Nonsurgical Local Therapies for Lung Metastases and Non–Small Cell Lung Cancer

Clinical data examining the use of available treatment options for selected lung cancer cases.

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Today, nonsurgical local therapies are available for patients with non–small cell lung cancer (NSCLC) and oligometastatic lung disease from various cancers. The two most common approaches are thermal ablative therapies delivered through percutaneously inserted applicators under imaging guidance or stereotactic ablative radiotherapy (SABR) delivered via external beam radiation. Various thermal ablation technologies, such as radiofrequency (RF) ablation, microwave (MW) ablation, and cryoablation, are used for the treatment of pulmonary tumors.[1-7] The lung has some organ-specific differences favoring thermal ablation, including insulation and low electric conductivity due to the lung tissue around the tumor,[3] which necessitates a larger volume of ablation in the lung than in subcutaneous tissues or the kidneys for a given quantity of RF current.[8]

RF ablation before resection demonstrated 100% necrosis at histopathology for nine of nine lung metastases treated.[9] Lung RF ablation for NSCLC and lung metastases demonstrated a median rate of complete ablation of 90%, with a variability from 38% to 97% in a review of 17 of the most recent publications.[10] Selecting tumors that measure < 2 cm provides a 78% to 96% rate of complete ablation.[3,11-14] Safety margins matter, as demonstrated by a 96% complete ablation rate when the ratio is ≥ 4 in between the area of RF ablation-induced ground-glass opacity and the targeted tumor.[3] Ground-glass opacity margins receiver-operator characteristic analysis confirmed the ablation zone as a predictor of recurrence, with an estimated cutoff of 4.5 mm for a specificity of 100% (ie, no local recurrence).[15]

In addition to RF ablation, MW ablation, cryoablation, and electroporation have become available for lung ablation. MW ablation has not demonstrated clear superiority over RF ablation in clinical practice,[16] even though it works at higher temperatures with lower convective cooling close to large vessels, as demonstrated in animal studies.[17,18] Electroporation is a nonthermal ablation process that has shown excellent preservation of vulnerable lung structure in animals,[19,20] but the local recurrence rate was a disappointing 61% in a multi-institutional study of 20 patients with lung metastases.[21] Cryoablation utilizes multiple probe treatments in which the tip of the probe creates ice crystals that destroy the tissue/tumor. Reports on cryoablation of lung metastases demonstrated a promising 94.2% local tumor control rate at 12 months in a phase 2 multicenter study that included 40 patients with 60 metastases.[22]

CLINICAL RESULTS

Lung Metastases

Local treatment of lung metastases with surgical resection has been accepted since the late 1990s, with actuarial 5-, 10-, and 15-year survival rates of 36%, 26%, and 22%, respectively, reported in an international registry.[23] However, the evidence for surgical metastasectomy remains controversial because the practice has never been subjected to a randomized trial, carries a risk of permanent loss of function, and has major cost implications.[24] RF ablation for oligometastatic lung disease was evaluated in studies by both Lencioni et al and de Baere et al, which included 61 and 566 patients with 15 months and 35.5 months of follow-up, respectively.[14,25] Lencioni et al reported 1-year local efficacy in 88% of patients. The study by de Baere et al was one of the largest reports to date of lung RF ablation for metastases, evaluating 566 patients with 1,037 lung metastases, including 52% with primary tumors of the colon or rectum and tumors at a median diameter of 15 mm

(range, 4–70 mm). Four-year local efficacy was 89%. Overall survival (OS) rates at 1, 2, 3, 4, and 5 years were 92.4% (standard error [SE], 1.2), 79.4% (SE, 1.9), 67.7% (SE, 2.4), 58.9% (SE, 2.8), and 51.5% (SE, 3.3), respectively.[25] Location of primary disease, disease-free interval, size > 2 cm, and metastases ≥ 3 were associated with OS in multivariate analysis.

A low complete local treatment rate of 37.5% in 32 tumors measuring up to 3.5 cm was achieved when RF ablation was guided by perioperative manual palpation during thoracotomy without any imaging guidance.[26] This result emphasizes the pivotal role of CT guidance and multiplanar reconstruction imaging due to the high contrast ratio related to the air density of the lung parenchyma, tissue density of the target tumor, and metallic density of the RF needle, which allows for optimal visualization and likely improved accuracy in targeting treatment delivery.

The 62-month OS rate reported in a large series of RF ablation for lung metastases is within the range of the best results obtained by surgical resection, with the same predictive factors for OS.[27-29] Surgical resection of lung metastases resulted in a 5-year OS rate of 53.5% in a multicenter registry by Iida et al[29] and between 27% and 68% in a meta-analysis by Pfannschmidt et al.[30] In lung metastatic patients, the challenge of disease control is more linked to the occurrence of new metastases distant from the ablation site as opposed to local recurrences. This was demonstrated with a 4-year progression-free survival rate of 13.1%, a 72.4% rate of patients who showed progression in the lungs, and retreatment up to four times with RF ablation in 24% of initially treated patients, resulting in a 4-year control rate of lung metastatic disease of 44.1%.[25] Thermal ablation is well tolerated and spares the lung parenchyma, as demonstrated by absence of post-RF ablation lung changes in respiratory function testing, which allows for high feasibility of retreatment when needed.[3,14]

Repeatability is definitively higher with thermal ablation than with any other local treatment, including surgery or SABR. Drawbacks of SABR are difficulties in treating several metastases in the same region with overlapping irradiation fields and near impossibility of retreatment with SABR for local progression after a previous SABR treatment. Reports of large series of SABR for lung metastases are scarce. One available large series that included 321 patients with 587 metastases (201 colorectal cancer metastases) treated with SABR over 13 years reported a median OS of 2.4 years (95% confidence interval [CI], 2.3–2.7) with 80%, 39%, 23%, and 12% OS at 1, 3, 5, and 7.5 years, respectively.[31] Three deaths were possibly procedure related. Of note, SABR is considered a noninvasive technique even though some complications are directly related to the treatment, but they are often difficult to attribute to SABR because they usually occur late after treatment, as with most postradiation toxicity. Moreover, it has been reported that placement of a fiducial marker was needed for SABR in 105 patients with tumors in the lung, resulting in 33.3% pneumothoraces (major, 13.3%; minor, 20%), 30.5% small peritumoral alveolar hemorrhage, and 2.9% of major bleeding,[32] which makes SABR invasiveness close to that of RF ablation in terms of pneumothoraces.

Non–Small Cell Lung Cancer

In NSCLC, surgical resection is the current standard of care for patients with stage I or II disease due to the benefit of associated lymphadenectomy. However, imaging-guided ablation and radiation therapy are increasingly offered as alternative therapies in nonsurgical candidates.[3,14,25,33-35] Impressive 1-, 3-, and 5-year OS rates of 97.7%, 72.9%, and 55.7%, respectively, have been reported in 44 consecutive patients treated with RF ablation for 51 recurrent NSCLC after surgery (mean diameter, 1.7 ± 0.9 cm).[36] The 1-, 3-, and 5-year OS rates were 100%, 79.8% (95% CI, 61.8%–97.8%) and 60.5% (95% CI, 32.5%–88.4%) in patients with tumors measuring < 3 cm. However, nearly 50% of reported deaths during follow-up of NSCLC treated with RF ablation were not related to cancer progression but rather comorbidities.[37,38]

Recent results of local ablation challenge surgery for stage IA and IB lung cancer combined with MW ablation showing similar therapeutic effect compared with lobectomy for stage I NSCLC but with fewer complications and less pain in a propensity-matched analysis.[39] Although randomized studies are needed, they will be difficult to complete due patient refusal to be randomized. Indeed, two independent, randomized, phase 3 trials of SABR in patients with operable stage I NSCLC (STARS and ROSEL) ended early due to slow enrollment. Pooled data from these trials, including 58 patients with T1/T2a(< 4 cm)N0M0, operable NSCLC who were randomly assigned in a 1:1 ratio to SABR or lobectomy with mediastinal lymph node dissection or sampling, showed an estimated 3-year OS of 95% (95% CI, 85%–100%) in the SABR group compared with 79% (95% CI, 64%–97%) in the surgery group (hazard ratio, 0.14; 95% CI, 0.017–1.190; log-rank $P = .037$).[40]

Of note, Lam et al reported findings from a the National Cancer Database analysis of RF ablation versus stereotactic body radiation therapy (SBRT) in stage IA and IB NSCLC.[41] The two cohorts were composed of 4,454 SBRT cases and 335 RF ablations and reported equivalent OS both for the unmatched groups and in

the propensity score–matched groups, with 1-, 3-, and 5-year OS rates of 85.5%, 54.3%, and 31.9% in the SBRT group versus 89.3%, 52.7%, and 27.1% in the RF ablation group (P = .835), respectively.

Pre- or postablation systemic therapy might improve outcomes of thermal ablation, and combination therapy has reported favorable outcomes.[42-44] The excellent tolerance of thermal ablation might render such a combination highly feasible, while only 70% of patients who undergo perisurgical systemic therapies are able to complete the scheduled regimen after lung surgery due to the long recovery time.[45]

CONCLUSION

Thermal ablation for lung tumors is gaining popularity because the rate of complete ablation is close to 90% for tumors up to 2 cm. Thermal ablation allows for excellent short- and long-term tolerance, which is an asset in metastatic disease that will likely recur and need retreatment as well as in NSCLC, which is often seen in patients with comorbidities that prevent surgery. The clinical data examining the use of available treatment options for lung metastases cannot favor surgery over thermal ablation for tumors < 2 cm. ■

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