THE VALUE OF TUMOR DEBULKING FOR PATIENTS WITH EXTENSIVE MULTI-ORGAN METASTATIC COLORECTAL CANCER

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Running head: Debulking in metastatic colorectal cancer

Author Statement

Elske Gootjes and Lotte Bakkerus were involved in conception and design, search and review of the literature and interpretation of the data therein, drafting and revising the article. Henk Verheul and Kees Verhoef were involved in conception and design, review of the literature and interpretation of the data therein, and drafting and revising the article. Albert ten Tije, Petronella Witteveen, Tineke Buffart, John Bridgewater and John Primrose were involved in review of the literature and critically revising the article. All authors gave final approval of this version to be published.

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Resection of oligometastases in mCRC is common practice. Preliminary evidence shows survival benefit from local treatment of metastases in extensive mCRC, which is increasingly being performed. Whether this 'tumor debulking' truly provides survival benefit for patients with mCRC undergoing palliative combination chemotherapy needs further investigation.

KEYWORDS

Metastatic colorectal cancer

Tumor debulking

Cytoreduction

Extrahepatic disease

Background

Local treatment of metastases by surgical resection or ablative techniques is technically feasible in an increasing number of patients with multi-organ metastatic colorectal cancer (mCRC). This results in a growing debate in multidisciplinary teams on whether or not local treatment of metastases should be performed. For selected patients with oligometastatic CRC, metastasectomy has become standard of care based on retrospective reports showing long term survival. Preliminary evidence suggests that patients with extensive mCRC may also benefit from local treatment of metastases, which could be considered as a 'tumor debulking' strategy, knowing that even after macroscopic complete resection disease will recur in the vast majority of patients.[1] There is an clinical need for more evidence whether tumor debulking leads to survival benefit when added to palliative chemotherapy.

Local treatment modalities

Developments in surgical procedures, combination with local ablative techniques and the use of conversion chemotherapy have increased the number of patients for whom local treatment of metastases is feasible. Multiple local treatment strategies, such as radiofrequency or microwave ablation (RFA, MWA), irreversible electroporation (IRE), local radioembolisation techniques (with or without cytotoxic or radiolabeled agents) and stereotactic radiotherapy are developing rapidly and finding their way into clinical practice.[2-4] One of the most crucial aspects to define the optimal strategy of therapy for patients with mCRC, is the evaluation on a case by case base in an expert multidisciplinary team. Solid evidence supporting decision-making is unavailable and hardly any randomized trials comparing local treatment modalities with each other or with systemic therapy have been performed. Large patient populations are needed to demonstrate statistically significant non-inferiority or survival benefit. Moreover, in daily clinical practice, it seems increasingly difficult to randomize patients for local treatment versus standard systemic treatment, due to lack of clinical equipoise in both patients and treating physicians.

Local treatment in multi-organ mCRC

By far the most debated contraindication to treatment of colorectal liver metastases is the presence of extrahepatic disease (EHD). For selected patients with extrahepatic oligometastases, a local treatment strategy is considered potentially curative based on retrospective reports. [1] Pulitanò et al. reported from an international multi-institutional database on 1629 patients who underwent resection of CLM , from which 10,4% had resection from EHD. If survival was stratified by the total number of metastases treated, the presence of extrahepatic disease still had a negative prognostic impact, but the relative impact of extrahepatic disease diminished as the total number of metastases treated increased.[5] Hadden et al. published a review and meta-analysis on resection of CRC liver metastases and extra-hepatic disease, including 15144 patients (from 52 studies), of which 2308 patients had extrahepatic disease (EHD). The five year OS rates were 26% , 17%, and 15% for extrahepatic lung, peritoneum and lymphnode involvement respectively.[1] These data suggest that in a subset of patients with extrahepatic disease tumor debulking may provide the possibility of long-term survival, but does not necessarily exceed survival times reached by systemic therapy only. Based on the available data, unequivocal selection criteria have not been established. Predictive models derived from retrospective series are suggested, but validation studies are lacking and they are currently not used in clinical practice.

Colorectal Cancer metastases

CRC generally metastasizes by lymphatic and hematogenous dissemination, as well as contiguous and transperitoneal spread. This significant difference from the predominantly abdominal dissemination pattern of ovarian carcinoma could explain why a treatment strategy aiming for tumor debulking is long standing in ovarian carcinoma and only of more recent focus in mCRC. The dissemination pattern of CRC from localized towards extensive metastatic disease can be considered as a continuum in which the chance of curation reduces with the extent of the disease (Figure 1).

Both the stage of the disease at the time of diagnosis as well as the underlying biological characteristics of the malignancy constitute important prognostic factors. At diagnosis, micro-metastases are already present in a subset of patients with localized CRC and in the majority of patients with oligometastases (reflected by the dotted line). Currently, surgical resection is mainly preserved for patients who are treated with curative intent, while in a palliative setting resections are only indicated to alleviate or prevent symptoms. In patients with mCRC confined to the liver, resection of liver metastases can lead to long term survival rates of approximately 40%. Although not formally proven in a randomized clinical trial, this approach is generally accepted as an effective treatment strategy with curative intent. Approximately one in six patients are actual ten-year survivors and could be considered to be cured.[6] It is however important to realize that an estimated 20% patients with liver metastases are eligible for surgical treatment, due to the extent of disease at the time of diagnosis.

Tumor debulking

There are theoretical benefits of cytoreduction for patients with extensive disease, but thus far there are no clinical data to support this. In patients with NSCLC, tumor size (by CT volumetric analysis) was correlated with plasma ctDNA,[7] generating the hypothesis that tumor debulking could reduce metastatic potential. Furthermore, one could postulate that organ dysfunction could possibly be prevented by reduction of tumor burden, thereby improving performance status and tolerance of systemic therapy. In addition, after removal of poorly vascularized tumors and drug resistant clonal cells, the limited tumor residue may be better perfused making it more responsive to cytotoxic agents. Moreover, reduction of the total tumor mass may alleviate associated immunosuppressive effects and thereby enhance host immunocompetence, all potentially improving overall survival.

Despite the lack of mechanistic proof, the combination of tumor debulking and chemotherapy is evidence-based standard of care or advanced ovarian cancer. For these patients overall survival

benefit from cytoreduction has been demonstrated including improved response to chemotherapy for patients undergoing tumordebulking.[8] Critics emphasize however that the biological behavior and extent of disease at diagnosis are leading in the course of the disease. Moreover it is speculated that the immediate postoperative low immune status and growth factors released after ablative interventions may actually facilitate tumor growth. Practical issues in considering the role of tumor debulking in extensive disease include the fact that effective systemic treatment needs to be interrupted for local treatment to take place. Procedure related morbidity and mortality, although improved by supportive care and development of minimal invasive techniques for local treatment, may impact quality of life and performance status of patients. Solid evidence showing favorable PFS or OS while maintaining quality of life is therefore required in order to make these local treatment strategies part of standard palliative treatment in combination with systemic treatment for patients with mCRC. Randomized trials in which metastasectomy for oligometastatic disease will be evaluated are unlikely to be performed since it is generally considered unethical to withhold patients this treatment strategy based on the favorable results from retrospective series. The way forward may be to explore tumor debulking by radical local treatment approaches in patients who respond to chemotherapy irrespective of complete resectability of the disease. Comparison of local treatment strategies with modern palliative systemic treatment including combination chemotherapy with 5-FU and oxaliplatin or irinotecan and anti-VEGF or anti-EGFR monoclonal antibodies that can result in a median OS of up to 30 months, are lacking at this point.[9] Patients with extensive multi-organ disease are generally considered to have a worse prognosis, estimated to be around 18 months.

Trials in progress

Several study groups are evaluation the role of tumor debulking in extra hepatic mCRC. Both in the Netherlands (NCT01606098), France (NCT02363049; NCT02314182) and in China (NCT02149784) multicenter randomized, phase III trials are recruiting patients with synchronous unresectable

metastases of CRC and randomizing between systemic therapy only and resection of the primary tumor followed by systemic therapy. In the multicenter phase III ORCHESTRA trial patients with multi-organ CRC metastases, are randomized between the combination of chemotherapy and maximal tumor debulking by a combination of surgery, radiotherapeutic or thermal ablation (at least 80% of tumor lesions is considered to be resectable), *versus* chemotherapy alone (NCT01792934). Safety and feasibility is demonstrated after inclusion of 100 patients. [10] The LUNA trial (NCT02738606), is a phase II single-institution randomized trial randomizing patients with resectable liver metastases and unresectable, (but low volume) lung metastases between liver resection plus chemotherapy or chemotherapy without liver resection.

Conclusion

Solid evidence is needed to value the preliminary evidence gathered from retrospective series, suggesting that patients with extensive metastatic colorectal cancer may experience clinical benefit when already established and innovative tumor debulking approaches are combined with standard palliative systemic therapy. Especially the fast development of new local treatment options requires evidence-based implementation of these strategies in daily clinical practice for patients who are considered to be incurable due to the extent of the metastatic disease. Although debulking might be feasible with current local treatment modalities in an increasing portion of patients with mCRC, only overall survival benefit can confirm that these patients actually profit from this strategy. The ongoing trials will provide strong clinical evidence for multidisciplinary decision-making in patients with mCRC.

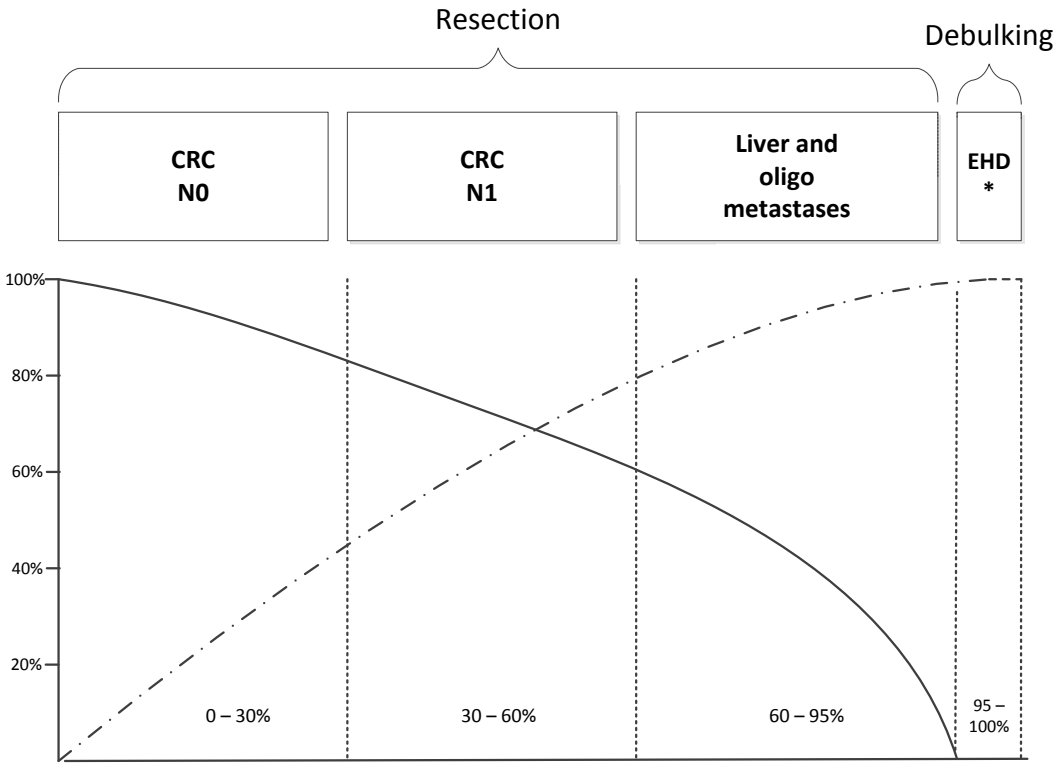

Figure 1. Resection or debulking in colorectal cancer

Different stages of colorectal carcinoma, CRC with no positive lymphnodes (Stage I and II), pathological lymphnodes present (stage III) and stage IV disease, separated in liver and oligometastases and multi organ extra hepatic disease (≥ 2 different organs with ≥ extrahepatic lesions)

Solid line showing the chance of curability and the dashed line showing the chance of presence of micro metastases

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