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The changing landscape of multimodal treatment for locally advanced oesophageal and junctional adenocarcinoma

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Members of the Rotterdam Oesophageal Tumour Study Group are co-authors of this study and are listed under the heading Collaborators.

Treatment with curative intent for oesophageal cancer has evolved over the last decades. Followers of the non-surgical school proposed radiotherapy alone in the 1970s. However, this led to cure in only the vast minority of patients[1]. Adding chemotherapy as a radiosensitizer improved survival and became a new standard in the 1990s when squamous cell histotype was still prevalent[2]. However, locoregional failure rates after definitive chemoradiation remained high and the addition of salvage surgery in selected patients with residual or recurrent disease arised[3]. On the other hand, primary surgical treatment was applied before the twenty-first century. In just over half of patients, a radical resection could be achieved with an in-hospital mortality rate of 13%, ultimately not curing more than 20% of patients[4]. Improvements in clinical staging, perioperative care, surgical techniques, and centralization of low-volume complex procedures led to better patient selection and surgical outcomes. Survival further improved by administering neoadjuvant chemotherapy or chemoradiation, enabling tumour downstaging and treatment of micrometastases. Today, combinations of radiotherapy, systemic therapy, and surgery are applied in a personalized multimodal setting.

Although locally advanced oesophageal squamous cell carcinoma is still best managed with chemoradiotherapy with or without surgery, optimal multimodal treatment for oesophageal adenocarcinoma is debated. Although the effectiveness of perioperative chemotherapy was mainly shown in gastric and junctional cancers, genomic similarities between junctional and oesophageal adenocarcinoma provide a rationale for applying chemotherapy to oesophageal adenocarcinoma[5]. Neoadjuvant therapy delays surgical treatment and may compromise patient condition, underscoring the importance of prehabilitation to mitigate surgical risks[6]. Although chemotherapy is associated with higher toxicity than neoadjuvant chemoradiotherapy (CRT), over 90% of the patients after chemotherapy or CRT proceed to surgery with comparable surgical outcomes, including an in-hospital mortality rate of 2–3% and severe complications in 22–27% of patients[7,8].

How can we choose wisely between CRT and chemotherapy when survival is often seen as the primary metric for efficacy and success? The Neo-AEGIS trial showed that chemotherapy and CRT offer equivalent overall survival in an era where radical transthoracic oesophagectomy is standard[9]. This trial achieved only 70% of its enrolment target, undermining its statistical power, and only 15% of patients in the chemotherapy arm received the current standard of FLOT (5-FU, oxaliplatin, docetaxel) chemotherapy. In the ESOPEC randomized trial, patients who received FLOT had better overall survival compared than those who received CRT[8]. Patients in the CRT arm (without adjuvant nivolumab) had a median overall survival of 37 months, which is markedly less than the reported 49 and 43.2 months in the Neo-AEGIS and CROSS trials[8–10]. Differences in study populations may explain this, as 81.6% of the patients had clinical positive nodal disease in the ESOPEC trial compared to 56% and 65% in the Neo-AEGIS and CROSS trials respectively[8–10]. Nevertheless, until the publication of the full trial data there remain outstanding questions on radiotherapy quality assurance, treatment adherence, treatment-related toxicity, and pathology data.

CRT induces locoregional tumour shrinkage and as such facilitates a radical tumour resection. Chemotherapy is believed to exert a more potent systemic effect and eradicates distant micrometastases. Conceptually, this should affect the pattern of recurrence after treatment. In the CROSS trial, distant recurrence rates were similar to surgery alone, but isolated locoregional recurrences were significantly lower following CRT plus surgery[10]. The Neo-AEGIS trial did not show gross differences in sites of treatment failure between CRT and chemotherapy, although there was a lower proportion of patients with lung and liver metastases in the chemotherapy arm[9]. Patterns of recurrence in the ESOPEC trial did differ, with lower rates of distant recurrence following chemotherapy, which supports the perceived distinct working mechanisms of both modalities (ISDE meeting 2024, personal communication). These observations allow for personalisation of treatment. Patients with advanced nodal stage (cN2–3) have a high risk of distant recurrence, implying that they carry a greater systemic micrometastatic burden and are more likely to benefit from chemotherapy. Conversely, chemoradiation makes radical surgery feasible even in bulky T4 tumours, but may also limit the metastatic potential

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of the primary tumour to some extent by inducing apoptosis and fibrosis. Although none of the aforementioned trials were powered to analyse tumour characteristics and recurrence patterns, a network meta-analysis including RCTs comparing CRT with chemotherapy showed no differences in locoregional and distant recurrence. However, data were insufficient to assess the effect of tumour or nodal categories and did not include the recent Neo-AEGIS and ESOPEC trials[11]. An update with these recent trials might provide new insights to better guide multimodal treatment. Based on the 23% pathological complete response (pCR) rate after CRT and surgery, CRT may allow for an active surveillance strategy in patients with a clinical complete response[10]. In contrast, pCR rates following chemotherapy have historically been lower, not exceeding 7–9% in real-world data[12]. The possibility of avoiding surgery and its associated risks and impact on quality of life may favour CRT. This advantage is challenged by more recent data, where FLOT was associated with a pCR rate of 16%[8].

The discussion on optimal multimodal treatment will continue as immune-modulating and targeted therapies may shift the debate. The efficacy and benefit of immune-modulating therapies may depend on the backbone therapy they are paired with. CRT induces the release of neoantigens, which are needed for tumour cell recognition of T cells[13]. Adjuvant nivolumab after CRT plus surgery improves disease-free survival by reducing both locoregional and distant recurrence and has been adopted in many countries as the standard of care. Adding PD-L1 inhibitors to neoadjuvant chemotherapy increases pCR, but data showing this results in less recurrence or improved survival are awaited[14,15]. The toxicity of FLOT could, however, limit its compatibility with other therapies[15]. In parallel, safety and efficacy of targeted therapies for HER2-positive tumours in the curative setting remains to be determined. Analogous to total neoadjuvant treatment for rectal cancer, combining CRT with chemotherapy aiming to increase treatment efficacy in oesophageal adenocarcinoma is currently being investigated. A combination of FLOT and CROSS CRT was tolerable in a small phase II study, instigating the upcoming TNT-OES-2 trial that will investigate whether this regimen reduces systemic failure while providing optimal locoregional control and improves survival in patients with node-positive adenocarcinoma[16].

Current data support the use of FLOT chemotherapy and this may be the preferred treatment for oesophageal and junctional adenocarcinoma. Personalized strategies based on tumour and patient characteristics could refine oncological outcomes, aligning therapeutic objectives with the approach that best achieves this. Emerging therapies and combination strategies hold promise to further improve efficacy while managing treatment-related toxicity.

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Data availability

No data was used or collected for this manuscript.

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