Discussion

Optimising the surgical treatment of oesophageal cancer patients consists of different strategies: early diagnosis, optimal patient selection, optimal peri-operative care, and possibly the application of (neo)-adjuvant chemo-radiation therapy. Oesophageal surgery is highly complex, and oesophageal carcinoma warrants a multidisciplinary approach. Gastro-enterologists, surgeons, pathologists, anaesthetists, radiologists and other (para) medical staff should collaborate closely to optimise care for these patients. This thesis is mainly concerned with the surgical aspects of oesophageal carcinoma, focussing on the extent of the surgical resection.

Performing a more extended resection serves three purposes: improving staging of the tumour, and postponing or even preventing tumour recurrence. As we have shown, staging is improved in 23% of the patients after extended resection. This effect of a more extended resection on staging has also been described for other tumours, such as gastric carcinoma. The subsequent stage migration might influence the stage by stage comparison of different resection forms, but does not influence comparison of overall survival rates.

In accordance with the previous literature and our own retrospective work, performing a more extended resection does lead to an increase in complications and a prolonged ICU/MCU and hospital stay. Improved peri-operative care might be able to (slightly) decrease morbidity and mortality after an extended procedure. However, an extended resection does not lead to significantly improved disease-free or overall survival rates. So far, we have not been able to demonstrate in a large randomised trial that there is a statistically significant survival benefit of an extended transthoracic resection over a limited transhiatal resection for adenocarcinoma of the oesophagus or gastric cardia involving the distal oesophagus. After two years, a strong trend towards a survival benefit for the extended approach emerges in the survival curves, estimated five-year disease-free survival rates are 27% and 39% resp., while five-year overall survival rates are 29% and 39% resp. Although this is suggestive for a survival benefit for the extended approach, these numbers fail to reach statistical significance. At present, median potential follow-up is 4.7 years, and extending the follow-up might lead to significant results. Further follow-up of the patients in this study might clarify whether the long-term survival benefits of the extended approach will outweigh the increase in early morbidity and associated costs, and thereby more clearly define the role of transthoracic resection with extended en-bloc lymphadenectomy in this population.

Some, mostly Japanese, surgeons argue that an extended two-field lymphadenectomy is not even sufficient due to the possibilities of cervical lymph node metastases, and one should therefore perform
a three-field lymphadenectomy. It should be noted that there is considerably more morbidity after a
two-field lymphadenectomy when compared with a limited transhiatal resection. Also, cervical
recurrence is a rare event in our population, occurring in only 6% of patients after a transhiatal
resection. Adding a formal cervical dissection would only add to the already increased morbidity, and
until large randomised trials demonstrate a clear survival benefit, (also taking in consideration quality
of life), a three-field lymphadenectomy is therefore not warranted.

Another option would be to minimise the already limited transhiatal procedure even further to
diminish post-operative morbidity and mortality. First reports of minimally invasive oesophagectomy
are emerging, with decreased morbidity and mortality, less post-operative pain, a shorter hospital stay
and earlier return to work as the alleged advantages. However, long-term results are not known yet,
and until these resection forms have been put to the test in a randomised study they should not be used
on a routine basis.

Finally, small tumours (T1im) might be removed endoscopically with endoscopic mucosal resection or
thermoablaive techniques such as photodynamic therapy. This way, the morbidity and mortality
associated with oesophagectomy are avoided. The main problem with these new modalities is the
tissue longitudinal lymphatic dissemination. While lymph node metastases are almost never found in
tumours confined to the mucosa (T1im), lymph node metastases are present in up to 20-30% of
patients with tumours extending into the submucosa (T1sm). A thorough work-up, consisting of
reliable endosonography and external echography (both when necessary combined with fine needle
aspiration) is therefore essential. In the AMC, the negative predictive value of endoscopic
ultrasonography for submucosal infiltration is and lymph node metastases is high. Based on these
data, endoscopic ultrasonography can be used reliably to assess T and N stage, and subsequently
identify patients with T1imN0 tumours, which might be candidates for local ablative therapies. On
option currently in use is to perform endoscopic mucosal resection (EMR) when a T1 tumour is
identified. In the EMR specimen the extent of infiltration can subsequently be assessed. When a T1
im tumour is found, the EMR can be considered as therapeutical, while in case of a T1 sm tumour the
patients will undergo surgical resection of the oesophagus. These new therapies are still to be
considered experimental, as no long term results are available yet. For patients with small tumours, an
individually tailored approach is therefore to be recommended.

There might be certain subgroups of patients in which one or the other surgical resection form does
offer benefit. In the present studies, these subsets have not been identified yet. However, for instance
patients with positive paratracheal or aorta-pulmonary nodes might be identified by pre-operative
endoscopic ultrasonography combined with fine-needle aspiration. These patients might benefit from
an extended resection, removing the tumour positive lymph nodes that can not be reached via the
transhiatal route. This staging technique is becoming a standard procedure in our institution. Although
there is an intuitive rationale for this strategy, strong evidence supporting this strategy is still lacking.
On the other hand, there are suggestions that it is the patient-group with small tumours without lymphatic (macro)metastases, that may benefit most from an extended resection. The present study was not designed for such an analysis, and a randomised trial comparing transhiatal resection with transthoracic resection for early tumours seems hardly feasible due to the low number of patients. In these patients, the occurrence of a loco-regional recurrence is unlikely, especially when an extended lymphadenectomy is performed, removing all possible micrometastases. The presence and clinical significance of micrometastasis therefore warrants our interest, and studies have been started in collaboration with other surgical groups with a wide experience in the analysis of micrometastasis.

Another possibility to improve surgical care is to perform complex surgical procedures such as oesophagectomy only in specialised centres. As we have shown, mortality after oesophagectomy is almost threefold higher in low-volume hospitals when compared with high-volume hospitals (12% and 5% resp.). Of course, there are smaller hospitals with excellent results, and these centres should certainly not be forced to stop performing these operations. And although early results are significantly better in high volume centres, nothing is known about the long-term survival rates. We would therefore stimulate all surgeons performing oesophagectomies to examine their surgical outcomes.

Survival might also be improved by performing surgery at an earlier stage. This would imply a surveillance program for patients known to have a Barrett’s segment. Such programs may or may not be (cost) effective and many patients present with an advanced tumour outside the surveillance programs. The presence of specialised columnar epithelium confers a 30-125 fold increased risk for oesophageal adenocarcinoma compared with the normal population. Most recent risk estimates suggest a cancer incidence among patients with a Barrett’s segment of approximately 1 per 200 patient years. Although reports from our institution as well from others suggest that outcomes are significantly better for patients developing carcinoma in a surveillance program because they are diagnosed with low-stage disease, large trials or population-based studies are lacking. Whether Barrett surveillance is effective lies beyond the scope of this thesis.

In the IKA region, a multidisciplinary Barrett Advisory Committee exists, offering advice on difficult cases of Barrett’s oesophagus. In 50% of cases this committee, consisting of expert gastroenterologists, pathologists and surgeons, disagrees with the original grading of dysplasia as diagnosed in the referring centre. In 40% of cases this meant a decrease in the severity of dysplasia. Most changes occurred after an original diagnosis of low-grade dysplasia. These findings confirm the well-known intra- and inter-observer variation in judging the grade of dysplasia in Barrett’s oesophagus, altering management in 17% of cases. This re-emphasises the difficulties arising in the diagnosis and subsequent management of difficult cases of Barrett’s oesophagus, and thereby the need for the centralisation of diagnosis and treatment of this disease in dedicated centres.
Another possible therapeutic target is the network of molecular changes involved in the metaplasia–dysplasia–carcinoma sequence. This might be investigated in longitudinal follow-up studies, but also in animal models. We have used two previously described rat-models for the development of Barrett’s oesophagus. One year after the performance of an oesophago-gastro-jejunostomy without gastric resection we identified a Barrett segment of 10-mm (including the hallmark of specialised intestinal metaplasia, i.e. the goblet cell). Dysplasia in these Barrett’s segments was not observed. Within three to four months tumours appear at the anastomotic site, which at first resemble benign human tumours found in the colon and stomach, called proctitis or gastritis cystica profunda. These tumours are probably due to mechanical forces introducing mucosal glands into the submucosa, which subsequently develop into large well-differentiated cyst-forming tumours. At one year, these tumours have enlarged and show more pronounced cytologic characteristics of malignancy. As they are confined to the submucosa without infiltrative growth or dissemination, and precursor lesions can not be found, these tumours are more likely to develop via a mechanical process than via reflux. These models are therefore useful for the study of Barrett’s oesophagus, but not for Barrett’s carcinoma.

The metaplasia-dysplasia-carcinoma sequence in the oesophagus resembles the adeno-carcinoma sequence of the colon. In this thesis we have also analysed the role for the Wg/Wnt pathway in Barrett’s oesophagus and adenocarcinoma of the oesophagus and gastric cardia. The Wg/Wnt pathway, of great importance in both familial and sporadic colon cancers, is also activated in oesophageal adenocarcinoma, as shown by the presence of nuclear β-catenin in 93% of these carcinomas. The presence of TCF-4, one of its effectors, which is under normal circumstances present in the small and large intestines but not in the oesophagus, gives further credit to the concept of intestinalisation of the oesophagus. As yet, it is not clear what causes this activation of the Wg/Wnt-pathway. Different mechanisms, including both extra-cellular and intra-cellular mechanisms may be involved. Aberrant expression of (extra-cellular) proto-oncogenes, e.g. the Wnt-family of proteins, results in activation of this path. In addition, other growth factors like EGF may also affect β-catenin levels. A recent study indicates that crosstalk exists between EGFR signalling and the Wg/Wnt path. This suggests that the increased presence of EGFR and one of its ligands, TGF-α, upregulated in oesophageal adenocarcinoma, could also play a role in the increased nuclear presence of β-catenin in this cancer. Constitutive Wnt activation can be caused by mutations which impair β-catenin degradation like mutations affecting binding of Axin and APC to β-catenin or mutations in β-catenin which affect its degradation. Also, hypermethylation of the APC promoter region might result in dysfunction of the APC complex. In addition, mutations in the receptor for Wnt signalling, Frizzled, or the absence of a transcriptional repressor can result in activation.

There are some early reports describing a possible relation between COX-2 expression and the Wnt-path. COX-2 expression may participate in intestinal carcinogenesis by inhibiting apoptosis, by
inducing angiogenesis and by promoting dissemination. In a recent study from Buskens and co-workers, COX-2 immunoreactivity was negative to weak in 21% and moderate to strong in 79% of oesophageal adenocarcinomas. Patients with high COX-2 expression were more likely to develop distant metastases and locoregional recurrences, and survival was significantly reduced (p=0.002) among patients with high COX-2 expression. Five-year survival rates were 35% in patients with high COX-2 expression and 72% in patients with low COX-2 expression. Furthermore, expression of COX-2 was recognised as an independent prognostic factor by multivariate analysis. These findings support the effort to initiate clinical studies to investigate the effect of COX-2 inhibitors as a novel (adjuvant) chemotherapeutic modality for the treatment of adenocarcinoma arising from Barrett’s oesophagus.

General conclusions

Surgery is still the mainstay of potentially curative treatment for carcinoma of the oesophagus and gastric cardia. A transthoracic resection with extended en-bloc resection can not be recommended on a routine basis, because long-term survival benefits do not yet compensate the increased early morbidity and mortality when compared with a relatively limited transhiatal resection. However, after three years a trend towards superiority of the extended approach emerges, and further follow-up is needed to more clearly define the precise role of extended resection in this population. Increasing or decreasing the extent of the surgical procedure might be of benefit in certain subgroups, but this is only based on theoretical reasoning, all evidence hereof is yet lacking. Early diagnosis would be of great benefit, but the efficacy of surveillance programs remains to be seen. Centralisation of oesophagectomy would probably reduce early mortality, but whether it increases long term survival has not been investigated yet. Little survival benefit is probably to be gained by improving surgical care.

A better understanding of the malignant degeneration of Barrett’s oesophagus might enable us to prevent the development of oesophageal carcinoma. Intervention at the molecular and/or genetic level might give new impulses to the treatment and prevention of this disorder. Prevention of the development of intestinal metaplasia itself should perhaps be our main concern, by intervening in the common disorder that is duodeno-gastro-oesophageal reflux disease.