

# Mediastinal lymphadenectomy for esophageal cancer: Differences between two countries, Japan and the Netherlands

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## Abstract

Extent of mediastinal lymphadenectomy during esophagectomy is clearly different between two representative countries of the Eastern and Western world, such as Japan and the Netherlands. In Japan, a clear policy is the standard complete two- or three-field type of lymphadenectomy whereas, in the Netherlands, a limited form is usually carried out. Reasons for these differences can be found in the different types of tumor, 80% of adenocarcinomas in the West and almost 95% of squamous cell cancer in Japan. Moreover, location of the tumors, distally located in the Netherlands whereas, in Japan, the majority are located in the middle and proximal thoracic esophagus. Also, type of neoadjuvant therapy, namely chemoradiotherapy in the Netherlands, and chemotherapy in Japan, are different. Arguments for more extended mediastinal lymphadenectomy are currently challenged in the West, first by the systematic use of chemoradiotherapy as neoadjuvant therapy and, second, the retrospective analysis of large data. According to two studies, the importance of extended lymphadenectomy is shown to be relative and less clear, especially in esophageal adenocarcinomas after neoadjuvant therapy. International efforts such as the TIGER study will help to standardize and find a relationship between the type and location of esophageal cancer, use of neoadjuvant therapy, extent of lymphadenectomy and survival.

## KEYWORDS

clinical-malignant, east vs west, esophagus, mediastinal lymphadenectomy

## 1 | INTRODUCTION

There is no European consensus concerning mediastinal lymphadenectomy during esophageal resection for cancer. This is despite the rapid change of tumor type (more adenocarcinomas), located

principally in the distal esophagus and esophagogastric junction (EGJ). This also ignores advancements in the increased use of neoadjuvant therapies, especially chemoradiotherapy, and the increased use of different types of minimally invasive esophagectomy (MIE). All of these changes have influenced the extent of mediastinal lymphadenectomy in Europe, thereby warranting consensus and a uniform policy. In this article, we point out the significance of these changes and discuss the rationale of the current approach.

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## 2 | WHAT ARE THESE CHANGES, ESPECIALLY IN NORTHERN EUROPE?

Lymphadenectomy has two aims, first to provide a therapeutic survival benefit and, second, to achieve accurate staging of the tumor. Traditionally, lymph node status (and lymphadenectomy) was considered an important parameter of stage in esophageal cancer (EC) and an independent predictor of survival. Distribution of metastatic lymph nodes (LN) may vary with different factors such as tumor location, tumor histology and biology, tumor invasion depth, length of the tumor (stage) and use of neoadjuvant therapy.<sup>1</sup> Surgical strategy depends on the distribution pattern of nodal metastases, but consensus on the extent of lymphadenectomy differs worldwide.<sup>2,3</sup>

## 3 | WHAT ARE THE DIFFERENCES IN ESOPHAGEAL CANCER BETWEEN THE NETHERLANDS AND ASIA?

There are several important differences: (i) the incidence is higher in Japan (more than two-fold higher); (ii) the type of tumor is different: in the Netherlands (NL) and other countries of North Europe, the rate of esophageal adenocarcinoma (Adc) is steadily increasing in incidence to almost 80% of all esophageal cancers (squamous cell cancer [SCC] remains at 19.4%), whereas in Japan, the rate of SCC is 93%, and Adc accounts for only 2.5%; (iii) in NL, distally located EC and esophagogastric junction (EGJ) tumors account for 86.5%, whereas in Japan, tumors located in the upper and middle esophagus account for more than 65%.<sup>4,5</sup>

Furthermore, in Japan, there is an active screening program for esophageal and gastric cancer whereas in the Netherlands and in the rest of Europe this program does not exist.<sup>6</sup>

## 4 | INCREASE OF ESOPHAGEAL ADENOCARCINOMA

In the Netherlands, the rise of adenocarcinoma significantly started during the middle of the 1990s and has progressively increased almost fivefold; this holds especially for male patients and clearly less so for female patients.<sup>7</sup> Factors of influence for these changes may be an increase in obesity, gastroesophageal reflux disease (GERD), alcohol abuse and smoking.<sup>6</sup> These factors have favored the appearance of Barrett's esophagus (BE). In NL, nearly one-third of patients with EC have a body mass index (BMI) of more than 30. In Japan, the majority of patients with SCC have a lower BMI.

## 5 | NEOADJUVANT THERAPIES

The neoadjuvant therapy of choice in NL and in the majority of the countries in continental Europe is chemoradiotherapy (CRT) according to the CROSS trial (neoadjuvant chemoradiation followed by

surgery vs surgery alone for patients with adenocarcinoma or squamous cell carcinoma of the esophagus) scheme for stages II and III<sup>8</sup>; whereas in Japan, neoadjuvant chemotherapy alone (JCOG9907) may be used for the same stages.<sup>9</sup> The MAGIC trial (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) scheme of therapy is used in the UK and Ireland for stages II and III, and also in other countries for type 2 Siewert EGJ tumors.<sup>10</sup> In Japan, the use of adjuvant therapy after surgery is broadly used.<sup>11,12</sup>

## 6 | TYPE OF LYMPHADENECTOMY IS ALSO DIFFERENT

In the Netherlands, the majority of esophageal surgeons carry out the so-called two-field lymphadenectomy in different extensions, never the total mediastinal lymphadenectomy as done in Japan, where the three-field lymphadenectomy is currently used for upper and middle SCC.<sup>3</sup>

The rationale for these differences is based on the histological type of tumor and the different locations in which the majority of tumors are found, being mainly the lower third of the esophagus in NL and Western Europe. For a proper understanding, we consulted the studies carried out in 1994 by Akiyama et al.<sup>13</sup> on thoracically located SCC. The authors observed that any SCC in the thoracic location can metastasize to three areas (cervical, mediastinal and abdominal along the celiac trunk) although in different percentages. However, in the classical study of Siewert et al. in 1999 regarding EGJ tumors and, according to this classification, they showed that type 1 will metastasize supracarinally in only 5% of patients and subcarinally in 10%, whereas types 2 and 3 do not metastasize supracarinally and only metastasize subcarinally in a low percentage (1%) of patients.<sup>14</sup>

### 6.1 | Different types of mediastinal lymphadenectomy

In 1994, and updated in 2003, the International Society for Diseases of the Esophagus (ISDE) defined different types of mediastinal lymphadenectomy currently still in use: (i) standard: lymphadenectomy up to the subcarinal lymph nodes; (ii) extended type: also includes paratracheal lymphadenectomy on the right side; (iii) total mediastinal: including both paratracheal and both recurrent nerves lymph nodes; and (iv) three-field lymphadenectomy.<sup>15</sup>

### 6.2 | What do we do about the type of mediastinal lymphadenectomy globally?

In 2015, the European Society of Esophageal Diseases (ESDE) organized an inquiry (unpublished), inviting 57 esophageal surgeons worldwide to confer on different subjects such as: the classification used for EC, the use of neoadjuvant therapy, and the extension of lymphadenectomy for Adc and SCC including the three types of EGJ tumor according to the Siewert classification.

The conclusion of this inquiry was that in Europe no consensus existed on the preferred classification system for EC, neither on the use of neoadjuvant therapy for both SCC and Adc, nor on the extent of lymphadenectomy (abdominal and mediastinal) in the different EC situations. However, in Japan, clear guidelines exist for all these points,<sup>4</sup> hence a stark difference.

## 7 | EVOLUTION OF ESOPHAGECTOMY IN THE NETHERLANDS (AND EUROPE)

Some 15 years ago, the 5-year survival rate of resected EC patients in Europe was only around 25%;<sup>16</sup> the transhiatal approach was used in 70% of all esophageal resections; a limited two-field mediastinal lymphadenectomy was carried out through the right transthoracic approach; the esophageal resections were not centralized in high-volume centers and mortality was around 10% with a hospital stay of 21 days on average.

Nowadays, the 5-year survival rate in centralized high-volume centers is around 45% (majority of patients have stage III), mortality is 3.5%, hospital stay is 10 days, esophageal resections are centralized in high-volume centers, neoadjuvant therapy is given in stages II and III; and MIE is implemented in 85% of patients with EC.<sup>5,17</sup> Moreover, registration of all resected patients is (anonymously) obligatory with a verification system and special care is paid to the quality of resections per center.<sup>5</sup> Moreover, the Dutch use the American Joint Committee on Cancer (AJCC) classification, at present, the 7th edition.<sup>18</sup>

## 8 | WHAT ARE THE REASONS FOR IMPROVEMENT IN SURVIVAL OF EC IN THE NETHERLANDS?

Four Dutch studies show how improvements in survival of EC can have worldwide implications:

1. The HIVEX trial comparing the transhiatal versus the transthoracic approach for distal and EGJ tumors in the era before the implementation of neoadjuvant therapy.<sup>16,19</sup>
2. Use of CRT according to the CROSS trial concerning the use of neoadjuvant therapy.<sup>8,17</sup>
3. Distribution of lymph nodes in EGJ tumors.<sup>20</sup>
4. Use of minimally invasive esophagectomy, the TIME study that compared total transthoracic MIE with the open procedure.<sup>21–23</sup>

### 8.1 | The HIVEX trial

Long-term follow up of the HIVEX trial (extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus) has indicated that for Siewert tumors type 1, the transthoracic approach has advantages for survival when compared with the transhiatal route; whereas for Siewert

type 2 tumors, there are no survival differences between the two approaches. Moreover, the overall survival rate in patients with one to eight metastasized lymph nodes is better using the transthoracic approach than with the transhiatal approach, although it should be noted that if the number of affected nodes exceeded this number, then no differences in survival can be found between the two approaches.<sup>16,19</sup>

### 8.2 | The CROSS trial

According to the CROSS study, neoadjuvant use of CRT has important diffusion and application worldwide. In this randomized controlled trial, there were two arms: the first one was treated with neoadjuvant CRT (paclitaxel and carboplatin on days 1, 8, 15, 22 and 29 and radiotherapy (41.4 gray) followed by surgery (transthoracic or transhiatal) after 6–8 weeks after completion of the neoadjuvant therapy; and the second arm was treated directly by surgery.

Pathological complete response rate was 29% of all primary tumors, being 23% in Adc and 49% in SCC. Furthermore, there were also fewer total numbers of resected nodes and resected positive nodes after CRT followed by surgery than when compared to the group of patients who had surgery alone.<sup>8</sup>

In the long term, it is clear that the total group of patients treated by CRT followed by surgery had a progression-free survival rate of 40% vs of 25% in the untreated group. If the two groups are split into both types of cancer, we observe that SCC treated with neoadjuvant therapy shows an important superiority in survival rate compared with the surgery-alone group (60% vs 28%), whereas for Adc this difference was more limited but was still statistically significant (42% vs 28%).<sup>17</sup>

### 8.3 | Distribution of affected supracarinal lymph nodes in EGJ adenocarcinomas

Using an extensive cohort of patients with EGJ tumors, Parry et al. compared lymphatic dissemination in types 1 and 2 according to Siewert. They found that in type 1, 10.4% of affected LN were located supracarinally, 1.5% in the aorta window and almost 15% subcarinally; whereas in type 2, those located supracarinally were only 0.8%, in the aorta window, 1.7%, and those located subcarinally almost 10%. Moreover, the group of patients with affected LN supracarinally located had a worse prognosis with a survival rate less than 10% after 5 years.<sup>20</sup>

This means that for Adc Siewert type 1 and for Adc located in the thoracic esophagus, transthoracic extended or total lymphadenectomy of the mediastinum will need to be carried out after neoadjuvant therapy, whereas for Siewert type 2 only a standard, more limited mediastinal lymphadenectomy up to subcarinal LN should be sufficient.

The TIGER study is a significant attempt to establish consensus on standardizing the type of lymphadenectomy for every specific esophageal tumor. In this study, all lymph node stations will be excised and separately sent for pathological examination. Additional analysis is aimed at identifying patterns of metastases in relation to

tumor location, tumor histology, tumor invasion depth and neoadjuvant therapy, thereby providing a roadmap for optimal lymphadenectomy based on its characteristics (Clinicaltrials.gov, trial number NCT03222895).

#### 8.4 | Transthoracic open versus minimally invasive esophagectomy

The TIME study constituted a multicentric randomized trial that compared the total MIE approach carried out by thoracoscopy in the prone position and laparoscopy with the standard approach carried out by posterolateral right thoracotomy and laparotomy followed by cervical (McKeown three-stage) or intrathoracic anastomosis (Ivor Lewis two-stage procedure). Included patients had stages 2 and 3 with intrathoracic or EGJ tumors (Siewert types 1 and 2) after neoadjuvant therapy and were treated in five experienced European centers.

The first aims of the study were postoperative respiratory infection at 2 weeks and in-hospital stay. Secondary aims were perioperative and postoperative data including quality of life (QoL) studies and oncological data after 1 and 3 years after operation. Short-term outcome was in favor of MIE concerning: (i) fewer respiratory infections (pneumonia) (9% vs 29% after 2 weeks and in-hospital stay 12% vs 34%); (ii) shorter hospital stay (11 vs 14 days); (iii) QoL scores being better at 2 weeks concerning pain (EORTC and visual analog scale [VAS]) and talking ability; (iv) whereas the pathology reports were similar for the two groups having R0 of 95% with the same number of resected LN.<sup>21,22</sup>

Moreover, technical complications, including anastomotic leakage were not different between the two groups. After year 1 and year 3, oncological data—including overall and disease-free survival—was similar between the two groups, entailing a better QoL after 1 year in some scores, such as physical condition and pain, thereby indicating that avoiding thoracotomy is an important advantage of total MIE.<sup>22,23</sup> Furthermore, these data, with limitation of power of this study for this analysis, show that MIE is an oncologically safe approach.

Based on these studies, surgeons in NL give neoadjuvant CRT in stages 2 and 3 followed by MIE as a first procedure for resection of EC. Concerning the area of anastomosis, 50% are intrathoracic (Ivor Lewis procedure, and the other 50% are cervical anastomosis), although a shift towards more intrathoracic anastomoses is observed.<sup>5</sup>

### 9 | CHALLENGING THE OBJECTIVE RULES

Nonetheless, these objective unwritten rules have been challenged in the last 5 years by two remarkable studies: one on the importance of lymphadenectomy after neoadjuvant chemoradiotherapy (the CROSS study) and the other on the outcome of retrospective large data on esophageal cancer.

Talsma et al. analyzed the data of LN after the CROSS study and found that the total number of resected nodes was significantly

associated with survival only for patients in the surgery-alone arm whereas after CRT the number of resected nodes was not associated with survival. These data importantly question the indication for maximization of mediastinal lymphadenectomy after CRT.<sup>24</sup>

Lagergren et al. retrospectively studied a series of esophageal resections between 2000 and 2012 at a large referral center in the UK. They analyzed 606 patients, the majority of patients had Adc, being 83.5% resected by transhiatal or transthoracic approaches. They studied the extent of lymphadenectomy in relation to all-cause and disease-specific 5-year mortality rates. Four groups were assembled according to nodes resected: 0-10, 11-14, 15-20 and 21-52 LN. General survival rate was 47% after 5 years.<sup>25</sup>

Mediastinal lymphadenectomy was not statistically associated with all-cause or disease-specific mortality. Patients with 21-52 nodes removed did not show a statistical difference in all-cause 5-year mortality compared with those in the lowest group of 0-10 nodes. The authors concluded that the extent of lymphadenectomy during surgery for EC might not influence the rate of 5-year all-cause or disease-specific survival.<sup>25</sup>

These results challenge the current clinical guidelines. Based on these studies, many European esophageal surgeons may think that mediastinal lymphadenectomy is important for staging only and not for patient survival. Consequently, they may carry out a limited form of mediastinal lymphadenectomy, especially in distal Adc and EGJ tumors after neoadjuvant therapy. This, again, causes diversity in type of lymphadenectomy carried out in the Netherlands.

### 10 | WHAT WE DO DIFFERENTLY IN JAPAN AND THE NETHERLANDS REGARDING EC?

In Japan, upper and middle thoracic SCC constitute 65% of all EC whereas in NL the numbers are approximately 12.3% (SCC 75% and 25% Adc). Tumors in upper and middle thoracic locations mostly metastasize to cervical and high mediastinal areas. Therefore, in Japan, for stage 2 and 3, surgeons advise the use of neoadjuvant chemotherapy followed by three-field lymphadenectomy.<sup>4</sup> However, in Europe, for patients with these tumors, neoadjuvant CRT or chemotherapy followed by total or extended two-field lymphadenectomy is done. Regarding lower thoracic localized EC, in Japan, 24.2% are all SCC, whereas in the Netherlands, 60% of EC are localized in this region (being 85.3% Adc and 14.6% SCC).<sup>4,5</sup> Concerning these lower thoracic cancers, in Japan neoadjuvant chemotherapy is used in stages 2 and 3, being the extension of mediastinal lymphadenectomy under discussion: two-field is the rule, three-field lymphadenectomy is exceptional, because LN metastasis in the cervical area is clearly less frequent. In Europe, neoadjuvant CRT followed by resection (Ivor Lewis approach is increasingly used) with standard or extended mediastinal lymphadenectomy is used.<sup>4</sup>

In the Netherlands, EGJ tumors are increasingly important, being 24% of all EC (involving Siewert types 1 and 2 adenocarcinoma in 95.7% of all

tumors, the rest SCC at only 4.3%). However, in Japan, only 4.5% of SCC are "abdominally" located and less than 3% of all EC are Adc.

Concerning neoadjuvant therapy, surgeons in Japan use chemotherapy, whereas surgeons in Europe give CRT or chemotherapy for Siewert types 1 and 2.

Definitions for EGJ tumors also differ between Europe and Japan. In Japan, esophagogastric junction is defined as a tumor localized in an area within 2 cm above and below the EGJ junction. Also, esophagogastric junction cancer (abdominal esophageal carcinoma) has its center located in this region.<sup>4</sup> In Europe, the AJCC 7th edition defines this tumor as including cancers whose epicenter is in the distal thoracic esophagus, esophagogastric junction or within the proximal 5 cm of the stomach (cardia) that extend into the esophagogastric junction or distal esophagus. Seen in this way, types 1 and 2 are considered as esophageal cancers whereas type 3 is gastric.<sup>18</sup>

Treatment in the Netherlands for Siewert 2 is commonly neoadjuvant chemotherapy or CRT in stages 2 and 3 followed by two-stage Ivor Lewis or transhiatal esophagectomy, whereas for Siewert 1, CRT as neoadjuvant therapy in stages 2 and 3 followed by a two- or three-stage transthoracic approach or transhiatal approach is carried out. In Japan, various techniques are available, including right thoracotomy with dissection including the upper mediastinal lymph nodes if necessary and reconstruction using a gastric tube, lower esophagectomy with proximal gastrectomy or lower esophagectomy with total gastrectomy through the left thoracotomy or serial left thoracic and abdominal incisions, and a transhiatal approach to the lower mediastinum without thoracotomy. The most commonly used technique is intrathoracic anastomosis using a gastric tube or the jejunum.

Ivor Lewis approach is the ideal surgical intervention for this Adc located distally of the carina in order to achieve practically 100% R0 resection, especially in the proximal margin, doing the anastomosis in a not-radiated esophagus. Implementation of MIE Ivor Lewis in the Netherlands has importantly increased from 13.5% of all transthoracic approaches in 2011 to 59.5% in 2015.<sup>5</sup> Moreover, there are some concerns about the extension of the mediastinal lymphadenectomy, especially in the supracarinal areas. To carry out a lymphadenectomy at this level, some form of esophageal dissection should be done. Even if this is possible, surgeons are afraid to extend the dissection proximally in order to avoid devascularization of the proximal esophagus. As a consequence, extension of the lymphadenectomy is usually more limited, in this way frequently missing the possible non-radiated but affected supracarinal LN.

The hurdle in this operation is the difficult anastomosis. There are different possibilities: manual anastomosis, end-to-side anastomosis using a conventional or specific circular Orvil® stapler (Medtronic, Medline Industries inc., Arnhem, the Netherlands) and, finally, the linear stapler to carry out a side-to-side anastomosis.<sup>26,27</sup> The possibility of carrying out the anastomosis very high in the thoracic cavity is more difficult and will be facilitated by the use of the ergonomics of the robot.<sup>28</sup>

## 11 | IMPLEMENTATION OF MIE

According to the national register, the percentage of MIE increased in the Netherlands between 2011 (42%) and 2015 (84%).<sup>5</sup> MIE is carried out unselected not only in the initial stage (from T1b) but also in stages II and III, 6-8 weeks after CRT.<sup>5,17</sup>

There is also an increased introduction of RAMIE (robot-assisted minimally invasive esophagectomy).<sup>29</sup> Answering the question of whether MIE is an adequate intervention for a reasonable lymphadenectomy, the Dutch register indicates that average LN resected in MIE were 21 and 16 in open and minimally invasive procedures, respectively. Radical R0 resection was accomplished in 91.5% of open and in 94% of MIE.<sup>5</sup>

## 12 | CONCLUSIONS

Good localization and clinical staging are essential factors for choosing the optimal treatment strategy, which consist of use of neoadjuvant therapy, the corresponding surgical approach, extent of resection and extent of mediastinal lymphadenectomy.

Adequate staging is important for prognosis and, if indicated, for the use of adjuvant therapy. Mediastinal lymphadenectomy in EC has two aims: survival and adequate staging. Extent of mediastinal lymphadenectomy may seem to be clear in SCC, but it is still unclear in distal and EGJ Adc.

Minimally invasive esophagectomy Ivor Lewis operation seems the ideal operative technique for distal and EGJ Adc concerning the extension of resection, but, according to scientific reports, its mediastinal lymphadenectomy may be limited.

For Siewert type 2 tumors, the transthoracic or transhiatal route has the same survival rate. For Siewert type 1 tumors, the transthoracic route seems to enable better survival than the transthoracic approach.

The role of adequate extension of mediastinal lymphadenectomy has been challenged in Adc by the use of neoadjuvant CRT and the analysis of retrospective big data studies. In the next few years, it should be demonstrated whether or not these challenges have been met.

The TIGER study is a significant attempt to establish a consensus on standardizing the type of lymphadenectomy for every specific esophageal tumor. Participation in this study should be encouraged.

In Europe, the combination of more standardized mediastinal lymphadenectomy in combination with a better selection of esophageal cancer patients for surgery and proper neoadjuvant therapy will probably help to increase the survival rate of esophageal cancer in the coming years.

## DISCLOSURE

Authors declare no conflicts of interest for this article.

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