Impact of multimodal treatment on patient outcomes and prognosis in colorectal peritoneal metastases

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Introduction / Research aims

This thesis focused on patients with peritoneal metastases of colorectal origin, with most emphasis on patients with limited intraperitoneal disease. These patients may be eligible for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC), a surgical procedure in which all visible tumor is resected by the surgeon (CRS), followed by the circulation of heated chemotherapy solution throughout the abdomen (HIPEC). Since about twenty years, this treatment has increasingly been applied in selected patients with this severe type of metastatic colorectal cancer. Still, recurrent disease unfortunately occurs in most patients and survival after this treatment is about 3 years on average. However, it is the best available treatment for these patients resulting in the best survival so far. This illustrates the need for further improvement of treatment options for these patients.

In other types of cancer like gastric cancer or esophageal cancer, much research is performed on perioperative treatment strategies, i.e. administration of neoadjuvant (prior to surgery) or adjuvant (after surgery) systemic chemotherapy. As the administration of systemic chemotherapy is usually associated with better survival, it is nowadays routinely administrated in patients with these types of cancer. For colorectal peritoneal metastases, this was never investigated, although many clinicians expect that also in these patients, systemic chemotherapy prior to and after surgery may be beneficial. Therefore, the CAIRO6 trial was initiated in 2017. This multicenter trial randomizes patients with colorectal peritoneal metastases into two treatment groups: a) upfront CRS-HIPEC without any perioperative systemic chemotherapy, being the standard of treatment for all patients in the Netherlands and b) neoadjuvant systemic chemotherapy (prior to CRS-HIPEC) and adjuvant systemic chemotherapy (after CRS-HIPEC) in addition to CRS-HIPEC. This thesis comprises a descriptive article about how the study is executed in the Netherlands, as well as the results of the phase II study, which showed this treatment to be safe and feasible in these patients, without worsening quality of life. Also, these treatments have the same impact on quality of life as frequently performed surgeries for primary colorectal cancer. Other parts of this thesis focused on patients with peritoneal (or ovarian) metastases in general, with data retrieved from the Netherlands Cancer Registry. These nationwide data provide insight in the risk factors and incidence of colorectal (or ovarian) metastases from
colorectal cancer, and provide insight into the severity of this disease. Several aspects of the treatment of these patients (i.e. the chemotherapeutic regimens used during HIPEC or the administration of chemotherapy after surgery) were investigated on a nation-wide level.

**Target population**

Firstly, the results of this thesis are of interest for patients who are diagnosed with colorectal peritoneal metastases and their doctors treating them. As the CAIRO6 trial aims to directly investigate the efficacy of an experimental treatment strategy (perioperative systemic chemotherapy in addition to CRS-HIPEC) and compare it to the currently standard of care in the Netherlands (CRS-HIPEC without perioperative systemic chemotherapy), the results of this trial will be of great value for these patients. The phase III trial which aims to show whether this additional perioperative systemic therapy is beneficial in terms of prognosis is still ongoing. Nevertheless, studies included in this thesis already show that perioperative systemic chemotherapy is safe and feasible in these patients, as no increased risk for postoperative complications was seen in these patients as compared to patients who did not receive systemic chemotherapy. Furthermore, systemic chemotherapy did not worsen quality of life. Also, CRS-HIPEC in general did not have a greater impact on quality of life than conventional colorectal surgery. These results are valuable for patients undergoing these treatments and their clinicians determining the patients’ treatment strategies.

Secondly, the results of this thesis are of interest for patients with colorectal cancer without (peritoneal) metastases, as three population-based studies in this thesis focused on patients with colorectal cancer in general, and investigated their risk factors for peritoneal or ovarian metastases. These results are informative for patients who are diagnosed with colorectal cancer and may also enhance clinical decision making with regard to follow-up, as these risk factors may be considered by the treating clinicians.

Thirdly, two chapters in this thesis focused on the treatment of patients with colorectal peritoneal metastases on a nationwide level. Both the types of chemotherapy used during CRS-HIPEC (the chemotherapeutic regimen which is used to circulate through the abdomen) and the routinely administration of
systemic chemotherapy after CRS-HIPEC (adjuvant systemic therapy) were investigated. It showed that both HIPEC regimens which are currently being used in the Netherlands (oxaliplatin and mitomycin C) are equally effective, and that systemic chemotherapy after CRS-HIPEC may be beneficial to prolong prognosis. As all of these studies were performed on nationwide databases, its results present real world data and therefore provide reliable information which can be translated to clinical practice.

Relevance

Ever since the implementation of CRS-HIPEC as standard of care for selected patients, colorectal peritoneal metastases are considered a curative disease with possible long-term survival in selected patients. Still, this disease remains aggressive with high relapse-rates despite extensive surgical procedures. Perioperative systemic therapy might prolong relapse-free survival and overall survival (as investigated in the CAIRO6 trial), which would subsequently lead to an increasing group of peritoneal metastases-survivors. This could possibly lead to new challenges and needs in the future (e.g. altered post-operative quality of life, strategies on duration and intensity of follow-up) which must be anticipated by clinical health care and research. Furthermore, this thesis described that the number of patients with peritoneal metastases within the total group of colorectal cancer patients in the Netherlands has increased over the last years, which would make this research even more relevant for the patient population with colorectal cancer. Also, quality of life studies in this thesis showed that additional systemic therapy in patients undergoing extensive surgery does not worsen quality of life. These findings might also be valuable for clinical decision-making in patients with other severe malignancies in whom a comparable multimodality treatment strategy is considered.

Finally, possible changes in the treatment of patients with colorectal peritoneal metastases as a result of the CAIRO6 trial will also influence hospital policies, health insurances, and the pharmaceutical industry. If perioperative systemic chemotherapy would become standardized, this would lead to modifications in care paths and increase costs. In patients with ovarian metastases from colorectal cancer, CRS-HIPEC appeared to be the most efficient treatment strategy. Although some experts already advocated CRS-HIPEC in these patients, others did not.
This has led to a variation among treatment strategies of colorectal ovarian metastases. If all patients with ovarian metastases eligible for CRS-HIPEC would routinely undergo this procedure, it would increase health care costs accordingly. A cost-effectiveness analysis is designated to investigate whether the routinely administration of CRS-HIPEC would be viable in this patient group.

**Activities / Innovation**

Since half of the studies included in this thesis are population-based, the results from this thesis are informative for a wide range of clinicians, patients, and researchers from different countries around the globe. As the treatment of colorectal peritoneal metastases is more and more changing into a multimodality approach, clinicians from different areas of expertise, such as surgery, oncology, radiotherapy, and radiology may find results of the studies included in this thesis useful in their clinical work. Furthermore, findings from the studies in this thesis may serve as a base for future clinical research as they present an accurate overview of incidences, risk factors and currently applied treatment strategies which reflect real-world, contemporary clinical practice in the Western world.

Although the systemic treatment regimens being administered in the experimental arm of the CAIRO6 trial are well-known chemotherapeutics which are broadly administered in patients with (metastatic) colorectal cancer, this trial is the first randomized controlled trial to investigate its efficacy in patients with colorectal peritoneal metastases undergoing CRS-HIPEC. While CRS-HIPEC is also recommended in most international guidelines for the treatment of this disease, no evidence for the efficacy of systemic chemotherapy exist yet. Besides, this thesis comprises the first comparison of patient-reported outcomes (quality of life) between patients who did, and patient who did not undergo perioperative systemic chemotherapy. The CAIRO6 phase III trial will eventually show whether perioperative systemic chemotherapy is beneficial in patients with colorectal peritoneal metastases undergoing CRS-HIPEC. The results of this study may lead to changes in (inter)national guidelines about treating these patients, therewith changing clinical care for patients with colorectal peritoneal metastases worldwide.