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The treatment of rectal cancer with synchronous liver metastases: A matter of strategy

Fabio Gelsomino[a,*], Andrea Spallanzani[a], Ingrid Garajovà[b]

[a] Division of Oncology, University Hospital of Modena, Via del Pozzo 71, 41124, Modena, Italy
[b] Medical Oncology Unit, University Hospital of Parma, via Gramsci 14, 43126, Parma, Italy

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ABSTRACT

Around one fifth of patients with rectal cancer (RC) have synchronous metastatic disease at the diagnosis. The optimal treatment sequence for patients with RC and synchronous liver metastases (LM) is complex and unclear, missing strong, evidence-based recommendations. From a clinical point of view, this situation is highly heterogeneous and the treatment strategy is generally determined by a number of factors, such as the potential resectability of primary tumor and LM, patients' characteristics, the presence of primary tumor-related symptoms and the response to therapies. Treatment options for these patients include systemic therapy, short-course radiotherapy (SC-RT), long-course chemoradiotherapy (LC-CRT) and surgery of the primary tumor and LM. The principal goal is to render the patients eligible to radical surgery, thus offering a chance of cure at least for some of them. This review summarizes the most appropriate treatment strategies which should be recommended in the different clinical scenarios of this heterogeneous condition.

1. Introduction

Colorectal cancer (CRC) represents one of the leading cause of cancer-related death worldwide, with RC accounting for about one third of cases (Siegel et al., 2018). Nearly 20% of cases of RC are diagnosed with synchronous metastatic disease, with three-quarter of them having LM and half of them liver-limited disease (LLD) (Lutz et al., 2016; Noren et al., 2016). Furthermore, as compared to colon cancer, RC has a higher incidence of lung metastases (Qiu et al., 2015). In the past 20 years, with the adoption of a multimodal approach, the refinement of preoperative staging and the improvements in surgical skills, considerable progress has been achieved in the outcome of patients with locally advanced RC.

Conversely, the treatment of RC with synchronous LM remains an area of significant controversy, since many trials have been published, often mixing patients with colon and rectal cancer as a unique entity, with heterogeneous endpoints, treatment strategies and patients' selection (Feng et al., 2014; Lykoudis et al., 2014).

However, this condition is highly heterogeneous and encompass a broad spectrum of different clinical scenarios, ranging from easily resectable LLD to non-resectable liver disease with or without extra-hepatic involvement.

Therefore, as a consequence of the lack of strong, evidence-based recommendations, the goal of the treatment along with the timing of each therapy (systemic therapy, RT, surgery of primary tumor and metastases) should be defined on a case-by-case discussion within an experienced multidisciplinary team, in a shared-decision approach with the patients.

In patients with resectable or potentially resectable metastatic disease, a radical resection of the primary tumor and LM may hopefully offer a chance of cure to some patients. Historically, among patients eligible for surgery, different strategies have been developed: the 'classical strategy' (rectum first), the 'reverse strategy' (liver first) and the 'simultaneous' strategy. A forth strategy is the so-called 'interval strategy', in which the resection of metastases is performed in the interval period between the end of the neoadjuvant chemoradiotherapy and the rectal surgery (Salvador-Roses et al., 2018). On the contrary, in patients with never-resectable metastatic disease, the prolongation of survival, the minimization of tumor-related symptoms and the improvement in quality of life are the main goals of the treatment.

In order to categorize the heterogeneity of the clinical reality in this setting, we propose 4 different clinical scenarios:

1) Resectable primary tumor and metastases.
2) Non-resectable primary tumor and resectable metastases.
3) Resectable primary tumor and non-resectable metastases.
4) Non-resectable primary tumor and metastases.

* Corresponding author.
E-mail addresses: gelsomino.fabio@aou.mo.it (F. Gelsomino), andrea.spallanzani@gmail.com (A. Spallanzani), ingegarajova@gmail.com (I. Garajovà).

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These categories mainly refer to patients with LM, although they might conceptually be applied to patients with other metastatic sites. Our narrative review aims at summarizing the issues and the strategies for each clinical scenario, discussing the available literature evidence and providing a useful algorithm for clinicians treating patients with RC and synchronous LM.

2. Resectable primary tumor and metastases (SCENARIO 1)

Although less frequent, this scenario is the most favorable in terms of prognosis. An accurate evaluation of the risk of local and systemic progression will dictate the sequence of the various treatments. The aim of the treatment in this setting is the complete removal of the primary tumor and the metastatic disease. Patients need to be optimally staged, possibly with a chest CT scan, a pelvic magnetic resonance (MRI), and hepatic MRI and, in selected cases, an FDG-PET scan.

Although the majority of patients will receive chemotherapy as the initial treatment, selected cases could receive immediate surgery both of primary tumor and metastases. In particular, the prognosis of patients with LLD should be accurately evaluated, according to the well-known published risk scores (Fong et al., 1999). Fong and colleagues demonstrated that a composite score including node positivity in the primary tumor, disease-free interval from primary tumor to metastases < 12 months, number of hepatic metastases > 1, largest hepatic tumor > 5 cm, and carcinoembryonic antigen (CEA) level > 200 ng/ml can accurately predict the outcome of patients with LM from CRC (Fong et al., 1999). In patients with resectable LM (up to four) from CRC, the EPOC trial demonstrated that perioperative chemotherapy with FOLFOX4 increased the rate of progression-free survival (PFS) at 3 years from 28.1% to 35.4% (HR 0.79; p = 0.058) as compared to surgery alone (Nordlinger et al., 2008). Although long-term follow up did not demonstrate any difference in overall survival (OS) between the two arms (Nordlinger et al., 2013), perioperative chemotherapy became the standard of care in this setting. Despite patients with synchronous easily resectable LM from RC have 1 adverse prognostic factor of the Fong criteria (disease-free interval from primary tumor to metastases < 12 months), selected cases without any other risk factor could receive immediate surgery. A careful discussion within an experienced multidisciplinary team is of paramount importance to define a personalized strategy for every patient.

In this setting, SC-RT is the preferred modality of preoperative treatment of the primary tumor since, owing to its shorter duration, it can be easily integrated with chemotherapy and surgery. LC-CRT should be reserved to patients with high-risk features RC, such as those with predicted mesorectal fascia (MRF) involvement, extramural vascular invasion (EMVI) or low-lying tumors, especially when sphincter-saving surgery is pursued (Xie et al., 2014; Siddiqui et al., 2017).

In modern clinical trials enrolling patients with metastatic CRC, a median survival of 30 months has been achieved and sometimes exceeded (Venook et al., 2017; Heinemann et al., 2014; Schwartzberg et al., 2014). The introduction of monoclonal antibodies in the therapeutic repertoire of CRC made a substantial contribution to achieve this goal (Sobrero, 2016). However, in the setting of perioperative treatment of patients with resectable metastatic disease (especially for those with LM), no clear role has been established neither for anti-VEGF nor for anti-EGFR monoclonal antibodies. In this regard, the NEW EPOC trial randomized patients with KRAS exon 2 wild-type (WT) resectable or suboptimally resectable LM from CRC to receive chemotherapy with or without Cetuximab. Unexpectedly, the addition of cetuximab to chemotherapy and surgery resulted in a shorter PFS (Primrose et al., 2014). Although this trial has been subject to fierce criticism concerning its design, patients' selection, quality of surgery, some missing data (i.e post-operative complications), the imbalance of prognostic and surgical factors between the two arms and the lack of a centralized surgical, radiological and pathological review (Hasegawa et al., 2014; Fong, 2014; Primrose, 2014), chemotherapy alone (FOLFOX) remains the standard of care in this setting of patients.

3. Non-resectable primary tumor and resectable metastases (SCENARIO 2)

In this setting the aims of the treatment are both local control and the opportunity to promptly start an effective systemic therapy. The use of endoscopic palliation or temporary colostomy should be avoided if not strictly indicated to prevent complications (Tyc-Szczepaniak et al., 2016). The palliative efficacy of SC-RT was highlighted in a small Italian trial: complete symptoms resolution was observed in 38.9% of patients and partial response in 50.0% of cases (Picardi et al., 2016). LC-CRT (45–50 Gy/25–28 fractions in combination with fluoropyrimidine) is effective in downstaging the primary tumor with R0 resection in more than 60% of patients but may results in under-treatment of the metastatic disease (Rodel et al., 2015).

In the Polish and in the Trans-Tasman Radiation Oncology Group (TROG) trials, LC-CRT was associated with a higher tumor downstaging compared to SC-RT (with surgery performed after 1 week). In fact, a pathological complete response (pCR) rate of 16.1% and 15% after LC-CRT vs 0.7% and 1% after SCRT were observed, respectively, in the two trials and with the greatest difference in the subgroup of patients with lower RC (Ngan et al., 2012; Bujko et al., 2006). Conversely, in the Stockholm III trial there was a higher tumor downstaging after SC-RT (with surgery delayed after 4–8 weeks) compared to LC-RT (43% vs 29% ypT0/1) (Erlandsson et al., 2017), with no difference in terms of local relapse. Another feasible approach is the use of consolidation chemotherapy after standard SC-RT. In a recent phase III trial the group of patients randomized to SC-RT plus consolidation chemotherapy with FOLFOX and delayed surgery achieved a pCR rate of 17% as compared to 12% in the LC-CRT group (Bujko et al., 2016).

The role of primary neoadjuvant chemotherapy in this setting is highly debated, because of the lack of efficacy on primary tumor control. However, in a recent Spanish phase II trial, patients treated with capecitabine, oxaliplatin and bevacizumab obtained an overall response rate (ORR) of 78% without RT (Fernandez-Martos et al., 2014).

Further confirmatory data from FOWARC trial reported a pathological downstaging (ypT0/1) with mFOLFOX6 alone in 35% of patients (Deng et al., 2016).

Based on these data, the suggested options in this setting are:

1) SC-RT – consolidation chemotherapy – delayed surgery (after 8–12 weeks).
2) (Intensified) neoadjuvant chemotherapy – LC-CRT – surgery.
3) LC-CRT (with or without oxaliplatin) – surgery (in selected cases with limited metastatic disease).

The feasibility and efficacy of the first strategy in this setting was evaluated in a small Dutch experience with capecitabine, oxaliplatin and bevacizumab as consolidation chemotherapy: radical surgical treatment of all tumor sites (84% of patients with LM) was completed in 36 patients (72%). Simultaneous TME and surgical treatment of metastases were carried out in 26 patients. In seven patients, liver first approach was carried out, followed by TME. In 12 patients, the primary tumor was resected before liver surgery (van Dijk et al., 2013).

The tolerability and efficacy of an intesified neoadjuvant chemotherapy on the primary tumor was recently investigated in a phase II trial with the mFOLFIRINOX regimen: the treatment was feasible and active, with a partial RR based on MRI evaluation of the primary tumor of 49% after 4 cycles and 63% after 8 cycles with a good response also on LM (Bachet et al., 2018).

The third strategy should be considered only in case of limited liver disease: data on the role of oxaliplatin as radiosensitizer in combination with 5-FU supported benefit in terms of pathological response (RR = 1.24, 95% CI: 1.02–1.51; p = 0.03) and low incidence of distant metastasis rate (RR = 0.79, 95% CI: 0.67-0.94, p = 0.007) with

polichemotherapy compared to 5-FU alone (Fu et al., 2017). Therefore, the addition of oxaliplatin to 5-FU and RT could be an option.

4. Resectable primary tumor and non-resectable metastases (SCENARIO 3)

In this setting the primary goal is the control of the systemic disease. In case of potentially resectable metastases, conversion chemotherapy with the most active regimens should be considered according to the molecular profile of the disease: doublet chemotherapy plus anti-EGFR monoclonal antibodies in RAS and B-RAF WT disease (FOLFOX plus panitumumab or cetuximab) or doublet/triplet chemotherapy and bevacizumab (in absence of bleeding) in RAS or B-RAF mutated population (Gruenberger et al., 2015). Although preliminary, data about combinations of triplets (FOLFOXIRI) and anti-EGFR seem encouraging, but should be considered only within clinical trials (Garufi et al., 2010; Cremolini et al., 2018).

In patients with LLD converted to resectability, the “liver first” approach should be probably the preferred one: a radical approach of the primary tumour should be evaluated only in case of potentially curative liver resection. Palliative treatment such as endoscopic stenting or radiotherapy could be alternative approaches to avoid terminal colostomy in case of symptomatic disease in patients with no chance of a liver curative approach (Fiori et al., 2012).

Many trials investigated the best first-line chemotherapy regimen in metastatic CRC, but only few of them were randomized controlled trials specifically designed to investigate conversion chemotherapy as a treatment strategy.

In the phase II CELIM trial, 106 patients with unresectable or suboptimally resectable ($\geq$5 liver metastases) LM from CRC were treated with FOLFOX or FOLFIRI plus Cetuximab. The ORR after centralized radiological revision was 68% with FOLFOX and 57% with FOLFIRI. Of those patients who were not considered to be resectable before study treatment, 34% finally underwent R0 resection (Folprecht et al., 2014).

In a subsequent Chinese phase II trial, 138 patients with unresectable KRAS exon 2 WT LLD were randomized to mFOLFOX/mFOLFIRI plus or minus Cetuximab. In the anti-EGFR group the ORR and the conversion rate were respectively 57% and 26% vs 29% and 7% in the chemotherapy alone group (Ye et al., 2013).

The triplet regimen (FOLFOXIRI) in association with anti-EGFR was evaluated in the phase II POCHER trial: 43 patients with unresectable LM (21% of them with RC) were treated with this regimen obtaining an ORR of 79% with macroscopical radical resection achieved in 26 patients (60%) (Garufi et al., 2010).

Efficacy data of FOLFOXIRI plus bevacizumab in patients with LLD in terms of conversion therapy were reported in the phase II OLIVIA trial. In this trial 80 patients (17 of them with RC) were randomized to mFOLFOX6 plus bevacizumab or FOLFOXIRI plus bevacizumab. The ORR was increased from 62% to 81% and the resection rate from 49% to 61% with the addiction of irinotecan to the standard regimen mFOLFOX6 plus bevacizumab (Gruenberger et al., 2015).

In conclusion, in this setting systemic therapy with the most active regimens according to the molecular tumor profile represents the mainstay of the treatment strategy. After the conversion to resectability of LM, a simultaneous or staged resection (preferably liver first strategy) should be performed. Resection of primary tumor should be preceded by SC-RT or LC-CRT according to staging and location (high-mid vs low rectum). In case of uncontrolled LM, RT on primary tumor could be considered with a palliative intent.

5. Non-resectable primary tumor and metastases (SCENARIO 4)

This situation represents the most unfavorable clinical scenario. In patients with never-resectable disease, prolonging the survival and maintaining the quality of life become the main aims of anticancer therapy.

In case of symptomatic disease with obstructive symptoms, the use of endoscopic stents (particularly in cases of tumors located at the level of the middle-high rectum) or decompression with a colostomy could be considered (Fiori et al., 2012; Kuhlmann and Poston, 2015; Park, 2018). However, Tyc-Szczepaniak and colleagues demonstrated that SC-RT can be used for palliative and cytoreductive purposes, allowing most patients (even those with a near-obstructing lesion) to avoid surgery (Tyc-Szczepaniak et al., 2016). In asymptomatic patients, resection of primary RC does not significantly prolong survival as compared to upfront systemic treatment and should therefore be avoided (Pfeiffer et al., 2018).

In patients with symptomatic and/or with high burden disease, chemotherapy with highly active regimens could be the best choice with the aim to relieve symptoms and improve quality of life as well as prolong survival. The choice of the chemotherapy regimen depends on a number of patient- and tumor-related factors. Tumor response increases resection rate and prolong survival in patients with initially unresectable LM (Folprecht et al., 2005; Okuno et al., 2017). This high antitumor effect can be exploited also in this palliative setting, especially in patients at high risk of occlusion. In general, doublets (FOLFOX/XELOX or FOLFIRI) and triplets (FOLFOXIRI) produce higher RRs as compared to monotherapy (Van Cutsem et al., 2016). Moreover, addition of anti-EGFR or anti-VEGF monoclonal antibodies should be considered according to molecular tumor profile. ORR in patients with metastatic disease is around 50% (Van Cutsem et al., 2016). However, with the combination of FOLFOXIRI plus anti-EGFR a higher ORR can be achieved (86–89%) (Fornaro et al., 2013). In selected cases initially deemed unresectable with a relevant shrinkage of LM, surgery of primary tumor can be considered, with or without SC-RT or LC-CRT.

When 5-FU is used as a radiosensitizer, metastatic disease can be undertreated with the consequent risk of hepatic and extrahepatic progression. Given this premise, Bird and colleague published their retrospective series of 78 patients with LM from RC (63 of them with unresectable metastatic disease) treated with a split-course pelvic chemo-radiation (with concurrent 5-FU and oxaliplatin) alternated with FOLFOX. They demonstrated the feasibility and the efficacy of this strategy, with a durable pelvic control for the majority of patients without the need for additional local treatment (only 7% of patients required further RT or endoscopic stent for worsening local symptoms) (Bird et al., 2017).

Conversely, in patients with asymptomatic disease and/or with low burden and/or with extrahepatic metastases, who do not need a rapid shrinkage of the disease and, reasonably, will never become resectable, less active regimens, according to patients’ preference, can be used with the aim to slow tumor progression and maintain quality of life (Van Cutsem et al., 2016).

In conclusion, prompt initiation of systemic chemotherapy should be considered for patients with non-resectable primary RC and non-resectable LM. In patients with symptomatic disease, SC-RT or standard RT combined with systemic treatment could avoid surgery in most of the cases. In selected cases with LM initially deemed unresectable who achieve a significant shrinkage, surgery for RC and metastases should be considered, with or without addition of SC-RT of LC-CRT. Table 1 summarizes the most relevant studies published according to the different clinical scenarios above mentioned.

6. Conclusions

The optimal treatment of patients with RC with synchronous LM is complex and a multimodal approach including RT, systemic therapy and surgery is mandatory. The recommendations for clinical practice mainly rely on expert opinion, essentially based on data of trials in which patients with RC represent a small fraction as compared to those with colon cancer. Therefore, since there are no evidence-based recommendations, the best strategy should be defined on a case-by-case discussion within a multidisciplinary meeting, taking into account both

Table 1
Summary of clinical trials of patients with RC and synchronous LM.

Author	Proportion of RC (%)	Treatment	Main conclusions
SCENARIO 1: resectable primary tumor and metastases			
Nordlinger et al. (2008)	152/364 (42)	perioperative FOLFOX vs surgery	Longer PFS with peri-operative FOLFOX 4 vs surgery alone
Primrose et al. (2014)	Not known	perioperative FOLFOX/FOLFIRI/XELOX plus or minus cetuximab	Shorter PFS with the addition of cetuximab to perioperative FOLFOX/XELOX/ FOLFIRI
SCENARIO 2: non-resectable primary tumor and resectable metastases			
Picardi et al. (2016)	18/18 (100)	SC-RT	Complete and partial symptomatic response in 38.9% and 50% of patients, respectively
SCENARIO 3: resectable primary tumor and non-resectable metastases			
Folprecht et al. (2014)	49/111 (44.1)	FOLFOX or FOLFIRI plus cetuximab	Confirmed partial or complete response in 68% of patients treated with FOLFOX plus cetuximab and 57% in those treated with FOLFIRI plus cetuximab
Ye et al. (2013)	56/138 (40.5)	FOLFOX or FOLFIRI plus cetuximab	R0 resection rates for liver metastases were 25.7% in cetuximab arm and 7.4% in chemotherapy alone arm
Garufi et al. (2010)	9/43 (21)	chrono-IFLO plus cetuximab	Macroscopically complete resections performed in 60% of patients
Gruenberger et al. (2015)	17/80 (21.2)	FOLFOXIRI vs FOLFOX plus bevacizumab	Higher response and resection rates with FOLFOXIRI plus bevacizumab vs FOLFOX6 plus bevacizumab (81% and 61% vs 62% and 49%, respectively)
SCENARIO 4: non-resectable primary tumor and metastases			
Fornaro et al. (2013)	11/37 (30)	FOLFOXIRI plus panitumumab	FOLFOXIRI plus panitumumab feasible and highly effective (89% of ORR)
Bird et al. (2017)	78/78 (100)	Split-course LC-CRT (concurrent 5-FU and oxaliplatin) and FOLFOX	Rates of radiological complete or partial response for local and metastatic disease of 90% and 66%

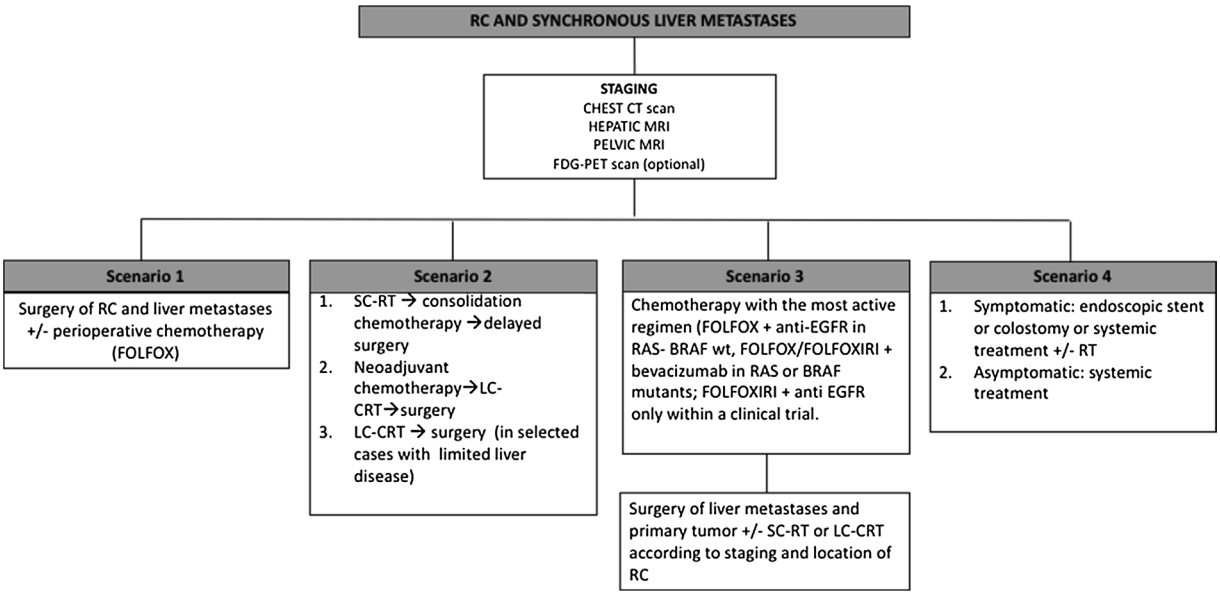

Fig. 1. Treatment algorithm for patients with RC and synchronous LM.

tumor-related factors (potential resectability of primary tumor and LM, risk of progression, molecular profile, response to therapies) and patient-related factors (performance status, comorbidities, presence of primary tumor-related symptoms). Since patients with LM are potential candidates for either simultaneous or staged resection of the primary tumor and metastases, they should be optimally staged, possibly with a chest CT scan, a pelvic magnetic resonance (MRI), and hepatic MRI and, in selected cases, an FDG-PET scan. For staged resection, there is growing evidence to support the "liver first" strategy because enables more patients to complete full treatment protocols. Fig. 1 provides a practical treatment algorithm for clinicians dealing with patients with RC and synchronous LM, according to the different clinical scenarios. Anyway, the optimal sequence of these treatments remain unclear and continues to evolve, deserving further evaluations in *ad hoc* clinical trials.

Conflict of interest

The authors declare that they have no conflicts of interest.

Author contribution

FG conceived and designed the manuscript. All authors analysed and interpreted the data, and drafted the article. All authors revised it critically for important intellectual content and finally approved the version to be submitted.

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References

Bachet, J.B., Lucidarme, O., Levache, C.B., Barbier, E., Raoul, J.L., Lecomte, T., et al., 2018. FOLFIRINOX as induction treatment in rectal cancer patients with synchronous metastases: results of the FFCD 1102 phase II trial. Eur. J. Cancer 104, 108–116.

Bird, T., Michael, M., Bressel, M., Chu, J., Chander, S., Cooray, P., et al., 2017. FOLFOX and intensified split-course chemoradiation as initial treatment for rectal cancer with synchronous metastases. Acta Oncol. (Madr) 56, 646–652.

Bujko, K., Nowacki, M.P., Nasierowska-Guttmejer, A., Michalski, W., Bebenek, M., Kryj, M., 2006. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br. J. Surg. 93, 1215–1223.

Bujko, K., Wyrwicz, L., Rutkowski, A., Malinowska, M., Pietrzak, L., Krynski, J., et al., 2016. Long-course oxaliplatin-based preoperative chemoradiation versus 5 x 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Ann. Oncol. 27, 834–842.

Cremolini, C., Antoniotti, C., Lonardi, S., Aprile, G., Bergamo, F., Masi, G., et al., 2018. Activity and Safety of Cetuximab Plus Modified FOLFOXIRI Followed by Maintenance With Cetuximab or Bevacizumab for RAS and BRAF Wild-type Metastatic Colorectal Cancer: A Randomized Phase 2 Clinical Trial. JAMA Oncol. 4, 529–536.

Deng, Y., Chi, P., Lan, P., Wang, L., Chen, W., Cui, L., et al., 2016. Modified FOLFOX6 With or Without Radiation Versus Fluorouracil and Leucovorin With Radiation in Neoadjuvant Treatment of Locally Advanced Rectal Cancer: Initial Results of the Chinese FOWARC Multicenter, Open-Label, Randomized Three-Arm Phase III Trial. J. Clin. Oncol. 34, 3300–3307.

Erlandsson, J., Holm, T., Pettersson, D., Berglund, A., Cedermark, B., Radu, C., et al., 2017. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncol. 18, 336–346.

Feng, Q., Wei, Y., Zhu, D., Ye, L., Lin, Q., Li, W., et al., 2014. Timing of hepatectomy for resectable synchronous colorectal liver metastases: for whom simultaneous resection is more suitable–a meta-analysis. PLoS One 9, e104348.

Fernandez-Martos, C., Brown, G., Estevan, R., Salud, A., Montagut, C., Maurel, J., et al., 2014. Preoperative chemotherapy in patients with intermediate-risk rectal adenocarcinoma selected by high-resolution magnetic resonance imaging: the GEMCAD 0801 Phase II Multicenter Trial. Oncologist 19, 1042–1043.

Fiori, E., Lamazza, A., Schillaci, A., Femia, S., Demasi, E., Decesare, A., et al., 2012. Palliative management for patients with subacute obstruction and stage IV unresectable rectosigmoid cancer: colostomy versus endoscopic stenting: final results of a prospective randomized trial. Am. J. Surg. 204, 321–326.

Folprecht, G., Grothey, A., Alberts, S., Raab, H.R., Kohne, C.H., 2005. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. Ann. Oncol. 16, 1311–1319.

Folprecht, G., Gruenberger, T., Bechstein, W., Raab, H.R., Weitz, J., Lordick, F., et al., 2014. Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). Ann. Oncol. 25, 1018–1025.

Fong, Y., 2014. Adjuvant therapy after hepatectomy for colorectal metastases. Lancet Oncol. 15, 544–545.

Fong, Y., Fortner, J., Sun, R.L., Brennan, M.F., Blumgart, L.H., 1999. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann. Surg. 230, 309–318 discussion 18-21.

Fornaro, L., Lonardi, S., Masi, G., Loupakis, F., Bergamo, F., Salvatore, L., et al., 2013. FOLFOXIRI in combination with panitumumab as first-line treatment in quadruple wild-type (KRAS, NRAS, HRAS, BRAF) metastatic colorectal cancer patients: a phase II trial by the Gruppo Oncologico Nord Ovest (GONO). Ann. Oncol. 24, 2062–2067.

Fu, X.L., Fang, Z., Shu, L.H., Tao, G.Q., Wang, J.Q., Rui, Z.L., et al., 2017. Meta-analysis of oxaliplatin-based versus fluorouracil-based neoadjuvant chemoradiotherapy and adjuvant chemotherapy for locally advanced rectal cancer. Oncotarget. 8, 34340–34351.

Garufi, C., Torsello, A., Tumolo, S., Ettorre, G.M., Zeuli, M., Campanella, C., et al., 2010. Cetuximab plus chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin as neoadjuvant chemotherapy in colorectal liver metastases: POCHER trial. Br. J. Cancer 103, 1542–1547.

Gruenberger, T., Bridgewater, J., Chau, I., Garcia Alfonso, P., Rivoire, M., Mudan, S., et al., 2015. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. Ann. Oncol. 26, 702–708.

Hasegawa, K., Oba, M., Kokudo, N., 2014. Cetuximab for resectable colorectal liver metastasis: new EPOC trial. Lancet Oncol. 15, e305–6.

Heinemann, V., von Weikersthal, L.F., Decker, T., Kiani, A., Vehling-Kaiser, U., Al-Batran, S.E., et al., 2014. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol. 15, 1065–1075.

Kuhlmann, K.F.S., Poston, G., 2015. Managing synchronous rectal cancer and liver metastases. Colorect Cancer. 4 (3), 115–118.

Lutz, M.P., Zalcberg, J.R., Glynne-Jones, R., Ruers, T., Ducreux, M., Arnold, D., et al., 2016. Second St. Gallen European Organisation for Research and Treatment of Cancer Gastrointestinal Cancer Conference: consensus recommendations on controversial issues in the primary treatment of rectal cancer. Eur. J. Cancer 63, 11–24.

Lykoudis, P.M., O'Reilly, D., Nastos, K., Fusai, G., 2014. Systematic review of surgical management of synchronous colorectal liver metastases. Br. J. Surg. 101, 605–612.

Ngan, S.Y., Burmeister, B., Fisher, R.J., Solomon, M., Goldstein, D., Joseph, D., et al., 2012. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J. Clin. Oncol. 30, 3827–3833.

Nordlinger, B., Sorbye, H., Glimelius, B., Poston, G.J., Schlag, P.M., Rougier, P., et al., 2008. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 371, 1007–1016.

Nordlinger, B., Sorbye, H., Glimelius, B., Poston, G.J., Schlag, P.M., Rougier, P., et al., 2013. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol. 14, 1208–1215.

Noren, A., Eriksson, H.G., Olsson, L.I., 2016. Selection for surgery and survival of synchronous colorectal liver metastases; a nationwide study. Eur. J. Cancer 53, 105–114.

Okuno, M., Hatano, E., Nishino, H., Seo, S., Taura, K., Uemoto, S., 2017. Does response rate of chemotherapy with molecular target agents correlate with the conversion rate and survival in patients with unresectable colorectal liver metastases?: A systematic review. Eur. J. Surg. Oncol. 43, 1003–1012.

Park, Y.Y.K.N., 2018. Treatment strategies for locally advanced rectal cancer with synchronous resectable liver metastasis. Formos J Surg. 51, 1–8.

Pfeiffer, P., Gruenberger, T., Glynne-Jones, R., 2018. Synchronous liver metastases in patients with rectal cancer: can we establish which treatment first? Ther. Adv. Med. Oncol. 10, 1758835918787993.

Picardi, V., Deodato, F., Guido, A., Giaccherini, L., Macchia, G., Frazzoni, L., et al., 2016. Palliative short-course radiation therapy in rectal Cancer: a phase 2 study. Int. J. Radiat. Oncol. Biol. Phys. 95, 1184–1190.

Primrose, J.N., 2014. Cetuximab for resectable colorectal liver metastasis: new EPOC trial–author's reply. Lancet Oncol. 15, e306.

Primrose, J., Falk, S., Finch-Jones, M., Valle, J., O'Reilly, D., Siriwardena, A., et al., 2014. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. Lancet Oncol. 15, 601–611.

Qiu, M., Hu, J., Yang, D., Cosgrove, D.P., Xu, R., 2015. Pattern of distant metastases in colorectal cancer: a SEER based study. Oncotarget 6, 38658–38666.

Rodel, C., Graeven, U., Fietkau, R., Hohenberger, W., Hothorn, T., Arnold, D., et al., 2015. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 16, 979–989.

Salvador-Roses, H., Lopez-Ben, S., Casellas-Robert, M., Planellas, P., Gomez-Romeu, N., Farres, R., et al., 2018. Oncological strategies for locally advanced rectal cancer with synchronous liver metastases, interval strategy versus rectum first strategy: a comparison of short-term outcomes. Clin. Transl. Oncol. 20, 1018–1025.

Schwartzberg, L.S., Rivera, F., Karthaus, M., Fasola, G., Canon, J.L., Hecht, J.R., et al., 2014. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J. Clin. Oncol. 32, 2240–2247.

Siddiqui, M.R.S., Simillis, C., Hunter, C., Chand, M., Bhoday, J., Garant, A., et al., 2017. A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) vs mrEMVI-negative cases. Br. J. Cancer 116, 1513–1519.

Siegel, R.L., Miller, K.D., Jemal, A., 2018. Cancer statistics, 2018. CA Cancer J. Clin. (68), 7–30.

Sobrero, A., 2016. A tribute to biologics in advanced colorectal cancer treatment. Ann. Oncol. 27, 1372–1374.

Tyc-Szczepaniak, D., Wyrwicz, L., Wisniowska, K., Michalski, W., Pietrzak, L., Bujko, K., 2016. Palliative radiotherapy and chemotherapy instead of surgery in symptomatic rectal cancer with synchronous unresectable metastases: long-term results of a phase II study. Acta Oncol. (Madr) 55, 1369–1370.

Van Cutsem, E., Cervantes, A., Adam, R., Sobrero, A., Van Krieken, J.H., Aderka, D., et al., 2016. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann. Oncol. 27, 1386–1422.

van Dijk, T.H., Tamas, K., Beukema, J.C., Beets, G.L., Gelderblom, A.J., de Jong, K.P., et al., 2013. Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer. Ann. Oncol. 24, 1762–1769.

Venook, A.P., Niedzwiecki, D., Lenz, H.J., Innocenti, F., Fruth, B., Meyerhardt, J.A., et al., 2017. Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial. JAMA 317, 2392–2401.

Xie, H., Zhou, X., Zhuo, Z., Che, S., Xie, L., Fu, W., 2014. Effectiveness of MRI for the assessment of mesorectal fascia involvement in patients with rectal cancer: a systematic review and meta-analysis. Dig. Surg. 31, 123–134.

Ye, L.C., Liu, T.S., Ren, L., Wei, Y., Zhu, D.X., Zai, S.Y., et al., 2013. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. J. Clin. Oncol. 31, 1931–1938.

Gelsomino Fabio is currently Medical Oncologist at University Hospital of Modena. He is involved in clinical research on gastrointestinal tumors. He is member of gastrointestinal tumors multidisciplinary Team (MDT).

Andrea Spallanzani is currently Medical Oncologist at University Hospital of Modena. He is involved in clinical research on gastrointestinal tumors. He is member of gastrointestinal tumors multidisciplinary Team (MDT).

Ingrid Garajovà is currently Medical Oncologist at University Hospital of Parma. She is involved in clinical research on gastrointestinal tumors. He is member of gastrointestinal tumors multidisciplinary Team (MDT).