Editorial Commentary

The importance of loco-regional control in metastatic rectal cancer

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The number of new cases of rectal cancer (RC) estimated per year is across 704,000 worldwide. Approximately 310,000 death cases are reported per year among RC patients, globally (1). Roughly 20% of patients with RC present with metastatic disease and their prognosis depends on the extent of tumor burden (2). The optimal treatment strategies, in this oncological setting, remain a challenge and the therapeutic choices are largely based on extension of local and systemic disease. Several studies have demonstrated that the treatment of the primary tumor and of all metastatic sites may lead to a better prognosis and, in some cases, curative intent (2,3). Clinical data suggest that resecting the primary tumor using total mesorectal excision (TME), as surgical choice, in properly selected patients affected with stage IV RC is a prognostic factor for favorable progression-free survival (PFS) and overall survival (OS) (4). While the role of pre-operative treatments [radiotherapy (RT) and chemotherapy (CT)] in patients with locally-advanced (LA) disease is well established, in metastatic RC the contribution of RT is not clearly defined.

A proper staging, especially with respect to the primary disease, is essential for both locally advanced and metastatic patients. The most precise imaging methodic to define locoregional clinical staging is magnetic resonance imaging (MRI), with an important contribution also in patients with metastatic disease, given the importance of local control (LC) in this setting. In order to detect extra-mural vascular invasion (EMVI), determining the T substage, the distance from the mesorectal fascia (MRF), MRI is considered the most reliable tool, with the possibility to also predict the risk of local recurrence (LR) and synchronous/metachronous distant metastases (DM) (5,6). Involved MRF (fascial distance ≤1 mm) and good quality TME are consistently impacting on oncological outcomes (5,6). Advanced T-stage, distal rectal presentations (<8 cm from the anal verge) and elderly age are associated with moderate to poor TME quality (5).

LA primary tumors require down-staging/sizing pre-operative procedures (RT alone, chemo-RT, peri- or pre-operative CT) in order to enable resection with adequate margins. Of notice, the circumferential margin (CRM) status is an important predictor of local and distant recurrence together with survival (7). Two different schedules for neoadjuvant RT (NRT) are usually employed: long-course RT (LCRT, total dose of 45–50.4 Gy in 25 to 28 fractions) combined with CT or short-course RT (SCRT, total dose of 25 Gy in 5 fractions, during 1 week). Neoadjuvant LCRT schedule with concurrent CT is widely used, especially when down-staging/-sizing are required [risk group "bad" according to the latest European Society for Medical Oncology (ESMO) guidelines: cT3c/d tumor or very low localization levators threatened, MRF clear; or cT3c/d mid-rectum, cN1–N2 extranodal, EMVI+; or limited cT4acN0; risk group "ugly": cT3 with any MRF involvement; any cT4a/b, lateral node involvement] (5).

The optimal timing for surgical resection after

preoperative chemoradiotherapy (CTRT) tends to be at 11 to 16 weeks, in order to favor down-staging/-sizing peak, allowing for a higher rate of complete response (CR). Combining RT and CT preoperatively can lead to higher chance for tumor regression grading (TRG) 4 (complete regression), with a remarkable prognostic significance due to the impact on DM and disease-free survival (DFS) (8).

In LA disease, when down-staging/-sizing are not required and a radical resection is possible (CRM negative), SCRT with immediate surgery (<10 days from RT start) is indicated, with the aim of reducing LR. "Intermediate-risk-group patients" are eligible for SCRT (cT3a/b very low, levators clear, MRF clear or cT3a/b in mid- or high rectum, cN1-2 not extranodal, no EMVI) (5). Recent studies highlighted that SCRT with delayed surgery (6–8 weeks from the end of RT) is a useful alternative to conventional SCRT allowing for the possibility to obtain down-staging/sizing, with similar oncological outcomes and lower postoperative complications (9). In patients unfit for CTRT (elderly and/or severe comorbidities), if down-staging/sizing are required, SCRT-delay approach can be proposed.

The optimal treatment strategy for the specific cluster of patients affected with stage IV RC is still unclear. Approximately 2% to 5% of RC are diagnosed with one or a few synchronous metastases in one organ. The most common metastatic sites are usually liver and lungs (2). Although CT and biologic agents remain the backbone of therapeutic strategies in this setting, loco-regional aggressive treatments of both metastatic disease and primary tumor can play a key role. In this oncological setting, long-term survivors have been observed following surgical resection of the primary tumor and of all isolated metastatic sites (3). Recurrence of disease can either occur in distant organs (usually within the first 2 years following resection), either in the resected primary tumor site (LR after radical resection ranges from 3% to 30 %) (3). Therefore, both local and systemic relapses should be considered in order to improve the prognosis. The role of pelvic RT for LC in stage IV RC and its timing are important aspects that still need to be thoroughly defined. The role of LCRT and SCRT to increase loco-regional control in stage IV RC deserves further investigation

The study by Agas *et al.* (10) from the Benavide Cancer Institute, attempted to review the current evidence regarding the therapeutic approach for patients affected with RC and synchronous metastatic spread (stage IV) comparing neoadjuvant pre-operative RT (NRT) to no pre-operative radiation (no RT). The authors conducted a systematic review of the literature selecting eight studies, published between 2000 and 2018. One randomized clinical trial (RCT), five retrospective cohorts, two population-based studies were included. Among the eligible studies, perioperative CT was allowed in case of either NRT or no RT.

Both LCRT combined with CT and SCRT were allowed in the group of NRT. In terms of RT, intensity-modulated RT (IMRT) and less conformal techniques were allowed. Local recurrence-free survival (LRFS) and OS were the primary outcomes.

In the only RCT analyzed, the "Dutch TME Trial" (11,12), 1,861 patients with resectable RC were randomized between TME preceded (1-week interval) by 5×5 Gy or TME alone in order to evaluate the efficacy of preoperative SCRT. Five-year LR risk of patients in SCRT arm was 5.6% in opposite to a 10.9% in patients undergoing up-front TME (P<0.001). At 5 years OS was 64.2% and 63.5%, respectively (P=0.902).

As showed in subgroup analyses, RT reduced LR risk in nodal positive patients, in distal and mid-rectum primaries and for patients with uninvolved CRM.

In this trial, up to 7% of patients was stage IV at diagnosis and this cluster was randomized in the 5×5 Gy arm or in the TME alone arm. No statistically significant differences in terms of 5-year LR (15.9% 5×5 Gy arm, 26.9% TME alone).

Among the remaining seven studies in the analysis (13-19), focused glimpse can be taken on the five retrospective studies, properly selected by the Authors for the pooled analysis (13-17). These studies included stage IV patients undergoing TME.

In the study by Fossum *et al.* (13) all patients received neoadjuvant treatments followed by curative-intent surgery with metastasectomy (liver and/or lung), performed, in some cases, simultaneously. Forty-seven patients received NRT (LCRT + CT or SCRT) and 46 patients did not (CT alone). Among patients who received NRT, 35 patients had LCRT (surgery interval 6–8 weeks) whereas 12 patients had SCRT (surgery interval 1 week). In 12 patients (26%) who did not receive radiotherapy, LR was observed, while no LR developed in those who received NRT (P<0.001). In the study by Huh *et al.* (14) among 140 patients with LA mid-to-lower RC and resectable stage IV enrolled, 69 received CTRT (26 preoperatively and 43 postoperatively) while 71 did not. Benefits in LR were observed in the preoperative RT arm compared with the postoperative RT arm, but this did not translate in a better survival outcome. In general, the employment of RT was more beneficial in distal RC.

Nevertheless, OS curves had a better trend in patients undergoing RT, either pre- or post-operatively, but without statistical significance (P=0.057), when compared with the no RT population.

The study by Kim *et al.* (15) compared neoadjuvant LCRT combined with CT and postoperative CT (including FOLFOX4, FOLFIRI, 5-FU/LV and Capecitabine). No statistical differences and similar data were reported in terms of LR, PFS and OS.

In study by Manyam *et al.* (16) 64 patients underwent LCRT and perioperative CT while for 45 patients just perioperative CT was administered. No significant differences were observed in terms of LR or OS. The use of LCRT in the preoperative setting led to optimal downstaging and clearer margins but overall did not impact on recurrence. In the RT arm more G2 complications were reported.

The study from Viganò *et al.* (17) analyzed the outcomes for 36 patients who underwent rectal and liver resection LA mid-low RC with synchronous metastases. Among this population, 15 patients underwent preoperative CT, 7 patients neoadjuvant LCRT with CT, 6 patients CT followed by CTRT preoperatively, 8 cases of upfront surgery. Subsequently to curative liver resection all patients underwent adjuvant CT. No LR occurred among patients who correctly completed treatment strategy. All patients receiving neoadjuvant CTRT were alive and disease-free; 5-year OS and DFS of patients receiving neoadjuvant CT were 59.3% and 25%, respectively.

The pooled analysis from these studies (13-17) showed that 2-year LRFS rates were significantly higher for the neoadjuvant pre-operative RT group.

Three studies were also eligible for statistical pooling regarding survival outcomes (13-15).

Pooled 5-year OS showed a statistically significant benefit for NRT, which was not seen in the subgroup who underwent metastasectomy.

The authors reported, in conclusion, a LRFS benefit with NRT over no RT in patients with stage IV RC and suggested a possible OS benefit.

The study by Agas *et al.* highlights how the available literature can be controversial regarding the optimal strategy in RC patients with synchronous metastases.

CT alone might not guarantee favorable outcomes in all RC patients with synchronous metastases. In this setting of patients, LCRT combined with CT provides a long interval between the start of treatment and surgery, during which DM may progress (20). On the other hand, SCRT can enable an early start of the systemic treatment within 2 weeks from the beginning of RT. Two phase III trials highlighted the benefits of SCRT with delayed surgery as alternative to conventional SCRT with immediate surgery (9,21). In a randomized phase III study by Bujko *et al.* (21), patients with fixed cT3 or cT4 RC were randomized either to 5×5 Gy and 3 cycles of FOLFOX4 (group A) or LCRT with CT (group B). Of interest, R0 resection rates and pathological CR rates in groups A and B were, respectively, 77% *vs.* 71% (P=0.07), and 16% *vs.* 12% (P=0.17) (21). These results highlight the potential role of SCRT followed by CT in non-metastatic patients.

Actually, there are no evidences, in the metastatic setting, favoring SCRT over LCRT with CT, however, combining 5×5 Gy and dose-dense CT seems fairly a reasonable treatment regimen to intensify systemic treatment and avoid delays (5). Moreover, this can be of particular interest considering the remarkable rate of CR, that could lead to organ-sparing strategies, such as a Watch & Wait approach on the primary tumor, in order to focus on metastases directed-therapy.

The benefits of a similar alternative schedule were highlighted in a phase II trial (22), that showed the positive effect, on achieving a higher number of CR, by adding modified-FOLFOX6 between long course CTRT and surgery. Similarly, polychemotherapy showed significant benefits in other solid tumors presentations, for example pancreatic cancer (23).

Following a similar multimodality treatment strategy, the ongoing Rapido trial (24), randomizes high-risk RC patients to standard CTRT followed by selective post-operatory CT or to SCRT (5 Gy ×5) followed by full-dose CT (capecitabine and oxaliplatin) in 6 cycles before TME.

Intensifying local therapy, in order to achieve LC, can influence survival. This rationale has been widely recognized in other solid tumors, such as breast cancer, since failure to achieve initial LC can allow late dissemination to distant sites, reducing patient's chance for long-term survival (25). This has not been the case for RC so far, especially in the setting of locally advance disease.

This review suggests the possible survival benefit with NRT in stage IV RC patients. Multi-institutional phase III studies, investigating the role of NRT in this setting, are warranted.

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Footnote

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