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Original research

Comparison of postoperative immune function in patients with thoracic esophageal cancer after video-assisted thoracoscopic surgery or conventional open esophagectomy

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HIGHLIGHTS

- We compare postoperative immune function between VATS and conventional surgery.
- Immune parameters were compared in same group or two groups at different time.
- VATS experience less postoperative immune suppression than conventional surgery.
- VATS recover preoperative immune function more quickly than conventional surgery.

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ABSTRACT

Aim: The aim of the study was to compare postoperative immune function in patients with thoracic esophageal cancer (EC) after video-assisted thoracoscopic surgery (VATS) or conventional open esophagectomy.

Patients and methods: Medical records were retrospectively analyzed for 228 patients with thoracic EC treated at a single hospital using VATS (n = 52) or conventional open esophagectomy (n = 176). Proportions of $CD3^+$, $CD4^+$, $CD8^+$, and natural kill (NK) cells, as well as the ratio of $CD4^+$ to $CD8^+$ cells, were measured in the two groups using flow cytometry on preoperative day (PrD) 1 and postoperative days (PoD) 1 and 7.

Results: Proportions of $CD3^+$, $CD4^+$, and NK cells as well as the CD4+/CD8+ ratio decreased significantly from PrD1 to PoD1 in both the VATS and open esophagectomy groups. In the VATS group, these parameters had returned to preoperative levels (PrD1) by PoD7. These parameters in open esophagectomy group increased from PoD1 to PoD7 but also lowered significantly to PrD1 by PoD7. The proportion of $CD8^+$ cells was similar between the two groups at all time points tested.

Conclusion: Patients may experience less postoperative immune suppression after VATS than after conventional open esophagectomy, and they may recover preoperative immune function more quickly.

1. Introduction

Esophageal cancer (EC) is the sixth-leading cause of cancer-related deaths worldwide, and more than 440,000 new cases of EC are reported globally every year [1]. Esophagectomy with systematic lymphadenectomy is widely accepted as the standard treatment [2], although conventional open esophagectomy, such as the Ivor-Lewis or McKeown procedures, is associated with

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potentially severe trauma and a high rate of postoperative morbidity. Studies suggest that conventional open esophagectomy may be associated with postoperative mortality of up to 7% in patients with EC [3].

Surgical trauma can trigger a systemic inflammatory response and influence postoperative systemic immune function [4]. Conventional open surgery is associated with more severe postoperative immune suppression than minimal invasive surgery carried out using laparoscopy [5]. For example, open colorectal resection is associated with significant suppression of postoperative cell-mediated immune function, whereas laparoscopic colorectal resection is not [6]. A similar relationship between treatment invasiveness and postoperative immune suppression has been shown for patients with pulmonary malignancies [7]. Minimally invasive procedures, by helping maintain immune function, may reduce incidence of postoperative infection, shorten postoperative re-hospitalization, reduce risk of long-term tumor recurrence and improve long-term survival [8–11]. For patients with EC, a small randomized trial indicated that minimally invasive procedure could be associated with fewer respiratory infections, better acute phase s and stress response than conventional open esophagectomy [12].

Video-assisted thoracic surgery (VATS) has emerged as a much less invasive option than conventional open esophagectomy for treating patients with EC. VATS has become popular with patients and clinicians in part because it appears to offer faster recovery, less postoperative pain and better cosmesis [13]. What remains unclear is whether VATS is associated with similar or less postoperative immune suppression than open esophagectomy. This question is important to address given the risk of postoperative morbidity and mortality associated with the open procedure, as well as the fact that both VATS and open esophagectomy involve risk of cervical, thoracic and abdominal trauma.

To compare VATS and open esophagectomy in terms of postoperative immune suppression, we retrospectively reviewed outcomes from EC patients at a single large medical center treated with either procedure.

2. Material and methods

2.1. Study population

Medical records were retrospectively analyzed for patients diagnosed with thoracic EC in stages T1-3, N0-1, and M0 who were treated between January 2005 and December 2014 at the Affiliated Tumor Hospital of Guangxi Medical University, China. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Affiliated Tumor Hospital of Guangxi Medical University. To be included in our study, patients had to be (a) 20–75 years old and (b) in clinical stage I, II or III based on the 6th edition of the guidelines of the American Joint Committee on Cancer; and they had to have (c) ECOG performance status of 0 or 1, as well as (d) adequate hematological, renal, hepatic, and pulmonary function. Patients were excluded from the study if they (a) showed evidence of distant metastases or T4 stage, (b) were pregnant or breastfeeding, (c) had a history of antitumor therapy, or (d) were originally scheduled to undergo VATS but were switched to conventional open esophagectomy.

Patients were staged before treatment based on clinical examination, which included computed tomography of the neck, chest, and upper abdomen, as well as endoscopic ultrasonography (EUS) with biopsy. When necessary, positron emission tomography/computed tomography was performed to assist in staging.

2.2. Study design

Patients were assigned to VATS or the conventional open esophagectomy group. The primary outcome was postoperative immune function, measured in terms of proportions of $CD3^+$, $CD4^+$, $CD8^+$, and NK cells, as well as the ratio of $CD4^+/CD8^+$ cells. Postoperative immune function was compared within each treatment group at different time points or between the two groups at the same time point. The time points were preoperative day (PrD) 1 and postoperative days (PoD) 1 and 7. The two groups were also compared in terms of demographic and clinicopathology factors, as well as postoperative morbidity and mortality.

2.3. Surgical procedures

Open transthoracic esophagectomy was performed as right fifth or sixth thoracotomy with two-field lymph node dissection. Either intrathoracic or cervical anastomosis was performed depending on tumor location.

For VATS, three incisions were made in the upper abdomen, right transthoracic region, and right neck. Four ports with a diameter of approximately 12 mm were used to perform thoracoscopic esophagectomy [14]. Patients were placed in a supine position at the end of thoracoscopy. Laparoscopy-assisted gastric tube reconstruction was performed in this group, and anastomosis was carried out at the right neck position.

2.4. Measurement of immune cell proportions

On PrD 1 and PoD 1 and 7, we used tubes containing EDTA as anticoagulant to collect peripheral venous blood samples (2 ml). To label lymphocyte subsets, an aliquot of blood (100 μl) was incubated at room temperature for 30 min with either the combination of FITC-conjugated monoclonal antibody against human $CD3^+$ and PE-conjugated monoclonal antibody against human $CD56^+$, or the combination of FITC-conjugated monoclonal antibody against human $CD4^+$ and PE-conjugated monoclonal antibody against human $CD8^+$. Then labeled lymphocytes were analyzed by flow cytometry. All antibodies were purchased from eBioscience (San Diego, CA, USA).

Red blood cells were lysed using FACS Lysing Solution (BD Bioscience, CA, USA), and the cell suspension was centrifuged at 400 *g* for 5 min. A cell counter (MAXM-Retic; Coulter, Beckman, USA) was used to determine total leukocyte number and lymphocyte proportions.

2.5. Statistical analysis

Data for continuous variables were expressed as mean ± SD or as median (range). Categorical data were expressed as number (%). All statistical analyses were performed using SPSS 17.0 (IBM, Chicago, IL, USA). $P < 0.05$ was considered statistically significant for all analyses.

3. Results

3.1. Study population characteristics

From January 2005 to December 2014, 612 patients with thoracic EC were prospectively enrolled in the database of the Tumor Hospital of Guangxi Medical University. Of these, 228 patients were included in the final analysis based on the inclusion criteria, of whom 52 (23%) underwent VATS and 176 (77%) underwent conventional open esophagectomy (Fig. 1). At baseline, patients in the VATS group were at earlier T and N stages than patients in the open