

# Video-Assisted Thoracic Surgery for Early Stage Lung Cancer — Can Short-Term Immunological Advantages Improve Long-Term Survival?

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**The development of video-assisted thoracic surgery (VATS) in the past decade has changed the way many pulmonary conditions are being treated. VATS has gained popularity among clinicians due to faster recovery following surgery, less postoperative pain and better cosmesis. It is well known that surgical trauma can induce a systemic inflammatory response and affect postoperative systemic immunity. Minimal access VATS has been shown to be associated with a reduced postoperative systemic inflammatory response. Recent evidence suggests VATS is also associated with better cellular immunity, and produces less immunochemokine disturbance following surgery, when compared with the thoracotomy approach. Circulating natural killer (NK) cell numbers and levels of insulin growth factor binding protein (IGFBP) are found to be higher, and plasma levels of matrix metalloproteinases are lower following VATS than that after thoracotomy. Maintenance of immune function with VATS may have important clinical implications in lung cancer surgery. (Ann Thorac Cardiovasc Surg 2006; 12: 308–12)**

**Key words:** immunosuppression, insulin growth factor binding protein, interleukin, video-assisted thoracic surgery

## Introduction

For decades, surgery has been known to induce significant postoperative inflammatory responses and immunosuppression, which are closely interrelated. The degree of access trauma relating to the surgical procedure is considered to be the most important factor in determining the degree of inflammation and immunosuppression.<sup>1)</sup> Inflammatory response and immune dysfunction following surgery can also be affected by the type and duration of procedure, and whether blood transfusion was administered.<sup>1)</sup> In the past, most clinicians have been concerned about the effects of postoperative immunosuppression on the incidence of wound or prosthesis infection, recovery

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following surgery, and hospital stay. Recent evidence suggests that minimal access approach may be associated with improved patient survival after oncological surgery, such as major lung resection for early stage non-small cell lung carcinoma (NSCLC) and colonic resection for colorectal carcinoma.<sup>2,3)</sup> In this article, we explore the recent evidence on immunological advantages following video-assisted thoracic surgery (VATS) for lung cancer, and its potential impact on long-term survival.

## Does VATS Carry a Short-Term Immunological Advantage?

### Plasma composition

Surgical trauma has a negative impact on the immune function, physiology, and serum protein composition, to create a postoperative immunocompromising environment that may influence tumor biology.<sup>1)</sup> It is well known that surgical trauma induces the release of acute-phase response mediators including C-reactive protein (CRP),

**Table 1. Some recently published clinical studies on postoperative immune cell response after lung cancer resection: minimal access versus open surgery**

Study	No.	Surgical procedure	Immune cell response: minimal access versus open
Leaver et al. <sup>18)</sup>	41	Lobectomy by VATS or thoracotomy for bronchogenic CA	POD2: less suppression of CD4 cell number & lymphocyte oxidation activity in VATS POD7: less suppression of NK cell in VATS
Craig et al. <sup>6)</sup>	35	Lobectomy by VATS or thoracotomy for bronchogenic CA	POD2 & POD7: more neutrophil ROS production in open
Ng et al. <sup>8)</sup>	21	Lobectomy by VATS or thoracotomy for bronchogenic CA	POD1: total T cell, T4 cell & lymphocyte numbers reduced in open POD7: NK cell numbers lower in open

VATS, video-assisted thoracic surgery; CA, carcinoma; POD, postoperative day; NK, natural killer; ROS, reactive oxygen species.

interleukin (IL)-1, IL-6 and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>4)</sup> Serum IL-6 concentration, an early marker of surgical or other trauma, can rise as early as 1 hour after the start of surgery, and peaks between 2 to 4 hours postoperatively.<sup>5,6)</sup> Moreover, serum IL-6 levels may remain elevated above baseline for several days postoperatively.<sup>5,6)</sup> The reduced access trauma associated with VATS has been shown to attenuate the postoperative inflammatory cytokine response compared with open thoracotomy. Several clinical trials have detected lower postoperative levels of CRP,<sup>6)</sup> IL-6,<sup>5-7)</sup> IL-8,<sup>5)</sup> and IL-10 following VATS lobectomy when compared with that accomplished through a thoracotomy. However, no differences in postoperative TNF- $\alpha$  or IL-1 $\beta$  levels were found between the two approaches.<sup>5)</sup>

Part of the interest in the production of IL-6, apart from its value as a surgical trauma marker, lies in its role on postoperative immunosuppression. IL-6 impacts upon the immune system via its effects on IL-1 $\beta$  and TNF- $\alpha$  production which are necessary for effective cellular immunity and immunosurveillance.<sup>8)</sup> In addition, recent studies have shown that elevated plasma levels of IL-6 may encourage cell proliferation in certain subtypes of NSCLC,<sup>9)</sup> and contribute to an environment favouring tumor growth by promoting the activity of insulin growth factor (IGF) and inhibiting IGF binding protein (IGFBP)-3.<sup>1)</sup>

High IGF-1 has been implicated in the progression of numerous cancers due to its ability to stimulate tumour proliferation and reduce tumour cell apoptosis.<sup>10)</sup> IGFBP-3 is the natural antagonist protein that binds and attenuates the activity of IGF-1, thereby inhibiting tumorigenesis. Low circulating levels of IGFBP-3 have been linked to advanced prostate carcinoma<sup>1,11)</sup> and in-

crease risk of developing colonic carcinoma.<sup>10)</sup> IGFBP-3 was also shown to have independent apoptosis inducing effect on all colon carcinoma cell lines,<sup>12)</sup> as well as many NSCLC cell lines.<sup>13)</sup> In addition, IGFBP-3 can impair DNA synthesis in poorly differentiated tumor cells.<sup>1)</sup> These anti-oncogenic properties of IGFBP-3<sup>12,13)</sup> may be even more important given that lung resection surgery is known to be associated with postoperative seeding of tumor cells into the circulation.<sup>14)</sup> Recently, we found in a prospective study that circulating levels of IGFBP-3 were higher on postoperative day 3 following VATS major lung resection for NSCLC compared with the open approach.<sup>15)</sup> Furthermore, the circulating levels of MMP-9 (which can cleave and deactivate IGFBP-3) were reciprocally lower in the VATS lung resection group during the same period. Elevated levels of MMP-9 have also been implicated in facilitating tumor invasion and metastasis in various tissues through its proteolytic properties against type IV collagen within the basement membrane.<sup>16,17)</sup> These observations may have important implications for postoperative tumor cell behavior.

### Cellular immunity

Major surgery is immunosuppressive and causes alterations in multiple immune parameters, including changes in the circulating blood lymphocyte subsets, and modulation of cell-mediated immunity.<sup>8)</sup> Most of the studies on postoperative cell-mediated immunosuppression were based on open and laparoscopic abdominal surgery.<sup>1,8)</sup> Only limited studies have been conducted so far on effects of thoracic surgery on postoperative cellular immunity (Table 1). Recently, VATS has been shown to produce less immunosuppression of lymphocyte activity, and

less suppression of lymphocyte, total T cells and CD4 T cells numbers in the early postoperative period, when compared with thoracotomy in patients undergoing lobectomy for NSCLC.<sup>8,18)</sup> Another interesting aspect of immunity is the natural killer (NK) cell response to VATS and open surgery. NK cells are well known to be essential in tumour immunosurveillance although its ability to recognize, target and directly kill tumor cells without prior sensitization was found to be significantly lower on postoperative day 7 following open lobectomy when compared with VATS approach. This suggests that the VATS method is associated with a quicker NK cell recovery than conventional thoracotomy.<sup>8,18)</sup> The higher plasma IL-10 levels detected following open lobectomy,<sup>5)</sup> in addition to being a T-helper type 2 (Th-2) type cytokine which, in general, suppress cell mediated immunity, they can also help tumor cells escape from the host immune system by directly inhibiting NK-cell-mediated cytotoxicity, and increase resistance of certain tumor cell lines to NK cell destruction in experimental setting.<sup>8,19)</sup> Furthermore, postoperative neutrophil phagocytic activity, in terms of reactive oxygen species (ROS) production was less affected following VATS lung resection than after thoracotomy.<sup>6)</sup> The relationship between cellular immunity, cytokines and plasma immunomodulatory mediators is a complex one and will require further evaluation. However, it should be noted that the differences for almost all of the immune parameters tested thus far are short lived, in order of hours or days. The clinical importance of better preserved immune function following VATS has yet to be proven in the setting of a generally healthy patient population that is immunocompetent preoperatively.

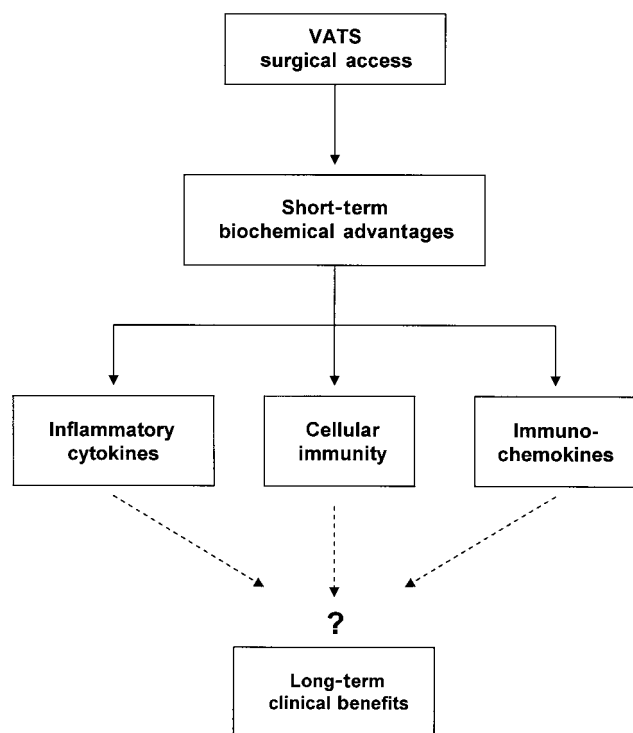
It is also worth noting that in addition to IL-6, IL-10 and IGFBP-3, there are other plasma mediators of interest including IL-12, IL-17 and IL-23 which are critical in T cell-dependent immune responses, including mobilization of NK cells and neutrophils.<sup>20)</sup> It is highly likely that many more immune mediators are involved in altering the composition of plasma following VATS and open surgery. Using lymphocyte oligonucleotide microarrays to study circulating lymphocyte gene activation in a clinical pilot study, we were able to detect changes in expression of over 100 genes following VATS or open major lung resection (unpublished data). Identifying these gene products may hold the key to our understanding of surgery-related cell-mediated immune dysfunction, and its effects on tumor biology. Furthermore, future novel pharmacologic strategies to limit the immunologic adverse effects of surgery may be devised.

## Can Surgical Access Impact on Survival?

In a non-randomized prospective study in patients undergoing stage I lung cancer resection, a significant 5-year survival benefit was reported in the VATS group (97%) compared to the thoracotomy group (78.5%).<sup>2)</sup> Other clinical series from numerous VATS centres have also shown survival following VATS for early stage lung cancer, are at least equivalent to, if not better than, those after the open procedure.<sup>21,22)</sup> However, there remains significant controversy over improved survival following VATS resection for early lung cancer. Recently, Yamashita et al.<sup>14)</sup> reported shorter survival in patients undergoing VATS lung cancer resection compared with their historical thoracotomy results, which the authors attributed to increased postoperative seeding of tumor cells into the circulation during the VATS procedure. Interestingly, it has been shown in other tumors, such as colonic carcinoma, that detection of circulating tumor cells following surgical resection with curative intent have had no prognostic significance.<sup>23)</sup> Discrepancies in survival data may be explained by reporting bias, technical differences in VATS, pathological staging (variations in mediastinal lymph node sampling) and patient selection. Nevertheless, there are several proposed mechanisms behind the possible survival advantages associated with minimal access techniques which include decreased alterations in serum protein composition, attenuated cytokine-acute phase responses, and better preserved postoperative immune function leading to improved tumor immunosurveillance as described (Fig. 1).<sup>3,8,21)</sup> Future large randomized prospective studies with longer follow-up are needed before conclusions can be drawn.

## Summary

VATS lung resection for early stage NSCLC is known to be associated with clinical benefits including less postoperative pain and quicker recovery following surgery. In the past few years, long term follow up data have shown comparable, and in some series improved survival following VATS lung cancer resection. The mechanisms behind such differences are likely multi-factorial. Recent observations indicated that VATS is associated with better preserved cellular immunity and less immunosuppression when compared with conventional thoracotomy during the immediate postoperative period. Less disturbance of inflammatory and immunomodulatory mediators following VATS may have additional impact upon tumor bio-



**Fig. 1.** Possible mechanisms on how minimal access surgery could lead to clinical benefits.

VATS, video-assisted thoracic surgery.

logical behavior. Potential clinical benefits relating to these differences warrant further confirmation.

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