

THE IMPORTANCE OF CHEMOTHERAPY IN THE MANAGEMENT STRATEGIES REGARDING HEPATIC METASTASES IN COLORECTAL CANCER

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Abstract

The liver is the most common site for haematogenous metastases in colorectal cancer. Over the past ten years the survival rate in patients with hepatic metastases has significantly improved, mostly because of the development of new chemotherapy protocols, as well as new therapeutic agents. Overall, these are strengthening the effects of surgery, which in case of radical resection offers the best survival. Moreover, surgical control of liver metastatic extensive disease can combine resection with ablation therapies or staged methods.

Today, the treatment of colorectal cancer liver metastases is essentially multi-disciplinary, the medical oncologist together with the surgeon and the gastro-enterologist deciding the therapeutical sequence individualised for each patient.

Rezumat

Ficatul este organul cu cea mai frecventă localizare a metastazelor în cancerul colorectal.

În ultimii zece ani, supraviețuirea pacienților cu metastaze hepatice din cancerul colo-rectal s-a îmbunătățit semnificativ, în special datorită dezvoltării unor noi protocoale de chimioterapie, precum și a utilizării unor noi agenți terapeutici. Acestea nu fac decât să consolideze efectele chirurgiei, care în condițiile unei rezecții radicale (marginii negative macroscopice) oferă cea mai lungă supraviețuire.

În ceea ce privește chimioterapia, perfecționarea protocoalelor precum și adăugarea terapiei cu anticorpi monoclonali a ajutat la consolidarea efectelor chirurgiei.

Astăzi, tratamentul metastazelor hepatice este eminent multi-disciplinar, oncologul alături de chirurg și gastroenterolog stabilesc secvența terapeutică personalizată pentru fiecare pacient.

Keywords: colorectal cancer, hepatic metastases, chemotherapy.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed type of cancer in males and the second in females. The liver is one of the favourite target organs for metastases in CRC, with portal circulation as major means for providing the venous return flow for subdiaphragmatic digestive *viscera* and its distribution at port system level favouring the settlement in the liver of migrated tumour cells [1, 2]. Prognosis of patients with untreated liver metastases is generally poor [3-6].

Just as important for patients with metastatic liver disease, new chemotherapeutic agents such as irinotecan and oxaliplatin, as well as new targeted agents such as cetuximab and bevacizumab added to current protocols have improved response and survival rates [6, 7]. A combined therapeutic approach has shown the most important promise, especially for the patients previously considered unresectable, and achieve survival rates similar to those for patients deemed resectable from the onset [8-10].

Diagnosis of liver metastases

A decisive role in the selection of therapeutic options take the lesion assessments carried out by cascading imaging tests, including preoperative, classical or contrast, ultrasound, computer tomography (CT) or magnetic resonance imaging and, last but not least, positron emission tomography with fluorine 18 fluorodeoxyglucose. The last cornerstone in order to obtain a free resection margin is the intraoperative ultrasound [11, 12].

Imaging methods are also a “must” in post-therapeutic monitoring of metastases, in order to detect recurrence or new liver determinations. Combined with increased carcinoembryonic antigen colorectal cancer specific tumour markers, imagistic methods achieve optimal surveillance of progression of liver secondary processes [13-15].

Therapeutic options in colorectal cancer liver metastases

The therapeutic approach in patients with liver metastases is multimodal, and the therapeutic cornerstones are surgical treatment, including resection or local ablative therapies, and chemotherapy, administered in personalised sequence and, in some cases, despite the relatively small tolerance of the liver to radiation, conformational radiotherapy [16] for reduced liver volumes may also be considered.

In the therapeutic protocol must be defined the resectability (primary or secondary after various conversion therapies) or non-resectability of liver metastases, with a major role in prescribing the procedural cascade.

Resection of liver metastases

Surgical resection is the "golden standard" in the treatment of liver metastases, as the only potentially curative method able to provide 20-40% survival [17]. The essential in putting into value the potential of the method is to obtain a complete resection ("R0"), as incomplete resections with outstanding micro- and macroscopic tumor residues (R1, R2 – "R1" = resection indicates that the margins of the resected parts show tumor cells when viewed microscopically, "R2" = resection indicates that portions of tumor visible to the naked eye were not removed) do not provide long-term survival.

Immunotherapy and chemotherapy

As shown above, increased resectability is a crucial opportunity for better survival and the problem now arises for finding means to enhance this possibility. Thus, chemotherapy has proved very useful in that respect, such targeted regimens as FOLFIRI (leucovorin, 5-fluorouracil and irinotecan) and FOLFOX (leucovorin, 5-fluorouracil and oxaliplatin) having resulted in increases between 10% - 35% of resectability [18-21].

Hepatic resectability was the focus of several extensive recent studies such as the Intergroup trial 40983 carried out by the European Organization for Research and Treatment of Cancer (EORTC) and the study performed on 1600 patients in the Memorial Sloan-Kettering Center on whom hepatic resection was performed for CRC, both studies showing improved rates of both progression free survival and overall survival [22, 23]. According to these studies, such results seem to be due to the combined effects of better targeted chemotherapy, better quality of chemotherapy agents as well as more careful selection of eligible patients according to their chemotherapeutic response [24].

After decision on lesion resectability, the problem arises of whether to use chemotherapy before surgery or not. In that respect, opinions are divided, some mentioning the beneficial effect of pre-surgery chemotherapy to help control the micrometastatic disease, reduce tumour size, additionally evaluate chemotherapeutic activity and tolerance, and finally serve as a predictor of potential liver surgery success [22-24].

On the other hand, those against the use of chemotherapy prior to surgery in resectable patients emphasise the dangers of potential evolution or growth at different sites, liver toxicity by Chemotherapy Associated Steatohepatitis (CASH), election of resistant clones. Last but not least, the possibility should also be considered that response to prior chemotherapy may increase the difficulty of subsequent surgery [25-27].

Considering all the above, practice seems to indicate that the first to be performed should be the resection, followed by chemotherapy, which is however not suitable in the case of metachronous lesions and borderline resectability.

An alternative mean to improve adjuvant approach of colorectal liver metastases consists of immunotherapy, which relies on the valuable liver immune system.

Development of further clinically established metastases may originate in the presence of deposits consisting of microscopic size tumour cells in the liver [28].

In addition, surgery itself may have a tumourigenic outcome, which may be the result of the healing process, which involves generation of angiogenesis mediators, factors of growth, chemokines and inflammatory cytokines by the healing tissues [29].

Further at the liver level, chronic inflammation or intrinsic tumour pathways determine *in vivo* expansion of dendritic cells and macrophages with modified stimulatory activity, as well as myeloid-suppressor cells and regulatory T cells, which exert potent inhibitory effects on anti-tumour immunity.

The assumption is that antibodies could be used to stimulate inherent liver immunity to check development of metastatic tumour deposits at the level of the liver.

In that respect, an anti-tumour vaccine has been developed consisting of heat shock-induced protein 96 extracted from liver metastases. Administration of this vaccine in patients with CRC induces a tumor-specific response mediated by CD8 and results consist of decreased tumour recurrence and longer survival rates [30, 31].

For more powerful tumour control mediated by the immune system, combinations of anti-cancer vaccines with antibodies can be used. For improving the effectiveness of adjuvant therapy in relation to surgery, further studies remain to focus on vaccine timing.

Radiofrequency ablation and combination therapy

Local control of tumors with radiofrequency ablation is an option for patients not eligible for conventional surgery and in small metastases with central locations, whose excision would entail significant elimination of liver tissue.

In the case of more advanced stages of colorectal liver metastatic disease, when a more aggressive approach is needed, a combination of therapeutic methods can be used. Such combinations of resection, cryotherapy and hepatic arterial chemotherapy have been attempted in high

risk patients with predominant high number of multiple (≥ 5) liver lesions developed bilaterally [32-34]. The combination resulted in such rates as 87%, 43% and 23% in 1-, 3-, and 5-year survival rates, respectively.

Conclusions

Surgery has been proved to be the most important therapeutic approach likely to be successful in patients with CRC induced hepatic metastases.

Unlike earlier times, recent developments make it now possible for more helpful chemotherapy regimens and it is now up to the surgeon and his medical team to choose from the extended range of novel therapeutic means and decide on the most suitable treatment for their individual patients.

Further development for the benefit of patients however requires healthcare professionals to work together in data collection and sharing as well as the use of a multitude of protocols and involvement of multicentric trials.

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