Mediastinal lymphadenectomy influences postoperative immune response after lung cancer surgery

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【Abstract】The aim of the study was to calculate the amount of surgical injury caused by systematic lymphadenectomy of mediastinum in patients operated on due to non–small cell lung cancer, with uneventful postoperative course. The study group consisted of 11 patients with cancer of the right lung (Group 1). The control group consisted of 12 patients with left lung cancer (Group 2). In patients with right lung cancer systematic lymphadenectomy, while in patients with left lung cancer systematic sampling was performed. Serum IL-6 and IL-1ra concentration was measured before and after surgery, and on postoperative day 1, 3, and 7, as well as in sputum at the end of surgery and in pleural fluid on postoperative day 1, by ELISA test. Peripheral blood lymphocyte (PBL) count was measured with flow cytometry. Time of surgery was higher in patients with right than left lung cancer [(154.1±31.29) vs (119.6±24.81) min; P=0.008)]. The number of resected mediastinal lymph nodes was higher in patients with right than left lung cancer [(27.6±7.6) vs (11.1±8.1); P=0.00006)]. Postoperative decrease of PBL was significantly higher in group 1 than 2 [(1.25±0.37) vs (1.75±0.64) ×10^3/μL; P=0.04)]. No significant differences were found in serum, pleural fluid and sputum concentration of IL-6 and IL-1ra between groups. Negative correlation between concentration of these cytokines in pleural fluid and number of resected mediastinal lymph nodes was found (Spearman test for IL-6: r=-0.723; P<0.001; for IL-1ra: r=-0.768; P<0.001). Number of "positive" N2 lymph nodes did not correlate with pleural fluid concentration of cytokines. Systematic lymphadenectomy of the mediastinum causes immunosuppression, as measured by decreased count of PBL and a negative correlation between number of resected mediastinal lymph nodes and concentration of cytokines in pleural fluid.

【Key words】Lung neoplasms Mediastinal lymphadenectomy IL-6 IL-1ra IL-1F3

1 Background and objectives

Systematic mediastinal lymphadenectomy is a recommended completion of radical surgical resection of lung cancer1). However, with the introduction of computerized tomography for lung cancer screening, a growing number of small pulmonary neoplasms, which could be treated with less invasive methods is observed. Minimizing surgical injury concentrates on three fields: surgical approach, extent of pulmonary resection and extent of mediastinal lymphadenectomy. The first goal was achieved by developing technique of VATS lobectomy2-4). To reach the second goal, multicenter surgical trials assessing the value of conservative pulmonary resections (segmentectomies and wedge resections) for lung cancer are organized5-8). To achieve the third goal, sentinel node technique has been investigated9), to establish in which cases mediastinal lymphadenectomy could be avoided. Avoiding
lymphadenectomy would not merely decrease the time of operation, but – even more importantly – it is believed to diminish the amount of surgical injury. Even with good availability of immunological tests, it is still difficult to establish what amount of immune response is the result of lymphadenectomy, because lymphadenectomy is not a separate procedure, but is always performed together with thoracic incision and pulmonary resection.

The aim of this study was to calculate the amount of surgical injury caused by systematic lymphadenectomy of mediastinum in patients with cancer of the right lung, comparing with surgical injury in patients with cancer of the left lung, where systematic sampling of mediastinal lymph nodes was performed.

2 Methods

Clinical data were collected prospectively from 69 patients [12 women, 57 men, age (61.8 ± 8.02) years], treated with anatomical pulmonary resections (at least lobectomy) due to lung cancer. Twenty–one patients developed complications, and in 48 the postoperative course was uneventful. Out of 23 patients with complications, 17 (74%) were operated on due to cancer of the right lung. Because anticipated immune response to lymphadenectomy was much smaller than immune response which accompanies complications, for further analysis only patients with an uneventful postoperative course were included. To avoid influence of different surgical approach and different type of anesthesia, only patients who were operated through muscle–sparing posterolateral thoracotomy and without epidural analgesia were selected. Immunological studies were performed only in patients with lung cancer of the right lung (Group 1) and in patients with cancer of the left lung who had systematic sampling (Group 2). Patients who had preoperative invasive staging more extensive than bronchoscopy and transthoracic fine needle aspiration (mediastinoscopy, mediastinotomy, thoracoscopy, Daniels procedure) within a month before curative resection, were excluded. Finally, out of the primary group, 23 patients who underwent uncomplicated resections [3 women, 20 men; age (58.3 ± 8.8) years] fulfilled inclusion and exclusion criteria for immunological studies. Sixteen lobectomies (1 left lower, 3 right lower, 7 left upper, 4 right upper, 1 right lower bilobectomy) and 7 pneumonectomies (3 right and 4 left) were performed. In all patients mediastinal nodal dissection was performed by the same surgeon (TS).

Serum IL–6 and IL–1ra concentrations were measured before surgery, at the end of surgery and on postoperative day 1, 3 and 7, as well as in sputum at the end of operation and in pleural fluid on postoperative day 1. After obtaining, venous blood and pleural fluid were cooled to 4 °C, centrifuged at a speed 2 500 rpm for 10 min, and then preserved in temperature –80 °C until further investigations. Sputum was obtained just before extubation, by washing routinely used catheter with saline. Diluted sputum was frozen at –80 °C. Before freezing, mucus was removed by centrifuging and filtering through gauze. Concentrations of IL–6 and IL–1ra were determined using enzyme immunoassay kits (Quantikine R&D Systems Europe Ltd, Barton Lane Abingdon, Oxon, UK). Immunological studies were performed with STAT FAX 2 100 device.

Degree of dilution of sputum was assessed by comparing concentration of urea in sputum and serum, both collected at the end of operation, with urease method (Olympus Diagnostica GmbH, Lismeehan, O’Callaghan Mills, Co. Clare, Ireland). Tests were performed with OLYMPUS AU400 device. The number of peripheral blood lymphocytes was measured with flow cytometry on postoperative day 1 with ACT 5DIFF Beckman–Coulter device.

Informed consent was obtained from every patient accrued. The study was approved by the local Ethics Committee.

Results were expressed as median and first and third quartile, or Mean±SD, or as number and percentage. To evaluate statistical significance of difference between preoperative and postoperative results of cytokines concentration, Wilcoxon test was used. Fisher exact test for categorical parameters was used. The differences between groups were analyzed with the Mann–Whitney U test. Computations were performed using SPSS 12.0 statistical package.

3 Results

Clinical characteristics of patients from analyzed groups are presented in Tab 1. Among analyzed parameters, time of surgery and a number of resected mediastinal lymph nodes were higher in patients with cancer of right lung. Squamous
Before surgery, number of peripheral blood lymphocytes (PBL) in the whole group, and in patients with cancer of the right and left lung was [(1.9 ± 0.6); (1.9 ± 0.4) and (2.0 ± 0.5)] × 10⁹, respectively. Differences between groups were not significant. After operation, the number of PBL was [(1.5 ± 0.6); (1.2 ± 0.4) and (1.7 ± 0.6)] × 10⁹, respectively. Patients from group 1 had lower postoperative number of PBL than patients from group 2 (P=0.04). Decrease in PBL was significant (P=0.3).

A significant negative correlation between number of resected mediastinal (N2) lymph nodes and concentration of cytokines in pleural fluid was observed in 23 analyzed patients (for IL-6: r=-0.44; P=0.04; for IL-1ra: r=-0.57; P=0.01) (Fig 4). No significant correlation between concentration of cytokines and number of resected hilar and intrapulmonary lymph nodes (N1), number of "positive" N2 nodes and number of "positive" N1 lymph nodes was observed.

4 Discussion

Measuring serum concentration of immune response mediators is a widely recognized method of quantitative assessment of the amount of surgical injury[8-10].

Mediastinal lymph node dissection, first described over 50 years ago[11,12] is a different procedure in patients with cancer of right and left lung, due to two main reasons: (1) predominant lymphatic drainage of both lungs through right paratracheal lymph nodes and (2) impaired access to paratracheal lymph nodes through left thoracotomy, due to aortic arch and its vicinity.
large branches. In patients with cancer of the left lung, systematic lymphadenectomy consists of transsection of superior pulmonary ligament and removal of all fatty tissue including lymph nodes. This procedure does not allow remove the predominant route of lymphatic drainage, which from left lung goes through right paratracheal lymph nodes. Therefore in patients with cancer of the left lung, lymphadenectomy does not influence the late outcome as much as lymphadenectomy in patients with cancer of the right lung. As a result, in patients with cancer of the left lung, systematic sampling is widely accepted, which consists of removal of 2–3 lymph nodes from stations 5 (aorto–pulmonary window), 6 (paraortic), and 7 (subcarinal), without transsection of superior pulmonary ligament, and without removal of left inferior paratracheal lymph nodes (station 4L). On the background of this study was the assumption that systematic sampling, as a less extensive procedure, causes smaller immune response than systematic lymphadenectomy, and therefore can serve as a control group in the study evaluating amount of surgical injury caused by systematic lymphadenectomy of the right mediastinum.

From the analysis of patients with complications (who were excluded from the current study) we learned that elevated concentrations of IL–6 and IL–1ra in pleural fluid on postoperative day 1 are sensitive early markers of postoperative complications. According to conclusion of that paper, negative correlation between number of resected N2 lymph nodes and concentration of these cytokines in pleural fluid (Fig 4) might be erroneously interpreted as lower risk of complications after more extensive lymphadenectomy.

Among several explanations of this negative correlation two are the most possible: ① Lymphadenectomy removes or transsects lymphatic routes which contain the lymph from lungs, where cytokines are extensively produced during surgical procedure even in uncomplicated cases, resulting in smaller leakage of lymph from pulmonary parenchyma, which includes these cytokines. By the way: in cases where
surgical injury causes especially high secretion of cytokines by pulmonary parenchyma (pneumocytes, macrophages, monocytes), concentration of IL-6 and IL-1ra in pleural fluid is rapidly elevated, preceding development of postoperative complications. 

② Removal of all fatty tissue from the mediastinum decreases the amount of loose tissue where immunocompetent cells can easily migrate after surgery, resulting in inflammatory infiltration and local secretion of cytokines.

The fact that no significant correlations were found between concentration of IL-6 and IL-1ra in pleural fluid and number of "positive" N1 and N2 lymph nodes, suggests that negative correlation between concentration of cytokines in pleural fluid and the number of resected lymph nodes was not the result of higher number of resected lymph nodes in more advanced lung cancer cases, where immunosuppression is expected.

Another symptom of immunosuppression in patients after systematic lymphadenectomy of the right mediastinum may be significant decrease of PBL after surgery. Decrease of PBL was highly significant in patients after surgery of right lung and not significant in patients after resections of cancer of left lung. This finding supports the interpretation of negative correlation between concentration of IL-6 and IL-1ra in pleural fluid and number of resected N2 lymph nodes as immunosuppression (predisposing to postoperative complications), not as decreased risk of development of postoperative complications.

5 Conclusion

Systematic lymphadenectomy performed in patients with cancer of the right lung, in comparison with patients with cancer of the left lung, does not result in elevation of IL-6 and IL-1ra concentration in serum, pleural fluid and sputum, which indicates that this procedure is not a major factor influencing changes in the immune response. Systematic lymphadenectomy is accompanied by slight immunosuppression, as measured by negative correlation between number of resected N2 nodes and by decreased number of peripheral blood lymphocytes in comparison with patients after systematic sampling. In certain cases, this immune response can tip the balance and trigger processes leading to development of postoperative complications.

Conflict of interest statement

Authors state that there were no financial or personal relationships with producers of tests or equipment used for this study, which could bias results of this study.

References


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