Thermal Ablation for Lung Metastases

Percutaneous alternatives when surgery is not an option.

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Local treatment of lung metastases has been accepted since the late 1990s when an international registry reported actuarial 5-, 10-, and 15-year survival rates of 36%, 26%, and 22%, respectively.[1] The evidence for surgical metastasectomy remains weak and is controversial because the practice has never been evaluated in a randomized trial. Furthermore, it has some short-term morbidity, can be responsible for permanent loss of function, and can have major cost implications.[2] Today, in addition to surgery, other local therapies are available for patients with oligometastatic disease, including stereotactic body radiation therapy and ablative therapies. Even if surgical resection remains the standard of care when circumstances allow, surgery is not an option for many patients due to advanced age, comorbidities, limited respiratory function, previous pulmonary resection, or surgery refusal. For these patients, image-guided ablation and radiation therapy are increasingly offered as alternative therapies.[3-8]

Early reports, including case series and small clinical trials, demonstrate the potential of various ablation technologies, including radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, and irreversible electroporation, for the treatment of pulmonary tumors.[3,9-14]

The characteristics of tissue (eg, vascularity, electric conductivity, etc) that surround the tumor affect heat and electricity diffusion and, consequently, ablation outcomes. The lung has some organ-specific differences favoring thermal ablation. The heat insulation and low electrical conductivity provided by lung tissue around the tumor are responsible for a larger volume of ablation in the lung than in subcutaneous tissues or in the kidney for a given quantity of radiofrequency current.[15] A consequence is that the delivery of RFA must be adapted to the tumor location, because impedance before ablation differs significantly between the tumors with more than 50% of the tumor abutting the pleura (86.5 ± 29.9 ohm) and the tumors that are not abutting the pleura (121.3 ± 42.8 ohm).[3] A tumor surrounded by the air-filled lung parenchyma is well-insulated electrically and thermally and will therefore require less energy deposition.

Several experimental studies have demonstrated that RFA can completely destroy an area of healthy lung or malignant lung tumors in an animal tumor model.[16,17] A study of RFA before surgical resection demonstrated 100% necrosis at histopathology for all (9 of 9) targeted lung metastases.[18]

DATA REVIEW

Currently, the largest report of RFA for lung metastases includes 566 patients (52% with primary tumors in the colon or rectum) who received 642 RFA treatments for 1,037 lung metastases with a median diameter of 15 mm (range, 4–70 mm).[7] Fifty-three percent of patients had one metastasis, 25% had two, 14% had three, 5% had four, and 4% had five to eight. Overall survival (OS) was 62 months, which compared favorably with previously published lung ablation data that showed a median OS of 51 months (95% confidence interval, 19–83 months) in one study of 148 patients and 41 months in another involving 122 patients.[19,20] The better outcomes found by de Baere et al can be explained by the very restricted inclusion criteria, resulting in more favorable predictive factors (ie, size of metastases, number of metastases, extrapulmonary disease, disease-free interval [DFI]). Extrapulmonary disease was present in 51% in the study by Gillams et al versus 22% for de Baere et al.[7,20] DFI was shorter than 12 months' duration for 52% of patients in the study by Gillams et al versus 21% for de Baere et al.[7,20]

The rate of OS after RFA of lung metastases is within the range of the best results obtained by surgical resection of lung metastases, with a 5-year OS rate of 53.5% in a multicenter registry and between 27% and 68% in a meta-analysis by Gonzalez et al.[21,22] Pfannschmidt et al evaluated 5-year OS in a literature review of 11 publications and 1,307 patients and found rates between 32.7% and 56%, with rates increasing to between 39.1% and 67.8% for patients who underwent R0 resection.[23]

Predictive factors of OS reported in major RFA series (ie, primary origin, DFI, size and number of metastases, and progression at RFA site)[7] were similar to what was reported in a large surgical series. Reported predictive factors of OS after surgery included complete resection, location of primary disease, and DFI in 5,206 patients[24]; DFI, number of metastases, and positive lymph nodes at pathology in a meta-analysis of 2,925 patients[22]; and number of metastases, completeness of resection, and preresection carcinoembryonic antigen level in 1,030 patients with colorectal lung metastases. RFA 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 discovery of tumor involvement of lymph nodes is a negative predictive factor of OS.[25,26]

RFA is highly repeatable when needed, due to the high acceptability of the treatment by patients in the short term and the long-term preservation of lung function with no change reported between pre– and post–lung RFA respiratory function tests.[3,8] In the study by de Baere et al, 24% of treated patients were retreated up to four times, allowing for a 4-year lung disease control rate of 44.1%.[7]

Four-year local tumor control was 89% for Lencioni and de Baere in 61 and 566 patients at 15 and 35.5 months of follow-up, respectively.[7,8] Excellent results of lung RFA are driven by strict selection criteria, with an extensive pre-RFA imaging workup that guarantees a low rate of local tumor progression in the range of 10%, which is similar to that reported after surgery.[27,28] The size of the target tumor is a main driver for local recurrences in most studies; in addition, RFA has a lower efficacy when tumors are close to vessels ≥ 3 mm,[29,30] due to the so-called heat sink effect, which is convection cooling by the vessel of the ablated zone. A low rate of complete local treatment was found (62.5% in 32 tumors measuring up to 3.5 cm) when RFA was guided by perioperative manual palpation during thoracotomy without any image guidance.[31] These results emphasize the pivotal role of CT guidance and multiplanar reconstruction, which, due to the high contrast ratio between the air density of the lung parenchyma, tissue density of the target tumor, and metallic density of the radiofrequency needle, allow for optimal visualization and accuracy in treatment targeting and delivery.

Cone beam CT is under evaluation for use in RFA in the lung. Cone beam CT allows for puncture at any angulation, but lacks the real-time imaging capability available with CT (where an image can be acquired and reconstructed within a second), thus targeting of lung nodule is probably less accurate and can be impossible in case of pneumothorax, which will displace the targeted tumor.[32] Such delays in imaging can be problematic if the target is moving either due to needle insertion or pneumothorax.

LIMITATIONS

Limitations of RFA related to tumor size or proximity of vessels may be addressed by new ablation technologies. For example, microwave energy produces a larger volume of ablation than RFA; however, the results in clinical practice were disappointing in that tumors > 3 cm remain a predictive factor of success.[12] Early MWA systems seem to suffer from lack of consistency and nonspherical ablation zones, but more recent technology seems to improve consistency and spherical ablation zones.[33] Perhaps these new technologies will help to break the "3-cm barrier." Microwave, which has a better thermal profile by working at a higher temperature with a more rapid increase in temperature, is less susceptible to convection cooling, and thus there is less distortion of the spherical geometry.

Animal experiments evaluating tumors close to large vessels have demonstrated less deflection of the ablation zone in contact with the large vessels with MWA as compared with RFA.[34] To our knowledge, this advantage has never been confirmed in clinical practice, either in the liver or the lung. Irreversible electroporation has been evaluated in a pilot study for tumors close to large vessels, but it demonstrates a high rate of incomplete ablation (probably due to nonhomogenous deposition of the electric energy, which is highly sensitive to exposure of the probes to air).[35] More recently, cryoablation of lung metastases with promising local tumor control (94.2%) at 12 months has been reported in a phase 2 multicenter study, including 40 patients with 60 metastases measuring 1.4 ± 0.7 cm (range, 0.3–3.4 cm).[36]

In addition to surgery or ablation, a competing technology is stereotactic ablative radiotherapy (SABR). Okunieff et al reported 83% local control with SABR in 50 patients with 125 tumors at a median of 18.7 months (mean tumor diameter, 2.5 cm).[6] SABR is considered noninvasive, but complications resulting from radiation to the lung usually occur later. Moreover, it has been reported that placement of the fiducial marker needed for SABR has resulted in a 33.3% rate of pneumothorax (major, 13.3%; minor, 20%), with small amounts of peritumoral alveolar hemorrhage in 30.5% and 2.9% of major bleeding in 105 patients with tumors to the lung.[37] This is close to RFA in terms of rate of pneumothorax.

Even if thermal ablation of lung metastases is mostly used as a stand-alone technique (with the main objective being complete destruction of tumor cells in the targeted volume), its impact on patients might make it easier for them to undergo systemic therapy before or after RFA in an effort to decrease recurrences. Sorafenib has the potential to increase the efficacy of RFA, as demonstrated in an animal model of renal tumor.[38] Patient selection for combined or adjuvant systemic therapy should take into account progress in histology, immunohistochemistry, and molecular biology to define a personalized strategy for each patient.

Follow-up imaging can be complex after thermal ablation in the lung because involution of the ablation zone is slow. As a result, diagnosis of incomplete ablation may be delayed, as shown in a study that reported progression of 82 local tumors at the site of RFA in 54, 21, five, and two patients at 1-, 2-, 3-, and 4- or 5-year follow-up, respectively.[7] PET-CT can be useful but should be performed more than 3 months after ablation due to glucose uptake of the periablation zone.[39,40] On CT, cryoablation has a much faster involution in the size of the ablation zone, which facilitates identification of local treatment failure with most incomplete ablation found by 6-month follow-up.[41]

CONCLUSION

In the future, it is likely that surgical management of small-size oligometastatic lung disease will decrease and minimally invasive techniques will replace surgery for such indications. The optimal technique will have to demonstrate efficacy, tolerance, and cost-effectiveness, even if randomized studies will be difficult, as highlighted by the early closure of randomized clinical trials trying to compare surgery and SABR in non–small cell lung carcinoma (STARS and ROSEL) due to slow accrual.[42] The size of the target tumor remains the main driver of success, and selection of patients with limited tumor size allows for an 89% local control rate, even if new technologies may increase the size of the tumor amenable to local ablation. ■

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