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Original Research

Challenging the dogma of colorectal peritoneal metastases as an untreatable condition: Results of a population-based study

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Abstract ***Purpose:*** To determine the impact of the implementation of novel systemic regimens and locoregional treatment modalities on survival at population level in colorectal cancer (CRC) patients presenting with peritoneal metastases (PMs).
Methods: All consecutive CRC patients with synchronous PM (<3 months) between 1995 and 2014 were extracted from the Eindhoven area of the Netherlands Cancer Registry. Trends in treatment and overall survival were assessed in four time periods. Multivariable regression analysis was used to analyse the impact of systemic and locoregional treatment modalities on survival.
Results: A total of 37,036 patients were diagnosed with primary CRC between 1995 and 2014. Synchronous PM was diagnosed in 1,661 patients, of whom 55% had also metastases at other sites (n = 917) and 77% received anticancer therapy (n = 1,273). Treatment with systemic therapy increased from 23% in 1995–1999 to 56% in 2010–2014 ($p < 0.0001$). Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) was applied since 2005 and increased from 10% in 2005–2009 to 23% in 2010–2014. Surgery for lymphatic or haematogenous metastases increased from 2% to 10% in these periods. Median overall

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survival of the complete cohort improved from 6.0 months in 1995–2000 to 12.5 months in 2010–2014 ($p < 0.0001$), with a doubling of survival for both PM alone and PM with other involved sites. The influence of year of diagnosis on survival (hazard ratio, 2010–2014 versus 1995–1999; 0.5, 95% confidence interval: 0.43–0.62; $p < 0.0001$) disappeared after including systemic therapy and locoregional treatment modalities in subsequent multivariable models. ***Conclusion:*** CRC patients presenting with PM are increasingly offered a multidisciplinary treatment approach, resulting in an increased overall survival for the entire cohort.

1. Introduction

Peritoneal dissemination is a common manifestation of metastases in patients with colorectal cancer (CRC), affecting approximately 10% of CRC patients [1–3]. Responses to 5-fluorouracil are poor, and results after only palliative surgical interventions are disappointing [4], resulting in an invariable fatal prognosis with conventional treatment [2,3,5]. Therefore, patients with peritoneal metastases (PMs) are considered to be virtually untreatable by many physicians, often resulting in only best supportive care in a palliative setting.

The introduction of novel systemic regimens combing chemotherapy and monoclonal antibodies may offer new treatment possibilities for CRC patients with PM. However, results from randomised studies on the efficacy of these systemic regimens in patients with PM are lacking, as these patients are often excluded from clinical trials given the problems in disease measurability by computed tomography imaging.

The hypothesis that PM may be regarded as locoregional tumour spread rather than systemically metastasised CRC resulted in the development of a locoregional treatment strategy combining cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC). Although promising results have been demonstrated with this treatment, the efficacy of CRS and HIPEC in CRC patients with PM remains a matter of debate with only one RCT supporting its beneficial value [6].

Due to the grim prognosis and the lack of solid evidence on both the systemic and locoregional treatment of PM, peritoneal disease still has a reputation of an untreatable condition. In spite of this, patients with PM in the Netherlands are treated with increased frequency and intensity [7]. We performed a population-based analysis to provide insight on the impact of this practice on survival in CRC patients presenting with PM.

2. Methods

2.1. Patients and data

Data from the Eindhoven area of the population-based Netherlands Cancer Registry (NCR) were used. This registry collects data of all patients with newly diagnosed cancer in a large part of the south-eastern Netherlands and covers an area of approximately 2.4 million inhabitants and is notified by six pathology departments, 10 community hospitals at 17 locations and two large radiotherapy institutions. Specially trained administrators of the cancer registry extract data on patient and tumour characteristics from medical records after notification by pathologists and medical registration offices, resulting in high quality of the data. Primary tumours are classified according to the Tumour Node Metastases (TNM) classification of malignant tumours. In case of missing pathological data, clinical TNM is used. Subsites of systemic metastasis at the time of diagnosis are registered according to the International Classification of Diseases for Oncology. Synchronous metastases were defined as metastases diagnosed within 3 months after the initial CRC diagnosis. Systemic treatment (yes versus no) was defined as prescription of either cytostatic drugs or targeted agents of any kind at the initial diagnosis. A distinction in surgical procedures was made between primary tumour resection (either open or laparoscopic), surgery for metastases (surgical procedures aiming to remove lymphatic or haematogenous metastases) or CRS-HIPEC. Four periods (1995–2000, 2000–2005, 2005–2010 and 2010–2014) were defined based on year of diagnosis to analyse time trends in the application of systemic therapy and locoregional treatment modalities for metastatic CRC as well as overall survival.

All consecutive patients diagnosed with primary CRC (C18.0–C20.9) between 1995 and 2014 were extracted ($n = 37{,}036$). Subsequently, all patients presenting with PM at the time of the initial CRC diagnosis were included ($n = 1{,}661$). In all patients, follow-up of vital status was complete until January 2015. This information was obtained from the municipal administrative databases, in which data on all deceased and emigrated persons are collected in the Netherlands.

2.2. Statistical analyses

Descriptive statistics were used to provide an overview of the total study population of patients with synchronous PM from CRC. Trends in treatment across the