

## GENERAL INTRODUCTION

The global incidence of esophageal cancer has increased in the past two decades; in 1990, 316,000 people were diagnosed with esophageal cancer while in 2008, 482,300 new cases of esophageal cancer were recorded<sup>1,2</sup>. Surgical resection with radical lymphadenectomy—usually after neoadjuvant chemotherapy or chemoradiotherapy—is the cornerstone in the treatment of resectable esophageal cancer.<sup>3,4,5</sup>

Open esophagectomy (OE), performed through a right thoracotomy and laparotomy, puts at least half the patients at risk for developing pulmonary complications, henceforth necessitating protracted stays in intensive care units (ICU) and hospital wards leading to subsequent consequences for quality of life during convalescence. Current mortality rates of esophageal resection are less than 5%.<sup>6</sup>

Minimally invasive esophagectomy (MIE), avoiding thoracotomy and laparotomy, may reduce the rate of pulmonary infections, thereby resulting in a shorter hospital stay.<sup>7,8</sup> Because of these potential advantages, MIE should be increasingly implemented for all patients with resectable esophageal cancer according to the current principles of esophageal surgery. Concerning this implementation of MIE in daily practice, there are important issues to be addressed.

One of the most important issues is the extension of the resection. and the use of neoadjuvant therapy. There is a general consensus in literature that all esophageal cancers should be operated with a two fields lymphadenectomy, in order to obtain an adequate radical resection with negative margins (including circumferential resection margins)<sup>9-15</sup>. This can be done through a transthoracic or a transhiatal approach. However, a transhiatal approach is associated with a limited lymphadenectomy. Therefore a patient with suspected thoracic lymphadenopathy and in a relative good condition is operated by a transthoracic approach. Only for cardiac or respiratory compromised patients or elderly patients with tumors located distal in the esophagus or in the gastro-esophageal junction, a transhiatal approach after neoadjuvant therapy should be considered as an adequate procedure. Nowadays esophagectomy is usually done after neoadjuvant chemoradiotherapy or chemotherapy alone. In transthoracic minimally invasive approach adequate lymphadenectomy and radical margins should therefore be aimed for<sup>15-18</sup>.

If we focus on thoracoscopic phase of the esophageal resection, there are two thoracoscopic approaches, those performed in the lateral position and those in the prone position<sup>7,8</sup>. In contrary with the lateral thoracoscopic approach, during the prone position it is not necessary to block the lung by double intubation. Normal intubation with ventilation plus a limited insufflation of the right thoracic cavity by means of CO<sub>2</sub> (7-8 mm Hg) is enough for a good visualization. Disadvantages may arise here if quick conversion is necessary, as the patient will have to be turned to the lateral position. Also, a change of position from prone to supine is necessary for the laparoscopic phase. The Ivor Lewis minimally invasive procedure may be performed in both lateral and in prone position. However, in prone position the ipsilateral lung will need to be temporarily blocked for a mini-thoracotomy in order to facilitate anastomosis and for the retrieval of specimen<sup>19-21</sup>.

The potential advantages of MIE are a reduction of trauma, with no necessity for laparotomy and thoracotomy incisions; a better visualization; no necessity of total pulmonary block if performed in prone position; and less postoperative complications. Regarding the latter we especially expect fewer pulmonary infections; less pain; faster recovery; and a better quality of life..

These perspectives in esophageal surgery encourage surgeons to search for an evidence based implementation of the minimally invasive procedure. With regard to these important issues in treatment of esophageal cancer addressed above, three meta-analysis compared minimally invasive esophagectomy with open esophagectomy<sup>22-24</sup>. These studies indicate an increasing role for MIE with potentially fewer postoperative complications and a shorter hospital stay as compared to OE. However, randomized prospective data was lacking.

Therefore, among others, these three meta-analyses generated the initiative for a randomized-controlled trial focusing on the short- and longterm and importantly the oncological outcome of MIE to investigate the potential advantages while maintaining the current principles of open esophageal surgery.

## AIM OF THE THESIS

The aim of this thesis is to chart the current developments on operative techniques, scientific evidence and impact of minimally invasive esophagectomy for cancer.

## OUTLINE OF THE THESIS

**Part I** of this thesis focuses on different techniques of minimally invasive esophagectomy for cancer. In **chapter 1** the transhiatal route for esophageal resection with cervical anastomosis is addressed. A comparison is made between the open transhiatal esophagectomy and the minimally invasive transhiatal esophagectomy. Two cohorts of 50 consecutive patients with cancer of the distal esophagus and gastro-esophageal junction are analyzed.

In **chapter 2** the level of anastomosis is being debated for the transthoracic approach. In this systematic review the aim is to compare cervical with intrathoracic anastomosis in case of distal esophageal tumors. Beside the level of the anastomosis, there are many different techniques used worldwide to perform an anastomosis. An overview of the different intrathoracic anastomotic techniques for the minimally invasive procedure is given in **chapter 3**. In the western world this 2-stage Ivor Lewis esophagectomy becomes of more interest since the increasing incidence of distal adenocarcinoma. **Chapter 4** describes a series of 103 patients operated by the minimally invasive Ivor Lewis esophagectomy. The main focus of the study is the postoperative complications and their treatment.

**Part II** is in search for the evidence of minimally invasive esophagectomy over open esophagectomy for patients with resectable esophageal cancer. **Chapter 5** outlines the preliminary results of minimally invasive esophagectomy in a single center. The first 40 patients operated in prone position are described and formed the basis for initiating a randomized trial comparing minimally invasive esophagectomy to

open esophagectomy for esophageal cancer. The short-term results of this first randomized trial named the TIME-trial (Traditional Invasive vs. Minimally invasive Esophagectomy) are presented in **chapter 6**. A total of 115 patients were included and randomly assigned to receive either open esophagectomy or minimally invasive transthoracic esophagectomy. The one-year results are the subject of **chapter 7**. The quality of life one-year post-surgery is analyzed for both groups and attention is paid to survival, disease-free survival and late complications.

In **part III** the impact of minimally invasive esophagectomy is discussed. In **chapter 8** the immunological changes after the open and minimally invasive procedure are analyzed as a substudy of the randomized trial. **Chapter 9** evaluates the healthcare costs for both surgical procedures until 30 days postoperatively. The total costs were compared and a cost-effectiveness analysis was performed to justify the possibility of the introduction of minimally invasive esophagectomy for esophageal cancer as a standard procedure.



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