

Minimally invasive surgery in cancer. Immunological response

A.C. Bobocea¹, B. Trandafir², C. Bolca¹, I. Cordoș^{1,2}

¹Ist Thoracic Surgery Clinic, "Marius Nasta" Institute of Pneumology, Bucharest, Romania

²"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Rezumat

Chirurgia minimal-invazivă în cancer. Răspunsul imun

Chirurgia minimal invazivă a adus schimbări majore în tratamentul neoplaziilor abdominale și al cancerului pulmonar în stadii incipiente. Laparoscopia și toracosopia sunt mai puțin traumatizante decât procedurile deschise: permit recuperarea rapidă a pacientului, reducerea duratei spitalizării și evitarea cicatricilor inestetice. Deși toate aceste avantaje sunt importante, pentru pacienții oncologici un interval liber de boală crescut, supraviețuirea pe termen lung cu creșterea calității vieții sunt principalele ținte ale tratamentului chirurgical. Chirurgia deschisă produce modificări semnificative ale răspunsului imun, care au semnificație deosebită la pacienții cu neoplazii, deoarece imunosupresia postoperatorie este direct legată de complicațiile septice, diseminarea tumorală, metastazarea și scăderea supraviețuirii. Studii clinice au demonstrat că laparoscopia menajează funcțiile imune ale pacientului. Concentrațiile plasmatiche postoperatorii ale IL-6, IL-10, proteina C reactivă (PRC) și TNF- α au fost mai scăzute după rezecțiile colonice laparoscopice. Studiile clinice prospective de lobectomie prin chirurgie toracică video-asistată (CTVA) au arătat păstrarea funcțiilor limfocitelor T, revenirea rapidă a răspunsului proliferativ limfocitar la normal, concentrații mai scăzute ale PRC, tromboxan și prostaciclina. Funcția imună este influențată de extensia actului chirurgical. Chirurgia

minimal invazivă permite diminuarea răspunsului imun de fază acută comparativ cu procedurile clasice, și conservarea mecanismelor imune celulare ale organismului.

Cuvinte cheie: chirurgie minimal invazivă, laparoscopie, toracosomie, răspuns imun

Abstract

Minimally invasive surgery produced major changes in treating abdominal malignancies and early stage lung cancer. Laparoscopy and thoracoscopy are less traumatic than open surgery: allow faster recovery, shorter hospital stay, better cosmesis. Although these clinical benefits are important, prolonged disease-free interval, long-term survival with improved quality of life are most important endpoints for oncologic surgery. Major surgery causes significant alteration of immunological response, of particular importance in oncologic patients, as postoperative immunosuppression has been related to septic complications, lower survival rate, tumor spread and metastases. Clinical studies have shown laparoscopic surgery preserves better the patient's immunological function. Postoperative plasma peak concentrations of IL-6, IL-10, C-reactive protein (CRP) and TNF- α were lower after laparoscopic colonic resection. Prospective thoracoscopic VATS lobectomy trials found better preservation of lymphocyte T-cell function and quicker return of proliferative responses to normal, lower levels of CRP, thromboxane and prostacyclin. Immune function is influenced by the extent of surgical trauma. Minimally invasive surgery show reduced acute-phase responses compared with open procedures and better preservation of cellular immune mechanisms.

Corresponding author:

Andrei Cristian Bobocea, MD
Ist Thoracic Surgery Clinic
"Marius Nasta" Institute of Pneumology
Bucharest, Romania
E-mail: andrei.bobocea@gmail.com

Key words: minimally invasive surgery, laparoscopy, thoracoscopy, immunological response

Introduction

Minimally invasive surgery produced major changes in the treatment of benign and malignant diseases, especially because it limits surgical trauma (1). The laparoscopic approach has developed as a therapeutic alternative for surgery of various abdominal malignancies and the thoracoscopic procedures as first choice in early stage lung cancer (2).

Minimally invasive procedures

Both laparoscopic colorectal resection and thoracoscopic pulmonary resections limit surgical trauma and have certain tremendous clinical benefits: reduce postoperative pain, restore faster normal bowel activity, allow rapid return to current activities with significantly shorter hospitalization and better cosmetic results, when compared to conventional surgery (3). Recent studies indicate reduced rates of postoperative ileus and wound infection, preservation of pulmonary function and faster recovery after minimally invasive surgery when compared with the open approach (1).

Although these clinical benefits are important and reflect reduced surgical trauma, prolonged disease-free interval, long-term survival with improved quality of life are most important endpoints for oncologic surgery (3).

Minimally invasive surgery in cancer

The minimally invasive surgery found its way rapidly throughout the world and its utility in the surgical treatment of neoplastic diseases. From major abdominal procedures, especially in colorectal malignant diseases, to early stage lung cancer resections in general thoracic surgery, laparoscopy and thoracoscopy are now the primary line in oncologic surgery.

Operative stress may develop the basic phenomenon of local or metastatic tumor growth during surgery. Some authors were not convinced as to the applicability of minimally invasive surgery for oncologic patients and some disadvantages have been postulated, as port sites metastasis and locally recurrence of neoplastic disease came up front, trying to minimize and restrain the widespread of "minimally invasive surgery stream" (4).

However, more recent data do not support those fears, reassuring actual port-site metastasis rates to be approximately 1%. Empiric, tumor handling with laparoscopic approach is greatly diminished and so the risk of contaminating the peritoneal cavity by continuity is fairly reduced. Metastases at port sites are a reality, but that can be merely a coincidence, as other wall determinations appear (4,5).

Recurrence, when it occurs, is systemic in approximately 80% of cases. This implies tumor dissemination during surgery or the presence of micrometastatic disease at the time of resection. It is almost impossible to handle or squeeze the lung

during thoracoscopic surgery, the risk for intraoperative dissemination being reduced with this technique (5).

Anyway, all of these facts have been thoroughly infirmed by now.

Advantages

Major surgery is known to cause significant modifications of immune function and immunological response appears to correlate with the severity of trauma. These postoperative changes in immunologic function seem to be of particular importance in oncologic patients, because immunosuppression may be responsible not only for postoperative infections but also for tumor spread and metastases (6).

The most important reason for the clinical benefits of minimally invasive surgery may be that immunological response is better after laparoscopic surgery than it is following conventional surgical procedures (3).

Immunological response

Immunological response to surgery has been increasingly studied since the introduction of minimally invasive techniques. Alterations of systemic immune response are known to be proportional to the extent of injury. As laparoscopic technique reduces the magnitude of operative trauma, the immune response to will be less altered when compared with conventional surgery (7).

Comparative studies between these two techniques offer biological foundation of what is frequently described as advantages of MIS. Clinical trials have shown laparoscopic surgery preserves better patient's immunological function (8).

Means of Immune Response Quantification

The magnitude of surgical trauma after laparoscopic and open colonic resection was evaluated by examining postoperative serum values of interleukin-6 (IL-6), IL-10, C-reactive protein (CRP), and granulocyte elastase (GE) (9).

Immunologic function was assessed by a count of lymphocyte subsets (CD3, CD4, CD8, CD19, CD57) and monocytes expressing human leukocyte antigen DR (HLA-DR) (10).

Impairment of cell-mediated immune function after surgery was demonstrated by testing delayed-type hypersensitivity (DTH) responses, especially in patients treated by laparotomy, as compared with those treated by laparoscopy. DTH is an easily to perform method that assesses cell-mediated immune function (10).

Literature review

Major abdominal surgery has been shown to result in significant postoperative immunosuppression. Open surgery causes a reduction in lymphocyte and neutrophil chemotaxis, natural killer cell activity, lymphocyte and macrophage interactions. It is estimated that after major open abdominal surgery immune function is suppressed for six to nine days. Immune function is better preserved after laparoscopic procedures (11).

The following parameters have been demonstrated to remain unaltered after laparoscopic vs. open surgery: T cell mitogen response, monocyte release of tumor necrosis factor and monocyte release of superoxide ion. A temporary deficiency of CD4+ T cells ability to recognize the presented antigen could count for DTH suppression. Decreased cytokine elaboration or impaired response to cytokines by effector cells could result in diminished DTH responses (12).

Conventional procedures resulted in an increase in the total number of peripheral blood leukocytes. Postoperatively peak concentrations of white blood cells were significant lower in the laparoscopic group than the conventional group, but there were no relevant changes between the two subpopulation of lymphocytes (CD4+, CD8+). The laparoscopic group showed higher values in cytokine production of mononuclear blood cells (13).

Postoperative plasma peak concentrations of IL-6 and TNF- α were lower after laparoscopic resection (14). The cytokine production was positive correlated between IL-6 level with hypercoagulability. Only mild hypercoagulability was observed in patients who had undergone laparoscopic surgery (15).

IL-6 and granulocyte elastase are ideally suited for monitoring surgical trauma. By using these parameters, surgical trauma after laparoscopic surgery is significantly reduced as compared to the open procedure (9).

Postsurgical changes have been detected in almost all elements of both the acute inflammatory reaction and the specific immune system (16). There is evidence that suggests acute immune faze reactants have the same evolution as in the sepsis condition (17). Sepsis based experimental models clearly showed resemblance with immunologic response in acute pancreatitis (18).

Immunosuppression has been related to septic complications and a lower survival rate. In oncologic surgery, it has been suggested that if immunosuppression caused by surgery could be attenuated or eliminated, it may be possible to improve survival and decrease the incidence of postoperative complications (16).

Surgical trauma represents an addition effect of incisions, dissection and organ removal. Most often, any patient is exposed to the systemic inflammatory response which appears postoperative, typically facing relative systemic immunosuppression. As time passes, understanding the mechanisms of perioperative immunologic changes can determine precise identification of patients which have a raised risk to develop surgical complications. Once the knowledge of intimate mechanism is fully understood, intervening with pharmacologic means for attenuation of immune system inadequate response may decrease the negative effects of surgical trauma (4).

The modulation of immune response has a very important significance especially for patients undergoing laparoscopic procedures for oncologic diseases, as the protection offered by an unaltered immune system can decrease perioperative tumor spread. Even if laparoscopy is considered "minimally invasive procedure", the immune system responses are under no doubts activated, proving there is still a stress. Laparoscopic surgery

induces a smaller injury compared to the open procedures, and thus resulting less decreased immunologic changes, so less alteration of immune system response. Beyond better cosmesis and faster functional recovery, an oncologic patient treated by laparoscopic surgery benefits from this kind of immunologic advantage, which will be later seen in the development of the disease (4).

Comparing classic open thoracic procedures to VATS (video assisted thoracoscopic surgery) approaches investigators have noted significant differences: less generation of IL-6 and CRP, and reduced leucocytosis (5).

There are few immunologic reviews that have been cited concerning VATS cases. The most relevant studies that concern thoracoscopic surgery concentrate on comparisons between open procedure and VATS lobectomy. Prospective studies for thoracoscopic lobectomy found better preservation of lymphocyte numbers, T-cell function and quicker return of lymphocyte proliferative responses to normal and also that CRP, thromboxane, and prostacyclin levels are lower comparing the group that underwent open procedure vs. the VATS lobectomy group (19).

It may reflect differences in incisional trauma, important differences in intraoperative lung manipulation, as the lung is a major site for generating cytokines and local mediators. Corresponding to their systemic levels, pleural fluid samples of IL-6 levels following lobectomy raised 100 times higher. Following VATS lobectomy compared with open procedure, the increase of IL-6 pleural fluid levels measured 3 hours after surgery was significantly lower. The group that underwent VATS was less suppressed immunological as lymphocyte oxidation in this group was significantly lower (20).

Limitation of Methods

Reproduction and reviewing studies between open and minimal procedure surgery is very difficult as they have important limitations. The plasma cytokines and various immunomodulatory factors which display active tissue roles have limited levels and sampling may miss their levels and its effects. Immunomodulatory signals are affected by many various noncellular metabolism mediators like secretory circulating binding proteins, other cytokines, receptor specific factors. Comparing to that, usually isolated plasma levels of any of these circulating cytokines has merely no significance. Nevertheless, VATS studies have low numbers of patients, include multiple testing, and not prospective randomized trials (5).

Conclusions

The available evidence suggests that minimally invasive approach has effect on endocrine responses, and laparoscopic and thoracoscopic procedures show reduced acute-phase responses compared with open procedures and better preservation of cellular immune mechanisms (21,22). This effect is mainly represented by a faster recovery of HLA-DR expression, a normal function of cell capacity, and a lower increase in IL-6 plasma levels (23).

The immune function is influenced by the extent of the surgical trauma. The better results after laparoscopic and thoracoscopic surgery might be related to a better preservation of immunologic response to the minimally invasive approach. Postoperative cell-mediated immunity and cellular cytokine production was better preserved after laparoscopic than after conventional colorectal resection (24).

Even for early stage cancers, recurrence occurs. This suggests tumor dissemination occurring during surgery or that there is previous existence of micrometastatic disease at the time of resection. As handling the tumor is almost nule during minimally invasive surgery, the risk for intraoperative dissemination should be reduced with this technique. Regarding micrometastases, reduced trauma associated to minimally invasive procedures and better preservation of immune response will provide better patient immunologic status (25).

Targeting specific immunologic and stress response pathways may result in novel strategies to attenuate tumor development (26). Postoperative immune suppression follows both conventional and minimally invasive surgery, but the impact on the postoperative systemic immune response is less than that seen with the conventional approach. Laparoscopic and thoracoscopic surgery has clinically relevant advantages and it also causes less impairment of the immune system than conventional operations (27).

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