# Predicting the risk of disease recurrence and death following curative intent radiotherapy for NSCLC: the development & validation of two scoring systems from a large multicentre UK cohort

Matthew Evison[1], Emma Barrett[1], Andrew Cheng[1], Arafat Mulla[1], Gerard Walls[2], David Johnston[3], Jonathan McAleese[3], Karen Moore[4], Jonathan Hicks[4], Kevin Blyth[4], Mary Denholm[5], Lavina Magee[5], David Gilligan[5], Sabrina Silverman[6], Crispin Hiley[7], Muneeb Qureshi[8], Hugh Clinch[9], Matthew Hatton[8], Lara Philipps[10], Sean Brown[11], Mary O'Brien[10], Fiona McDonald[10] and Corinne Faivre-Finn[11,12]

*[1]Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK; [2]Northern Ireland Cancer Centre, Belfast, Northern Ireland, UK; [3]Cancer Centre Belfast City Hospital, Belfast Northern Ireland, UK; [4]NHS Greater Glasgow & Clyde, Glasgow, Scotland, UK; [5]Cambridge University Hospitals NHS Trust, Cambridge; [6]University College London Hospital, London, UK; [7]CRUK Lung Cancer Centre of Excellence, UCL Cancer Institute, London, UK; [8]Weston Park Hospital, Sheffield, UK; [9]The University of Sheffield Medical School, Sheffield, UK; [10]Royal Marsden Hospital, London, UK; [11] The University of Manchester, Manchester, UK; [12]The Christie NHS Foundation Trust, Manchester, UK*

Corresponding Author: Dr Matthew Evison – m.evison@nhs.net

**Abstract:**

**Introduction:** There is a paucity of evidence on which to produce recommendations on neither the clinical nor the imaging follow-up of lung cancer patients after curative intent radiotherapy. In the 2019 NICE lung cancer guidelines further research into risk stratification models to inform follow up protocols was recommended.

**Methods: A** retrospective study of consecutive patients undergoing curative-intent radiotherapy for NSCLC from 01/10/2014 to 01/10/2016 across nine UK trusts. Twenty two demographic, clinical and treatment-related variables were collected and multivariable logistic regression used to develop and validate two risk stratification models to determine the risk of disease recurrence and death.

**Results:** 898 patients were included in the study. Mean age was 72yrs, 63% (562/898) were good PS (0-1) and 43% (388/898), 15% (134/898) & 42% (376/898) were clinical stage I, II and III respectively. 36% (322/898) suffered disease recurrence and 41% (369/898) in the first two years following radiotherapy. The ASSENT score (**A**ge, performance **S**tatus, **S**moking status, staging **E**BUS, **N**-stage, **T**-stage) was developed that stratifies the risk for disease recurrence within 2 years with an AUROC for the total score of 0.712 (0.671-0.753) and 0.72 (0.65-0.789) in the derivation and validation set respectively. The STEPS score (**S**ex, Performance status, staging **E**BUS, **T**-stage, N-**S**tage) was developed that stratifies the risk of death within 2 years with an AUROC for total score of 0.625 (0.581-0.669) and 0.607 (0.53-0.684) in the derivation and validation set respectively.

**Conclusions:** These validated risk stratification models could be used to inform follow-up protocols after curative intent radiotherapy for lung cancer. The modest performance highlights the need for more advanced risk prediction tools.

**Introduction:**

Follow-up after curative-intent treatment for non-small cell lung cancer (NSCLC) is universally recommended across international guidelines (1-6). The purpose of this follow-up is to monitor and treat underlying co-morbidities (including tobacco addiction), provide patient support and information, prevent acute crisis admissions, manage treatment-related complications, detect treatable relapse of cancer and detect second primary cancers that could undergo further curative-intent treatment. However, international guidelines also universally acknowledge a paucity of high quality evidence on which to make specific recommendations on the type and intensity of both imaging surveillance and clinical review.

The evidence review conducted by the National Institute for Health and Care Excellence (NICE) Lung Cancer Guideline Group identified only three poor quality studies relating the follow up after lung cancer treatment and all related to follow up after lung resection with no data relating to curative-intent radiotherapy (2). Similarly a literature search of 3412 citations for the American College of Chest Physicians (ACCP) guidelines on the follow up after curative-intent treatment of lung cancer failed to produce adequate evidence to produce recommendations specific to radiotherapy (6). International guidelines from the National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO) and European Society of Radiation Oncology (ESTRO) all recommend routine contrast-enhanced computed tomography (CT) of the chest following curative intent-radiotherapy for stage I-III NSCLC at 3-6 month intervals for 2-3 years, based only on expert consensus (1, 3, 5). This lack of high quality evidence on which to base recommendations led the NICE guideline group to recommend further research into 'the use of prognostic factors to develop risk stratification models to determine the optimal follow up pattern' in their 2019 lung cancer guidelines.

The aim of this study was to understand the outcomes from a large cohort of patients across the United Kingdom (UK) undergoing curative-intent radiotherapy for NSCLC including disease recurrence, patterns of recurrence, treatment of recurrence, metachronous primary cancer diagnosis, and death

from both cancer and co-morbidities. Using a broad range of patient-related, cancer-related and treatment-related parameters we aimed to produce separate risk-stratification models to predict the risk of disease recurrence and death following radiotherapy. Such models might prove useful in designing personalised follow-up strategies for patients undergoing curative-intent radiotherapy for NSCLC in the future.

**Methods:**

Retrospective data was collected for consecutive patients that underwent curative-intent radiotherapy for NSCLC from 1st October 2014 to 1st October 2016 at nine trusts across the United Kingdom (Wythenshawe Hospital, The Christie NHS Foundation Trust, Royal Marsden NHS Foundation Trust, University College London Hospitals, Papworth Hospital NHS Foundation Trust, Addenbrokes Hospital, Sheffield Teaching Hospitals Trust, NHS Greater Glasgow and Clyde Trust and Northern Ireland Cancer Centre, Belfast). The data were collected in early 2019 ensuring a minimum of two years follow-up data for all patients and the database locked in April 2019 for analysis. The data were retrieved from case note and electronic patient record review. The following 22 demographic, clinical and treatment-related parameters were collected: age, gender, pre-treatment performance status, BMI, smoking status, emphysema (none, mild, moderate or severe based on CT imaging), interstitial lung disease (none, mild, moderate or severe based on CT imaging), forced expiratory volume in one second (FEV1, as percentage of predicted), diffusing capacity for carbon monoxide (DLCO, as percentage of predicted), pathological diagnosis of NSCLC (versus clinical diagnosis without pathological confirmation), pre & post-treatment absolute lymphocyte count, pre & post-treatment neutrophil-lymphocyte ratio, T-Stage (8th Edition TNM clinical staging), N-stage (8th Edition TNM clinical staging), primary tumour size (mm), primary tumour SUV, lymph node SUV (maximal SUV value in any thoracic lymph node), completion of a staging endobronchial ultrasound (EBUS, yes/no), presence of an ipsilateral pleural effusion (yes/no) and the type radiotherapy treatment used (continuous hyperfractionated accelerated radiotherapy (CHART), stereotactic ablative radiotherapy (SABR), conventional radical radiotherapy (including an accelerated schedule 55Gy/20 fractions/4 weeks), sequential chemoradiotherapy (sCRT) or concurrent chemoradiotherapy (cCRT)). In addition, the following outcome data was collected: disease recurrence, date of disease recurrence, pattern of disease recurrence (local, nodal or distant where local recurrence is defined as isolated to the lung in the area of the original primary tumour and radiotherapy field), symptomatic versus asymptomatic detection of recurrence, further treatment for disease recurrence, diagnosis of metachronous primary tumour during follow-up (diagnosis of metachronous tumour based on local MDT decision considering

factors such as separate histology, disease free survival ≥2years, developing from carcinoma-in-situ, or different lobe with N0 M0 as supporting a diagnosis of metachronous primary tumour (7)), treatment of metachronous tumour, overall survival and cause of death (cancer related versus non-cancer related).

The first objective of the analysis was to report relevant outcomes from a large cohort of patients undergoing curative-intent radiotherapy across the UK including: the prevalence, distribution and type of treatment for disease recurrence, the prevalence and treatment of metachronous primary tumours and overall survival following curative-intent radiotherapy for NSCLC including the proportion of deaths attributed to lung cancer and the proportion attributed to and non-cancer death. The second objective was to develop separate risk stratification models to categorise patients into different levels of risk for disease recurrence and death.

**Statistical methods:**

Patient characteristics and comorbidities are summarised as means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. To assess the relationship between these variables and the outcomes of interest, disease recurrence and death within 2 years of commencing treatment, two separate but identical statistical analyses were performed for each outcome. For validation purposes, a pseudorandom number generator was used to partition the data into training and testing sets at an approximate 3:1 ratio. Differences in distributions and proportions of baseline characteristics between the two sets were tested, and found not to be significant at $p<0.05$. Single variable logistic regression with all 22 demographic, clinical and treatment-related variables was used. A multivariable logistic regression model was used to develop the risk score system, with all variables used in the single variable analysis considered. Variables with more than 20% missing data were excluded from the multivariable analysis, and multiple imputation was used to deal with missing data for the remaining variables. The R package ‘mice’ was used to create 5 imputated datasets by; predictive mean matching for numeric data, proportional odds model

for ordered categorical data, logistic regression and polytomous regression imputation for binary and unordered categorical data respectively. Optimal cut-off values were found for continuous variables, by maximising the Youden index, with respect to predicting recurrence and death, separately. Subsequently, all variables included in the multivariable analyses were categorical.

The final model was selected via backward stepwise elimination, pooled across the imputed datasets, starting with all variables and then removing the least significant variable and running the model again. This process continued until all remaining variables were significant at the 5% level. The scoring system for predicting both outcomes within 2 years was devised from the coefficient estimates of the final models. After initially assigning scores according to the ORs from the multivariable model, comparisons were made for various Score models & the model with the highest Area Under the Receiver Operating Characteristic curve (AUROC) was used**.** Scores were categorised into three risk categories, low, moderate, and high-risk, according to the optimal cut-off locations, based on likelihood ratio tests and the maximal (AUROC). Survival analysis was performed using Kaplan-Meier curves and log-rank tests for the three risk categories. Performance of the risk models was assessed using the testing dataset. All analyses were performed using R 3.5.1. Ethical approval was not required given the observational nature of the study, confirmed via discussion with the local ethics committee.

**Results:**

A total of 898 patients underwent curative intent radiotherapy for NSCLC in the study period and were included in the analysis. The median follow up period was 763 days. A summary of the patient

demographic and clinical parameters is provided in Table 1. Mean age was 72 years and 54% (485/898) were female. Sixty three percent (562/898) were of good performance status prior to treatment (WHO PS 0-1). Overall 43% (388/898) were 8th Edition TNM clinical stage I and 42% (376/898) were clinical stage III with the remainder being clinical stage II. The pathological sub-types were adenocarcinoma 26% (235/898), Squamous cell carcinoma 27% (242/898), NSCLC Not Otherwise Specified 4% (34/898), NSCLC other 1% (13/898) and 18% (163/898) where the data field was completed as 'yes' to pathological diagnosis of NSCLC but did not provide sub-typing. The remaining 24% (211/898) did not have pathological diagnosis. The majority of patients with no pathological diagnosis had stage 1 lung cancer (82%, 173/211). The type of radiotherapy treatment delivered was as follows: CHART 4% (32/898), conventional radical radiotherapy 42% (380/898), SABR 27% (242/898), sCRT 20% (180/898) and cCRT 7% (64/898).

In total 45% (403/898) of patients suffered disease recurrence following curative intent treatment within the study period and 36% pf patients suffered disease recurrence within the first two years (80%, 322/403, of all disease recurrences were within the first two years). Fifty-two percent of disease recurrences were detected due to symptomatic presentation and 48% were detected through routine surveillance imaging in the absence of symptoms. The pattern of disease recurrence was as follows: local recurrence in 30% (120/403), nodal recurrence in 8% (31/403) and distant recurrence in 62% (244/403). Patients with disease recurrence underwent the following treatment: surgical resection 2% (6/403), other radical local treatment (e.g. microwave ablation, brachytherapy) 1% (5/403), radical radiotherapy for nodal recurrence 1% (5/403), 'radical' treatment for metachronous oligometastatic disease (local ablative therapy or surgical resection) 3% (10/403) and palliative systemic anti-cancer treatment 36% (141/403). The commonest management strategy for disease recurrence was best supportive care alone (58%, 228/403).

During the follow up period 4% (39/898) of patients developed a metachronous primary lung cancer and 64% (25/39) were diagnosed in the first two years following radiotherapy. The majority were stage

1 (67%, 26/39) and detected incidentally during routine surveillance imaging in the absence of symptoms (85%, 33/39). In those patients with a metachronous lung cancer 13% (5/39) underwent surgical resection, 47% (18/39) underwent curative-intent radiotherapy and 8% (3/39) underwent palliative systemic anti-cancer therapy and 32% (12/39) were managed with best supportive care alone.

Across the study cohort the median overall survival following radiotherapy was 921 days. A total of 533 (59%) patients had died at the time of analysis and 41% (369/898) of patients died within the first two years (69%, 369/533, of all deaths were within the first two years). The cause of death was available in 418 patients in whom death was attributed to lung cancer in 65% (270/418), non-lung cancer related causes in 32% (134/418) and treatment related in 3% (14/418).

Type of radiotherapy delivered, crude recurrence rates both at 2 years and overall, pattern of recurrence, treatment of recurrence and deaths both at 2 years and overall stratified according to overall TNM stage I-III is provided in Table 2.

**Risk stratification for disease recurrence:**

76 patients were excluded from the original 898 due to missing data on disease recurrence. From this 822, the data was randomly split into Training (618) & Testing (204) sets. Using the training set, single variable analysis found 12 variables to have statistical significance at the 5% level. Multivariable analysis identified 6 variables as having independent associations with recurrence within 2 years (**A**ge, performance **S**tatus, **S**moking status, staging **E**BUS, **N**-stage and **T**-stage). From this final model, a scoring system (the **ASSENT** score) was produced using the regression coefficients (Table 3). Scores range from 0 to 6, categorised as follows: Low-risk (Score ≤3), moderate-risk (Score 3-4) and high-risk (Score ≥4). 20% (54/272) of patients in the low-risk group were diagnosed with disease recurrence within 2 years, compared to 46% (105/228) and 64% (75/118) in the moderate-risk and high-risk groups respectively. The data held back for assessing model performance, the validation dataset, consisted of 204 patients whose baseline characteristics had similar distributions to the derivation

dataset (Appendix 1). In the validation dataset, 21% (18/87) of patients in the low risk group were diagnosed with disease recurrence within 2 years, compared to 46% (36/79) and 61% (23/38) in the moderate risk and high risk groups respectively. The AUROC for Total score in the derivation cohort was 0.712 (95%CI: 0.671-0.753) and 0.72 (95%CI: 0.65-0.789) in the validation cohort. The Kaplan-Meier survival curves for the derivation and validation cohorts are provided in Figure 1. Log rank tests for difference between survival curves was significant across the two cohorts ($p<0.001$) confirming a consistent, statistically significant difference in survival between the three risk groups.

**Risk stratification for death:**

69 patients were excluded from the original 898 due to missing data on disease recurrence. From this 829, the data was randomly split into Training (623) & Testing (206) sets. Using the training set, Single variable analysis found 16 variables to have statistical significance at the 5% level. Multivariable analysis identified 5 variables as having independent associations with death within 2 years (**S**ex, **T**-stage, staging **E**BUS, **P**erformance status, N-**S**tage). From this final model, a scoring system (the '**STEPS'** score) was produced using the regression coefficients (Table 4). Score range from 0 to 8.5, categorised as follows: Low-risk (Score <1), moderate-risk (Score 1-2.5) and high-risk (Score >2.5). 31% (29/95) of patients in the low-risk group had died within two years of radiotherapy, compared to 39% (145/373) and 63% (98/155) in the moderate-risk and high-risk groups respectively. The data held back for assessing model performance, the validation dataset, consisted of 206 patients whose baseline characteristics had similar distributions to the derivation dataset (Appendix 2). In the validation set, 27% (8/30) of patients in the low-risk group had died within two years of radiotherapy compared to 40% (50/125) and 63% (32/51) in the moderate-risk and high-risk groups respectively. The AUROC for Total score in the derivation cohort was 0.625 (95%CI: 0.581-0.669) and 0.607 (0.53-0.684) in the validation cohort. The Kaplan-Meier survival curves for the derivation and validation cohorts are provided in Figure 2. Log rank tests for difference between survival curves was significant across the

two cohorts ($p<0.001$) confirming a consistent, statistically significant difference in survival between the three risk groups.

**Discussion:**

***Key findings.*** This multi-centre UK study of nearly 900 patients undergoing curative intent radiotherapy for NSCLC has shown approximately one third of patients suffered a recurrence of their cancer and two in every five patients died in the first two years following radiotherapy. Three in every

five patients with disease recurrence were managed with best supportive care alone. These outcomes are despite two-thirds of patients being of good performance status prior to treatment (PS 0-1), two-thirds being clinical stage I or II and approximately half of all disease recurrence being detected via routine surveillance imaging in the absence of symptoms. Risk stratification scores have been identified that can categorise patients into a low, moderate or high level of risk for disease recurrence (ASSENT) or death (STEPS) in the two years following radiotherapy treatment. These scores could have clinical utility in describing risk during patient discussions and facilitating shared decision making as well as informing personalised, risk stratified follow up protocols whereby the frequency of imaging is intensified for those at highest risk of recurrence and the frequency of clinical assessment is intensified in those at highest risk of death. Conversely, such protocols could facilitate de-intensifying regimes in low risk categories. As an example, the ASSENT score classified less than 20% of patients as high risk in both derivation and validation cohorts yet >60% of patients in this high risk group across both cohorts suffered disease recurrence. The ASSENT score could, therefore, lead to more efficient use of radiological resource in the follow-up of lung cancer patients after curative-intent radiotherapy.

***Discussion.*** Whilst out of the two models, the ASSESNT score for disease recurrence appears to perform the best; the performance of both the ASSENT and STEPS scores is modest overall. Furthermore, in an unplanned post-hoc analysis there was no statistically significant difference in the performance of ASSENT/STEPS scores when compared to overall stage ($8^{th}$ edition TNM clinical stage I,II,III) in the validation cohorts (Appendix 3 and 4). The AUROC values for both the risk stratification models and overall stage remain suboptimal and highlight a lack of effective risk stratification tools following lung cancer treatment.

It is noted that poor performance status and increasing age are associated with reduced risk of recurrence after radiotherapy in these models. This study included all forms of curative radiotherapy and therefore likely contained two distinct groups: older and frailer patients with early stage disease that are not fit enough for surgery and undergo radiotherapy and younger fitter patients with

unresectable stage III disease treated with multimodality treatment including radiotherapy. The former older and frailer group will have a lower risk of recurrence from early stage disease. Furthermore, the older and frailer group are more likely to die from non-cancer related causes before the cancer has had the opportunity to recur. This highlights one of the benefits of the ASSENT score whereby those with a poorer performance status score lower and are more likely to classified as low risk where follow-up protocols might be de-escalated, particularly if suitability for further treatment is in doubt.

Staging EBUS is an independent predictor of disease recurrence and death and appears in both models. This is an interesting finding and may reflect a higher risk of nodal metastases coupled with an association of underlying co-morbidities and pro-inflammatory states that manifest as lymph node enlargement or elevated metabolic activity on PET-CT necessitating staging EBUS.

***Strengths of the study*.** This is a multicentre study across the UK with a large study cohort of nearly 900 patients. These data have been collected from high volume expert cancer centres. A significant breadth of data was collected spanning fitness, co-morbidities, physiological indices, cancer specific parameters and treatment specific information. Coupled with detailed outcome data has allowed this study to look in depth at the potential impact of host and cancer related factors on outcomes following curative intent radiotherapy. Looking only at disease recurrence and cancer related survival can neglect competing causes of death in often co-morbid patients diagnosed with lung cancer. This level of detail and understanding adds significant weight to the conclusions we can draw from these data. The statistical analysis is robust including both derivation and validation cohorts. This study has included all forms of curative intent radiotherapy and not focused on specific sub-groups such as stage III (8) or those undergoing chemoradiotherapy (9, 10) thereby increasing the clinical utility.

***Weaknesses of the study*.** This is a retrospective study reliant on data recall using patient records. As the centres contributing to this study are tertiary referral regional cancer centres not all information was available from investigations completed at the referring hospitals. The study methodology

stipulated that variables with >20% missing data were excluded from the multivariable analysis. This excluded 9 of the 22 variables which could have impacted on the resulting performance of the risk stratification scores. However, to have clinical utility these scores must include variables that are readily available to either treating or referring centres and by excluding those variables that are consistently difficult to identify will inherently create a scoring system that can be reliably calculated from readily available information. Furthermore, an unplanned post-hoc analysis using a cut-off of >30% missing data for exclusion was performed (which allowed inclusion of emphysema, ILD, DLCO and primary tumour SUV) but none of the additional variables were chosen for the final scoring system (unpublished data). We also included patients within this study that did not have a pathological diagnosis of NSCLC. Therefore there may have been patients with benign disease or small cell lung cancer included and this could impact on the rate of recurrence and death for a study targeting those with NSCLC. However, including these patients reflects real-life practice and patients without a pathological diagnosis would still benefit from risk stratification post treatment and these models account for this cohort. There are also variables that could have been included in this or any future work, particularly Gross Tumour Volume which has been shown to have a negative prognostic impact (11). This study cohort is likely to be representative of UK, and probably European, practice but the results may not be generalizable to other regions and countries. Lastly but most importantly is considering what conclusions can be drawn from the low rate of further active treatment following the diagnosis of recurrence. This retrospective study does not capture patient choice, post-treatment performance status or presence of targetable mutations all of which impact on treatment decisions and would be needed to truly examine these results. Furthermore, there may be emerging therapies for disease recurrence following radiotherapy that could impact on treatment rates (such as salvage surgery, radical re-irradiation and emerging systemic therapies such as immunotherapy) which could alter the balance of risk and benefit to routine surveillance and is not accounted for in this data.

***Future impact.*** These results present a clinical dilemma. One interpretation might be that the low rate of further treatment for disease recurrence could question the effectiveness of intensive surveillance

imaging. Another interpretation might be that current surveillance imaging is failing to adequately identify or identify early enough disease recurrence particularly distant disease. Given that the majority of disease recurrence was distant should differing imaging modalities be considered such as PET-CT and brain imaging? In other words, just because further treatment wasn't delivered in this retrospective cohort doesn't mean it couldn't be in carefully selected patients in whom an intensive imaging surveillance protocol might be helpful. Either way, what is clear form this data is that disease recurrence, morbidity and death are common in this patient cohort which supports the need for comprehensive clinical review and survivorship service following radiotherapy. The risk stratification models presented here could be used as part of a holistic assessment that covers patient choice, post treatment fitness and risk stratification to define a personalised follow-up protocol. Future studies to help answer these questions and dilemmas are required.

**Conclusion**

We have developed and validated risk stratification models to predict the risk of disease recurrence and death following curative intent radiotherapy based on clinical, physiological and cancer-related parameters. However, the performance of these models remains modest and further studies into the optimal imaging programme and optimal clinical surveillance following radiotherapy as well as more advanced tools for predicting outcomes following treatment are required. A shift in focus from routine imaging-based follow-up to Patient Reported Outcome Measure-based survivorship services requires exploration. Ultimately the search for better risk stratification following curative intent radiotherapy continues and there is a clear need for better prognostic predictors of outcome.

**Figure Legends:**

**Figure 1:** Kaplan-Meier survival curves for low, moderate and high risk of disease recurrence groups (ASSENT Score) in (A) derivation and (B) validation cohorts

**Figure 2:** Kaplan-Meier survival curves for low, moderate and high risk of death groups (STEPS Score) in (A) derivation and (B) validation cohorts

**References**


1. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv1-iv21.
2. NICE. Lung cancer: diagnosis and management

NICE guideline [NG122]. NICE Clinical Guideline. 2019.
3. Guckenberger M, Andratschke N, Dieckmann K, Hoogeman MS, Hoyer M, Hurkmans C, et al. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. Radiother Oncol. 2017;124(1):11-7.
4. Huang K, Dahele M, Senan S, Guckenberger M, Rodrigues GB, Ward A, et al. Radiographic changes after lung stereotactic ablative radiotherapy (SABR)--can we distinguish recurrence from fibrosis? A systematic review of the literature. Radiother Oncol. 2012;102(3):335-42.
5. Network NCC. Non-small cell lung cancer. NCCN Clinical Practice Guidelines in Oncology. 2019;Version 7.

6. Colt HG, Murgu SD, Korst RJ, Slatore CG, Unger M, Quadrelli S. Follow-up and surveillance of the patient with lung cancer after curative-intent therapy: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e437S-e54S.
7. Martini N, Bains MS, Burt ME, Zakowski MF, McCormack P, Rusch VW, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. J Thorac Cardiovasc Surg. 1995;109(1):120-9.
8. Oberije C, De Ruysscher D, Houben R, van de Heuvel M, Uyterlinde W, Deasy JO, et al. A Validated Prediction Model for Overall Survival From Stage III Non-Small Cell Lung Cancer: Toward Survival Prediction for Individual Patients. Int J Radiat Oncol Biol Phys. 2015;92(4):935-44.
9. Dehing-Oberije C, De Ruysscher D, van der Weide H, Hochstenbag M, Bootsma G, Geraedts W, et al. Tumor volume combined with number of positive lymph node stations is a more important prognostic factor than TNM stage for survival of non-small-cell lung cancer patients treated with (chemo)radiotherapy. Int J Radiat Oncol Biol Phys. 2008;70(4):1039-44.
10. Dehing-Oberije C, Yu S, De Ruysscher D, Meersschout S, Van Beek K, Lievens Y, et al. Development and external validation of prognostic model for 2-year survival of non-small-cell lung cancer patients treated with chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2009;74(2):355-62.
11. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015;16(2):187-99.

**Table 1**: Patient demographics and clinical parameters

| | | |
|---|---|---|
| Age | Mean (SD) | 72.0 (+/-9.41) |
| | Missing n (%) | 10 (1) |
| Gender<br>n (%) | Male | 413 (46) |
| | Female | 485 (54) |
| | Missing | 0 (0) |
| Pre-treatment WHO Performance Status<br>n (%) | 0 | 123 (14) |
| | 1 | 439 (49) |
| | 2 | 276 (31) |
| | 3 | 41 (4) |
| | Missing | 19 (2) |
| BMI | Mean (SD) | 25.89 (+/-5.86) |
| | Missing n (%) | 568 (63) |
| Smoking Status<br>n (%) | Never smoker | 49 (6) |
| | Ex-smoker | 539 (60) |
| | Current smoker | 263 (29) |
| | Missing | 47 (5) |
| Emphysema<br>n (%) | None | 370 (41) |
| | Mild | 138 (15) |
| | Moderate | 152 (17) |
| | Severe | 38 (4) |
| | Missing | 200 (22) |
| Interstitial lung disease<br>n (%) | None | 623 (70) |
| | Mild | 45 (5) |
| | Moderate | 19 (2) |
| | Severe | 0 (0) |
| | Missing | 210 (23) |
| FEV1 % predicted | Mean (SD) | 74.67 (+/-32.33) |
| | Missing n (%) | 110 (12) |
| DLCO % predicted | Mean (SD) | 62.32 (+/-25.78) |
| | Missing n (%) | 267 (30%) |
| Pathological diagnosis of NSCLC<br>n (%) | Yes | 687 (76) |
| | No | 211 (24) |
| | Missing | 0 (0) |
| Pre-treatment lymphocyte count | Mean (SD) | 1.83 (1.09) |
| | Missing n (%) | 322 (36) |
| Pre-treatment lymphocyte:neutrophil | Mean (SD) | 3.9 (4.0) |
| | Missing n (%) | 317 (35) |
| Post-treatment lymphocyte count | Mean (SD) | 0.92 (0.63) |
| | Missing n (%) | 424 (47) |
| Post-treatment lymphocyte:neutrophil | Mean (SD) | 8.39 (9.29) |
| | Missing n (%) | 424 (47) |
| T-stage<br>n (%) | T1 | 330 (37) |
| | T2 | 243 (27) |
| | T3 | 158 (18) |
| | T4 | 151 (17) |
| | T0/x | 15 (2) |
| | Missing | 1 (<1) |
| | N0 | 496 (55) |

| | | |
|---|---|---|
| N-stage<br>n (%) | N1 | 108 (12) |
| | N2 | 252 (28) |
| | N3 | 42 (5) |
| | Missing | 0 (0) |
| Primary tumour size (mm) | Mean (SD) | 34.44 (+/-20.05) |
| | Missing n (%) | 80 (9) |
| Primary Tumour SUV | Mean (SD) | 11.24 (+/-7.07) |
| | Missing n (%) | 270 (30%) |
| Maximum lymph node SUV | Mean (SD) | 2.49 (+/-1.98) |
| | Missing n (%) | 1 (<1) |
| Staging EBUS<br>n (%) | Yes | 201 (22) |
| | No | 696 (78) |
| | Missing | 1 (0) |
| Ipsilateral pleural effusion<br>n (%) | Yes | 58 (6) |
| | No | 840 (94) |
| | Missing | 0 (0) |
| Treatment type<br>n (%) | CHART | 32 (4) |
| | Conventional XRT | 380 (42) |
| | SABR | 242 (27) |
| | Sequential CRT | 180 (20) |
| | Concurrent CRT | 64 (7) |
| | Missing | 0 (0) |

**Table 2:** Outcomes stratified according to overall TNM stage

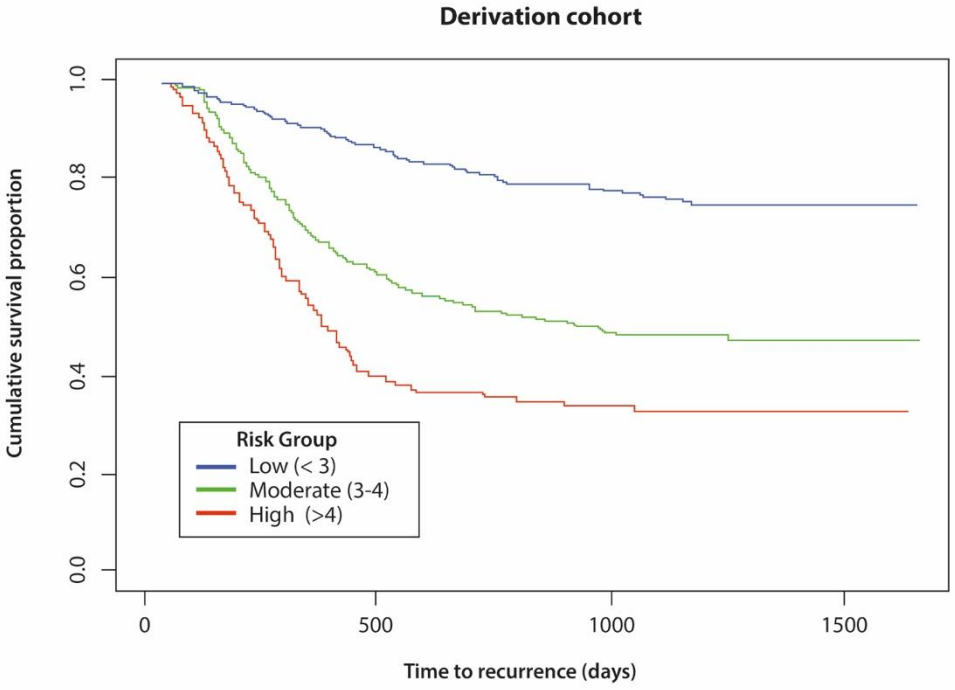
| | | 8th Edition TNM Stage I (n=388) | 8th Edition TNM Stage II (n=134) | 8th Edition TNM Stage III (n=376) |
|---|---|---|---|---|
| Radiotherapy Regime n (%) | CHART | 12 (3) | 6 (4) | 14 (4) |
| | Conventional XRT | 145 (37) | 96 (72) | 139 (37) |
| | SABR | 228 (59) | 13 (10) | 1 (<1) |
| | Sequential CRT | 1 (<1) | 14 (10) | 165 (44) |
| | Concurrent CRT | 2 (<1) | 5 (4) | 57 (15) |
| Recurrence rate within 2 years, n (%) | | 85 (22) | 48 (36) | 189 (50) |
| Overall recurrence rate, n (%) | | 111 (29) | 56 (42) | 228 (61) |
| Pattern of recurrence n (%) | Local | 44 (40) | 13 (23) | 63 (28) |
| | Nodal | 11 (10) | 4 (7) | 16 (7) |
| | Distant | 56 (51) | 39 (67) | 149 (65) |
| Recurrence treatment type n (%) | Resection | 3 (3) | 1 (2) | 2 (<1) |
| | Other local curative | 4 (4) | 0 (0) | 1 (<1) |
| | Radical XRT (nodes) | 3 (3) | 1 (2) | 1 (<1) |
| | Oligometastatic Rx | 2 (2) | 0 (0) | 8 (4) |
| | Palliative SACT | 28 (25) | 15 (26) | 98 (43) |
| | Best supportive care | 73 (65) | 38 (66) | 117 (52) |
| Deaths within 2 years, n (%) | | 112 (29) | 59 (44) | 198 (53) |
| Overall death rate, n | | 182 | 89 | 262 |

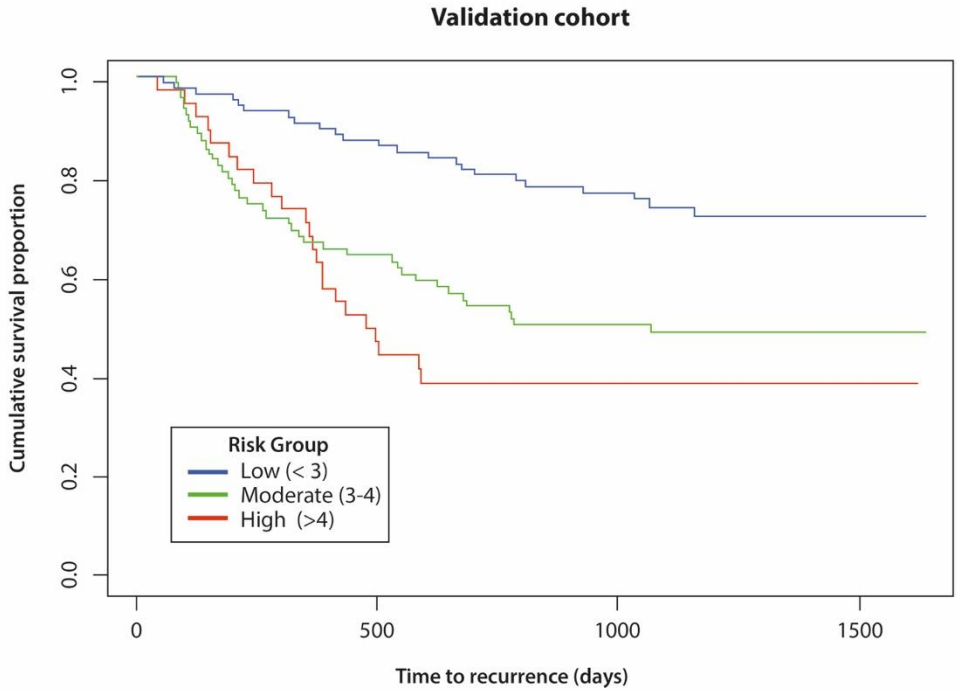
**Table 3:** Multivariate analysis & scoring system for the risk of recurrence within 2 years of radiotherapy (ASSENT Score)

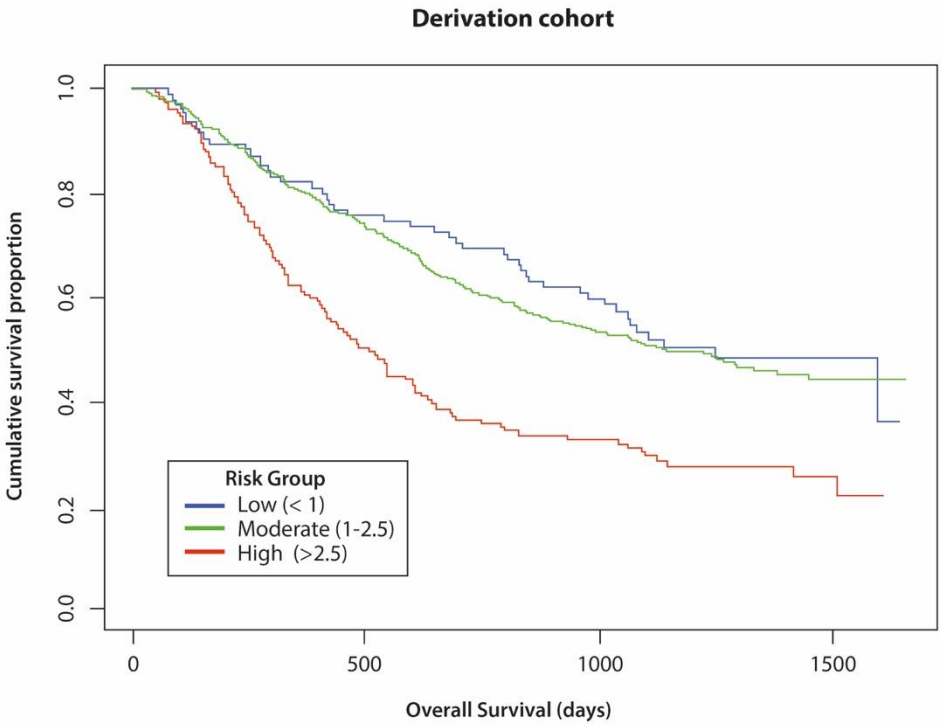
| Variable | | Patient numbers n (%) | OR (95% CI) | p-value | Score |
|---|---|---|---|---|---|
| **A**ge | <75yrs | 364 (59) | 1 | | 0.5 |
| | ≥75yrs | 254 (41) | 0.66 (0.45-0.96) | 0.032 | 0 |
| Performance **S**tatus | 0 | 90 (15) | 1 | | 1 |
| | 1 | 304 (49) | 0.66 (0.39-1.1) | 0.11 | 0.5 |
| | 2 | 190 (31) | 0.8 (0.45-1.42) | 0.44 | 0.5 |
| | 3 | 34 (5) | 0.27 (0.09-0.72) | 0.013 | 0 |
| **S**moking status | Never | 34 (5) | 1 | | 0 |
| | Ex-smoker | 393 (64) | 2.29 (0.97-5.94) | 0.068 | 1 |
| | Current | 191 (31) | 2.64 (1.08-7.0) | 0.04 | 1 |
| Staging **E**BUS performed | No | 475 (77) | 1 | | 0 |
| | Yes | 143 (23) | 1.78 (1.16-2.73) | 0.008 | 0.5 |
| **N**-stage (clinical staging) | N0 | 361 (58) | 1 | | 0 |
| | N1 | 78 (13) | 2.25 (1.29-3.94) | 0.004 | 1 |
| | N2 | 157 (25) | 1.82 (1.13-2.93) | 0.014 | 1 |
| | N3 | 22 (4) | 1.05 (0.4-2.68) | 0.92 | 1 |
| **T**-stage (clinical staging) | T1a-c | 235 (38) | 1 | | 0 |
| | T2a-b | 173 (28) | 2.05 (1.3-3.24) | 0.002 | 1 |
| | T3 | 109 (18) | 2.03 (1.19-3.48) | 0.01 | 1 |
| | T4 | 101 (16) | 3.09 (1.77-5.41) | <0.001 | 2 |
| **Overall Risk Score** | **Low** | **272 (44)** | **2yr recurrence 20%** | | **≤3** |
| | **Moderate** | **228 (37)** | **2yr recurrence 46%** | | **3 - 4** |
| | **High** | **118 (19)** | **2yr recurrence 64%** | | **≥4** |

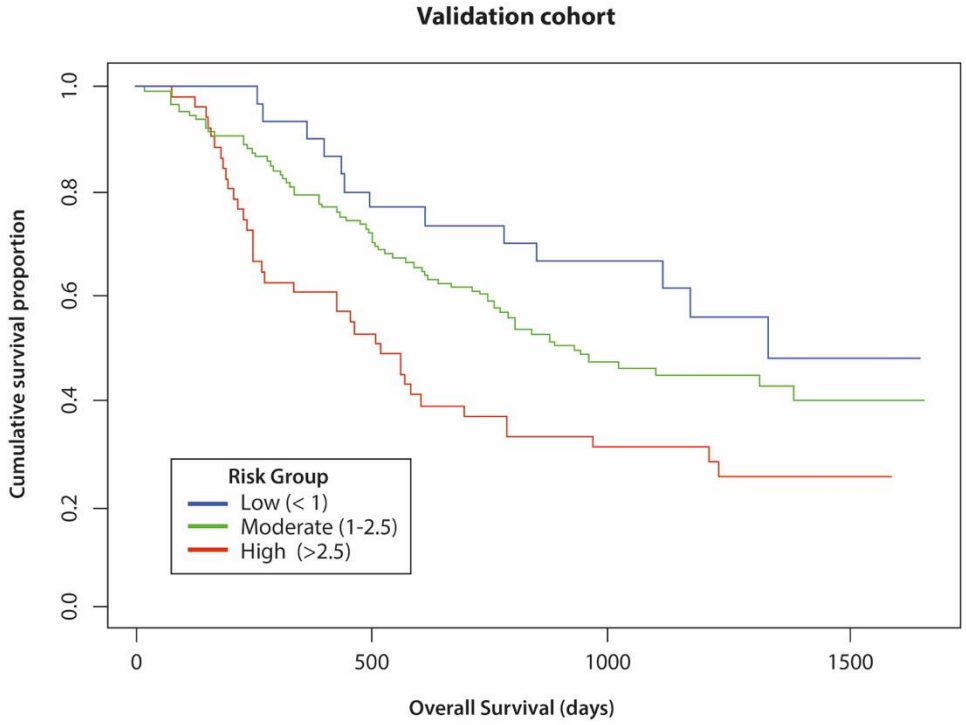
**Table 4:** Multivariate analysis & scoring system for the risk of death within 2 years of radiotherapy (STEPS Score)

| Variable | | Patient numbers n (%) | OR (95% CI) | p-value | Score |
|---|---|---|---|---|---|
| **S**ex | Female | 283 (45) | 1 | | 0 |
| | Male | 340 (55) | 2.19 (1.55-3.12) | <0.001 | 1 |
| **T**-stage | T1 | 236 (38) | 1 | | 0 |
| | T2 | 180 (29) | 1.58 (1.03-2.43) | 0.035 | 0.5 |
| | T3 | 110 (18) | 2.36 (1.41-3.96) | 0.001 | 1 |
| | T4 | 97 (15) | 4.36 (2.47-7.84) | <0.001 | 3 |
| Staging **E**BUS | No | 471 (76) | 1 | | 0 |
| | Yes | 152 (24) | 1.60 (1.07-2.51) | 0.024 | 0.5 |
| **P**erformance status | 0 | 82 (13) | 1 | | 0 |
| | 1 | 306 (49) | 1.56 (0.9-2.74) | 0.12 | 0 |
| | 2 | 200 (32) | 2.69 (1.47-5.02) | 0.002 | 1 |
| | 3 | 35 (6) | 2.67 (1.08-6.58) | 0.033 | 1 |
| N-**S**tage | 0 | 344 (55) | 1 | | 0 |
| | 1 | 81 (13) | 1.38 (0.8-2.39) | 0.25 | 0 |
| | 2 | 169 (27) | 1.94 (1.22-3.1) | 0.005 | 1 |
| | 3 | 29 (5) | 1.22 (0.5-2.89) | 0.66 | 1 |
| **Overall risk score** | **Low** | **95 (15)** | **2yr mortality 31%** | | **<1** |
| | **Moderate** | **373 (60)** | **2yr mortality 39%** | | **1-2.5** |
| | **High** | **155 (25)** | **2yr mortality 63%** | | **>2.5** |


Derivation cohort
Cumulative survival proportion
0.0
0.2
0.4
0.6
0.8
1.0
0
500
1000
1500
Time to recurrence (days)
Risk Group
Low (< 3)
Moderate (3-4)
High (>4)


Validation cohort
Cumulative survival proportion
0.0
0.2
0.4
0.6
0.8
1.0
0
500
1000
1500
Time to recurrence (days)
Risk Group
Low (< 3)
Moderate (3-4)
High (>4)


Derivation cohort
Cumulative survival proportion
0.0
0.2
0.4
0.6
0.8
1.0
0
500
1000
1500
Overall Survival (days)
Risk Group
Low (< 1)
Moderate (1-2.5)
High (>2.5)


Validation cohort
Cumulative survival proportion
0.0
0.2
0.4
0.6
0.8
1.0
0
500
1000
1500
Overall Survival (days)
Risk Group
Low (< 1)
Moderate (1-2.5)
High (>2.5)