What is the extent of the advantage of video-assisted thoracoscopic surgical resection over thoracotomy in terms of delivery of adjuvant chemotherapy following non-small-cell lung cancer resection?

Elaine Teh, Udo Abaha, David Church, Wasir Saka, Denis Talbot, Elizabeth Belcher and Edward Black

INTRODUCTION

Over the past two decades, the role of video-assisted thoracoscopic surgery (VATS) in the treatment of early-stage lung cancer has increased. There has been no randomized controlled trial to compare the results of VATS versus open lobectomy. However, the non-randomized evidence has consistently shown that VATS lobectomy is safe and feasible and is associated with less postoperative pain, fewer postoperative complications, reduced acute-phase reactants and cellular immune response, with faster recovery of respiratory function and shorter hospital stay. The 1- and 3-year survival is at least equivalent to open lobectomy, with a trend towards better survival at 5 years with a VATS approach [1-4]. Lately, a recent meta-analysis comparing VATS with thoracotomy demonstrated a reduced systemic recurrence rate and improved 5-year mortality rate with VATS resection [5].

Apart from very early-stage disease, complete treatment for non-small-cell lung cancer (NSCLC) is surgery with adjuvant chemotherapy. A meta-analysis published in 1995 showed that, in trials comparing surgery versus surgery combined with adjuvant chemotherapy, there was a 13% reduction in the relative risk of death with an absolute benefit of 5% at 5 years [6]. More recent trials showed evidence that there was an overall survival benefit and disease-free interval in patients with Stage II and III diseases, with complete surgical resection undergoing adjuvant chemotherapy [7-10]. Following complete surgical resection, current British Thoracic Society’s (BTS) ‘Guidelines on the Radical Management of Patients with Lung Cancer’ advocate adjuvant chemotherapy.
with the aim of eliminating micrometastases and preventing disease recurrence, for T1–3, N1–2 and tumours ≥4 cm [11].

Any method that facilitates the delivery of chemotherapy may confer additional survival advantage and should be adopted. Therefore, the strategy of the surgical team is directed towards safe resection and early recovery, so that suitable patients can complete their treatment with chemotherapy in a timely fashion. To date, there is very limited evidence comparing tolerance to adjuvant chemotherapy with either open or VATS resection. We hypothesize that the decreased surgical stress of the VATS approach may result in a shorter interval between surgery and commencement of chemotherapy and an increased tolerance of adjuvant chemotherapy.

**MATERIALS AND METHODS**

A retrospective study of all lung resections (which included lobectomy, segmentectomy and wedge resections in the VATS group and all lung resections including pneumonectomy in the open group) for primary NSCLC in a single surgical centre was undertaken, between October 2008 and August 2013. In our centre, all patients are considered for VATS lung resection if tumours are less than 7 cm, do not require complex reconstructions or pneumonectomies regardless of other comorbidities as we believe the sickest patients will derive the most benefit from reduced surgical insult. Surgical and chemotherapy databases were reviewed to extract data on patient characteristics, operative details, pathological stage, chemotherapy delivery and toxicity.

**Operative techniques**

VATS lobectomy was performed via two 11 mm ports and a 5-cm non-rib spreading anterior utility incision. Hilar structures were individually divided and fissures completed (where necessary) with endostaplers. Thoracotomy was performed via a posterolateral, serratus-sparing approach in the fourth to sixth intercostal space, without rib transection. Systematic nodal dissection was the same in both VATS and thoracotomy groups (right lobectomy = stations 4R, 7, 8, 9, 10, 11 and 12; left lobectomy = stations 4L, 5, 6, 7, 8, 9, 10, 11 and 12). The surgical strategy was determined by tumour size and position. Patients converted from VATS approach to open thoracotomy (n = 2) were analysed in the thoracotomy group. Analgesia was provided by means of thoracic epidural or paravertebral block based on patient preference, in addition to intercostal and phrenic nerve blocks.

**Adjuvant chemotherapy**

Postoperative histology was discussed in a multidisciplinary team including pathologists, respiratory physicians, thoracic surgeons, lung cancer specialist nurses and oncologists within 2 weeks following lung resection. Patients were staged using the 7th edition (American Joint Committee on Cancer and the Union Internationale Contre le Cancer) TNM Staging system; those with tumours above 4 cm or nodal disease and a performance status (PS) of 0–1 were automatically sent to discuss adjuvant chemotherapy with the oncologists. Commencement of chemotherapy was determined by the oncologists’ assessment of PS, patients’ pre-existing comorbidities and evidence of acute infection. Formal assessment of acute-phase reactants, cellular immune response or recovery of respiratory function was not the oncologist’s routine practice. Four cycles of chemotherapy were intended in all patients who were eligible and agreed to receive adjuvant chemotherapy. The majority of patients received four cycles of cisplatin 80 mg/m² and vinorelbine 50 mg/m², on Days 1, 22, 43 and 64. Dose intensity (DI) is calculated as the actual dose given over the intended treatment period as a percentage of the planned dose. The DI takes into consideration dose reductions and dose delays. For example, if four doses of 100 mg were planned to be given every 3 weeks and 75 mg administered on time for four cycles, the DI would be 75%. If 100 mg doses were given but Cycles 2, 3 and 4 were each delayed by 1 week, the period of treatment would be 12 weeks instead of 9, thus meaning a DI of 75. Dose reduction was determined by the oncologist on the basis of PS and evidence of haematological toxicity, classified according to the National Cancer Institution Toxicity Criteria listed in Table 1 and directed by their treatment protocol. Typical dose reductions are 25% of the DI calculation taking into account the sizes of dose reduction and dose delay. Chemotherapy was terminated if there was unacceptable toxicity as assessed by treating oncologists, at patients’ request or if recurrent disease was found during treatment.

**Statistical analysis**

Statistical comparisons were made by standard parametric (t-test and \( \chi^2 \) test), non-parametric (Fisher’s exact test and Mann-Whitney) tests, with \( P <0.05 \) indicating statistical significance. Data analysis was carried out using the Prism Graphpad software (CA, USA).

**RESULTS**

There were 323 NSCLC cases identified; 142 (44%) underwent VATS resection and 181 (56%) underwent posterolateral thoracotomy. There were two patients, in whom VATS was attempted but required conversion to thoracotomy (in one patient, dissection of the pulmonary vein was difficult and in another patient, initial assessment with VATS found that pneumonectomy was required). There were no emergency conversions and so they were analysed in the open group. In the VATS groups, 15 patients underwent

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count</td>
<td>4.0</td>
<td>3.0–3.9</td>
<td>2.0–2.9</td>
<td>1.0–1.9</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Platelet</td>
<td>Within normal limits</td>
<td>75.0–normal limits</td>
<td>50–74.9</td>
<td>25–49.9</td>
<td>&lt;25</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Within normal limits</td>
<td>10–normal limits</td>
<td>8.0–9.9</td>
<td>6.5–7.9</td>
<td>&lt;6.5</td>
</tr>
<tr>
<td>Granulocytes/lymphocytes</td>
<td>2.0</td>
<td>1.5–1.9</td>
<td>1.0–1.4</td>
<td>0.5–0.9</td>
<td>&lt;0.5</td>
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anatomical lobe resection and one had a sublobar wedge resection. In the open group, 23 patients underwent anatomical lobe resection and five had pneumonectomies. Review of final histology at lung multidisciplinary team meeting showed that 35/142 (24.6%) patients in the VATS and 91/181 (50.3%) in the open group fulfilled the criteria for adjuvant chemotherapy (P < 0.001) as per criteria mentioned in the Materials and Methods section and had automatic referral to our medical oncologists. Some patients declined adjuvant chemotherapy for personal reasons, some were treated elsewhere and, in a handful of patients, it was not clear why patients did not have adjuvant chemotherapy, resulting in 16/142 (11.3%) and 28/181 (15.5%) of VATS and open groups, respectively, receiving adjuvant chemotherapy in the end. Patient demographics and tumour stage between VATS and thoracotomy groups are summarized in Tables 2 and 3. There was no significant difference in the extent of systematic lymph node dissection carried out whether lung resections were performed via VATS or open thoracotomy (Table 4).

All patients received platinum/vinorelbine therapy. Chemotherapy was initiated significantly earlier in the VATS group (mean 55.7 ± 3.1 vs 68.2 ± 4.3 days from surgery, P = 0.046) (Table 5). Although not statistically significant, 50% of patients who had VATS completed four cycles of chemotherapy at 100% of planned doses for both platinum and vinorelbine therapy compared with 42.9% of patients who had thoracotomy. Additionally, more patients in the VATS group completed four cycles of the combination chemotherapy compared with open surgery. In patients where chemotherapy was terminated before four cycles, all were due to intolerance of side effects or unacceptable toxicity as determined by treating oncologists. There were fewer reports of toxicity in patients who had undergone VATS. Grade 3/4 haematological toxicity was reported in 12.5% of patients in the VATS group compared with 39.5% in the open group (P = 0.09).

**DISCUSSION**

In this retrospective study, we have shown that, by adopting VATS for primary lung cancer resection, patients were able to commence adjuvant chemotherapy earlier than those who had thoracotomy. In addition, there was a trend towards fewer complications and greater delivery of the planned dose. This is probably due to the decreased morbidity following VATS surgery compared with open. This is a reasonable speculation since several studies directly comparing the perioperative morbidity between VATS and open surgery found that the total complication rate was consistently lower in VATS; with some studies showing shorter duration of air leak, and lower incidence of arrhythmia and pneumonia [12]. Decreased morbidity could result in a shorter hospital stay and quicker recovery of function. Consequently, patients are better able to endure postoperative chemotherapy regimens.

Besides lower morbidity, a few studies have shown that, biologically, the VATS approach may confer certain additional advantages. Minimally invasive general surgery, established much earlier compared with VATS, showed that there was attenuated inflammatory response in terms of decreased production of interleukin (IL) IL-6 and C-reactive protein (CRP) [13]. Studies comparing VATS and lobectomy also consistently found that there were reduced inflammatory markers (IL-6, IL-8, IL-10 and CRP), consistent with the theory that the minimally invasive surgical technique results in reduced surgical stress [12].

There are only a few other studies specifically addressing the role of VATS compared with open thoracotomy, which indicated improved tolerance and/or delivery of adjuvant chemotherapy following the procedure. No such study has been done in Europe before. In a North American retrospective study spanning a period of 6 years, Petersen et al. [14] found that VATS resulted in higher compliance (26 vs 49%) and less delay in starting chemotherapy (18 vs 58%). More recently, two Asian studies also reported better compliance with chemotherapy when VATS resection was carried out. Jiang et al. [15] reported that, in their cohort of patients, more patients with VATS completed more cycles (3.6 vs 3.0), with a higher proportion of patients receiving the full dose on schedule (57.4 vs 33.9%) and ≥75% planned dose (88.9 vs 71.4%). Lee et al. [16] in Korea also found that, in patients who underwent VATS compared with the propensity-matched cohort of patients who had thoracotomy, there was a higher proportion of patients who received four cycles of chemotherapy (95.9 vs 82.4%). Interestingly, although the length of hospital stay ranged from 7 to 13 days in these two Asian studies, the mean days to initiation of adjuvant chemotherapy ranged between 27 and ~34 days. By contrast, our results were more comparable with that reported by Petersen and colleagues; the length of hospital stay was shorter, but the mean days to initiation of adjuvant chemotherapy was ~50 days. In our cohort of patients presented here,
we also found a trend suggesting that patients who underwent VATS resection were able to tolerate four cycles of chemotherapy. Commencement of adjuvant chemotherapy was decided between the treating oncologists and the patients after clinical assessment and time considering the side effects and risk–benefit information received. Our routine practice does not include measurement of biochemical variables or respiratory function prior to starting chemotherapy, relying on preoperative lung function tests. Any bias that may exist (as this is a retrospective study) will be equivalent between the two groups.

Our hypothesis is that the delivery of the treatment package (surgery plus chemotherapy) is dependent on the reduced trauma associated with minimally invasive surgery. We have observed an underestimation of the importance of this factor in considering whether VATS lobectomy should be the standard operation for most lung cancer patients. The number of surgeons in the UK who regularly perform VATS lobectomy is increasing, but we still have some way to go before we reach the ideal proportion [17]. In the USA, VATS lobectomy is performed in 45% of resection for primary lung cancers [18]. In recent years, in our institution, it has reached 56% of primary lung cancer resections.

Our study is not without its limitations. First, the number of patients was small. Second, it was a retrospective study and the patients were not randomized or matched in any way. There was undoubtedly bias that could not be completely accounted for in a retrospective study; however, it is likely that the bias is equal in the VATS and open cohorts.

There were two patients who were converted from VATS to open thoracotomy. These two patients were converted semi-electively (and not urgently due to complications) after early intraoperative assessment made it clear that open thoracotomy will be necessary. Therefore, we felt it appropriate to analyse them in the open rather than VATS group. Other reasons for patients being offered thoracotomy rather than VATS may have been related to tumour size or position. N2 disease was significantly higher in the open group. Larger or more disseminated tumours may invariably have increased biological burden and this could potentially impact on patients’ tolerance towards

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**Table 4: Systematic lymph node dissection carried out perioperatively divided by anatomical resection**

<table>
<thead>
<tr>
<th></th>
<th>VATS (n = 3)</th>
<th>Open (n = 8)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>SMN (%)</td>
<td>100</td>
<td>100</td>
<td>ns</td>
</tr>
<tr>
<td>Subcarinal (%)</td>
<td>100</td>
<td>62.5</td>
<td>0.049</td>
</tr>
<tr>
<td>Para-aortic (%)</td>
<td>66.7</td>
<td>37.5</td>
<td>0.55</td>
</tr>
<tr>
<td>IMN (%)</td>
<td>100</td>
<td>75</td>
<td>1.00</td>
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**Table 5: Adjuvant chemotherapy data**

<table>
<thead>
<tr>
<th></th>
<th>VATS (n = 16)</th>
<th>Open (n = 28)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval from surgery to chemotherapy mean ± SEM (days)</td>
<td>55.7 ± 3.1</td>
<td>68.2 ± 4.3</td>
<td>0.046</td>
</tr>
<tr>
<td>Dose intensity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Planned platinum dose (%)</td>
<td>76</td>
<td>78</td>
<td>0.84</td>
</tr>
<tr>
<td>Planned vinorelbine dose (%)</td>
<td>78</td>
<td>78</td>
<td>1.00</td>
</tr>
<tr>
<td>No. of patients (%) who completed four cycles at 100% of platinum-based and vinorelbine</td>
<td>8 (50)</td>
<td>12 (42.9)</td>
<td>0.76</td>
</tr>
<tr>
<td>No. of patients (%) who completed four cycles of platinum-based and vinorelbine</td>
<td>11 (68.8)</td>
<td>17 (60.1)</td>
<td>0.75</td>
</tr>
<tr>
<td>Haematological toxicity (Grade 3–4), no. of patients (%)</td>
<td>2 (12.5)</td>
<td>11 (39.3)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Dose intensity was calculated as the actual dose given over the intended treatment period as a percentage of the planned dose.

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SMN: superior mediastinal nodes; IMN: inferior mediastinal nodes; RUL: right upper lobectomy; RLL: right lower lobectomy; LUL: left upper lobectomy; LLL: left lower lobectomy; R pneumonectomy: right pneumonectomy; L pneumonectomy: left pneumonectomy.
chemotherapy. Finally, we do not have long-term survival data available as yet due to the fact that thoracic service in our department was only recently established. It would be very informative if we could determine whether early initiation of adjuvant chemotherapy could in fact be translated to better mid- and long-term survival.

Nonetheless, our study is the first European study to contribute to the trend observed in other reported series that VATS enables early delivery of adjuvant chemotherapy, with better compliance and reduced toxicity. It is now vital for ongoing data collection and review to see how this impacts on long-term survival.

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Conflict of interest: none declared.

REFERENCES


eComment. Can video-assisted thoracoscopic surgery or open thoracotomy alter the compliance to adjuvant chemotherapy and the oncologic prognosis of patients with non-small-cell lung cancer?

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We have read with great interest the article by Teh et al. The authors analyzed the impact of video-assisted thoracoscopic surgery (VATS) lobectomy and open thoracotomy for non-small cell lung cancer (NSCLC) on compliance to adjuvant chemotherapy [1]. They concluded that adjuvant chemotherapy was started significantly earlier in patients following VATS lung resections compared with open thoracotomy. However, this retrospective study includes a small number of patients. Moreover, there was a disparity between the number of patients in each pathology stage of NSCLC, i.e. preoperative pathology stage was 12.5% vs 30.8% for stage III in VATS and open group, respectively. The above led to a very weak trend towards VATS superiority.

On the other hand, selection criteria for open thoracotomy imply, by definition, more advanced local disease and heavier systematic malignant burden making re-habilitation longer and carrying a greater possibility of major adverse events. In addition, fewer reports of toxicity were observed in the VATS group (12.5%) compared with the open group (39.3%). Is this phenomenon correlated with the type of procedure or with the stage of the disease? A recent report using a larger cohort (n = 189) found no significant difference between the VATS and open thoracotomy approach for adjuvant chemotherapy compliance. On the contrary, significant factors proved to be the patient’s age, comorbidity and pathologic N status [2]. Recently, Booth et al. showed that NSCLC patients who underwent adjuvant chemotherapy beyond 10 weeks from surgery did not appear to be associated with inferior survival [3]. Besides, it should be analyzed whether the main factor responsible for early administration of adjuvant chemotherapy is the less postoperative surgical stress or the less complication rate of VATS over open thoracotomy. The real difference between VATS and open thoracotomy is possibly due to the shorter hospital stay. Adjuvant chemotherapy compliance may not be the strongest benefit for thoracoscopic surgery. Controlled prospective studies should be planned stage-for-stage matched, to clarify the real impact of VATS on overall oncologic management.

Conflict of interest: none declared.

References