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Mini Review

Perspectives on Minimally Invasive Approach to Resection of Colorectal Liver Metastases

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1. Abstract

Surgical resection is the most effective treatment approach in colorectal liver metastases. The improved survival in stage IV colorectal cancer is associated with a better diagnosis and evaluation, proper decision making, improved chemotherapy, and the adoption of parenchymal-sparing hepatic resections. Liver surgery was one of the last frontiers reached by minimally invasive surgery. Surgical techniques and specialized equipment evolved to overcome the technical limitations making Laparoscopic Liver Resections (LLR) safe and feasible. This will be relevant in these elderly cohort of patients with comorbidities, chemotherapy associated steatohepatitis and probale prior liver resections. The rationale for, and efficacy of minimally invasive surgery for colorectal liver metastases are briefly discussed.

2. Keywords: Minimally invasive surgery; Colorectal; Liver metastases

3. Background

The liver is the most common site for Colorectal Cancer (CRC) metastases accounting for 80% of stage IV patients and 40% as the only site of distant disease. 20-25% of patients with CRC present with synchronous metastases and 50-60% will develop metachronous disease [1]. Although neo-adjuvant chemotherapy such as FOLFOX (folinic acid plus fluorouracil plus oxaliplatin) as first line treatment then single agent irinotecan as second-line treatment has improved tumour response, the median survival for patients with unresectable disease is poor and there is no 5-year survival. Resection, when feasible confers a higher chance of cure and can improve 5-year survival to 34-60% [1, 2]. The resectability criteria for colorectal liver metastases (CRLM) is expanded in an advanced multidisciplinary team (MDT) meeting alongside the evolution of imaging, neo-adjuvant and adjuvant techniques such as thermal ablation, selective internal radiation therapy (SIRT) and transarterial chemoembolisation (TACE) [2]. Unresectable unilobar disease may be treated by neoadjuvant chemotherapy followed by extended liver resection with or without portal vein embolisation to stimulate the size of the future liver remnant (FLR). For multiple bilobar colorectal liver metastases, the strategies for improved margin clearance includes stage resection which entails a first-stage local resection of metastases of the future left remnant liver followed by portal vein embolisation/ ligation and then a second-stage right hepatectomy 4 weeks later after the left remnant has hypertrophied [1, 2]. Although high-quality contrast-enhanced Computed Tomography (CT) and liver Magnetic Resonance Imaging (MRI) are commonly used preoperatively, laparoscopic ultrasonography (LUS) usually performed with a high-resolution 7.5 -10 MHz probe allows direct visualization of liver metastases in regard to segmental anatomy (Figure 1), local vascular involvement and regional nodal disease.LUS improves the diagnostic accuracy of staging laparoscopy alone, provides additional information on resectability in 14-25% of patients, and detects occult metastases and new findings in 40-55% of cases [2, 3]. Intra-operative ultrasound (IOUS) via real-time imaging aid planning at the time of resection and allow safe removal of all viable tumour with a clear margin of >1cm. It facilitates liver-sparing and microwave / radio-frequency (RF) thermal ablation techniques in patients with compromised parenchyma (chemotherapy associated steatohepatitis (CASH), prior

liver resection), and avoids the small for size syndrome [2-4]. Anatomical liver resections follow anatomical planes and thus have better oncological clearance than non-anatomical liver resections. Major anatomical resections have better oncological clearance than limited segmental resections with reduced recurrence rate and improved survival. However, segmental liver resection of focal cancers based on Couinaud's liver segmental classification (Figure 1), would improve vascular control (less blood loss), minimize the risk of recurrence from intrahepatic spread, and reduce the amount of normal liver unnecessarily removed [3]. Fortunately, liver secondary metastases from colorectal cancers have better biology than metastases from other gastrointestinal sites, and are amenable to non-anatomical surgical resections. Thus, the oncologically safe non-anatomical, parenchymal-sparing resections are used for colorectal liver metastases to achieve a complete metastatectomy. There is, however, 20% recurrence. Which are also amenable to repeat resections [1-3]. It is appropriately utilized in the modern setting of multimodal treatments and repeat resections. It may, however, result in compromise of vascular supply of the remaining tissue. Simple wedge excision of peripheral lesions is not appropriate since it compromises the resection margin and risks the danger of leaving satellite metastases [1, 5]. There is controversy as to the significance of resection margin status as ablation with haemostatic devices will destroy the margin to some extent (1-3mm) giving an appearance of a 'R0' margin (no tumour cells)in the patient remnant but an 'R1' margin (tumour cells present) in the pathological specimen [1, 4, 5].

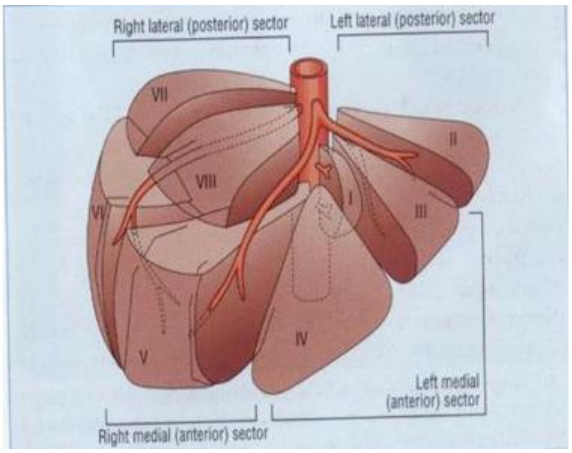

Figure 1: Couinaud's segmental anatomy of the liver [4] (with permission).

4. Minimally Invasive Surgery

Laparoscopic surgery had been slowly introduced in surgical oncology because of the concern of inadequate margins or lymph node sampling, tumour seeding, missing small metastases, and poor pathological and oncological outcomes. The only randomized controlled trial (the OSLO-COMET study) showed that in patients undergoing parenchyma- sparing liver resection for colorectal metastases, laparoscopic surgery was associated with significantly less postoperative complications compared to open surgery, was cost effective (early recovery, short hospital stay and early return to work) and, the rate of free resection margins was the same [6].The concerns of the rare air embolism is met by putting the patient in 150 Tredelenberg position and careful surgical technique [1, 7]. In the current COVID-19 pandemic just as with surgery in HIV/AIDS [8], care should be taken during laparoscopy upon using disposable ports with a vestibular flange to prevent splash back, and by deflating the abdomen prior to port withdrawal because any aerosol emanating from the port entry wound will harbor COVID-19 [9, 10]. In addition to the currently advised Personal Protective Equipment (PPE) to healthcare staff in the operating theatre, this simple method would further lessen the risk of occupational transmission [10]. COVID-19 patients would benefit from the reduced surgical stress of minimally invasive surgery, but it would be important to know the effect of immuno suppression from major LLR on COVID-19 disease progression. During the 1990's minor resections of two or fewer easily accessible Couinaud's liver segments had been the standard of care. The posterior-superior segments (VII, VIII) and segments S1, IV a were excluded as they posed a higher surgical challenge from the extensive mobilization required to bring those segments to the operative field. Resections of lesions located on anterolateral segments (S II, III, IVb, V, VI) and left lateral sectionectomy (S II, III) were performed systematically by laparoscopy in hepatobiliary centres. The posterior-superior resections had been indicated as 'major operations' despite including only two segments (VII, VIII). This was corroborated by the associated higher conversion rates, higher blood loss, prolonged operative times and narrower surgical margins [11]. Resection of lesions located on posterior- superior segments and major liver resections were shown to be feasible but remain technically demanding and reserved for experience surgeons in high volume hepatobiliary centres. Laparoscopy- assisted, and transthoracic port placement are useful strategies applied to difficult resections [7, 11]. Nearly 10,000 minor and major LLRs as an alternative to open surgery have been reported in the literature since 2000, showing the wide acceptance and safety [11, 12]. Currently, the indications for LLR do not differ from those for open surgery [12]. A recent meta-analytic study [13] showed laparoscopic liver resection (LLR) having better perioperative outcome than open liver resection (OLR) for recurrent liver cancer without compromising oncological outcome. With longer overall and median survival rates following recurrent resections, the indications for surgery are increasing with R1 surgery (complete tumour resection without safe margins) being justified for patients with a response to preoperative chemotherapy [1, 2, 5]. It makes sense that minimally invasive procedures are made available to these elderly patients who may also have CASH, prior liver resections, and other co-morbidities [5-7]. In addition, despite the relatively higher local recurrence rate, adjunctive treatment such as laparoscopic RF/microwave ablation is acceptable for patients of high surgical risk for liver resection, or with small solitary colorectal liver metastases [1, 2]. Therefore, the favourable biology of CRLM has enabled patients to live with their disease with repeat resections for recurrence. However, oncogenic mutations of

RAS (N-ras and K-ras) genes controlling cell proliferation have been associated with worse disease- free and overall survival following CRLM resection even with adjuvant anti-epidermal growth factor (EGFR) cetuximab therapy. Thus, the rationale for neoadjuvant chemotherapy even for resectable patients, and biologic agents for the k-ras exon 2 wild-type, is to destroy occult micrometases and increase progression-free survival [1, 2]. Where CRLM are unresectable chemotherapy may downsize tumours and improve biological selection for resection. This is seen as a complete radiological response which depends on the quality and completeness of preoperative imaging, or as "missing" metastases. As complete radiological response does not signify a complete pathological response, liver resection of curative-intent would include all initial and currently known sites of disease [1, 2]. Robotic-assisted resections are feasible as demonstrated in reported case series. The three dimensional (3-D) view and greater range of movement can be useful for complex resections [14]. The dynamic applicability of the 3-D planning to navigation during operation may also improve operative results [15].

5. One Stage (Simultaneous) Or Staged Procedure?

The decision as to whether the operations for the primary tumour and liver metastases are done at the same time (simultaneous) or separately (staged) is made at the advanced MDT meeting and in discussion with the patient [1]. The advantages of a one stage (simultaneous) operation are (a) the decreased risk of disease dissemination (transperitoneally), (c) no repeated postoperative immunosuppression causing increased tumour growth [15], and (c) lower costs. A staged procedure would (1) allow assessment of biological behavior of metastases, (2) avoid operating on patients who are progressing while on chemotherapy, and (3) allow more precise selection for curative surgery. Delayed hepatic resection may not impair survival but help select those patients most likely to benefit from hepatic resection i.e. stable disease. For mid and low rectal primary tumours, chemoradiotherapy is often needed and in addition to a difficult resection a one stage surgery is not recommended. One stage surgery is not advocated for complex colonic and upper rectal primary tumours, for high risk patients or when hepatectomy is major (> 3 segments). Minor liver resections (2 segments or less) may be safely performed at the same time as colorectal resection (open or laparoscopic) when both the primary tumour and the metastases are easily resectable. The outcomes are similar to sequential surgery in this scenario [1,2].

6. The Four Clinical Scenarios of Stage IV CRC

The management of the four clinical scenarios are as follows (i) for the asymptomatic CRC and resectable synchronous CRLM, chemotherapy is first with or without radiotherapy for rectal cancer, followed either by surgery in a one-stage procedure for patients with limited hepatic disease and easy to resect primary tumour, or by staged (liver-first) surgery for other patients; (ii) for asymptomatic CRC and non-resctable synchronous CRLM, the consensus is for optimal chemotherapy first, with the aim of making the liver metastases (LM) resectable. This is followed by hepatic surgery and then resection of the primary; (iii) for symptomatic CRC and resectable synchronous CRLM, recommendations are for resection of the primary tumour for perforated or occlusive tumours (but not for tumours with bleeding causing anaemia), followed by chemotherapy and then surgery for LM; (iv) for symptomatic CRC and non-resectable synchronous CRLM, recommendations are for resection of the primary tumour for perforated or occlusive tumours, followed by chemotherapy and then surgery for LM if tumour shrinkage is achieved. For tumours with bleeding causing anaemia, induction chemotherapy is recommended to downsize both the primary and LM, followed by surgery at the site with the most significant tumour load which is usually the liver, i.e. a reverse approach [1, 2].

7. Conclusions

Both proper selection of patients who will benefit from liver resection and a high experience in minimally-invasive surgery are warranted in a hepatobiliary unit. Improved imaging techniques, identification of genomic markers and advances in chemotherapy will further improve the outcome of minimally-invasive surgery in the management of stage IV CRLM.

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