Improvement of the multimodality treatment of oesophageal cancer
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Summary
The general aim of the studies described in this thesis was to improve the combined modality treatment of oesophageal cancer. The results are summarized in three parts, PART I entitled “Chemoradiotherapy and surgery for oesophageal cancer”, PART II entitled “Use of pathological markers in oesophageal cancer treatment”, and PART III entitled “Quality assessment in oesophageal cancer treatment”.

PART I: Chemoradiotherapy and surgery for oesophageal cancer

In chapter 1, a systematic review of publications between 2000 and 2008 on the benefits and risks of neoadjuvant chemoradiation for oesophageal cancer patients was undertaken. Thirty-eight papers comprising 3640 patients met the inclusion criteria. One of the most striking findings was the large variety of chemoradiation regimens that have been applied worldwide. From 12 studies, it could be calculated that 84 per cent of patients proceeded to surgery after neoadjuvant chemoradiation. A microscopically radical resection was achieved in 88 per cent of patients. The average pathological complete response was 26 per cent in evaluable operated patients. There was little uniformity in the reporting on postoperative morbidity. Overall survival after neoadjuvant chemoradiation followed by surgery varied from 16 to 59 per cent at 5 years. The results of this review have shown that more uniformity in the reporting of results is needed. Besides the traditional outcome measures (such as survival), other parameters should receive more attention (for example, toxicity). Only then, one can reliably judge whether the risks of neo-adjuvant chemoradiation are sufficiently compensated for by its benefits.

The role of chemoradiation in the treatment of oesophageal cancer is increasing, not only in the neoadjuvant setting but also as definitive treatment modality. Therefore, efforts to minimize toxicity and maximize efficacy are more and more important. In chapter 2, the toxicity and efficacy of three chemoradiation regimens were evaluated in a group of 94 patients treated in the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital (NKI-AvL) between 1997 and 2007. In the first group, radiotherapy (36-50 Gray in 18-25 fractions) was combined with two cycles of cisplatin 75 mg/m² and 5-fluorouracil 800 mg/m². For patients with hearing loss or diminished renal function, an alternative regimen was given consisting of radiotherapy (50.4 Gray in 28 fractions) in combination with carboplatin targeted at an “area under the curve” of 2, and paclitaxel 50 mg/m², administered on days 1, 8, 15, 22, 29 and 36. The third regimen combined radiotherapy (up to 66 Gray in 33 fractions) with low-dose daily cisplatin 6 mg/m², and was given to patients with cancer of the cervical oesophagus. Twenty-four (25%) patients experienced grade 3 or 4 (non-) haematological toxicity during treatment (25%, 38%, and 15% in the first, second, and
third group, respectively). Two patients died during or shortly after their chemoradiotherapy. Overall, 81 (86%) patients completed the planned treatment. Re-evaluation of the patient’s clinical condition together with re-assessment of the extent of disease after chemoradiation altered the original treatment plan in 14 out of 92 (15%) patients. Pathological complete response was seen in 12 (27%) operated patients. With a median follow-up of 15 (range, 1–108) months, the 3-year survival was 41% for all patients, and 56% for operated patients. These results show that acceptable rates of toxicity and efficacy of chemoradiotherapy for oesophageal cancer can be achieved in selected patients.

In chapter 3, the outcome of surgically treated oesophageal cancer patients in the NKI-AVL was described. During the study period (1995-2007), only a minority of the patients presenting with oesophageal cancer at our institute was eligible for potentially curative treatment (163 out of 828; 20 per cent). This low percentage was the result of the large number of patients who were referred for palliative treatment only. Potentially curative treatment measures included local endoscopic therapy (n=5), definitive chemoradiotherapy (n=71) and surgery (n=87). Oesophageal resection was accompanied by a low postoperative mortality rate (1 per cent) and an acceptable rate of postoperative complications (53 per cent). Overall 5-year survival was achieved in more than 40% of patients. Comparing these results with data from the literature, it was concluded that outcome of low-volume oesophageal cancer surgery can be comparable to published data from high surgical volume hospitals. The results highlight the need to identify more relevant factors other than operative volume alone to improve the outcome of oesophageal cancer surgery.

PART II: Use of pathological markers in oesophageal cancer treatment

In chapter 4, the prognostic value of the tumour-stroma ratio (TSR) in resected adenocarcinoma of the oesophagus was evaluated. With a cut-off value of 50% tumour/stroma, tumours were classified as TSR high (n=60) or TSR low (n=33). By multivariate analysis, TSR was identified as a significant prognostic factor for overall survival (HR 2.0; P=0.010), independent of known prognostic factors. TSR was determined easily on original H&E stained sections of the resected tumour. Implementing this novel parameter could have additional value in identifying patients with a dismal prognosis who do not benefit from surgical resection (alone). The biological background is as yet unknown but the study results emphasize that the stromal part of a tumour is related to clinical outcome and should therefore also be explored in the search for new targeted therapies.

In chapter 5, we have elaborated on these results. In the same patient series, TSR was investigated on biopsy specimens. We assessed the inter- and intraobserver agreement for
TSR scoring on biopsies and correlated these biopsy results with the results derived from the corresponding surgical specimens. Again, TSR scores were classified into two groups (<50% and ≥50%). Interobserver correlations ranged between 0.372 and 0.886 (P<0.001 for all) and intraobserver agreement was substantial to near-perfect (κ=0.780–0.848; P<0.001 for all). The definitive TSR biopsy score revealed moderate correlation with TSR scores on surgical specimens (κ=0.506). Also on biopsy material, TSR was an independent prognostic factor for survival. This finding together with the reproducibility and ease of TSR scoring support a role for TSR in clinical practice.

In chapter 6, the incidence of EGFR, K-ras and BRAF gene mutations in oesophageal cancer was studied in pretreatment biopsies from patients who underwent neoadjuvant chemoradiotherapy plus surgery. In none of the 30 patients, mutations in K-ras and BRAF were found. One deletion of EGFR in exon 19 was identified in one patient with a pathological complete response of the tumour in the surgical resection specimen, but this deletion could not be confirmed by fragmentation analysis. Pathological complete response (pCR) was observed in 10 out of 30 (33%) patients. Following these study results, prudence is warranted when introducing targeted therapies based on EGFR, K-ras or BRAF gene mutations in the treatment of potentially curable oesophageal cancer.

PART III: Quality assessment in oesophageal cancer treatment

In chapter 7, an overview of the literature on quality aspects of oesophageal cancer surgery is given. One hundred and thirty papers published between January 1990 and October 2009 met the inclusion criteria. There was strong evidence that both hospital and surgeon volume are important determinants of postoperative mortality. Other structural measures, such as infrastructure, have been investigated less frequently. The most commonly reported process measures were determinants of patient selection for surgery (for example, patients’ age). Other process indicators with considerable evidence were found (such as multidisciplinary team management), though the number of studies was small. Finally, the level of evidence for pathological outcome measures was high. This review indicated that there was considerable variation in the evaluation of quality of care. The uniform use of well-defined quality-of-care indicators to measure and document practice performance holds the promise of improving outcome in patients who undergo oesophageal cancer surgery.

In chapter 8, a study was undertaken to investigate the quality of care for 821 oesophageal cancer patients who were seen at the NKI-AVL between 2003 and 2008. Waiting times throughout this study period improved and planning of appointments at the outpatient clinic was more efficient in recent years. Assessment at the multidisciplinary meeting was above
80% in patients who received potentially curative treatment. Outcome results of potentially curative treatment were good and remained unchanged over time. By evaluating different dimensions of healthcare quality, we have identified which steps in the multidisciplinary care path need more attention in order to raise the whole level of care.

**Chapter 9** is a quality-of-life study among 36 patients who underwent potentially curative treatment for oesophageal cancer (neoadjuvant therapy followed by surgery, surgery only, or chemoradiation only) at least one year earlier. These patients reported a better health-related quality of life than a large reference group of 1031 oesophageal cancer patients, but a worse quality of life as compared to a reference sample of 7802 persons from the general population. A variety of symptoms continued to persist in a majority of patients. The results of this study can be used when informing patients with oesophageal cancer about the long-term effects of potentially curative treatment.