Proximal esophageal cancer

Impact paragraph

In this thesis, we explored a number of scientific questions in an attempt to provide answers for clinical problems which may be encountered in everyday practice in (proximal) esophageal cancer. In this chapter, the relevance of the results described in this thesis and their scientific and social impact will be discussed.

Reinforced real-world data

Esophageal cancer is the seventh leading type of cancer worldwide (572.034 new cases in 2018), and tenth in the Netherlands (2.456 new cases in 2018).[1] Although the absolute number of deaths has decreased, esophageal cancer covers the sixth place in cancer-related mortality globally and in the Netherlands.[1] Over the past decades, several developments in esophageal cancer care have been established, such as the implementation of neoadjuvant chemoradiation,[2,3] definitive chemoradiation,[4] and centralization of care in the Netherlands.[5] Cancer of the proximal esophagus is a distinct and rare entity. Due to its location, i.e. adjacent vital structures, the treatment approach of these cancers differs from cancers from lower parts of the esophagus, by predominantly performing non-surgical therapy. In addition, patients with proximal esophageal cancer are frequently excluded from esophageal trial participation and, as a result, no separate high level evidence has been achieved. Hence, research data from large populations in Western countries are necessary to optimize patient counseling in the Netherlands. This thesis has added value to clinical practice as it provides insights in the characteristics of proximal esophageal cancer patients, their treatment options, and it offers real-world survival data.

Overall, outcome of patients with (proximal) esophageal has improved over the past decades. We revealed that the broad implementation of combined modality treatment with chemoradiation was associated with this progress. We found that in proximal esophageal cancer, outcome in patients treated with surgery, with or without neoadjuvant therapy, was comparable with patients treated with the non-surgical strategy of definitive chemoradiation. Concerning high morbidity rates and decreased quality of life associated with the surgical procedures for proximal esophageal cancer, it is essential to focus on the multimodality treatment of chemoradiation, appreciating patients' quality of life but yet maintaining survival prospects.

Enhanced chemoradiation strategies

Accordingly, this thesis focused on the identification of an optimal chemoradiation regimen for patients with proximal esophageal cancer. By performing a comparative effectiveness study of four contemporary chemoradiation schedules, we provided relevant information regarding risks of toxicity, and concerns of non-adherence mainly caused by adverse events. Furthermore, we demonstrated a suboptimal outcome based on high rates of locoregional residual disease or recurrence, with limited salvage treatment options.

Superiority of carboplatin plus paclitaxel versus cisplatin in definitive chemoradiation schedules for the treatment of proximal esophageal cancer could not be established in terms of overall survival. However, the toxicity profile was significantly better in patients treated with carboplatin plus paclitaxel compared with cisplatin. Hence, we concluded that carboplatin plus paclitaxel-based chemoradiation should be regarded as the standard of care in proximal esophageal cancer. This statement was supported by the Dutch Upper GI Cancer Group (DUCG) and the National Working Group Head Neck Cancer (NWHHT), following national scientific discussion sessions. In December 2020, a survey during a DUCG meeting following the presentation of our study results, demonstrated that 22 out of 24 Dutch physicians involved in esophageal cancer treatment, implemented carboplatin plus paclitaxel in chemoradiation for proximal esophageal cancer nowadays. This is a significant increase compared with 53% of the patients included in our study being treated with carboplatin plus paclitaxel between 2004 and 2014, enrolled from 11 centers in the Netherlands. The decision to implement carboplatin plus paclitaxel based regimens is strengthened by the conveniences and reduced direct healthcare costs associated with a shift towards outpatient treatment and lower numbers of high grade adverse events expected to minimize treatment-related hospitalization days, contributing to economic gain.

More importantly, patients will benefit directly from the substantial reduction of toxicities of carboplatin plus paclitaxel compared with cisplatin-based backbone used in chemoradiation. Specifically, in a disease like (proximal) esophageal cancer with this poor outcome it is essential that patients maintain the best achievable quality of life during treatment. This includes as little as possible hospitalization days for treatment and/or due to serious treatment-related side effects.

Various strategies have been addressed in the ‘Future perspectives’ paragraph for further optimization of chemoradiation. We are awaiting efficacy data of proton therapy, MRI guided radiotherapy, and immunotherapy in definitive chemoradiation schedules for esophageal cancer. However, in other cancers, the implementation of

these innovative treatment options are subject of debate to balance high quality health care programs and keeping health care budget within limits, in order to maintain accessibility of care for the total population.

Treatment counseling

Several aspects have been explored in our studies that may help to optimize quality of patient care. We offer input to improve patient counseling in esophageal cancer, and implement the most optimal chemoradiation schedule in proximal esophageal cancer. Particularly in patients with resectable proximal esophageal cancer, the provided information is crucial for treatment counseling. For each individual patient, clinically meaningful treatment possibilities can be depicted in a more careful way. By discussing potential treatment options, higher satisfaction rates of patients in terms of awareness of side effects and survival outcome are obtained, considering patient values, treatment preferences and restrain psychological distress.[6] Hence, as a result narrowing the perception-reality gap. It is known that treatment tolerance and adherence amongst patients is highest when patients are extensively informed of the risks of the distinct treatment trajectories.[7]

Follow-up after initial curative treatment

In this thesis, we further explored outcome of the subgroup of patients with the best perspective, i.e. clinical complete responders following chemoradiation. We showed that most recurrences in this subset of patients with proximal esophageal cancer occurred within the radiation field and within the first three years after primary definitive chemoradiation therapy. Whether or not follow-up after definitive chemoradiation for esophageal cancer is useful remains controversial. Hence, recommendations by NCCN and ESMO guidelines are inconsistent regarding follow-up strategies and duration of surveillance.[8,9] Considering the burden of prolonged follow-up on patients quality of life and health care costs, we state that restricting follow-up to three years following definitive chemoradiation for proximal esophageal cancer is to be considered. Unless other factors regarding patients recovery, e.g. repeated dilatations, dietary or psychosocial needs, require continued surveillance. It would be of great interest to study the influence of different novel methods of follow-up on the timing and rate of detection of residual disease or locoregional recurrence, e.g. diffusion-weighted magnetic resonance imaging (MRI),[10] a radiomics nomogram model,[11] or

circulating tumor DNA.[12] In addition, benefits and strains of salvage treatments should further be addressed, reinforcing quality of life. Better pre-selection of patients will lead to less (avoidable) burden of invasive strategies for patients and their multidisciplinary expertise team.
Furthermore, research aiming to establish the effect of surveillance for early detection of second primary tumors may be of importance, considering the high occurrence of a second squamous cell cancer due to the close association of alcohol and smoking disposition.[13]

To optimize awareness amongst physicians in esophageal cancer care, the findings of this thesis were presented at the scientific meetings of DUCG and NWHHT, and at the national congress of the Netherlands Medical Oncology Working group (NVMO). Moreover, it is proposed to insert a separate paragraph in the national guideline of esophageal cancer treatment, highlighting the therapeutic options and their burden in patients with proximal esophageal cancer.

The preceding aspects delineate that further research in (proximal) esophageal cancer is not only crucial from a patients' point of view by providing progress in treatment and subsequent outcome, but also has the potential to result in an economic and societal benefit. Accordingly, we consider the results of our research as a step forward in esophageal cancer patient care.

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