EDITORIAL

Rectal cancer and synchronous metastases: Resection of primary tumor or not?

Cancer rectal et métastase synchrones : résection ou non de la tumeur primitive ?

In patients with rectal cancer and synchronous metastasis, the value of timing and surgical extend of a resection of the primary tumor has been discussed very controversially in the past. On the one hand, an upfront resection of the primary tumor might prevent local complications due to tumor progression if occurring under systemic therapy, such as obstruction and bleeding, potentially requiring urgent surgery, a situation which is associated with a worse prognosis due to higher morbidity and mortality; on the other hand, surgery might delay systemic treatment due to potential postoperative complications, with the risk of tumor progression – especially in those patients with high tumor load or unfavourable tumor biology. Furthermore, in the past, we have discussed these topics more or less in the light of palliative treatment only with prolongation of survival at its best, whereas now we have to consider that some of those patients with rectal cancer and synchronous metastases might have a potential option for "cure" by integrating all instruments of interdisciplinary management, such as surgery, radiotherapy and systemic treatment, which might change our opinion about former more traditional sequences and algorithms in this special situation.

In his article, Tougeron et al. reported a retrospective analysis of 96 patients with rectal cancer and synchronous metastases that initially underwent either a surgical resection of their primary tumor (S), radiotherapy with/without chemotherapy followed by surgery (CRTS), chemoradiotherapy without surgery (CRT) or chemotherapy only (CT). Pelvic symptoms including obstruction, pelvic pain/tenesmus or rectal bleeding requiring blood transfusions or endoscopic treatment were evaluated using patients’ reports. In the different treatment groups, the duration of a pelvic symptom-free period relative to the overall survival observed was 93% (S), 83.1% (CRTS), 53.0% (CRT) and 53.2% (CT), respectively. Average hospital stay for surgery patients was acceptable with 16.5 ± 2.6 days. The median time between surgery and beginning of chemotherapy in those patients with primary surgical resection was 39 ± 28 days, with a maximum interval between surgery and initiation of chemotherapy of 113 days. In multivariate analysis, only surgical treatment correlated with a significant pelvic symptom-free period (p < 0.01). Additionally, in univariate analysis, rectal resection, performance status of 0 or 1 and a Köhne score of 1 were found to be significantly correlated with a high relative pelvic symptom-free period. The authors concluded that resection of the primary tumor is the most effective treatment in selected patients with rectal cancer and synchronous metastases. Thus, do those results offer a proof of principle indicating that primary surgery should be standard treatment for this patient group? The answer is clearly "no"; although those data give good evidence for such an approach by the nature of this retrospective analysis, the most relevant alternative to primary surgery – which is a therapeutic sequence of primary chemotherapy followed by ± radiation and ± surgery – has not been evaluated at all in this study.

Recently, Poultsides et al. – again retrospectively – analysed 155 colon and 78 rectal cancer patients with synchronous metastasis that received combination chemotherapy with or without the addition of the VEGF antibody bevacizumab [1]. Only 7% of patients required palliative surgery for their primary tumor during the whole course of their disease. This finding was identical for the subgroups of colon and rectal cancer. Thus, 6% operative and 9% nonoperative emergent interventions, such as stent or radiotherapy, were described in patients with the location of their primary in the rectum. Those data do not support the resection of the primary tumor in rectal cancer patients with synchronous...
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metastases, but underline the importance of an effective upfront chemotherapeutic regimen for this patient group.

But what might be the most effective systemic treatment option and sequence for rectal cancer patients with synchronous metastases not only in terms of quality of life and symptom control, but also and in particular, in terms of best overall survival and maybe curative intention?

To answer this question, it is of utmost importance that a multidisciplinary team defines, whether metastases, mostly liver metastases, are initially resectable or potentially might become resectable after chemotherapy. In terms of resectable metastases, perioperative chemotherapy has been explored in the EORTC-40983-Intergroup trial [2]. In that study, 364 patients with up to four initially resectable hepatic metastases of colorectal cancer received either six cycles combination chemotherapy with oxaliplatin, 5-fluoruracil and leucovorin (FOLFOX 4) before and after surgery or surgery alone. The final analysis presented at ASCO 2009 showed a significant improvement of progression-free survival in the perioperative treatment arm (p = 0.025).

Therefore, taking into account comorbidities and liver function, in patients with initially resectable liver metastases the current European standard of perioperative chemotherapy should be discussed in a multidisciplinary team before surgery of primary tumor and metastases, or first resection of the primary, followed by chemotherapy and secondary resection of the metastases.

In case of initially unresectable metastases, it is important to consider that resectability and thereby cure might be achieved implementing neoadjuvant systemic treatment. Thus, Adam et al. reported a conversion of initially unresectable liver metastases into resectability in 12.5% of patients after neoadjuvant chemotherapy with FOLFOX, which resulted in a 5-year survival of 33% [3]. In a phase III study, Falcone et al. treated 244 patients with metastatic colorectal cancer with either irinotecan, 5-FU, leucovorin (FOLFIRI) or irinotecan, oxaliplatin, 5-FU, leucovorin (FOLFOXIRI), resulting in response rates of 41% and 66%, respectively [4]. Secondary resection of metastases was observed in 6% versus 15%, in case of liver metastases only even in 12% versus 36%. Whether the addition of the EGFR antibody cetuximab could further improve response and resection rates was explored by Folprecht et al. in the CELIM study. In that trial, 106 patients with initially unresectable liver metastases received either FOLFIPIR plus cetuximab or FOLFOX plus cetuximab. A general response rate of 62% was observed resulting in a secondary resection rate of 34% [5]. Currently, it is under investigation, if the addition of the VEGF antibody bevacizumab might further improve those results; Masi et al. reported 80% response and 28% R0-resection in patients with “lower” only metastases after receiving FOLFOXIRI plus bevacizumab [6].

Following resection of metastases, the question of integrating neoadjuvant radiochemotherapy before resection of a locally advanced rectal tumor to minimize the risk of local recurrence in a maximal curative approach is under discussion. In a small prospective study, patients with colorectal cancer (11 rectal/nine colon) and hepatic metastases (Fong ≥ 3) received FOLFOXIRI or Cape/Ox/Iri [7]. Following hepatic metastasectomy, patients with tumor node metastasis (TNM) stage 2 rectal cancer were irradiated with a total dose of 50 Gy or a biologically equivalent dose before resection of their primary tumors. Seven of 11 patients with rectal cancer and all nine patients with colon cancer underwent this therapeutic sequence resulting in a 2- and 3-year survival of 93% versus 79% and 81% versus 71% compared with the whole patient population treated.

Those results are promising and at least demonstrate the feasibility of such a combined interdisciplinary approach with maximal curative intention. Nevertheless, trials systematically addressing and evaluating treatment algorithms in the setting of rectal cancer with synchronous metastases as described above are urgently warranted. Until such prospective trials are completed, we are left with individual decisions within a multidisciplinary GI oncology team based on the conditions and options described. A potential algorithm for definitive procedures and decision tree must be developed separately for patients with a potentially "curative" situation including all available treatment modalities with aggressive 3- or 4-drug chemotherapy, surgery of primary tumor and metastases and definitive local (chemo-)radiation. Founding factors for the decision about the priority initial treatment are the local extent of the primary tumor, the general patient condition and the potential for metastases-resectability in case of major response under chemotherapy.

For those patients judged to be definitely unresectable, e.g. due to massive or multiple metastases or patient’s condition and comorbidities, therapy should focus on optimal systemic palliation with least invasive treatment burden for the patient; it is mandatory to take into account that in such a patient “radical” local tumor resection including disruption of continence or colostoma is not changing survival at all, but has major negative impact on quality of life for the rest of the patient’s life.

Finally, the authors of this manuscript [8] have to be congratulated that they analysed and reported this series of patients as contribution to the discussion. However, those data should not implicate primary surgery of the rectal tumor to be the standard treatment in all patients with synchronous metastases. But this series again highlights that prospective trials in a clearly defined patient population with distinguished approaches for the different subpopulations are urgently needed.

References


