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EDITORIAL

Clinical Studies

Liver transplantation for non-resectable colorectal liver metastases: the thin red line

Transplantation for non-resectable colorectal liver metastasis (CRLM) has become accepted for a few, select patients following stringent criteria. With improved understanding of the selective indications, enhanced curation of the donor pool, and by further insight into cancer biology, novel avenues for research may be developed and eventually benefit more patients with non-resectable CRLM.

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In Edinburgh, at the National War Museum, there is an oil on canvas called 'The Thin Red Line'. The painting refers to a battle of Balaclava during the Crimean war (1853–1856). In the 1854 event, an outnumbered and outpowered two-line deep defence of Scottish infantry soldiers at a hilltop was formed to face the Russians. The line counted 500 men from the Highland brigade against 2500 of the Russian cavalry. Thinking the infantry could not stand alone without support hidden from their sight, the Russians never charged, eventually leading to their defeat despite their superiority. The incident was a small one, both in the context of the battle and in the Crimean war overall. However, the event became the focus for celebrating the stoicism and steadfastness of the British Army, as well as the source of poems, marches, and paintings. It also very much inspired the epic 1998 movie with the same title, portraying the complexities of humans and war during the Guadalcanal Campaign in World War II.

Now, personally, I am no great enthusiast for the use of the 'war analogy' in cancer treatment and research. I dislike the expression of patients 'losing the battle against cancer', as if a victory was theirs to decide had they only mustered the strength and force. However, in the current issue of the *Journal*, the comprehensive review of liver transplantation for colorectal liver metastasis (CRLM) [1] by the Barcelona Liver Transplant Unit brought the analogy of the 'Thin Red Line' to mind. Like the evolution of liver transplantation as such, the re-emergence of liver transplantation for CRLM is truly a story of stoicism and steadfastness. Yet, still, it is also a reminder of how thin the defence line against CRLM really is.

Colorectal cancer (CRC) is a global health burden with a concerning increase in early-age onset cancers. About half of all patients with CRC will develop metastases with the liver as the most frequent site for spread. Currently, about one in every five patients with CRLM may be eligible for resection aimed for cure. Evolution of combined treatment strategies have made more patients amenable to interventions—including improvements in systemic therapy and targeted therapy; the adjunct use of liver-modifying techniques, such as portal vein embolisation; ablative techniques alone or in combination with surgery [2]; and parenchyma-sparing resections and extended indications (e.g. select patients with lung metastasis).

Indications are being stretched as liver surgery for CRLM has become safer and currently performed with low morbidity and mortality. The pendulum for 'resectable' has swung from 'what needs to be taken out' (in the past: max 3 lesions, all <3 cm in size) to 'what is left' (currently: an adequate size and function of the future liver remnant). Beyond the limits of technical resectability lies the reflection of what is believed to be sound oncological boundaries. Notably, these boundaries are increasingly hard to define and, as a consequence, we are increasingly making decisions in a 'grey zone' (Fig. 1). However, there are limits—structural, technical, and biological. There are considerable variations in both referrals for evaluation of liver surgery and in the assessment of resectability [3, 4]. While the resection rate for CRLM seems to hover around 20–25% (Fig. 1), most patients are never considered candidates for surgery. The share volume of patients outnumbers the surgical options for cure, as it stands.

Hence, for the group of patients with unresectable CRLM, getting a new liver by transplantation has re-emerged as an attractive option. The concept has largely been revitalised through the Second Cancer (SECA) trials [5]. Liver transplantation is now an accepted treatment for very select patients using stringent criteria (Fig. 1), with recommendations endorsed through international consensus guidelines [6].

Indeed, the enthusiasm for liver transplantation in unresectable CRLM is spreading globally. In a recent report, at least 15 centres in the United States reported having transplanted patients with CRLM with a further handful of centres having patients listed for transplant [7]. In the UK, transplant services for CRLM has aimed to commence by end of 2022 [8]. Other centres and countries prepare to follow suit. The question addressed by the Barcelona group is thus timely [1]—are we ready for it?

One expressed concern is an overuse of transplantation in an era with shortage of graft donors in most countries, particularly with a surge in centres providing this treatment. However, the collective US experience of 46 current transplants for CRLM is done in a period with an estimated 165,000 new metastatic colorectal cancers in the US [7] and during a period for which 1000s of liver resections were done. Hence, the share volume of transplantation represents an overall small part of treatment offered to patients with CRLM (Fig. 1). Critics and contestants have

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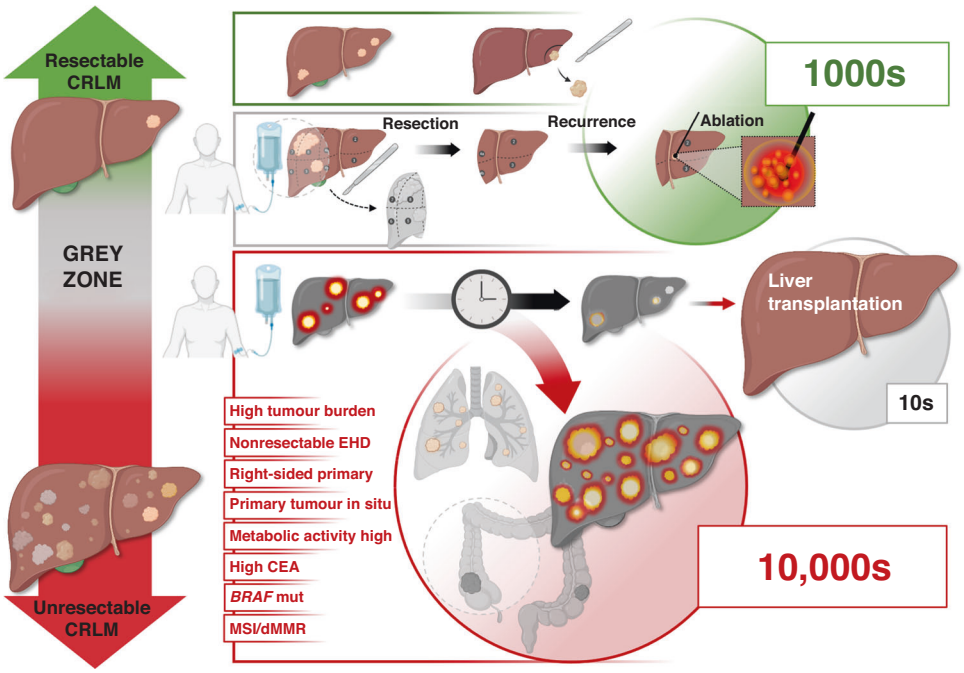

Fig. 1 Resectable and non-resectable colorectal liver metastasis. The resectable (green area) and non-resectable (red area) colorectal liver metastasis (CRLM) is overlapped by a 'grey zone' in which indications and protocols are being stretched to expand criteria for 'resectable' or 'treatable' CRLM by different modalities. Initial resection may be followed by new local treatment, e.g. ablation for a recurrence. Transplantation is a modality, for which selection of candidates is based on time-dependent criteria and avoiding unfavourable biological factors (such as BRAF mutation) to prevent futility. Also, in unresectable CRLM with MSI/dMMR the use of first-line immunotherapy has proved to be an efficient treatment hence competing with the efficacy of transplantation. For every transplant, the numbers of patients who undergo resection is in the thousands and for non-resectable CRLM in the tens of thousands. Hence, transplantation for non-resectable CRLM represents a 'thin red line' and not the main defence for treating non-resectable CRLM. CEA carcinoembryonic antigen, EHD extrahepatic disease, MSI microsatellite instability, dMMR defect mismatch repair. Created in part with Biorender.com.

argued that the donor pool will be exhausted by introducing new indications like CRLM. However, the change in epidemiology and treatment of other diseases (e.g. for viral hepatitis now amendable to medical cure) and development of new techniques (ex situ machine preservation; suboptimal grafts previously discarded) can expand the current pool of grafts available in particular to patients with CRLM [9, 10]. However, unwise, undocumented, and too liberal use may truly break down the thin red line.

Indeed, the feat of liver transplantation for non-resectable CRLM forms a thin red line, very visible on the hilltop, compared to the deeps of trenches. It adds to the stretch in indications that has pushed biological boundaries over the years. In resectable CRLM, a high 10-year overall survival can be achieved in a considerable number of patients, conditional of favourable prognostic factors [11]. In resected CRLM [12], poor prognostic factors tend to diminish in their role over time, as patients drop out of survival analyses early and hence other factors become more prominent for the remaining survivors over time. For example, $BRAF^{V600E}$ mutations are considered an early predictor of poor outcome but has less impact in long-term survivors. Indeed, there is recognised 'good', 'bad' and 'ugly' biology in CRLM [13] largely driven by molecular and morphological features in the tumour–liver microenvironment interface [14]. Currently, the understanding of these is limited at best and we are only able to treat but a minority of the features involved. The dynamic, altered, and disruptive biological behaviour of CRLMs is essential to understand at a cellular level, such as the image-based metabolic response that appears essential also for selection from the SECA cohort [15].

Transplantation for CRLM may indeed form a thin red line against the increasing volume of non-resectable CRLMs. In keeping with the analogy—it is but a battle in the war. However, improved understanding of the selective indications, by curating the pool of donors, and harnessing the biological behaviour implied in its success it might just give the source of inspiration for—if not poems, paintings, and movies—new avenues for research and innovations that eventually will benefit the larger group of patients with non-resectable CRLM.

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DATA AVAILABILITY

Not applicable.

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Not applicable.

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