Special Report

Open surgical treatment for esophageal cancer: transhiatal *vs.* transthoracic, does it really matter?

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Introduction

Esophageal cancer has become a global health problem; it is the sixth cause of death related to malignant neoplasms around the world (1). Squamous cell cancer (SCC) and adenocarcinoma (AC) occur as a result different factors for each histology, therefore, they have different biological behavior and affect the esophagus in different anatomical sites. Surgical treatment options are diverse, depending on the anatomical site affected by the tumor, extension and the preference and experience of the surgeon, Ivor Lewis esophagectomy, McKeown esophagectomy, minimally invasive variants of Ivor Lewis or McKeown, transhiatal esophagectomy, or thoracoabdominal approaches are some of the options available.

A study that surveyed 618 esophageal surgeons on the United States and around the world (2) determined that the most used approaches are transhiatal esophagectomy in 35–44% of the cases and transthoracic esophagectomy (Ivor-Lewis) in 36–50% of the cases, with some variations depending on the location of the tumor. In 14–18% of the cases surgeons performed *en bloc* resections and minimally invasive approaches are used only in 3.9–6.5% of the cases. This variability in terms of surgical approaches is a reflection of the lack of consensus that exists in this issue (3). The extent of lymphadenectomy is defined by fields, where the first field refers to the abdominal portion, the second field to the thoracic portion below the azygos vein and the third field refers to the upper thoracic portion and cervical nodes. Most of the surgeons dissect at least the first and the second field, while a minority dissects the third field.

Since open approaches continue to be practiced more often than minimal invasive approaches, the objective of this review is to answer the questions on which of the open approaches confers greater morbidity, which one have advantage in terms of doing a more extensive lymphadenectomy and to present the evidence supporting the assertion that an extensive lymphadenectomy confers a better outcome in terms of survival; all this based on the available scientific evidence

What do the clinical practice guidelines say about surgical treatment for esophageal cancer?

The management of esophageal cancer depends on patient's and tumor's characteristics. In early stages, these neoplasms can be treated endoscopically, when it presents as a locally advanced disease, the treatment will be based on chemotherapy, chemo radiotherapy, surgery or a combination of all the above.

The National Comprehensive Cancer Network (NCCN) guidelines for the treatment of esophageal and gastroesophageal junction cancers (4) and the European Society of Medical Oncology (ESMO) guidelines for the treatment of esophageal cancer (5) establish that prior to surgical treatment it is necessary to assess the resectability of all esophageal tumors with of a tomography of the thorax and abdomen, positron emission tomography and endoscopic ultrasound. It is important the evaluation by an esophageal surgeon to determine the feasibility of performing an esophagectomy in each patient. According

to the Siewert classification (6), type I and II tumors should be treated as esophageal, while type III should be treated as gastric tumors. It is not the purpose of this review to talk about type III tumors.

Surgical procedures accepted for treatment of esophageal cancer vary. Broadly speaking, the two options are the transabdominal approach and the transthoracic approach. The recommended reconstruction will be, if possible, a gastric conduit, followed by colon or jejunum. NCCN guidelines (4) do not stand on a specific recommendation on the type of esophagectomy to be performed, while the ESMO guidelines (5) recommend performing an three field esophagectomy, Ivor Lewis type, based on the findings reported in the study from Hulscher *et al.* (7), which will be discussed later in this review.

Which of the open approaches confer greater morbidity and mortality?

Within the controversies of treatment for esophageal cancer, the morbidity and mortality of the different approaches to resection have been and continue to be one of the most controversial (8). It seems logical to think that an approach where only an abdominal incision is made will be less morbid than one in which a thoracic incision and another abdominal incision is made. The evidence has been convincing and has shown that morbidity and mortality are similar in both approaches, with some exceptions that will be discussed below. We will present the evidence divided in large cohort studies, randomized clinical trials and meta-analysis.

Large cohort studies assessing morbidity and mortality in esophagectomies

There are many cohort studies published around the world, the three largest of them were done in the United States, and their characteristics and findings will be described below.

The first cohort study was performed by Connors *et al.* (9), this paper included patients from the Nationwide Inpatient Sample (NIS) database. It included 17,395 patients that underwent esophagectomy between 1999 and 2003. Of the total number of patients, 11,914 underwent transhiatal esophagectomy and 5,481 underwent transthoracic esophagectomy. Morbidity and mortality were not different between the two groups. The overall morbidity was 50.7% (49.3% for the transhiatal group and 53.5% for the transthoracic group). The weaknesses of this study are the fact of being retrospective and not specifying data about the tumors or the indication of the esophagectomy in the patients.

Khullar *et al.* (10) used the Surveillance, Epidemiology and End Results database from Medicare (SEER) from 2002 to 2009. It included a total of 942 patients that underwent esophagectomy for AC in the distal third of the esophagus, 537 were enrolled in the transthoracic esophagectomy group and 405 in the transhiatal esophagectomy group. The complication rates (46.7% *vs.* 50.8%) and operative mortality (7.9% *vs.* 7.1%) were similar, as were the readmission rates (30.5% *vs.* 32.5%). The most common complications were pulmonary with 25% in both groups, without statistical difference. The only significant differences were the hospital stay (13 *vs.* 11.5 days) and the length of stay in the intensive care unit (7 *vs.* 5 days) favoring the transhiatal approach. Weaknesses of the study include being retrospective and including only patients older than 65 years old.

In 2017, Schlottmann *et al.* (11) analyzed the National Surgical Quality Improvement Program database (NSQIP) from the American College of Surgeons. They included 4,053 patients undergoing esophagectomy (the diagnosis was not specified) between the 2005 and 2014. They found 58.3% of the patients underwent transthoracic esophagectomy and 41.7% underwent transhiatal esophagectomy. Transhiatal esophagectomy was associated with a higher rate of surgical site and urinary infections. Transthoracic esophagectomy was associated with a higher incidence of pneumonia and bleeding requiring transfusions. The anastomotic leak rate was similar with 7.6% for transhiatal esophagectomy and 9.4% for transthoracic esophagectomy with no difference in mortality. The weaknesses of this study are its retrospective nature and because it is a national database, concise data of the patients' surgical indication were not obtained.

Randomized studies assessing morbidity and mortality in esophagectomies

Randomized clinical trials comparing transhiatal esophagectomy with transthoracic esophagectomy agree that pulmonary complications are higher in transthoracic esophagectomy, as well as the length of stay in intensive care units appear to be higher in patients undergoing transthoracic esophagectomy (7,12-15). Other complications such as surgical site infection or pneumonia do not have a significant difference. Omloo *et al.* (16) did

not report the morbidity of the surgical treatment in their published study.

Meta-analysis

Three meta-analyses have been performed to compare the results of transhiatal esophagectomy versus transthoracic esophagectomy. Boshier *et al.* (17) included 52 studies and 5,905 patients, Hulscher *et al.* (18) included 50 studies and 7,584 patients and Wei *et al.* (19) included 8 studies with 1,155 patients. The three studies agree on the conclusions, transthoracic esophagectomy has greater pulmonary morbidity and longer stay in the intensive care unit compared with transhiatal esophagectomy. Perioperative mortality does not have a statistically significant difference.

What is the better approach for an extensive lymphadenectomy?

Regarding the topic of lymphadenectomy through different surgical approaches, the deduction that can be made is that a limited approach such as a transhiatal esophagectomy will have a diminished number of lymph nodes dissected compared to having an extended field, as in the case of transthoracic. To analyze this hypothesis we will present the data obtained from the following studies.

Cohort studies assessing extent of lymphadenectomy

Not all the cohorts conducted with the United States databases describe the extent of lymphadenectomy obtained in the patients included in their analysis (9,11,20). The only cohort that describes this variable is the one performed by Khullar *et al.* (10) where it was found that the average difference between lymphadenectomy performed with the two different techniques was 2 lymph nodes more in transthoracic esophagectomy (11 lymph nodes) compared to transhiatal esophagectomy (9 lymph nodes) (P=0.003).

Randomized studies assessing extent of lymphadenectomy

Randomized clinical trials describing the extent of lymphadenectomy will be described in detail. The rest of the randomized trials comparing transhiatal and transthoracic esophagectomies (13-16) do not describe their finding on this issue.

Hulscher *et al.* (7) published in 2002 a randomized clinical trial that included 220 patients with gastroesophageal junction AC classified as Siewert I and II tumors and treated with transhiatal esophagectomy (106 patients) or transthoracic esophagectomy (114 patients). Lymphadenectomy in patients treated with transthoracic esophagectomy was statistically greater compared to those treated with transhiatal esophagectomy (31±14 *vs.* 16±9 nodes).

In 2006 Sasako *et al.* (12) conducted a randomized clinical trial in Japan that included 167 patients diagnosed with AC of the gastroesophageal junction. The tumors were classified as Siewert II and III types and were randomized to be treated either with transthoracic or transhiatal surgery. The number of lymph nodes dissected for the transhiatal group was 68 [14–147] and for the transthoracic group was 60 [16–160]. They did not find a significant difference in overall or disease-free survival. It should be noted that these patients had tumors of the distal esophagus or the cardia, as an important difference compared with the clinical trial conducted by Hulscher *et al.* (7).

It is important to mention that unlike the cohorts based on SEER, NSQIP and NIS (9-11,20), patients included in these randomized clinical trials were diagnosed with esophageal cancer, this could be the reason for increased number of lymph nodes obtained in the lymphadenectomy in the randomized studies compared to the cohort studies.

Meta-analysis

Hulscher *et al.* (18) do not include data comparing lymphadenectomy between the two approaches. Boshier *et al.* (17) found that four of the 52 studies that were included in their analysis adequately reported the lymphadenectomy results of the patients. Transthoracic esophagectomy had an average of eight more lymph nodes compared to transhiatal esophagectomy (P=0.02; 95% CI, 1–14), although heterogeneity was significant (P<0.001, I^2=94%), and finally Wei *et al.* (19) reported in their analysis 4 articles describing lymphadenectomy (2 randomized clinical trials and 2 nonrandomized studies). In the individualized analysis of both types of studies (randomized and nonrandomized) there was no statistically significant difference in the number of resected nodes.

Effect of adjuvant treatment on survival and lymphadenectomy

It is well known that surgical resection as monotherapy in esophageal cancer was the gold standard a long time ago, nowadays its usefulness is questionable. Chemotherapy

and neoadjuvant radiotherapy play a very important role; this was demonstrated in the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS), where chemo and radiotherapy plus surgery were compared to surgery alone for the treatment for esophageal cancer. In this study, it was observed that the overall survival was 49.4 months for patients with neoadjuvant therapy plus surgery compared with 24 months in patients who underwent surgery alone (21). With this overwhelming evidence, it was postulated that esophagectomy as initial treatment should be proposed to patients with T1N0M0 lesions and T2N0M0 tumors in some hospitalary centers. All patients with T3 tumors and some patients with T4a tumors should undergo neoadjuvant chemo radiotherapy.

Adjuvant treatment with chemoradiotherapy has also been subject of multiple research studies. Castoro *et al.* (22) performed a prospective study where they included 402 patients with locally advanced esophageal tumors. It compared patients who received neoadjuvant treatment with 5-FU a platinum and radiotherapy plus esophagectomy against those who were treated with surgery alone. Staging was performed prior to treatment with chest tomography, endoscopic ultrasound and in some patients with positron emission tomography. It is an interesting finding that in the pathology examination, it was observed that there were significantly fewer lymph nodes affected in the patients who received neoadjuvant treatment compared to those who did not.

The Will Rogers effect in surgical treatment of esophageal cancer: does lymphadenectomy really confers a better survival to esophageal cancer patients?

The Will Rogers effect in medicine is well known. Comedian and American actor who was characterized by his political jokes, Will Rogers expressed that "When the habitants of Oklahoma moved to California, they raised the average of intelligence in both states" (23). Mathematically, this could be if it is explained in the following way: if the average value of a variable is higher in one population than in another (in this case, the intelligence of Oklahoma subjects compared against the intelligence of California subjects) subjects with a value below the average that move from the population with the highest average value to one with a lower average value will increase the mean values in both populations. In medicine, specifically in oncology it is known as stage migration.

To talk and establish an opinion about lymphadenectomy in esophageal cancer, it is necessary to remember the dissemination pathways of this neoplasm. The loco regional growth of esophageal cancer is characterized by extending into the submucosal layer, invading at the beginning regional lymph nodes and then spreading in distant lymph nodes and organs.

The main routes of dissemination are direct extension, lymphatic and the hematogenous. Speaking specifically of lymphatic spread, the vast submucosal lymphatic vessels predisposes to early spread of the disease. There are positive lymph nodes in 10% of patients with tumor limited to the mucosa (T1) and in 38% to 60% of patients in whom the tumor reached the muscularis propria (T2). The lymphatic drainage of the cervical esophagus drains to the supraclavicular and jugular lymph nodes. The proximal thoracic esophagus neoplasms spread through mediastinal lymph nodes, paraesophageal, peritracheal, periaortic, and celiac trunk in up to 40% of cases. The distal esophagus neoplasms involve the celiac trunk and perigastric lymph nodes in more than 50% of the cases. The incidence of lymph node involvement in the neck in patients with tumors in the middle or distal third of the esophagus is as high as 20% to 30%.

All of the above would suggest that lymphadenectomy plays a fundamental role in the treatment of esophageal cancer patients, and in a certain way it does. We will now analyze the role of lymphadenectomy in survival.

In a retrospective study conducted by Peyre *et al.* (24), where they included 2,303 patients with diagnosis of esophageal cancer (1,381 with AC and 922 with squamous cell carcinoma) from nine international centers who underwent esophagectomy with an R0 resection, it was observed that the mean number of resected lymph nodes was 17 [interquartile range (IQR) 10–29]. The 5-year global survival was 40% and the Cox regression analysis showed that the number of resected lymph nodes was an independent predictor factor of survival ($P<0.0001$). This benefit was observed with a resection of at least 23 lymph nodes. Weaknesses of this study include its retrospective nature and the fact that none of the patients included in the analysis received neo or adjuvant chemotherapy.

On the other hand, Lagergren *et al.* (25) analyzed a prospective cohort from 2000 to 2014 of esophageal cancer patients undergoing esophagectomy with lymphadenectomy. A total of 606 patients were included, the extension of lymphadenectomy was not statistically associated with disease related mortality or mortality from any other cause. Those patients with the highest number of resected nodes

(21–52 nodes) had no reduction in mortality at 5 years compared with those with the lowest number of resected nodes (0–10 nodes) (HR 0.86; 95% CI, 0.63–1.17). A higher number of metastatic lymph nodes and a higher positive lymph nodes/negative lymph nodes ratio was associated with an increase in mortality.

Another study that we consider relevant to mention is the one conducted by Koen Talsma *et al.* (26), in which the same patients included in the CROSS study were included, in this work, the authors found in the Cox multivariate analysis that the number of resected lymph nodes in those patients who underwent esophagectomy only had a positive impact on survival (HR 0.76 for every 10 additionally resected nodes P<0.01), while those patients that received chemoradiotherapy and surgery did not have a better survival associated with lymphadenectomy (HR 1.00, P=0.87).

From these studies it could be concluded that a more extensive lymphadenectomy helps to identify patients with occult ganglion metastases in whom the prognosis is probably better than those with evident nodal disease. It is necessary to carry out randomized studies to test the hypothesis that extended lymphadenectomy confers a better survival to patients with esophageal cancer.

Conclusions

Open surgical treatment for esophageal cancer continues to be essential in the therapy of patients with esophageal cancer. Morbimortality rates are comparable between transhiatal and transthoracic approaches. Lymphadenectomy tends to be more extent in transthoracic approaches although its benefit remains in doubt, since it could be effect of stage migration. Treatment modality and lymphadenectomy should be individualized in each patient.

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Footnote

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

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