

## Current Standards and New Trends in Oesophageal Cancer

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### Abstract

Oesophageal squamous cell cancer has a constant or even decreasing incidence rate in many regions in Europe, while oesophageal adenocarcinoma and oesophagogastric junction (OGJ) cancer have shown an increasing incidence over the past three decades. If diagnosed at an early stage (stage I), which is rarely the case, these cancers have a good prognosis. Endoscopic resection can then be recommended in selected cases where the submucosal layer is not reached. In these cases, surgical resection is regarded as the standard of care. In contrast, in stages II and III, the prognosis is more critical. Local relapses and distant metastases occur frequently during post-surgical follow-up, leading to long-term survival being as poor as 20–30 %. For locally advanced tumours, multimodal treatment has been established as the new standard of care. Neoadjuvant chemotherapy or chemoradiation have proven efficacy in adenocarcinoma of the oesophagus. Neoadjuvant chemoradiation (followed by surgery) and definitive chemoradiation are two proven and equivalent options with comparable outcomes in oesophageal squamous cell cancer. In metastatic disease, chemotherapy on the basis of cisplatin and 5-fluorouracil can be offered in order to achieve better symptom control, although prolongation of survival has not formally been proven due to a lack of randomised controlled clinical studies.

### Keywords

Oesophageal cancer, oesophagogastric junction, chemotherapy, chemoradiotherapy, neoadjuvant, peri-operative, targeted, antibody, positron emission tomography

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Oesophageal adenocarcinoma and oesophagogastric junction (OGJ) cancer have shown an increasing incidence over the past three decades in many European countries and other regions of the world with a Western lifestyle, indicating strong environmental influences on pathogenesis. Oesophageal adenocarcinoma and OGJ cancer are among the most common cancers in Europe and other parts of the world. In many countries, they are found more frequently than oesophageal squamous cell cancer.<sup>1</sup> If diagnosed at an early stage (stage I), which is rarely the case in Europe, oesophageal adenocarcinoma and OGJ cancer have a relatively good prognosis. Endoscopic resection can be recommended in selected cases where the infiltration does not go beyond the mucosal layer. Alternatively, surgical resection leads to a cure in the vast majority of patients in early stages. In contrast, in stages II and III, the prognosis is more critical. Local relapses and distant metastases occur frequently in the post-surgical follow-up. The five-year survival rate used to be as poor as 20–30 %.<sup>1</sup> Using the increasing opportunities of multimodal treatment and the experience gained at specialised centres, the outcome of oesophageal cancer can be significantly improved. In Western societies, oesophageal squamous cell cancer is generally associated with a more dismal prognosis than adenocarcinoma.<sup>2</sup>

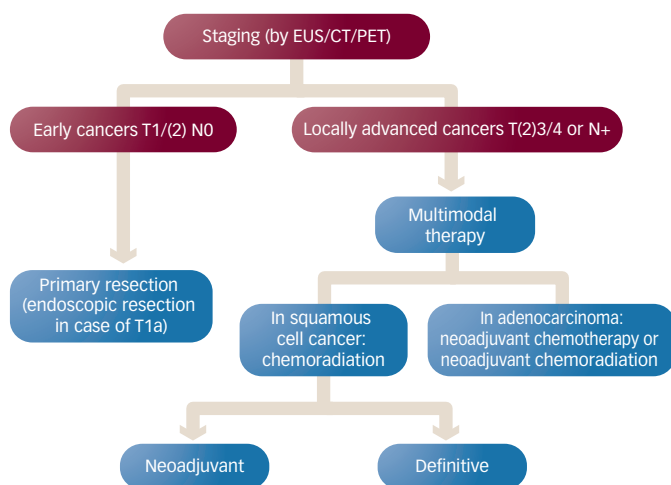
### Treatment Strategies

Randomised studies have shown that neoadjuvant and peri-operative chemotherapy lead to an improved outcome in patients with adenocarcinoma of the oesophagus and OGJ. On the basis of current

meta-analyses, patients are now treated with pre- and peri-operative chemotherapy. In some centres, neoadjuvant concurrent chemoradiation is the preferred approach.<sup>3</sup> Combined chemoradiation has not shown superior outcomes when compared with neoadjuvant chemotherapy alone<sup>3</sup> and, according to some studies, it may lead to increased morbidity and increased peri-operative mortality. This is why many European centres regard peri-operative chemotherapy without radiation as their standard approach. In the recently published European Society for Medical Oncology (ESMO) guidelines, peri-operative chemotherapy is recommended in patients with T3/T4 oesophageal and OGJ cancer. Neoadjuvant chemoradiation is regarded as an alternative approach.<sup>4</sup>

In locally advanced squamous cell cancer of the oesophagus, pre-operative chemoradiation has shown some benefit.<sup>3</sup> It is a matter of debate when oesophageal resection should be performed and in which particular subgroups of patients definitive chemoradiation may lead to satisfying long-term outcomes. Comparative studies have shown comparable survival.<sup>5</sup> Functional imaging and molecular prognostic markers may support decision-making in the future. Currently, it is recommended that patients presenting with resectable squamous cell carcinoma and without limiting cardiorespiratory, hepatic and other co-morbidities should be offered oesophagectomy. Neoadjuvant concurrent chemoradiation can be recommended in tumour categories  $\geq$ T3.<sup>3,4</sup> The currently suggested treatment algorithm for localised oesophageal cancer is illustrated in *Figure 1*.

**Figure 1: Suggested Treatment Algorithm for Patients with Localised Oesophageal Cancer**



CT = computed tomography; EUS = endoscopic ultrasound; PET = positron emission tomography.

Despite the improved outcomes that have been demonstrated in studies investigating multimodal treatment, some patients do not respond to pre-operative chemotherapy or radiation therapy and therefore have no benefit, but experience a time delay and side effects. Positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) offers the opportunity to monitor responses early in the course of pre-operative treatment. Early changes in tumour glucose uptake can also serve as a prognostic marker. In patients who do not respond to treatment at an early time point, we have shown that treatment can be modified and alternative approaches can be offered.<sup>6</sup> Such innovative strategies are currently being validated in clinical trials and should still be regarded as investigational.<sup>7</sup>

In addition to conventional chemotherapy, the role of biologically targeted drugs has been studied in resectable oesophageal cancer.

At the time being, the most interesting targets from studies performed in metastatic oesophagogastric cancer appear to be the inhibition of human epidermal growth factor receptor-1 (HER-1) and HER-2, two members of the epidermal growth factor receptor (EGFR) family, by cetuximab (anti-HER-1)<sup>8,9</sup> or trastuzumab (anti-HER-2),<sup>10</sup> respectively. These targeted drugs are currently being investigated in the peri-operative setting in a couple of already started or planned European and North American studies.

In metastatic disease, platin plus fluoropyrimidine-based drug combinations form the backbone of treatment. These can be combined with a third cytotoxic drug, e.g., epirubicin<sup>11</sup> or docetaxel.<sup>12</sup> Due to the lack of randomised controlled trials in advanced oesophageal cancer, the true value of palliative chemotherapy remains unknown. However, on an individual basis, treatment is often recommended in order to improve symptom control. Many centres treat adenocarcinoma of the oesophagus and OGJ according to gastric cancer guidelines. In oesophageal squamous cell cancer, the addition of cetuximab, an anti-EGFR HER-1-directed antibody, has shown promising Phase II results in a study conducted by the Arbeitsgemeinschaft Internistische Onkologie (AIO).<sup>8</sup> Panitumumab, another anti-EGFR antibody, is being further investigated in a European Phase III study performed within the European Organisation for Research and Treatment of Cancer (EORTC) network.<sup>13</sup>

## Conclusions

The prognosis of patients with localised oesophageal cancer can be improved by optimal surgery and peri-operative treatment provided in specialised referral centres. The consequent use and further improvement of the existing multimodal treatment options will enhance the chances of cure for patients. Further progress can be expected from more sophisticated guidance of treatment by functional response imaging, by a better understanding of predictive and prognostic tissue biomarkers and by the integration of molecularly targeted drugs into peri-operative treatment. ■

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