Original Article

Immune effects after uniportal nonintubated video-thoracoscopic operations

Tommaso Claudio Mineo[1], Vincenzo Ambrogi[1,2]

[1]Department of Surgery and Experimental Medicine, [2]Department of Thoracic Surgery, Official Awake Thoracic Surgery Research Group, Policlinico Tor Vergata University, Rome, Italy

Contributions: (I) Conception and design: All authors; (II) Administrative support: TC Mineo; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: V Ambrogi; (V) Data analysis and interpretation: V Ambrogi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Tommaso Claudio Mineo. Department of Surgery and Experimental Medicine, Official Awake Thoracic Surgery Research Group, Policlinico Tor Vergata University, Rome 00133, Italy. Email: mineo@med.uniroma2.it.

Background: We hypothesized that uniportal video-assisted thoracic surgery (VATS) under nonintubated anesthesia may have a lesser immunological impact than same procedures under general anesthesia.

Methods: Between December 2005 and October 2016, a total of consecutive 878 patients underwent VATS operations under nonintubated anesthesia. In a subset of 542 patients we assessed lymphocyte subpopulations at 1, 7 and 14 days postoperatively and matched with a control group of 106 patients who underwent uniportal intubated surgery.

Results: Global time spent in the operative room was significantly longer in intubated group (85±41 *vs.* 118±34 minutes; P=0.03). The total lymphocytes count showed a lesser drop in the nonintubated group at post-operative day 7 (P=0.04) and 14 (P=0.05) with a significant lesser reduction of natural killer lymphocytes at day 7 (P=0.03) and 14 (P=0.04). 30-day mortality (0.9% *vs.* 4.7%; P=0.04), major morbidity (9.5% *vs.* 19%; P=0.03) and hospital stay (4.2±2.8 *vs.* 6.1±2.6 days; P=0.04) were significantly lower in the nonintubated group. Survival rate in the subset of patients operated for malignant effusion was significantly higher in the nonintubated group (P=0.03).

Conclusions: Uniportal nonintubated operations demonstrated a significant lower impact on immunological response compared to the traditional procedure in general anesthesia. This impacted postoperative 30-day mortality, major morbidity and hospital stay. We also found a significant influence on long-term survival in a consistent subset of patients operated for malignant pleural effusion.

Keywords: Thoracic surgery; non-intubated surgery; video-assisted thoracic surgery (VATS)

Received: 21 December 2017; Accepted: 06 January 2018; Published: 17 January 2018.
doi: 10.21037/vats.2018.01.02
View this article at: http://dx.doi.org/10.21037/vats.2018.01.02

Introduction

It is well and consolidated belief that surgical injury may lead to transient depression of the immune function that can potentially cause infective complications as well as cancer spread (1,2). The biological basis of this statement might likely be due to both surgical and anesthesiological proceedings (3,4). Among all immunological effectors the lymphocytes represent one of the most important elements and namely, natural killer cells (CD16/CD56) play a key role against tumors and infections thank to their cytotoxic activity (5,6). General anesthesia and especially one lung ventilation combined with surgical stress and extensive tissue trauma affect negatively the response lymphocytes and natural killer population (7-9). These effects are accomplished by decreasing the basal cytotoxicity action, predisposing to post-operative alteration of wound healing processes (10), facilitating infections and increasing the risk

of tumor progression and metastases (11). On the other hand, a minimization of surgical trauma in thoracic surgery demonstrated to preserve the immune defense (12).

The increasing evolution of non-intubated thoracic surgery allowed the execution of progressively more elaborate operations in patients with different pathologies (13). Nonintubated surgery revealed a potential in reduction of inflammation (14), a better preservation of immunological function (15) compared to the traditional approaches. Our program of non-intubated thoracic surgery named the Awake Thoracic Surgery Research Group was specifically created for this purpose by one of us (Tommaso Claudio Mineo), who is still the main mentor and coordinator (16). To date, more than one thousand non-intubated procedures have been carried out in our department (13). Early operations were done under epidural anesthesia and three-port video-assisted thoracic surgery (VATS) (17) but starting from 2005, operations have been preferably accomplished through a unique thoracoscopic access under intercostal block and non-intubated anesthesia (18).

In this study our aim is to analyze the variations in the different immune patterns after uniportal VATS operations under nonintubated anesthesia compared to an intubated group that in the same period underwent similar procedures.

Methods

From December 2005 to December 2016, a total amount of 878 patients underwent uniportal VATS operations under nonintubated anesthesia. This combined approach was applied to a variety of nononcologic (pneumothorax, diffuse and bullous emphysema, pleural infection and interstitial lung disease) and oncologic conditions (pleural effusion, peripheral lung nodules and mediastinal masses) (13,18) including both minor (biopsies and wedge resections) as well as major (decortications, segmentectomies and lobectomies) operations.

Inclusion criteria for nonintubated surgery were generic indications to VATS surgery such as normal mass body index <30 kg/m^2, no imaging or clinical suspect for obliterated pleural cavity and hemodynamic stability, combined with patient's cooperation and absence of excessive anxious attitude.

Indeed, all patients released written fully informed consent after having listened, read and understood the explanations of the main details including theoretical pros and cos of nonintubated operations. In particular, the form advised that during a nonintubated procedure, surgical maneuvers might be somewhat demanding and less tolerated with the risks of hypercapnia and intolerance. Conversely, the immediate postoperative course was predicted to be smoother than that after intubated procedures given the absence of weaning-related side effects.

Technique

During the procedure patients were continuously monitored by pulse oximeter, arterial blood gases, body temperature, electrocardiogram, systemic and central venous blood pressure, bispectral index and end-tidal CO_2. A 5-mL solution of 2% lidocaine was aerosolized for 5 min, before the procedure, in order to prevent cough reflex. Furthermore, the patient inhaled O_2 during the operation through a ventimask to maintain saturation greater than 90%.

Uniportal procedures were done by intercostal block with separate infiltration of lidocaine 2% (4 mg/kg) and ropivacaine 7.5% (2 mg/kg). Intraoperative intravenous administration of benzodiazepine (midazolam 0.03–0.1 mg/kg) or opioids (remifentanil 15 μg/kg/min) allowed the patients to tolerate all of the intrathoracic phases. Unexpected anxiety or panic occurring intraoperatively were sedated without interfering with spontaneous breathing by increasing propofol (0.5 mg/kg) continuous infusion.

At the end of the procedure one 28# chest tube was collocated at the posterior limit of the surgical wound. Drinking, eating, and walking was generally allowed in the same day of surgery. Patients were discharged after radiological evidence of complete lung re-expansion, limited pleural effusion (no more than 100 mL/day), and no air leakage. Patients with protracted air leakage (>5 days) were discharged with a Heimlich valve.

Laboratory assessment

Venous blood samples were taken in the morning prior the operative session from antecubital vein, and it was repeated at postoperative days 1, 7, and 14. The Laboratory of Onco-hematology of our institution performed the immediate real-time tests without need of storage. Total lymphocytes count was assessed with a cell counter (Coulter Beckmann, MedLab, Cupertino, CA, USA). Lymphocyte-subset were analyzed with FACSCanto II esa-color flow cytometry

Table 1 Features of the two groups

Variables	Nonintubated group (n=542)	Intubated group (n=106)	P value
Age (range), years	60 [41–85]	60 [34–80]	0.1
Sex (m:f)	311:231	58:48	0.9
Procedures			
Primary pneumothorax	38	8	0.09
Secondary pneumothorax	9	–	–
Emphysematous bullae	25	2	0.8
Empyema thoracis	8	2	0.1
Interstitial lung disease	16	1	0.08
Lung volume reduction surgery	37	3	0.6
Malignant pleural effusion	225	43	0.8
Benign nodules	39	5	0.7
Malignant nodules	18	4	0.2
Lung metastases	51	13	0.1
Anterior mediastinal biopsies	72	21	0.08
Lung anatomical resections	4	4	0.05

(BD Biosciences, San Diego, CA, USA) using monoclonal antibodies specific to the cell markers. Before, samples were incubated with monoclonal antibodies and then processed with the erythrocyte lyse-wash technique (ammonium-chloride solution 1×; BD Biosciences). The identification of phenotypes of lymphocyte population was made by anti-CD3-FITC, anti-CD4-APC-H7, anti-CD8-PE-Cy7, anti-CD56(3-)-PE, anti-CD19-APC, and anti-CD45-PercPCy5.5 (BD Biosciences).

Study design and statistics

The study was designed as retrospective and approved by our Institutional Review Board, which allowed the review of all laboratories values. We were able to retrieve data about lymphocyte subpopulations for 542 patients. Clinical features of this cohort of patients are summarized in *Table 1*. Furthermore, only on observational basis we compared these data to those measured in 106 patients, who had been scheduled for nonintubated procedure in the same period but who refused this option preferring intubation and general anesthesia. Statistical analysis was performed with the SPSS software package (SPSS® 18 version, Chicago, IL, USA). Data were expressed as mean and standard deviation. Significant level was considered $P<0.05$. Non-parametric tests were prudentially preferred using Wilcoxon for within group and Kruskal-Wallis for between-group evaluations, respectively. Survival analysis was conducted with the Kaplan-Meier method and significance between group was assessed with the log rank test.

Results

As shown in *Table 1*, all main variables resulted homogeneously distributed between groups. Postoperative results of the patients are shown in *Table 2*. We did not experience intraoperative mortality. Global time spent in the operative room including induction and awake time was significantly longer in intubated group (85±41 *vs.* 118±34 minutes; P=0.03), whereas operative time was still shorter in the intubated group (68±29 *vs.* 53±41 minutes) yet not significant.

Immunological impact

Postoperative immunologic trends are shown in *Figure 1* and *Table 3*. As expected, total leukocytes count increased after surgery in both groups. The total lymphocytes count

Table 2 Features of the two groups

Variables	Nonintubated group (n=542)	Intubated group (n=106)	P value
Operative room stay time (min)	85±41	118±34	0.03
Operative time (min)	68±29	53±41	0.7
30-day mortality, n (%)	5 (0.9%)	5 (4.7%)	0.04
Major morbidity, n (%)	52 (9.5%)	20 (19%)	0.03
Postoperative pneumonia, n (%)	27 (4.9%)	13 (12%)	0.01
Air leakage (day)	3.4±2.9	4.1±2.4	0.1
Hospital stay (day)	4.2±2.8	6.1±2.6	0.04

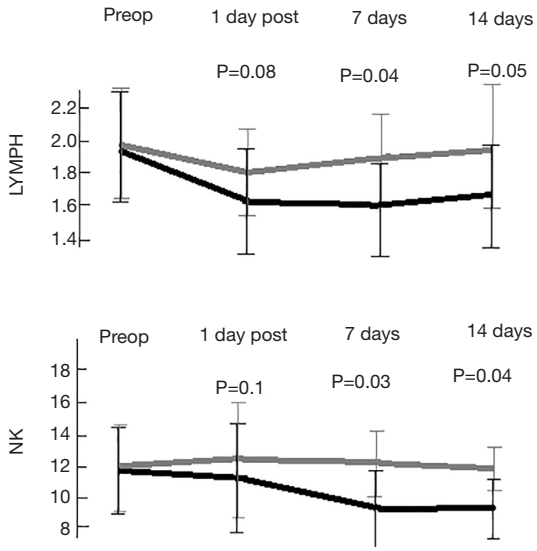

Figure 1 Mean ± standard deviations postoperative values lymphocytes subpopulations for intubated (black line) and nonintubated (gray line) patients. Between group P values at different intervals are indicated. LYMPH, lymphocytes; NK, natural killer.

showed a lesser drop in the nonintubated group in both post-operative day 7 (P=0.04) and post-operative day 14 (P=0.05), with the nonintubated group also displaying a nearly-significant more rapid restoration of the baseline value. Among the subpopulations in the nonintubated group, there was a significant lesser reduction of natural killer lymphocytes at 7 (P=0.03) and 14 (P=0.04) days following the procedure compared to the intubated group (*Figure 1*). On the other hand, the other subpopulations did not present significant difference between groups.

Morbidity

We had 5 deaths (0.9%) within 30 days from the operation, which was significantly lesser than the 5 deaths (4.7%; P=0.04) occurred in the intubated group. Major morbidity rate was significantly higher in the intubated group 52 (9.5%) *vs.* 20 (19%) (P=0.03). The favorable ratio was mainly due to the lower number of postoperative pneumonia: 27 patients (4.9%) in the nonintubated group versus 13 patients (12%) in the intubated one (P=0.01). This more uncomplicated postoperative course had an impact on mean hospital stay (4.2±2.8 *vs.* 6.1±2.6 days), which was significantly faster in the nonintubated group (P=0.04).

Long term effects in malignant effusion

We also evaluated long term survival in a consistent cohort of patients with malignant pleural effusion, which represents the vast majority of the neoplastic pathologies operated. The subset included 217 patients undergoing a nonintubated procedure and 43 patients an intubated procedure, respectively. Survival rate was significantly higher in the nonintubated group (P=0.03) (*Figure 2*).

Discussion

Lymphocytes, and mainly natural-killer cells (CD16+/CD56+), are important effectors of the immune response (5). This action largely depends on their cytotoxic activity as well as on their capability to release regulatory cytokines (6). Traditional intubated surgery (10) especially under one-lung ventilation (8,9) may create many significant side effects in the immunologic sphere decreasing basal natural-killer cytotoxicity. In addition,

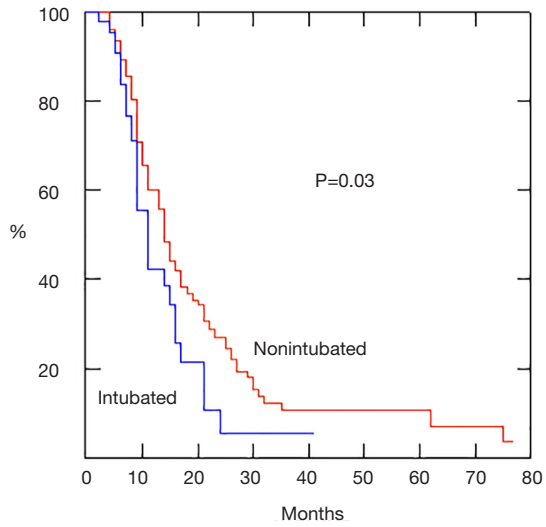

Figure 2 Overall survival calculated by the Kaplan-Meier curve of the patients with malignant pleural effusion operated with uniportal nonintubated and intubated anesthesia.

surgical stress and the extensive tissue trauma may reduce the amount of circulating lymphocytes and namely the rate of natural-killer cells (3). As a result, the impairment of the immune function may favor post-operative infections and hinder postoperative healing processes (19). Furthermore, reduced cytotoxic activity of peripheral-blood lymphocytes may increase the risk of tumor progression and metastatic spread (11). Even though lessened by the uniportal approach (20) and one-lung ventilation might evoke a cascade of many oxidative changes, eventually resulting in a compartmental release of pro-inflammatory mediators (19,21,22) including interleukin 6 (23).

As far as we know, our program of awake VATS operations is the oldest surgical program specifically created for this purpose. In many studies we demonstrated that nonintubated thoracic surgery allows a faster recovery, with shorter hospital stay and lesser economical expenses (13-18). In the present one, we found that the nonintubated

Table 3 Postoperative mean ± standard deviation dosages of lymphocyte subpopulations

Variables	Baseline	Day 1	Between-group, P value	Day 7	Between-group, P value	Day 14	Between-group, P value
Total leucocytes (n 10^9/L)							
Nonintubated group	5.74±1.45	7.92±2.43	0.1	7.14±1.37	0.08	6. 71±1.57	0.06
Intubated group	5.88±1.31	8. 16±1.53		7.87±1.69		7.54±2.02	
Total lymphocytes (n 10^9/L)							
Nonintubated group	1.97±0.27	1.81±0.24	0.08	1.93±0.27	0.04	1.95±0.33	0.05
Intubated group	1.92±0.29	1.61±0.22		1.60±0.23		1.68±0.24	
B lymphocytes (%)							
Nonintubated group	12.1±5.7	12.5±5.7	0.9	11.7±3.9	1	9.7±2.14	0.9
Intubated group	12.4±5.4	12.4±5.5		11.8±5.9		9.4±1.32	
T lymphocytes (%)							
Nonintubated group	73.4±11.1	71.0±13.3	0.06	72.6±8.9	0.05	73.1±9.1	0.07
Intubated group	70.2±9.5	67.3±16.7		62.6±6.5		68.7±11.2	
T helper/T suppressor (ratio)							
Nonintubated group	2.5± 1.1	2.4±1.2	0.9	2.3±0.7	1	2.3±1.6	0.9
Intubated group	2.3±1.3	2.3±1.3		2.3±0.9		2.2±1.2	
Natural killer (%)							
Nonintubated group	11.9±2.4	12.4±3.7	0.1	12.1± 1.8	0.03	11.4±1.0	0.04
Intubated group	11.7±2.6	11.2±2.9		9.4±2.1		9.5±0.6	

procedure can reach successful results with a significantly lower 30-day mortality and major morbidity rates. We would also remark the lower rate of postoperative pneumonia that is directly connected to bilateral lung ventilation and the lack of re-expansion after one lung ventilation (16). As a result, we reported a lesser duration of the hospital stay. At the same time, we experienced a significantly lower decrement of natural killer lymphocytes at day 7 and 14 in the nonintubated group and bilateral lung ventilation may explain this trend.

Spontaneous bilateral ventilation might have also improved the oncological outcomes. The frequent postoperative onset of undiagnosed metastases may be likely due to the rapid growth of occult metastases to the lack of immune control related to postoperative immunologic depression (6,24,25). In a previous study, we did not report significant differences in postoperative survival among patients undergoing colorectal pulmonary metastasectomy (26). This finding can be probably explained with the short sample size of the study groups. On the contrary, the positive effect of nonintubated surgery could now be visible on the larger population of patients with malignant pleural effusion.

The present study presents obvious and crucial limitations. First of all, the non-randomized nature of the two study groups and the absence of a proper propensity score approach. Second, the group allocation based on patient's preference. Third, the peculiar features of the neoplastic patients extrapolated among those with advanced disease and influenced by a so heterogeneous number of interfering factors. Fourth, the lack of similar comparison for patients with other neoplastic disease, unsuitable because of scant sample size. Fifth, the study is restricted to lymphocyte subpopulation, whereas immunological spectrum is so wide and would require the analysis of more factors.

Despite these evident flaws, we think that this observational study can provide interesting information in a consistent sample size. According to these supplemental data about immunological effect of nonintubated surgery we would endorse the diffusion of this kind of anesthesia especially in neoplastic conditions.

Conclusions

In the last decades, increasing attention has been dedicated to the importance of immune-competence in the postoperative period. Uniportal operations under nonintubated anesthesia demonstrated a significant lower impact on immunological response compared to the uniportal procedures in general anesthesia with selective intubation and one-lung-ventilation. This may have effects on both postoperative 30-day mortality and morbidity with a significant shorter hospital stay. We also found a significant influence on long-term survival in a consistent subset of patients operated for malignant pleural effusion.

Acknowledgements

This research was supported by the Italian Health Ministry (title of the project: 'Profilo genetico associato al fenotipo metastatico e alla prognosi nei tumori polmonari'). We thank so much Daniela Fraboni from the Laboratory of Onco-hematology of our institution for her precious and qualified cooperation in evaluating the blood samples.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was submitted and approved by the Internal Review Board at Tor Vergata University of Rome with the authorization code 628/15.

References

1. Meakins JL. Surgeons, surgery, and immunomodulation. Arch Surg 1991; 126: 494–498.
2. Griffis CA, Page G, Kremer M, Yermal S. Implications of immune function to anesthesia care. AANA J 2008; 76: 449-454.
3. Marik PE, Flemmer M. The immune response to surgery and trauma: implications for treatment. J Trauma Acute Care Surg 2012; 73: 801-808.
4. Whitehead T, Slutsky AS. The pulmonary physician in critical care: ventilator induced lung injury. Thorax 2002; 57:635–642.
5. Herberman RB, Ortaldo JR. Natural Killer cells: their role in defenses against disease. Science 1981;241:24–30.
6. Imai K, Matsuyama S, Miyake S, Suga K, Nakachi K. Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population. Lancet 2000; 356(9244): 1795–1799.
7. Tønnesen E, Hohndorf K, Lerbjerg G, Christensen NJ, Huttel S, Andersen K. Immunological and hormonal responses to lung surgery during one-lung ventilation. Eur

J Anaesth 1993;10:189–195.
8. Schilling T, Kozian A, Huth C, Bühling F, Kretzschmar M, Welte T, Hachenberg T. The pulmonary immune effects of mechanical ventilation in patients undergoing thoracic surgery. Anesth Analg 2005; 101: 957–965.
9. Gothart J. Lung injury after thoracic surgery and one-lung ventilation. Curr Opin Anaesthesiol 2006; 19: 5–10.
10. Kutza J, Gratz I, Afshar M, Murasko DM. The effects of general anesthesia and surgery on basal and interferon stimulated natural killer cell activity of humans. Anesth Analg 1997; 85: 918–923.
11. Lee HH, Kang H, Cho H. Natural killer cells and tumor metastasis. Arch Pharm Res 2017; 40: 1037-1049.
12. Koltun WA, Bloomer MM, Tilberg AF, AF, Seaton JF, Ilahi O, Rung G, Gifford RM, Kauffman GL Jr. Awake epidural anesthesia is associated with improved natural killer cell cytotoxicity and a reduced stress response. Am J Surg 1996;171: 68–72.
13. Mineo TC, Tamburrini A, Perroni G, Ambrogi V. One thousand cases of tubeless video-assisted thoracic surgery at the Rome Tor Vergata University Future Oncol 2016; 12: 13–18.
14. Mineo TC, Tacconi F. From "awake" to "monitored anesthesia care" thoracic surgery: A 15-year evolution Thoracic Cancer 2014; 5: 1–13.
15. Vanni GL, Tacconi F, Sellitri F, Ambrogi V, Mineo TC, Pompeo E. Impact of awake videothoracoscopic surgery on postoperative lymphocyte responses. Ann Thorac Surg 2010;90:973–978.
16. Mineo TC, Ambrogi V Efficacy of awake thoracic surgery, J Thorac Cardiovasc Surg 2012; 143: 249–250.
17. Mineo TC. Epidural anesthesia in awake thoracic surgery. Eur J Cardiothorac Surg 2007; 32: 13–19.
18. Mineo TC, Ambrogi V, Sellitri F. Non-intubated video-assisted thoracic surgery from multi to uniport approaches: single centre experience. Eur Med J Respir 2016; 4: 104–112.
19. Baker EA, El-Gaddal S, Williams L, Leaper DJ. Profiles of inflammatory cytokines following colorectal surgery: relationship with wound healing and outcome. Wound Repair Regen 2006; 14: 566–572.
20. Harris CG, James RS, Tian DH, Yan TD, Doyle MP, Gonzalez-Rivas D, Cao C. Systematic review and meta-analysis of uniportal versus multiportal video-assisted thoracoscopic lobectomy for lung cancer. Ann Cardiothorac Surg 2016; 5: 76-84.
21. Wrigge H, Zinserling J, Stüber F, von Spiegel T, Hering R, Wetegrove S, Hoeft A, Putensen C. Effects of mechanical ventilation on release of cytokines into systemic circulation in patients with normal pulmonary function. Anesthesiology 2000; 93: 1413–1417.
22. Funakoshi T, Ishibe Y, Okazaki N, Miura K, Liu R, Nagai S, Minami Y. Effect of re-expansion after short-period lung collapse on pulmonary capillary permeability and pro-inflammatory cytokines gene expression in isolated rabbit lung. Br J Anaesth 2004; 92: 558–563.
23. Mineo TC, Sellitri F, Vanni G, Gallina FT, Ambrogi V. Immunological and inflammatory impact of non-intubated lung metastasectomy. Int J Mol Sci 2017; 18, (7). doi: 10.3390/ijms18071466.
24. Ghanim B, Schweiger T, Jedamzik J, Glueck O, Glogner C, Lang G, Klepetko W, Hoetzenecker K. Elevated inflammatory parameters and inflammation scores are associated with poor prognosis in patients undergoing pulmonary metastasectomy for colorectal cancer. Interact Cardiovasc Thorac Surg 2015; 21: 616–623.
25. Abdelnour-Berchtold E, Perentes JY, Ris HB, Beigelman C, Lovis A, Peters S, Krueger T, Gonzalez M. Survival and local recurrence after video-assisted thoracoscopic lung metastasectomy. World J Surg 2016, 40, 373–379.
26. Ambrogi V, Sellitri F, Perroni G, Schillaci O, Mineo TC. Uniportal video-assisted thoracic surgery colorectal lung metastasectomy in non-intubated anesthesia. J Thorac Dis 2017; 9: 254-261.

doi: 10.21037/vats.2018.01.02
Cite this article as: Mineo TC, Ambrogi V. Immune effects after uniportal nonintubated video-thoracoscopic operations. Video-assist Thorac Surg 2018;3:4.

