Value of wide-margin wedge resection for solitary pulmonary nodule: a single center experience

Balakrishnan Mahesh, Christopher Forrester-Wood, Aftab Yunus, Rauf Ahsan, Khalid Amer, Anthony Morgan, Raimondo Ascione*

Division of Thoracic Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

Received 3 December 2003; received in revised form 15 March 2004; accepted 19 March 2004; Available online 2 July 2004

Abstract

Objective: Despite refinements of the diagnostic procedures, often surgery remains the only option to ascertain the histopathological nature of solitary pulmonary nodules (SPN). Aim of the present study was to ascertain the value of wide-margin wedge resection (WMWR) with curative intent in a consecutive cohort of patients afflicted by SPN. Methods: From January 1995 to January 2002, 129 patients (74 male, mean age 60.5 ± 14.4 years) underwent WMWR of a SPN. In-hospital outcome was prospectively collected and retrospectively analyzed. Incidence of malignancy was obtained by histology. Patients found to be afflicted by primary lung cancer (PLC) were sub-grouped according to their preoperative cardiopulmonary status (CPS). In-hospital and mid-term clinical outcome of all the patients is presented. Results: There were 3 (2.3%) in-hospital deaths. Distribution of histology included 61 (47.3%) PLC (41 poor CPS), 20 (15.5%) secondary lung cancer (SLC), and 48 (37.2%) miscellaneous benign lesions. Twenty patients with PLC were fit and underwent completion lobectomy within 2 weeks following WMWR. Hospital length of stay was longer in patients with PLC as compared to patients with SLC (P = 0.04). There were 17/61 (27%) recurrences in the PLC group. Of these, 2 occurred in fit patients undergone previous WMWR-lobectomy, and 15 in patients with poor baseline CPS. All these patients were referred for adjuvant therapy. Overall 5-year survival of the PLC group was 66% (61.1% for those with poor CPS and 82.5% for those with good CPS (P = NS). Seven out of 20 (35%) patients with SLC had late recurrent disease, leading to 1 re-operation. The overall 5-year survival in this group was 58.8%. There was only 1 non-related late death in the benign group. Conclusions: The WMWR resection of a primarily malignant SPN determines a valuable 5-year survival but a relatively high incidence of late recurrence. WMWR is a safe and effective surgical option for patients presenting with poor cardiopulmonary reserve. © 2004 Elsevier B.V. All rights reserved.

Keywords: Solitary pulmonary nodule; Wedge resection; Frozen section; Lobectomy

1. Introduction

Solitary Pulmonary Nodule (SPN) is found in 0.1–0.2% of chest radiographs [1–5]. Various modalities have been available to aid in the diagnosis of SPN including flexible bronchoscopy [1,3–5], sputum cytology [3], endobronchial and transbronchial biopsy [3,5], computerised tomography (CT) guided percutaneous, fine needle aspiration biopsy (FNAB) [1,3,5,6], helical CT, and Positron Emission Tomographic (PET) scanning [1–5,7]. However, in the absence of a definitive diagnosis, surgery remains the only option. Wide-margin wedge resection (WMWR) of SPN is a surgical alternative and can be performed through a mini-thoracotomy or minimally invasive approaches including video assisted thoracoscopy (VATS) technique [1–4,8,9]. We present the in-hospital and mid-term clinical outcome of a consecutive series of patients undergoing WMWR of SPN with a curative intent.

2. Materials and methods

2.1. Patient selection, data collection, and definitions

Data were collected prospectively into a database for all patients undergoing a thoracic surgical procedure between January 1995 and January 2002 and retrospectively...
analyzed. The database was queried for consecutive patients who had undergone WMWR of a SPN. The baseline imaging of all the patients was reviewed by an independent radiologist and the definition of SPN was restricted to lesions of any size less than 3 cm, peripheral but completely surrounded by lung parenchyma, with no evidence of atelectasis or pneumonia in the lung parenchyma distal to it together with absence of mediastinal lymphadenopathy [1,2]. Local control of the primary site when appropriate, and absence of other metastases was a pre-requisite for patients with history of previous primary lesions.

Pulmonary lung function was defined poor in presence of a FEV1 <1.5 or <50% predicted. Poor cardiopulmonary status (CPS) was defined as the simultaneous presence of two or more of the following factors: age >75 years, WHO Performance status >3, poor pulmonary functions (FEV1 <1.5 or <50% of predicted), co-morbid factors (previous myocardial infarction, current angina, uncontrolled diabetes), poor nutritional status, previous lung resection. The definition of WMWR was of a liberal wedge containing the nodule ensuring at least 2 cm palpable tumor free margins [10,11], macroscopically free of tumor.

2.2. Anaesthetic and operative technique

Anaesthetic technique was standardized in all patients. Analgesia was provided by either epidural analgesia or intercostal nerve blocks and/or paravertebral nerve blocks followed by postoperative patient-controlled analgesia to ensure early mobilization in the postoperative period. After obtaining informed consent, WMWR was performed through a minithoracotomy through the 5th or 6th rib bed, depending on the location of the SPN. Since 1999 the majority of these procedures was carried out via VATS technique. The WMWR was achieved by the use of a linear stapler, fired on more than one occasion if required. In case the resection was not achievable with a linear stapler, two angled clamps were applied at the predefined distance from the lesion and resection performed. The completeness of resection was based on ensuring at least 2 cm palpable tumor free margins macroscopically free of tumor. The healthy surrounding lung margins were over sewn with a polidioxanone absorbable suture. Following resection, an accurate inspection of the chest cavity was carried out. Only visible lymphonodes with a size >1 cm on the longer axis were separately sent for histology.

2.3. Postoperative management

At the end of surgery, patients were extubated in theatre, transferred to the recovery and managed according to a standard unit protocols. Prophylactic antibiotics, aggressive physiotherapy and frequent saline nebulisers were provided to clear sputum and secretions with a view to prevent respiratory infection. In-hospital mortality was defined as any death that occurred within 30 days of operation. Pulmonary complication included chest infection, ventilation failure, re-intubation and tracheostomy. Post-operative blood loss was defined as total chest tube drainage. Infective complication were as defined by positive culture and requiring antibiotic therapy. Complete histology report was obtained within 3–4 days following surgery and in case of fit patients with PLC completion lobectomy was carried out within 2 weeks. All PLC patients not amenable to completion lobectomy were referred to oncologist for adjuvant therapy.

2.4. Follow-up

All 129 patients were regularly followed up at the thoracic out-patient clinic. Patients with benign lesion were discharged after 3 months and their survival data was obtained by contacting their GP. Patients with malignant lesion were followed up at 1, 3, 6, 9, 12 months during the first year, six-monthly in the second year, and at yearly intervals thereafter. At each follow-up visit, symptoms were reviewed, clinical examination was performed and chest radiographs were taken. Suspected recurrence was systematically investigated with computed tomography (CT) scan and CT guided FNAB if needed.

2.5. Statistical analysis

Statistical analysis was carried out using the SPSS 11.0 statistical package. Statistica (StatSoft Inc.) was used to construct the Kaplan Meier survival and event free curves [12]. Chi-square ($\chi^2$) was calculated using Fisher’s exact test for parametric distributions and the Mann Whitney $U$ test for non-parametric distributions. Patients affected by PLC were divided in sub-groups depending on baseline CPS to ascertain the effect of this variable on late events.

3. Results

Distribution of baseline characteristics is summarized in Table 1. The majority of SPNs was detected on routine chest radiograms on asymptomatic patients (40%). Other type of presentations included cough, shortness of breath, hemoptysis, chest pain and pneumonia. All lesions were peripheral according to both baseline CT scan and intraoperative findings. All patients underwent routine video-bronchoscopy which was inconclusive in all patients. Fourteen patients (10.8%) underwent inconclusive FNAB and 12 patients (9.3%) underwent positron emission tomography (PET).

Distribution of type of histology included 61 (47.3%) primary lung cancer, 20 (15.5%) secondary lung cancer and 48 (37.2%) benign miscellaneous causes (Table 2). Preoperative CT size of the lesion ranged from 0.8 to 2.9 cm with a mean of 2.3 ± 1.2, 2.2 ± 1.2, and 2.13 ± 0.9
for the PLC, SLC and benign groups, respectively ($P = NS$).

The surgical procedure was carried out via mini-thoracotomy in 98 patients (75.9%), while the remnant 31 patients (24.1%) underwent VATS technique. Out of 61 patients of the PLC group only 26 had macroscopically abnormal lymph node stations which were intra-operatively sampled for histology (all N1, 6 with VATS technique). Of these, only 6 (25%) were found to have metastases. Within the PLC group, the pathological stage of the lesions was as follow: T1N0 in 55, and T1N1 in 6. Out of 68 patients with either SLC or benign lesions, 15 had macroscopically abnormal lymph node stations, which were intra-operatively sampled for histology (all N1, 4 with VATS technique). All these stations did not show any evidence of malignancy.

Patients with PLC were on average more likely to be older, smokers, and symptomatic when compared to patients with SLC or benign lung disease ($P < 0.05$). SOB, shortness of breath; NYHA, New York Heart Association; TB, Tuberculosis.

### 3.1. Late clinical outcome

Follow-up was completed in all patients. Mean duration of follow-up was $38 \pm 13.2$ months. The overall 5-year survival of the entire population is presented in Table 4 .

**Table 1**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Overall no. (%)</th>
<th>Primary no. (%)</th>
<th>Secondary no. (%)</th>
<th>Benign lesions no. (%)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>74/55 (57/43)</td>
<td>36/25 (59/41)</td>
<td>15/5 (75/25)</td>
<td>23/25 (48/52)</td>
<td>NS</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>52 (40.3)</td>
<td>22 (36.1)</td>
<td>16 (80)</td>
<td>14 (29.2)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Weight loss</td>
<td>6 (4.7)</td>
<td>6 (9.8)</td>
<td>0</td>
<td>0</td>
<td>0.042</td>
</tr>
<tr>
<td>Cough</td>
<td>19 (14.7)</td>
<td>5 (8.2)</td>
<td>4 (20)</td>
<td>10 (20.8)</td>
<td></td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>19 (14.7)</td>
<td>9 (14.8)</td>
<td>0</td>
<td>10 (20.8)</td>
<td></td>
</tr>
<tr>
<td>SOB</td>
<td>18 (14.1)</td>
<td>12 (19.6)</td>
<td>0</td>
<td>6 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10 (7.8)</td>
<td>4 (6.6)</td>
<td>0</td>
<td>6 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>5 (3.9)</td>
<td>3 (4.9)</td>
<td>0</td>
<td>2 (4.2)</td>
<td></td>
</tr>
<tr>
<td>NYHA III/II</td>
<td>(79.8/17.1/3.1)</td>
<td>48/11/2</td>
<td>(79/18/3)</td>
<td>(95/50)</td>
<td>(75/20/84/2)</td>
</tr>
<tr>
<td>Tobacco</td>
<td>72 (55.8)</td>
<td>49 (80.3)</td>
<td>5 (25)</td>
<td>18 (37.5)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Asbestos</td>
<td>5 (3.9)</td>
<td>4 (6.6)</td>
<td>0</td>
<td>1 (2.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Radiation</td>
<td>1 (0.8)</td>
<td>1 (1.6)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>TB</td>
<td>5 (3.9)</td>
<td>3 (4.9)</td>
<td>0</td>
<td>2 (4.2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* $P$ value for the difference between primary and secondary malignant nodules; NS, not significant, when $P > 0.05$. SOB, shortness of breath; NYHA, New York Heart Association; TB, Tuberculosis.

### Table 2

<table>
<thead>
<tr>
<th>Type of nodule</th>
<th>Histology</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary lung cancer</td>
<td>Squamous cell carcinoma</td>
<td>20 (32.8)</td>
</tr>
<tr>
<td>Secondary lung cancer</td>
<td>Secondary adenocarcinoma</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>TB</td>
<td>16 (33.3)</td>
</tr>
<tr>
<td></td>
<td>Hamartoma</td>
<td>7 (14.6)</td>
</tr>
<tr>
<td></td>
<td>Cyst</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td></td>
<td>Sarcoideis</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td></td>
<td>Sarcoidis</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td></td>
<td>Adenoma</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td></td>
<td>Fibrous scar</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td></td>
<td>Bronchocentric granulomatosis</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td></td>
<td>Bronchiectasis</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td></td>
<td>Organizing infarct</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td></td>
<td>Normal lung</td>
<td>1 (2.1)</td>
</tr>
</tbody>
</table>

AVM, Arterio venous malformation; MFH, Malignant fibrous histiocytosis; TB, Tuberculosis.
survival was 65.9 and 58.8% for PLC and SLC patients respectively (NS) (Fig. 1). The overall 5-year cumulative freedom from recurrence was 56.2 and 58.8% in the PLC and SLC groups, respectively (NS).

Late recurrence was noted in 17 (27.8%) patients of the PLC group, of whom 2 in the fit sub-group (undergone previous WMWR-completion lobectomy) and 15 in the poor CPS sub-group. One of the 2 previously fit patients underwent completion pneumonectomy, while the second one was referred for adjuvant therapy together with the remaining 15 patients of the poor CPS sub-group. All these 16 patients suffered late death. The 5-year survival of the PLC group, split by CPS, is shown in Fig. 2.

Seven out of 20 (35%) patients with SLC had late recurrent disease, leading to 1 re-operation. The overall 5-year survival in this group was 58.8%. Only 1 late death occurred in the benign pathology group, due to complications associated to a pre-existing status of chronic renal failure.

4. Discussion

Management of SPN when a preoperative tissue diagnosis is not available remains a controversial issue. Observation for growth, biopsy, and resection are the available options, while aiming to avoid delay in the diagnosis and treatment of lung cancer, false negative results, and resection of benign lesions.

The overall incidence of PLC in our series was of 47.3%. The further presence of 15.5% incidence of SLC gives an overall malignant incidence of our SPN series of 62.8%. This seems rather high when compared with literature (1–3). However, our incidence of malignancy is about a group of patients referred for surgery, and does not include all those patients managed conservatively by respiratory physicians.
The incidence of morbidity and mortality in our series is almost as high as in lobectomy. However, of the 3 deaths observed, 2 were due to acute postoperative myocardial infarction, and one to septicemia resulting from severe nosocomial pneumonia. We believe that this is a reflection of the rather high incidence of patients with poor CPS in our series.

Keagy et al. have recommended that lobectomy but not a pneumonectomy can be performed safely without violating the principles of cancer surgery in a suspicious but inaccessible lesion. However, 32% of their patients who underwent lobectomy without a definitive diagnosis had a benign lesion [13].

Standard lobectomy with mediastinal lymph node sampling has been described as the gold standard operation for stage I lung cancer with a free survival at 5-year of 80% [10,14–15]. Although the survival rate of our overall PLC group at 5-year do not compare favourably to these results, yet 67.8% of our patients had poor CPR status, and more extensive surgery was not an option. In fact, the PLC subgroup presenting with good baseline CPS had a 5- survival comparable with what is reported in literature for standard lobectomy [10,14–15]. Ginsberg et al. reported a 75% increase in recurrence rates in patients undergoing limited resection, 30% increase in overall death rate, and a 50% increase in cancer-related death when compared to patients undergoing lobectomy. They attributed this to failure to identify occult intrapulmonary microscopic and lymphatic spread [10]. They also stressed the importance of intraoperative mediastinal lymph node sampling, as 25% clinically stage (Ia) lesions were found to have mediastinal involvement at the intraoperative assessment [10], for which standard lobectomy with lymph node dissection has been advocated as the treatment of choice [16–18]. In keeping with this policy, we also carried out intraoperative lymph node sampling of interlobar and hilar macroscopically abnormal nodes. However, in our series only 6 out of 26 patients of the PLC group had a malignant involvement.

Limited lung resection for cancer patients with compromised pulmonary or cardiac reserves continues to be a controversial matter. Several authors have been in favor of using lesser forms of resections such as wedge resection and segmentectomy in patients who would not tolerate a lobectomy [11,19–21]. Kodama et al. [16] suggested that segmentectomy was acceptable for stage I lung cancer in patients with poor PFT. There was an increased risk of locoregional recurrence with limited resection, but they felt that since most patients with locoregional recurrence died of distant metastases, survival was not affected.

Further analysis of our PLC group highlighted the importance of co-morbidity in this cohort of patients. A strong trend to a worse survival rate (61.1 vs. 82.5%) was observed for those patients who had a WMWR on grounds of poor overall cardiopulmonary status. These results are consistent with previously published series [16,19].

There are a variety of diagnostic approaches to patients presenting with SPN of undetermined origin. This may include the use of bronchoscopy, trans-thoracic fine needle aspiration (FNA), and positron emission tomography (PET). Although all patients of our series underwent preoperative video-bronchoscopy, only 14 had baseline FNAB while 12 had PET. All these investigations were however, inconclusive. The use of PET may enable a functional approach to the evaluation of lung cancer that complements the anatomic assessment provided by chest radiography, CT scanning, and magnetic resonance imaging. PET has excellent sensitivity and good specificity for the determination of malignancy of lung lesions with a very high reported predictive value [22]. These data however must be weighed against the evidence of instances of false-positive results because of inflammatory lesions and false-negative results in small- or low-metabolism neoplasms [23]. FNAB is an invasive diagnostic procedure, which could be used to obtain diagnosis of SPN. Such procedure is widely adopted, although is difficult to perform in the presence of very small lesion, and it is associated with a variable risk of pneumothorax depending on the location of the lesion. Most importantly, however, is that with this technique there is a risk of delaying the diagnosis and treatment of a malignant lesion. SPN considered to be either benign or nondiagnostic at FNA have been subsequently found to be malignant in as high as 29% of the cases [24].

An alternative surgical approach to patients with SPN is to perform an intraoperative frozen section prior to resection. This is particularly true for those centrally located lesion, where justification of pneumonectomy for benign disease may not be widely supported. Nashef et al. [25] recommended systematic use of frozen section diagnosis for SPN, followed by lung resection. This approach reduces the morbidity and mortality associated with unnecessary major lung resection.

There are several limitations to this study, which deserve mention. The first is the lack of routine intraoperative frozen
section to promptly ascertain the histology and to ensure completeness of resection by sampling the remaining margins. However, we would like to point out first that intraoperative frozen section histology was not available at the start of this study in 1995 due to limited resources. Secondly, all patients with good pulmonary and cardiac reserves who turned out to have cancer were operated upon within 2 weeks from the first operation, whereas for those 41 out of 61 PLC patients afflicted by poor CPS, a completion lobectomy would have not been an option anyway. Finally, we are using routine intraoperative frozen section histology since December 1998.

A further limitation of the present study is that only 31 patients underwent WMWR via VATS technique. This is a reflection of the fact that VATS has not been available for a long period due to limited resources. However, although this approach might have affected the early outcome in terms of pain control and wound healing and/or infection, the fact remains that a VATS approach could not have affected the mid-term survival and incidence of recurrence of the PLC group.

In conclusion, our study confirms that the WMWR resection of a primarily malignant SPN determines a valuable 5-year survival but a relatively high incidence of late recurrence. WMWR is a safe and effective surgical option for patients presenting with poor cardiopulmonary reserve.

Acknowledgements

We wish to thank the patients and all nursing staff of the Bristol Cardiothoracic Centre. We also thank the Garfield Weston Trust for its support.

References