Review Article

Treatment algorithm of metastatic rectal cancer

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Abstract: Around 50% of patients suffering from colorectal cancer will develop metastasis within their lifetime. Some liver and lung metastases are amenable to surgical resection, and these patients can enjoy an improved overall survival (OS), although up to 65% will develop some form of recurrence. In the era of precision surgery, with personalised medicine for each individual, a multi-disciplinary approach is required to ensure we are optimising the patient's treatment. Whilst we know that surgical resection is often a matter of technical limitations, it is not always the correct choice. With the advances in oncotherapy, surgical resection should be reserved for those in whom it is clear will benefit from this. The surgical approach to the synchronous approach of metastatic rectal cancer has created controversy in whether to tackle the primary first, or deal with the metastasis first, or the benefits of neoadjuvant chemotherapy, with or without radiotherapy. In this review article, we aim to summarise the current practices and treatment options for management of metastatic rectal cancer, as well as patient selection.

Keywords: Metastatic rectal cancer; multidisciplinary discussion (MDT); synchronous; simultaneous resection

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Introduction

Colorectal cancer is the third most commonly diagnosed cancer among both men and women, and second most common cause of death in the UK. In 2018, the global incidence was approximately 1.8 million cases, and accounted for almost 700,000 deaths, making it the fourth leading cause of cancer death worldwide (1). Metastasis is a concern for patients and clinicians alike as they may be fatal. The liver and lung are the most common sites of spread for rectal cancer. This is thought to be due to the venous drainage of the rectum. Up to 25% of patients present with metastasis at initial diagnosis, and around 50% of patients will develop liver or lung metastasis during the course of the disease (2,3).

For solitary or confined liver or pulmonary metastases, surgical resection remains the standard of care, though around 65% will develop intra-hepatic recurrence within 3 years (4). Surgical resection improves median overall survival (OS) to approximately 40–55 months, and a 5-year survival of up to 40% (2), compared to a mere 1% with treatment with systemic chemotherapy (4).

In the era of precision surgery, patient selection remains the key to maximise the benefit of surgical resection. The question of "who should be operated on" has progressed to a multifactorial assessment of technical and oncological factors, with decisions made in a multidisciplinary approach, which is now a mandatory legal requirement in the UK. The importance of a multidisciplinary discussion (MDT) and decision making is well recognised as the optimal approach to determine management (5,6).

Who should be operated on?

With resectable colorectal liver metastases (CRLM), surgical resection remains the standard of care. There

is a general consensus as to which patients will benefit from surgical resection. Those with a small solitary liver metastases, in which an adequate margin (1 cm) is achievable, whilst leaving a significant volume of remnant liver, would be suitable for surgical therapy and can enjoy a long-term disease free survival (DFS) with a meta-analysis finding rates of 40% alive at 5 years, and 25% at 10 years (7). For those with metastasis unsuitable for surgical resection, neoadjuvant chemotherapy have similar survival rates to those "straight to surgery" (8). Advances in systemic chemotherapy and molecular therapy provides a potential median survival of over 25 months (4).

Lung is the second common place for metastatic rectal cancer. Up to 15% of cases are found to be advanced, i.e., multiple or bilateral metastasis, and only 7% a single lesion. There are no prospective controlled or randomised trials to date regarding the benefit of surgical therapy, but pulmonary metastectomy is regarded as treatment of choice providing 5-year survival rates of up to 58%, in those suitable (9). Despite the advances in multi-agent chemotherapy, median survival remains only around 2 years.

Simultaneous *vs.* staged resection

The role of surgery in the combined liver and lung metastasis is not yet well defined. With 5-year survival rates of up to 50%, surgical resection is often offered to many patients. The decision to operate, however, lies at the heart of the MDT. Whilst there no prospective studies looking into this, several retrospective studies have all come to the conclusion that simultaneous resection offers prolonged survival, with a 5-year rate of up to 55% (10-13).

Liver

CRLM can present either synchronously, or metachronously. Around 20% will present synchronously, and of these, around 20% will be suitable for surgical resection. There are no current strict criteria to define the resectability, but follows the general rule of ability to obtain an R0 resection, whilst leaving sufficient remnant liver volume. For synchronous presentations, there is the option a simultaneous or a staged resection. The options for synchronous presentations include treating the primary first, synchronous resections, or treating the liver first.

The classical approach, primary first, involved resection followed by chemotherapy, and then 3–6 months later, a liver resection.

Lung

Pulmonary metastases are treated sequentially. To date there are only retrospective studies evaluating the benefit of pulmonary resection for colorectal metastases. However, they have all shown an increased OS with resection (9,14-16). Few prognostic indicators have been summarised, which include the site of the primary tumour, R0 resection, disease-free interval, serum carcino-embryonic antigen level, metastasis number, size and lymph node metastasis (17,18). Simultaneous pulmonary metastectomy and primary resection has not yet been explored, despite advantages of a simultaneous resection. Whilst there are no trials comparing surgical *vs.* non-surgical management in resectable disease, obtaining ethics to set up a trial may prove difficult given how strong the evidence for surgical resection is.

Simultaneous liver and lung

Previously combined liver and lung segmentectomy required two separate incisions or a thoracoabdominal extension, and this was associated with significant post-operative morbidity, and as a result not undertaken very often. Blumgart revolutionised the simultaneous approach by conceptualising the trans-abdominal-transdiaphragmatic approach. Ko *et al.* went onto describe a thoracic transdiaphragmatic approach for hepatectomies in patients with hepatocellular carcinoma (19). This method was then adopted by Delis *et al.* and extended to treat metachronous and right-lung metastases. The major benefit of this method was the reduced post-operative morbidity, without compromising clearance, when compared to the two incision approach (20).

Mise *et al.* compared outcomes between their transdiaphragmatic simultaneous resection and conventional lung mastectomy and found reduced estimated blood loss and reduced length of stay in the simultaneous group (21). One limitation they found was the technical complexity of the procedure given the narrow visual field in the thoracic cavity. However, a learning curve exists with all new procedures. An added benefit of the procedure was detection by manual palpation of lung metastases. Manual palpation is the most sensitive method for small lung lesions (22), and theoretically, long-term prognosis should be improved, although not compared in the study.

One other aspect which should be considered is the availability of thoracic surgeons at the same time as liver

surgeons. This requires coordination of what is already an understaffed rota, and so it may be difficult to provide this joint service.

Multimodal therapy

The treatment algorithm for locally-advanced rectal cancer without distant metastasis is well established (23). Neoadjuvant chemoradiotherapy followed by total mesorectal excision (TME) is the current standard of care, and is known to reduce rates of local recurrence. For metastatic rectal cancer, a form of neoadjuvant therapy is required, in the form of radiotherapy, chemotherapy or a combination.

Initially irresectable liver limited disease

The primary aim of chemotherapy in irresectable liver limited metastasis is the conversion to resectability. Approximately 70% are unresectable at diagnosis and required a combination of loco-regional therapy (chemoembolization, hepatic arterial infusion, ablation or radiation). The UK National Institute for Clinical Excellence (NICE) currently recommend the use of FOLFOX (folinic acid, fluorouracil, oxaliplatin) as first line therapy for irresectable disease, and combination with irinotecan as second line therapy (24).

The optimum combination of cytotoxic and biological agents is still under investigation. The introduction of bevacizumab when associated with FOLFOXIRI (folinic acid, fluorouracil, oxaliplatin, irinotecan) as first line chemotherapy showed a slight gain in response rate. Loupakis *et al.* randomised 508 patients to either FOLFIRI plus bevacizumab or FOLFOXIRI plus bevacizumab, and showed a progression-free survival (PFS) of 9.7 *vs.* 12.1 months (HR 0.75; 95% CI, 0.62–0.90; P=0.003). The response rate was 53% *vs.* 65% (P=0.006), and rate of resection was 12% *vs.* 15% (25). Of note though they recorded an increased rate of toxicity from the FOLFOXIRI plus bevacizumab group.

The OLIVIA trial compared FOLFOXIRI plus bevacizumab *vs.* mFOLFOX-6 plus bevacizumab and found higher response and resection rates and prolonged PFS in the FOLFOXIRI plus bevacizumab group (26). In the German phase II trial, the resection rates of FOLFIRI plus panitumumab treatment are 15% and 7% in the KRAS wild type and mutant groups respectively (27). The PRIME study compared FOLFOX4 with and without panitumumab and found increased PFS (9.6 *vs.* 8.0 months; HR 0.80; 95% CI, 0.66–0.9; P=0.02), as well as reduced PFS in mutant KRAS (HR 1.29; P=0.02) and longer median OS (15.5 *vs.* 19.3 months, HR 1.24; P=0.068) (28). The CRYSTAL trial found resectability rates of 7% *vs.* 3.7% in the FOLFIRI plus cetuximab arm *vs.* FOLIRI alone with R0 resection rate of 4.8% *vs.* 1.7% (P=0.002) (29).

The effects of chemotherapy associated liver injury (CALI), resulting from multiple lines of chemotherapy, were studied by Vauthey *et al.* and demonstrated a clear and significant increase in post-operative mortality (30), the chance of cure from surgical resection still provides a viable option (31). Whilst the most beneficial combination of chemotherapeutic agents is yet to be determined, many have shown its advantages for conversion to resectability, and should be used.

Resectable CRLM

Relapse has been reported as high as 60% after complete surgical excision. Adjuvant chemotherapy has been shown to increase OS when compared to surgery alone, although not proven to be statistically significant (32). NICE now recommend 6 months of chemotherapy for resectable metastatic liver lesions. The National Comprehensive Cancer Network (NCCN) guidelines advocate the use of more than one chemotherapy line. New anti-epidermal growth factor receptors (such as cetuximab and panitumumab) and anti-angiogenic drugs (bevacizumab, regorafenib and aflibercept) are available to complement the classic cytotoxic agents.

The NCCN guidelines suggest the use of FOLFOX, FOLFIRI (irinotecan plus leucovorin and short-term infusional fluorouracil) or XELOX (capecitabine and oxaliplatin) with or without bevacizumab; FOLFIRI with or without cetuximab or panitumumab; or FOLFOX with or without panitumumab or cetuximab.

The European Organisation for Research and Treatment of Cancer (EORTC) 40983 trial randomised 364 patients to 12 cycles (6 before and 6 after) of perioperative FOLFOX or surgery alone. The primary endpoint was 3-year PFS and in the experiment arm, the 3-year PFS was 36.2% compared to 28.1% compared to the surgery alone arm. The 5-year OS was not significantly better in the chemotherapy group (52% *vs.* 48%), however the study was not powered to that effect (29).

Lung

The role of adjuvant chemotherapy in colorectal lung

metastasis has yet to be defined. To date, no trials have evaluated the use and benefits of chemotherapy after pulmonary metastectomy. Shiomi *et al.* completed a retrospective review and found adjuvant chemotherapy strongly affected relapse-free survival and OS compared to surgery alone [recurrence free survival (RFS): HR 0.49; P=0.016 and OS: HR 0.35; P=0.014] (33). Kim *et al.* showed improved DFS but no improved OS in the adjuvant chemotherapy group when compared to surgery alone (32.7 *vs.* 11.2 months; and 89.6 *vs.* 86.8 months respectively) (34). Imanishi *et al.*, however, showed no benefits in terms of OS (HR 1.00; P=1.00) and DFS (HR 1.07; P=0.62) (35).

Radiotherapy

Radiotherapy is effective in controlling disease-related symptoms (36). However, its role in metastatic rectal cancer is not completely clear. When combined with neoadjuvant chemotherapy, several studies point towards improved OS and PFS, although optimal timing is yet to be determined (37). The recognised benefits of neoadjuvant chemoradiotherapy for resectable spread include downsizing lesions allowing lesser resections, early treatment of micrometastatic disease, better selection of patients for resection, and evaluation of response. Potential drawbacks include the risk of progression of disease and CALI.

Buwenge *et al.* not only found greater OS and DFS with the use of neoadjuvant radiotherapy, but found it provided great palliation from symptoms of pain, bleeding and obstruction, with response rates of 79, 87 and 78% (36). Furthermore, Fossum *et al.* reported the benefits of neoadjuvant radiotherapy finding also decreased incidence of local recurrence, as well as improved OS (5-year OS 43.3% *vs.* 58.3%) and DFS (5-year rate 49.6% *vs.* 60.5%) (32).

Long vs. short-course chemoradiotherapy

In rectal cancer with synchronous metastases, the primary tumour almost always has progressed to a more locally advanced stage. Downstaging is often attempted in the form of neoadjuvant radiotherapy or chemoradiotherapy. The current standard is for long-course chemoradiotherapy followed by TME. However, this poses the potential threat of further systemic spread whilst completing the course, and subsequently turning resectable metastasis into irresectable metastasis.

EORTC 22921 found a significantly higher pathological complete response rate in patients undergoing preoperative chemoradiotherapy *vs.* radiotherapy alone (14% *vs.* 5%), as well as significantly less advanced pT and pN stages (P<0.001), and few cases with venous, perineural, or lymphatic invasion (P<0.008) (38).

Ngan *et al.* randomly assigned 326 patients to either short-course or long-course neoadjuvant radiotherapy for rectal cancer. They found no statistically significant difference between the two arms for local recurrence after 3 years (39). Latkauskas *et al.* randomized patients with resectable stage II and II rectal cancers to receive either short-course radiotherapy or long-course chemoradiotherapy and found statistically significant greater tumour downsizing and downstaging in the long-course arm, but no difference in the R0 resection rates (40). In the final results however, Latkauskas *et al.* reported a better 3-year DFS in the long-course group compared to the short-course (75.1% *vs.* 59%; P=0.022) but no difference in OS (82.4% *vs.* 78%; P=0.145) (41).

Conclusions

The definitive pathway to treat metastatic rectal cancer requires refinement. What is clear is the role of surgery in technically resectable metastasis, and the use of perioperative chemotherapy. For those unsuitable for resection, chemotherapy can convert irresectable to resectable and should be attempted. As advances in chemotherapeutic agents are made, tumour biology should also be taken into account (anti-EGFR and anti-angiogenesis drugs), although this can only be done retrospectively. Patients with metastatic rectal cancer should all have a careful staging and individualised treatment approach including a selective combination of surgery, chemo- or radiotherapy.

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