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

Anna Maria Ierardi[1], Aldo Carnevale[2]^, Serena Chiarello[2], Martino Cavazza[2], Elvira Stellato[3], Paolo Mendogni[4], Alessandro Palleschi[4], Davide Tosi[4], Melchiore Giganti[2], Gianpaolo Carrafiello[1,5]

[1]Radiology Unit, Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Department of Translational Medicine, Section of Radiology, University of Ferrara, Ferrara, Italy; [3]Postgraduate School of Diagnostic and Interventional Radiology, University of Milan, Milan, Italy; [4]Thoracic Surgery and Lung Transplantation Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [5]Department of Health Sciences, Università degli Studi di Milano, Milan, Italy

Contributions: (I) Conception and design: AM Ierardi, G Carrafiello; (II) Administrative support: P Mendogni, A Palleschi, D Tosi; (III) Provision of study materials or patients: A Carnevale, M Giganti; (IV) Collection and assembly of data: S Chiarello, M Cavazza; (V) Data analysis and interpretation: A Carnevale, S Chiarello, M Cavazza; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Aldo Carnevale. Radiology Unit, Translational Medicine Department, University of Ferrara, via L. Ariosto 35, 44121 Ferrara, Italy. Email: aldocarnevale@hotmail.it.

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; percutaneous ablation; microwaves; radiofrequency; cryoablation (CRA); chemoembolization; sterotactic radiotherapy

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

^ ORCID: 0000-0001-8191-6042.

predict, identify and cure life-threatening advanced disease.

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://dx.doi.org/10.21037/asj-21-36).

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 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 stereotactic body radiotherapy (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 patients with long-standing COPD (24). In a large cohort of pulmonary metastatic patients, the authors documented severe complications ≥ 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	N patients	Age	Primary tumor	Number 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. 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 et al. (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
Palussièr et al. (34), 2011	29	51y	Sarcoma	47	9 mm	50 m	1y 92%; 3y 65%	N.A.	N.A.	0%	59% PNX drained
Von Meyenfeldt et al. (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 et al. (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 et al. (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 et al. (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 et al. (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 et al. (40), 2014	10	67.5y	Esophgeal	17	15 mm	20 m	1y 77.8%; 2y 62.2%	1y 83%	N.A.	0%	30% PNX
de Baère et al. (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 et al. (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 et al. (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 et al. (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 et al. (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 et al. (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 et al. (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 et al. (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 et al. (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 et al. (50), 2020	70	66y	CRC	100	10 mm	57 m	3y 84%	1y 91%	N.A.	1% (hemorragic pleural effusion)	20% PNX treated with chest tube
Lassandro et al. (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 et al. (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. 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 metanalysis (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 as 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	N. of lesions	Lesion size	Follow-up length	Overall survival	Local control	Progression-free survival	Mortality	Morbidity
Cheng et al. (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 et al. (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 et al. (57), 2018	50	58.5y	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 et al. (58), 2017	22	56.05y	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 et al. (59), 2015	17	45.7y	HN	29	0.8–4.2 cm	14 m	NA	1y: 88.2%	NA	0%	2 pts: PNX; 4 pts: parenchimal bleeding
Vogl et al. (60), 2011	80	59.7y	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. 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 et al. (61), 2015	40	62.6	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 et al. (62), 2011	24	62	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. CRC, colorectal cancer; N.A., 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.

Acknowledgments

Footnote

and AP served as the unpaid Guest Editors of the series and serve as unpaid editorial board members of *AME Surgical Journal* from January 2021 to December 2022. PM served as an unpaid Guest Editor of the series. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Stella GM, Kolling S, Benvenuti S, et al. Lung-Seeking Metastases. Cancers (Basel) 2019;11:1010.
2. Schirren J, Schirren M, Lampl L, et al. Surgery for pulmonary metastases: quo vadis? Eur J Cardiothorac Surg 2017;51:408-10.
3. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg 1997;113:37-49.
4. Handy JR, Bremner RM, Crocenzi TS, et al. Expert Consensus Document on Pulmonary Metastasectomy. Ann Thorac Surg 2019;107:631-49.
5. Macbeth F, Fallowfield L. The myth of pulmonary metastasectomy. Br J Cancer 2020;123:499-500.
6. Gonzalez M, Poncet A, Combescure C, et al. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. Ann Surg Oncol 2013;20:572-9.
7. Qi H, Fan W. Value of ablation therapy in the treatment of lung metastases. Thorac Cancer 2018;9:199-207.
8. Petrella F, Diotti C, Rimessi A, et al. Pulmonary metastasectomy: an overview. J Thorac Dis 2017;9:S1291-8.
9. Binkley MS, Trakul N, Jacobs LR, et al. Colorectal Histology Is Associated With an Increased Risk of Local Failure in Lung Metastases Treated With Stereotactic Ablative Radiation Therapy. Int J Radiat Oncol Biol Phys 2015;92:1044-52.
10. Franceschini D, Cozzi L, De Rose F, et al. Role of stereotactic body radiation therapy for lung metastases from radio-resistant primary tumours. J Cancer Res Clin Oncol 2017;143:1293-9.
11. Aoki M, Hatayama Y, Kawaguchi H, et al. Stereotactic body radiotherapy for lung metastases as oligo-recurrence: a single institutional study. J Radiat Res 2016;57:55-61.
12. Baschnagel AM, Mangona VS, Robertson JM, et al. Lung metastases treated with image-guided stereotactic body radiation therapy. Clin Oncol (R Coll Radiol) 2013;25:236-41.
13. Baumann BC, Nagda SN, Kolker JD, et al. Efficacy and safety of stereotactic body radiation therapy for the treatment of pulmonary metastases from sarcoma: A potential alternative to resection. J Surg Oncol 2016;114:65-9.
14. Baumann BC, Bernstein KA, DeLaney TF, et al. Multi-institutional analysis of stereotactic body radiotherapy for sarcoma pulmonary metastases: High rates of local control with favorable toxicity. J Surg Oncol 2020;122:877-83.
15. Berkovic P, Gulyban A, Defraene G, et al. Stereotactic robotic body radiotherapy for patients with oligorecurrent pulmonary metastases. BMC Cancer 2020;20:402.
16. De Rose F, Cozzi L, Navarria P, et al. Clinical Outcome of Stereotactic Ablative Body Radiotherapy for Lung Metastatic Lesions in Non-small Cell Lung Cancer Oligometastatic Patients. Clin Oncol (R Coll Radiol) 2016;28:13-20.
17. Filippi AR, Badellino S, Guarneri A, et al. Outcomes of single fraction stereotactic ablative radiotherapy for lung metastases. Technol Cancer Res Treat 2014;13:37-45.
18. Helou J, Thibault I, Poon I, et al. Stereotactic Ablative Radiation Therapy for Pulmonary Metastases: Histology, Dose, and Indication Matter. Int J Radiat Oncol Biol Phys 2017;98:419-27.
19. Jingu K, Matsuo Y, Onishi H, et al. Dose Escalation Improves Outcome in Stereotactic Body Radiotherapy for Pulmonary Oligometastases from Colorectal Cancer. Anticancer Res 2017;37:2709-13.
20. Jung J, Song SY, Kim JH, et al. Clinical efficacy of stereotactic ablative radiotherapy for lung metastases arising from colorectal cancer. Radiat Oncol 2015;10:238.
21. Kessel KA, Grosser RCE, Kraus KM, et al. Stereotactic body radiotherapy (SBRT) in patients with lung metastases - prognostic factors and long-term survival using patient self-reported outcome (PRO). BMC Cancer 2020;20:442.

22. Kinj R, Bondiau PY, François E, et al. Radiosensitivity of Colon and Rectal Lung Oligometastasis Treated With Stereotactic Ablative Radiotherapy. Clin Colorectal Cancer 2017;16:e211-20.

23. Navarria P, Ascolese AM, Cozzi L, et al. Stereotactic body radiation therapy for lung metastases from soft tissue sarcoma. Eur J Cancer 2015;51:668-74.

24. Oh D, Ahn YC, Seo JM, et al. Potentially curative stereotactic body radiation therapy (SBRT) for single or oligometastasis to the lung. Acta Oncol 2012;51:596-602.

25. Osti MF, Carnevale A, Valeriani M, et al. Clinical outcomes of single dose stereotactic radiotherapy for lung metastases. Clin Lung Cancer 2013;14:699-703.

26. Qiu H, Katz AW, Chowdhry AK, et al. Stereotactic Body Radiotherapy for Lung Metastases from Colorectal Cancer: Prognostic Factors for Disease Control and Survival. Am J Clin Oncol 2018;41:53-8.

27. Ricardi U, Filippi AR, Guarneri A, et al. Stereotactic body radiation therapy for lung metastases. Lung Cancer 2012;75:77-81.

28. Ricco A, Davis J, Rate W, et al. Lung metastases treated with stereotactic body radiotherapy: the RSSearch® patient Registry's experience. Radiat Oncol 2017;12:35.

29. Rieber J, Streblow J, Uhlmann L, et al. Stereotactic body radiotherapy (SBRT) for medically inoperable lung metastases-A pooled analysis of the German working group "stereotactic radiotherapy". Lung Cancer 2016;97:51-8.

30. Siva S, Kirby K, Caine H, et al. Comparison of Single-fraction and Multi-fraction Stereotactic Radiotherapy for Patients with 18F-fluorodeoxyglucose Positron Emission Tomography-staged Pulmonary Oligometastases. Clin Oncol (R Coll Radiol) 2015;27:353-61.

31. Yamashita H, Niibe Y, Yamamoto T, et al. Lung stereotactic radiotherapy for oligometastases: comparison of oligo-recurrence and sync-oligometastases. Jpn J Clin Oncol 2016;46:687-91.

32. Zhang Y, Xiao JP, Zhang HZ, et al. Stereotactic body radiation therapy favors long-term overall survival in patients with lung metastases: five-year experience of a single-institution. Chin Med J (Engl) 2011;124:4132-7.

33. Hiraki T, Yamakado K, Ikeda O, et al. Percutaneous radiofrequency ablation for pulmonary metastases from hepatocellular carcinoma: results of a multicenter study in Japan. J Vasc Interv Radiol 2011;22:741-8.

34. Palussière J, Italiano A, Descat E, et al. Sarcoma lung metastases treated with percutaneous radiofrequency ablation: results from 29 patients. Ann Surg Oncol 2011;18:3771-7.

35. von Meyenfeldt EM, Prevoo W, Peyrot D, et al. Local progression after radiofrequency ablation for pulmonary metastases. Cancer 2011;117:3781-7.

36. Li X, Wang J, Li W, et al. Percutaneous CT-guided radiofrequency ablation for unresectable hepatocellular carcinoma pulmonary metastases. Int J Hyperthermia 2012;28:721-8.

37. Gillams A, Khan Z, Osborn P, et al. Survival after radiofrequency ablation in 122 patients with inoperable colorectal lung metastases. Cardiovasc Intervent Radiol 2013;36:724-30.

38. Petre EN, Jia X, Thornton RH, et al. Treatment of pulmonary colorectal metastases by radiofrequency ablation. Clin Colorectal Cancer 2013;12:37-44.

39. Matsui Y, Hiraki T, Gobara H, et al. Percutaneous radiofrequency ablation for pulmonary metastases from esophageal cancer: retrospective evaluation of 21 patients. J Vasc Interv Radiol 2014;25:1566-72.

40. Baba Y, Watanabe M, Yoshida N, et al. Radiofrequency ablation for pulmonary metastases from gastrointestinal cancers. Ann Thorac Cardiovasc Surg 2014;20:99-105.

41. de Baère T, Aupérin A, Deschamps F, et al. Radiofrequency ablation is a valid treatment option for lung metastases: experience in 566 patients with 1037 metastases. Ann Oncol 2015;26:987-91.

42. Ferguson J, Alzahrani N, Zhao J, et al. Long term results of RFA to lung metastases from colorectal cancer in 157 patients. Eur J Surg Oncol 2015;41:690-5.

43. Tongdee T, Tantigate P, Tongdee R. Radiofrequency Ablation of Lung Metastasis Not Suitable for Surgery: Experience in Siriraj Hospital. J Med Assoc Thai 2015;98:1019-27.

44. Wang Y, Lu X, Wang Y, et al. A prospective clinical trial of radiofrequency ablation for pulmonary metastases. Mol Clin Oncol 2015;3:559-62.

45. Wang Y, Lu X, Wang Y, et al. Clinical Effect of Percutaneous Radiofrequency Ablation for Residual Lung Metastases from Breast Cancer After Systemic Chemotherapy. J Coll Physicians Surg Pak 2015;25:602-5.

46. Fanucchi O, Ambrogi MC, Aprile V, et al. Long-term results of percutaneous radiofrequency ablation of pulmonary metastases: a single institution experience. Interact Cardiovasc Thorac Surg 2016;23:57-64.

47. Sato T, Iguchi T, Hiraki T, et al. Radiofrequency ablation of pulmonary metastases from sarcoma: single-center retrospective evaluation of 46 patients. Jpn J Radiol 2017;35:61-7.

48. Gonnet A, Salabert L, Roubaud G, et al. Renal cell

carcinoma lung metastases treated by radiofrequency ablation integrated with systemic treatments: over 10 years of experience. BMC Cancer 2019;19:1182.

49. Hiyoshi Y, Miyamoto Y, Kiyozumi Y, et al. CT-guided percutaneous radiofrequency ablation for lung metastases from colorectal cancer. Int J Clin Oncol 2019;24:288-95.

50. Hasegawa T, Takaki H, Kodama H, et al. Three-year Survival Rate after Radiofrequency Ablation for Surgically Resectable Colorectal Lung Metastases: A Prospective Multicenter Study. Radiology 2020;294:686-95.

51. Lassandro G, Picchi SG, Bianco A, et al. Effectiveness and safety in radiofrequency ablation of pulmonary metastases from HCC: a five years study. Med Oncol 2020;37:25.

52. Zhong J, Palkhi E, Ng H, et al. Long-Term Outcomes in Percutaneous Radiofrequency Ablation for Histologically Proven Colorectal Lung Metastasis. Cardiovasc Intervent Radiol 2020;43:1900-7.

53. Yuan Z, Wang Y, Zhang J, et al. A Meta-Analysis of Clinical Outcomes After Radiofrequency Ablation and Microwave Ablation for Lung Cancer and Pulmonary Metastases. J Am Coll Radiol 2019;16:302-14.

54. Hiraki T, Tajiri N, Mimura H, et al. Pneumothorax, pleural effusion, and chest tube placement after radiofrequency ablation of lung tumors: incidence and risk factors. Radiology 2006;241:275-83.

55. Cheng G, Shi L, Qiang W, et al. The safety and efficacy of microwave ablation for the treatment of CRC pulmonary metastases. Int J Hyperthermia 2018;34:486-91.

56. Ferguson CD, Luis CR, Steinke K. Safety and efficacy of microwave ablation for medically inoperable colorectal pulmonary metastases: Single-centre experience. J Med Imaging Radiat Oncol 2017;61:243-9.

57. Kurilova I, Gonzalez-Aguirre A, Beets-Tan RG, et al. Microwave Ablation in the Management of Colorectal Cancer Pulmonary Metastases. Cardiovasc Intervent Radiol 2018;41:1530-44.

58. Li L, Wu K, Lai H, et al. Clinical Application of CT-Guided Percutaneous Microwave Ablation for the Treatment of Lung Metastasis from Colorectal Cancer. Gastroenterol Res Pract 2017;2017:9621585.

59. Qi H, Wan C, Li X, et al. Computed tomography-guided percutaneous microwave ablation treatment for lung metastases from nasopharyngeal carcinoma. Indian J Cancer 2015;52 Suppl 2:e91-5.

60. Vogl TJ, Naguib NN, Gruber-Rouh T, et al. Microwave ablation therapy: clinical utility in treatment of pulmonary metastases. Radiology 2011;261:643-51.

61. de Baere T, Tselikas L, Woodrum D, et al. Evaluating

Cryoablation of Metastatic Lung Tumors in Patients-- Safety and Efficacy: The ECLIPSE Trial--Interim Analysis at 1 Year. J Thorac Oncol 2015;10:1468-74.

62. Yamauchi Y, Izumi Y, Kawamura M, et al. Percutaneous cryoablation of pulmonary metastases from colorectal cancer. PLoS One 2011;6:e27086.

63. Vogl TJ, Mekkawy AIA, Thabet DB, et al. Transvenous pulmonary chemoembolization (TPCE) for palliative or neoadjuvant treatment of lung metastases. Eur Radiol 2019;29:1939-49.

64. Londero F, Grossi W, Morelli A, et al. Surgery versus stereotactic radiotherapy for treatment of pulmonary metastases. A systematic review of literature. Future Sci OA 2020;6:FSO471.

65. Milosevic M, Edwards J, Tsang D, et al. Pulmonary Metastasectomy in Colorectal Cancer: updated analysis of 93 randomized patients - control survival is much better than previously assumed. Colorectal Dis 2020;22:1314-24.

66. Treasure T, Farewell V, Macbeth F, et al. The Pulmonary Metastasectomy in Colorectal Cancer cohort study: Analysis of case selection, risk factors and survival in a prospective observational study of 512 patients. Colorectal Dis 2021;23:1793-803.

67. Prud'homme C, Deschamps F, Moulin B, et al. Image-guided lung metastasis ablation: a literature review. Int J Hyperthermia 2019;36:37-45.

68. Ierardi AM, Carnevale A, Rossi UG, et al. Percutaneous microwave ablation therapy of renal cancer local relapse after radical nephrectomy: a feasibility and efficacy study. Med Oncol 2020;37:27.

69. Ierardi AM, Piacentino F, Pesapane F, et al. Basic embolization techniques: tips and tricks. Acta Biomed 2020;91:71-80.

70. Cao C, Wang D, Tian DH, et al. A systematic review and meta-analysis of stereotactic body radiation therapy for colorectal pulmonary metastases. J Thorac Dis 2019;11:5187-98.

71. Yilmaz MT, Elmali A, Yazici G. Abscopal Effect, From Myth to Reality: From Radiation Oncologists' Perspective. Cureus 2019;11:e3860.

72. Lewis SL, Porceddu S, Nakamura N, et al. Definitive Stereotactic Body Radiotherapy (SBRT) for Extracranial Oligometastases: An International Survey of >1000 Radiation Oncologists. Am J Clin Oncol 2017;40:418-22.

73. Dupuy DE, Zagoria RJ, Akerley W, et al. Percutaneous radiofrequency ablation of malignancies in the lung. AJR Am J Roentgenol 2000;174:57-9.

74. Floridi C, Carnevale A, Fumarola EM, et al. Percutaneous

Lung Tumor Biopsy Under CBCT Guidance with PET-CT Fusion Imaging: Preliminary Experience. Cardiovasc Intervent Radiol 2019;42:1644-8.

75. Vogl TJ, Shafinaderi M, Zangos S, et al. Regional chemotherapy of the lung: transpulmonary chemoembolization in malignant lung tumors. Semin Intervent Radiol 2013;30:176-84.

76. Vogl TJ, Wetter A, Lindemayr S, et al. Treatment of unresectable lung metastases with transpulmonary chemoembolization: preliminary experience. Radiology 2005;234:917-22.

77. Hori A, Ohira R, Nakamura T, et al. Transarterial chemoembolization for pulmonary or mediastinal metastases from hepatocellular carcinoma. Br J Radiol 2020;93:20190407.

78. Gadaleta CD, Solbiati L, Mattioli V, et al. Unresectable lung malignancy: combination therapy with segmental pulmonary arterial chemoembolization with drug-eluting microspheres and radiofrequency ablation in 17 patients. Radiology 2013;267:627-37.