Lung metastases from hepatocellular carcinoma: multidisciplinary approach—narrative review

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Objective: To describe and discuss the different treatment approaches concerning the management of lung metastasis from hepatocellular carcinoma (HCC).

Background: HCC is the sixth most commonly diagnosed cancer and the third leading cause of cancer related deaths worldwide. Lungs are the most common site of extrahepatic metastases from HCC. Opposite to local recurrence, extrahepatic metastasis has to be considered a terminal-stage cancer with poor prognosis.

Methods: The authors review the most recently published works regarding the different treatment approaches for lung metastasis from HCC.

Conclusions: In this article, the authors review the surgical management of lung metastasis from HCC, with a particular focus on the outcomes and prognostic factors associated with long term survival after resection. Pulmonary metastasectomy seems to be the most effective treatment with most of the published experiences reporting a 5-year survival rate ranging from 17% to 46%. Resection of lung nodules from HCC in well-selected patients (tolerable risk; feasibility of a complete resection; sufficient expected pulmonary reserve after surgery; primary tumor under control) has the potential of improving long-term survival. Main areas of controversy regard the selection of surgical candidates and the operative approach. Chemotherapy offers only a limited benefit in metastatic disease while other local ablative techniques and hybrid therapies have been described as palliative techniques. Moreover, the new therapeutic approaches are described. A multidisciplinary setting is of paramount importance for choosing the most appropriate treatment within each case.

Keywords: Hepatocellular carcinoma (HCC); lung metastases; surgery

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Introduction

Globally, hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer and the third leading cause of cancer related deaths worldwide in 2020, representing the second leading cause of cancer-related deaths in men and the sixth cause among women (1). Different approaches are considered in the treatment of HCC, such as curative hepatic surgery, liver transplantation, transcatheter hepatic arterial chemoembolization, radiotherapy including local ablation by radiofrequency or percutaneous ethanol injection, and chemotherapy also with targeted therapy, like sorafenib. The use of the aforementioned multimodality treatments has greatly improved the survival of patients affected by HCC (2).

Despite these different approaches, HCC has a high recurrence frequency rate, with Poon *et al.* reporting a cumulative 5-year recurrence rate of 75–100%, both in

terms of local relapse and distant metastasis (3). Lungs are the most frequent site of extrahepatic metastases (47%) followed by lymph nodes (45%), bone (37%) and adrenal glands (12%) (4). Opposite to local recurrence, extrahepatic metastasis has to be considered a terminal-stage cancer, and because of the lack of effective treatments prognosis continues to be poor. Indeed, for patients with extrahepatic metastasis the median survival is 9.6 months and the overall 1-, 3-, and 5-year survival rates are 31%, 7%, and 4% respectively (5).

Furthermore, concerning patients with untreated pulmonary metastases (PM), mean survival is 3.3 months from diagnosis (6). To further improve long-term survival of HCC patients, more active treatments of extrahepatic recurrence seem to be required. The aim of this review is to evaluate the significance of surgical resection for PM from HCC and the integration of surgery with other treatment options.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://asj.amegroups.com/article/view/10.21037/asj-21-54/rc).

Methods

A literature search was undertaken to identify published studies regarding treatment of PM from HCC. Candidate studies in English were sought for up to February 2021 via a computerized search of PubMed, Embase, Cochrane Central, Web of Science, and Google Scholar databases. Keywords and meSH terms entered in the search were 'pulmonary metastasectomy', 'pulmonary resection', 'lung metastases', 'surgical approach', 'radiation therapy', 'chemotherapy', 'Sorafenib', and 'Hepatocellular Carcinoma', or 'liver transplant'.

The reference lists of all the relevant retrieved articles were evaluated manually for further relevant studies.

Studies were considered for inclusion and further analysis on the basis of the following criteria:

(I) Patients diagnosed with lung metastases from HCC who received surgery, chemotherapy, radiation therapy or targeted therapy either alone or in combination;
(II) Randomized controlled trials or observational studies (cohort and case-control studies);
(III) Studies providing sufficient perioperative and oncologic outcome data.

Also, studies with inextractable data, review articles, editorials, comments, letters, case reports, and animal experimentation were excluded from analysis.

The study outcomes analyzed included: number of patients, number of lesions, surgical approach, overall survival (OS) (median), and disease-free survival (DFS) (median).

Two independent analysts (GZ and LM) identified the publications based on title and abstract according to the above-mentioned eligibility criteria. Any disagreement was resolved by a third analyst (GMC). Thereafter, the full texts of potentially relevant studies were reassessed to determine their conformity with the criteria. Relevant data from included articles were extracted and entered into a standardized data table. The following data were extracted from each included study: first author, publication year, treatment of primary tumor, median disease-free interval (DFI), number of lesions, number of patients, surgical approach and median OS. Survival data were extracted directly from the text. Information used to write this paper was collected from the sources listed in *Table 1*.

Discussion

Pulmonary metastasectomy for HCC

Advances in surgical techniques and perioperative management has markedly improved the survival rate of patients with HCC, however it hasn't been clarified the role of surgery for PM from HCC yet (40).

In thoracic surgery pulmonary metastasectomy is the second most frequently performed procedure after primary lung cancer surgery, and it represents a major part of thoracic surgeons profession (15–50%) (41). The original surgical indications for lung metastasectomy were proposed in 1965 by Thomford *et al.* (42) and summarized as follows: feasibility of a complete resection of all known disease; tolerable general and functional risk; primary tumor under control; no evidence of extrathoracic disease.

Although HCC was not included in the study of Thomford, subsequent studies reported pulmonary metastasectomy for HCC following criteria based on a modification of the principles of Thomford (12,18,21). For example, many authors agree that primary or recurrent HCC with synchronous PM shouldn't be considered as a contraindication for pulmonary resection if hepatic nodule is thought to be controllable, in patients with adequate general physical condition and sufficient expected pulmonary function after pulmonary metastasectomy (12,25,37).

Indeed, many patients with HCC with PM are not

Table 1 Summary of previously reported pulmonary metastasectomy for HCC

Authors	Patients (n)	Treatment of primary tumor	Median DFI (months)	Number of lesions	Surgical approach	Median survival (months)	Summary
Lam *et al.*, 1998, (7)	9	R (100%)	21.8	1 (100%)	NR	42	Report of long-term survival in highly selected patients with solitary PM
Chen *et al.*, 2004, (8)	6	R (100%)	17.5	1 (17%), ≥2 (83%)	NR	47.2 (mean)	For patients with multiple lung metastases in different lobes or different lungs, aggressive surgical resection is recommended if complete resection can be achieved
Gwak *et al.*, 2004, (9)	4	R (50%), Lx (50%)	10.3	1 (75%), ≥2 (25%)	NR	NR	Report of long-term survival was achieved after pulmonary metastatectomy in highly selected HCC patients
Nakamura *et al.*, 2004, (10)	2	R (50%), Lx (50%)	33	1 (50%), >2 (50%)	VATS (100%)	NR	Feasibility of pulmonary metastasectomy for selected patients with HCC, even those with multiple lung nodules as long as there is no concurrent liver recurrence
Nakajima *et al.*, 2005, (11)	20	R (95%), Lx (5%)	13.3 (mean)	1 (65%), ≥2 (35%)	VATS (50%), open (50%)	16	Favorable factors for HCC-free survival: negative liver cut-end involvement and multiple lung surgeries
Tomimaru *et al.*, 2006, (12)	8	R (100%)	32 (mean)	1 (50%), 2 (50%)	Open (100%)	29 (mean)	Survival of pulmonary metastasectomy resection group was better than non-resection group
Nakagawa *et al.*, 2006, (13)	25	R (100%)	16.3	1 (44%), 2 (25%), >2 (31%)	Open (100%)	51.8	Favorable factors for survival: DFI >12 months, AFP before metastasectomy <500 ng/mL
Kuo *et al.*, 2007, (14)	34	R (100%)	11.5	≤2 (47%), ≥3 (53%)	VATS (44%), open (56%)	56	Unfavoarble factors for survival: AFP ≥100 ng/mL, hepatic margin <1 cm, DFI <12 months
Koide *et al.*, 2007, (15)	14	R (100%)	NR	NR	NR	21.6	Favorable factor for survival: no history of transarterial chemoembolization
Bates *et al.*, 2008, (16)	5	LT (100%)	16.7	1 (100%)	VATS (20%), open (80%)	28	Survival times of patients who underwent to liver transplantation for HCC with PM are similar to those of patients who underwent to hepatectomy for HCC with PM
Chen *et al.*, 2008, (17)	12	R (83%), LT (17%)	12	1 (75%), 2 (25%)	VATS (67%), open (33%)	33	Favorable factor for survival: maximum PM size <3 cm
Kwon *et al.*, 2008, (18)	16	R (31%), LT (44%), interventional (25%)	14±4 (mean)	1 (56%), ≥2 (44%)	VATS (94%), open (6%)	20	Favorable factors for survival: liver transplantation, good differentiation of HCC, negative HBV infection
Kawamura *et al.*, 2008, (19)	61	R (100%)	28.7	1 (52%), 2 (25%), 3 (12%), 4 (3%), ≥5 (8%)	NR	NR	In multivariate analysis: survival of patients with number of lesions ≤2 was better than patients with three or more lesions

Table 1 (*continued*)

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Authors	Patients (n)	Treatment of primary tumor	Median DFI (months)	Number of lesions	Surgical approach	Median survival (months)	Summary
Liang *et al.*, 2008, (20)	12	R (100%)	28	1 (60%), >2 (40%)	NR	24	When intrahepatic recurrence is effectively controlled, HCC patients with 1 or 2 PMs might benefit from pulmonary resection and achieve prolonged survival
Lee *et al.*, 2010, (21)	32	R (66%), LT (3%), Lx (31%)	24.1	2.2±2.5 (mean; range, 1–13)	VATS (9%), open (91%)	10.7	Favorable factors in multivariate analysis: HCC controlled by surgery, number of lesions ≤2
Han *et al.*, 2010, (22)	41	R (69%), LT (29%), Lx (2%)	11	1 (46.3%), ≥2 (53.7%)	VATS (29%), open (71%)	77	Unfavorable factors for survival in multivariate analysis: presence of extrahepatic/extrapulmonary recurrence after pulmonary metastasectomy
Yoon *et al.*, 2010, (23)	45	R (100%)	NR	1.4±0.7 (mean; range, 1–4)	VATS (53%), open (47%)	40.7	Favorable factors for survival: first recurrence in lung, long DFI, solitary pulmonary mestastasis
Cho *et al.*, 2010, (24)	17	R (100%)	21.2	3.8 (mean; range, 1–17)	Open (100%)	28.9	Favorable factors for survival: AFP after metastasectomy <100 ng/mL, DFI >24 months
Kitano *et al.*, 2012, (25)	45	R (87%), LT (6%), Lx (7%)	14.3	1 (58%), ≥2 (42%)	VATS (69%), open (31%)	26.5	Unfavorable factors in multivariate analysis: history of recurrence and des-gamma-carboxy prothrombin >40 mAU/mL
Hwang *et al.*, 2012, (26)	23	LT (100%)	NR	1 (56.5%), ≥2 (43.5%)	NR	NR	After LT for HCC, surgery should be performed for resectable PM-HCC, because it may provide a chance of long term survival
Ohba *et al.*, 2012, (27)	20	R (60%), LT (15%), Lx (25%)	10.5	1 (55%), ≥2 (45%)	NR	NR	Both the overall and cancer specific survival rates were significantly worse for patients with AFP >500 ng/mL
Zhu *et al.*, 2013, (28)	34	R (100%)	NR	1 (100%)	NR	NR	Favorable factors: primary tumor controllable, no evidence of extra-hepatic or extra-pulmonary lesions, solitary PMs with a diameter <3 cm, no mediastinal lymph nodes metastasis, AFP <500 ng/mL
Zhou *et al.*, 2014, (29)	9	R (100%)	23	NR	NR	37	Surgical resection is a safe and effective treatment in patients with PM from HCC. Such long-term survival cannot be achieved by non-surgical treatment
Chok *et al.*, 2016, (30)	46	R (100%)	NR	NR	NR	40	In the unresectable group (sorafenib/chemotherapy) the median survival was 7.46 months, and 40.36 months in the resectable group
Ogawa *et al.*, 2015, (31)	7	NR	14	NR	VATS (100%)	41	Surgical resection of metachronous PMs is associated with a favorable outcome in selected patients
Kow *et al.*, 2015, (32)	30	R (100%)	12	NR	Open (100%)	30	Resection of lung metastasis improves survival in patients with resected HCC. Favorable outcomes could be obtained for peritoneal metastasis as well

Table 1 (*continued*)

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Authors	Patients (n)	Treatment of primary tumor	Median DFI (months)	Number of lesions	Surgical approach	Median survival (months)	Summary
Mizuguchi *et al.*, 2016, (33)	19	R (%), Lx (%)	18.1	1 (42%), ≥2 (58%)	NR	65	Surgical resection is a safe and effective treatment even in patients with multiple lung nodules from HCC. Repeated locoregional therapy for lung recurrence might help to improve OS
Takahashi *et al.*, 2016, (34)	93	R (100%)	17.0	1 (83%), ≥2 (17%)	NR	39	DFI is an independent prognostic factor in patients who undergo pulmonary resection for metastasis from HCC
Hau *et al.*, 2016, (35)	10	R (50%), LT (50%)	19.3	2 (median; range, 1–3)	VATS (40%), open (60%)	38.8	Pulmonary metastasectomy for HCC recurrence in lung can be performed safely with a reasonable morbidity even in immunosuppressed patients after LT
Kuo *et al.*, 2017, (2)	28	R (100%)	22.7	2.2±2.2 (mean)	VATS (43%), open (57%)	40	Favorable factors: remission status in the liver before pulmonary metastasectomy and long DFI
Hu *et al.*, 2017, (36)	26	R (100%)	17.6	<4 (88%), ≥4 (12%)	NR	28.2	Pulmonary metastasectomy might provide potential survival benefits in well selected PM-HCC patients who underwent liver transplantation
Nakamura *et al.*, 2019, (37)	30	NR	18.5	1 (60%), ≥2 (40%)	VATS (66%), open (33%)	25.0	Favorable factors: no evidence of viral hepatitis, solitary PM and no evidence of recurrence before metastasectomy
Wang *et al.*, 2019, (38)	103	NR	22	1 (72.8%), 2 (21.4%), ≥3 (5.8%)	VATS (84%), open (16%)	NR	Favorable factors: no liver recurrence, single site of PM, tumor size <2 cm, tumor located on one side or one lobe, long free-disease interval and maintenance of normal liver function
Invenizzi *et al.*, 2020, (39)	25	LT (100%)	34	1 (68%), 2 (20%), ≥3 (12%)	VATS (64%), open (36%)	51	Pulmonary metastasectomy could be efficacious in selected patients with isolated pulmonary HCC-recurrence after LT
Lee *et al.*, 2021, (40)	134	R (82.8%), Lx (17.2%)	19.1	1.0 (median; range, 1–11)	VATS (63%), open (37%)	38.7	Prognostic factors for OS: local recurrence of HCC, liver cirrhosis, and preoperative AFP level. VATS metastasectomy had outcomes comparable to those of open metastasectomy

HCC, hepatocellular carcinoma; DFI, disease-free interval; R, resection; Lx, locoregional therapies; LT, liver transplantation; NR, not reported; VATS, video-assisted thoracoscopic surgery; PM, pulmonary metastasis; AFP, alpha-fetoprotein; HBV, hepatitis B virus.

considered fit for surgery due to a reduced functional status, advanced disease stage and severe liver dysfunction (37).

Nowadays, the decision to proceed with surgical resection must consider the relative risks and benefits. For this reason, a multidisciplinary group should be discussing each case with a dedicated oncologist, surgeon, radiotherapist, radiologist and pathologist.

The aim of the surgery is to completely remove lesions preserving as much lung tissue as possible, therefore taking with it a 0.5- to 1.0-cm margin of normal lung tissue in all directions (R0 resection) (43). From a technical point of view, lung metastatic lesions are resected through wedge resection for peripheral lesions, whereas anatomical resections (segmentectomy, lobectomy or bilobectomy) are preferred when metastatic lesions are located deeper in the pulmonary parenchyma (lesion involving the lobar or pulmonary hilum) or in case of larger lesions or in the presence more nodules in same segment/lobe (12,37,40).

Standard thoracotomy is the preferred access for unilateral metastasis or as staged thoracotomies for bilateral lesions (44). An open approach consents an adequate visualization and access of the organ surface and the possibility to fulfill a whole lung parenchyma palpation to identify occult nodules undetected by preoperative computed tomography (CT) scan.

Video-assisted thoracoscopic surgery (VATS) has progressively become more popular for resection of pulmonary lesions since its introduction in the 1990s. Advantages of a minimally invasive approach include limited skin incision, a decrease in postoperative pain and hospitalization time (44). The most remarkable limitation is the difficulty lung palpation in its entirety, possibly leading to incomplete metastasectomy (45,46). Despite this limitation, VATS is being utilized more and more frequently; since the majority of PM are located peripherally, nodules are the perfect candidates for this technique while the use of localization techniques (hook wires, methylene blue injection, indocyanine green injection) makes it possible to resect also deeper metastases. In addition, VATS minimizes adhesion formation and makes repeated resection more feasible, especially for patients with chronic disease such as liver cirrhosis (40). Finally, in contrast to the inaccuracy of old-generation CT scans, new high-resolution CT (HRCT) has a higher detection rate of metastatic pulmonary nodules, possibly becoming a substitute for manual palpation (40). even if other studies show that manual palpation still has a higher detection rate (47).

Many studies have been published to date comparing thoracoscopic versus open surgery approach concerning lung metastases from colorectal cancer: case-matched studies showed that survival after VATS pulmonary metastasectomy is not inferior to open thoracotomy (48), and some authors even showed better OS using thoracoscopic metastasectomy than the open approach (49). A recent study by Markowiak *et al.* compared video-assisted pulmonary metastasectomy to thoracotomy, experiencing that histologically complete resection (R0) was achieved in 90.5% of patients who underwent VATS and thus was comparable to the resection status after thoracotomy. Moreover, VATS metastasectomy revealed to be equally successful to thoracotomy in regard to lymph node status, recurrence-free survival and OS (50).

Furthermore, in a study by Prenafeta Claramunt *et al.* no significant difference was noted in ipsilateral recurrence rates between VATS and open surgery considering the treatment of colorectal cancer lung metastases, so that VATS approach in the current era is widely accepted for resection of PM from colorectal cancer (51).

On the contrary, there is still a lack of studies specifically focusing on the best surgical approach to lung metastasectomy from HCC. Recently Lee *et al.* investigated surgical outcomes of HCC patients who underwent pulmonary metastasectomy according to the surgical approach, showing that VATS provides results comparable to those by open metastasectomy (thoracotomy or sternotomy) in terms of OS rate, DFS rate and pulmonary-specific DFS rate (40).

Concluding, VATS metastasectomy proved to have outcomes comparable to those of open metastasectomy (40,50), but conversion to open approach should still be considered if the lesion detected by CT-scan can't be palpated or resected by VATS approach. Further studies are still required on this topic. Regardless of the type of surgical approach used, the principal requirement for pulmonary metastasectomy remains radical resection of the lesion (40).

Lymph node dissection

According to a radiological study, HCC rarely metastasizes to mediastinal lymph nodes. Only 4.7% of extrahepatic metastasis are located in mediastinal lymph nodes and 0.6% are in subcarinal ones (52). Mechanisms for mediastinal lymph node involvement may be related to the intra-pulmonary lymphatic drainage of a lung metastasis from HCC or a direct spread from the hepatic portal region to the mediastinal lymph-nodes (53).

To date, there is no agreement concerning the need for dissection of the mediastinal lymph nodes during surgery

for PMs from HCC.

Kawamura *et al.* described only 4 cases (9%) of lymphatic metastases proven histologically in patients undergoing metastasectomy for HCC, but did not analyze the impact of positive lymph nodes on prognosis (19).

A study by Han *et al.* reported mediastinal lymph node dissection in 75% of cases of pulmonary metastasectomy in a series of 41 patients, and found 19.4% of patients presenting metastatic mediastinal lymph nodes. Hence it was concluded that dissection of mediastinal lymph nodes is required and should be carried out as a routine procedure in pulmonary metastasectomy for HCC (22). Despite this, mediastinal lymph nodes were not routinely dissected in most cases reported in literature, unless preoperative examination particularly through fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT scans identifies enlarged lymph-nodes (14,21,23,36,40,54), but no study focused on the impact that positive lymph nodes have on prognosis. Thus, it is advisable that more studies should be produced on this topic.

Prognostic factors after pulmonary metastasectomy

Over the last few years many authors aimed to evaluate the prognostic factors related to PM from HCC.

According to a recent work by Nakamura *et al.* three risk factors influence the prognosis in patients with lung metastasis from HCC: number of pulmonary nodules, viral hepatitis and presence of other site recurrence before pulmonary metastasectomy (37).

Regarding the number of lesions and based on the consideration that in most cases PM from HCC were multiple and, even when a metastasis seemed solitary, it was commonly supposed that occult metastases were present, PM from HCC were not considered amenable of surgical resection (55). Lam *et al.* were among the first who demonstrated that a prolonged survival is possible in selected patients after surgical resection of isolated PM from HCC reporting a median survival after lung resection of 42 months (7).

However subsequent studies showed conflicting results. Nakagawa *et al.* for instance, found that the number of lesions (single or multiple) and their location (unilateral or bilateral) showed no correlation to cancer-specific survival in a significant way (13).

On the contrary, in a study by Kuo *et al.*, bilateral distribution and multiple PM were described as adverse factors for DFS at univariable analysis, and only the number of PM was seen to be an independent prognostic factor at multivariable analysis (14). The same results were obtained by Kawamura *et al.*, in particular a stepwise regression analysis identified three or less PM to be an independent factor of better prognosis, with no other factors influencing the outcomes (19). Lee *et al.* showed that pulmonary metastasectomy in HCC patients might be beneficial if primary tumor was controlled by surgery and with less than three pulmonary nodules (21). Yoon *et al.* found that long DFI, lung as first site of recurrence and solitary PM were associated with better OS by univariate analysis (23).

More recently, in a retrospective study considering 103 patients who underwent surgical resection for PM from HCC, a correlation was highlighted between patients with a single lesion, tumor size <2 cm, tumor located on one side or one lobe, and a significantly better OS (38).

Secondly, with regard to viral hepatitis and hepatic status in general, absence of hepatitis B virus (HBV) infection was described as a favorable predictive factor for survival in a study by Kwon *et al.* (18). Indeed, median survival is longer for patients with a Child-Pugh score A at the moment of surgery (21), and the maintenance of normal liver function after pulmonary metastasectomy tends to be associated with favorable OS (38), whereas history of liver cirrhosis has been described as an independent negative prognostic factor (40).

Thirdly, it is widely accepted that the presence of extrahepatic/extrapulmonary recurrence is an unfavorable factor for survival. An analysis of recurrence by Han *et al.* revealed poorer survival rate in patients with recurrence in organs besides, liver or lung, which suggests that a scrupulous search for distant metastasis is necessary for patient selection before pulmonary metastasectomy (22). The proportion of patient with inoperable disease has increased in parallel with the development of PET, allowing for a better selection of surgical candidates (56).

Liver recurrence at the time of pulmonary metastasectomy is also significantly associated with unfavorable OS after surgery (38) and in a recent study by Lee *et al.* local recurrence or progression of HCC and high preoperative level of alpha-fetoprotein (AFP) were described to be independent negative prognostic factors (40).

Regarding the correlation between preoperative levels of AFP and OS after pulmonary metastasectomy, a study by Nakagawa *et al.* showed a mean survival of 15.9 months for patients with levels of AFP of 500 ng/mL or more, and 39.2 months for those with AFP less than 500 ng/mL (P=0.015) (13).

Similar results were obtained by Ohba *et al.*, who pointed

out that significantly poorer OS and cancer specific survival rates were acquired in patients with preoperative AFP ≥500 ng/mL in comparison to those with AFP <500 ng/mL (P<0.05) (27).

Furthermore, an AFP level after metastasectomy <100 ng/mL has been described as a favorable prognostic factor (14,24).

Almost of the studies are based on a small study population, prognostic factors should be seen with caution.

Pulmonary metastasectomy from HCC after liver transplantation

HCC is the only solid cancer that can be cured by transplantation, and this evidence completely changed the strategy of treatment for this tumor. Nonetheless, HCC recurrence post-transplant persists as the primary cause of death in these patients, associated with a high incidence of extrahepatic metastasis.

In one large, single center study, HCC-recurrences after liver transplantation has been detected in 18% of patients and in patients who experienced recurrence the 5-year survival was significantly worse (from 64% to 22%) but, despite shortened survival, significant benefit was described in patients who underwent surgical resection for recurrence (57).

Bates *et al.* retrospectively studied a cohort of five patients who underwent orthotopic liver transplantation for HCC and subsequent resection of the pulmonary recurrences, concluding that survival times of patients who underwent LT for HCC with PM treated by surgery are similar to those of patients who underwent hepatectomy for HCC with PM (16).

In a further assessment, Hwang *et al.* evaluate the effect of resection of PM from HCC after liver transplantation comparing outcomes in patients who underwent pulmonary metastasectomy after liver transplantation, and patients who did not due to multiple lung nodules (>5), comorbidity or residual extrapulmonary metastases (26). The OS rate was significantly improved in patients who underwent surgery, hence the conclusion that pulmonary metastasectomy should be performed for resectable PM-HCC, even following LT, as it may provide an improved chance of long-term survival.

More recently, an Italian multicenter experience considering 25 patient who developed PM after liver transplantation for HCC, showed that the 1-, 3-, and 5-year OS from pulmonary recurrence is about 100%, 66% and 43% respectively, with a median OS of 51 months after surgery (39). They concluded that in selected patients with solitary PM from HCC after LT and showing conserved hepatic function, surgical approach may be effective and that repeated pulmonary metastasectomies are not a risk factor for long-term survival in these patients (*Table 1*).

Non-surgical local ablative therapies

Radiation therapy is considered a palliative therapy that purposes to improve local control and reduce symptoms (58).

External beam radiotherapy (EBRT) is known as one of the most effective options for local control of lung cancer in patients unsuitable for surgical resection, but it has rarely been employed in lung metastatic cases from HCC, and published data on this topic is scarce. Some authors reported that PM from HCC is sensible to EBRT when administered at 50–60 Gy in conventional fractions, with an objective response observed by CT in 76.9% of subjects, leading to median progression-free survival for all patients of 13.4 months, and 2-year survival rate from PMs of 70.7%. Hence EBRT can be considered an effective palliative therapy with a reasonable safety in patients with multiple PMs that were not considered fit for surgery (58).

An additional study by Li *et al.* reported a series of 29 unresectable cases with PM from HCC that were treated using percutaneous CT-guided radiofrequency ablation sessions, and revealed that 1-, 3-, and 5-year OS rates were 71.6%, 27.9% and 9.3% respectively, with a median survival of 26.3 (range, 3–66) months (59).

Other studies showed that ^{125}I brachytherapy combined with sorafenib treatment in patients with multiple lung metastases guarantees an overall 1-, 2-, and 3-year survival rates of 100%, 50% and 12.5%, respectively, with a median survival time of 21 months (60). However, more recent studies, suggested that the combined therapy of sorafenib and radiotherapy lead to an overall incidence of adverse events in 93.3% of patients, and an incidence of severe adverse events in 20% of patients (61). To date there is a lack of information in literature regarding stereotactic radiotherapy in the treatment of HCC lung metastases (62). Li *et al.* performed a meta-analysis comparing pulmonary metastasectomy and stereotactic body radiotherapy (SBRT) in patients with PM from solid tumors, and no significant difference was observed between the two cohorts of patients in terms of OS and DFS rate (62). Moreover, SBRT was described as a good option for patients with PMs from colorectal cancer who refuse to undergo surgery

or considered medically inoperable (63). However, the small sample size, heterogeneity of SBRT protocols and incomparable follow-up periods between the two treatment groups together with the selection bias made the conclusions particularly weak.

Therefore, stereotactic ablative radiotherapy is an arising competitive treatment modality for the management of lung metastases but there is still no evidence of its specific efficacy in PM from HCC (63).

Chemotherapy

Despite extensive efforts, systemic therapy for recurrent HCC has proven ineffective (64,65), and metastatic HCC is generally considered a chemo-refractory tumor (66). Many drugs tested both as single agents or in combination have provided unsatisfactory results, never achieving solid evidence of efficacy.

In fact, for the patients with PM that underwent chemotherapy treatment median survival is 4.6–14 months and 1-year survival rate is only 20–42%, compared to a reported 24–41.4% and 5-year survival rate for patients that underwent metastasectomy (40).

These data can be explained by the difficulty to manage patients with PM from HCC as they commonly show advanced liver disease, so that systemic chemotherapy can rarely be successfully tolerated, and it must be considered that patients not qualifying for surgery generally present a more advanced disease and poorer performance status (67,68). Only in a retrospective study by Chok *et al.* (30) patients with resectable lung metastases from primary HCC were compared to patients deemed unresectable and treated with systemic therapy. Predictably, patients undergoing surgery showed a better OS than those with unresectable PM (31). However, it shouldn't be forgotten that the study was influenced by many biases, as previously mentioned (31).

Therefore, local treatments, when feasible, are always preferred to chemotherapy. Additionally, no data are available regarding the role of chemotherapic treatments before or after local therapies.

A novel treatment for PM from HCC is represented by targeted chemotherapy with sorafenib, a multikinase inhibitor approved for the treatment of advanced HCC only in 2008. Anyhow, published results are not homogeneous, and further research is needed.

Some authors validated the use of sorafenib in eradicating multiple lung metastasis, providing a new perspective for patients with recurrent HCCs (69).

In this case, a series of 602 patients with advanced HCCs receiving either sorafenib or placebo have been evaluated in the international phase III placebo-controlled sorafenib HCC assessment randomized protocol trial. Within the sorafenib group, the median OS was 10.7 months, and 7.9 months in the placebo group, and median time to progression was significantly less in patients receiving sorafenib than in those treated with placebo (70).

Despite this, systemic therapy with sorafenib revealed ample variability in terms of prolonged survival, even though not many patients truly profit from this therapy.

It is interesting to point out that, in the study by Chok *et al.* (30), among unresectable patients, no differences were noted in terms of survival in patients treated with first line sorafenib and patients with standard chemotherapy. Notably, in the former group the improvement in survival was very modest, and the percentage of response to sorafenib in the treatment of advanced HCC was low, 2–3% only (33).

Recently, multimodal therapies merging sorafenib and other treatments, like transarterial chemoembolization or everolimus have been evaluated (67,68). Apparent profits seem promising, but it is auspicable that the future advent of new effective systemic therapy will further improve the survival of the patients (71,72).

Another study by Xiong *et al.* investigated the effect of saracatinib (a tyrosine kinase inhibitor selective for Src) on PM from HCC, and results indicated that Src inhibition reduces lung metastases effectively (73).

Sheng *et al.* described in a case report the eradication of multiple bilateral lung metastases from HCC after ablation of primary tumor by transarterial infusion with recombinant adenovirus p53 gene (74).

Moreover, a study by Lu *et al.* investigated the effect and the underlying mechanisms of ZLDI-8, an inhibitor of ADAM-17 (a key cleavage enzyme of Notch pathway), that seems to inhibit the metastasis of HCC both *in vitro* and *in vivo* (75).

Other studies are trying to find new pathways to prevent and cure PM from HCC, and it is fundamental to increase research and trials in this area.

Conclusions

Despite the absence of randomized controlled trials, the results acquired from retrospective case-series suggest that surgical approach to PM from HCC is a valid treatment option.

Collectively, these studies indicate that resection of lung nodules from HCC in well-selected patients (tolerable risk; feasibility of a complete resection; sufficient expected pulmonary reserve after surgery; primary tumor under control) has the potential of leading to long-term survival.

Furthermore, the longer OS after pulmonary metastasectomy from HCC might be achieved in patients with a long DFI, reduced number of lung metastases (≤5 nodules), no presence of liver dysfunction or viral hepatitis at the time of surgery, and no presence of other sites of recurrence before metastasectomy. To date, there is no evidence in literature that open versus VATS approach or routine mediastinal lymph node dissection could present a real advantage in terms of survival, but more studies need to be done in this regard.

Assumed the relative shortage of effective systemic and target therapies, on the basis of available retrospective data, it seems legitimate to perform pulmonary metastasectomy for resectable lung nodules from HCC as it is the only treatment that may provide an improvement of long-term survival, in the hope that more effective therapies will be discovered in the near future.

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