
Management of Low Rectal Cancer with Synchronous Liver Metastases

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Introduction

One-quarter of patients with rectal adenocarcinoma have stage IV disease at presentation, and over two-thirds of patients have metastases limited to the liver. Unresectable liver colorectal liver metastases (CRLM) are associated with only 30% 1-year survival, and long-term survival is worse for patients presenting with synchronous disease [1].

Successful completion of treatment to all sites of disease is the only chance of cure and is associated with 5-year survival of 55% [2, 3]. Indeed 5-year survival rates of 67% [4] have been achieved with the addition of neoadjuvant systemic therapy to control micrometastatic disease and select biologically favorable disease [5, 6].

Uncertainty remains regarding the optimal sequencing of therapy, the applicability of synchronous resections and the role of pelvic radiotherapy in stage IV rectal adenocarcinoma [7–11]. The overall goal of treatment is surgical resection of disease and minimizing delay in systemic treatment.

Case Presentation 1

A 65-year-old man with a background of chronic obstructive pulmonary disease and type 2 diabetes presented with diarrhea and 10 g of unwanted weight loss over 2 months. Colonoscopy revealed an obstructing low rectal tumor. MRI of the

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rectum was suggestive of a T3N1 tumor with threatened circumferential resection margin. CT scan revealed a 13 mm hypodense lesion in segment 3 of the liver. CEA was elevated at 3.22 $\mu\text{g/L}$.

Clinical Pearls

- Pelvic radiation for locally advanced low rectal cancers improves local control and disease-free survival and may facilitate a liver-first approach.
- In the setting of synchronous metastatic disease, neoadjuvant radiotherapy regimens should include oxaloplatin-based chemotherapy.
- Consider performance status prior to synchronous resection. Major hepatic resections, when combined with synchronous rectal resection, are associated with high morbidity.
- For large-volume liver disease, neoadjuvant “sandwich” chemotherapy (+concurrent pelvic radiotherapy) and a liver-first approach is favored.
- For low-volume liver disease, multimodal treatment of the rectal disease, followed by completion chemotherapy is favored. Hepatic resection may be combined with reversal of ileostomy.

Multidisciplinary Management

Neoadjuvant chemoradiation was undertaken with short-course radiation therapy to the rectum (5×5 Gray over two weeks). At the completion of week 2, systemic FOLFOX was delivered for six cycles over 6 weeks. CT imaging was repeated showing no progression of disease but no objective tumor response in the pelvis. Laparoscopic low anterior resection with colo-anal anastomosis and diverting ileostomy was completed. The postoperative course was uneventful and pathological analysis confirmed complete tumor extirpation (T3N1bR0). Eight weeks after rectal resection, synchronous laparoscopic left lateral sectionectomy and reversal of ileostomy was performed. Again, the postoperative recovery was uneventful, both rectal and hepatic resections were complete, and no further systemic therapy was required (Figs. 6.1 and 6.2).

Case Summary

The background of a patient with a symptomatic primary tumor, low volume CRLM, and limited performance status requires careful consideration. Long-course radiation to the pelvis combined with combination chemotherapy was considered too toxic for this patient [12]. Short-course radiotherapy (SCRT) followed by combination chemotherapy only delayed receipt of systemic therapy by 2 weeks and

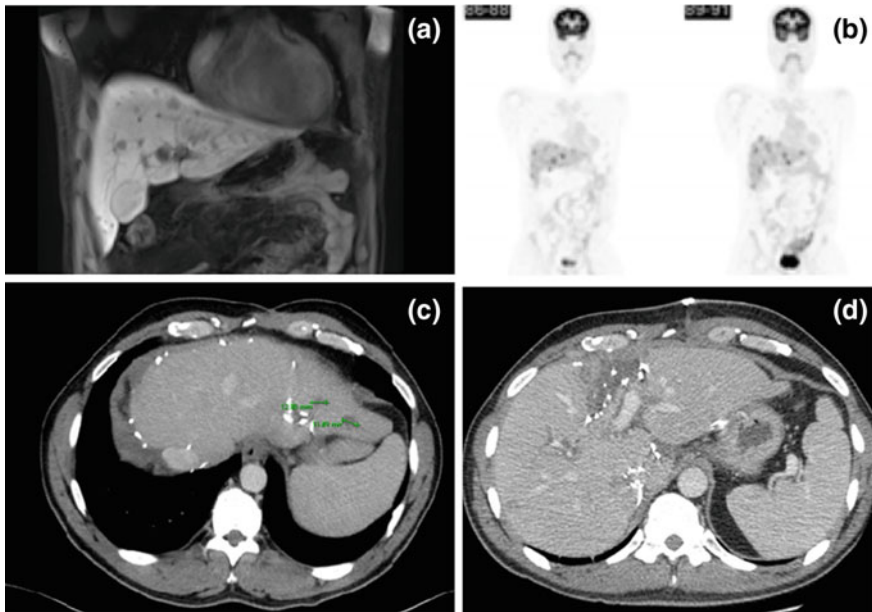


Fig. 6.1 Case 3. **a** Contrast enhanced T1 weighted MRI of the liver showing multiple liver metastases and segment 4 lesion threatening left portal vein margin. **b** FDG-18 Positive emission topography showing multiple liver metastases and primary in pelvis. **c** Computed tomography 6 months after surgery revealing 2 recurrent lesions in the left lobe of the liver which were subsequently resected. **d** Computed tomography scan of the liver following first ALLPPS procedure showing dissection along portal vein margin and ligation of right portal vein

allowed good control of the symptomatic primary disease [13]. Low anterior resection (with diverting ileostomy) and left lateral sectionectomy were both surgically amenable to a combined laparoscopic approach. This was not undertaken due to the higher risk of complications from combined liver and rectal resection, in a comorbid patient [14], as well as the fact that an ileostomy reversal could be combined with laparoscopic left lateral sectionectomy.

Controversies in Management

- Complete extirpation of malignant disease is possible for patients undergoing minor liver resections and left-sided bowel resections, although not always appropriate.
- Patient fitness and performance status is the main determinant of whether this approach is appropriate.

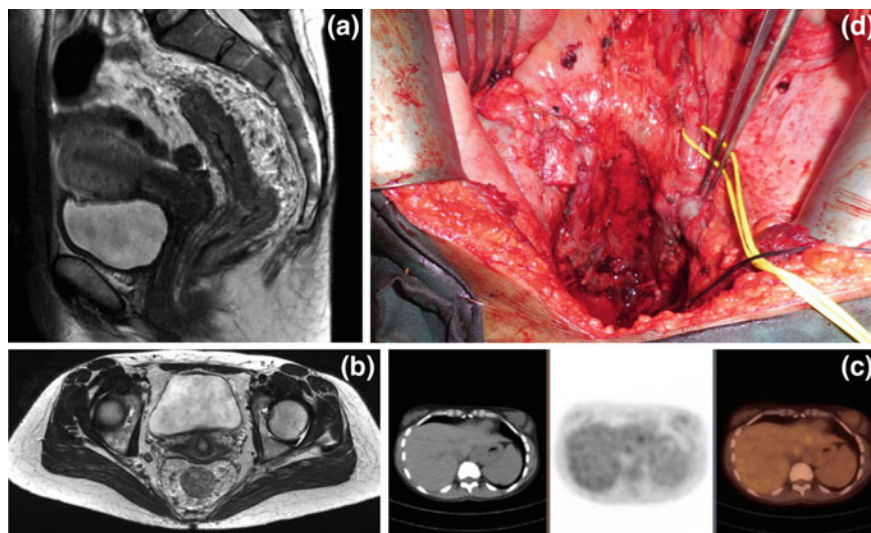


Fig. 6.2 Case 2. **a, b** T2 weighted MRI of the pelvis showing extensive low rectal adenocarcinoma with multiple enlarged mesorectal and iliac lymph nodes. **c** FDG-18 PET/CT showing increased uptake in segment 2/3 of the liver, this lesion was not identifiable on imaging following chemotherapy. **d** Operative photograph following partial anterior exenteration and bilateral ileac node dissection

Case Presentation 2

A 35-year-old woman, with no significant past medical history, presented to her general practitioner with lethargy and was found to have iron-deficiency anemia. A history of intermittent rectal bleeding was elucidated. Digital rectal examination revealed a firm anteriorly fixed mass, 6 cm from the anal verge. Colonoscopy confirmed a nonobstructing rectal mass and biopsy proved adenocarcinoma.

Computed tomography of the chest, abdomen, and pelvis, and magnetic resonance imaging of the pelvis was performed for staging. A 2 cm hypodense lesion in segment 2/3 was observed, with no evidence of extrahepatic disease. Pelvic MRI revealed a very large low rectal tumor with invasion to the rectovaginal septum as well as extensive mesorectal and iliac lymphadenopathy (T4b, N2b, M1a). Staging was completed with 18F-FDG PET/CT, which confirmed oligometastatic disease in the left lateral section of the liver. CEA levels were not elevated at 1.2 µg/L.

Multidisciplinary Management

Neoadjuvant long-course chemoradiation was commenced. Fractionated external beam radiation was delivered to the rectum and pelvic side walls for a total of five

weeks and 50 Gray. The chemosensitizer 5-FU was delivered in combination with oxaloplatin, irinotecan, leucovorin, and bevacizumab for 7 months.

Repeat MRI of the pelvis and CT of the chest, abdomen, and pelvis showed significant response to neoadjuvant therapy in the pelvis, “ghosting” of the lesion in the left lobe of the liver, and no new metastatic deposits.

Synchronous ultralow anterior resection (incorporating the posterior wall of the vagina), diverting loop ileostomy, bilateral iliac node dissection, and left lateral sectionectomy of the liver was performed. The liver lesion was not detectable on intraoperative high definition ultrasound, and there was minimal iliac nodal tissue and a fibrotic rectovaginal septum.

Pathological analysis revealed a moderate response to neoadjuvant therapy of the primary lesion, extensive necrosis was seen in most lymph nodes sampled, with viable tumor cells in only three of 31 mesorectal nodes. A complete pathological response was observed in the liver lesion, with no viable tumor.

The perioperative course was complicated by severe thrombocytopenia and a return to theater for suspected pelvic bleeding, subsequent abdominal and pelvic collections requiring percutaneous drainage, and intravenous antibiotics. Postoperative chemotherapy was delayed for 4 months due to complications from surgery.

Case Summary

The extensive nature of the pelvic disease, despite limited symptoms, meant that the potential for downstaging with standard radiotherapy was favored [15]. The patient was able to tolerate combination chemotherapy, radiotherapy, and a biological agent with minimal toxicity and excellent response. Synchronous open resection was performed, but due to the extensive nature of the pelvic dissection, multiple complications were observed. Clear surgical margins, minimal lymph node involvement, and complete response to disease in the liver were good prognostic indicators.

Controversies in Management

- Longer durations of chemotherapy prior to surgery increase the risk of perioperative complications.
- Systemic recurrence is the most likely determinant of long-term survival and this may be improved with a longer duration of preoperative chemotherapy.
- Preoperative chemotherapy allows assessment of the biology of the disease.

Case Presentation 3

A 42-year-old man presented to his general practitioner with epigastric pain. He underwent an ultrasound scan of the abdomen, which revealed multiple bilobar solid liver lesions. Subsequent digital rectal examination revealed a mid-to-low rectal mass. Referral to colonoscopy and an examination by a colorectal surgeon confirmed a low rectal adenocarcinoma. MRI of the rectum revealed the tumor to focally extend beyond the muscularis propria, with multiple enlarged lymph nodes confined to the mesorectum. CT imaging of the liver revealed hypodense lesions in all segments of the liver, but no evidence of peritoneal or extrahepatic spread. 18FDG PET/CT confirmed the innumerable FDG-avid lesions in the liver, but with no extrahepatic disease. CEA level was elevated at 9.0 µg/L.

Multidisciplinary Management

Systemic chemotherapy with palliative intent was commenced and, given his excellent performance, two cycles of FOLFOX were delivered. Repeat CT scan revealed a measurable reduction in size of the liver lesions. There was also some objective evidence of shrinkage of the primary lesion. Referral to a specialist liver surgeon prompted primavist MRI of the liver and consideration of staged hepatectomy. The two superficial lesions in segments 2 and 3 of the liver were resectable prior to portal vein embolization, with extended right hemi-hepatectomy as a second-stage procedure. However, a 2 cm segment 4 lesion was close to the left portal inflow, which if enlarged following the first-stage hepatectomy, may have precluded extended right hemi-hepatectomy. Dissection on the plane of the left portal pedicle and the requirement to minimize time without chemotherapy made an ALLPPS procedure ideal. The patient completed five further cycles of FOLFOX chemotherapy, suffering only with fatigue and mild peripheral neuropathy. Repeat imaging was completed before proceeding to surgery three weeks after the seventh cycle of chemotherapy. Six wedge resections of segments 2 and 3 were performed at the first stage along with caudate lobectomy, liver partition along the left portal pedicle, and ligation of the right portal vein. Of the six lesions, only one contained viable adenocarcinoma, with necrosis, inflammation, and fibrosis, indicating a good response to neoadjuvant chemotherapy. Extended right hemi-hepatectomy was performed 11 days later, revealing more than 40 lesions of the liver with a maximum diameter of 25 mm. Pathological analysis revealed no metastasis in portal lymph nodes and no lymphovascular invasion. Postoperatively, chemotherapy was recommenced at 6 weeks with a further six cycles of FOLFOX. MRI of the pelvis at 6 months revealed a complete radiological response in the rectum, and this was confirmed at proctoscopy. Repeat primovist MRI of the liver revealed two new lesions in segment 2 of the liver (in a watershed of a wedge resection). A third hepatectomy was performed to remove segment 2. After a further 3 months with no chemotherapy, a single-stage low anterior resection was performed, and pathological review of the specimen analysis revealed a complete pathological response.

Case Summary

Hepatic metastases defines the prognosis of the patient. The patient was initially deemed unresectable at colorectal MDT and started “palliative” chemotherapy. After a response to initial chemotherapy was observed, referral to a specialist HPB surgeon was performed. The risk of involved margins at hepatectomy favored prolonged systemic therapy and a short interval to aggressive two-stage hepatectomy removing approximately 50 liver lesions. Early low-volume recurrence in the left lateral section has necessitated further chemotherapy and a third liver resection. The primary tumor has undergone near-complete response and can be observed, as further metastatic disease will dictate outcome.

Controversies in Management

- Longer durations of preoperative chemotherapy may improve tumor response at the expense of causing liver injury as a consequence of sinusoidal obstructive syndrome and steatohepatitis.
- Liver-first surgery is appropriate when the burden of disease is high, or the surgery to remove the tumors is complicated.

Discussion: Symptomatic Primary Tumors

The referral pattern of patients diagnosed with primary rectal cancer often dictates sequencing of therapy, with a primary first approach still favored by most centers [8]. Symptomatic disease is often cited as the reason for upfront resection, prior to systemic therapy. Sporadic rectal bleeding and anemia are common symptoms, but bleeding requiring ongoing transfusion is rare. Large bowel obstruction due to a low rectal tumor is also a rare event and should be managed with diverting colostomy followed by neoadjuvant therapy rather than upfront resection. For partially obstructed or endoscopically obstructed rectal adenocarcinoma, colostomy can be avoided in 96% of patients who are able to undergo radiation therapy prior to surgery [16]. This results in less delay to neoadjuvant therapy, and should reassure oncologists that treatment is unlikely to be interrupted.

Neoadjuvant Therapy

In nonmetastatic rectal cancer, short-course radiation therapy (SCRT) followed by surgery and long-course radiation therapy (LCRT) with chemosensitization (5-FU)

then surgery, is associated with decreased rates of local recurrence [17]. LCRT has the added benefit of downstaging primary tumors for sphincter-sparing resections, and can increase R0 resection rates and local control [15]. In stage IV disease the use of standard SCRT/LCRT regimes followed by rectal surgery can delay the provision of effective systemic therapy by over 3 months. This delay may be dramatically increased should complications be encountered following rectal resection, which risks disease progression in the liver and subsequent unresectability [5]. Similarly, untreated rectal disease and a systemic therapy/liver-first approach is associated with 26% of rectal tumors being found to be unresectable [18].

The addition of more effective systemic therapy to LCRT (typically oxaloplatin compounds and leucovorin) is an aggressive approach of neoadjuvant treatment to the liver and rectum. It is associated with increased toxicity and may be poorly tolerated in patients with comorbidities [12].

A less toxic approach is short-course radiotherapy with surgery delayed until systemic therapy can be completed. This is associated with radiological response rates in 74% of patients [19] and this allows for modifications in subsequent treatment sequence, i.e., liver-first approach. The sequence of radiation therapy—systemic therapy then repeat imaging—may also be reversed with the advantage of early assessment for disease progression and avoiding radiation therapy in patients with progressive unresectable liver disease [17].

Aggressive systemic therapy may be applied in patients with excellent performance status, and may convert initially stage IV unresectable disease in 15% of patients [20]. Response rates of the primary tumor to standard combination chemotherapy rates are in the order of 55% [20], however, a proportion of patients may progress despite treatment [18]. The addition of biological agents in eligible patients increases response rates. Meta-analysis has revealed that overall response rates are around 64% and conversion to R0 resectability possible in 22.5% [21].

Combination chemotherapy may be complicated by nonalcoholic steatohepatitis, steatosis, and liver cell injury. This may delay or preclude major liver resection, especially in patients with borderline liver function, or necessitate a two-stage procedure. Even successful chemotherapy with a complete or near-complete response may cause radiological “ghosting” of lesions, making resection complex.

Surgical Resection

The classical approach (primary first) to synchronous colorectal cancer and CRLM remains the most widely accepted and commonly practiced approach [7, 22]. This may in part be due to patterns of referral and can allow the full metastatic burden of disease be appreciated. The liver-first approach incorporating neoadjuvant chemotherapy, in which the metastatic disease is prioritized and not delayed by local treatment to the primary tumor, is a newer approach. The requirement and effect of rectal chemoradiation and the higher risk of septic complications with rectal resection, compared to colonic resection make a liver-first approach ideally

suited to synchronous rectal adenocarcinoma [23]. Although no benefit has been proven in overall survival, and morbidity and mortality appear to be similar in both groups [7, 8], a higher proportion of patients complete all treatment in a liver-first approach [5]. Meta-analysis has shown that only 19% of patients progress in their liver disease prior to hepatic resection with neoadjuvant chemotherapy [5]. Although 55% response rates are observed in the rectal primary [24], a high proportion of patients (26%) are observed to have progression in the pelvis after completion of all therapy to the liver [18]. The addition of radiotherapy (either short-course immediately followed by systemic therapy, or long-course with effective systemic therapy) may negate the risk of an unresectable primary [12, 13].

Conclusion

A synchronous approach to colorectal resection of all tumor sites at one operation would seem the ideal approach, with similar mortality and morbidity to staged resections, as published by multiple authors [7, 10, 14, 23, 25, 26]. However, these studies are biased by the limited numbers of rectal resections included and the low-volume of metastatic disease (i.e., need for major hepatectomy). One study limited to patients with undergoing synchronous resection in the setting of a rectal primary showed it is safe, but that 5-year survival is lower than other published studies [25]. This study was also limited by less than 1/3 of patients undergoing low anterior resection and only 22% major hepatectomy [25]. Other studies have reported high rates of complications (58%) and lower overall survival (32%) [14]. There is general consensus that in all but the fittest patients, combined low rectal resection and hepatectomy should be avoided.

The decision to perform a primary or liver-first approach should be impacted by the volume of disease at both sites. The likelihood of involved margins or progression preventing resection at each site must be assessed, and treatment prioritized, to avoid positive margins or unresectable disease.

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