Editorial

Role of image-guided percutaneous thermal ablation in the management of colorectal cancer liver metastases

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Colorectal cancer (CRC) is the second most common cause of cancer death in the developed world and the third most common malignancy worldwide, with more than 1 million people affected. Approximately half of this population develops colorectal liver metastases (CLM) with a significant increase in morbidity and mortality, yet only a minority of these patients (10–15%) can undergo hepatectomy (1). Image-guided percutaneous thermal ablation (TA) destroys cancer cells by delivering heat directly into the tumor using radiofrequency (RFA) or microwave (MWA) energy, via special needles/electrodes.

Early experience of TA in the management of CLMs was in the form of RFA and was used to treat tumors not amenable to resection due to patient inability to undergo surgery or tumor characteristics precluding complete resection with margins (R0). Despite the limitations of RFA, including smaller and inconsistent ablation volumes, prolonged ablation times and poor performance in perivascular tumors (due to the heat-sink phenomenon), there is level I evidence that aggressive local treatment with RFA (with or without hepatectomy) combined with FOLFOX significantly prolongs overall survival (OS) in patients with initially unresectable CLMs (2).

The increasing knowledge of factors impacting oncologic outcomes after TA of CLM and the understanding of the importance of patient selection has allowed patients with resectable small volume disease to be treated by TA with curative potential. The wide implementation of MWA that overcomes most limitations of RFA has also contributed to this paradigm shift. TA has been incorporated into oncologic guidelines and is recommended alone or in combination with surgery as long as all visible disease is eradicated (3). Despite decreasing mortality rates, hepatectomy entails a relatively increased morbidity that negatively impacts patient progression-free and OS (1,4). In particular for low-risk, potentially surgical candidates with a tumor size <3 cm, <3 CLMs and no extrahepatic disease, percutaneous TA with ablation margins over 10 mm (A0) can offer a chance for local cure similar to hepatectomy avoiding the surgical morbidity (5).

The question of where image-guided TA fits in the overall management of patients with CLM is still being debated. Recurrence or new CLMs will occur in up to 50% of patients after any therapy, including hepatectomy. Percutaneous TA can be repeated with no added liver toxicity, either for local tumor progression (LTP) or new CLMs, and can achieve survival similar to patients without recurrence and no new metastases (6,7). Repeat TA combined with close imaging and clinical follow-up can delay metastasectomy, allowing for a better understanding of tumor biology while concomitantly sparing patients that will develop multifocal liver disease from potentially unnecessary and morbid hepatectomy (8). Image-guided TA minimizes the destruction of healthy liver tissue and is preferred than hepatectomy in patients with underlying cirrhosis or steatohepatitis resulting from prolonged chemotherapy exposure, and those who have previously undergone extensive liver resection. Often, patients can undergo TA as outpatients with a rapid recovery to normal activities.

Despite the very favorable safety profile of TA and a curative potential, the historically relatively high LTP rates ranging between 2.8–60% after TA, remain the main limitation to its widespread use for the treatment of CLMs (1). Similarly to the surgical clinical risk score, a modified ablation clinical risk score was proposed and indicated that certain patient and disease characteristics are more likely to predict oncologic outcomes after TA (6). Precisely, tumor biology expressed as lymphovascular invasion at the time of primary resection, disease-free interval from initial diagnosis to the detection of liver metastasis under 12 months, more than one CLM, tumor size over 3 cm, and CEA level higher than 30 ng/mL are associated with decreased OS and local tumor progression-free survival (PFS) after TA (6).

Moreover, the ability of ablation to eradicate the tumor with a sufficient margin has been shown by different investigators to be the most important technical factor contributing to local tumor control and liver PFS (6,9). Specifically, it has been shown that a 5 mm margin all around the target CLM is critical in order to achieve local tumor control, whereas when a 10 mm margin can be created, long term liver PFS can be over 95% (5,6,10,11). This 10 mm ablation margin, named A0, corresponds to the surgical resection margin R0 and is supported by the fact that the majority of intrahepatic micrometastases are usually found within 1 cm away from the boundary of the grossly detected CLM. A study comparing RFA to MWA indicated that A0 was associated with no LTP regardless of ablation modality used, within a 24-month follow-up period (5). In addition, MWA, unlike RFA, was not affected by the heat sink effect and was able to create adequate margins even in perivascular tumors.

Disease biology and embryonic origin of the primary tumor can further impact oncologic outcomes of patients with CLM treated by ablation. It has been proven that patients with primary tumors originating from the right colon had diminished PFS and OS when compared to patients with left site origin CRC (12,13). Moreover, several publications have pointed out the importance of genetics, as well as their implication on ablation techniques (10,11). The status of the RAS gene (wild *vs.* mutant) is a significant factor affecting ablation outcomes in all margin categories (10). In addition, an ablation margin under 5 mm for RAS mutant tumors was associated with significantly higher LTP rates compared to RAS wild tumors (11), implying that a heat resistant mechanism is possibly associated with the RAS mutant status.

The importance of complete tumor ablation with margins cannot be emphasized enough. To ensure that appropriate margins are achieved during image-guided TA procedures, several methods of ablation zone assessment have been proposed. Treatment effectiveness is generally evaluated with post-procedural anatomic contrast-enhanced imaging [computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US)], metabolic imaging [positron emission tomography (PET)/CT] and specialized 3D softwares. Although additional TA can be offered at the same sitting for patients with visible residual tumor, LTP often occurs even in the face of complete tumor ablation confirmed by imaging. Residual viable tumor cells still "escape" the spatial resolution of currently available morphologic and metabolic imaging methods.

On the other hand, despite the classic teaching that even morphologically intact tumor cells will eventually undergo irreversible apoptosis and cell death after TA, more recent investigations showed that the detection of cytosolic (G6PD) or prolific (Ki67) markers in cancer cells from the ablation zone independently predicted LTP and even patient survival after TA (14,15). Subsequent work prospectively validated these results showing that immediate post-ablation biopsy of the ablation zone center and margin could predict LTP. Notably, it was demonstrated that pathologically confirmed complete tumor necrosis accompanied by a >5 mm margin, was associated with >95% local PFS at over 30 months after RFA of CLM (16).

To further optimize outcomes of image-guided TA and promote its application as standard therapy for well-selected small CLM, real-time morphological surrogates of complete tumor ablation have been implemented to confirm complete tumor eradication or detect residual viable disease even in the face of radiographically complete ablation (17). If immediate additional ablation is not feasible, patients at risk for LTP will receive at least a short course of systemic therapy and will be followed-up closely. Such steps improve the outcomes of image-guided TA and can identify patients at risk for local failure, similar to the assessment of resected tumors with positive margins by pathology.

The belief that the only chance of cure of CLMs lies with resection is no longer valid since image-guided TA can and does result in cure in selected patients. Patient selection can no longer be based on retrospective data, reminiscent of the era when TA was only offered to patients who were expected to fare less well than those who were eligible for resection. A recent meta-analysis indicated that RFA might have been inferior to surgery when it comes to LTP despite similar OS rates, but MWA resulted in similar oncologic outcomes as metastasectomy (18). Since ablation margins were not reported in the studies included in this metanalysis, a prospective randomized controlled trial of metastasectomy *vs.* TA and specifically MWA for small tumors that can undergo ablation with wide margins (A0) would be of utmost importance. To this direction, a prospective RCT comparing surgery to TA for CLMs ≤3 cm is currently enrolling patients, and the first results are expected at the end of 2025 (19).

The role of image-guided thermal ablation in the management of CLM has evolved significantly. The definition of the patient population that will most benefit from TA is now clear and supports the use of TA as the first local therapy with the potential to cure patients with small-volume disease that can undergo A0. Close monitoring with imaging is essential and will allow for early detection of any recurrence that can be treated with repeat TA or hepatectomy if there is no development of multifocal or extrahepatic disease. Continuous technological evolutions, understanding of tumor variability through disease biology and genetics, and development of intraprocedural guidance methods will further improve the application of TA and expand its use to a larger patient population.

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Footnote

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