SCC

12%  42%
Figure 4: Scatter plot showing the relationship between predicted risk of lesion failure and observed lesion failure. The plot includes confidence intervals for the observed data points. A dashed line indicates a theoretical linear relationship.
<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient and Treatment Characteristics</th>
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<table>
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<td><strong>GTV</strong></td>
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<td><strong>SUV peak, T-sites</strong></td>
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| Outcome 2: Distant metastases as first site of failure |
| **Co-variable** | **Unit** | **HR, p; base model** | **HR, p; Model with GTV** | **HR, p; Model with SUVpeak** |
| **Age** | Year | 0.99 [0.97;1.01] | 0.99 [0.96;1.01] | 0.99 [0.97;1.02] |
| **Histology** | AC vs SCC | 2.12 [1.37;3.27], p<0.001 | 2.43 [1.56;3.78], p=0.001 | 2.21 [1.41;3.48], p=0.001 |
| **PS** | PS1 and higher vs. PS 0 | 0.84 [0.57;1.25], p=0.40 | 0.77 [0.52;1.14], p=0.20 | 0.77 [0.51;1.17], p=0.22 |
| **Clinical Stage** | III vs. I and II | 1.56 [0.81;3.03], p=0.20 | 1.34 [0.69;2.63], p=0.40 | 1.09 [0.54;2.22], p=0.80 |
| | IV vs. I and II | 3.35 [1.47;7.62], p=0.004 | 3.22 [1.42;7.31], p=0.005 | 3.19 [1.37;7.44], p=0.007 |
| **GTV** | per 50 cm3 increase | NR | 1.16 [1.07;1.26], p<0.001 | 1.18 [1.09;1.28], p<0.001 |
| **SUV peak, N-sites** | NR | NR | 1.03 [1.00;1.06], p=0.035 |

| Outcome 3: Dead, NED as first event |
| **Co-variable** | **Unit** | **HR, p; base model** | **HR, p; Model with GTV** | **HR, p; Model with SUVpeak** |
| **Age** | Year | 1.02 [0.98;1.07] | 1.02 [0.98;1.07] | 1.02 [0.98;1.07] |
| **PS** | PS1 and higher vs. PS 0 | 1.59 [0.78;3.24], p=0.21 | 1.59 [0.78;3.24], p=0.21 | 1.59 [0.75;3.35], p=0.22 |
| **Gender** | Female vs Male | 1.07 [0.52;2.20], p=0.85 | 1.07 [0.52;2.20], p=0.85 | 1.17 [0.55;2.50], p=0.68 |
Table 2. Sub distribution of hazard ratios in competing risk models. Loco-regional or Distant metastases as first site of failure. Dead, NED as first event. AC: Adenocarcinoma. SCC: Squamous cell carcinoma. HR: hazard ratio, P: P-value, <0.05 is significant. NR: not relevant. GTV: Gross tumor volume. PS: Performance Status. SUVpeak: Standardized Uptake Value. T-sites: Tumor sites. N-sites: Lymph nodes. NED: No evidence of disease.
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