

Evaluation of Immediate Inflammatory Response in Thoracoscopic Esophageal Resection versus Open Approach – A Prospective Study

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Rezumat

Evaluarea răspunsului inflamator imediat postoperator în esofagectomia toracoscopică versus toracotomie – studiu prospectiv

Introducere: studiile recente au demonstrat existența unui răspuns imun și inflamator după chirurgia majoră, și că acestea au un impact direct asupra ratei de morbiditate și mortalitate. În prezent, nu există modalități de predicție la care subgroup de pacienți se va dezvolta o astfel de complicație. Scopul acestui studiu a fost de a evalua dinamica proteinei C reactive (CRP), presepsinei și a procalcitoninei imediat postoperator la pacienți cu esofagectomie efectuată fie videotoracoscopic, fie prin abord deschis.

Metode: A fost efectuat un studiu prospectiv ce a inclus 27 de pacienți cu o vârstă medie de $61,48 \pm 6,80$ ani, 13 pacienți cu VATS și 14 pacienți cu abord classic. Marea majoritate a pacienților au fost în stadiul III (81%) și în toate cazurile a fost efectuat tratament neoadjuvant.

Rezultate: au fost decelate valori crescute ale CRP, presepsina și procalcitonină la ambele grupuri de pacienți cu valori semnificative mai mari în grupul operat clasic, având curbe relative similare. În 3 cazuri au fost decelate valori foarte mari ale procalcitoninei în primele 24 de ore postoperator, în absența unei complicații septice, la acești pacienți o complicație majoră a fost dezvoltată.

Concluzii: esofagectomia efectuată prin toracoscopie induce un răspuns imun diminuat chiar atunci când este asociată cu o laparotomie. Valorile postoperatori crescute ale procalcitoninei, pot fi indicatori ai dezvoltării unei complicații majore postoperatori.

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Cuvinte cheie: cancer esofagian, esofagectomie, răspuns imun, toracoscopie, VATS

Abstract

Introduction: There is an immune response after major surgery and inflammatory complications following complex surgery have a direct impact on morbidity and mortality. Currently, we do not have clinical tools to predict in which subset of patients a major complication will occur. The aim of this study was to evaluate the immediate dynamics of C-reactive protein (CRP), presepsin and procalcitonin in patients in which esophagectomy was performed either through video assisted thoracic surgery (VATS) or open approach

Methods: We conducted a prospective study on 27 patients with a mean age of 61.48 ± 6.80 years, 13 patients with VATS and 14 with open approach, most of the patients were on stage III esophageal cancer (81%) and in all cases neoadjuvant treatment was performed.

Results: There were increased levels of CRP, presepsin and procalcitonin after both arms of the study with significantly higher values for the open approach and with the same dynamic curves. In 3 cases there were extremely elevated levels of procalcitonin in the absence of a septic complication, in all cases a major complication occurred.

Conclusion: Video assisted thoracoscopic esophageal mobilization induces a less immune response, even with the association of laparotomy. An elevated postoperative procalcitonin level can be an early indicator of a major postoperative complication.

Key words: esophageal cancer, esophagectomy, immune response, thoracoscopy, VATS

Introduction

Surgery represents a controlled trauma which induces local tissue damage and together with the exposure to the external elements including the germs can induce an overexpressed inflammatory response. Also, an extensive trauma can lead to a degree of immunosuppression (1). The combination of an overexpressed inflammatory response and immunosuppression can increase the risk of infections and sepsis. Currently, there are no accurately tools to identify the subgroup of patients who will develop postoperative complications, especially infectious complications, which are harder to manage or to prevent. The incidence of postoperative inflammation varies between type of surgery, elective versus emergency surgery, trauma versus transplantation (2). With the introduction of minimally invasive surgery, there was an increased interest in evaluation of immunological response after

surgery, the rationale for this was that laparoscopic surgery reduces the magnitude of operative trauma, especially at the level of abdominal wall and during this procedure there is a smaller risk of tissue damage during mobilization and dissection (3).

One of the most studied cytokines and acute phase proteins are C-reactive protein (CRP), interleukin-6 and interleukin-8 after surgical trauma (4, 5). Procalcitonine is one of the most used and studied biomarker for the diagnosis of sepsis and it is considered to be superior to CRP (6). Those markers are more useful in order to exclude sepsis than to diagnose it and also dynamic evaluation of serum levels can give an insight regarding the response to treatment.

The levels of presepsin in free circulation may reflect de systemic inflammation and can give an insight regarding the septic patient or can be used as an indicator of early sepsis (7).

Video assisted thoracoscopic surgery

(VATS) represents a variant of conventional open esophagectomy for patients with esophageal cancer and is associated with faster recovery and less pain, nevertheless far better cosmetic results (8). The conclusions of many studies are that VATS can induce a less postoperative immune suppression and that the immune function is recovered more quickly (9).

The aim of this study was to compare the immune response after surgery in two subgroups of patients diagnosed with esophageal cancer in which surgery was performed either by open thoracotomy or VATS by evaluate de immediate postoperative levels of CRP, procalcitonin and presepsin.

Material and Methods

We conducted a prospective study that included all the patients diagnosed with esophageal cancer in which surgery was performed during 2014 and 2017 on the 1st Surgical Department of the Regional Institute of Oncology Iasi. A subgroup of patients was selected from the 1st Surgical Clinic of University Hospital "St. Spiridon" Iasi, in which a video assisted thoracoscopic approach was performed. All selected patients had a positive histopathological diagnosis of either squamocellular adenocarcinoma of lower esophagus. We excluded the patients with Siewert II and III oesophago-gastric junction adenocarcinoma and included in the analysis only the Siewert type I junction adenocarcinomas. In all patient's preoperative evaluation after the positive confirmation included contrast enhanced CT scan of the cervical, thoracal and abdominal region. Patients with advanced tumours based on the current guidelines and the multidisciplinary team decision were referred to neoadjuvant radio and chemotherapy. Functional evaluation included in all patient's pulmonary test, thoroughly cardiac tests and nutritional status evaluation. In all patients an informed consent was obtained and this study was approved by the ethics board committee.

Surgical technique for the classic McKeown

esophagectomies consisted in primary right thoracotomy and left lung blockade with complete esophageal dissection and thoracic lymphadenectomy, followed by a medial laparotomy with gastric conduct preparation and cervical incision with esophageal dissection, transection and retrograde retraction, final preparation of gastric conduct and finally cervical pull-up and anastomosis. This was accompanied by a two-field lymphadenectomy with removal of the left gastric and celiac nodes in the abdomen and the peri-esophageal and subcarinal nodes in the chest. For the patients in which the thoracic part of the surgery was performed using video assisted thoracoscopic surgery, we preferred the prone position, the same principles were respected (esophageal mobilization and lymphadenectomy). The procedure in these cases is continued in the same manner as previously described.

After the surgery all patients were referred in the Intensive Care Unit for surveillance and treatment. We collected peripheral blood and serum samples at 6, 12 and 24 hours after the surgery, and we compared the dynamics of CRP, procalcitonin and presepsin in a comparative group of patients with open and video-assisted thoracoscopic surgery.

Statistical Analysis

Descriptive statistics were computed with frequencies, means and medians and statistical analysis was performed using MedCalc v9.2.0.1. The quantitative variables were done using mean and standard deviation, the categorical variables by way of percentages. A P-value less than 0.05 was considered to be statistically significant.

Results

We included in this study a total of 27 patients, 13 patients in the minimally invasive group and 14 patients in the open group. Baseline characteristics of the included patients are shown in *Table 1*. No statistically significant differences were observed between groups in

Table 1. Characteristics of the patients included in the study, depending on the surgical approach used for esophagectomy

	VATS esophagectomy patients	Open esophagectomy patients	P-value
Age	61.75±5.36	64.13±7.38	NS
Male	10 (76.92%)	12 (85.71%)	
Performance status (ECOG scale)			NS
0	8(61.5%)	8(57.1%)	
1	4(30.7%)	4(28.5%)	
2	1(7.69%)	2(14.2%)	
Histological tumor type:			NS
Adenocarcinoma	2(15.4%)	2(14.3%)	
Squamous cell	11(84.3%)	12(85.7%)	
Tumour location			NS
Upper third esophagus	1(7.7%)	2(14.3%)	
Middle third esophagus	8(61.5%)	9(64.2%)	
Lower third esophagus and Gastroesophageal junction	4(30.8%)	3(21.4%)	
Stage TNM			NS
I	1 (7.7%)	1(7.1%)	
II	2 (15.4%)	2(14.2%)	
III	10 (76.9%)	11(78.6%)	
Total	13	14	

Abbreviations: NS - not significant, VATS - Video Assisted Thoracic Surgery esophagectomy, TNM - Tumor Nodes Metastasis, ECOG - Eastern Cooperative Oncology Group

Note: Every TNM stage includes a total of corresponding stages and substages (e.g. IA and IB) for squamous cell carcinomas and adenocarcinomas.

respect with age, sex, tumour location, histological subtype or tumour stage. In all patients neoadjuvant treatment was performed. Overall, mean age of the patients was 61.48 years, 23 patients (85.18%) had squamous type carcinoma and the other 4 cases (14.81%) had adenocarcinoma of the lower esophagus or type I Siewert tumours. Stage repartition based

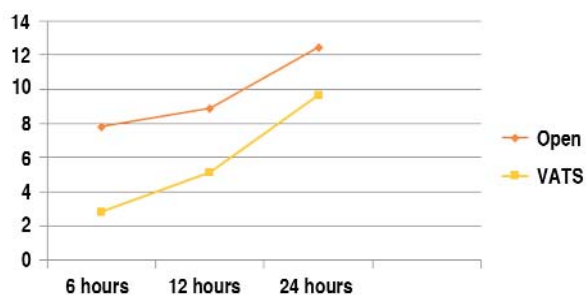
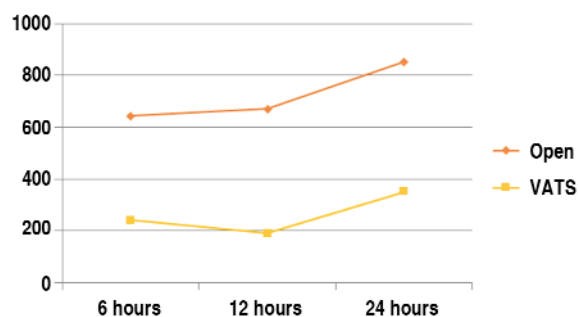

Figure 1. C-reactive protein dynamics in hours after surgery ending VATS - Video Assisted Thoracic Surgery

Table 2. Values of postoperative markers and time of sampling; mean value

	Time interval when blood samples were taken (calculated from the surgery ending)		
	6 h	12h	24 h
CRP (mg/dl)			
Open	7.26±0.79	8.90±1.38	10.12±0.83
VATS	2.82±1.79	5.14±1.11	5.24±1.23
Procalcitonin (ng/ml)			
Open	0.23±0.023	0.85±0.038	1.23±0.12
VATS	0.35±0.08	1.01±0.26	1.46±0.31
Presepsin (pg/ml)			
Open	644±61.29	670±66.23	693±68.34
VATS	241±54.01	190±52.43	178±49.65

Abbreviations: CRP - C-reactive protein, Open - open esophagectomy, VATS - Video Assisted Thoracic Surgery esophagectomy

on histopathological evaluation of resected specimens for all patients was: stage I – 2 patients (7.4%), stage II – 4 patients (14.8%), stage III 21 patients (77.7%). Individual and mean values of CRP and presepsin were significantly different in-between the two groups of patients as shown in *Table 2*. Moreover, the dynamics of analyzed markers was relatively similar, with increasing values after surgery, but with lower values for VATS group, as shown in *Fig. 1* and *2*. The most important difference was for the mean values of the CRP and presepsin which showed a more than double mean values at each time interval. There were two patients with elevated procalcitonin levels at all postoperative determinations, which required surgical reintervention and a prolonged intensive care unit treatment and surveillance.


Figure 2. Presepsin dynamics in hours after surgery ending VATS - Video Assisted Thoracic Surgery

Discussions

Currently, there are many clinical hypotheses regarding the alteration of immune response after the surgery, but one thing is clear, that there is an immunologic response to surgery, the extent of this response varies between open and minimally invasive surgery, there are currently several modalities to evaluate the immune response and the clinical impact. Some of the research studies regarding the impact on pneumoperitoneum on inflammatory response were conducted on animals showing lower levels of interleukin 6 after CO₂ pneumoperitoneum (10), a reduced level of alpha-2 macroglobulin mRNA and beta fibrinogen (11). Open surgery is associated with temporary suppression of variety of cells involved in the innate and specific immune response (lymphocytes, neutrophils, monocytes and macrophages). Moreover, interaction between cells and cellular functions are influenced and the ability to mount a positive delayed type hypersensitivity is suppressed after the surgery (1,12). In one study comparing open and laparoscopic colectomy, it was shown that the delayed type hypersensitivity after laparoscopic procedures was the same as in preoperative measurement, but after open surgery the response was smaller (13).

We used in our approach a hybrid minimally invasive esophagectomy, with the thoracoscopic mobilization of the esophagus as previously described by Collard (14), followed by laparotomy and preparation of gastric conduit. Another modification of thoracoscopic approach that we used is the prone position (15) which gives advantages regarding the visualization of esophagus, not limited by the lung and the accumulation of blood using three to four ports. The results of the cited study showed a median intensive care unit stay of 1 day, an overall mortality of 1.5%, an anastomotic leak rate of 3% with an overall morbidity of 11%.

The results of our study show that video assisted thoracoscopy induces lower levels of inflammatory markers in the immediate time after surgery. We conducted the study in the first 24 hours after surgery, because we do not

want to have a possible septic complication development that can act directly influence the serum markers values. Our results are relatively similar with another study that showed that thoracoscopic esophagectomy induces a less immune suppression and a faster immune function recovery (9). In this study the proportions of CD3, CD4 and NK cells and the CD4/CD8 ratio decreased significantly from the first preoperative day to first postoperative day in both open and thoracoscopic groups, but they returned to preoperative levels in the 7th postoperative day for the minimally approach. These parameters in open esophagectomy group increased from first postoperative day to the 7th postoperative day. One explanation was that this response might be due to inhibition of the release of immunosuppressive cytokines. The results of a sub-study of a larger randomized study comparing minimally invasive with conventional esophagectomy (3) showed significantly lower numbers of leucocytes after 1 week, without any difference in IL-6, IL-8 and CRP levels, however CRP levels peaked at 72 hours after surgery for both groups and IL-6 and IL-8 increased at 24 hours compared to baseline measurements. There were no differences between groups in terms of dynamics of cortisol, prolactin and growth hormone.

To our knowledge there is no study regarding the early dynamics of presepsin and procalcitonin levels after esophagectomy. The results of our study showed that there is a net difference in between open and thoracoscopic esophagectomy regarding serum levels of those markers. Moreover, in patients with higher levels of procalcitonin after surgery, in the first postoperative day, there is a higher chance for the occurrence of a septic complication. Basically, all the patients with higher levels of procalcitonin developed a grade 4 to 5 complication.

There are some limitations of this study regarding the smaller samples of patients and the lack of randomization. We tried to conduct a pilot study in order to see if we can extend the research area in the future. We included a consecutive series of patients with a relative

similar tumor stage and preoperative evaluation and treatment, and both surgeries were performed by the same surgical team.

Conclusions

Inflammatory response after major surgery have significant effects on morbidity, mortality and perhaps on overall survival of oncological patients. It is essential to identify the subset of patients in which such a major complication will occur in order to prevent or to early treat the patient. Although we found small differences, higher values are correlated with the occurrence of a major complication, and indicate that less surgical trauma can lead to better results. Further studies are needed in order to verify our results perhaps using larger series of patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

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