A multimodality approach to improve oesophageal and gastric cancer treatment
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GENERAL DISCUSSION AND FUTURE PERSPECTIVES
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Oesophageal and gastric cancer treatment has considerably changed in the last decade. Comprehensive molecular analysis led to the identification of four molecularly different gastric cancer subtypes and defined the differentiating molecular features of oesophageal squamous cell carcinomas and adenocarcinomas. Short-term surgical outcomes improved by the centralisation of oesophageal (2011) and gastric cancer surgery (2013), in combination with the increasing use of neoadjuvant and perioperative chemotherapies. For both oesophageal and gastric cancer, the one-size fits all treatment approach is outdated. Since 2012 it is commonly known that oesophageal squamous cell carcinomas respond better to chemoradiotherapy than adenocarcinomas. Complete response rates are 50% and 23%, respectively, which translates into a median survival difference of 39 months after neoadjuvant chemoradiotherapy and surgical resection (82 versus 43 months, respectively). In addition, evidence is increasing that chemotherapy in diffuse histological subtypes is less effective than in intestinal subtypes. As valuable treatment alternatives are lacking, these cancer types (squamous cell carcinomas/adenocarcinoma, diffuse/intestinal) are currently still treated as if being the same disease entity.

Individualised treatment is the ultimate goal of current cancer research, and small steps are made. The introduction of trastuzumab for example, resulted in a 3 months increase in survival for patients with HER2 positive (only 7–34% of patients) irresectable or metastatic squamous cell carcinomas. However, for the majority of patients, survival over the years only slightly improved in case of oesophageal cancer, and remained stable in case of gastric cancer. In this thesis, current and new treatment strategies for oesophageal and gastric cancer were evaluated, together with potential new starting points for further tailoring treatment.

PATIENT SELECTION FOR MULTIMODALITY TREATMENT

Despite outcome-enhancing measures, both oesophagectomy and gastrectomy remain complex surgical procedures associated with considerable morbidity, and even postoperative mortality. After surgery, it takes up to 12 months to regain pre-surgical quality of life, while 20% of patients dies in this first year after surgery. As surgery is the cornerstone for potentially curative treatment, it is a rewarding challenge to select those patients that actually get the chance to benefit from it.

Elderly

The Dutch population is aging; the proportion of individuals aged above 70 grew from 6% in 1960 to 13% in 2017. As elderly are often excluded – or underrepresented – in clinical trials because poorer treatment tolerance is expected, the extrapolation of study results to the elderly population can be questioned. Therefore, new treatment strategies are fairly underutilised in elderly patients potentially resulting in poorer overall outcomes than necessary.

Growing evidence suggests that securely selected elderly patients can benefit from intensive treatment strategies. Similar long-term outcomes can be achieved in younger and elderly oesophageal cancer patients after neoadjuvant chemoradiotherapy followed by surgery or definitive chemoradiotherapy. As it might improve their outcome, elderly should be considered for potentially curative treatment.

With increasing life-expectancy, management of elderly cancer patients becomes a challenge. Selection of elderly patients suitable for intensive cancer treatment should focus on the complete package. It should be based on a combination of a comprehensive frailty assessment together with patient- and tumour related clinical factors such as tumour stage, histological subtype, comorbidity scores, performance status, and, last but not least, a patient’s individual preferences.

Histological subtypes

Subtyping gastric adenocarcinomas according to Laurén distinguishes prognostically different patient groups. This phenomenon appeared translatable to oesophageal adenocarcinomas (Chapters 2 and 3): diffuse subtypes (20%) were less sensitive to chemoradiotherapy, and showed a significantly worse patients’ prognosis than intestinal subtypes. This finding is particularly interesting in the light of current organ-sparing treatment initiatives as it seems plausible that (near)complete responders to chemoradiotherapy can do without oesophageal resection. In addition, those who do not respond, or those at risk for early disease recurrence, might be unnecessarily exposed to the toxicity of neoadjuvant treatment and the morbidity of subsequent surgery.

Identification of (non)complete responders will become the ultimate goal. For this, multimodal response assessment (imaging, endoscopy) is essential, but should be combined with patient- and tumour characteristics for risk stratification. Response assessment after chemoradiotherapy might be enhanced by measuring tumour markers (Chapter 5) or circulating tumour DNA, by improving sampling accuracy during oesophagogastroduodenoscopy (bite-in-bite biopsies), by implementing routine PET-CT, or by implementing other staging modalities such as magnetic resonance imaging during chemoradiotherapy or prior to surgery (PRIDE study: NCT03474341 at ClinicalTrials.gov).
Molecular subtypes
Especially for those patients who do not respond to current treatment regimens, there is an urgent need for the exploration of alternative treatment options. Efforts from The Cancer Genome Atlas (TCGA) and The Oesophageal Cancer Clinical and Molecular Stratification (OCCAMS) consortium provided molecular characterisation of oesophageal and gastric cancers. This revealed starting points for targeted agents, but have as yet not resulted in clinical implications. For example in gastric cancer, the molecular subtypes as described by the TCGA that are positive for Epstein–Barr virus (EBV) or microsatellite unstable tumours (MSI) seem good targets for immune-based therapy, which is currently being investigated (PANDA study, ClinicalTrials.gov: NCT03448835). There is as yet no molecular explanation for the clinical association between the histological subtypes according to Laurén and treatment response. Furthermore, it is unsure whether the phenotypical similarity between diffuse oesophageal and gastric adenocarcinomas can be transferred to the molecular level. In gastric cancer, diffuse types have a strong association with the genomically stable molecular TCGA subtype (73%), and they are diagnosed at an earlier age than intestinal types. In oesophageal adenocarcinomas, the genomically stable (i.e., diffuse) molecular subtype only accounts for 1% of TCGA cases, while 18–21% of patients exhibited the phenotypical characteristics of a diffuse subtype in Chapters 2 and 3. Furthermore, not in oesophageal, but in gastric cancer diffuse types were diagnosed at a younger age than intestinal types (Chapter 3). These findings suggest molecular differences between oesophageal and gastric diffuse types. Further research needs to determine whether there is a common genetic defect resulting in this diffuse phenotype on different locations (oesophagus/stomach). Or, whether diffuse type oesophageal adenocarcinoma is a more advanced tumour that lost its capability of cell differentiation resulting in the typical diffuse type-like loss of epithelial architecture. Biobank initiatives collecting pre- and posttreatment oesophageal and gastric cancer biopsies together with clinical data are needed to provide further insight in the genetic pathways and the biological processes that underlie tumour dissemination and response to therapy.

TREATMENT
Surgical treatment
The outcomes after oesophagogastric cancer surgery have improved the last decades. In-hospital mortality after oesophagectomy declined from 14% in the early nineties to 4% in 2014, and radical resection (R0) rates increased from 70% to 95%. For gastric cancer, comparable trends were seen with current in-hospital mortality rates of 4%, and R0 resections in almost 90%. By introducing minimally invasive surgery, efforts were made to reduce hospital-stay and postoperative complication rates. Current research in the potentially curative setting focuses on the whole care path, from neoadjuvant treatment via surgery to postoperative recovery.

For example, in the CRITICS II study, the aim is to evaluate which neoadjuvant multimodal treatment strategy is optimal before gastrectomy: chemotherapy, chemoradiotherapy or chemotherapy with subsequent chemoradiotherapy (ClinicalTrials.gov: NCT02931890). In the surgical field, minimally invasive surgery evolves rapidly. New techniques such as 3D instead of 2D vision in endoscopic surgery were developed, and became available for implementation (Chapter 8). In addition, multi-institutional efforts are made to determine the ultimate benefit of minimally invasive (robot-assisted) surgical techniques over open techniques, such as: the ROBOT, LOGICA and STOMACH trials. Enhanced postoperative recovery is studied in the NUTRIENT II trial, and outcomes after an oesophagectomy with a cervical versus an intrathoracic anastomosis are assessed in the ICAN trial.

As staging modalities improve, it is expected that the percentage of patients diagnosed at stage IV disease will increase. Since the incorporation of FDG-PET/CT scans for re-staging after chemoradiotherapy in oesophageal cancer, surgery is precluded in 8% of patients in whom interval metastases become apparent. For gastric cancer, in the most recent Dutch guidelines, FDG-PET and diagnostic laparoscopy are advised in patients with potentially resectable cT3-cT4 and/or N+ tumours. This combination is thought to reveal metastases in 27% of patients who will thus not proceed to potentially curative gastrectomy. The Dutch PLASTIC-study will determine the cost-effectiveness of this additional staging combination and its clinical impact. Besides more strict patient selection for potentially curative surgery, indications are broadened for surgery in the (oligo)metastatic setting.

In gastric cancer, the PERISCOPE I trial (Chapters 9 and 10) has been a first step towards the much-needed standardisation of HIPEC in gastric cancer patients. Peritoneal carcinomatosis is considered locoregional extension of disease, suggesting that by eliminating both micro- and macroscopic disease, long-term survival should be possible. Following the beneficial outcome in colorectal and ovarian cancer (amongst all) and promising results in non-randomised gastric cancer patient series, the applicability of HIPEC in gastric cancer patients is increasingly investigated in both the prophylactic- and curative setting (GASTRIPEC and GASTRICHP). The procedure itself is associated with a high complication risk, as was seen in the PERISCOPE I, which underlines the need for proper patient selection. Survival and quality-of-life benefit should outweigh the accompanying morbidity of the procedure. Young and fit patients with limited spread of disease appear the ideal candidates. The results of the recently opened PERISCOPE...
II trial (ClinicalTrials.gov: NCT03348150) together with the results of the GASTRIPEC (ClinicalTrials.gov: NCT02158988) and GASTRICHIP (ClinicalTrials.gov: NCT01882933) studies will determine the role of HIPEC in gastric cancer patients.

In our healthcare system there is an increasing demand for transparency, and nationwide non-hospital dependent high quality of care. Improving oesophagogastric cancer care as a whole remains a major challenge, not in the least because a multimodal and multidisciplinary treatment approach is needed which is difficult to coordinate on a national level. As a result, the probability of receiving potentially curative treatment and subsequent survival vary per hospital of diagnosis. In 2011 the Dutch Upper gastrointestinal Cancer Audit (DUCA) was launched. By enabling continuous monitoring and feedback of short-term surgical outcomes, rapid quality-enhancing changes in clinical practice are stimulated and hospital-variation can be reduced. After initiation of the DUCA there was a nationwide reduction in time between diagnosis and treatment, the quality of surgery improved at certain points, and mortality after gastric cancer resection decreased.

Textbook outcome is a composite outcome measure for oesophagogastric cancer surgery which was developed based on national audit data, and validated on a single hospital level (Chapter 6). Textbook outcome justifies the multidimensional nature of oesophagogastric cancer surgery in a single parameter. Its association with patients’ survival (Chapter 6) indicates that by optimising patient selection, quality of surgery and postoperative care, long-term outcome can be improved. Using textbook outcome provides new possibilities for quality assurance in all different levels of healthcare. Individual hospitals might improve themselves at underperforming parameters, patients might use it for choosing their hospital of preference, and in the bigger picture it can be used to identify outliers in quality of care.

In the Western world, increasing survival is no longer accepted at all costs. Quality of life becomes increasingly important, and the paternalistic health care system makes room for shared decision making. An example is given in this thesis for patients with HDGC, in whom counselling is crucial to determine the proper timing of prophylactic surgery (Chapter 7). Increasing quality and transparency are expected by the patient in his role as a consumer of care. Analogous to the private sector, the healthcare sector should strive for the most efficient (in terms of costs) delivery of a perfect product (care) to the consumer (patient). The major problem thus far is the lacking definition of perfect care. Measures as textbook outcome provide a way to summarise perfect care from the healthcare perspective, but lack routine consumer reviews, i.e., patient reported outcomes measures (PROM). Routine collection of PROMs in oesophagogastric cancer care was recently initiated (https://pocop.nl/). The outcomes will provide insight in the patients need rather than the doctor’s will to cure. Combining outcomes of care such as textbook outcome with PROMs will eventually result in a viable healthcare system where the needs of all stakeholders are in balance.
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