Immune response after video-assisted thoracic surgery in non-small cell lung cancer patients

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Abstract: The effects of immunomodulation processes in patients undergoing video-assisted thoracic surgery (VATS) lobectomy are still debated; although, the reduced surgical stress of minimally invasive surgery is evident. The immunological repercussions could also influence the evolution of the disease and the prognosis of patients. The article aims to raise some points of reflection by considering available evidences and reiterating, once again, the prognostic utility of a minimally invasive procedure rather than classical approach.

Keywords: Non-small cell lung cancer (NSCLC); immunology; video-assisted thoracic surgery lobectomy (VATS lobectomy); interleukine

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Minor surgical stress with an early discharge represents a cornerstone of video-assisted thoracic surgery (VATS). However, the immediate post-operative period is a crucial moment for the patients, since both adaptive and rehabilitative processes with modifications in lung dynamics occur due to neurovegetative and immunological responses. The response to a surgical trauma is complex and involves an early activation of a cascade of intercellular factors resulting in leukocyte activation and changes in the vascular endothelium. Although the inflammatory stimulus represents a protective factor for the organism, it can assume pathological connotations at the onset of an immunological imbalance, as a dysregulated response to a pathogenic noxae, such as in the case of surgery. Several studies have demonstrated the benefits associated with thoracoscopic access compared to thoracotomy in terms of cytokine and immune cellular response (1), by minimizing the ineluctable post-operative stress. In our opinion, this aspect needs reflection, even more by considering the increasing incidence of pulmonary neoplasms and, therefore, of the surgical interventions that must be tackled.

The modulation of the adaptive response of the organism as a sequential aspect of the surgery requires a profound knowledge, which could reduce or at least anticipate the onset of dreadful post-operative complications. Even more fascinating would be to investigate if and how much postoperative inflammatory responses influence the prognosis of patients with non-small cell lung cancer (NSCLC). In this regard, a pioneering study was published by Yim *et al.* (2) involving 36 patients with stage I NSCLC and comparing the proinflammatory and anti-inflammatory cytokine effects according to surgical access (VATS *vs.* open). Interestingly, both the levels of proinflammatory cytokines (IL-6, IL-8) and anti-inflammatory (IL-10) were significantly reduced post-operatively in the VATS group. Moreover, an elevated IL-6 and IL-8 correlated with an increased risk of complications (3) due to the onset of an immune dysregulation with alteration of the inflammatory/anti-inflammatory balance and the production of oxygen-free radicals with both local and systemic effect. Furthermore, among the systemic effects, the proinflammatory cytokines increase synaptic excitability of the sensory fibers modulated by the activation of vagal afferents resulting in hyperalgesia. This last aspect, we believe is an element to be taken into consideration and confirms the superiority of minimally invasive access for surgical treatment of lung cancer.

Similar results were published by Nagahiro *et al.* (4) in a trial of 22 NSCLC patients. In fact, serum IL-6 levels appeared significantly increased at POD 0 in the thoracotomy group when compared to the VATS one (21.6 *vs.* 4.1 pg/mL, P<0.03, respectively). In addition, both surgical and inflammatory stress present high mitogenic and apoptotic stimuli, whose dysregulation may result in a "skip effect" leading to hyperstimulation of cell membranes and the activation of uncontrolled cellular turnover processes. In this regard, Ng *et al.* (5), about a decade ago, hypothesized a fundamental role of some transcription of growth factors in the prognosis of patients with early stage NSCLC. Furthermore, by comparing VATS versus classical approaches, the Authors found significant differences in post-operative serum levels of insulin-like growth factor binding protein (IGFBP)-3, that, like the insulin growth factor (IGF)-1, promotes cell apoptosis. Moreover, surgical stress seemed to activate the synthesis of matrix metalloproteinase (MMP)-9 with chelating effects on insulin-like growth factors. Regarding IGFBP-3, its levels appeared significantly higher in the VATS group at POD 1; while the levels of MMP-9 were doubled in thoracotomy patients compared to those minimally invasively treated (1,311 *vs.* 628 ng/mL). Similar conclusions were reported by Zhang *et al.* (6) in the largest published randomized trial including 122 patients. In particular, in the VATS group, IGFBP-3, VEGF and IL-6 levels at each time point after surgery were dramatically lower than in the thoracotomy brace. It would seem, therefore, that a standard approach represents rather a risk for the persistence of a pro-inflammatory microenvironment with the production of growth factors, cytokines and soluble factors, whose consequences still require further investigation. In the view of a systemic disease, however, inflammation could significantly influence patients' prognosis, as a multi-organ macroenvironments, through systemic manifestations as the onset of cachexia (7), protidemic depletion, increased risk of postoperative complications. In conclusion, the choice of a minimally invasive strategy finds its concrete rational in the preservation of the homeostasis of the organism by minimizing the predictable effects of a standard thoracotomy.

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Footnote

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