



Long-term survival of surgical treatment of esophageal squamous cell carcinoma in Europe: the story of current practice in multimodal treatment

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Abstract: Squamous cell carcinoma is still the most common histological subtype of esophageal carcinoma in Europe, although its incidence is decreasing, while incidence of adenocarcinoma is rapidly increasing, especially in Western and Northern countries. Curative treatment is still surgery based, but unlike in most Asian countries, most patients receive multimodal treatment. Based on recent randomized trials, European guidelines mention neoadjuvant chemoradiation therapy followed by surgery or definitive chemoradiation followed by salvage resection when needed as treatment options in locally advanced esophageal squamous cell carcinoma patients. The trend towards more definitive chemoradiation can be explained by the possibility to have an organ-sparing treatment on one hand, but on the other hand also by the fact that most European esophageal surgeons are visceral surgeons who are less familiar with lymph node dissections in the upper mediastinum and neck. Nevertheless, surgical treatment with adequate lymph node dissection as part of a multimodal treatment still offers the best chances on long term survival with 5-year survival rates of up to more than 40 percent.

Keywords: Esophageal cancer; combined modality therapy; squamous cell carcinoma; survival

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Incidence of esophageal squamous cell carcinoma (ESCC) in Europe

Squamous cell carcinoma is the most common histological subtype of esophageal carcinoma worldwide (1). Also, in Europe, with age adjusted incidence rates of 2.9 in men and 0.8 in women, ESCC is still more frequent than the rapidly increasing esophageal adenocarcinoma (EAC) with incidence rates of 1.9 and 0.3 respectively (2). In Western and Northern European countries, incidence of EAC is already surpassing that of ESCC and other countries are expected to follow this trend in the coming years (3).

Not only good surgery is important: the quest for the ideal treatment

ESCC has a different biological behavior as compared to EAC (4). Therefore, a specific treatment is mandatory: patients with early stage ESCC can undergo immediate resection, either endoscopically, or surgically, depending on depth of tumor and risk of lymph node involvement (5). However, most ESCC patients in Europe present with more advanced stadia and have worse prognosis after surgery alone, compared to their EAC counterparts (4). Several randomized trials were performed in Europe in the last

25 years which tried to answer the question on how to improve long-term survival in ESCC.

The first one was a German trial by Zieren *et al.*, published in 1995, comparing 35 ESCC patients who underwent surgical treatment alone with 33 ESCC patients who underwent esophagectomy followed by adjuvant radiation therapy (6). Three-year overall and disease-free survival were not different between the two groups, being 20% and 22% respectively. However, the formation of anastomotic strictures after 1 year postoperatively was doubled in the adjuvant radiotherapy group. Therefore, adjuvant radiotherapy was left as a potential therapy for ESCC.

In 2009 the updated results of the British OEO2 trial were published comparing patients with both ESCC and EAC between primary surgical treatment in one arm and neoadjuvant chemotherapy followed by esophagectomy in the other arm (7). Chemotherapy regimen comprised 2 cycles of cisplatin on day 1 and fluorouracil (5FU) as a continuous infusion over 96 hours repeated every 3 weeks. A total of 124 and 123 ESCC patients were included respectively. Five-year overall survival was 17.0% in the primary surgery arm versus 25.5% in the neoadjuvant chemotherapy arm. However, the difference did not reach a statistically significant level in ESCC alone [hazard ratio (HR), 0.81; 95% CI, 0.61–1.07] and the major drawback of this study design was that neoadjuvant radiotherapy was allowed in both arms, resulting in 9% of patients included in the study potentially influencing survival numbers by their radiotherapy treatment.

The idea of trimodality treatment was born and in 2012, the Dutch CROSS trial was published comparing primary surgical treatment with neoadjuvant chemoradiation therapy followed by esophagectomy in ESCC as well as in EAC patients (4). Neoadjuvant therapy consisted of 41.4 Gy radiotherapy (23 fractions of 1.8 Gy on week days during 5 weeks) and two cycles of carboplatin/paclitaxel on week 1 and week 5. Updated results were published in 2015 and although only 43 ESCC patients were included in the primary surgery arm and only 41 ESCC patients in the neoadjuvant therapy followed surgery arm, results were striking (8): median overall survival of 81.6 months for the multimodality treatment group versus only 21.1 months for the primary surgery group (HR, 0.48; 95% CI, 0.28–0.83). Median disease-free survival was comparable with 74.7 versus 11.6 months respectively (HR, 0.48; 95% CI, 0.28–0.82).

Since then, CROSS trial regimen neoadjuvant therapy is widely used as standard of care in ESCC patients with locally advanced disease. However, the success

of the CROSS trial and earlier trials with neoadjuvant chemoradiations therapy raised another question in these patients: since pathological complete response of the tumor in the resection specimens was found in 49% of all ESCC patients, one could argue that surgical therapy is not necessary anymore in all patients.

To answer this question, the French FFCD 9102 trial was conducted some years before comparing neoadjuvant chemoradiation therapy followed by esophagectomy in one arm with definitive chemoradiation in the other arm (9). A total of 130 ESCC patients were included in the surgical arm and 129 ESCC in the medical arm. Two-year survival rates showed no significant differences with 33.6%±4.5% and 39.8%±4.5%, respectively, in the intent-to-treat analysis.

Therefore, the European Society of Medical Oncology proposed both therapies (neoadjuvant chemoradiation followed by esophagectomy and definitive chemoradiation) as a valuable option in her 2016 guidelines (5).

However, the major problem with the FFCD 9102 trial was that actually all patients received the same neoadjuvant scheme of 46 Gy radiotherapy (23 fractions of 2 Gy) with 2 cycles of cisplatin/5FU. Randomization was only performed thereafter in fit patients having response on the treatment. So, the next question is: “what happened to the non-randomised patients who started their neoadjuvant therapy?”. Vincent *et al.* answered this question with the very interesting result that non-randomised patients from the FFCD 9102 trial who underwent esophageal resection had exactly the same survival curve as the randomized patients (10). So, the so-called non-responders had the same outcome after surgery, which means that surgery can still cure more patients than chemoradiation alone.

But good surgery is still the best option: the importance of the lymph nodes

Although the quality of the surgical treatment in ESCC patients is essential, surgical quality is not well defined in all previously described trials going from “no type of surgery was recommended” in the FFCD 9102 trial and “procedure selected according to tumor site and local practice” in the OEO2 trial, to “transthoracic approach with two-field dissection for tumors at or above the level of the carina” in the CROSS trial (7-9).

Similarly, as in Japanese ESCC patients, up to 25 percent of European ESCC patients can present with metastatic cervical lymph nodes after primary surgical

treatment (11). Therefore, these patients will need more extensive lymph node dissection than the usually performed standard 2-field lymph node dissection up to the level of the carina. However, since most surgeons dealing with esophageal carcinoma in Europe are visceral surgeons, they are less familiar with lymph node dissections in the upper mediastinum and neck (12).

Nevertheless, adequate lymphadenectomy in these patients will improve staging, which in turn can more accurately predict survival. Depypere *et al.* showed in a recent multicentric European study covering 576 ESCC patients with a mean number of 22.6 resected lymph nodes after neoadjuvant chemoradiation therapy, that not only lymph node invasion is a prognosticator for survival (13). The extent of lymph node invasion beyond the lymph node capsula seems to be a strong prognosticator for overall survival in these patients. Five-year overall survival in ESCC patients without lymph node invasion, with intracapsular lymph node invasion and with extracapsular invasion was 47.4%, 39.5% and only 10.6% respectively. Furthermore, the study showed no survival difference between patients with incomplete tumor response but no residual lymph node disease and patients with limited (one or two metastatic lymph nodes without spread beyond the capsula) lymph node disease. This means that residual metastatic lymph nodes in ESCC patients after neoadjuvant chemoradiation therapy do not necessarily mean a poor prognosis in these patients.

Summary of current evidence-based practice in ESCC surgical treatment in Europe

- ❖ ESCC incidence is decreasing in Europe while EAC is increasing;
- ❖ European guidelines suggest neoadjuvant chemoradiation followed by surgery or definitive chemoradiation and salvage surgery when needed as evidence-based treatment options;
- ❖ Esophageal surgery in Europe is mostly performed by visceral surgeons;
- ❖ Not all ESCC patients with residual positive lymph nodes have a poor prognosis by definition;

Therefore, adequate surgery with properly performed lymph node dissection remains important to obtain the best staging and results with 5-year overall survival expected to be up to more than 40%.

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Footnote

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