Resection and Ablation for Colorectal Liver Metastases

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Abstract

The surgical approach combining resection and ablation allows for a greater number of patients with colorectal liver metastases who would otherwise be considered to have unresectable disease to be given an opportunity to undergo a curative attempt surgery. Ablation results in local destruction of tumour and is often employed in lesions that are in locations which are not easily resectable. This may involve the use of radiofrequency ablation that causes thermal destruction or cryotherapy that freezes tumours. This review examined the literature reporting resection and ablation of colorectal liver metastases.

Keywords: Resection; Radiofrequency; Cryotherapy

Introduction

Surgical resection remains the gold standard treatment for CLMs, achieving 10-year survival rate of 22% in a selected group of patients [1]. However, only 20% of CLMs are amenable to resection at time of diagnosis. Despite the increased resectability in advanced CLMs with two-stage heptectomy, approximately 20% of patients may fail to go through with the planned treatment [2]. The rate of resectability had also expanded over the years owing to the availability of better chemotherapy agents permitting improved local disease control and down staging of tumor burden allowing subsequent resection.

Post-operative hepatic functional reserve remains the main limitation to surgical resection, hence the attractive alternative of employing the adjunctive use of ablative therapies. There are multiple methods of percutaneous imaging-guided ablation. The simplest of these is alcohol injection but this has a role limited to small hepatocellular carcinoma. Cryotherapy and radiofrequency ablation will be discussed in detail. The role of these treatments are probably best limited to unresectable tumors or patients who are unfit for resection because we have been ultimately led to believe that ablation can ensure the long-term survival results of resection. The application of cryotherapy is not limited to lesion ablations but also may be used to treat suboptimal or involved margins of resection in patients precluded from extended resections. Long-term data following thermal ablation are scarce. Till date, the superiority of either thermal ablative method remains unclear and further sizeable comparative studies would be required to determine this.

Radiofrequency Ablation

Radiofrequency ablation (RFA) is currently the most frequently utilized thermal ablative modality. The radiofrequency energy conducted through the electrodes induces localized ionic agitation, which is converted into heat energy with an end-result of a zone of coagulation necrosis [3]. The clinical safety and efficacy of different approaches of RFA (open/laparoscopic/percutaneous) in eradication of hepatic malignancies had been demonstrated in early studies, extending curative treatment to non-resectable diseases [2,4,5]. RFA further gained popularity from its proven superiority over ethanol injection [6], and comparable results to surgical resection from randomized trials in treatment of hepatocellular carcinomas [7]. Its benefits in treatment of unresectable CRLMs was further supported by the EORTC trial comparing RFA plus systemic chemotherapy to systemic chemotherapy alone, whereby a prolonged median DFS by 7 months was observed in the combined treatment group albeit not translated into overall survival [8]. The present literature on RFA for the treatment of colorectal liver metastases, nonetheless, leaves limitations to interpretation, largely owing to the heterogeneity in study designs with majority of comparative trials being retrospective.

Delivery of RFA

RFA is better suited to percutaneous approach because of small probe diameter; however, better data exists for laparoscopy and open therapy. Although the approach of RFA was not shown to influence survival, there was a trend towards a higher rate of recurrence with percutaneous RFA (PcRFA) (15.1%) compared to open (6.7%) and laparoscopy (9%) in a study by Bleicher et al. of 153 patients treated for a total of 447 liver tumours [8]. In addition, several studies had consistently reported significantly higher complication rates with PcRFA relative to operative approaches [9,10]. Despite the perceived technical simplicity with PcRFA, the cooperation of patients’ respiratory effort following sedation poses difficulty in accurate probe placement [11]. The percutaneous approach as it’s minimally invasive, of course, avoids most of the morbidity of operative approaches resulting in shorter hospital stay [12].

The advantages of operative approaches translated by the eventual oncological outcome are undeniable as they allow accurate disease staging (undiagnosed on pre-operative imagings) via visualization, manual palpation and intraoperative ultrasonography (IOUS) [13-16]. In a study by Elias et al., surgical management was altered in 41.3% of patients with colorectal liver metastases (CLM) (total of 209) based on additional disease found intraoperatively - extrahepatic (16.2%), intrahepatic (30%), and both (4.9%) [16]. The subsequent analysis on 124 patients who could have had undergone PcRFA (<3 cm diameter, ≤ 3 lesions) revealed 21.7% with additional extrahepatic metastases [16]. Surgical access also protects adjacent structures from thermal injury and enables vascular occlusion to be performed; allowing control of hemorrhage and increasing the possibility of complete tumor ablation of lesions in close proximity to hepatic vasculature by minimizing the cooling effect [10,12,17-19].

Image-controlled ablation is dependent on IOUS experience and on 3-D probe-placement expertise. Our senior author (DLM) has till date performed up to 2000 IOUS, and it’s still technically challenging.

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Regardless of the approach of RFA employed, treatment outcomes are indeed operator dependent. Experience with RFA determines complete ablation and post-operative morbidities, as demonstrated by Poon et al. [20]. On the other hand, Bale and colleagues demonstrated that experience did not influence treatment outcome of stereotactic radiofrequency ablation as the technology allows accurate multiple needle placements, however, with compromised complication rates of up to 17% [21,22].

Survival following Radiofrequency Ablation for Unresectable Colorectal Liver Metastases

Overall survival

The heterogeneity in study designs with regards to inclusion criterion has rendered difficulty in interpretation of survival data within the current RFA literature. These data analysed a collective of tumour types, which differ in natural history. CLMs treated with RFA have poorer survival outcome compared to hepatocellular carcinomas and neuroendocrine metastases [10]. There is simply insufficient data on individual tumours. The best estimate of median, 1-, 2-, 3-, 4-, and 5-year survivals achieved with RFA in CLMs are 27-38 months [12,23,24], 71% - 94% [11,17,23-30], 60% - 78% [17,23-27,29], 21% - 72.7% [11,17,23-25,27,29,31-33], 27% - 36% [26,27], and 14% - 43% [11,12,23,28,29,34,35], respectively (Figure 1).

Traditionally, unresectable hepatic disease was defined by multinodularity (>4 lesions), presence of extrahepatic disease, anatomical location of metastatic deposits, and presence of bilobar disease resulting in inadequate functional hepatic reserve post-resection. Recent advancements have led to the belief that these factors are merely of prognostic value. As early as 1996, incorporation of neoadjuvant systemic chemotherapy into treating initially unresectable CLMs has expanded curability with sequential surgical resection [36]. Most centres have, therefore, adopted an aggressive multimodal approach in treating CLMs; offering surgical resection alone or in combination with thermal ablation provided complete tumor extirpation can be achieved with sufficient functional post-operative hepatic parenchyma [9-11,15,17,20,23,25-27,31,35-44]. How RFA fits into the expanded unresectable criteria today is unclear. Several studies have also included patients who have refused surgical resection into their analysis along with those ineligible for resection.

Disease recurrence

Disease recurrence following surgical interventions is a common phenomenon. Contrary to the belief, needle-track seeding following RFA is a sporadic event [23]. Data on recurrence within the available literature were variably reported, either by per patient or per lesion. The median, 1-, 2-, 3-, and 5-year disease-free survivals reported were 6 - 12 months [24,26,43], 43% - 92%, 38% - 55%, 8% - 34.1%, and 0% - 15% (Figure 2) [17,25,28,33,43,45]. The application of RFA influenced both overall and intrahepatic recurrence rates with most studies reporting poorer recurrence-free survival in CLMs treated with RFA alone [17,25,31]. Abdalla et al. observed an increased risk of recurrence in patients receiving RFA alone compared to RFA in combination with resection, and the occurrence of intrahepatic recurrence was 4 times more than resection alone [31]. Although statistically insignificant, Gleisner and colleagues demonstrated otherwise [33]. Treatment failure as depicted by local recurrence following any form of ablative therapy remains a concern. A wide range of local recurrence rates at RFA-treated sites had been reported, from as low as 2% up to 60% [9,11-15,17,19,23-29,32,35,37-39,42,43,45,46]. The majority of these were diagnosed within the first 12 months post-RFA, with virtually none observed after 18 months [24,26,43].

Prognostic Determinants

The following are significant prognostic determinants identified thus far. However, these factors are also related to the underlying biology of the tumor.

Tumour size

Local recurrence is largely predicted by the maximal diameter of
ablated metastatic deposits [14,32,39]. Although there is a wide range of RF devices available, the established literature on RFA is largely on monopolar RF device; its use limited to small lesions (<3 cm) to ensure optimal local tumor control [14,32,39,45,47]. Several studies have included treatment of larger lesions (>3 cm) with multiple overlapping ablation demonstrating a high rate of local recurrence owing to the inaccuracy of real-time imaging with ultrasound [13,39,48,49]. This is due to the presence of microbubbles obscuring the actual tumour margin during the process of RFA by creating an enlarged hypechogenic area on sonographic images [49]. Kennedy et al. reported their laparoscopic experience a 3.6% local recurrence in lesions <3 cm, in contrast to 19.6% in lesions >3 cm [45]. In a study by Veltri, ablation of lesions larger than 4 cm with RFA not only doubles the rate of treatment failure but also significantly reduces median survival (23.2 vs. 36.2 months) [23].

Bipolar RF device has expanded treatment to lesions of 5 cm in diameter though early studies on its efficacy have been contradictory [50,51]. In a more recent study by Baldwin et al. on a small cohort with mean lesion size of 3.6 ± 1.3 cm, only 1 of 22 patients developed recurrence at the site of ablation [52].

**Tumour margin**

The aim of RFA is to induce coagulative necrosis of the target lesion with a margin of normal hepatic parenchyma. Ablated margins of less than 1 cm was associated with a 1.6 fold increased risk of local recurrence [17]. Similarly, another study demonstrated a trend towards higher local recurrence rate of 22.2% in CLM patients with post-ablation margin of less than 0.4 cm [48]. Therefore, a circumferential rim of 0.5 to 1.0 cm of ablation is required for best tumour control [9,35].

**Proximity to vascular structures**

Treatment failure is also determined by the anatomical location of metastatic lesions. Unlike small vessels, larger vessels (4 - 5 mm) are resistant to thermal injury induced by RFA. A rim of viable tumour adjacent to the vessel wall often persists following RFA as a result of convective cooling effect exerted by blood flow. Most studies analysing the manipulation of blood flow have found no difference in local tumour control. The effects of vascular occlusion with Pringle's manoeuvre in surgical RFA have been controversial. Percutaneous portal or hepatic vein balloon occlusion has also been employed. This, however, did not demonstrate any benefit with regards to local tumour progression. In addition, one patient amongst the 10% who developed asymptomatic complete venous thrombosis, experienced left lobe atrophy owing to permanent left portal branch thrombosis [9,17,25,49,53].

**Tumor number**

The number of tumours ablated was associated with survival outcome. The median survival in unresectable CLMs with more than 3 lesions had a significantly lower median survival (29.7 months) compared to those with fewer than 3 lesions (41.3 months) [15]. This however, was reflective only in patients treated with RFA alone. Patients who were treated in RFA in combination with surgical resection were unaffected [31]. In general, patients who were treated with RFA and resection had better prognosis relative to those receiving RFA alone [13,14,16,31,32,53]. Even when cases with solitary disease were taken into consideration, the outcome was worse overall [31]. Similar pattern of survival was described in a study of 30 patients where 10 (33.3%) underwent RFA due to significant comorbidities precluding safe hepatic resection -5-year survival of 72% (surgically resected) vs. 18% (RFA) (p=0.006) [32].

**RFA-Related Morbidity and Mortality**

A wide range of morbidity rates following RFA for unresectable CLMs have been reported, ranging from 1.7% to 27% [13,15,22-24,26,30,37-47]. Morbidity following RFA is inversely proportional to the experience of the proceduralist [4]. Most studies have classified their morbidities into major and minor complications based on the Therapy-Oriented Severity Grading Systems (TOSGS) classification.

Of the major complications, abscess formation by far, has the highest prevalence; comprising of 7.5% within 308 tumours ablated in one study [14]. Major complications as a result of thermal injury include biliary stricture and leaks, and viscous perforation. Biliary injury frequently occurs in patients with bilioenteric anastomoses and biliary strictures. The consequential severe morbidity following these thermal-induced complications has led to lesions within 1 cm range from the hepatic hilum, gallbladder and gastrointestinal structures a contraindication to RFA [15]. Cases of abdominal wall burn requiring surgical debridement have been reported. Other major complications related to RFA include haemorrhage and multiorgan failure [38]. Poon et al. described one multiorgan failure syndrome post-RFA, and similar to the cryoshock phenomenon was notioned to be related to systemic cytokine response [20]. Navarra et al. reported one case of perioperative multiorgan failure and one DIC. However, no further details were provided regarding these cases [15]. Further studies may be required to validate these possible incidents.

Minor complications happen more frequently after RFA. These include asymptomatic pulmonary complications (pneumothorax, pleural effusion), uncomplicated intra- and perihepatic haematomas, self-limiting hepatic failure, post-ablation syndrome, grounding pad burns, brachial plexopathy, and myoglobinuria [9,11,13,15,20,24,25,27,37,47,54,55].

Mortality rates of RFA have been nil in many studies and very low in all - 0% to 3.4% [13,14,16,23,25,26,30,35,37-39,41,45,47,48,54,56]. The clinical safety and efficacy of RFA in oncological outcome along with its popularity has encouraged the ongoing exploration of its role in treatment of CLMs as an alternative to hepatic resection.

**Cryotherapy**

**Introduction**

Destroying tumours by freezing has a long history but it really only became practical in the liver using imaging-guided placements of vacuum-insulated coaxial probes. There are 2 types of available systems for clinical purpose - using liquid nitrogen (Erbe Tubingen Germany; Spembly, Andover, UK; Cryotech, Ripley, UK; Cryomedical Science Inc, MD, USA; Candela, Eindhoven, The Netherlands) [56-65] and argon gas (Endocare, CA USA) [62,66,67]. Some have reusable probes which very significantly reduces costs.

**Method**

The vast majority of literature on hepatic cryotherapy is from open surgery. It has also been used laparoscopically and percutaneously but RFA has the distinct advantage in the latter technique because of the smaller diameter probe. We routinely use spinal needle trial placement at surgery under intraoperative ultrasound control before finally introducing the probe or multiple probes. The use of ultrasound in monitoring the progress of cryoablation is easy owing to the distinctive ice ball appearance - hypechoic rim with posterior acoustic shadowing. We essentially aim to achieve a 1 cm circumferential margin, confirmed with multiposition imaging, to ensure adequate
coverage of tumour ablation. Incomplete ablation is no better than supportive treatment [68]. We do not monitor temperature of ablation site - temperature at the centre of the ice ball where the probe is located is of no real interests. Studies have demonstrated significant temperature discrepancies between the ablated centre and edge. For simplicity, we use the sonographic margin appearance as a surrogate.

After freezing, most systems have an active rewarthing feature to remove the probe more rapidly and haemostatic material is packed into the probe track. Multiple probes can be used at the same time and, unlike RFA, will meld together rather than leaving small untreated areas which is a common predicament with multiple/overlapping application of RFA. A twin freeze thaw cycle is undoubtedly more effective but also has safety concerns [65]; hence; we recommend just refreezing the edge (least well treated area) by allowing 1 cm to thaw then refreeze.

Perioperative risks

Apart from the risks of any surgery there are a few specific ones related to cryotherapy. Cryoshock is a rare but significant phenomenon related to cytokine release, presenting clinically as multiorgan failure syndrome and disseminated intravascular coagulation. Early elevated liver function (AST/ALT) and thrombocytopenia warn of this syndrome. In practice, however, it is simply not a problem unless a very large volume (perhaps a third of liver), is frozen [66]. Unfortunately, treatment merely consists of supportive therapy. Other more treatable cryotherapy-related complications include hepatic abscess formation, haemorrhage, biliary injury and pleural effusion. Hepatic abscess is common (0.9% - 11.8%) but usually seen when combined colonic resection and liver cryotherapy are performed synchronously [57,61,64,66,71-72]. Bleeding from liver cracks can easily be controlled by pressure or suture [58,66,69]. The susceptibility of biliary tree to thermal injury may complicate cryo-treatment with biloma or bile fistula [57,58,63,64,66,69,71,72]. Pleural effusion is common, as it is after other liver surgeries, and may very often be treated conservatively [63,69-71,73].

Survival

As for radiofrequency ablation, cryotherapy is either used alone or in combination with hepatic resection. Comparative studies on cryotherapy and surgical resection had demonstrated long-term survival in patients with CLMs with acceptable mortality rates (0% - 7%) [57-88]. Seifert et al. achieved 5-year survival rates of 26% in the hepatic cryotherapy group and 23% in the resection group; accompanied by mortality rates of 2% and 5%, respectively [59]. Similar survival results can be achieved when using cryotherapy as an adjunct to resection to treat non-resectable CLMs, with 5-year overall survival of 32% following resection alone, and 24% following cryotherapy and resection (p = 0.206) [80]. Application of hepatic cryotherapy has undoubtedly extended treatment to otherwise incurable CLMs. The curative potential with cryotherapy in CLMs had been further demonstrated by the 10-year survival of 13% [82]. The available literature on treatment of CLMs with hepatic cryotherapy reports median, 1-, 2-, 3-, 4-, 5-, and 10-year overall survivals of 18 - 33 months [56,57,59-61,63,64,66,70-73,77,78,80-83,85], 78% - 92% [56,58,61,63,66,70-72,80,82,83,86], 47% - 66% [61,63,66,70-72,80,82,83,86], 29% - 50% [56,58,60,63,66,72,80,82,86-88], 21% - 38% [58,66,67,72,80,86], 13% - 23% [56,60,63,66,72,74,80,82,84,87], and 13% [82], respectively (Figure 3).

Recurrence

Margin clearance following surgical resection is essential for both recurrence-free and long-term survivals. In some centres, edge cryotherapy had been employed to suboptimal resection margins obtaining median and 5-year survivals of 39 months and 36% [69,82,88,89], respectively; resembling that of clear-margin resections [82,84,88-90]. The median, 1-, 2-, 3-, 5-, and 10-year disease-free survivals reported were 9 – 27 months [59,72,77,78,81,82,84,86,88], 38% - 41% [58,78,82,86], 16% - 35% [58,78,86], 8% - 17% [78,82,86], 12% - 13% [59,82], and 11% [82], respectively (Figure 4).

Approximately 80% of surgically treated CLMs will develop some form of recurrence; and the pattern of recurrence had been variably described [61,64,70,71,78,80,82,86]. Metastatic pulmonary disease was the most common initial site of extrahepatic recurrence observed. Whilst the extent and site of extrahepatic recurrence were similar following both hepatic cryotherapy and resection, this was not the case with intrahepatic recurrences. CLM patients treated with cryotherapy were noted to have higher rates of intrahepatic recurrences, partly due to disease recurrence at cryoablated sites [59]; the appearance of which may be detected as late as 39 months post-cryotherapy, and rarely up to 98 months [69,86]. Cryosite recurrence frequently occurs - rates of up to 44% have been reported by two different institutions [74,86]. The risk factors for local recurrence are similar to RFA’s - proximity to major vasculature related to the heat-sink effect, and size, as previously described [58,61,63,74,84].

Prognostic factors

Tumour number and size: More number of lesions is predictive of poorer disease-free survival following hepatic cryotherapy [63,71,72,80,86,87,89,91]. Nonetheless, the efficacy of this ablative modality is undeniable. The survival data on cryotherapy merely revolves around CLM patients with advanced disease, which is untreatable with the conventional surgical resection. Although the present literature on hepatic resection for CLM has improved over the years, with 5-year and 10-year survival of 58% and 22%, respectively; this represents only
required to validate the use of RFA as first-line treatment in colorectal treatment alternative to surgical resection. Further studies are still "technical simplicity" has led to further investigation of RFA as a Comparison of Ablative Modalities demonstrated otherwise, do not apply cryotherapy to lesions larger compared to cryotherapy alone [71,72,80]. Seifert and colleagues, who survival is inversely proportional to size [60,61,63,66,80,86,89]. All there is sufficient post-operative functional hepatic parenchyma, though more studies would be required to validate this hypothesis following hepatic cryotherapy.

While number is not a limitation to surgical intervention provided there is sufficient post-operative functional hepatic parenchyma, survival is inversely proportional to size [60,61,63,66,80,86,89]. All except one study have described better or equivalent survival outcome in patients undergoing synchronous hepatic resection and cryotherapy compared to cryotherapy alone [71,72,80]. Seifert and colleagues, who demonstrated otherwise, do not apply cryotherapy to lesions larger than 5 cm [59].

Serum CEA-level: The correlation of serum CEA-level with tumour burden has long been established. Nonetheless, no consistent cut-off value prognostic of outcomes has been identified, with preoperative serum CEA-levels above 5 ng/mL [72,80,86,87], 100 ng/mL [66,78] and 200 ng/mL [82] reflecting on worse survival. Decrement in CEA-level following cryotherapy may be observed over a period of 6 weeks to 3 months but when detected, indicates improved intrahepatic, local and overall recurrence-free survival [86,89-92].

Comparison of Ablative Modalities

The positive clinical and oncological outcome along with its "technical simplicity" has led to further investigation of RFA as a treatment alternative to surgical resection. Further studies are still required to validate the use of RFA as first-line treatment in colorectal hepatic metastases as most data within the literature express concerns regarding the significant risk of recurrence, both local tumour progression and new hepatic metastases. Even with the attempt to nullify the potential effects of tumour biology by comparing only solitary metastases, treatment efficacy of RFA with surgical resection have been variably described [67,88,93].

Of the available thermal ablative methods, RFA is widely favoured over cryotherapy, mainly due to its minimally invasive percutaneous approach. Relative to RFA, cryotherapy is associated with higher morbidities and longer hospital stays, as the open approach had been required for application of cryotherapy until recent years. These have been consistently demonstrated in the few comparative studies [59,73,94,95]. Also, there was a non-statistically significant trend towards poorer survival post-cryotherapy compared to RFA [94,95]. Nevertheless, Bilchik et al. [14] showed that the treatment efficacy of cryotherapy is superior to RFA, limiting treatment of RFA only to lesions smaller than 3 cm [59].

More recently, there has been an increase in the clinical application of microwave ablation (MWA) in treatment of hepatic malignancies. Its administration, like RFA, can be performed via the percutaneous, laparoscopic or open/laparotomic approach. Early studies comparing RFA and MWA in HCCs demonstrated comparable outcomes relating to local tumor control, long-term survival and treatment-related complications [96]. Unlike RFA, microwave energy is capable of propagating through tissues without a conductive medium resulting in relatively higher intratumoural temperatures allowing larger zone of ablations over a short treatment interval. While MWA has been designed to achieve larger area of necrosis, treatment of larger lesions is associated with a higher rate of complications [97]. Overall, the occurrence of complications post-MWA is similar to that of RFA [97-101].

Conclusion

Although surgical resection remains the goal of modern cancer therapy that achieves a cure, ablation provides a non-surgical but curative option. It may be used as an alternate local therapy for patients who are considered non-surgical candidates and may be used in combination with resection as a local option to expand the boundaries of resection for patients with multiple metastases. The efficacy of both radiofrequency ablation and cryotherapy are largely user dependent and its availability varies with each centre depending on local expertise.

There is now a substantial body of data to demonstrate its safety and efficacy and future directions should be aimed at improving the usability of these technologies, reduce its invasiveness to improve recovery times and continued investigations in combination with other multi-modality options for which will be the only way forward to improve the outcomes of patients with metastatic disease.

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