Tailoring ablation strategies for colorectal liver metastases based upon rat sarcoma viral oncogene mutation status

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Abstract: Rat sarcoma viral oncogene (RAS) is one of the most well-known tumor genes implicated in the oncological and surgical management of patients with colorectal liver metastases (CLM). More recently, RAS mutational status has also emerged as a relevant factor affecting the oncological outcomes of CLM treated with ablation procedures, a well-established local therapy modality routinely utilized in the oligometastatic disease (OMD) setting. Available evidence suggests that RAS mutation is a prognosticator of shorter local tumor progression free survival (LTPFS) following liver ablation, and that mutant RAS patients with CLM treated with ablation should have wider minimal ablation margins. In this review, we aim to discuss the current literature on the influence of RAS mutational status on ablation outcomes, as well to provide a perspective on the future research on the impact of tumor molecular biology on liver ablation procedures and the potential synergies between local and systemic therapies.

Keywords: Colorectal cancer; liver metastasis; ablation techniques; minimal ablation margin; rat sarcoma viral oncogene (RAS) proteins

Introduction

Colorectal cancer is the second most common cause of cancer-related death in both sex (1). Approximately 20% of the patients with colorectal cancer present with metastasis at the initial diagnosis, and up to 60% will develop metastasis during the course of disease. The liver plays a crucial role in the natural history of the disease as being the most common site of metastases, with progression of colorectal liver metastases (CLM) accounting for the main cause of mortality in 53% of the patients (2). Surgical eradication of the CLM is linked with improved overall survival (OS) rates and is warranted (3). Unfortunately, only 20–30% of the patients with CLM are resectable (4).

Ablation is a well-established local therapy for patients with limited CLM extension. In such population subset, the combination of ablation with systemic chemotherapy has demonstrated improved OS when compared to systemic chemotherapy alone, as showed by the latest results of the CLOCC trial (5). Accordingly, the last version of the European Society for Medical Oncology Consensus guidelines (6) acknowledges for the first time the role of ablation for patients with CLM presenting with oligometastatic disease (OMD). Moreover, ongoing trials are currently investigating the use of ablation as a first approach for the treatment of CLM (7). To correctly select patients for ablation, it is of paramount importance to identify the factors that affect its outcomes.

Rat sarcoma viral oncogene (RAS) mutational status is a key factor for the clinical management of colorectal cancer

patients (8). Specifically, RAS mutation is a downstream component of the epidermal growth factor receptor (EGFR) signaling network, and it has been associated with resistance to medical treatments with EGFR antibodies. Furthermore, RAS mutation has been associated with higher incidence of disease recurrence and shorter OS following resection for CLM (9). Similarly, recent findings in the interventional radiology literature suggest interactions between RAS mutational status and image-guided ablation outcomes (10). Therefore, in this review, we aim to discuss the current literature on the influence of RAS mutational status on ablation outcomes, as well to provide a perspective on the future research on the impact of tumor molecular biology on liver ablation procedures.

Percutaneous image-guided ablation

Percutaneous image-guided ablation is routinely used as a safe and effective loco-regional therapy for the treatment of patients with CLM. Among the imaging modalities, computed tomography, ultrasound, and magnetic resonance imaging are the most commonly utilized. Its minimally invasive nature has several advantages: it can be easily repeated to treat progression; it does not impact surgical eligibility for those that can be eventually resected; it does not require prolonged chemotherapy interruption; and finally, it has minimal or no impact on patients' quality of life (11). Such facts are particularly important in view of the recurrent nature of CLM, which brings a high likelihood of requiring repeated local treatments even after successful resection or ablation.

From the early reports on the use of image-guided ablation for the treatment of patients with CLM in the late 90s (12) to the present time, technical developments and a deeper understanding of the oncologic mechanisms have led to improved therapeutic strategies and increased survival rates. During the last three decades, several ablative technologies have been proposed and reported in the literature: radiofrequency (RF), laser, cryoablation, microwave (MW), and irreversible electroporation (IRE). The two most used technologies are by far radiofrequency ablation (RFA) and, more recently, microwave ablation (MWA).

RF systems induce coagulative necrosis resulting from thermal energy delivered by an alternating electrical current through the needle probe placed within the target tumor. An electrical circuit is completed through grounding pads, normally attached to the thighs. Temperatures range between 60 to 100 ℃, resulting in coagulation necrosis. The major portion of the final ablation zone is due to thermal conduction into more peripheral areas around the electrode (13). MWA uses electromagnetic waves between 900 and 2.4 GHz through the MW probe, which is called the antenna. These high-frequency electromagnetic waves cause oscillation and friction of water molecules with subsequent heat, resulting in tissue destruction by coagulation necrosis. MWA presents some theoretical advantages over RFA, such as reduced 'heat-sink' effect (lower heat dissipation in a vessel's proximity) and larger ablation zones in a reduced period of time. For these reasons, MWA is thought to be more efficient in the treatment of larger lesions and for targets located near large vessels when compared to other thermal ablation modalities. However, presently, there is no clear evidence in favor of one technology over the other in the CLM ablation setting.

Factors affecting ablation outcomes

Local control of the ablated tumor is the main goal for an effective image-guided ablation. Presence of residual disease or development of tumor recurrence at the ablation zone is considered a treatment failure that the interventional radiologists should prevent. In the ablation literature, local recurrence is termed as "local tumor progression" (LTP), which is defined as the appearance of tumor foci at the edge of the ablation zone or within 1 cm from it (14). In order to differentiate LTP from residual tumor, it is necessary to have at least one contrast-enhanced follow-up study after ablation documenting adequate ablation and an absence of viable tissue in the target tumor by imaging criteria. Low LTP rates are desirable given the relationship between local disease control and disease-free survival, which is thought to ultimately influence OS (15).

Tumor size and ablation margins

Several factors have been described to be associated with local outcomes of ablation (16). Among the most relevant factors, tumor size and the minimal ablation margins are the two most widely recognized in several published series (16-20).

The impact of tumor size—normally defined as the maximum longitudinal diameter in the uni-dimensional axial plane—on ablation outcomes has been extensively investigated. The literature supports the evidence that the smaller the lesion is, the most favorable the local outcome

Table 1 Published studies on RAS mutational status and image guided ablation of colorectal liver metastases

Authors/year	Type of study	Number of patients/ lesions	Mean lesion size (cm)	RAS evaluation	3 years LTPFS rate (RAS mut vs. RAS wt)	Other findings
Odisio et al. 2017 (10)	Retrospective	92/137	1.6	KRAS codons 12,13, 61 and 146 and NRAS codons 12, 13, 61	35% vs.71%	Minimum ablation margin of less than 5 mm was found as negative predictors of local tumor progression-free survival
Calandri et al. 2018* (25)	Two institutions/ retrospective	136/218	1.7	KRAS codons 12,13 in all patients, KRAS codons 59, 61, 117 and 146 and NRAS codons 12, 13, 18, 59, 61, 117 and 146 in the majority of them	35% vs.77%	Minimal ablation margins >10 mm and RAS status interact as independent predictors of LTPFS following CLM ablation
Shady et al. 2017 (27)	Retrospective	97/148	1.9	K-RAS (exon 2)	37% vs. 57%	KRAS mutation was a significant predictor of new liver metastases (P=0.037) and peritoneal metastases (P=0.015)
Jiang et al. 2019 (28)	Retrospective	76/154	NA	K-RAS (codons 12 and 13)	36.2% vs. 11.1%**	m-CS (P=0.033) was an independent prognostic factor for LTP

*, overlapping series with Odisio 2017; **, LTP rates. RAS, rat sarcoma viral oncogene; LTPFS, local tumor progression free survival; CLM, colorectal liver metastases; m-CS, modified clinical score; LTP, local tumor progression.

will be. According to Veltri et al. (17), complete ablation was achieved in 66.7% of CLM <3 cm vs. 33.3% of CLM >3 cm (P<0.0001). More recently, these findings were confirmed by other investigators (18-22). Although 3 cm is the most commonly utilized tumor size cut-off for image-guided ablation eligibility in several institutions, the largest tumor size amenable to be effectively treated with thermal ablation is still a matter of debate. Indeed, image-guided ablation of CLM up to 5 cm can be acceptable in selected cases (20), and effective local tumor control rates can be achieved with adequate procedure planning and monitoring (23).

Ablation margins are another critical factor affecting ablation outcomes. Several studies have demonstrated the importance of achieving minimal ablation margins that extend beyond the tumor in a three-dimensional plane at least 5 mm. According to Wang et al. (19), 2-year local tumor progression free survival (LTPFS) rates for ablated CLM with minimal ablation margins of 0, 1–5, 6–10, and 11–15 mm were 26%, 46%, 74%, and 80%, respectively (P<0.011). In a recent report by Shady et al., CLM treated with minimal ablation margins >10 mm had no recurrence in a series including 110 patients (24). Thus, minimal ablation margin of >10 mm in all planes is considered with strong consensus as the optimal technical goal by an expert meeting position paper (16). Despite its criticality, achieving minimal

ablation margins >10 mm is relatively difficult, as shown by some reports in the literature. Shady et al. reported ablation margins >10 mm were successfully obtained in only 12% (21/174) of their historical series (18), while a two-institution retrospective study showed that 28% (60/218) of the ablated CLM had ablation margins >10 mm (25). Nevertheless, it should be mentioned that these two published studies (18,25) consisted of retrospective patient series that pre-dated the most current evidence in regards optimal results associated with minimal ablation margins >10 mm.

RAS mutation and thermal ablation

Mutations in the RAS family of proto-oncogenes (KRAS, NRAS, HRAS) are present in 30–45% of the patients with colorectal cancers (8). These mutations cause a constitutive activation of the MAPK pathway, leading to resistance to treatment with EGFR antibodies. RAS mutations are the most well-recognized and relevant prognostic biomarker among patients undergoing CLM resection (26). More recently, published data also suggests an equivalent role in the image-guided ablation setting, as discussed below and summarized in *Table 1*.

In 2017, Odisio et al. showed that mutant RAS patients (both NRAS and KRAS) had shorter 3-year LTPFS

following liver ablation compared to wild-type RAS patients (35% versus 71% respectively; P=0.001) (10). In this same study, the authors also showed that among all the ablated CLM that presented with LTP, patients with mutant RAS recurred earlier and in smaller tumors when compared with those in wild-type RAS patients. In the same year, Shady *et al.* also showed mutant RAS as a significant predictor of LTP after CLM ablation with margins of 1–5 mm (P=0.018), with an LTP rate of 80% versus 41% for wild-type (27). The findings of these two seminal papers have been also confirmed by a recent paper, which found lower LTP rates in wild-type RAS patients (9.8%) when compared with mutant RAS patients (27.8%, P=0.004) (28).

The relationship between RAS mutational status and minimal ablation margins has also been investigated (25,27). Calandri *et al.* (25) performed a two-institutional retrospective analysis of 136 patients submitted to CLM ablation. The authors demonstrated that 3-year LTPFS was significantly better among wild-type RAS tumors compared with mutant RAS tumors, irrespective of the minimal ablation margins achieved (≤10 mm ablation margins: 29% mutant RAS *vs.* 70% wild-type RAS, P<0.001; >10 mm ablation margins: 48% mutant RAS *vs.* 94% wild-type RAS, P=0.006). Based on their analysis, achieving minimal ablation margins >10 mm in mutant RAS tumors would provide similar 3-years LTPFS as achieving ≤10 mm ablation margins in wild-type RAS tumors (P=0.36). In the previously mentioned series published by Shady *et al.* (27), the authors identified KRAS mutation as a significant independent predictor of LTP following RF ablation of CLM with minimal ablation margins of 1–5 mm (P=0.018). The authors also showed that mutant RAS tumors carried a risk of progression of 15.6-fold higher when compared with wild-type RAS tumors ablated with ablation margins of ≥6 mm. Therefore, the authors suggested that minimal ablation margins of ≥6 mm should be absolutely required (27), especially for mutant-type RAS tumors, and proposed minimal ablation margins of ≥10 mm as the treatment endpoint to offer the best possible local tumor control (25,27).

Discussion

Ablative and surgical techniques and RAS: similarities and differences

Surgical data regarding CLM management have shown the role of RAS mutational status as both a prognostic factor of OS and as predictor of recurrence following surgery (9). Proposed strategies in the surgical literature for improving the outcomes of CLM resection according to the mutational RAS status are (I) the identification of specific predictive factors (in the mutant RAS patients); (II) a better understanding of the minimal resection margins required. Passot *et al.* (29), stratified mutant RAS patients who underwent surgery according to node-positivity of the primary tumor, CLM size >3 cm, and more than 7 cycles of preoperative chemotherapy, showing different OS in the subgroup analyses and proposed a pre-procedural scoring system.

Brudvik *et al.* demonstrated in a retrospective series that RAS mutations were associated with positive margins in patients undergoing resection of CLM, underlying a more infiltrative tumor behavior (30). Likewise, as for resection of tumors in proximity to vessels, if vascular R1 can be considered as R0 parenchyma in case of wild-type RAS tumors, this is not acceptable for mutant RAS tumors (31,32). Very recently, these and other studies have led to a specific modified clinical score (m-CS) that includes the mutational RAS status, modified from the traditional risk-score (t-cs); m-CS has been successfully validated, becoming a useful tool to predict survival after resection of CLM (33).

In the ablation literature, evidence concerning the role of RAS mutational status is more recent than the surgical literature. For more than a decade, publications concerning image-guided ablation have focused attention on its safety and efficacy, paying specific attention to the technical aspects. In recent years, the need to overcome the persistent relatively high LTP rates associated with ablation when compared with the recurrence rates reported in the surgical literature have led the interventional community to try to understand the role of tumor biology, highlighting that beyond technology, patient selection is of paramount importance (10). Despite this, presently, there is no consensus in regards to patient selection and ablation margins according of RAS mutational status (6,16).

Although the RAS mutational status is not considered a contraindication to image-guided ablation, care should be exercised in the selection of the patients. Thus, considering the relationship between ablation margins, mutational status and LTPFS, we recommend that mutant RAS patients should be considered candidates for ablation only if adequate ablation margins can be planned and obtained. Specifically, a three-dimensional minimal ablation margins of ≥5 mm is always required in patients with mutant RAS, and, ideally, a minimal ablation margin of ≥10 mm should be highly desirable. Further refinements on imaging fusion
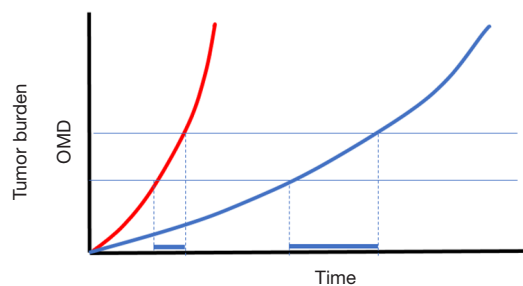
Figure 1 Oligometastatic disease definition (based only on tumor burden) does not identify the best responders for local therapies. Red line represents aggressive tumors with rapid kinetic growth (RAS+, BRAF+, MSI+, Right colon origin, etc.). Blue line represents tumors with favorable prognosis and slow kinetics growth (RAS–, BRAF–, MSI– Left colon etc.). These less aggressive tumors can meet criteria as OMD for a longer period of time during their natural history. OMD, oligometastatic disease; RAS, rat sarcoma viral oncogene.

Figure 2 Oligometastatic disease definition (based only on tumor burden) does not reflect the potential differences of different OMD conditions during the natural history of the tumor and during local and systemic therapies. OMD, oligometastatic disease.

and biomechanical deformation methods should provide more accurate methods to assess minimal ablation margins intra-procedurally in order to improve the ability of achieving sufficient minimal ablation margins on a three-dimensional plane.

The understanding of the relevance of tumor biology on local ablation outcomes may lead, in the near future, to unique tailored approaches for interventional procedures (especially in the case of mutant RAS patients) consisting of sequential treatments between systemic therapies (global treatment) and image-guided ablation (local treatment), in a so-called "glocal" approach (34).

RAS and other biomarkers in the OMD setting

Hellman proposed the term oligometastases for the first time in 1995 (35), suggesting that in some patients with a limited number of clinically detectable metastatic tumors, a limited tumor burden reflects a transitional state before widespread systemic disease. In this setting, local treatments of oligometastases would have the potential to yield improved systemic control (36). According to ESMO consensus guidelines, the oligometastatic condition is defined as the presence of metastases "at up to 2 or occasionally 3 sites and 5 or sometimes more lesions, predominantly visceral and occasionally lymphonodal." This definition focuses on the global radiological tumor burden without including any tumor biology information.
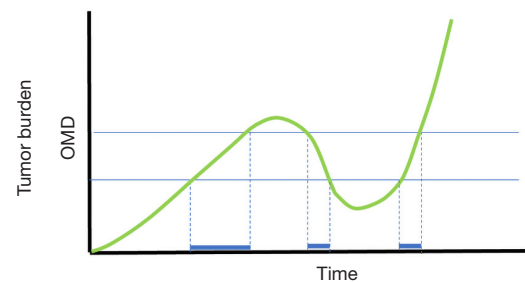
However, tumor biology deeply impacts the OS of all CRC patients including those who fit the OMD criteria, as shown by different aggressiveness and tumor growth kinetics (*Figure 1*). Furthermore, patients may be potentially considered in the OMD setting at different times during their disease history, even after selective selection of systemic therapies that may have changed the global genetic tumor profile and subsequently its aggressiveness (*Figure 2*). In the near future, efforts should be made to identify prognosticators for OMD. For instance, the use of circulating tumor DNA analysis in a longitudinal manner might prove to be a valuable surrogate of tumor aggressiveness in the OMD setting. In order to better select patients, a deeper knowledge of tumor genetics is required. Also, as recently understood and demonstrated, not all RAS mutations are equal (37,38), potentially with different impact on disease free survival and OS after local therapies. Finally, efforts are required to understand the interactions between different genes mutations, such as the case of co-mutations of TP53 and RAS, which lead to a decreased OS after CLM resections (39).

Conclusions

RAS mutational status is emerging as a relevant prognosticator for LTP and OS after CLM image guided ablation. Available evidence suggests wider minimal ablations margins should be obtained in mutant RAS CLM patients in order to obtain improved LTPFS rates. Further studies are required to investigate specific interactions between RAS and other gene mutations, specific predictive factors of poor outcomes in the OMD setting in the mutant RAS CLM patient population and synergies between local

and systemic therapies.

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Footnote

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