Video-assisted thoracic surgery lobectomy for lung cancer is associated with less immunochemokine disturbances than thoracotomy

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Abstract

Objective: Major surgery is immunosuppressive and could have an impact on postoperative tumor immunosurveillance and recurrence in cancer patients. Low circulating levels of insulin growth factor binding protein (IGFBP)-3 have been linked to advanced prostate and the development of colonic cancers. This prospective study examined the early postoperative circulating levels of IGFBP-3, matrix metalloproteinase (MMP)-9, and tissue inhibitor of metalloproteinase (TIMP)-1 in early stage non-small cell lung cancer (NSCLC) patients undergoing major lung resection by VATS versus thoracotomy. Methods: Forty-two consecutive patients with resectable primary NSCLC were assigned to VATS or thoracotomy approach over a 7-month period. Blood samples were collected preoperatively and postoperatively on days (POD) 1 and 3 for enzyme linked immunosorbent assay determination of IGFBP-3, MMP-9 and TIMP-1 levels in the serum. Results: There were no demographic differences between the two groups. VATS lung resection was associated with lower levels of MMP-9 and TIMP-1 on POD1 (median 628 vs 1311 ng/ml, p = 0.009; and 131 vs 211 ng/ml, p = 0.004, respectively) but higher levels of IGFBP-3 on POD3 (1366 vs 1144 ng/ml, p = 0.02), when compared with the thoracotomy approach. There was no perioperative mortality. Conclusions: VATS major lung resection for NSCLC is associated with higher circulating levels of IGFBP-3, and lower levels of MMP-9 and TIMP-1, compared to the thoracotomy approach. The clinical relevance of these postoperative changes on tumor biology following lung resection for cancer warrants further investigation.

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1. Introduction

The development of video-assisted thoracic surgery (VATS) over the past decade has led to a paradigm shift in the approach to managing a number of chest conditions including lung cancer. Several studies have demonstrated considerable benefits relating to VATS compared with the thoracotomy approach, including an attenuated inflammatory cytokine response [1], less disturbance of postoperative cellular immunity [2], shorter hospital stay, less pulmonary [3] and shoulder dysfunction [4] and reduced postoperative pain [1]. These advantages have been attributed to the reduced access trauma related to VATS.

It is generally accepted that the 5-year survival of patients undergoing major lung resection for early stage lung cancer by the VATS approach and open method are comparable. There is recent evidence to suggest that long-term survival and recurrence outcomes following VATS lobectomy for clinical stage I and II non-small cell lung cancer (NSCLC) may be better than that achieved with thoracotomy [3], although significant controversy still exists [3,5]. Interestingly, survival benefits associated with minimal access surgery for colorectal cancer have also been reported [6]. One explanation was that minimal access approach reduces surgical trauma, which has been known to cause immunosuppression in the early postoperative period [7]. For instance, the difference in the serum levels of insulin-like growth factor binding protein (IGFBP)-3 may be at least partially related to surgical access [7]. In addition to binding insulin growth factor (IGF)-1, which is an important cell growth promoter, IGFBP-3 can independently induce apoptosis in many colonic, prostatic, as well as in some NSCLC tumor cell lines [8,9]. Furthermore, surgical trauma has been associated with increased levels of matrix metalloproteinase (MMP)-9, which can deactivate IGFBP-3 [7].
The objective of this prospective study was to examine
the postoperative circulating levels of IGFBP-3 and MMP-9 in
patients with early stage NSCLC undergoing major lung
resection by VATS or thoracotomy. The circulating levels of
the MMP-9 antagonist, tissue inhibitor of metalloproteinase
(TIMP)-1, were also measured.

2. Materials and methods

Forty-two consecutive patients with resectable primary
NSCLC were recruited over a 7-month period in 2005. Ethical
approval was given by the research ethics committee of the
Chinese University of Hong Kong. Informed consent for the
study was obtained from all patients. Standardized pre-
operative investigations included fiber-optic bronchoscopy,
computer tomography of the thorax and mediastinoscopy.
Bone scans and positron emission tomography (PET) were
selectively performed. In addition, the results from histology
were used for tumor (T), nodal (N), metastatic (M) staging.
VATS resection was carried out whenever it was technically
feasible. Patients with fused fissures and marked pleural
adhesions were assigned to undergo the conventional
posterolateral thoracotomy approach. Major lung resection
using individual ligation technique, followed by mediastinal
sampling in at least four lymph node stations has been
previously described [5]. (Fig. 1) Both groups of patients
received identical anesthesia with selective one lung
ventilation. Our VATS lung resection technique uses 6—
8 cm utility minithoracotomy (Fig. 2a) with no rib spreading
compared with conventional posterolateral thoracotomy.
(Fig. 2b) Intraoperative intercostals block with 0.5% bupivacaine
(Astra, North Ryde, Australia) was given to both groups
of patients at the conclusion of the procedure. Pain control
during postoperative days 1 and 2 was achieved by
standardized patient controlled analgesia with meperidine
hydrochloride (Antigen Pharmaceuticals Ltd., Roscrea,
County Tipperary, Ireland), and subsequently by oral analge-
sics paracetamol 640 mg and dextropropoxyphene 65 mg four
times per day.

Peripheral venous blood was collected in plain serum
Tubes (Vacuette®, Greiner Bio-One, Kremsmuenster, Austria)
before anesthetic induction as baseline, and at the same
time on postoperative days (POD) 1 and 3. The sample was
allowed to stand for 30 min for clotting of blood, followed by
centrifugation at 3,000 rpm for 10 min at 4 °C. The serum
collected was stored at −70 °C until assay. The concentra-
tions of IGFBP-3, MMP-9, and TIMP-1 were determined by the
same technologist who was blinded to the clinical data, using
commercially available enzyme-linked immunosorbent
assays kits (R&D Systems, Minneapolis, MN, USA).

Fig. 1. Flow diagram of the 42 patients recruited for the study.

Fig. 2. (a) VATS utility minithoracotomy wound, (b) posterolateral thoracot-
omy wound.
3. Results

3.1. Clinical findings

The final study consisted of 20 patients in the VATS group and 22 patients in the thoracotomy group. No demographic differences were found between the two groups (Table 1). None of the patients received mediastinal lymphadenectomy. In the VATS group, 19 patients underwent a lobectomy and one patient a bilobectomy. There were 14 patients with pathological TNM stage I, four patients with stage IIa, and two patients with stage IIIa. There were 13 adenocarcinomas, five squamous cell carcinomas (SCC), and two other carcinomas.

In the thoracotomy group, 20 patients underwent a lobectomy and two patients a bilobectomy. There were 13 patients with pathological TNM stage I, five with stage IIa, two with stage IIb and two with stage IIIa disease. There were 15 adenocarcinomas, four SCC, and three other carcinomas. There was no significant difference between the two groups on the date of resection over the study period, excluding potential effect of seasonal variation in the measured parameters.

The duration of surgery in the VATS and the thoracotomy groups were not significantly different, although there was a tendency towards a slightly longer procedure in the latter. The mean tumor size for patients in the VATS group was 3 cm, and for patients in the thoracotomy group was 3.8 cm (Table 1). The number of lymph node stations dissected and sampled were comparable between the groups. No blood transfusion or blood product was required for any patient. There was no perioperative mortality. One patient in the thoracotomy group developed significant sputum retention requiring repeated bronchoscopic toileting, and one patient in the VATS group had prolonged airleak for 4 days, which was self limiting.

3.2. Intra-group differences in chemokines

Comparing to the baseline, the levels of IGFBP-3 were significantly higher at POD 1 following VATS resection, and significantly lower at POD 3 following thoracotomy (Table 2). MMP-9 and TIMP-1 levels at POD 1 were significantly elevated in both groups of patients.

3.3. Inter-group differences in chemokines

The baseline values of the measured chemokines were comparable in the two groups. The IGFBP-3 levels at POD 3 were significantly higher in the VATS group than that in the thoracotomy group (Table 2 and Fig. 3). In contrast, both MMP-9 and TIMP-1 levels at POD 1 were significantly lower in the VATS group when compared with those in the thoracotomy patients.

4. Discussion

Although considerable controversy remains [5,10], recent observations from non-randomized trials on VATS resection for stage I lung cancer suggested equivalent or better intermediate to long-term survival compared to conventional thoracotomy [3,5,7]. Such differences in outcomes, if any, may be influenced by disease severity, treatment effectiveness, or chance. Hence, large prospective randomized studies with longer follow-up are certainly needed before any conclusions could be drawn. Nevertheless, the potential survival advantages following VATS major lung resection have led to numerous speculations on the possible mechanisms, including attenuated cytokine-acute phase responses [1] and better preserved immune function leading to improved tumor immunosurveillance [2,7].

High IGF-1 has been implicated in the progression of numerous cancers due to its ability to stimulate tumor proliferation and reduce tumor cell apoptosis [11]. IGFBP-3 is the natural antagonist protein that binds and attenuates the activity of IGF-1, thereby possess anti-tumorogenesis

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**Table 1**

<table>
<thead>
<tr>
<th>Variables</th>
<th>VATS</th>
<th>Open</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>65.1 ± 10.2</td>
<td>68.5 ± 6.3</td>
</tr>
<tr>
<td>Male/female</td>
<td>15/5</td>
<td>15/7</td>
</tr>
<tr>
<td>Smoker</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Tumor diameter (cm)*</td>
<td>3.0 ± 1.32</td>
<td>3.8 ± 1.4</td>
</tr>
<tr>
<td>Tumor histology (adeno/SCC/other)</td>
<td>13/5/2</td>
<td>15/4/3</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>IGFBP-3 (ng/ml)</th>
<th>Preop*</th>
<th>Day 1*</th>
<th>p</th>
<th>Day 3*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VATS</td>
<td>1322 (992–1927)</td>
<td>1355 (1180–2292)</td>
<td>0.009</td>
<td>1366 (1056–1857)</td>
<td>0.6</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>1155 (785–1471)</td>
<td>1259 (706–1649)</td>
<td>0.2</td>
<td>1144 (570–1272)</td>
<td>0.04</td>
</tr>
<tr>
<td>MMP-9 (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VATS</td>
<td>412 (202–604)</td>
<td>628 (259–1080)</td>
<td>0.03</td>
<td>458 (40–1000)</td>
<td>0.6</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>580 (439–937)</td>
<td>1311 (1143–1377)</td>
<td>≤0.0001</td>
<td>724 (433–1177)</td>
<td>0.4</td>
</tr>
<tr>
<td>TIMP-1 (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VATS</td>
<td>118 (98–137)</td>
<td>131 (114–170)</td>
<td>0.02</td>
<td>139 (106–153)</td>
<td>0.1</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>130 (89–220)</td>
<td>211 (167–245)</td>
<td>0.02</td>
<td>167 (110–235)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

* Median (interquartile range).
properties. Low circulating levels of IGFBP-3 have been linked to advanced prostate carcinoma [12] and risk of developing colonic carcinoma [13]. Interestingly, IGFBP-3 have been shown to have independent apoptosis-inducing effect on all colon carcinoma cell lines [9], as well as many NSCLC cell lines [8]. In addition, IGFBP-3 can impair DNA synthesis in poorly differentiated tumor cells [7]. These properties of IGFBP-3 may be important following lung cancer resection when tumor cells may be shed into the circulation [10].

We observe that circulating levels of IGFBP-3 were higher on postoperative day 3 following VATS major lung resection for NSCLC compared with the thoracotomy approach. Furthermore, the blood levels of MMP-9, which can cleave and deactivate IGFBP-3, were reciprocally lower in the VATS group on postoperative day 1. It is interesting to note that the MMP-9 inhibitor, TIMP-1, was also significantly lower on postoperative day 1 following VATS major lung resection compared to the open approach. Apart from MMP-9 acting as IGFBP-3 antagonist, elevated levels of MMP-9 have been implicated in facilitating tumor invasion and metastasis in various tissues through its proteolytic properties against type IV collagen within the basement membrane [14,15]. Therefore, higher MMP-9 levels following thoracotomy may adversely affect postoperative tumor cell immunosurveillance.

It is also worth mentioning briefly that elevated levels of inflammatory cytokine interleukin (IL)-6 may promote IGF and antagonize IGFBP-3 activities [16]. The level of circulating IL-6 is well known to reflect the degree of surgical trauma [7]. The release of IL-6 in the early postoperative period has been found to be significantly lower in patients undergoing VATS major lung resection for NSCLC than in those receiving thoracotomy [1], citing a potential relationship between access trauma and circulating IGFBP-3 levels. Our experience also indicates that in centers where VATS is well established, the operative duration of VATS lung resection is similar or even shorter than that of thoracotomy. Whether such a difference could partially affect postoperative immune function remains to be elucidated.

Limitations of the study include the low patient numbers, and non-randomized nature of the study. Although the demographics and pathology of the two groups of patients were comparable in the current study, and randomizing patients into VATS or thoracotomy groups may be difficult when patient’s choice preclude one or the other, our findings should be validated in a randomized trial. It would also be interesting to explore whether some of these changes in postoperative circulating chemokines are sustained. Furthermore, quantifying local IGFBP-3 responses in the pleural cavity and lung tissue may be important in determining local tumor immunosurveillance. It is still premature to associate better preserved immune function following lung resection for cancer to improved survival, particularly when other surgical and tumor related factors can have even more significant influence on outcome.

In short, VATS major lung resection for NSCLC is associated with higher levels of circulating IGFBP-3, and lower levels of MMP-9 and TIMP-1 in the early postoperative period when compared to the thoracotomy approach. The underlying mechanisms are likely multi-factorial, while access trauma may play an important role. The potential impact of postoperative changes in chemokine levels on tumor immunosurveillance following lung cancer resection warrants further investigation.

Acknowledgment

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References

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