Advanced colorectal cancer: Exploring treatment boundaries
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General introduction and outline of the thesis
Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide, with more than 1.200.000 new diagnoses every year and resulting in 600.000 deaths/year\(^1\)-\(^3\). In Europe alone, CRC is responsible for 200.000 deaths/year\(^4\). The International Agency for Research on Cancer published European cancer figures in 2006: the estimated age-standardized incidence rate per 100.000 was 55.4 for men and 34.6 for women, with estimated age-standardized mortality rates per 100.000 of 27.3 in men and 16.6 in women, respectively\(^5\).

As with the majority of cancers, long-term survival is dependent on the stage of the disease at diagnosis. The average 5-year overall survival (OS) ranges from approximately 90% for stage I disease to 5% or less for stage IV (metastatic) CRC\(^6\).

The scope of this thesis mainly focuses on advanced and metastatic CRC. About 20-30% of CRC patients present with stage IV disease at diagnosis and about 50-60% of CRC patients will eventually develop metastases at some point in the course of their disease\(^4,7\). Peritoneal carcinomatosis (PC) is reported to occur in about 12-13% of patients with CRC\(^8-10\). Often, it presents in combination with other sites of disease, such as liver and/or lung metastases\(^10,11\). In general, about 50% of CRC patients will develop colorectal liver metastases (CRLM)\(^4,12\).

Two decades ago, (palliative) systemic chemotherapy was the only available treatment option for metastatic CRC, resulting in a very poor outcome. But over the last 15 to 20 years, there has been a significant evolution in systemic treatment modalities for CRC, with more efficient systemic chemotherapy (e.g. oxaliplatin- or irinotecan-based chemotherapy) and the addition of biologicals (e.g. bevacizumab, cetuximab) to the treatment regimens\(^13-31\). Furthermore, there has been a major surgical effort to expand the indications of surgical resection for metastatic
disease, resulting in longevity in a significant subset of patients. Also, the concept of neo-adjuvant chemotherapy has significantly increased the number of patients who are suitable for metastasectomy.\textsuperscript{4,32-47}

This clinical thesis aims to explore the boundaries of treatment in advanced CRC. It is subdivided in 3 parts:

In the first part, we focused on unresectable PC from colorectal origin. We retrospectively studied all patients that were diagnosed with unresectable PC from a single center (the Netherlands Cancer Institute/Antoni van Leeuwenhoek-hospital in Amsterdam [the Netherlands]) over the last 5 years. We analyzed survival data and risk factors potentially influencing prognosis. Subsequently, we performed a prospective pilot study to evaluate whether neo-adjuvant chemotherapy can increase resectability in a subgroup of patients with unresectable PC, as this is already a validated strategy for CRLM. We also reviewed literature to evaluate the incidence and clinical significance of Bevacizumab-related non-surgical and surgical serious adverse events in metastatic CRC: we explored at what morbidity and mortality cost bevacizumab can be added to the neo-adjuvant chemotherapy regimens for patients with stage IV CRC?

In the second part, we focused on resectable PC from colorectal origin. Complete cytoreductive surgery (CCRS) followed by Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) has progressively become an accepted combined treatment modality for this subgroup of patients. A prospective, multicenter, observational study was performed in Belgium to evaluate the outcome of CCRS and HIPEC with Oxaliplatin in patients with resectable PC from CRC. Is this very invasive combined treatment modality worthwhile? And what is the clinical cost in morbidity and mortality that comes with it’s survival benefits?
We then performed a retrospective analysis of prospectively gathered data from 2 HIPEC centers: the Netherlands Cancer Institute/Antoni van Leeuwenhoek-hospital in Amsterdam [the Netherlands] and the University Hospitals Gasthuisberg in Leuven [Belgium]. Morbidity and mortality, as well as survival data were compared after CCRS and HIPEC with Mitomycin C and Oxaliplatin, respectively. Which intraperitoneal agent should be prefered for HIPEC?

And finally, a reflection was made on the potential role for ‘prophylactic’ HIPEC in patients with T4a colon cancer, who are at high risk of developing PC. The burden of PC in T4a tumors was assessed, as well as the risk for local intraperitoneal recurrence as the only site of metastatic disease. This is crucial to adequately estimate the potential benefits of HIPEC as an adjuvant treatment strategy in T4a colon cancer patients.

In the third part, we focused on the additive value of RFA in the treatment of CRLM. Does RFA push treatment boundaries for CRLM?

A review of literature assessed RFA with and without chemotherapy, RFA with and without liver resection, RFA for solitary unresectable CRLM, surgical and percutaneous imaging-guided RFA and RFA compared with chemotherapy. The reported survival and recurrence data, as well as morbidity and mortality data in these different settings were analyzed. Furthermore, the review reflects on a possible role for RFA in resectable CRLM.

A retrospective analysis of RFA for liver lesions compared morbidity and mortality data after laparoscopic versus open RFA.

And finally, RFA is evaluated as a coagulative tool to prepare liver resection planes: is this a useful strategy to reduce intra-operative blood loss?
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