



A narrative review on pulmonary metastases management by non-surgical local techniques: where do we stand?

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Objective: To analyze the existent evidence regarding local non-surgical therapies of lung metastases in terms of prognostic outcomes, control of disease and safety of treatment.

Background: The rationale of local therapies for pulmonary metastases is either to increase the patient's chance of survival or cure the disease, depending on the origin and histology of the tumour. Metastasectomy still represents the preferred local treatment for lung metastases; however, due to the obvious drawbacks of almost any surgical intervention, many patients are not considered eligible for surgery.

Methods: An extended search with a priori selection criteria was performed on the treatment of pulmonary metastases with stereotactic radiotherapy, percutaneous ablation via radiofrequency, microwaves, cryoablation (CRA) and chemoembolization. Two reviewers independently screened the titles and abstracts of all retrieved papers; the reference lists of eligible studies were checked with the aim to find further studies not identified by the initial search. After final selection, 52 original articles were included.

Conclusions: A discrete number of minimally invasive non-surgical methods has been developed for tumor patients who are ineligible for surgical treatment. Among the available techniques, stereotactic radiotherapy and percutaneous ablation are currently the most commonly used local therapies. They have emerged as valid alternatives in case of surgical or medical inoperability, and may offer cancer patients the possibility for controlling unresectable pulmonary metastases with opportunities for improved survival.

Keywords: Lung metastases; microwaves; radiofrequency; cryoablation (CRA); chemoembolization

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Introduction

Metastasis is the fundamental biological characteristic of malignant neoplasms, feature which is responsible for poor prognosis of affected patients and eventually

leads to treatment failure or death. The molecular and cellular mechanisms underlying the metastatic spread of malignancies are the topic of intense research efforts because of obvious implications for the possibility to predict, identify and cure life-threatening advanced disease.

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The lungs are the second most prominent site of metastases after the liver, detected in 20–54% of metastatic patients (1). Pulmonary involvement may result through the following routes: lymphatic spread, hematogenous spread, direct invasion, and transcoelomic (i.e., transpleural) diffusion.

In adults, the most common primary tumors that disseminate to the lungs include breast, colorectal, renal carcinoma, and uterine leiomyosarcoma. In limited cases, the primary tumor is not identifiable in spite of a thorough diagnostic work-up (namely, cancer of unknown primary, CUP).

Broadly speaking, the rationale of local therapies for pulmonary metastases is either to increase the patient's chance of survival or cure the disease, depending on the origin and histology of the tumour. Another possible goal of such approaches is to provide the patient, who has been prescribed long-lasting systemic treatment, with a well-earned break from that therapy (2).

Pulmonary metastasectomy has been gradually accepted as a strategy of proved therapeutic value in selected cases (3). Historically, the goal of lung metastasectomy has been cure; therefore, it is generally assumed that local therapies make little sense if other sites of disease remain unaddressed (4).

Surgery for lung metastases has long been practiced, albeit a robust evidence in the literature regarding prolonged survival is still lacking (4,5). Indeed, gains in life expectancy attributable to surgery are not irrefutable, and there is no consensus on selection of patients who may actually benefit the most from such a treatment, in the absence of evidence-based data (4,6).

Systemic chemotherapy still remains the cornerstone of treatment for malignant tumors metastasized to the lungs. Indeed, in recent years the efficacy of chemotherapy has drastically improved due to advances in treatment strategies and the emergence of molecular targeted drugs; the fight against cancer with immune-stimulation has opened a new era of immunotherapy. However, some patients still experience tumor progression, or are not tolerant to systemic therapy due to its side effects (1,2,7).

The role of pulmonary metastasectomy has been widely investigated by the 1970s, representing the preferred local treatment for lung metastases and being routinely performed in thoracic surgery units (8). However, due to the obvious drawbacks of almost any surgical intervention and the requirement of adequate patient lung function, many patients are considered not eligible for surgery. Moreover, the recurrence rate after lung metastasectomy remains high,

thus entailing repeat surgical treatments (7).

A discrete number of minimally invasive non-surgical methods for treating pulmonary metastases has been consequently developed for tumor patients who are ineligible for surgical treatment. Among the available techniques, stereotactic radiotherapy and percutaneous ablative techniques are currently the most commonly used local therapies.

Our review aims to analyze the existent evidence regarding local non-surgical therapies of lung metastases in terms of prognostic outcomes, control of disease and safety of treatment. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://asj.amegroups.com/article/view/10.21037/asj-21-36/rc>).

Methods

Search strategy

An extended systematic search was performed in Medline database (via PubMed), including articles written in English, related to human medicine, and published in the last 10 years to April 2021.

Only studies dealing with pulmonary metastases were considered eligible, with no restrictions to primary tumors.

The search strategy was elaborated to include the greatest number of references dealing with the populations and the interventions object of the study by using the following keywords in combination with the Boolean operators OR and AND: “lung,” “pulmonary,” “metastasis,” “metastases,” “ablation,” “radiotherapy,” “embolization,” “chemoembolization”.

Two reviewers (SC, MC) independently screened the titles and abstracts of all retrieved papers and selected the studies to be included in this review, after removing duplicates. All the articles selected by at least one of the reviewers were retrieved for full text evaluation. Reviews, case reports and case series were excluded. Studies dealing with the treatment of both primary and metastatic lesions, or employing multiple techniques were excluded from the analysis.

In case of disagreement between the reviewers, a further author (AC) was consulted to achieve a consensus.

Primary aim of this review was the analysis of outcomes in terms of local control (LC), overall survival (OS), and progression-free survival (PFS) of the different treatment approaches. LC was defined as no progressive disease of the

tumor within the treated area. PFS was generally defined as the lack of progression or relapse at any site after the commencement of stereotactic body radiotherapy (SBRT).

Selected articles were retrieved and all data were extracted using a form designed to respond to the objectives of this work.

Results

The search generated 367 results; the reference lists of eligible studies were checked with the aim to find further studies not identified by the initial search. Finally, 52 studies were included in this review.

Among them, 24 papers dealt with stereotactic radiotherapy, mainly with retrospective study design.

Pulmonary metastases from different tumors were treated through SBRT in the articles selected: non-small cell lung cancer, colorectal cancer (CRC), renal cell carcinoma, hepatocarcinoma, head & neck cancer, melanoma, oesophagus, pancreas, prostate, rectal carcinomas, soft tissue sarcomas, salivary gland, uterine, thyroid cancers, and other less frequent histologies.

Some authors have correlated the primary type to local failure of the treatment (9,10): CRC metastases were found to carry a significantly higher cumulative incidence of local failure at 12 and 24 months (25.5% and 42.2%), compared to all the other histologies (4.4% and 9.9%; $P < 0.0004$) (9). The presence of extrapulmonary disease and the number of the lesions were also identified as predictor of poor outcome (10).

Outcomes of treatment were reported in an exhaustive manner in most papers (see details in *Table 1*). The variability of OS may be explained by different exclusion criteria applied in the retrospective series analyzed: some authors had enrolled only oligometastatic patients with controlled primary tumor, or only patients with limited number of metastases or sites.

Rieber *et al.* (29) reported the larger retrospective cohort of patients with oligometastatic disease, in which pulmonary metastases were treated by SBRT; they found 2-year LC of 81.2% and 2-year OS of 54.4%.

Different cut-off values have been proposed to obtain satisfactory LC; some authors have postulated a metastatic gross tumor volume threshold of 10 cc (15). However, optimal LC was achieved even for larger sized lesions (5 cm) in a cohort of oligometastatic sarcoma patients (14).

SBRT was generally well tolerated. Adverse events

were frequently reported using the Common Terminology Criteria for Adverse Events (CTCAE), and are mostly detailed as grade 1 or grade 2 toxicity, without the need for further treatment or requiring only minor supportive measures. Most common complications included pneumonitis, dyspnoea, pulmonary fibrosis, atelectasis, chest wall pain, bronchial stenosis, pleural effusion, pneumothorax, rib fracture, fatigue, and nausea. One patient treated for a large (6.7 cm) central metastasis died due to grade 5 pneumonitis (29). Another death was described in a patient with long-standing chronic obstructive pulmonary disease (COPD) (24). In a large cohort of pulmonary metastatic patients, the authors documented severe complications \geq grade 3 in only 2.9% (6/207) within the first 6 months and in 2.5% (3/119) after 1 year (21).

Twenty studies concerning radiofrequency ablation (RFA) were analyzed, including 9 with prospective observational and 11 retrospective study design (*Table 2*).

Lung metastases from different types of primary tumors were treated with RFA: CRC, breast cancer, renal cell carcinoma, hepatocarcinoma, head & neck cancer, melanoma, esophageal, soft tissue sarcomas, thyroid cancers, and other less frequent histologies.

Most articles accurately analyzed the outcomes of the interventions.

The largest prospective series was reported by de Baère *et al.* (41), treating 566 patients with 1,037 lung metastases. Median OS was 62 months, 1-, 2-, 3-, 4- and 5-year OS rates were respectively 92.4%, 79.4%, 67.7%, 58.9% and 51.5%; PFS rates at 1-, 2-, 3- and 4-year were 40.2%, 23.3%, 16.4% and 13.1%, and LC rates were 89.6%, 85.5%, 82.5% and 81.9% at 1-, 2-, 3- and 4-year, respectively. Moreover, the authors identified primary tumor, disease-free interval, size and number of lesions as predictors of survival in multivariate analysis.

Another large study by Ferguson *et al.* (42) applied RFA in the treatment of 157 patients with 434 lung metastases from CRC; 1-, 3- and 5-year OS were 89%, 44% and 19.9%, whereas PFS at 1-, 3- and 5-year were 60.5%, 14.4% and 7%, respectively. The difference in terms of OS between the two largest study cohorts could be explained by different criteria used in patients' selection, especially in terms of lesion size. Indeed, 111 out of 157 patients in the Ferguson's cohort had tumors larger than 3 cm (mean size 44.5 mm), whereas most of the other studies used 35 mm as a size cut-off to include patients to be treated.

The procedures had negligible mortality, with some rare cases of high-grade complications. Pneumothorax was

Table 1 Characteristics of the studies dealing with SBRT included in this review

| Author, year | No. of patients | Age | Primary tumor | No. of lesions | Lesion size | Follow-up length | Overall survival | Local control | Progression-free survival | Total dose, fractions | Mortality | Morbidity |
|-------------------------|-----------------|--------------------|--|---------------------|------------------------------|------------------|--|---------------------------------|--|---------------------------------------|-----------|----------------------------|
| Aoki (11), 2016 | 66 | 71y | NSCLC: 47%; CRC: 19.7%; HN: 15.1%; Oe: 4.5%; uterus: 4.5%; others: 9.1% | 76 | ≤30: 92.1%; >30: 7.9% | 31.7 m | 3y: 76% | 3y: 90% | 3y: 53.7% | 50 Gy, 5 | 0% | 5% |
| Baschnagel (12), 2012 | 32 | 62y | CRC (n=10), sarcoma (n=4), H&N (n=4), M (n=3), bladder (n=2), NSCLC (n=2), RCC (n=2), thymoma (n=2), thyroid (n=1), endometrial (n=1), oesophageal (n=1) | 47 | 16 mm | 27.6 m | 1, 2 and 3y: 83%, 76% and 63% | 1, 2 and 3y: 97%, 92% and 85% | N.A. | 60 Gy, 4 | 0% | 3/30 patients |
| Baumann (13), 2016 | 30 | 56.3y | Sarcomas | 39 | 24 mm | 23 m | 1 and 2y: 76% and 43% | 1 and 2y: 94% and 86% | N.A. | 50 Gy, 4–5 | 0% | 2/30 patients |
| Baumann (14), 2020 | 44 | 59y | Sarcomas | 56 | 20 mm | 25 m | 1 and 2y: 74% and 46% | 1 and 2y: 96% and 90% | N.A. | 50 Gy, 4–5 | 0% | 3/30 patients |
| Berkovic (15), 2020 | 104 | 66.4y | NSCLC (n=49, 47.1%), gastro-intestinal (n=35, 33.7%), other (n=20, 19.2%) | 132 | 7.9 cc | 22 m | 1, 2, 3y: 92.2, 80.9% and 72.0% | 89.3, 80.0% and 77.8% | 1, 2, 3y lung: 66.3%, 50.0%, 42.6%; distant: 80.5%, 64.4%, 60.6% | 60 Gy, 3 | 0% | 7% (grade 1), 2% (grade 2) |
| Binkley (9), 2015 | 77 | 60y | NSCLC: 17.2%; CRC: 21.3%; S: 15.6%; others: 45.9% | 122 | N.A. | 22 | 1y: 93.7%; 2y: 74.6% | 1y: 91.3%; 2y: 83.8% | N.A. | 25 Gy, N.A. | 0% | N.A. |
| De Rose (16), 2016 | 60 | 70.5y | NSCLC | 90 | N.A. | 28 m | 1y: 94.5%; 2y: 74.6%; 3y: 64.3%; 5y: 22.1% | N.A. | N.A. | 48–60 Gy, 3–8 | 0% | N.A. |
| Filippi (17), 2014 | 67 | 71y | NSCLC: 37.4%; CRC: 40.3%; melanoma: 7.5%; HN: 4.5%; HCC: 2.9%; Oe: 2.9%; breast: 1.5%; RCC: 1.5%; Pr: 1.5% | 90 | 17 mm | 24 m | 1y: 85.1%; 2y: 70.5% | 1y: 93.4%; 2y: 88.1% | 1y: 72%; 2y: 55.4% | 26 Gy, 1 | 0% | N.A. |
| Franceschini (10), 2017 | 200 | 69y | RCC: 12%; M: 4.5%; HCC: 10%; Salivary gland: 3.5%; S: 20.5%; CRC: 49.5% | 1: 64%; >1: 36% | N.A. | 24.2 m | N.A. | 1y: 91%; 2y: 84.9%; 3y: 82% | 1y: 84%; 2y: 57.7%; 3y: 47% | 30–60 Gy, 1–8 | 0% | N.A. |
| Helou (18), 2017 | 120 | 67y | NSCLC: 31.3%; RCC: 25.3%; breast: 21.7%; others: 21.7% | 184 | 15 mm | 22 m | N.A. | 1y: 95.6%; 2y: 84.8% | N.A. | 48–52 Gy, 4–5 | <1% | 8.3% |
| Jingu (19), 2018 | 93 | 69y | CRC | 104 | 15 mm | 28 m | 3 and 5y: 55.9% and 42.7% | 3 and 5y: 65.2% and 56.2% | N.A. | N.A. | 0% | 2/93 patients |
| Jung (20), 2015 | 50 | 65y | CRC | 79 | N.A. | 42.8 m | 3y: 64% | 1y: 88.7%; 3y: 70.6% | 3 ys: 24% | 40–60 Gy, 3–4 | 0% | 4% |
| Kessel (21), 2020 | 219 | 68y | NSLC (n=56 17.7%), CRC (n=93, 29.4%), melanoma (n=11, 3.5%), breast cancer (n=20, 6.3%), others (n=136, 43.0) | 316 | N.A. | 16.5 m | 1, 2, 3y: 74%, 54% and 39% | 1, 2, 3y: 92%, 84% and 78% | N.A. | 35 Gy | 0% | 2.9% (≥ grade 3) |
| Kinj (22), 2017 | 53 | 69y | CRC | 87 | 16 mm | 33 m | 1y: 83.8%; 2y: 69.3%; 5y: 58.3% | 1y: 79.8%; 2y: 78.2% | 1y: 29.2%; 2y: 14.6% | 50–75 Gy, 3–5 | 0% | N.A. |
| Navarria (23), 2014 | 28 | 64y | Sarcomas | 51 | 6.5 cm ³ | 21 m | 2 and 5y: 96.2% and 60.5% | 5y: 96% | N.A. | N.A. (based on the site and the size) | 0% | 64% (grade 1 and 2) |
| Oh (24), 2012 | 57 | <60: 28%; >60: 72% | NSCLC: 49.2%; HCC: 13.4%; CRC: 10.5%; HN: 16.4%; others: 10.5% | 67 | <25 mm: 86.6%; >25 mm: 13.4% | 21 m | 2y: 59.7%; 5y: 56.2% | N.A. | N.A. | 50–60 Gy, 4–5 | 2% | N.A. |
| Osti (25), 2013 | 66 | 68y | NSCLC: 18%; CRC: 35%; breast: 17%; others: 30% | 103 | 10 cc: 62%; 10 cc: 38% | 15 m | 1y: 76.4%; 2y: 31.2% | 1y: 89.1%; 2y: 82.1% | 1y: 53.9%; 2y: 22% | 23–30 Gy, 1 | 0% | 3% (grade 3), 6% (grade 2) |
| Qiu (26), 2018 | 65 | <60: 60%; >60: 40% | CRC | 1: 36.9%; >1: 63.1% | <10 mm: 27.7%; >1: 72.3% | 6.4 m | 1y: 77.8%; 2y: 42.8% | 1y: 56.6%; 2y: 30.9% | 1y: 23.5%; 2y: 10.1% | 40–60 Gy, 5–11 | N.A. | N.A. |
| Ricardi (27), 2012 | 61 | 70y | NSCLC: 53.5%; CRC: 21.3%; Pa: 3.3%; HCC: 3.3%; HN: 3.3%; O: 12.8% | 77 | 20 mm | 20.4 m | 2y: 66.5% | N.A. | 2y: 32.4% | 26–45 Gy, 1-3 | N.A. | 4.92% |
| Ricco (28), 2017 | 447 | 69y | Breast: 9.2%; CRC: 25.7%; HN: 11.4%; NSCLC: 16.6%; RCC: 8.1%; melanoma: 6.5%; others: 22.1% | 1–3 per patient | 10.58 cc | 13 m | 1y: 74.1%; 3y: 33.3%; 5y: 21.8% | 1y: 80.4%; 3y: 58.9%; 5y: 46.2% | N.A. | 50 Gy, 3 | N.A. | N.A. |
| Rieber (29), 2016 | 700 | 67y | NSCLC (n=210), CRC (n=153), sarcoma (n=51), RCC (n=48) breast (n=43) | 1: 42.4%; >1: 57.6% | 22 mm | 14.3 m | 1y: 75.1%; 2y: 54.4% | 1y: 90.9%; 2y: 81.2% | N.A. | 12.5 Gy, 3 | 0.2% | N.A. |
| Siva (30), 2015 | 65 | 69y | CRC: 31%; NSCLC: 25%; HN: 11%; sarcomas: 8%; others: 25% | 1: 78.5%; >1: 21.5% | N.A. | 25 m | 1y: 93%; 2y: 71% | N.A. | N.A. | 18–50 Gy, 1–5 | 0% | 31% |
| Yamashita (31), 2016 | 96 | 72y | CRC: 26%; NSCLC: 25%; HN: 8%; uterus: 8%; others: 32% | 1: 79.2%; >1: 20.8% | 19 mm | 21 m | 3y: 53.2% | 3y: 74.2% | 3y: 32.2% | N.A. | 0% | N.A. |
| Zhang (32), 2011 | 71 | 59y | NSCLC: 18.3%; CRC: 15.5%; HN: 14.1%; sarcoma: 11.3%; HCC: 11.3%; RCC: 8.5%; breast: 7.0%; others: 14.1% | 172 | 21 mm | 24.7 m | 1y: 78.9%; 3y: 40.8%; 5y: 25.2% | 1y: 96.6%; 3y: 89.4%; 5y: 89.4% | N.A. | 36–60 Gy, 3–5 | 0% | N.A. |

Data are expressed as median or mean as reported in the original article. SBRT, stereotactic body radiotherapy; CRC, colorectal cancer; HN, head & neck; NSCLC, non-small cell lung cancer; N.A., not available; Oe, oesophageal; Pr, prostate; Pa, pancreas; RCC, renal cell carcinoma.

Table 2 Characteristics of the studies dealing with RFA included in this review

| Author, year | No. of patients | Age | Primary tumor | No. of lesions | Lesion size | Follow-up length | Overall survival | Local control | Progression-free survival | Mortality | Morbidity |
|---|-----------------|-------|---|----------------|-------------|------------------|--|--|---|-----------------------------------|---|
| Hiraki <i>et al.</i> (33), 2011 | 32 | 61.9y | HCC | 83 | 14 mm | 20.5 m | 1y 87%; 2y 57%; 3y 57% | 3 ys: 92% | N.A. | 0% | 25% PNx drained; 35% PNx conservative treated |
| Palussière <i>et al.</i> (34), 2011 | 29 | 51y | Sarcoma | 47 | 9 mm | 50 m | 1y 92%; 3y 65% | N.A. | N.A. | 0% | 59% PNx drained |
| Von Meyenfeldt <i>et al.</i> (35), 2011 | 46 | 57y | CRC (30%), sarcoma (26%), RCC (9%), melanoma (7%), breast (7%), other (21%) | 90 | 16 mm | 22 m | 1y 84%; 3y 69% | 1y 78%; 2y 65% | 1y 33%; 3y 11% | 0% | 25% PNx drained |
| Li <i>et al.</i> (36), 2012 | 29 | 56y | HCC | 68 | 19 mm | 23 m | 1y 74%; 2y 41% 3y 30% | N.A. | 1y 59%; 2y 28% | 0% | 9% PNx drained |
| Gillams <i>et al.</i> (37), 2013 | 122 | 68y | CRC | 398 | 17 mm | 18 m | 3y 57% | N.A. | N.A. | 0% | 15% PNx drained; 4% major complication (effusion, infection) |
| Petre <i>et al.</i> (38), 2013 | 45 | 63y | CRC | 69 | 4–35 mm | 18 m | 1y 95%; 2y 72%; 3y 50% | 1y 87% | N.A. | 0% | 6% effusion, infection; 19% PNx drained |
| Matsui <i>et al.</i> (39), 2014 | 21 | 66y | Esophageal | 31 | 17 mm | 22.4 m | 1y 85.7%; 2y 54.8%; 3y 38.4% | 4m 74.2% | 1y 85.7%; 2y 54.8%; 3y 38.4% | 0% | 29% PNx treated conservative; 7% Effusion, pnx, infection requiring treatment |
| Baba <i>et al.</i> (40), 2014 | 10 | 67.5y | Esophageal | 17 | 15 mm | 20 m | 1y 77.8%; 2y 62.2% | 1y 83% | N.A. | 0% | 30% PNx |
| de Baère <i>et al.</i> (41), 2015 | 566 | 63y | CRC (34%); RCC (12%); Sarcoma (9%); Thyroid (3%); Breast (3%); Others (22%) | 1,037 | 17 mm | 35.5 m | 1y 92.4%; 2y 79.4%; 3y 67.7%; 4y 58.9%; 5y 51.5% | 1y 89.6%; 2y 85.5%; 3y 82.5%; 4y 81.9% | 1y 40.2%; 2y 23.3%; 3y 16.4%; 4y 13.1% | 0% | 67% PNx (28% not treated, 58% chest tube, 14% simple aspiration during the RFA procedure) |
| Ferguson <i>et al.</i> (42), 2015 | 157 | 64y | CRC | 434 | N.A. | 28 m | 1y 89%; 3y 44%; 5y 19.9% | N.A. | 1y 60.5%; 3y 14.4%; 5y 7% | 0% | 53.8% PNx; 18.6% PNx that required chest tube |
| Tongdee <i>et al.</i> (43), 2015 | 14 | 50y | HCC 64.3%; CRC 21.4%; Thyroid 7.1%; Prostate 7.1% | 27 | 13 mm | 11.1 m | N.A. | N.A. | N.A. | 0% | 71% PNx |
| Wang <i>et al.</i> (44), 2015 | 67 | N.A. | CRC 38%; NSCLC 19%; sarcoma 10%; Esophageal 10%; HCC 7%; Others 16% | 115 | N.A. | 24 m | 1y 83.6%; 2y 46.3%; 3y 14.3% | 2y 87.8% | 6m 82.1%; 12m 55.7%; 18m 27.5% | 0% | 12% PNx; 2% PNx treated with chest tube; 10% effusion |
| Wang <i>et al.</i> (45), 2015 | 35 | N.A. | Breast | 67 | N.A. | 25 m | 1y: 88.6%; 2y: 59.3%; 3y: 48.2% | N.A. | N.A. | 0% | 8.6% PNx; 8.6% emottisi; 5.7% effusion |
| Fanucchi <i>et al.</i> (46), 2016 | 61 | 74y | CRC 47.5%; HN 13%; RCC 7%; Sarcoma 8%; Other 4% | 86 | 20 mm | 28 m | 1y 94.8%; 3y 49%; 5y 44.5% | N.A. | 1y 86.3%; 3y 70.3%; 5y 68% | 0% | 11%; PNx in 8.7%; Effusion on 2% |
| Sato <i>et al.</i> (47), 2017 | 46 | 54.5y | Sarcoma | 144 | 13.5 mm | 16.7 m | 1y 80.6%; 2y 70.1%; 3y 47.1% | 1y 83.5%; 2y 76.3% | N.A. | 0% | Grade 2 in 24% |
| Gonnet <i>et al.</i> (48), 2018 | 53 | 67y | RCC | 100 | 12mm | 61 m | 1y 94%; 3y 74.5%; 5y 61.8% | 1y 93.8%; 3y 82.6% | 1y 58.9%; 3y 35.2% | 0% | 26 drained PNx |
| Hiyoshi <i>et al.</i> (49), 2018 | 43 | 64.8y | CRC | 188 | 12 mm | 24.3 m | Median OS 52.7 m | N.A. | Median PFS 6.8 m | 0% | 55.8% (PNx, effusion, subcutaneous emphysema but chest tube drainage 14%) |
| Hasegawa <i>et al.</i> (50), 2020 | 70 | 66y | CRC | 100 | 10 mm | 57 m | 3y 84% | 1y 91% | N.A. | 1% (hemorrhagic pleural effusion) | 20% PNx treated with chest tube |
| Lassandro <i>et al.</i> (51), 2020 | 26 | 62.5y | HCC | 42 | 14 mm | N.A. | 1y 88.5%; 3y 69.8%; 5y 26.2% | N.A. | N.A. | 0% | 22.5% PNx, only 2.6% treated with chest tube insertion |
| Zhong <i>et al.</i> (52), 2020 | 60 | 69y | CRC | 125 | 14 mm | 45.5 m | 1y 96.7%; 3y 74.7%; 5y 44.1%; 7y 27.5%; 9y 16.3% | 1y 96.7%; 2y 91.7%; 3y 90%; 4y 90% | 1y 66.7%; 3y 31.2%; 5y 25.9%; 7y 21.2%; 9y 5.9% | 0% | 60% PNx (50% of them required chest tube insertion) 3% effusion that required chest tube |

Data are expressed as median or mean. RFA, radiofrequency ablation; CRC, colorectal cancer; HN, head & neck; NSCLC, non-small cell lung cancer; HCC, hepatocarcinoma N.A., not available; RCC, renal cell carcinoma; PNx, pneumothorax.

the most frequent and expected adverse event, with a wide range of probability between the different series, ranging from 10% to 60%, even though the vast majority of cases did not require any treatment.

Indeed, pneumothorax is one of the most common complications in the treatment of lung tumors through RFA, with an incidence reported between 8.5% and 50% by a metaanalysis (53). Several risk factors are correlated to pneumothorax, including lesion number, electrode position and trajectory through the lung parenchyma (54). In the aforementioned work by de Baère *et al.* (41), 67% of patients developed pneumothorax, and 2 cases of hemothorax related to intercostal artery puncture were treated by embolization during the same session. Other complications were pleural effusion, hemothorax, pneumonitis, and subcutaneous emphysema.

Six articles were included about the treatment of lung metastases through microwave ablation (MWA) (Table 3), mainly with retrospective study design: 4 studies dealt with pulmonary metastases from CRC, 1 with metastases from nasopharyngeal cancer and 1 with metastases from other malignancies, including CRC, hepatocarcinoma and breast cancer.

Percutaneous CT-guided MWA seems to be a safe therapy able to obtain local control of pulmonary metastases. Multiple lesions can be treated in a single session; furthermore, MWA is a repeatable method in the event of local recurrence or new metastases.

Vogl *et al.* (60) reported the largest cohort of patients (n=80) with metastatic CRC treated via MWA under CT-fluoroscopic guidance. Inclusion criteria were: no eligibility for surgical resection and the presence of 5 or fewer lesions with maximal diameter of 5 cm. Recurrence or residual tumor were identified in 26.9% of lesions. There were no intraprocedural deaths and the most common complications were pneumothorax (incidence of 8.5%), intraparenchymal hemorrhage (6.2%), and hemoptysis (4.6%). The survival rates at 12 and then 24 months were respectively of 91.3% and 75%. The authors concluded that peripheral lesions had lower incidence of recurrence after ablation than perihilar lesions, probably as a consequence of the “heat sink effect”.

Moreover, the study indicated a strong correlation between the size of metastases and procedural success: successful ablation was more probable for lesions smaller than 3 cm. No correlation was found between histology of primary tumor and ablation outcome, instead.

Interesting results emerged in the work by Kurilova *et al.* (57), in which a strong association was found between

tumor diameter, minimal ablation margin and local control of the lesion (local tumor progression was greater for lesions ≥ 1 cm ablated with minimal margin < 5 mm). However, they also reported that tumor location was a predictor for procedural success, as pleural-based tumors had a higher risk of progression. In their study, survival rates at 1-, 2- and 3-year were respectively of 94%, 84% and 60%.

In all the included articles, procedure-related mortality rate was 0%; the most common complications were represented by pneumothorax, mild pleural effusion, chest pain or mild hemoptysis.

Only 2 studies describing cryoablation (CRA) treatment of lung metastases were included, one with a prospective design and the other with a retrospective one (Table 4).

Yamauchi *et al.* (62) described a cohort of 24 patients with only metastases from CRC, in which ablation was performed under local anesthesia. OS rate at 12 months was 91%. In this study, local progression free interval was found to be significantly greater for lesions with a diameter < 15 mm.

Da Baere *et al.* (61) reported the largest cohort of patients (n=40) with a total of 60 lesions from different primary tumors (CRC being the most frequent origin) treated with CRA under general anaesthesia or conscious sedation, using a three-cycle freeze–thaw phase protocol. Overall local tumor control rate at 12 months for 49 out of 52 metastases was 94.2% (including complete response, partial response and stable disease), with an OS rate of 97.5%.

In both the aforementioned studies, no procedural-related death was observed. Pneumothorax was the most frequent adverse event, followed by pleural effusion and transient hemoptysis.

CRA offered the advantage (when compared with the heat-based technologies) of an easily monitoring procedure by using CT imaging, since the ablation zone appears as a well-defined area of low attenuation.

The incidence of procedural-related pain is generally low, thus the intervention can be performed under conscious sedation even in case of tumors located in the juxtapleural region.

Finally, a single retrospective study (63) regarding chemoembolization fulfilled the inclusion criteria of this review. The authors used transpulmonary chemoembolization (TPCE) with palliative or neoadjuvant intent in 43 patients presenting with pulmonary metastases from diverse primary tumors. Technical success was 100%. The mean survival time was estimated to be 24.3 ± 1.8 months with a median follow-up of 9.8 months. TPCE was

Table 3 Characteristics of the analysed studies dealing with MWA

| Author, year | No. of patients | Age | Primary tumor | No. of lesions | Lesion size | Follow-up length | Overall survival | Local control | Progression-free survival | Mortality | Morbidity |
|-----------------------------------|-----------------|---------|-------------------------|----------------|-------------|------------------|--------------------------------|----------------------------|---|-----------|---|
| Cheng <i>et al.</i> (55), 2018 | 32 | 63 y | CRC | 48 | <6 cm | 3y | 1y: 79.5%; 2y: 63.1%; 3y 44.4% | NA | NA | 0% | PNX (12.5%) |
| Ferguson <i>et al.</i> (56), 2017 | 14 | 65 y | CRC | 20 | 15.7 mm | 24.4 m | NA | 12/14 pz | NA | 0% | Asymptomatic PNX (42.1%); drained PNX (5.3%); pneumonia (5.3%); pleuritic pain (5.3%) |
| Kurilova <i>et al.</i> (57), 2018 | 50 | 58.5 y | CRC | 90 | 1 cm | 25.6 m | 1y: 94%; 2y: 82%; 3y: 61% | LTP in 9/90 lesions (10%) | 1y, 2y and 3y: 93%, 86% and 86% (local) | 0% | Minor 38%; Major 13% |
| Li <i>et al.</i> (58), 2017 | 22 | 56.05 y | CRC | 36 | <3.5 cm | 25.5 m | NA | LTP in 2/36 lesions at 6 m | 94.4% | 0% | PNX: 28% (mild 15%, severe 13%); chest pain: 21%; fever 5% |
| Qi <i>et al.</i> (59), 2015 | 17 | 45.7 y | HN | 29 | 0.8–4.2 cm | 14 m | NA | 1y: 88.2% | NA | 0% | 2 pts: PNX; 4 pts: parenchymal bleeding |
| Vogl <i>et al.</i> (60), 2011 | 80 | 59.7 y | CRC, HCC, breast, NSCLC | 130 | <3 cm | 6–24 m | NA | 73.1% (95/130 lesions) | NA | 0% | PNX: 8.5%; hemorrhage: 6.2%; hemoptysis: 4.6% |

Data are expressed as median or mean. MWA, microwave ablation; CRC, colorectal cancer; HCC, hepatocarcinoma; HN, head & neck; NSCLC, non-small cell lung cancer; N.A., not available; PNX, pneumothorax; RCC, renal cell carcinoma.

Table 4 Characteristics of the selected studies dealing with CRA of lung metastasis

| Author, year | No. of patients | Age | Primary tumor | No. of lesions | Lesion size | Follow-up length | Overall survival | Local control | Progression-free survival | Mortality | Morbidity |
|-----------------------------------|-----------------|--------|-------------------|----------------|-------------|------------------|------------------------|-----------------------------|---|-----------|--|
| de Baere <i>et al.</i> (61), 2015 | 40 | 62.6 y | CRC, RCC, sarcoma | 60 | 14 mm | 12 m | 97.5% | 96.6% at 6 m; 94.2% at 12 m | NA | 0% | No grade 4 and 5 complications. 18.8% PNX requiring drainage |
| Yamauchi <i>et al.</i> (62), 2011 | 24 | 62 y | CRC | 55 | 13 mm | 40 months (mean) | 91% (1 y), 59.6% (3 y) | NA | 3 y: lesions ≤15 mm, 79.8%; >15 mm, 28.6% | 0% | PNX (63%), pleural effusion (70%), hemoptysis (43%) |

Data are expressed as median or mean. CRA, cryoablation; CRC, colorectal cancer; NA, not available; PNX, pneumothorax; RCC, renal cell carcinoma.

well tolerated, with 0% mortality.

Discussion

Surgical resection of pulmonary oligometastases seems to improve cancer patients' outcomes in terms of survival, and is currently the first-choice approach (64). However, it is worth mentioning that the widespread belief in the value of metastasectomy has been challenged in recent years (5,65,66), since there is growing evidence that survival without surgery, even in CRC patients, may be higher than previously reported and largely dependent on patients' selection.

In case of surgical or medical inoperability, patients who may benefit from local treatment should not be denied metastases-directed therapy.

Alternative treatments have traditionally been reserved for poor surgical candidates or for patients who refuse surgery. In recent years, constant improvements and refinements in technology and more precise treatment strategies are widening the indications for these methods: curative intent, chemo-vacations and, more recently, treating metastases that present a dissociated or disproportional response to chemotherapy or new generation therapies represent the three widespread indications (67-69). In addition, ablation or radiotherapy may be considered an option for patients who present with ipsilateral metastases after prior metastasectomy (4).

Prognosis of local approaches is strongly dependent on the type of the primary tumor. Therefore, patients who may benefit most likely from local treatments are those with: long disease-free interval (>36 months) between the treatment of the primary tumor and the development of pulmonary metastases; oligometastatic disease; cases in which local treatment are likely to result in complete ablation/resection; small lesion dimension (up to 2–3 cm) (67).

There is growing evidence to support the hypothesis that radical treatment of pulmonary oligometastatic disease with SBRT can improve oncological outcomes: lung metastases are thus increasingly being treated by SBRT with minimal peri-procedural toxicity (70). SBRT not only may produce tumor necrosis, but also a tumor-specific response of the host immune system with possible inactivation of residual micrometastases (abscopal effect) (71). Rarely, regression of non-irradiated metastatic lesions at a distance from the primary site of irradiation may indeed take place as a systemic anti-tumor immune response. SBRT is a well-documented non-invasive substitute to metastasectomy for

a wide variety of primary tumors and metastatic sites (15).

However, previous studies have suggested different efficacies of SBRT based on the histology, and multigene expression models have been elaborated to predict the radiosensitivity index (RSI) of different tumors (64,70). A discrete number of prognostic factors were found to predict the risk of local recurrence for patients with pulmonary metastases, including increased size of target lesions, increased number of lesions, primary tumor and lower SBRT dosage (9,70). Hence, a biological effective dose (BED) at PTV periphery (BEDPTV) >100 Gy is generally considered necessary for optimal local control in early stage lung cancer, and this data was confirmed in a large cohort of patients treated by SBRT for pulmonary metastases from different primary neoplasms (29).

A metanalysis (70) has shown that SBRT applied to lung metastases from CRC demonstrated 3-year LC, OS and PFS rates of 60%, 52%, and 13%, respectively. Moreover, when comparing data of patients treated for CRC pulmonary metastases to non-CRC ones, significantly lower LC but higher OS were observed for patients in the first group.

When comparing SBRT to surgery, any substantial difference between the two approaches in terms of short-term survival results was registered; however, an advantage for surgery was suggested analyzing data on long-term outcomes (64).

Despite the constantly increasing use, general skepticism about the adoption of SBRT to treat oligometastases remains, mainly due to the lack of clinical data to support this practice (72). Ongoing randomized trials should help to clarify this relevant issue.

Ablation therapy is playing an increasingly relevant role as a local therapy in the comprehensive treatment of lung metastases. Ablation techniques, including radiofrequency, microwave and cryoablation, alone or combined with different treatment methods, are able to provide good therapeutic effects (7) with the advantage of sparing the lung parenchyma compared to surgery.

RFA was the first percutaneous technique used in this setting (73), and has shown similar efficacy as metastasectomy when used to treat patients with metastatic CRC (7).

All these interventions are performed under image-guidance: CT is the fundamental modality but, since the development of CT-fluoroscopy and Cone-beam CT (CBCT) (74), ablative procedures can be implemented using either of this guidance.

Among the available techniques, MWA may offer

several theoretical advantages over RFA which may result in a more reliable and predictable coagulative effect (68), including greater intratumoral temperatures, a more homogeneous and faster tissue damage over larger volumes, lesser susceptibility to zonal variation in tissue physical characteristics, also when the target lesion is closer to the vessels (in contrast to the heat-sink effect registered during RFA). Therefore, although in theory MWA is more optimal than RFA, the differing efficacies of the two modalities remain debated in the literature.

A recent metanalysis (53) has shown that RFA was superior to MWA with regard to the 1-, 2-, 3-, 4-, and 5-year OS for treating lung malignancies. However, the analysis of the 4- and 5-year OS rates between the two approaches only included small-sample study cohorts, which lowered the strength of such observation. Moreover, RFA led to better median OS compared to MWA when considering pulmonary metastasis only, with the same abovementioned limitations regarding the sample size.

On the other hand, CRA allows painless interventions under conscious sedation and/or local anesthesia, with the possibility to safely access difficult locations of the target lesions (67). Moreover, CRA better preserves the collagenous architecture of the lung parenchyma inside the ablation volume, which may be advantageous in treating lesions adjacent to the bronchi or in presence of emphysematous changes (67).

However, it should be borne in mind that a careful patient selection is crucial when evaluating the outcome of such procedures. In fact, disease control for lung metastatic patients is linked to the repeatability of these interventions, as PFS is generally low, and most treated patients will progress in a distant site over time. de Baère and colleagues (41) have found in a large prospective cohort that patients treated by RFA for lung metastases with a diameter below 4 cm had an OS of 62 months, associated with a 4-year local efficacy of 89%. Repeated ablations allowed a 4-year LC of 44.1%, with patient retreated safely up to 4 times.

Chemoembolization has been used successfully for treating primary and secondary liver malignancies, and it is under evaluation as a less invasive strategy for the treatment of lung malignancies (75). Since the first report in 2005 (76), TPCE has been used in limited cohorts as a locoregional technique for delivering chemotherapy in higher intratumoral concentrations and with reduced systemic toxicity (63,75), mainly with neoadjuvant or palliative intent. This method is performed via super-

selective catheterization of the tumor-feeding pulmonary arteries, blocking them by injection of cytotoxic drugs mixed with lipiodol and microspheres. This may result in a double effect: a prolonged deposition of the injected cytostatic drugs into the lesion with limited outflow into the circulation; on the other hand, an ischemic damage induced by temporary interruption of blood-flow similar to that reported after hepatic artery embolization.

Not unexpectedly, it has been recently studied in patients with hepatocellular carcinoma to treat intrathoracic metastatic spread (77). This technique may be employed either alone or prior to ablation in a multimodality strategy, with the aim to improve local disease control by eliminating eventual micrometastasis and reducing the need for a larger safety margin during subsequent percutaneous ablation (63,78).

Conclusions

Metastasectomy, when feasible, still represents the hallmark of local treatment for pulmonary oligometastases. Among the available options, SBRT and percutaneous ablation techniques have been used as valid alternatives in case of surgical or medical inoperability, and may offer cancer patients the possibility for controlling unresectable pulmonary metastases with potential opportunities for improved survival.

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