Should males ever undergo wedge resection for stage 1 non-small-cell lung cancer? A propensity analysis†

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Abstract

OBJECTIVES: Wedge resections are frequently performed for small peripheral lesions in patients unfit for a more extensive resection. We aimed to investigate whether patient sex and histology type are important factors determining survival in patients undergoing a wedge resection for stage I lung cancer.

METHODS: We retrospectively analysed a prospective thoracic database of patients (n = 2859) who had undergone potentially curative wedge resection for stage I non-small-cell lung cancer. Only patients with adenocarcinoma or squamous carcinoma were included (n = 540). We benchmarked our 5-year survival against the sixth International Association for the Study of Lung Cancer results. Kaplan–Meier, Cox multivariate regression analysis and propensity analysis were utilized to assess the effect of sex and histology on survival post-wedge resection with regard to long-term survival.

RESULTS: Cox regression of patients who had undergone wedge resection demonstrated that adenocarcinoma (odds ratio [OR]: 2.16, 95% confidence interval [CI]: 1.11–4.19), P = 0.02 was the only significant term determining long-term survival. Cox regression of male patients identified adenocarcinoma (OR: 3.29, 95% CI: 1.22–8.86), P = 0.02 as the only significant term determining long-term survival. Cox regression of female patients failed to identify any significant factors that determine long-term survival. Propensity matching based on gender identified that gender had no effect on survival, P = 0.46; however, histology was associated with a difference in survival, P = 0.02. This effect occurred in males, P = 0.02, but not females, P = 0.26. Propensity matching based on histology identified that gender had no effect on survival, P = 0.29; however, histology was associated with a difference in survival, P = 0.01. This effect occurred in males, P = 0.01, but not females, P = 0.26. Differing life expectancy between males and females was adjusted for by the use of the Framingham-predicted life expectancy.

CONCLUSIONS: Long-term survival of patients with stage I non-small-cell lung cancer who undergo a wedge resection is affected by gender and histological type. Male patients undergoing wedge resections for adenocarcinoma have outcomes inferior to those of patients with squamous carcinoma. Histology type does not affect survival in female patients undergoing wedge resections.

Keywords: Lung cancer • Wedge • Surgical treatment • Outcome

INTRODUCTION

Lobectomy is the gold standard for curative resection of non-small-cell carcinoma [1].

Debate, however, exists, particularly in high-risk patients with small peripheral lesions, as to the clinical advantage of lobectomy versus wedge resections [2]. The definition of high risk remains difficult to define and quantitate, and remains subjective.

Understanding risk factors for poor survival post-wedge resection may help clinicians select who is not suitable for wedge resections. We have previously described the importance of histology subtype and smoking status with regard to long-term outcomes following lobectomy and pneumonectomy after potentially curative resections of non-small-cell lung cancer [3, 4].

We sought to investigate via Cox regression analysis, propensity analysis and neuronal network analysis whether gender and histological subtype influences long-term survival of patients with stage I non-small-cell lung cancer undergoing wedge resections.

PATIENTS AND METHODS

Local ethics

Local institutional review board approval was granted for this study.
Protocol

We retrospectively analysed a prospective thoracic database of patients who had undergone potentially curative surgical wedge resection for stage I non-small-cell lung cancer (n = 540), from September 2001 to October 2012 in a single institution. Only patients with adenocarcinoma or squamous carcinoma were included. No patients received neoadjuvant or adjuvant chemo or radiotherapy. Wedge resection was defined as a non-anatomical stapler resection. The indication for wedge resection was at the surgeon’s discretion, based on predicted pulmonary function, co-morbid conditions, performance status and tumour location, with regard to the risk of lobectomy. No patients deemed fit enough for a lobectomy underwent a wedge resection. Patients with pure bronchoalveolar carcinoma were excluded.

Staging

Staging was defined as pathological staging to eliminate bias by ‘better’ preoperative staging due to current multislice computer tomography (CT) and positron emission tomography (PET) scanning. PET scanning became routine for all patients 6 years ago in our unit. Routine intraoperative mediastinal lymph node sampling has always been undertaken in our unit. All patients with mediastinal lymph nodes enlarged by CT criteria (>1 cm in the short axis) or hot on PET (standard uptake value greater than the blood pool as assessed by an independent specialist in nuclear radiology) were biopsied preoperatively via mediastinoscopy, mediastinotomy or endobronchial ultrasound. No difference in preoperative work-up exists between the wedge resection and lobectomy groups, with regard to staging.

Follow-up

Survival data for all patients are routinely obtained through the National Strategic Tracing Service, as previously described [5–7].

Benchmarking

We benchmarked our 5-year survival against the sixth International Association for the Study of Lung Cancer (IASLC) results [8].

Analysis

Univariate analysis was performed using the Kaplan–Meier survival for patients undergoing wedge resections for stage I non-small-cell disease. Univariate comparisons were made by means of Wilcoxon rank-sum tests and \( \chi^2 \) tests as appropriate. Multivariate analysis was performed via stepwise Cox regression analysis to determine significant factors determining survival. The entry criterion was \( P < 0.05 \), and the removal criterion was \( P > 0.1 \). The group survival was plotted at the mean of the covariates. The multivariate analyses were all repeated using forward, backward and the enter techniques for statistical rigour to confirm findings.

Propensity matching

Logistic regression for group membership, regardless of outcomes, was used to calculate the propensity score for 1:1 matching. Nearest neighbour matching without replacement with a calliper of 0.2 was utilized. Variables used in the propensity match included: age, lung function [forced expiratory volume in 1 s (FEV1)], sex, body mass index (BMI), diabetes, pack-years and alcohol consumption (units/week). Two separate matches were performed, by gender and by histology type.

A dotplot of standardized mean differences (Cohen’s d) for all covariates before and after matching, and Kaplan–Meier post-propensity matching survival curves were created.

Table 1: Characteristics of patients in study cohort and operative and disease characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wedge (n = 540)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td></td>
</tr>
<tr>
<td>Age at operation</td>
<td>72 (64–77)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>266 (49)</td>
</tr>
<tr>
<td>Adeno (% female)</td>
<td>216 (81)</td>
</tr>
<tr>
<td>Squamous (% female)</td>
<td>50 (19)</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>74 (59–86)</td>
</tr>
<tr>
<td>BMI &gt; 30 (%)</td>
<td>35 (7)</td>
</tr>
<tr>
<td>NYHA status (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>75 (13)</td>
</tr>
<tr>
<td>1</td>
<td>169 (31)</td>
</tr>
<tr>
<td>2</td>
<td>219 (41)</td>
</tr>
<tr>
<td>3 and 4</td>
<td>77 (15)</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>114 (21)</td>
</tr>
<tr>
<td>Emphysema (%)</td>
<td>21 (4)</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>128 (24)</td>
</tr>
<tr>
<td>Ex</td>
<td>305 (57)</td>
</tr>
<tr>
<td>Non</td>
<td>107 (19)</td>
</tr>
<tr>
<td>Pack-years</td>
<td>25 (23–26.7)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>116 (22)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>193 (36)</td>
</tr>
<tr>
<td>History of IHD (%)</td>
<td>136 (25)</td>
</tr>
<tr>
<td>PVD (%)</td>
<td>77 (14)</td>
</tr>
<tr>
<td>Operative and disease characteristics</td>
<td></td>
</tr>
<tr>
<td>Histopathology (%)</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>400 (74)</td>
</tr>
<tr>
<td>Squamous carcinoma</td>
<td>140 (26)</td>
</tr>
<tr>
<td>T stage (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>411 (76)</td>
</tr>
<tr>
<td>2</td>
<td>129 (24)</td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Tumour diameter (mm)</td>
<td>20.5 (15–25)</td>
</tr>
<tr>
<td>N stage (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>540 (100)</td>
</tr>
<tr>
<td>1</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Median follow-up (days)</td>
<td>1012</td>
</tr>
<tr>
<td>In-hospital mortality (%)</td>
<td>6 (1)</td>
</tr>
</tbody>
</table>

Categorical variables quoted as number (percentage). Continuous as median (interquartile range).

% FEV1: percentage forced expiratory volume in 1 s; BMI: body mass index; NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; PVD: peripheral vascular disease; IHD: ischaemic heart disease.
Statistical software

All statistical analyses other than the neuronal network and propensity matching were performed with MedCalc for Windows (version 12.1.4, MedCalc Software, Mariakerke, Belgium). The propensity matching was performed with SPSS (version 20.0 for Windows, SPSS, Inc., Chicago, IL, USA), SPSS Statistics Integration Plug-In for R, and R 2.12.2.

RESULTS

100% long-term follow-up was achieved. The overall institutional in-hospital mortality was 2.0% for all thoracic resections and 1% for wedge resections. The median survival was 2.78 years (range 0–13 years).

Study group

Study group preoperative, operative and pathological characteristics are given in Table 1.

Benchmarking

Benchmarking failed to reveal any significant differences between our institutions stage survival and the sixth IALSC results, P = 0.8.

Univariate analysis

Univariate survival analysis of patients undergoing wedge resections (n = 540) identified gender as a significant factor determining survival, P = 0.02, Fig. 1A. Histology subtype was not a significant factor for the study cohort, (adenocarcinoma n = 400, squamous n = 140), P = 0.15, Fig. 1B, in males (n = 274), P = 0.13, Fig. 1C and in females (n = 266), P = 0.46, Fig. 1D.

Multivariate analysis

Cox regression of patients who had undergone wedge resection demonstrated that adenocarcinoma (odds ratio [OR]: 2.16, 95% confidence interval [CI]: 1.11–4.19), P = 0.02 was the only significant term determining long-term survival. Age, postoperative FEV1, BMI, smoking status, cardiac disease, diabetes and a clinical diagnosis of emphysema were excluded by the stepwise regression model. The group survival plotted at the mean of the covariates is shown in Fig. 2A.

Cox regression of male patients who had undergone wedge resection demonstrated that adenocarcinoma (OR: 3.29, 95% CI: 1.22–8.86), P = 0.02 was the only significant term determining long-term survival.

Figure 1: Univariate survival of patients undergoing wedge resections (A) study group (n = 540), by gender, P = 0.02, (B) by histology, adenocarcinoma (n = 400), squamous (n = 140), P = 0.15, (C) the effect of histology type in males (n = 274), P = 0.13, and (D) the effect of histology type in females (n = 266), P = 0.46. Marks indicate censored data.
long-term survival, Fig. 2B. Cox regression of female patients who had undergone wedge resection failed to identify any significant factors that determine long-term survival, Fig. 2C.

**Propensity matching**

Matching based on patient gender matched 124 male patients 1:1 with female patients undergoing wedge resection. The dotplot, Fig. 3A, of standardized mean differences demonstrated that a good match was obtained, overall \( \chi^2 \) balance test \( \chi^2 (7) = 4.91, P = 0.67 \). Survival of wedge resections after propensity matching based on gender identified that gender had no effect on survival, \( P = 0.46 \), Fig. 4A; however, histology was associated with a difference in survival, \( P = 0.02 \), Fig. 4B. This effect occurred in males, \( P = 0.02 \), Fig. 4C, but not females, \( P = 0.26 \), Fig. 4D.

Matching based on histology matched 140 adenocarcinoma patients 1:1 with squamous carcinoma patients undergoing wedge resection. The dotplot, Fig. 4B, of standardized mean differences demonstrated that a good match was obtained, overall \( \chi^2 \) balance test \( \chi^2 (7) = 1.74, P = 0.97 \). Survival of wedge resections after propensity matching based on histology identified gender had no effect on survival, \( P = 0.29 \), Fig. 5A; however, histology was associated with a difference in survival, \( P = 0.01 \), Fig. 5B. This effect occurred in males, \( P = 0.01 \), Fig. 5C, but not females, \( P = 0.26 \), Fig. 5D.

Full details of both propensity matches are contained in the Supplementary material.

**DISCUSSION**

Long-term survival of patients with stage I non-small-cell lung cancer who undergo a wedge resection is affected by gender and histological type. Male patients undergoing wedge resections for adenocarcinoma have outcomes inferior to those of patients with squamous carcinoma. Histology type does not affect survival in female patients undergoing wedge resections. The agreement between Cox regression and neuronal network analysis and propensity matching increases the confidence in this finding; however, a randomized trial is still needed to avoid bias.

Previous work has defined lobectomy as the gold standard compared with wedge resections for curative treatment of early lung cancer [1]. This work was based in an era that did not utilize PET or high-resolution CT scans and failed to use advanced statistical techniques such as Cox multivariate regression and neuronal networks. More recent work has demonstrated that in stage I non-small-cell lung cancer, wedge resection may be equivalent to lobectomy with regard to long-term survival [9]. The high non-cure rate associated with wedge resections justifies the need to determine possible factors affecting poor survival.

Non-small-cell histological subtypes, in addition to adenocarcinoma and squamous carcinoma, and patient gender are known risk factors with regard to long-term survival post-lobectomy and pneumonectomy [3, 10]. To date, no study has analysed gender and histology subtype in patients undergoing wedge resections. We have restricted our analysis to adenocarcinoma and squamous carcinoma due to the small number of patients undergoing wedge resection with other histological subtypes. Mixed adenosquamous carcinoma is a known adverse histological subtype, but we did not have enough for a statistical analysis [11]. Previous work has demonstrated the importance of smoking status and histological subtype on long-term survival in patients undergoing lobectomy and pneumonectomy [4]. Smoking status made no difference with regard to long-term survival in patients having wedge resections in our series.

Patient gender is a well-known factor affecting survival in lung cancer patients; however, histological subtype (adeno or squamous) does not affect survival in patients undergoing lobectomy. We speculate, but are unable to provide any evidence, that the metastatic potential of adenocarcinoma is different in males compared with females. We are unable to comment on the role of
Figure 3: A dotplot of standardized mean differences (Cohen's d) for all covariates before and after propensity matching: (A) match based on gender and (B) match based on histology. ppoFEV1: postoperative predicted forced expiratory volume in 1 s; DM: diabetes; BMI: body mass index.

Figure 4: Survival of wedge resections after propensity matching based on gender. The effect of (A) gender in matched group, \( P = 0.46 \), (B) histology type in matched group, \( P = 0.02 \), (C) histology type in males, \( P = 0.02 \), and (D) histology type in females, \( P = 0.26 \). Marks indicate censored data.
epidermal growth factor receptor mutation status with regard to our findings. We have not included resection margin in our analysis. We only have this data field for 154 of the cohort. Only R0 resections were included in the analysis. Cox regression of this subgroup failed to demonstrate resection margin as important, but tumour diameter was a significant factor determining long-term survival despite all cases being stage 1 (data not shown). Resection margin, albeit in lobectomy and pneumonectomy, has previously been shown not to be an important factor in the absence of a positive resection margin [12, 13].

Only patients that are deemed to be high risk with regard to pulmonary function, age, performance status or concomitant medical conditions undergo wedge resection in our institution, and lobectomy is the preferred modality of treatment.

The identification of the effect of histology on survival strengthens the argument that a preoperative histological diagnosis is important in the management and decision-making process of patients with suspected lung cancer.

**LIMITATIONS**

This work is non-randomized, and the results need to be interpreted as such. Decision on operation type, wedge versus lobectomy, is partially based on preoperative staging, particularly the N1 lymph node status. The introduction of endobronchial ultrasound (EBUS) has enabled us to identify patients with preoperative N1 disease. These patients should not undergo a wedge resection. Pathological staging was utilized in this manuscript. Preoperative staging has improved during the period of this study, increased CT scan resolution, PET scanning and EBUS, and continues to improve; however, our pathological staging accuracy has remained constant, and hence its use. We do not have mode of death, local or distant recurrence data available for analysis. We do not have standard uptake values of PET scans available. The presence or absence of a bronchoalveolar component was not recorded on our database. Pulmonary diffusion is a known prognostic risk factor. Unfortunately, our database is incomplete for this variable.

**CONCLUSION**

Long-term survival of patients with stage I non-small-cell lung cancer who undergo a wedge resection is affected by gender and histological type. Male patients undergoing wedge resections for adenocarcinoma have inferior outcomes to patients with squamous carcinoma. Histology type does not affect survival in female patients undergoing wedge resections.

**SUPPLEMENTARY MATERIAL**

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.
REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr P. Ciriaco (Milan, Italy): It is reported in the literature that women develop lung cancer at an earlier age compared to men and that the outcome is worse for them. This is due to different factors, including the different genetic patterns. I know that you didn’t include any data about genetic mutations in your paper, but my comment is that, at the moment, it is very important to evaluate the different genetic mutations of patients to draw conclusions about survival.

My question is, did you analyse the age of onset of the disease between men and women, and did you analyse how much this affected the survival in the two groups?

Dr Poullis: That’s a difficult one, the age of onset of lung cancer, because you don’t know the doubling time to track back from when you were diagnosed as stage 1. It is an impossible question for anyone to answer because you don’t know the doubling time. They are all stage 1B, they are all about the same time, but we know they have a doubling time, and stage 1 can be between 30 days and 120 days with normal non-small-cell. So it is impossible to say when they actually developed it.

Dr Ciriaco: Well, it’s the time of diagnosis.

Dr Poullis: Oh, the time of diagnosis. We have the age. That was included in the analysis. That’s one of the things that worried us. The males and the females are significantly different age groups. That’s why we did two propensity matches, one based on the sex and one based on the histology and, of course, we had the normal Cox beforehand, which supposedly takes age into account. You are right, there is a difference, but you can’t propensity-match easily on a continuous variable. It has to be a dichotomous variable for a propensity match.

Regarding your original comment on the genetic mutations, I am sure you are completely right. With the adenocarcinoma, it is different in the males and females, probably because of some genetic mutation. This is a historical series, so those mutations were not analysed in half these patients.

Dr W. Klepket (Vienna, Austria): You applied very sophisticated statistics. Also, we are all aware that this is a retrospective series and it is difficult sometimes to go into details in long-extending retrospective series. However, it would have been interesting to look at whether there were more recent improvements in understanding early-stage lung cancer, the necessity to perform a wedge resection, segmentectomy, or lobectomy, the presence of ground-glass opacity, the relation of solid component to ground-glass opacity, and the differentiation between T1a and T1b. It would have been of interest to look for all of these in this really big series of patients. Were you able to do so or did you attempt it?

Dr Poullis: We don’t have the difference between ground-glass and solid, which is known to be an important factor. With regard to grades of stage 1 lung cancer, we have looked at that, and it is exactly as the TNM would say, the smaller the tumour, the better off you are. In terms of the time, just as normal clinical practice has evolved with the introduction of PET scanning and EBUS throughout the course of this, we have a marked change in our wedge resections. In the past, someone with a peripheral nodule and some central lymph nodes that were not accessible via mediastinoscopy would have a wedge resection, and quite often they were N1 and N2 when you sampled the lymph nodes at the time of the wedge resection. So we have a completely different practice now than we had 5, 10 years ago.

Dr K. Athanassiadi (Athens, Greece): I congratulate you, of course, on your statistical analysis, for which you are very well known, but if you see the percentage between 2800, let’s say 3000, cases and 500, more than 500, it is more than 18% wedge resections. I consider that a high number. Could you please comment on that?

Dr Poullis: Yes, it is a high number, and we have quite a lot of variation amongst the surgeons in my institution, and this is one of the reasons we have been looking quite closely at what we have been doing. When you look at just the unit, the wedge resection rate is high, but I work in an area called Merseyside in Liverpool, United Kingdom, and we have one of the highest resection rates in the United Kingdom for lung cancer and we have one of the best long-term survivals, which has just recently been published. A lot of these people we have been doing wedges on are really high-risk. You are right, it is a high percentage because we have a high resection rate.

Dr Athanassiadi: Do you propose to the younger patients to do wedge resections?

Dr Poullis: Well, it is interesting, actually. We have published on wedge resection and lobectomy for stage I lung cancer essentially no difference in long-term survival. The trouble is, we all know that there is the 40-year-old in whom you do a wedge resection and he will turn out to have disease with recurrence that would have been cured if he had a lobectomy. So I think with today’s staging, which is wrong - not wrong, but is inaccurate still with regard to N1 status, you should be doing a lobectomy in anyone who is fit enough to have a lobectomy, but in some people where they are a bit borderline and they could probably have a lobe or you could probably do a wedge, I think you have to box clever and pick the ones who have got more chance of recurrence to have the lobe, and the ones with less chance of recurrence, they maybe could have a wedge if you are really not sure what to do. I think there are very difficult decisions in some of these patients. I quite agree that young, fit, it’s a lobe every time, even for a centimetre peripheral lesion.

Dr Klepetko: I have a final question, and I think you should be very careful in answering it. Based on these results, do you really treat males and females differently in your department?

Dr Poullis: No.