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Prognostic impact of immune response in resectable colorectal liver metastases treated by surgery alone or surgery with perioperative FOLFOX in the randomised EORTC study 40983

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Abstract ***Aim:*** To investigate whether the immune response in colorectal liver metastases is related to progression free survival (PFS) and if this may be influenced by systemic therapy. ***Methods:*** A retrospective central collection of tumour tissue was organised for the European Organisation for Research and Treatment of Cancer (EORTC) study 40983, where patients with colorectal liver metastases were treated by either resection alone or resection with perioperative FOLFOX. Immunostaining on whole slides was performed to recognise

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B-lymphocytes
Macrophages
Mast cells

T-lymphocytes (CD3+, CD4+, CD8+), B-lymphocytes (CD20+), macrophages (CD68+) and mast cells (CD117+) inside the tumour, at the tumour border (TNI) and in normal liver tissue surrounding the tumour (0.5–2 mm from the TNI). Immunological response was compared between treatment arms and correlated to PFS.

Results: Tumour tissue and immune response profiles were available for 82 resected patients, 38 in the perioperative chemotherapy arm and 44 in the surgery alone arm. Baseline patient and disease characteristics were similar between the treatment arms. In response to chemotherapy, we observed increased CD3+ lymphocyte and mast cell counts inside the tumour ($p < 0.01$), lower CD4+ lymphocytes in the normal liver tissue ($p = 0.02$) and lower macrophage counts in normal tissue ($p < 0.01$) and at the TNI ($p = 0.02$). High number of CD3+ lymphocyte and mast cells, and high T-cell score were correlated with tumour regression grade (TRG). Prolonged PFS correlated with the presence of mast cells in the tumour (9.8 versus 16.5 months, Hazard ratio (HR) 0.54 $p = 0.03$), higher CD3+ lymphocyte count at the TNI (10.8 versus 22.8 months, HR 0.57, $p = 0.03$) and T-cell score >2 (10.8 versus 38.6 months, HR 0.51, $p = 0.04$).

Conclusion: Our analyses in the context of a randomised study suggest that chemotherapy influences immune cell profiles, independent of patient characteristics. Immune responses of lymphocytes and mast cells were associated with pathological response to chemotherapy and to increased PFS. High CD3+ lymphocytes at the tumour front and intratumoural mast cells appear to be prognostic for patients with colorectal liver metastases.

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1. Introduction

Colorectal cancer (CRC) is one of the top three most-frequent cancers with 446.000 (13.0%) new cases and 214.000 (12.2%) deaths in Europe each year [1]. About half of the patients diagnosed with CRC will eventually develop liver metastases (CRLM) and only 10–20% of these patients will be resectable resulting in five-year survival rates of up to 60% depending on the tumour characteristics, extent of the disease and resection margin [2,3].

The immune system seems to play an important role in CRC survival [4]. Tumour infiltrating lymphocytes (TILs) are associated with a better prognosis [5]. Although the complexity and extent of tumour-immune-modulation are still not fully understood, several mechanisms and cells have been identified to possess anticancer properties (e.g. cytotoxic and memory T cells), while others are immune suppressive and result in poor outcome (e.g. regulatory T cells) [6,7]. Especially (CD3+) TILs in colorectal cancer are associated with an improved survival and could potentially be more relevant for prognosis than conventional UICC-TNM classification [8]. Next to tumour infiltrating lymphocytes (TILs), other immune cells have been associated with colorectal cancer as well, e.g. macrophages and mast cells [9–12].

FOLFOX (5-FU with leucovorin and oxaliplatin) has a central role in the adjuvant treatment of colorectal cancer and resectable colorectal liver metastases. Next to an immune suppressive effect (neutropenia), it has also a stimulating effect on the peritumoural immune response [13,14]. Murine studies show oxaliplatin has a synergistic effect with an intact immune system, as immune competent mice treated by oxaliplatin have a better tumour survival than immune incompetent littermates [14,15]. In addition, 5-FU acts proinflammatory by inducing heat-shock proteins (also called stress proteins) that are involved in both the innate and adaptive immune responses and facilitates antigen uptake and subsequent cross-presentation of tumour antigens to various immune cells [16].

There have been several studies on different types of immune response in CRLM [7,17–24]. Generally a higher response is associated with an improved outcome, however these studies are not comparable as they have investigated different immune cells at various locations near or in the tumour with a diverse degree of systemic treatment regimen.

Recently it has been shown that an improved immune response (CD3+, CD8+ and granzyme B+ T-cells) at the tumour invasive margin of colorectal liver metastases is associated with response to chemotherapy (RECIST) and longer PFS and OS rates [22]. Although, whether this prolonged survival is a direct result of the improved immune response or solely attributed to systemic therapy is unknown as all patients received neoadjuvant treatment.

The aim of our study was to investigate the distribution and possible benefit of an immune response in relation to chemotherapy in patients with resectable CRLM with and without perioperative FOLFOX chemotherapy in a randomised trial.

2. Materials and methods

Patients from the European Organisation for Research and Treatment of Cancer (EORTC) intergroup

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