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REVIEW ARTICLE

Surgical Trauma and Immune Functional Changes Following Major Lung Resection

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Abstract Video-assisted thoracic surgery (VATS) has evolved greatly over the last two decades. VATS major lung resection for early stage non-small cell lung carcinoma (NSCLC) has been shown to result in less postoperative pain, less pulmonary dysfunction postoperatively, shorter hospital stay, and better patient tolerance to adjuvant chemotherapy compared with patients who underwent thoracotomy. Several recent studies have even reported improved long-term survival in those who underwent VATS major lung resection for early stage NSCLC when compared with open technique. Interestingly, the immune status and autologous tumor killing ability of lung cancer patients have previously been associated with long-term survival. VATS major lung resection can result in an attenuated postoperative inflammatory response. Furthermore, the minimal invasive approach better preserve patients' postoperative immune function, leading to higher circulating natural killer and T cells numbers, T cell oxidative activity, and levels of immunochemokines such as insulin growth factor binding protein 3 following VATS compared with thoracotomy. Apart from host immunity, the angiogenic environment following surgery may also have a role in determining cancer recurrence and possibly survival. Whether differences in immunological and biochemical mediators contribute significantly towards improved clinical outcomes following VATS major lung resection for lung cancer remains to be further investigated. Future studies will also need to address whether the reduced access trauma from advanced thoracic surgical techniques, such as single-port VATS, can further attenuate the postoperative inflammatory response.

Keywords Angiogenesis · Immune · Inflammation · Single port · Trauma · Thoracotomy · VATS

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Introduction

In the past two decades, video-assisted thoracic surgery (VATS) has undergone significant evolution and refinement, increasing its application in numerous thoracic conditions. Consequently, the degree of surgical access trauma experienced by patients undergoing VATS major lung resection has decreased as two-port and single-port VATS techniques are employed [1] (Fig. 1). VATS is now considered the approach of choice by many for major lung resection (lobectomy or pneumonectomy) in the management of early stage lung cancer. Initial skeptism and concerns about VATS safety, oncological clearance, long-term benefits, and cost-effectiveness are unfounded [2, 3]. On the other hand, the benefits associated with VATS major lung resection including less blood loss and transfusion requirements, less postoperative pain, better preserved pulmonary and shoulder function, shorter chest drain duration and hospital stay, as well as better patient tolerance and compliance to subsequent adjuvant chemotherapy, compared with the thoracotomy approach are increasingly being appreciated [3–7]. Moreover, improved intermediate to long-term survival in favor of VATS for early non-small cell lung cancer when compared to the open technique have been shown in nonrandomized studies [2, 3, 8, 9]. Nevertheless, such survival advantage from the minimal invasive technique has not been consistently demonstrated [10–12]. There is also growing body of evidence from studies on pro-and anti-inflammatory cytokines, immunomodulatory cytokines, circulating T (CD4) and natural killer (NK) cells, and lymphocyte function to suggest that the body's immune function may be

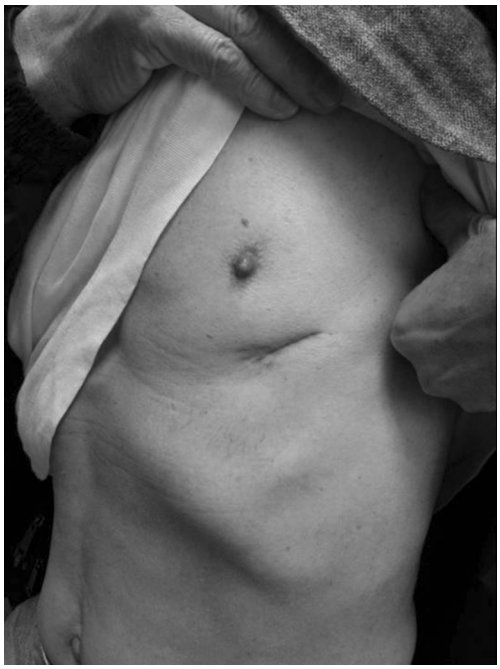

Fig. 1 Surgical access trauma is significantly reduced with the introduction of single-port video-assisted thoracic surgery for lobectomy

better preserved following VATS compared to thoracotomy [13]. Since immunosurveillance is believed to be important in tumor suppression, surgically induced immunosuppression may predispose to increase risk of tumor recurrence following surgery [13]. Most cases of lung cancer recurrence are at a distance from the primary tumor site, some of those are likely to be metastatic from initial exploration. Therefore, it is possible that minimal invasive VATS approach for lung cancer resection may allow better preservation of host immunity and optimize long-term survival.

Inflammatory Response

Cytokines

Surgical trauma can cause a systemic inflammatory cytokine response. Typically, circulating inflammatory cytokine levels, including interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α) are elevated in the early postoperative period [14]. Interestingly, minimal access abdominal surgery is associated with an attenuated serum IL-6 and C-reactive protein response compared with open approach [13, 15, 16]. Similarly, the reduced access trauma of VATS major lung resection compared with open thoracotomy resulted in a reduced postoperative CRP, IL-6, and IL-8 response [17–20]. Furthermore, the postoperative difference in IL-6 levels between the two approaches is likely related to difference in surgical access trauma rather than the extensiveness of the intrathoracic procedure [20, 21]. VATS lobectomy is also associated with reduced release of the anti-inflammatory cytokine IL-10 in the early postoperative period when compared with thoracotomy [18]. This finding may be important because IL-10, in addition to being a T helper type 2 cytokine, which, in general, suppress cell-mediated immunity, can help tumor cells evade from the host immune system by direct inhibition of NK cell-mediated cytotoxicity and increase resistance of certain tumor cell lines to NK cell destruction [22].

Interleukin 6 has an additional role in postoperative immunosuppression via its effects on IL-1β and TNF-α production, which are necessary for effective cellular immunity and immunosurveillance [23]. Interaction between IL-6 and insulin growth factor (IGF) also cause insulin growth factor binding protein (IGFBP) 3 inhibition, thereby contributing to an environment favoring tumor growth [13], which can encourage proliferation of certain subtypes of non-small cell lung carcinoma [24].

Immunomodulatory cytokine, IGF-1, is known to facilitate progression of numerous tumors due to its ability to stimulate cancer proliferation and reduce cancer cell apoptosis [25]. IGFBP3 is the natural antagonist of IGF-1 that binds and attenuates IGF-1 activity, thereby exert anti-tumorogenesis properties. Furthermore, IGFBP3 can independently induce apoptosis in several cancerous cell lines including colonic, prostatic, and certain non-small cell lung carcinomas (NSCLC) [26, 27], as well as impair DNA synthesis in some poorly differentiated tumors [13]. Appropriate activity of IGFBP3 may be important following lung cancer resection to reduce the risk of recurrence, especially when tumor cells may be shed into the circulation during surgery [10]. In a recent prospective study of patients with early stage NSCLC undergoing major lung resection, VATS was associated with higher levels of IGFBP3 in the early postoperative period when compared with thoracotomy [28]. Nevertheless, the study failed to find any clinical benefits in VATS patients during the short postoperative follow-up period. Another important immunochemokine matrix metalloproteinase (MMP-9), normally released from mononuclear cells in response to surgical trauma, was also found to be reciprocally lower in the group who underwent VATS major lung resection [28, 29]. Apart from the ability of MMP-9 to cleave and deactivate IGFBP-3, MMP-9 can also allow tumor invasion and metastasis by its proteolytic activity against basement membrane type IV collagen [28–31]. Early postoperative differences in inflammatory cytokines and immunochemokines between the different surgical approaches may be important in affecting tumor cell behavior.

Cellular Immunity

Major surgery can significantly affect host cellular immunity with potential impact on postoperative infection and tumor immunosurveillance [13]. In abdominal surgical procedures,

postoperative decrease in lymphocyte proliferation, altered circulating lymphocyte subsets, downregulation of T helper type-1 cytokine response which favors humoral rather than cellular immunity, and decreased delayed type hypersensitivity responses have been described [14, 32, 33].

VATS lobectomy for early stage NSCLC has been found to be less immunosuppressive compared with open thoracotomy, shown by less suppressed lymphocyte, total T cells, CD4 T cells, and NK cells numbers in the early postoperative period [23, 34] (Table 1). NK cells play an important role in tumor immunosurveillance by recognizing and directly destroying tumor cells. Interestingly, VATS major lung resection also resulted in less disturbed neutrophil phagocytic activity and reactive oxygen species production compared with thoracotomy [17]. Interestingly, in a rodent model of open versus minimal invasive thoracic surgical access, as well as thoracotomy versus VATS major lung resection, the thoracotomy groups were associated with significantly more lymphocyte suppression, including CD3+, CD4+, and CD8+ counts, when compared with their counterparts in the early postoperative period [20]. However, all these postoperative immune differences between VATS and thoracotomy groups are short lived, in the order of hours to a few days. In the context of oncological surgery, maintaining a functioning postoperative cellular immunity may have a role in reducing tumor growth and recurrence, although the clinical importance of better preserved immune function following VATS remains unproven.

Table 1 Studies comparing the systemic cellular immune responses following major lung resection for bronchogenic carcinoma in VATS and open thoracotomy patients

	No. of patients	Cellular immune response:
Clinical study		
Ng et al. [23]	21	Postoperative day 1: total T cell, T_4 cell, and lymphocyte numbers were reduced in open group
		Postoperative day 7: natural killer cell numbers were lower in open thoracotomy group
Craig et al. [17]	35	Postoperative days 2 and 7: more neutrophil reactive oxygen species production in open thoracotomy group
Leaver et al. [34]	41	Postoperative day 2: number of CD4 cells and lymphocyte oxidation activity was less suppressed in VATS group
		Postoperative day 7: natural killer cell suppression was less in VATS group
Experimental study		
Ito et al. [20]	32	Postoperative day 1: number of lymphocytes, including CD3+, CD4+, and CD8+ numbers, were less suppressed in VATS group

Immune Status: Storm in a Teacup?

To many, the association between a better preserved immune status following minimal invasive VATS resection for early stage NSCLC and improved survival remains a fantasy. In order to demonstrate such a relationship, a large randomized trial that measures a comprehensive range of postoperative immune markers and long-term survival following VATS and open lobectomy is needed. Such trials would not only be encounter logistical difficulties in measuring a large number of immune function markers but also pose problems in randomizing patients into minimal invasive and open groups in centers where VATS is well established because patient choice often precludes the open approach.

Potentially interesting prognostic immune parameters in lung cancer include delayed hypersensitivity skin test [35] and lymphoblastogenesis (LB) induced by mitogens [36]. Interestingly, the postoperative lymphocyte autologous tumor killing (ATK) and NK cell activity during the 2 weeks immediately following surgery for NSCLC was an important prognostic factor [37, 38]. Leukocytes identified to be involved in ATK include CD3(+), CD4(−), CD8(+), and CD11b(−) [38]. Patients with higher postoperative ATK were shown to have a lower 5-year tumor recurrence rate and also better survival in both early and more advance NSCLC stages [38]. More recently, Nakamura et al. [39] prospectively measured various cellular immunologic parameters including lymphocyte subsets, NK cell activity, and LB stimulation in peripheral blood samples taken from patients before the initiation of therapy (surgery or chemotherapy). The study found that no significant survival differences were associated with LB, NK activity, FcγRIII$^+$ T cells, CD3, CD4, CD8, and CD4/CD8 ratio [39]. However, upon subgroup analysis according to histologic type, an increase of HLA-DR+ cells and FcγRIII$^+$ T cell subset suggested a worse prognosis in squamous cell carcinoma. Similarly, an increase HLA-DR+ cells, and in addition a decreased CD4/CD8 ratio, were associated with worse prognosis in small cell carcinoma [39, 40]. Lately, it has been found that a high interferon-gamma+/CD4+ (Th1) to IL-4+/CD4+ (Th2) lymphocyte cell ratio in peripheral blood was also associated with a poor 5-year prognosis in NSCLC patients [41].

Studies so far suggest that certain immune parameters are associated with survival in lung cancer patients, its importance may depend in part to histologic type. Such association may partly explain the rare phenomenon of spontaneous tumor regression in squamous cell and small cell carcinoma [42, 43]. In addition, whether such association between immunity and survival can be extrapolated to early stage NSCLC

patients following VATS major lung resection needs further investigation.

Future Directions

Other mediators of interest which may be associated with postoperative immunity include IL-12, IL-17, IL-23, and IL-25 (IL-17E). Interleukins 12, 17, and 23 have been shown to play a role in T cell-dependent immune responses and mobilization of NK cells and neutrophils [44]. More specifically, IL-12 increases interferon-γ production and induce Th1-type cells development from naive helper T lymphocytes [45] changing Th1 and Th2 cells ratio which can potentially impact upon survival in NSCLC patients [41]. Another novel inflammatory cytokine IL-25 (IL-17E) was recently shown to have immunomodulatory and antitumoral properties through eosinophil activation and eotaxin cytokine release [46].

The angiogenic environment following oncological surgery may be important in affecting tumor biological behavior. The most potent inducer of angiogenesis is vascular endothelial growth factor (VEGF) which not only plays a significant role in wound healing but also acts as a strong tumor growth stimulator. VEGF release following surgery may be undesirable, since it may enhance tumor growth and metastasis formation on residual tumor cells. Elevated circulating levels of VEGF were found following major abdominal surgery from several days up till 4 weeks postoperatively [47, 48]. Interestingly, the release of VEGF were significantly higher in the open abdominal surgical patients compared with laparoscopic approach to colectomy, irrespective of whether surgery was for benign or malignant pathology [48]. Recently, postoperative changes in angiogenic factors were also found in patients undergoing major lung resection for early stage lung cancer [49]. Irrespective of lung resection approach, postoperative angiopoietin-1 and soluble VEGF receptor 2 levels were significantly decreased, while angiopoietin-2 and soluble VEGF receptor 1 levels markedly increased. Compared with open group, VATS had significantly lower plasma levels of VEGF in the early postoperative period, showing similar trends to abdominal surgical patients [49]. Therefore, major lung resection for early stage NSCLC leads to a pro-angiogenic status, and minimal invasive surgical access by VATS can attenuate angiogenic response with lower circulating VEGF levels compared with open approach. These studies suggest that the amount of surgical access trauma may play an important role in stimulating the release of angiogenic factors into the circulation, and by inference tumor behavior. In addition to ex vivo measurements, the clinical impact of these chemokines and factors should be investigated in in vitro assays to confirm whether postoperative plasma and plasma from surgery associated with large surgical access trauma can stimulate tumor proliferation and invasion.

Apart from surgical access trauma per se, other factors favoring VATS lung resection, such as reduced postoperative pain, may also have an important contribution in preserving postoperative cellular immunity by reducing lymphocyte suppression and attenuate proinflammatory cytokine responses [50]. Furthermore, VATS major lung resection encompasses a spectrum of techniques and is not a unified approach [11]; therefore, variations in the use of and size of utility thoracotomy, the number of incisions and port sites used [1], the practice of rib spreading and segmental rib resection [51], as well as the duration of surgery may all have addition effects on postoperative inflammatory and immune responses. The recent development of single-port VATS (uniportal) major lung resections may further reduce surgical access trauma, attenuating the postoperative inflammatory response when compared with standard three-port VATS [52, 53]. Future studies in these exciting areas are warranted.

Conflict of Interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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