Improvement of the multimodality treatment of oesophageal cancer
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Future perspectives
Improvement of the multimodality treatment of oesophageal cancer

There are several ways to improve outcome of oesophageal cancer treatment. First, individual treatment planning, multidisciplinary team assessment, and refinement of surgical and non-surgical therapies can improve the overall prognosis of patients with oesophageal cancer. Secondly, a better knowledge of pathological markers that are helpful in predicting treatment response and patient's prognosis may further ameliorate patient-tailored treatment approaches in oesophageal cancer therapy. Finally, improvements in quality assessment of cancer care will help to improve patients' outcome of oesophageal cancer treatment through auditing and benchmarking.

Improvement of combined modality treatment for oesophageal cancer

Even with improvements in preoperative staging, surgical techniques, and postoperative care, the overall survival of patients with oesophageal cancer remains low with 5-year survival rates ranging from 15% to 39%. The poor prognosis of patients with locally advanced disease initiated the use of neoadjuvant therapies in combination with surgery. In these initiatives, other parameters - besides traditional outcome parameters (such as survival) - should also be analysed (for example toxicity) to assess whether the risks of neoadjuvant treatment are sufficiently compensated for by its benefits. Recently, the results of a Dutch multicenter randomised phase III trial comparing preoperative chemoradiation (weekly paclitaxel and carboplatin with concurrent radiotherapy) followed by surgery versus surgery alone have been presented. Grade 3/4 haematological toxicity in the chemoradiation arm consisted of 7 per cent leucopaenia, and grade 3/4 non-haematological toxicities were all below five per cent. Pathological compete response rate was 33 per cent. Median survival was 47 months versus 26 months in the surgery alone group. With acceptable toxicity and good outcome results, this is one regimen that can be considered standard of care for patients with resectable oesophageal cancer.

Still, there is room for further improvement in the multimodality treatment of oesophageal cancer. One problem is the lack of non-invasive markers for response monitoring. Imaging modalities, such as endoscopy, endoscopic ultrasound, and computed tomography have been shown to be highly inaccurate in evaluating response to neoadjuvant therapy in patients with oesophageal cancer. In other studies, the potential role of fluorodeoxyglucose positron emission tomography (FDG-PET) was investigated. No significant association between metabolic imaging and response or prognosis has been demonstrated in patients who underwent neoadjuvant chemoradiation for oesophageal cancer. To date, the most accurate
method for response assessment is a histomorphologic regression grading system. The Mandard tumour regression grade has emerged as an important prognostic factor after neoadjuvant treatment in oesophageal cancer. But, it remains a major limitation that this method involves surgical removal of the tumour. Ideally, information on response to treatment is available before surgery.

**Improved use of pathological markers in the treatment of oesophageal cancer**

Significant progress in the prediction and early identification of responders to chemoradiation will likely come from further insight into the molecular biology of oesophageal cancer. The use of markers may help to select patients with early metastatic potential, to earmark patients who will be unresponsive to chemoradiation, and to individualize choices of chemotherapeutic regimens combined with radiotherapy.

**Tumour-stroma ratio**

Similar to all other malignant tumours, oesophageal cancer is composed of carcinoma cells admixed with stromal fibroblasts, lymphatic and vascular channels, and inflammatory cells, often referred to as the tumour micro-environment. This micro-environment has been recognised to play an important role in tumour cell invasion and metastatic behaviour. Recent results have shown that not only in oesophageal cancer, but also in breast cancer and colon cancer, a low proportion of tumour cells is related to poor survival. The identification of patients with a poor prognosis based on an estimate of the proportion of tumour obtained through simple, relatively inexpensive morphometrical measurements could easily be transferred into routine diagnostic practice. But, before this scoring system can be implemented, earlier results need to be validated in prospective studies.

**Gene expression analysis**

Microarray technology is a tool for genome-wide analysis of differences in the gene expression profile of (tumour) cell populations. This technology has improved our understanding of the molecular mechanisms of cancer development. Gene expression analysis in oesophageal cancer has been limited mostly to relatively small studies in patients with squamous cell carcinoma, with the focus on chemosensitivity and studies that investigated the progression from Barrett’s metaplasia to oesophageal adenocarcinoma. In a recent study, patients with oesophageal cancer who responded to neoadjuvant chemotherapy...
(n=28) were compared to those who did not respond (n=19). Significant differences in a profile of 86 genes were found. Such results deserve further evaluation. At our institute, a prospective biopsy study has been initiated to investigate whether gene expression profiling can improve individual treatment planning in patients who present with non-metastatic oesophageal cancer. It aims to provide further insight into genetic pathways that underlie the processes of tumour dissemination, response to radiation, and chemosensitivity in patients with locally advanced oesophageal cancer.

**Mutational analysis**
Integration of targeted therapy into current cancer treatment is increasing. Important molecular targets of these novel therapies are the epidermal growth factor receptor (EGFR), and the vascular endothelial growth factor (VEGF) and its receptor. Mutations in the EGFR gene have only rarely been detected in oesophageal cancer. In colorectal cancer, it is now well-established that the mutational status of KRAS, an oncogene downstream of EGFR, dictates responsiveness to anti-EGFR therapies. Patients whose tumours were found to have KRAS mutations derived no benefit from cetuximab or panitumimab, anti-EGFR antibodies. In addition, the V600E mutation in BRAF, an oncogene downstream of KRAS, was associated with lack of response to cetuximab in KRAS wild-type colorectal cancer patients. In oesophageal cancer, relatively little is known about the incidence of EGFR, KRAS and BRAF mutations, much less about their predictive value for response to targeted therapy. Yet, at this time, there are several ongoing phase III evaluations of anti-EGFR and anti-VEGF agents in oesophageal cancer patients. In the coming years, these trials should elucidate whether these targeted agents have a role in the multimodality treatment of oesophageal cancer. It is possible that other gene mutations need to be explored in the search for an effective targeted therapy for oesophageal cancer.

**Improvement of quality assessment in the treatment of oesophageal cancer**
In the past, surgical outcomes and causes of variation were largely unknown. More recently, the beneficial effects of auditing surgical outcomes and feeding back data to individual surgeons have been recognized and accepted. In the Netherlands, under the supervision of the Signalling Committee of the Dutch Cancer Society, a "Quality of Cancer Care" taskforce was formed in 2007, comprising medical specialists from all disciplines involved in the care of cancer patients. This taskforce was charged with the evaluation of quality
of cancer care in the Netherlands and the development of strategies for improvement. The experts first focused on the relation between procedural volume and patient outcome and later aimed to identify other factors associated with quality of care. Following the recommendations of this taskforce, valid case-mix adjusted outcome information should be collected in national audit programs and fed back to individual hospitals and physicians continuously. Professionals should determine which data are essential to assess the quality of care provided to each patient, and these ‘minimal datasets’ should be integrated in the Electronic Health Records of each hospital in the Netherlands. The European Society of Surgical Oncology initiated the international multidisciplinary outcome-based quality improvement program. The objective is to create a framework for every type of cancer and every cancer patient in Europe through which results are evaluated, audited and improved. These improvements in quality assurance for surgery but also for multidisciplinary care are expected to have a greater impact on survival than that of any of the (neo)adjuvant therapies currently under study. Moreover, a framework is created upon which clinical research can be conducted at a higher level.

In 2009, a start has been made by the Dutch Surgical Colorectal Audit to register all patients undergoing colorectal cancer surgery in the Netherlands. Plans to expand this population-based registry to other cancers - including oesophageal cancer - are currently being realized.
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