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MULTIMODAL TREATMENT OF RECURRENT COLORECTAL CANCER

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Abstract – *Introduction:* *Recurrent disease following colorectal cancer surgery will occur in about 30-50% of patients when considering both locoregional relapse and distant metastasis. For patients with rectal cancer, preoperative chemoradiotherapy followed by TME can provide durable 10-years overall survival (OS) of 58% and recurrence-free survival (RFS) of 62%.*

Background: *Despite optimal treatment with neoadjuvant therapy and a complete TME, some rectal cancers still recur locally. Over the last two decades, the rates of local recurrence have been reduced.*

Patients and Methods: *To identify the optimal treatment strategy patients can be divided into four clinical groups: resectable disease, potentially resectable, non-resectable with or without intensive treatment.*

Results: *In the case of a resectable disease, the option of upfront surgical intervention was offered to a selected subset of patients with a local recurrence. In the case of a potentially resectable disease with curative intention, there is no consensus about neoadjuvant therapy for recurrence. Options are chemotherapy, external beam radiotherapy (EBRT), brachytherapy or intraoperative radiotherapy (IORT). In non-resectable disease category with a disseminated disease, when it is necessary intensive treatment, the cytotoxic doublet in combination with a monoclonal antibody is the preferred option. In the non-resectable disease category with a disseminated disease when the patients have no cancer-related symptoms, the cytotoxic doublet or mono-chemotherapy with or without biological target agent is the preferred option.*

Discussion and Conclusions: *Surgical resection with microscopically negative margins is the only curative procedure for rectal cancer recurrence. Preoperative RT in association with chemotherapy offers significantly better survival compared with surgery alone. An accurate multidisciplinary approach to patients with recurrence of colorectal cancer should be performed in order to avoid unnecessary laparotomies and guarantee the best-tailored chance of cure to the individual patient.*

KEYWORDS: *Rectal cancer, Local recurrence, Radiotherapy, Chemotherapy, Multidisciplinary approach.*

INTRODUCTION

Recurrent disease following colorectal cancer surgery will occur in about 30-50% of patients, considering both locoregional relapse and distant metastasis[1].

Rectal cancer is more frequently associated with local failure than colon cancer, due to its distinctive behavior of spreading from the pelvis through the lymphatic and venous system. However, the introduction of total mesorectal excision (TME) and the association of neoadju-

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vant radiochemotherapy have dramatically reduced the local relapse rate to 6%[2].

Curative treatment of recurrence is possible and this improves prognosis and overall survival.

BACKGROUND

For patients with rectal cancer preoperative chemoradiotherapy followed by TME can provide durable 10-years overall survival (OS) of 58% and recurrence-free survival (RFS) of 62%[3]. Preoperative treatment is a highly controversial topic and some studies are ongoing.

One of these is V-shoRT trial, a phase 1/2 study of valproic acid and short-course radiotherapy plus capecitabine as preoperative treatment in low-moderate risk rectal cancer[4].

The purpose of this study is: 1) to determine the maximum tolerated dose of capecitabine given alone or in combination with valproic acid during preoperative short course radiotherapy (phase I); 2) to explore whether the addition of valproic acid or the addition of capecitabine to short-course radiotherapy before optimal radical surgery might increase the pathologic complete tumor regression rate in patients with low-moderate risk rectal cancer (phase II)[4].

A second trial with overlapping aims is the RAPIDO trial: Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer[5]. Current standard treatment for patients at high risk of failing locally and/or systemically includes pre-operative long course radiotherapy (5 weeks) in combination with chemotherapy (neoadjuvant). The neoadjuvant chemoradiotherapy demonstrated to improve local control but has no impact on the overall survival, since a substantial proportion of patients cannot receive chemotherapy postoperatively due to TME complications. An alternative approach is to administer the systemic therapy preoperative and short course RT to guarantee control of the rectum tumor. In this trial, the investigators compared this approach (short RT followed 6 cycles of chemotherapy with capecitabine + oxaliplatin, followed by TME) with the standard treatment of neoadjuvant chemoradiotherapy followed by TME surgery and optional adjuvant chemotherapy[5]. The RAPIDO trial showed that short-course radiotherapy combined with full-dose chemotherapy preoperatively can be a possible alternative that offers advantages compared to concomitant chemoradiotherapy with or without postoperative chemotherapy.

PATIENTS AND METHODS

Recurrence risk and surveillance strategies

Despite optimal treatment with neoadjuvant therapy and a complete TME, some rectal cancers still recur locally. Risk factors include bulky tumors (T3/T4), node positivity, and unfavorable pathologies such as lymphovascular invasion or perineural invasion[6]. Moreover, distance of mesorectal extension (DME), circumferential resection margin (CRM), lymphatic invasion (positive Ly), and venous invasion (positive V) are independent risk factors for local recurrence (LR) in patients who undergo curative resection for rectal cancer without preoperative CRT. Moreover, a combination of these factors can identify a group of patients who are at high risk of LR.

Surveillance strategies after curative treatment for primary rectal and colorectal cancer are controversial, and the optimum combination of timing has not been established. Among patients who underwent curative surgery for primary colorectal cancer, intensive imaging and Carcinoembryonic antigen (CEA) screening (CEA every 3 months for 2 years then every 6 months for 3 years + CT scan total body every 6 months for 2 years then annually for 3 years) each provided an improved rate of recurrence treated with curative intent compared with minimal follow-up (no scheduled follow-up except a single CT scan total body at 12 to 18 months); there was no advantage in combining both strategies. If there is a survival advantage to any strategy, it is likely to be small[7].

Over the last two decades, the rates of LR have been reduced in patients with rectal cancer. This has occurred through of a variety of different approaches including improved surgery, and the use of adjuvant chemotherapy and radiotherapy[8].

Surgical management of locally recurrent colorectal cancer evolved with improvements in surgical strategy and multimodal therapies[9]. Published series document 5-years survival rates of 30-60% with acceptable rates of morbidity and mortality[10].

Methods of managing these patients are contentious, with no established algorithms.

In order to identify the optimal treatment strategy, patients can be divided into four clinical groups: resectable, potentially resectable, and nonresectable with or without intensive treatment (Table 1).

TABLE 1. Therapeuthic algorithm for mCRC.

	Group 0 (resectable disease)	*Group 1 (potentially resectable disease)*	*Group 2 (disseminated disease not resectable with intensive treatment)*	*Group 3 (disseminated disease not resectable with no intensive treatment)*
Surgery upfront	•			
Chemotherapy perioperative	•			
Cytotoxic doublet + anti EGFR		•	•	
Cytotoxic doublet + anti VEGFR			•	
Cytotoxic triplet + anti VEGFR		•	•	
Mono-chemotherapy +/- biological targeted agents				•

Resectable disease

In this category, patients are further categorized as having resectable or potentially resectable disease:

- Group 0 resectable disease (usually this group includes liver or lung limited disease).

The option of upfront surgical intervention was offered to a selected subset of patients with a LR. The operative strategy was determined by the anatomical extension of the tumor as mapped by preoperative radiological imaging[11]. Curative resection was carried out safely in the majority of cases, since postoperative mortality and morbility rates were acceptable. Most reasons for unresectability were anatomically unresectable disease, the presence of distant metastasis or poor fitness for surgery[12]. The R0 resection rate following surgery for recurrent colorectal cancer was the best predictor of long-term survival. There was no survival difference between patients undergoing a palliative (R2) resection compared with non-operated patients. In liver-limited disease two chemotherapy options are available: 1) postoperative chemotherapy after surgical resection (six months); 2) perioperative approach (three months before and three months after surgical resection of liver metastases)[13].

- Group 1 potentially resectable disease with curative intention

There is no consensus about neoadjuvant therapy for recurrence. Options are chemotherapy, external beam radiotherapy (EBRT), brachytherapy or intraoperative radiotherapy (IORT). Many patients with previous rectal cancer received radiotherapy at the time of primary resection, so further irradiation was limited to a small subset of patients. Re-irradiation for pelvic recurrences is controversial due to concern of late toxicity. Brachytherapy, EBRT and IORT show promising single-center results but there is no evidence from randomized trials for the use of these modalities; further randomized trials are needed[14].

Chemotherapy treatment in this group of patients is similar to first-line chemotherapy for patients with mCRC. Recently, findings of several key studies on first line chemotherapy for CRC have been reported.

During the 2014 Annual Meeting of the American Society of Clinical Oncology (ASCO) were presented the results of expanded RAS analysis in the CALGB/SWOG 80405 study (phase III Trial of Irinotecan/5-FU/Leucovorin [FOLFIRI] or Oxaliplatin/5-FU/Leucovorin [mFOLFOX6] with bevacizumab (BV) or Cetu-ximab [CET] for patients with KRAS wild-type untreated metastatic adenocarcinoma of the colon or rectum [mCRC]). The conclusion of this trial is that FOLFIRI/cetuximab and mFOLFOX6/bevacizumab are equivalent in terms of overall survival (OS) in patients with previously untreated KRAS wild-type (codons 12 and 13) metastatic colorectal cancer and that both regimens are appropriate in first-line treatment. Expanded RAS was tested in all wild-type RAS exon 2 using beaming technology including KRAS exon 3,4 and NRAS exon 2, 3 and 4 showing a detection sensitivity of 0.01%. In expanded RAS wild-type population, the median OS was extended beyond 30 months. However, there was no significant difference between patients receiving cetuximab or bevacizumab in combination with chemotherapy (32 months *vs.* 31.2 months). There was no difference in the progression-free survival (PFS). However, in the expanded RAS population, there was higher response rate in the cetuximab arm (68.6% *vs.* 53.6%; $p < 0.01$).

A similar study, the FIRE-3 trial (FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer), compared first-line therapy with FOLFIRI plus either cetuximab or bevacizumab (1:1) in 150 centers in Germany and Austria. Extended RAS analysis was carried out in KRAS and NRAS exon 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) using the pyro-sequencing technique. Independent evaluation

in KRAS exon 2 wild-type population showed an ORR of 66.5% in the cetuximab arm and 55.6% in the bevacizumab arm ($p = 0.016$). In the final RAS wild-type population, the ORR was 72% in the cetuximab arm *vs.* 56.1% in the bevacizumab arm ($p = 0.003$). OS favored the cetuximab arm, 33.1 months *vs.* 25.0 months (HR 0.697, $p = 0.0059$). This trial showed that median OS was markedly superior in all-RAS wild-type patients receiving first-line therapy with cetuximab, and the authors demonstrated a significantly higher ORR in patients treated with FOLFIRI plus cetuximab compared with patients receiving FOLFIRI plus bevacizumab[15].

A further important contribution to the first-line therapy in mCRC was the TRIBE trial (Combination chemotherapy and bevacizumab as first-line therapy in treating patients with metastatic colorectal cancer). This trial, which evaluated FOLFOXIRI and bevacizumab versus FOLFIRI and bevacizumab, showed a significant difference in the primary end point of PFS (12.1 *vs.* 9.7 months, respectively). FOLFOXIRI plus bevacizumab was associated with a 25% reduced risk of progression compared with FOLFIRI plus bevacizumab. The response rate was 53.1% in the control group compared with 65.1% in the experimental group, but the was no statistically significant differences in the rate of R0 resection of metastasis[16,17].

The phase II PEAK trial (Panitumumab efficacy in combination with mFOLFOX6 against bevacizumab plus mFOLFOX6 in mCRC subjects with wild-type KRAS tumors) randomized patients with wild-type KRAS and NRAS to first-line panitumumab with FOLFOX or bevacizumab with FOLFOX. PFS for panitumumab with FOLFOX was 13.0 months, compared with 9.5 months for bevacizumab with FOLFOX. Median OS was 41.3 and 28.9 months respectively in the panitumumab and bevacizumab arms (HR, 0.63; 95% CI, 0.39 to 1.02 $p = 0.058$); objective response rate was 63.6% in the panitumumab arm and 60.5% in the bevacizumab arm. Results from PEAK trial indicate similar PFS and improved OS with panitumumab relative to bevacizumab plus mFOLFOX6 in patients with wild-type KRAS exon 2 mCRC, but patients who were wild-type by extended RAS analysis seemed more likely to benefit from anti-EGFR therapy[18].

Non-resectable disease

In the non-resectable disease category, patients are further categorized as receiving or not receiving intensive treatment.

- Group 2 disseminated disease, not resectable disease, intensive treatment.

In this setting, patients have cancer-related symptoms and the treatment goal is palliation. The cytotoxic doublet in combination with a monoclonal antibody is the preferred option.

- Group 3: disseminated disease, not resectable disease, not intensive treatment

In this setting, the patients have no cancer-related symptoms and treatment intention is to prolong survival and prevent disease progression. The cytotoxic doublet or mono-chemotherapy with or without biological target agent is the preferred option[19].

DISCUSSION

Colorectal cancer is one of the most frequent solid tumors in the western world. Treatment options depend on the stage of the disease, patient performance status, and – increasingly – molecular make-up of the tumor.

Treatment efficacy in the metastatic setting increased with the introduction of targeted substances.

These include: a) the anti-vascular endothelial growth factor-A (anti-VEGF-A) antibody bevacizumab; b) the anti-epidermal growth factor receptor (anti-EGFR) antibodies cetuximab and panitumumab; c) the anti-angiogenic multi-kinase inhibitor regorafenib, and d) the anti-angiogenic compound aflibercept.

Anti-EGFR antibodies have shown efficacy only in the sub-populations of tumors that do not have any mutation in KRAS and NRAS exon 2, 3, 4. Physicians now have the option of using biological agents in combination with chemotherapy based on treatment goals and patient performance.

The optimal treatment strategy for patients with metastatic CRC should be discussed in a multidisciplinary team of experts that includes the oncologist, the radiotherapist, the surgeon, the nutritionist, the expert in cancer pain's therapy in order to identify the optimal treatment strategy for patient and to preserve patient's quality of life.

CONCLUSIONS

Surgical resection with microscopically negative margins (R0) is the only curative procedure for rectal cancer recurrence. Preoperative RT in association with chemotherapy offers significantly better survival and local control rates

compared with surgery alone or surgery in association with postoperative treatments; data on IORT as part of multimodal treatments are inhomogeneous and inconsistent, necessitating randomized controlled trials.

Palliative R2 resection offers only poor survival outcomes and no prognostic benefits compared with non-operative palliative treatments; for this reason, an accurate multidisciplinary approach to patients with recurrence of colorectal cancer should be recommended and performed in order to avoid unnecessary laparotomies, spare morbidity rates and guarantee the best-tailored chance of treatment to the individual patient.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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