Thermal ablation in the management of oligometastatic colorectal cancer

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Abstract

Purpose: To review available evidence on thermal ablation of oligometastatic colorectal cancer.

Methods: Technical and cancer specific considerations for percutaneous image-guided thermal ablation of oligometastatic colorectal metastases in the liver and lung were reviewed. Ablation outcomes are compared to surgical and radiation therapy literature.

Results: The application of thermal ablation varies widely based on tumor burden, technical expertise, and local cancer triage algorithms. Ablation can be performed in combination or in lieu of other cancer treatments. For surgically non-resectable liver metastases, a randomized trial has demonstrated the superiority of thermal ablation combined with chemotherapy compared to systemic chemotherapy alone in terms of progression-free survival and overall survival (OS), with 5- and 8-year OS of 43.1% and 35.9% in the combined arm vs. 30.3% and 8.9% in the chemotherapy alone arm. As ablation techniques and technology improve, the role of percutaneous thermal ablation may expand even into surgically resectable disease. Many of the prognostic factors for better OS after local treatment of lung metastases are the same for surgery and thermal ablation, including size and number of metastases, disease-free interval, complete resection/ablation, negative carcinoembryonic antigen, neoadjuvant chemotherapy, and controlled extra-pulmonary metastases. When matched for these factors, thermal ablation for lung and liver metastases appears to provide equivalent overall survival as surgery, in the range of 50% at 5 years. Thermal ablation has limitations that should be respected to optimize patient outcomes and minimize complications including targets that are well-visualized by image guidance, measure <3 cm in diameter, and be located at least 3 mm distance from prominent vasculature or major bronchi.

Conclusions: The routine incorporation of image-guided thermal ablation into the therapeutic armamentarium for the treatment of oligometastatic colorectal cancer can provide long survival and even cure.

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer-related death in developed countries [1] and the third most common cancer worldwide. Metastatic disease is commonplace. An estimated 50% of patients with CRC develop liver metastases. Even though the clinical outcomes with systemic therapies have improved over the last 20 years, the median overall survival (OS) is roughly 2 years and 5-year survival remains below 15% [1].

To augment outcomes of systemic therapy, several locoregional treatment options have been advanced that include surgical R0 resection (complete resection with clear resection margins at pathology and no evidence of microscopic residual tumor), A0 ablation (evidence of ablation margin at follow-up imaging and non-evidence of disease at imaging), and radiation therapies such stereotactic body radiation therapy (SBRT). The success of these locoregional treatments has been most pronounced for oligometastatic disease (OMD) [2-4].

The European Society for Medical Oncology (ESMO) guidelines recommend the use of locoregional treatment for CRC OMD if eradication of all sites of primary and metastatic disease is possible [5]. Locoregional treatment may be performed before or after induction treatment with systemic therapy. Recent publications confirmed that long-term survival and cure can be attained in 20–50% of CRC OMD patients who undergo complete R0 resection [4] or A0 thermal ablation [6-8]. Outcome survival is improved when metastatic location is isolated to fewer organs, particularly the liver and lung, and worse for other locations, such as in the peritoneum, lymph nodes, bones, or brain [9], in patients with OMD involving more sites, namely peritoneum, nodes, bones, brain, ovary, and >4 organs, the value of a Local ablative therapy in this patients can be seen as controversial because local ablative therapies are curative in a small proportion of patients [4].

The selection of best locoregional treatment is largely regionally dependent upon local preferences and technical...
ability to address variations in metastatic disease number, location, and size, as well as the patient comorbidities and treatment-related morbidity. Despite the absence of randomized trials comparing outcomes with surgical resection for CRC OMD lesions smaller than 3 cm, although resection is considered the preferred local therapy, ablation is indicated as a stand-alone therapy or in combination with surgery as long as all visible disease can be eradicated according to NCCN Clinical Practice Guidelines in Oncology for colon cancer version 2.2021. Image-guided thermal ablation is considered for metastases in locations that are not easily resected, or in patients with co-morbidities that preclude surgery. SBRT is a reasonable option for local treatment of CRC metastases only if patients cannot undergo resection or thermal ablation [10].

In this manuscript, we review the technical and cancer-specific considerations for percutaneous image-guided thermal ablation of oligometastatic colorectal metastases in the liver and lung. Ablation outcomes are compared to surgical and radiation literature.

**General thermal ablation considerations**

Thermal ablation can be considered for liver or lung oligometastases alone or in conjunction with surgery, with the stipulation that all visible diseases can be treated with clear margins [10]. Several benefits are self-evident for image-guided thermal ablation over surgical resection. These include the ability to provide curative treatment at the time of pathologic needle biopsy [11], decreased post-procedure hospitalization, decreased recovery and healing period, minimized delay in initiation of systemic or radiation therapy.

Radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation are the most common technologies applied for image-guided thermal ablation. Of the two heat-based technologies, RFA has been performed for a longer period and thus has more safety and outcome data in the literature; however, MWA has rapidly gained in popularity due to its capability to rapidly reach higher temperatures with greater uniform consistency throughout the ablation zone. The isolation of critical adjuvant structures from the ablation zone can be accomplished with percutaneous injection of liquid or insufflation of carbon dioxide gas. New methods to assess ablation margins include fusion of pre- and post-ablation imaging using non-rigid registration software [20]. Such assessment of ablation can be improved using a volumetric 3D semi-automated assessment approach and a volume of the tumor plus 5-mm margin that remained untreated has the highest 2-year local tumor progression-free survival compared to ablation margins alone [19].

Advanced ablation techniques can be applied for more challenging metastases to improve outcomes given the technological challenges. Multiple probes or overlapping ablation zones can generate larger ablation zones or shape the ablation to amorphous metastases. The isolation of critical adjacent structures from the ablation zone can be accomplished with percutaneous injection of liquid or insufflation of carbon dioxide gas. New methods to assess ablation margins include fusion of pre- and post-ablation imaging using non-rigid registration software [20]. Such assessment of ablation can be improved using a volumetric 3D semi-automated assessment approach and a volume of the tumor plus 5-mm margin that remained untreated has the highest 2-year local tumor progression-free survival compared to ablation margins alone [19].

Recently, fluorescent assessment has offered a potential intra-procedural biomarker of complete tumor ablation [22].

Even with the best technique, cancer molecular differences can affect the outcome. For example, CRC OMD patients with RAS and BRAF mutations have overall worse clinical outcomes, with RAS mutations associated with an increased incidence of lung, bone, and brain metastases [23]. With this appreciation, the correlation between cancer molecular profile and ablation outcomes has begun to be explored. RAS mutation has been reported as a marker of local tumor progression after percutaneous radiofrequency ablation of CRC liver metastases [12,24,25]. Ki67 has been reported as an independent predictive biomarker of cancer-specific and local recurrence-free survival after lung tumor ablation [26], as well as an independent predictor of liver progression-free survival and OS after radiofrequency of liver malignancies [27]. The understanding of cancer molecular profile on treatment outcome and overall survival is still in a nascent stage, and treatment implications are under investigation. For example, some studies suggest a discordance in RAS and RAF mutation status may exist in between the primary disease site and the metastasis, and even between synchronous and metachronous metastases [28,29].

Others have demonstrated the utmost importance of margins when analyzing 415 CRC liver metastases treated with RFA or MWA where local tumor control was 100% when ablation margins were >10 mm, while local tumor control was 73% in patients with a margin of 6–10 mm [16]. Similarly, in a study for thermal ablation in CRC pulmonary metastases in 50 patients, no local tumor progression was reported for tumor size <1 cm and image documentation of >5 mm ablation margins [17]. In 293 CRC lung metastases, size >2 cm (HR = 2.10, \( p = 0.0027 \)) and several metastases \( \geq 3 \) (HR = 1.86, \( p = 0.011 \)) remained significantly associated with OS [6]. Similarly, ablation of tumors smaller than 2 cm has improved outcomes compared to tumors measuring 2.1–4 cm (median OS of 51 months with a 3-year survival of 64%, compared to 31 and 44%, respectively (\( p = 0.08 \)). The location of tumors also seems to affect the outcome. An algorithmic strategy to predict local tumor progression after RFA in 365 patients with 512 CRC liver metastases concluded that a multifactorial approach including tumor size and subcapsular location better predicted local tumor progression-free survival compared to ablation margins alone [19].
Thermal ablation of liver metastases

To date, direct comparisons of surgical resection and image-guided ablation have been marred by scientific bias. For example, a meta-analysis comparing surgery and thermal ablation of liver metastases report lower OS and a higher rate of local recurrence for thermal ablation [30], but underlined that ‘All the included studies were subject to possible patient selection bias and therefore randomized clinical trials are needed to accurately evaluate these treatment modalities’. Similarly, a 2013–2016 Swedish nationwide registry that compared unmatched cohorts of 82 MWA patients to 645 surgical resection patients treated for first intervention for CRC liver metastases measuring <3 cm demonstrated 3-year OS favoring resection over MWA (76% and 69%, p = 0.005); however, there were significant differences in age, American Society of Anesthesiologists (ASA) class, Charlson comorbidity index, primary tumor location, number of metastases and previous chemotherapy regimens [31]. After propensity score matching, 70 MWA patients and 201 resection patients had no difference in 3-year OS (76% and 76%, p = 0.253), with a median OS of 54.7 and 48 months, respectively. Overall, it appears that thermal ablation in a selected population can provide an equivalent control rate and overall survival rate than surgery. Analysis of current data paints an increasingly favorable portrayal of ablation as a rapidly advancing viable alternative for small CRC liver metastases.

The COLLISION trial is an ongoing randomized clinical trial with the objective to prove non-inferiority of thermal ablation compared to surgical resection in patients with at least one CRC liver metastasis and no extrahepatic disease (Clinical trials NCT03088150) [32]. In the past, several similar randomized studies that attempted to compare surgical resection and thermal ablation of CRC liver metastases have failed. For example, the recent LAVA trial (Current Controlled Trials ISRCTN52040363), screened a total of 366 patients with CRC liver metastases over 1 year, but only 59 were considered eligible and of these only nine participants were randomized [33]. The key issues inhibiting recruitment were misconceptions about the eligibility criteria for the trial, surgeons’ preference for one of the treatments with an unconscious bias toward surgery, and patient’s refusal of randomization preference for one of the treatments. Due to these seemingly unsurmountable failures in randomized trials, large registries have been advanced by the Society of Cardiovascular and Interventional Radiology of Europe (CIRCE) and Society of Interventional Radiology (SIR) that include the CIRSE Emprint Microwave Ablation (CIEMAR) registry and the ACCLAIM registry.

As direct comparison is an ongoing randomized COLLISION trial, the next best alternative has been reported by Tanis et al. that supports the excellent local control rate of RFA in patients with limited size and number of CRC liver metastases. The authors retrospectively evaluated subpopulations from two different prospective randomized control trials from the European Organization for Research and Treatment of Cancer (EORTC). Patients randomized to RFA + adjuvant FOLFOX (±bevacizumab) in the CLOC trial [7] were compared to patients randomized to surgical resection + perioperative chemotherapy in the EPOC trial [34]. Among the 81 patients treated with surgical resection, the local recurrence rate was 7.4% per patient and 5.5% per lesion. Among the 55 patients treated with RFA, the local recurrence rate was 14.5% per patient and 6.0% per lesion overall, but only 2.9% per lesion when lesion size was limited to 3.0 cm [35]. The authors conclude that the local control per lesion does not appear to differ greatly between RFA and surgical resection.

In patients who are not surgical candidates, ablation has been shown to complement the outcomes of systemic chemotherapy. A randomized phase II trial enrolled 119 patients with unresectable CRC liver metastases (<10 metastases) and no extrahepatic disease compared the outcome of systemic chemotherapy (FolFox ± bevacizumab) alone to chemotherapy combined with RFA as first-line therapy [7]. The primary end-point of the 30 months OS rate >38% were met, although the explanatory power of the study was ultimately limited by a lower than anticipated sample size primarily caused by a change in the standard comparator systemic chemotherapeutic agent mid-study. At the time of analysis, no differences were found in OS; however, the long-term analysis at a median follow-up of 9.7 years concluded that the combination approach significantly improved OS and PFS. The 3-, 5-, and 8-year OS was 56.9%, 43.1%, and 35.9% in the combined modality arm and 55.2%, 30.3%, and 8.9% in the chemotherapy alone arm. The trial showed an OS of 36% after 8 years, which compared well to surgical trials, and therefore recommended the use of a combination approach with chemotherapy and ablation in this non-resectable patient population. A recent meta-analysis reviewed 48 studies in the treatment of CRC liver metastases to assess the safety and outcome of RFA and MWA as compared to systemic chemotherapy and partial hepatectomy [32]. The authors concluded that further randomized comparisons of ablation to chemotherapy alone should be considered unethical, as ablation in combination with chemotherapy has superior long-term survival with low complication rates.

Thermal ablation of lung metastases

In comparison to surgery and radiation therapy, thermal ablation can achieve the same rate of local tumor control for small-sized metastases. The reported rate of R0 resection after surgical resection of lung metastases is roughly 90% [36–38]. Similar outcomes have been reported for thermal ablation [6,39]. The 51% 5-year OS of 56% and 49.6% reported after thermal ablation in 191 colon cancer patients and rectal cancer patients, respectively is within the range of the best results obtained by surgery. Indeed, the 5-year OS rates reported after lung metastasectomy for CRC lung metastases is 53.5% in a multicenter registry [40], between 27% and 68% in a meta-analysis [41], and between 39.1 and 67.8% after R0 resection in a literature review of 11 publications with 1307 patients [42]. SBRT has similar outcomes with local control rates at 1, 2, and 3 years estimated to be 81%, 66%, and 60%, respectively [43]. Interestingly, this SBRT meta-analysis reported significantly lower local control rates
for CRC lung metastases compared to non-CRC lung metastases (HR, 2.93; 95% CI, 1.93–4.45; \( p < 0.000001 \)), which has been noted in another study with local progression at 12 and 24 months for CRC lung metastases vs. the overall population reported as 25.5% and 42.2% vs. 8.7% and 16.2% [44].

One explanation for the similar results between surgery and ablation in lung metastases is more equitable selection criteria and work-up as recommended by NCCN guidelines [10]. Another consideration is that ablation in the lung is augmented by the surrounding normal air-filled alveoli that facilitate identification of tumor margins by imaging and also provide inherent thermal insulation to limit energy loss and a more homogenous and larger ablation [45]. In addition, the predictive factors for OS after surgery and thermal ablation in the lung have been shown to be similar. Surgical OS predictive fractures according to one large cohort of 5206 patients were complete resection, location of the primary disease, and DFI [46]; while another meta-analysis of 2925 patients reported DFI, several metastases, and positive lymph nodes at pathology [41]. Ablation OS predictive factors after RFA include primary origin, disease-free interval, size and number of metastases, and progression at the RFA site. Of course, thermal ablation does not allow for regional control of lymph nodes. However, the benefit of systematic lymph node resection during surgery of lung metastases remains unproven, even if the discovery of tumoral involvement of lymph nodes is a negative predictive factor of surgical OS [47,48].

Lastly, even with locoregional control, new sites of disease may present distance from the ablation site regardless if the initial therapy was surgical resection, radiation, or ablation. Ablation has been successfully applied to treat multiple areas of recurrence in the same patient spaced over time. In a series of 1037 lung metastases treated with RFA, 37 patients have retreated for tumor progression resulting in 61.7% of patients free of lung disease at 2 years [6]. Similarly, among 114 patients with 202 lung metastases treated with cryoablation, 11 patients with 12 tumors were retreated to achieve a secondary local tumor control in 184 of 202 lesions (91.1%) [49]. Compared to surgical resection and radiation thermal ablation might be a more favorable alternative for multifocal treatments due to the minimally invasive nature that targets the metastasis while sparing the surrounding lung parenchyma and prevents compromise to respiratory function in the short or long term [39,50,51]. Conversely, surgical metastasectomy reduces lung function depending on the amount of parenchyma resected, and SBRT has been correlated with delayed onset of decreased FEV1 by 4.1% at 1 year and 7.6% at 2 years [52].

Quality of life

Recent emphasis has highlighted the importance of quality of life for cancer patients. Ablation is well-tolerated, with a relatively low-risk profile due to its minimally invasive nature. Comparatively, chemotherapy and immunotherapies may be more caustic. A prospective study in 84 CRC patients compared local ablative therapy and chemotherapy for non-resectable CRC lung metastases showed that quality of life was better in the ablative therapy group (QALY OS = 317) than the chemotherapy group (165) (\( p < 0.001 \)) [53]. In comparison to surgical resection, ablation requires a shorter healing time and thus less delay should systemic therapies be indicated. Lastly, radiation therapy may create more locoregional damage along the path of the radiation beam that may result in regional pain or delayed functional organ damage.

With continued improvements in ablation local control outcomes, this minimally invasive technique can be considered as a separate line of treatment that can achieve long-term tumor control while minimizing the need for toxic chemotherapy or invasive surgery. In a consecutive series of 209 patients that underwent 323 thermal ablation procedures for 630 CRC lung metastases, the median chemotherapy-free survival in the global population was 12.2 months (95% CI: 10.3–17.7) [54]. Patients with no extra-pulmonary metastases showed a significantly better CFS than those who had extra-pulmonary metastases with a median of 20.9 and 9.2 months, respectively (\( p < 0.001 \)). This capability to achieve long chemotherapy-free survival with ablation suggests that ablation can be a separate line of treatment in select patient populations, thus improving quality of life and saving cytotoxic systemic therapy and invasive surgery should disease advance.

Conclusions

Image-guided thermal ablation for colorectal oligometastatic disease in the liver and lungs provides local control and overall survival that are similar to surgical resection. Outcomes are improved for metastases measuring \(<3\) cm that is treated with complete A0 ablation that achieves adequate tumor-free margins. Due to the minimally invasive nature that is well-tolerated by patients, thermal ablation can provide a reliable treatment alternative that can improve quality of life in comparison to other more caustic and invasive treatments.

Disclosure statement

T. de Baere is a consultant for Medtronic, Boston-Scientific, HD technologies, GE Healthcare. Dr. Deschamps is a consultant for Medtronic, GE Healthcare, and Dr. Tselikas is a consultant for Boston Scientific.

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