Lung cancer staging: a physiological update†

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Abstract

The tumour-node metastasis (TNM) classification system is anatomically based. We investigated whether the addition of simple physiological variables, age and body mass index (BMI), would affect survival curves, i.e. a composite anatomical and physiological staging system. We retrospectively analysed a prospectively validated thoracic surgery database (n = 1981). Cox multivariate analysis was performed to determine possible significant factors. Kaplan–Meier survival curves were constructed with combined anatomical and physiological factors. Cox multivariate analysis revealed age (P < 0.001) and BMI (P = 0.01) as significant factors affecting survival. Receiver operating curve analysis determined cut-off levels for age of 67 and BMI of 27.6. A composite anatomical and physiological survival curve based on TNM for BMI > 27.6 and age < 67 was produced. Age and BMI criteria resulted in significantly different survival curves, for stage I (P < 0.0001) and stage II (P = 0.0032), but not for stage III (P = 0.06). Neural network analysis confirmed the importance of BMI and age above cancer stage with regard to long-term survival. Combining age < 67, BMI > 27.6 and TNM anatomical classification results in very different estimated survival curves from the usual TNM system. Patients from stages I, II and III may have survival equivalent to a stage higher or lower depending on their age and BMI.

Keywords: Lung cancer • Staging • Physiology

INTRODUCTION

Staging of non-small-cell lung cancer is based on anatomical information with regard to tumour size, location and lymph node involvement and spread [1]. Factors other than stage can affect 5-year survival of lung cancer patients [2–4]. Using some of these factors may help predict high- and low-risk subgroups within a given stage. This may help select or indeed reject certain groups for neoadjuvant or adjuvant therapy.

We utilized a large prospective validated thoracic surgery database to evaluate simple, easily measured clinical factors that may have a significant contributing effect on long-term survival for a given stage.

METHODS

Ethics

Local institutional ethics board approval was obtained for this study.

Methodology

We retrospectively analysed a prospectively validated thoracic surgery database (n = 1981). The demographics of the study population are shown in Table 1. All non-anatomical resections were eliminated from the analysis.

Staging

Staging was defined as pathological staging to eliminate bias by ‘better’ preoperative staging due to current multi-slice computed tomography (CT) and positron emission tomography (PET) scanning. Routine intraoperative mediastinal lymph node sampling has always been undertaken in our unit. PET scanning became routine for all patients 5 years ago in our unit. All patients with mediastinal lymph nodes enlarged by CT criteria or avid on PET were biopsied preoperatively via mediastinoscopy, mediastinotomy or endobronchial ultrasound.

Follow-up

Survival data for all patients are routinely obtained through the National Strategic Tracing Service, as previously described [5].

Benchmarking

We benchmarked our 5-year survival against the Seventh International Association for the Study of Lung Cancer (IALSC) [1] (Supplementary material).
Survival factor identification

Univariate analysis of all variables was performed first, with the objective of identifying significant factors for inclusion in a multivariate Cox regression model. Stepwise Cox proportional hazards regression analysis was used for the study population and each stage separately, as previous work has identified different factors as being significant for each stage [2] (Supplementary material). Entry criterion was $P < 0.05$, and removal criterion was $P > 0.1$. Cox risk-adjusted survival curves were created to demonstrate the effect of age and body mass index (BMI) on long-term survival (Fig. 1). The covariates were plotted at their mean.

Receiver operating curve (ROC) analysis was performed to determine the cut-off values for Kaplan–Meier survival curves for any significant continuous variables.

Survival curves

Kaplan–Meier survival curves for all resection stages (I, II and IIIa) were constructed with combined anatomical and physiological factors (Fig. 2). The upper line of each stage contains patients with good (BMI > 27.6 and age < 67) prognostic factors identified above. The bottom line of each stage contains patients with poor (BMI < 27.6 and age > 67) prognostic factors identified above. Stage comparisons are shown in Fig. 3.

Adjuvant patients

Two hundred and eighty-seven patients had received adjuvant therapy. Analysis was performed with and without these patients included.
A neural network was then trained and run to create an ROC value to assess the network goodness-of-fit for predicting long-term survival to cross-validate the Cox regression analysis. All studied variables used in the Cox regression analysis were used as input variables for the neural network construction. The basis of this network is multilayer perceptions that have feed-forward back-propagation topology. The network consists of four layers as shown in Fig. 4.

1. The input layer is of neurons into which variables were entered following their normalization through a process of standard rescaling (subtracting the mean and dividing by the standard deviation).
2. Two hidden layers composed of neurons in which computation and differential weighing of the different variables are performed, using the hyperbolic tangent function.
3. The output layer is two neurons into which the end result is entered (alive or dead), via the Softmax function.

Figure 2: Kaplan–Meier survival curves for (A) stage I, (B) stage II and (C) stage IIIa. Good was defined as BMI > 27.6 and age < 67, and bad was defined as BMI < 27.6 and age > 67.

Figure 3: Comparison between (A) bad stage I and good II and (B) bad stage II and good IIIa. Good was defined as BMI > 27.6 and age < 67, and bad was defined as BMI < 27.6 and age > 67.

Neural network analysis

A neural network was trained and run to create an ROC value to assess the network goodness-of-fit for predicting long-term survival to cross-validate the Cox regression analysis. All studied variables used in the Cox regression analysis were used as input variables for the neural network construction. The basis of this network is multilayer perceptions that have feed-forward back-propagation topology. The network consists of four layers as shown in Fig. 4.
Normalized importance output

This was used to determine factors that are important in predicting long-term survival post-resection for potentially curative non-small-cell lung cancer (Fig. 5).

Statistical software

All statistical analyses other than the neural network were performed with MedCalc for Windows (version 11.4.2.0, MedCalc Software, Mariakerke, Belgium). The neural network analysis was
performed with SPSS (version 17.0 for Windows; SPSS, Inc., Chicago, IL, USA).

RESULTS

One hundred percent patient follow-up was obtained. Overall institutional in hospital mortality was 1.6% for all lobectomy and pneumonectomy resections.

Benchmarking

Benchmarking failed to reveal any significant differences between our institution’s stage survival and the Seventh IALSC results (Supplementary material).

Cox analysis

Cox multivariate analysis (Table 2) revealed age ($P < 0.001$) and BMI ($P = 0.01$) as significant factors affecting survival. ROC analysis determined cut-off levels for age of 67 (sensitivity 57.3%, specificity 56.9%) and BMI of 27.6 (sensitivity 72.8%, specificity 36.5%).

Cox risk-adjusted survival curves demonstrated the significant effect of age on long-term survival (Fig. 1).

Kaplan–Meier curves

A composite anatomical and physiological Kaplan–Meier survival curve based on tumour-node metastasis (TNM), BMI (cut-off 27.6) and age (cut-off 67) was produced. Good was defined as BMI $> 27.6$ and age $< 67$, and bad was defined as BMI $< 27.6$ and age $> 67$. Age and BMI criteria resulted in significantly different survival curves, for stage I ($P < 0.0001$) and stage II ($P = 0.0032$), but not for stage III ($P = 0.06$) (Fig. 3).

Kaplan–Meier curves comparing stages I and II, and II and IIIa are shown in Fig. 3. It can be seen that stage overlap occurs, making survival prediction based on stage alone potentially erroneous.

Adjuvant therapy

Inclusion and exclusion of patients who had received adjuvant therapy from the analysis did not affect the above results (data not shown).

Normalized importance output

The normalized predictive values of the neural network (Fig. 5) identified age and BMI were of higher predictive value than the TNM stage, with regard to survival.

Figure 5: Normalized importance output from neural network analysis. For key, see legend to Fig. 4.

Table 2: Cox regression analysis of factors affecting long-term survival (all stages)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Relative risk (RR)</th>
<th>95% CI of RR</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>BMI</td>
<td>0.98</td>
<td>0.96–0.99</td>
<td>0.01</td>
</tr>
<tr>
<td>Female</td>
<td>0.81</td>
<td>0.68–0.95</td>
<td>0.01</td>
</tr>
<tr>
<td>FEV1</td>
<td>0.99</td>
<td>0.99–1.00</td>
<td>0.0001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.42</td>
<td>1.18–1.69</td>
<td>0.0001</td>
</tr>
<tr>
<td>Stage Ia</td>
<td>0.67</td>
<td>0.55–0.83</td>
<td>0.0002</td>
</tr>
<tr>
<td>Stage II</td>
<td>1.52</td>
<td>1.22–1.88</td>
<td>0.0001</td>
</tr>
<tr>
<td>Stage IIIa</td>
<td>2.86</td>
<td>2.23–3.67</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.03–1.05</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
DISCUSSION

Simple, easily measured clinical variables such as age and BMI have significant effects on the survival of patients with non-small-cell lung cancer. This may have implications for survival curve analysis in neoadjuvant and adjuvant therapy trials.

The use of ROC curves to identify cut-off levels for the creation of the Kaplan–Meier survival curves was to aid graphical representation of the proposed concepts and for proof-of-principle only. In clinical practice, age and BMI are continuous variables and should be treated as such. To predict survival based on these variables, the parameter estimates obtained from the Cox regression analysis should be used, as described previously [6].

All non-anatomical resections were eliminated from this analysis. Previous work has demonstrated that wedge resections were an independent factor predicting poor outcomes [2, 7, 8].

The choice of age and BMI as segmentation variables was based only on three facts. First, the data set, despite its large size, is too small to subdivide patients into strata defined by all the significant factors identified by Cox regression analysis. Second, neural network analysis identified age and BMI as having higher importance in determining survival than TNM stage. Third, we have demonstrated via propensity matching that BMI is a significant determinant of long-term survival (Shackcloth et al, in press).

Combining age < 67, BMI > 27.6 and TNM anatomical classification results gives very different estimated survival curves from the usual TNM system. Patients from stages I, II and IIIa may have survival equivalent to a stage higher or lower depending on their age and BMI. This may have a significant effect when considering adjuvant therapy.

Quality control is an important part of modern thoracic surgery practice, with benchmarking against other units an important part of this [9]. The addition of simple clinical variables to the current TNM staging system may allow some of the contributing variables that exist between different institutions to be accounted for.

A number of molecular biology markers that are associated with a good or bad prognosis have been identified [10, 11]; however, these remain research tools and are not universally available, unlike the simple variables such as age and BMI.

Entry into oncologic trials is usually histology- and stage-based [12]; however, we have shown that simple physiological variables have a significant effect on long-term survival. The Adjuvant Lung Cancer Trial Collaborative Group studies include age and sex, amongst other variables, but do not include BMI as a contributing factor, despite Cox regression and neural network analyses demonstrating it to be a significant factor.

We were unable to include all other factors identified by regression analysis due to the limited size of our database, despite it containing nearly 2000 resections. Neural networks remain contentious due to their ‘black box’ technology; however, t-test results from the neural network normalized importance indicate that we have chosen the two most important variables. The aim of this concept paper was simplicity combined with clinical ease of applicability.

Patients who received adjuvant therapy potentially could have skewed the data; however, when analysed with or without these patients, the same results were reached. This could have been a source of bias as adjuvant patients tend to be younger and be less likely to be wasted, i.e. a BMI > 27.6, due to their selection usually based on performance status, of an appropriate TNM stage.

Adjuvant therapy increases survival by ~5% [12], whereas patient physiological variables alter survival by 15%. Identification of patient groups that do better or worse than average does not correlate with the response rate to neoadjuvant or adjuvant therapy. Further work is needed to identify for a given stage which physiological group(s) will benefit most from oncological therapy, which is currently anatomically selected via the TNM system and performance status guided.

In conclusion, the addition of simple physiological variables to the anatomical TNM staging system identifies large variations in survival for a given stage. Overlap in survival between stages occurs between ‘good’ and ‘bad’ patient physiological parameters.

SUPPLEMENTARY MATERIAL

Supplementary material is available at ICVTS online.

Conflict of interest: none declared.

REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr G. Cardillo (Rome, Italy): This well-written, quality-content paper coming from a well-known, high-volume UK institution, the Liverpool Heart and Chest Hospital, reports an analysis of 1,981 patients from the thoracic database with an impressive 100% follow-up.

I have two questions, the first regarding age and the second regarding BMI. Since the paper by Sugarbaker in 1999 which stated age to be a risk factor for death after thoracotomy, a large number of papers have shown the safety of lobectomy in patients older than 80 years. Furthermore, the age limit that you have chosen, 67.6 years, has a very low impact on our practice, since epidemiologic data have shown that 70% of lung cancers are diagnosed over 65 years and the median age is 71.4. Could you please comment on how this age limit could impact on our practice? Regarding BMI, I have seen that the limit that you have chosen is 27.6, but overweight is over 25 and obesity is over 30. What do you suggest, that we have to change our vision of BMI?

Dr Poullis: In the manuscript it’s carefully stated in the discussion. The reason I used the cut-off values was clearly for demonstration of the concept I was trying to present. It’s not for clinical practice where you become 70 and suddenly you can have a different operation or treatment. That’s not the game. You get the same treatment surgically no matter what your age or your BMI. Now, because we can depict very different survival curves in these two subsets of patients, it then has implications. Who should get the chemotherapy? Is it the bad group or is it the good group? We don’t know. When I looked at Agregado, I think it is, his latest adjuvant chemotherapy trials don’t include BMI. Age is included. So I’m not trying to alter the surgical therapy. I’m just saying that it’s not as simple at the moment where, if you have a fixed stage and you’re fit, you get chemo, and if you’re the wrong stage, you don’t get chemo.

The ROC curves I showed were purely for graphical representation of the concept. That’s not how it’s practised clinically. I made that clear in the discussion of the paper. It’s purely to show you the curves. I show you the Cox regression and the P-value of surgeons, but if I show you two Kaplan-Meier curves completely apart, the fact that you do better in stage II than you do in stage I, depending on your risk factors, is easier to see graphically than on a Cox. You are right in your point.

Dr M. Dusmet (London, United Kingdom): Looking at this and the previous presentation from your centre, there are some intriguing things that I’d like to hear your thoughts on. First of all, if I’m correct, both papers were based upon exactly the same database?

Dr Poullis: Yes.

Dr Dusmet: And yet the operative mortality in the first paper is 2.5% and in yours it’s just over 1.5%. That’s my first question.

Dr Poullis: It’s exactly the same database, but the timeframe that the data is taken from is different between the two studies. The two projects we did actually were completely independent, as in a typical department, not talking to each other. That’s why the total number of patients is different between the two. Also, I have excluded all people with residual disease in my dataset, which wasn’t done in the first paper.

Dr Dusmet: The second question leads on from what Giuseppe was just saying. What you’ve shown when you put the data of these two papers together is that when your BMI is higher, you have a better chance of survival, but, as Giuseppe just pointed out, statistically your chances of being older are also greater, and, secondly, you’ve demonstrated the chances of being diabetic and having renal impairment are greater. Therefore, by the time you’re older and you have renal impairment and you have diabetes, the likelihood of getting adjuvant chemotherapy is virtually nil because the oncologists do not like to kill patients who have been offered curative surgery. So your thoughts on that, please.

Dr Poullis: Well, you are exactly right. My point about what the oncologists do is based on stage and performance status. That’s the only two things that go through their minds. You have to be at the right stage and fit. And I’m saying, well, actually, it’s more complicated than that. You can be at the wrong stage and have a terrible survival, which might mean you need adjuvant therapy. It might not. We don’t know from the data. That’s the flaw in the adjuvant data. They looked at age only and they have looked at a lot of other factors, but they didn’t look at BMI. When I looked through the papers, I couldn’t find BMI as a matching factor in any of the adjuvant lung cancer trials.

Dr P. Van Schil (Antwerp, Belgium): An important factor that is often forgotten, even in the adjuvant therapy trials, is the smoking status of the patients. In our series this is a major prognostic factor. Did you look at it, as it can be an important factor influencing outcome.

Dr Poullis: Yes, I have looked at it, and that’s hopefully going to be work that I’ll be presenting soon, if I get it accepted. We looked at people who are still smoking, people who are ex-smokers, and people who have never smoked who have lung cancer: Dr Van Schil: And those who resumed smoking after the operation?

Dr Poullis: Well, we counted those as continuous smokers. Liverpool has quite a few. It’s a dedicated smoking city. It turns out that if you’ve never smoked or you’re still smoking, your survival is way, way worse than if you stop smoking.

Dr L. Spaggiari (Milan, Italy): I have a brief comment. We analysed a large series of patients who underwent pneumonectomy according to several parameters, including BMI, and we agree with your results. There is a strong correlation between survival in pneumonectomized patients and BMI.

Dr Poullis: Yes. The only argument for the cut-off for the BMI in the paper was that in the literature everyone uses 30, but in our database it wasn’t 30. It was reasonably close. So I didn’t know, do I just use 30, which everyone else is using, or do I use what our database showed? But really, at the end of the day, it’s just for demonstration of the point that BMI is important, age is important, and they are not factors usually considered. It’s usually if they’re really old, no adjuvant therapy, but there’s no other consideration in any of the decisions.

Dr Spaggiari: We need to study BMI.