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

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Abstract:

Introduction: There is a paucity of evidence on which to produce recommendations on the clinical and imaging follow-up of lung cancer patients after curative intent treatment, particularly radiotherapy. In their 2019 lung cancer guidelines, NICE have recommended further research into risk stratification models to inform follow up protocols.

Methods: This is a retrospective study of consecutive patients undergoing curative-intent radiotherapy for NSCLC from 01/10/2014 to 01/10/2016 across nine UK trusts. Outcomes recorded included disease recurrence and death (cancer vs non-cancer related). Twenty five different clinical parameters were collected and multivariable logistic regression used to develop two risk stratification models to determine the risk of disease recurrence and death.

Results: 898 patients were included in the study. Sixty three percent of patients were of good PS (0-1) and 43%, 15% & 42% were clinical stage I, II and III respectively. In total, 45% suffered disease recurrence, 80% of which occurred in the first two years following radiotherapy. Overall only 4% of patients with disease recurrence received further curative-intent treatment and 58% were managed with best supportive care alone. In total 59% of patients died during the study period, 69% of which were in the first two years. The ASSENT score (**A**ge, performance **S**tatus, **S**ize of primary tumour, staging **E**bus, **N**-stage, **T**-stage) was developed that stratifies patients into low, moderate and high risk groups for recurrence with an AUC of 0.71 (0.69-0.78) in the validation set. The POETS score (**P**erformance status, **O**verall stage, staging **E**bus, **T**-stage, **S**ex) was developed that also stratifies patients into low, moderate and high risk groups for death with an AUC 0.70 (0.63-0.77) in the validation set.

Conclusions: We present separate validated risk stratification models for predicting the risk of disease recurrence and death following curative intent radiotherapy for NSCLC. The performance of these models is modest despite analysis of an extensive list of prognostic factors. The modest performance highlights the need for more advanced risk prediction tools and the low rates of

treatment for disease recurrence highlights the need for further research into the effectiveness of follow-up protocols.

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 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, 8th edition TNM Staging (clinical staging; T-stage, N-stage, overall stage & 7th Edition staging was adjusted to 8th edition on an individual patient basis), 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), total radiotherapy dose (Gy), 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)) and radiotherapy techniques used (four dimensional radiotherapy (4DRT), intensity-modulated

radiotherapy (IMRT) and image-guide radiotherapy (IGRT)). 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. Single variable logistic regression with all 25 demographic, clinical and treatment-related variables was used. Data were partitioned into two sets, for training and testing purposes. 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 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. Three risk groups were decided from the scores, and survival analysis performed using Kaplan-Meier curves and log-rank tests. Performance of the risk models was assessed using the testing dataset. All analyses were performed using R 3.5.1.

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 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). Four dimensional radiotherapy planning was used in 58% (523/898) of cases, IMRT in 44% (391/898) and IGRT planning in 89% (802/898).

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:

A total of 618 patients were used in the training set to develop the risk stratification model. 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**ize of primary tumour, 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 2). The score range was 0 to 7.5. Scores were categorised into 3 risk categories according to

the optimal cut-off locations, based on likelihood ratio test and AUROC using the findcut() function*. The resulting categories are as follows: Low-risk (Score ≤ 2.5), moderate-risk (Score 3-3.5) and high-risk (Score ≥ 4). 82% (178/215) of patients in the low-risk group did not experience a recurrence within 2 years, compared to 62% (115/187) and 42% (91/216) in the moderate-risk and high-risk groups respectively.

The Kaplan-Meier survival curves for the three risk groups are shown in Figure 1. Log-rank tests show statistically significant differences in survival distributions between the three groups (overall log-rank test, and pairwise comparisons – low vs moderate, moderate vs high and low vs high, $p<0.001$). From the Cox proportional hazards models, the hazard ratios were 2.35 (95%CI: 1.64-3.37, $p<0.001$) for moderate vs low-risk, and 4.08 (95%CI: 2.92-5.7, $p<0.001$) for high vs low-risk. 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. The AUROC for the validation dataset was 0.71 (95%CI: 0.64-0.78). The hazard ratios from the Cox proportional hazards model were similar for the validation and derivation datasets, with HR=2.54 (95%CI: 1.35-4.8, $p=0.004$) for moderate vs low-risk and 4.28 (95%CI: 2.33-7.85, $p<0.001$) for high vs low-risk. The AUROC for Total score, 0.72 (95%CI: 0.68-0.76), was significantly higher than compared to overall stage alone in the derivation dataset (0.66, 95%CI: 0.62-0.71, $p<0.001$) but not in the validation dataset (0.71 vs 0.68, $p=0.27$). The AUROC for Risk group, 0.7 (95%CI: 0.66-0.74), was significantly higher than compared to overall stage alone in the derivation dataset (0.66, 95%CI: 0.62-0.71, $p=0.04$) but not in the validation dataset (0.7 vs 0.68, $p=0.53$). In the derivation dataset, the Cox proportional hazards model for risk groups was a better fit than the Overall stage model for both Rsquare (0.12 vs 0.089) and AIC (3133 vs 3154). A Hosmer-Lemeshow goodness of fit test was carried out on the validation dataset, which was not significant $p=0.3$.

Risk stratification for death:

A total of 618 patients were used in the training set to develop the risk stratification. 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 (**P**erformance status, **O**verall stage, staging **E**BUS, **T**-stage, **S**ex). From this final model, a scoring system (**POETS** score was produced using the regression coefficients (Table 3). The POETS score range was 0 to 8.5. Scores were categorised into 3 risk categories according to the optimal cut-off locations, based on likelihood ratio test and AUROC using the findcut() function*. The resulting categories are as follows: Low-risk (Score ≤ 2.5), moderate-risk (Score 3-4.5) and high-risk (Score ≥ 5). 77% (180/235) of patients in the low-risk group were alive after 2 years, compared to 52% (113/216) and 34% (58/172) in the moderate-risk and high-risk groups respectively.

The Kaplan-Meier survival curves for the three risk groups are shown in Figure 2. Log-rank tests show statistically significant differences in survival distributions between the three groups (overall log-rank test, and pairwise comparisons – low vs moderate, moderate vs high and low vs high, p≤0.001). From the Cox proportional hazards models, the hazard ratios were 2.09 (95%CI: 1.59-2.74, p<0.001) for moderate vs low-risk, and 3.28 (95%CI: 2.5-4.31, p<0.001) for high vs low-risk. 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. The AUROC for the validation dataset was 0.7 (95%CI: 0.63-0.77). The hazard ratios from the Cox proportional hazards model were similar for the validation and derivation datasets for moderate vs low-risk, with HR=2 (95%CI: 1.29-3.11, p=0.002), but only slightly higher for high vs low-risk, with HR=2.18 (95%CI: 1.39-3.41, p<0.001). The AUROC for Total score, 0.72 (95%CI: 0.68-0.76), was significantly higher compared to overall stage alone in the derivation dataset (0.64, 95%CI: 0.6-0.68, p<0.001) but not in the validation dataset (0.66 vs 0.64, p=0.3). The AUROC for the Risk group, 0.69 (95%CI: 0.65-0.73), was significantly higher compared to overall stage alone in the derivation dataset (0.64, 95%CI: 0.6-0.68, p=0.002) but not in the validation dataset (0.65 vs 0.64, p=0.6). In the derivation dataset, the Cox proportional hazards model for Risk group was a better fit than the Overall stage model for both

Rsquare (0.12 vs 0.062) and AIC (4163 vs 4201). A Hosmer-Lemeshow goodness of fit test was carried out on the validation dataset, which was not significant p=0.68.

Discussion:

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 the first two years following radiotherapy. Three in five patients died within the study period and the median overall survival was approximately 2.5 years. The disease recurred in distant organs in two-thirds of patients that suffered disease recurrence and three in every five disease recurrences were managed with best supportive care alone. The cause of death across the study was related to lung cancer in approximately two-thirds of deaths and non-cancer related in one third. 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 (POETS) in the two years following radiotherapy treatment. However, these scores do not appear to add significant additional value on top of clinical stage alone (stage I, II, III) in predicting these outcomes. The AUC 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. The validated risk stratification models presented in this paper could have clinical utility in describing risk during patient discussions and facilitating shared decision making as well as informing risk stratified follow up protocols whereby the frequency of imaging is intensified for those at high risk of recurrence and the frequency of clinical assessment is intensified in those at high risk of death. Conversely, such protocols could facilitate de-intensifying regimes in low risk categories.

It is noted that poor performance status and increasing age are associated with reduced risk of recurrence after radiotherapy in these models. This is likely explained by fact that 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.

Strengths and weaknesses

This study has a number of strengths. It 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 were collected spanning fitness, co-morbidities, physiological indices, cancer specific parameters including both staging and biological factors and treatment specific information such as techniques and technology employed. Coupled with detailed outcome data including disease recurrence, presentation of recurrence, survival and cause of death 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 and also includes a comparison to stage alone as 'standard of care' for assessing risk in current day practice. 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.

There are also weaknesses to address. 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. Specifically BMI (568 missing data points), absolute lymphocyte count pre-treatment (322 missing data points), neutrophil lymphocyte ratio pre-treatment (317 missing data points), absolute lymphocyte count post-treatment (424 missing data points) and neutrophil lymphocyte ratio post-treatment (424 missing data points) needed to be excluded from multivariate risk stratification analysis due to the high level of missing data. We have 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 is unlikely to add significant value over stage alone. Further studies into the optimal imaging programme and optimal clinical surveillance following radiotherapy and 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 the answers may lie in the evolving field of circulating tumour DNA and minimal residual disease.

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