Stage migration: results of lymph node dissection in the era of modern imaging and invasive staging for lung cancer†

Bilal H. Kirmania, Robert C. Rintoulb, Thida Winc, Cormac Mageea, Lavinia Mageeb, Cliff Choonga,d, Francis C. Wellsa and Aman S. Coonara,c,*

a Department of Thoracic Surgery, Papworth Hospital, Cambridge, UK
b Department of Thoracic Oncology, Papworth Hospital, Cambridge, UK
c Department of Respiratory Medicine and Thoracic Oncology, Lister Hospital, Stevenage, UK
d Department of Surgery (MMC), Monash University, Monash Medical Centre, Melbourne, Victoria, Australia

* Corresponding author. Papworth Hospital, Cambridge University Health Partners, Cambridge CB23 3RE, UK. Tel: +44-1480-364887; fax: +44-1480-364583; e-mail: aman.coonar@papworth.nhs.uk (A.S. Coonar).

Received 2 October 2011; received in revised form 10 February 2012; accepted 18 February 2012

Abstract

OBJECTIVES: Lung cancer staging has improved in recent years. Assuming that contemporary detailed preoperative staging may yield a lower rate of stage change after surgery, we were interested to determine the impact of our lymph node dissections performed at the time of surgical resection.

METHODS: We retrospectively analysed a database in our surgical unit that prospectively captured information on all patients assessed and treated for lung cancer. We reviewed the data on patients who underwent lung cancer surgery with curative intent between January 2006 and August 2010 so as to reflect contemporary practice. Prior to potentially curative treatment, patients systematically underwent staging computerized tomography (CT), integrated positron emission tomography (PET) with CT and brain imaging. Enlarged and/or PET-positive nodes were subject to invasive evaluation to establish the nodal status in line with the current guidelines. This was performed by needle aspiration or biopsy usually with ultrasound guidance, endobronchial or endo-oesophageal ultrasound with needle biopsy; mediastinoscopy; mediastinotomy; video-assisted or open surgery.

RESULTS: Three hundred and twelve lung cancer resections were performed (a mean age of 68 years [range 42–86] and a male-to-female ratio of 1.14:1). Despite thorough preoperative evaluations, 25.3% of patients had a change in nodal status after lung resection and lymph node dissection; of which 20.8% of patients had a nodal status upstaging. Occult N2 disease was identified in 31 (9.9%) of 312 patients. Patients with cT1 tumours showed a nodal upstaging of 12.3% compared with 25.3% in cT2 tumours. There was no difference in the rate of N2 disease for different tumour histological types.

CONCLUSIONS: Despite systematic preoperative staging, there continues to be a high rate of nodal status change following surgical resection and lymph node dissection. If considering non-surgical treatments for the early stage lung cancer, the impact of this discrepancy should be considered. If not, errors in prognosis and in determining correct adjuvant treatment may arise.

Keywords: Carcinoma • Non-small cell lung • Cancer staging • Metastasis • Operative • Lymph node

INTRODUCTION

Considerable improvements in lung cancer staging have been made in recent years. The increased availability of 18FDG positron emission tomography (PET) scanning in preoperative assessment has increased the sensitivity and specificity of mediastinal staging [1] compared with computerized tomography (CT) alone, but not to the extent that surgical staging was not required altogether [2]. New, less-invasive lymph node sampling techniques such as endobronchial ultrasound (EBUS) and endoscopic oesophageal ultrasound (EUS) with a fine-needle aspiration (FNA) have also become available in recent years. While these have a high specificity, the negative predictive value is lower and, therefore, surgical staging may still be indicated for negative results [3].

The current British Thoracic Society guidelines [4] recommend that, where available, PET scanning is used to indicate the presence of lymph node involvement. However, it is thought that between 4 and 16% of patients thought to be N2 negative at CT-PET staging preoperatively may have occult nodal metastasis at mediastinoscopy or surgical resection with curative intent [5–8]. The accurate staging of non-small cell lung cancer (NSCLC), in particular the identification of pathological N2 disease, significantly affects the outcomes and potential treatment strategies [9]. The resectability of lymph node groups can now often be anticipated radiologically, and en bloc lymphadenectomy as an
oncological procedure rather than purely advocated [10]. Concerns that radical mediastinal lymphadenectomy at the time of surgical lung resection might increase perioperative complications or mortality would appear to be unfounded [11], although the risks may be higher in the elderly [8].

Particularly, with respect to the early-stage lung cancer, there is increasing interest in the role of limited resections and especially for those who are less fit, non-surgical treatments such as radiofrequency ablation and stereotactic radiotherapy. These latter two techniques do not include lymph node dissection.

In this context, we were interested to examine the fidelity of modern preoperative staging with postoperative, histologically confirmed node status.

We examined the accuracy of the cN status following our contemporary clinical staging and compared this with the histological (pN) status determined from lymph node dissection at the time of surgical resection.

MATERIALS AND METHODS

Population

We retrospectively analysed records from a prospectively collected database on all patients assessed and treated for lung cancer in our tertiary referral centre. The inclusion criteria were all patients referred for curative surgical resection of suspected or confirmed primary lung cancer (not including those receiving neo-adjuvant chemotherapy) from January 2006 to August 2010. The exclusion criteria included: the pathological finding of non-primary lung cancer (including malignancies of non-lung origin and benign conditions originally referred as presumed cancer), ‘open-and-close’ thoracotomy for unresectable disease, tumours other than NSCLCs and patients undergoing neo-adjuvant therapy.

Clinical assessment

All patients were discussed at preoperative multi-disciplinary team meetings and work-up for surgery included thoracic and upper abdominal CT and a separate 18FDG PET-CT. Brain imaging, usually with CT but in some cases with magnetic resonance imaging, was also used in nearly all patients. If N2 or N3 lymph node involvement was suggested by radiological criteria (nodes >10 mm on CT; PET positive higher than background or otherwise considered suspicious), invasive staging was performed to confirm the nodal status. Techniques employed to biopsy lymph nodes for the pathological assessment of metastatic disease included:

- (radiologically guided—usually ultrasound) FNA or core biopsy
- bronchoscopy
- EBUS/EUS and FNA
- mediastinoscopy or mediastinotomy
- video-assisted thoracoscopic surgery (VATS)
- thoracotomy
- biopsy of other sites if indicated

Mediastinoscopy was performed with the intention of sampling from stations 7, 4R, 2R, 4L and 2L. At EBUS-EUS, the lymph nodes were systematically scanned. All PET-CT-positive nodes and any other enlarged or sonographically abnormal nodes that were accessible were sampled. It was not routine practice to sample small, sonographically normal and PET-CT-negative nodes.

Analysis

Data were compiled and analysed using commercially available statistics software (JMP 8.0 for Mac). The final clinical stage (cTNM), as established by the multidisciplinary team after all radiological, minimally invasive and/or surgical staging was compared with the pathological staging (pTNM), as determined from the surgical findings and the postoperative histology results. The demographical data were analysed using t-test or Fisher’s exact test for continuous data and ANOVA or $\chi^2$ for discrete variables. Log-rank tests were employed to compare the survival data.

RESULTS

Demographics

A total of 377 patients were identified from our database as fulfilling the inclusion criteria. Thirteen patients had a benign and 17 had an unresectable disease (six determined preoperatively and 11 (3%) undergoing open-and-close thoracotomy), and the 35 patients who were not NSCLC were excluded.

There were 312 patients remaining in the study group with a mean age of 68 years (range 42–86) and a male-to-female ratio of 1.14:1. Of this population, 61 (19.6%) required invasive lymph node staging and, following these investigations, were deemed to be suitable for surgical resection with curative intent.

The distribution of clinical and pathological stages based on the International Union Against Cancer (UICC) TNM classification, 6th edition, is outlined in Table 1.

Eight patients clinically assessed as possibly Stage IIIB or Stage IV disease were referred for surgery without induction treatment for a variety of reasons, usually due to uncertainty as to the full extent of disease and thereby giving the patient the ‘benefit of the doubt’ approach.

Seven patients staged as IIIA due to cN2 had surgery with curative intent without induction treatment for the following reasons:

- Pathologically confirmed cN2
- A fit patient with single-station low-volume disease who was motivated for surgery.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Preoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>236</td>
<td>180</td>
</tr>
<tr>
<td>II</td>
<td>32</td>
<td>43</td>
</tr>
<tr>
<td>IIIA</td>
<td>36</td>
<td>64</td>
</tr>
<tr>
<td>IIIIB</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 1: The distribution of clinical and pathological stages
Not-pathologically confirmed cN2

- One patient presenting incidentally with pneumothorax was found to have enlarged nodes on CT but required urgent surgery and did not therefore undergo further investigation with PET or invasive staging.
- One patient undergoing mediastinoscopy for clinical staging, required conversion to thoracotomy for bleeding and the decision was made to perform a concomitant lung resection.
- One patient in whom PET-positive para-oesophageal nodes were thought may be related to oesophagitis.
- One patient with positive station 5/6 nodes that were otherwise close to the tumour and motivated for surgery.
- Two patients in whom good performance status, young age and patient preference led to a 'benefit of the doubt' approach.

Surgery

A total of 312 surgical resections were performed for primary lung cancer. These constituted 249 lobectomies, 48 pneumonectomies and 15 segmentectomies or wedge resections. These data are presented in Table 2 and the proportions of the types of surgery are comparable with the UK national averages (as determined from the 2008 National Adult Cardiac Database Report of the Society for Cardiothoracic Surgery in Great Britain and Ireland). The surgical technique was operator dependent, but unit policy was to undertake an extensive lymph node dissection of all ipsilateral nodal stations. The mean number of lymph node stations sampled was 3.4 ± 1.4 (median 4, interquartile range 3–5).

Histology studies identified 159 adenocarcinomas, 122 squamous cell carcinomas, 13 broncho-alveolar carcinomas and 23 other non-small cell cancers (including one basaloid, two neuro-endocrine and five large cells). More than one tumour type was identified in some patients. Two patients had synchronous tumours.

Stage migration

The change from preoperative clinical node status was seen in 25.3% of all patients, with 20.8% pathologically staging higher than their preoperative assessment and 4.5% down-staged. Occult N2 disease was detected at the time of surgery in 9.9% (Table 3). The redistribution of nodal status is demonstrated graphically in Fig. 1.

N-status migration by T-status

Of 108 patients presenting for surgery with T1N0M0 disease, 14 (13.0%) were upstaged by a new nodal disease while 94 (86.2%) remained at the same N-status. From the 128 patients with clinical stage T2N0M0, 33 (25.7%) were upstaged on the N-status. Twenty patients with T3N0M0 disease saw six (30.0%) upstaged on the N-status. Recursive partition modelling identified T-stage as the most likely discriminator between those patients likely to be nodal upstaged at the time of surgery.

N-status migration by histology

In cases of histologically proven N2 disease, 23 of 37 (62%) patients had nodes that contained small or microscopic tumour deposits. In the remaining 14, one or more nodes were completely replaced by tumour. There was no statistically significant difference in the distribution of the tumour histology types between lymph nodes that had been largely replaced by tumour and those with small deposits only ($P = 0.68$). There was no difference in the rate of pN2 disease between adenocarcinomas and squamous cell carcinomas (11.6 versus 10.2%, $P = 0.85$), although the rate of N2 disease was higher in lung cancers of the unspecified histological type (21.7%) (Table 4). The histological subgroup had no statistically significant effect on nodal status migration ($P = 0.28$).

N-status migration by different invasive staging modalities

Of the patients who were nodal status upstaged at the time of surgery, 45 of 65 (69.2%) patients had not had any invasive staging (Fig. 2). In total, 61 patients underwent invasive lymph node evaluation by any modality (17 mediastinoscopy, 16 EUS, 32 EBUS and 3 had FNA of cervical or other non-mediastinal lymph nodes, with more than one investigation in some patients). The rate of nodal status up-migration was 32.7% (20/61) in patients invasively staged, when compared with 18.0% (45/251) in patients who proceeded directly to surgical resection following the radiological staging. This difference was statistically significant ($P < 0.022$ by Fisher’s exact test).

DISCUSSION

In patients being assessed for the radical treatment of lung cancer, the guidelines advise the use of staging CT, integrated
CT-PET and invasive evaluation if indicated [4, 12]. The accurate staging of NSLC affects treatment decisions, and in particular, it influences the decisions regarding adjuvant treatment in post-operative surgical patients.

Recognizing the limitations of mediastinoscopy to assess certain nodal stations (particularly posterior station 7, 8, and 9 on the Mountain-Dresler map), the less-invasive lymph node sampling techniques of EBUS/EUS with FNA were developed [13]. As predicted, the efficacy of these techniques was subsequently confirmed in randomized and other studies [14, 15]. However, needle sampling from nodes as well as mediastinoscopy may be less accurate when compared with histological examination of whole lymph nodes from surgical resection [16]. While minimally invasive techniques have a high sensitivity, the negative predictive value is lower and surgical staging is often still recommended for negative results [3, 14, 17, 18].

The combinations of endoscopic and surgical staging techniques may further increase the number of accessible nodes compared with the use of any one technique alone, and this would therefore increase sensitivity and specificity [19, 20]. The results of the recently published ASTER study took selected subjects and randomized them into lymph node staging by surgery alone or combined EBUS/EUS (and surgical staging if endoscopic results were negative) [14]. The authors reported a sensitivity for surgical staging alone of 79% (95% CI, 66–88%) versus 94% (95 CI, 85–98%) for EBUS/EUS (and surgical staging if endoscopic results were negative).

However, as our data demonstrate, in a whole unit population even contemporary, pragmatic preoperative staging consisting of staging CT and integrated CT-PET followed by the invasive evaluation of suspicious nodes has a relatively high error rate when compared with postoperative results.

**Relevance**

More than a quarter of patients in our study staged for primary lung cancer and operated on with curative intent were subsequently found to have a different node status. Surgery detected new pN2 disease in 9.9% of patients following multi-modal assessment based on the current guidelines. This is consistent with other reports which range from 4 to 16% of patients thought to be N2 negative at CT-PET staging preoperatively [5–8]. These studies did not, however, employ additional staging techniques such as EUS or EBUS, and comparison in some cases was made with lymph node biopsies from mediastinoscopy. It is important to note, however, that preoperative lymph node staging relies on the radiological identification of suspicious lymph nodes for biopsy. Our study demonstrates that even when there is no radiological suspicion of N2/3 disease, 18.0% of patients who proceeded to surgical resection without invasive staging were found to have a higher nodal status than determined preoperatively. Interestingly, we found a higher rate of nodal status migration in the invasively staged group rather than the non-invasively staged group. This probably indicates that we were correctly identifying patients who may have higher stage disease and putting them forward for invasive preoperative staging. This group, however, had disease which was detected only after surgical resection and formal lymph node dissection.

**Implication**

The significance of our observation rests on two factors: first, the importance assigned to N2 disease currently undetectable by contemporary preoperative staging and, secondly, implications
for patients who may undergo the non-surgical treatment of operable lung cancer.

What is the importance of N2 disease currently undetectable by contemporary preoperative staging?

A previous generation of work suggested that N2 disease found incidentally at the time of resection was associated with a better prognosis than other types of N2 disease excluded from surgery [21–23]. In many cases in the current era, this will be PET-negative low-volume N2 disease. Recent work has found an association between SUV and prognosis [24]. Extrapolating from these two positions, patients newly found to be pN2 may also have a better prognosis than patients excluded from surgery as a consequence of having proven N2 disease preoperatively. Further study could clarify this.

Implications for patients undergoing non-surgical treatment of operable lung cancer

The other important issue relates to the proportion of patients found to be newly staged as having nodal disease (pN1 or pN2). As currently only patients who undergo surgery can be fully staged, it follows that those cN0 patients who have non-surgical treatments on the grounds of unfitness or personal preference cannot be reliably allocated to adjuvant therapy.

The corollary of this is that because of the reduced morbidity associated with less-invasive thoracic surgery and improved peri-operative care, for patients with clinical Stage I–II lung cancer and in particular that subgroup with small peripheral tumours, there are relatively few who can safely undergo radical radiotherapy or radiofrequency ablation who could not safely undergo surgery. So, if the two former techniques are offered instead of surgery, patients should be informed that they are at risk of sub-optimal staging [25], which may impact on the correct allocation of adjuvant treatment. In part this may be countered if such patients more frequently underwent invasive staging, for example with EBUS to sample station 10 and 11 lymph nodes. Finer bronchoscopes may also allow even more distal biopsy. Conversely, if such patients are unfit for adjuvant treatment from outset, this becomes less important.

Limitations

We acknowledge the limitations of a retrospective, pragmatic, single-centre study with the inherent bias of a small study. This does, however, have the advantage of describing an actual whole unit experience.

Nodal dissection during surgery will have been surgeon dependent and, whilst our unit practice is to undertake a dissection of all ipsilateral stations rather than a more limited sampling, this too may have had some bearing on our results. However, the effect may have been to produce more conservative estimates of stage migration.

Suggestions for further study

The significance of CT-negative and/or PET-negative N2 disease should be investigated. If such a disease is not prognostically important, then there may be a less value in searching for it.

CONCLUSIONS

Despite systematic radiological and invasive staging, there continues to be a high rate of nodal status change following radical
surgical resection with lymph node dissection as practised in our unit. More liberal use of invasive staging may increase the concordance between clinical and pathological staging. However, currently, if patients undergo therapies without full operative staging, they will be at a statistically significant risk of incorrect staging and so may be disadvantaged by not being offered appropriate adjuvant treatment.

ACKNOWLEDGEMENTS

The authors thank Muhammed Khan for initial data collection and also the associated Departments of Pathology and Radiology and in particular those at Papworth Hospital NHS Trust and the East & North Hertfordshire NHS Trust, UK. These data series include some patients who were recruited into the multi-centre ASTER study [14]. We are grateful to the audit department of Papworth Hospital for their assistance.

Funding

Robert C. Rintoul is partly funded by the Cambridge Biomedical Research Centre.

Conflict of interest: none declared.

REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr G. Leschber (Berlin, Germany): Maybe before the questions I would like to clarify one thing. What do you understand by aggressive lymph node dissection?

Dr Cooman: I specifically used that term, or we used that term, because I think there is a great deal of difference in the nomenclature of what people understand. I think one person’s lymphadenectomy is very different to another person’s, and where does lymph node sampling stop and lymph node dissection begin? I would say what I understand by that in the current era is that we aim to achieve compliance, at least with ESTS guidelines, and I think that it would be fair to say that we would try to go beyond the ESTS guidelines. Now, my own practice is that unless there is a specific reason not to, or if I am very concerned about tissue fragility, I will try to remove the nodes with the associated fat. Unless I feel it is going to change my intraoperative management, I would do that at the end of my resection.
Dr Leschber: So it would be a systematic lymphadenectomy, that is what you understand, with an en bloc resection?

Dr Coonar: I think that is one way of describing it, but I would not, for example, remove the anterior mediastinal fat as part of that routinely, and I think some people when they talk about lymphadenectomy they mean that. There is enough concern about the language. That is why I chose a slightly different term.

Dr J. Schirren (Wiesbaden, Germany): You showed us that you had a change in the N status even with PET-CT in 22%, which shows us that with PET-CT also, you cannot have a good prognosis before operation. We will always have changes. You agree with this?

Dr Coonar: Yes, I do.

Dr Schirren: And the second point, I saw that by right-sided thoracotomy, if you dissect the nodes and the fatty tissue with the nodes en bloc, then normally by right-sided thoracotomy you get No. 4 left and No. 2 left, and I have never seen that you have dissected 4 and 2 left.

Dr Coonar: I am sorry. If it does say left when we are on the right, I apologize. It is a misprint.

Dr Schirren: Then you cannot say you do a compartment dissection. If you do a compartment dissection, from a right-sided thoracotomy you will get to position No. 4 and No. 2 left and right-sided.

Dr Coonar: Routinely, in our practice, unless I have misunderstood your question, and I apologize if I have, routinely we don’t excise nodal tissue from the contralateral side during lung resection. Is that your practice?

Dr Schirren: Yes.

Dr Coonar: Okay. Well, I accept that certainly sometimes taking the pre-tracheal tissue we will cross over and take left-sided tissue, but it is not part of our standard practice.

Dr Schirren: And how was the survival of the patients staged by PET-CT and lymph node dissection on the ipsilateral side?

Dr Coonar: This data is really very contemporary. I do not have the survival data. It started in 2006 and finished in April 2009.

Dr E. Nelson (Odense, Denmark): Did you find any correlation between the number of nodes you took for a patient and the N stage the patient had?

Dr Coonar: I am afraid I can’t tell you that at the moment. Our pathologists are retrospectively counting nodes. We count nodal stations, that has been our practice, but they have not been routinely counting number of nodes.

Dr Nelson: Did you find a correlation between the number of stations you biopsied from a patient and the N stage that you found the patient to have?

Dr Coonar: No. But it is reasonable to assume the more stations you biopsy, the greater the rate of stage migration. I think we all accept that.