



# New horizons in non-small-cell lung cancer patients with ipsilateral pleural dissemination (M1a): review of the literature

Hao Li<sup>#</sup>, Taorui Liu<sup>#</sup>, Zewen Sun, Zhenfan Wang, Xianping Liu, Fan Yang

Department of Thoracic Surgery, Centre of Thoracic Minimally Invasive Surgery, Peking University People's Hospital, Beijing, China

*Contributions:* (I) Conception and design: H Li, F Yang; (II) Administrative support: F Yang; (III) Provision of study materials or patients: H Li, T Liu; (IV) Collection and assembly of data: Z Wang, X Liu; (V) Data analysis and interpretation: Z Sun, T Liu; (VI) Manuscript writing: All authors. (VII) Final approval of manuscript: All authors.

<sup>#</sup>These authors contributed equally to this work.

*Correspondence to:* Fan Yang, MD. Department of Thoracic Surgery, Peking University People's Hospital, No. 11 Xizhimen South Street, Xicheng District, Beijing 100044, China. Email: yangfan@pkuph.edu.cn.

**Abstract:** Non-small cell lung cancer (NSCLC) with ipsilateral pleural dissemination (pM1a) is generally contraindicated for surgery owing to the extremely poor survival. However, some studies have demonstrated that primary tumor resection (PTR) may prolong the survival of these patients. Besides, with the development of systemic therapy, it is still hard to decide the best therapy model for pM1a patients. Thus, we reviewed essential studies about NSCLC with pleural disease and summarized the progress of new techniques in recent years, trying to provide promising new horizons about the management of pM1a patients. Firstly, we suggest performing PTR for highly selected pM1a patients, combined with appropriate systemic therapies and follow-up strategies. Secondly, hyperthermic intrathoracic chemotherapy (HITHOC) can control the symptoms and prolong the survival of NSCLC patients with malignant pleural effusion (MPE). It could also combine with PTR together. Finally, application of genetic testing and circulating tumor DNA (ctDNA) monitoring may furthermore make it possible for personalized management of pM1a patients in the future.

**Keywords:** Ipsilateral pleural dissemination; primary tumor resection (PTR); hyperthermic intrathoracic chemotherapy (HITHOC); circulating tumor DNA monitoring (ctDNA monitoring)

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## Introduction

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death around the world (1). Non-small-cell lung cancer (NSCLC) accounts for about 85% of lung cancer cases (2). Ipsilateral pleural dissemination is a special status of NSCLC which means tumor spread or metastasize to the ipsilateral pleural cavity, including malignant pleural/pericardial effusion and nodules, are defined as T4-IIIb in the sixth edition of the Union for International Cancer Control (UICC) lung cancer staging system (3). However, further survival data showed those patients have a similar poor prognosis as contralateral lung nodules, with median survival time (MST) of 4–11.5 months and a 5-year survival rate of

3–10% (4,5). Therefore, they are reclassified as M1a (stage IVA) together in the 7<sup>th</sup> edition of the lung cancer staging system (4).

Owing to the poor survival, NSCLC patients with ipsilateral pleural dissemination lesions (pM1a) were recommended to receive systemic treatment according to all current guidelines, while surgical intervention has been considered as contraindicated (6-10). However, those patients have great heterogeneity regarding different pleural extension severity. Their clinical features range from a single nodule with localized pleural nodules to huge mass concomitant with diffused seeding or obvious malignant pleural effusion (MPE) (11). There is still no uniform

therapy model applicable to all pM1a patients, making the treatment of pM1a patients full of controversy and challenges.

Recently, the survival of pM1a patients prolonged a lot with the development of systemic therapy, including targeted therapy and immune therapy. The progress of minimally invasive surgical technique makes surgery recapture an important role as a component of multimodal treatment. Besides, symptomatic treatments such as hyperthermic intrathoracic chemotherapy (HITHOC) achieve a positive effect and attract a lot of attention. Advances in diagnostic technology and genetic testing also lead researchers to explore genetic differences among pM1a patients (12), thereby making dynamic monitoring of tumor burden and personalized treatment possible in the future. In the following sections of this review, we will summarize the latest progress and provide promising new horizons about the management of pM1a patients. We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-6188>).

## Methods

PubMed was searched for the resulting articles referenced to create this review. Additional articles were included to summarize the existing literature or provide sufficient background.

## Results

### *The value of primary tumor resection (PTR) of pM1a patients*

As early as the 1990s, Reyes *et al.* (13) firstly report the result of neoadjuvant chemotherapy followed by extrapleural pneumonectomy (EPP) to treat pleural dissemination disease. Yamaguchi *et al.* (14) then designed a phase II trial to assess the effect of preoperative concurrent chemoradiotherapy followed by EPP. However, because of the slow registration pace, this trial was prematurely terminated after involved only 11 patients. Long-term follow-up showed a 5-year disease-free survival (DFS) rate as 11.1% and 5-year overall survival (OS) rate as 22.2%. Recurrence developed in 88.9% of patients who underwent EPP. With the deep understanding of pleural dissemination, EPP had almost abandoned by surgeons. Thus in the last decade, surgeons concentrated more on cytoreductive

surgery like PTR, but not radical resection for pM1a patients, and combination of systemic therapy to prolong patients' OS.

Thoracic surgeons usually encountered two different clinical scenarios about pM1a NSCLC patients. The first one was patients who staged as resectable preoperatively were diagnosed pleural dissemination unexpectedly during surgery [clinical stage M0 (cM0)]. Surgeons should decide on whether to continue the operation or perform biopsy only. Generally, these patients were characteristic as localized pleural seeding or minor MPE couldn't be detected by preoperative imaging examination. So some surgeons tried to perform PTR for these patients instead of exploratory only. Another scenario was that MPE or pleural seeding had already been detected by preoperative staging procedures [clinical stage M1a (cM1a)]. In this scenario, surgical intervention was mainly performed for diagnostic biopsy and symptomatic relief. We will review the application of PTR in different types of clinical scenarios.

### *For cM0 patients*

The majority of studies on surgical intervention in pM1a patients have focused on cM0 patients. The earliest study on PTR for pM1a patients accidentally found during surgery was a multicenter retrospective study conducted by Ichinose *et al.* (15) in 2000. They involved a total of 227 cases of NSCLC patients found pleural dissemination at thoracotomy through a multicenter questionnaire survey of the Japan clinical oncology group (JCOG). One hundred and ninety-four patients of the whole cohort underwent surgical resection, while thoracotomy alone without resection was performed for the other 34 patients. The resection group put up a significantly better survival compared with exploratory group (5-year OS 14.9% *vs.* 0%). The authors further analyzed the outcome of 100 patients with minimal carcinomatous pleuritis in PTR group. These patients yielded an unexpectedly good prognosis, with an MST of 20.6 months and the 3- and 5-year survival rates of 31.8% and 22.8%, respectively (16). This study proposed that PTR may bring survival benefits for patients with mild thoracic dissemination. However, Sawabata *et al.* (17) then reported a similar study but presented the opposite result. They found that patients with malignant minor pleural effusion detected at thoracotomy, even with complete gross resection of the tumor, had an MST of only 13 months. The opposite conclusions of the two similar studies might due to the differences in adjuvant treatment and surgical methods.

Then, in the last two decades, several single-center retrospective studies with sample sizes ranging from 25 to 138 also reported outcomes of unexpected M1a patients undergoing PTR, with MSTs ranging from 15–64 months and 3-year OSs ranging from 34.2% to 82.9%, 5-year OSs ranging from 16.3–42.7%, respectively (18–27). Most studies supported PTR as a significant prognostic factor for better survival for patients intraoperatively diagnosed as M1a. More details of these studies were listed in *Table 1*. There were trends in the increasing rate of minimally invasive surgery and normalized systemic treatment. For example, Li *et al.* (26) included 43 patients with lung adenocarcinoma with pleural seeding diagnosed unexpectedly during surgery using a prospectively collected database. PTR was performed in 30 patients while the remaining 13 patients underwent pleural nodule biopsy alone. The rate of video-assisted thoracoscopic surgery (VATS) was about 97.7% (n=42). Twenty-nine patients received epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) therapy (76%). The patients undergoing PTR demonstrated an extremely good survival, with an MST of 64 months, 3-year progression-free survival (PFS) of 44.5%, and 3-year OS of 82.9%. In the most recent study of Park *et al.* (27) from Seoul National University Hospital, 130 unexpected M1a patients were included. One hundred and ten patients (84.6%) administered systemic treatment. The result showed that 5-year OS of the PTR group was superior to the biopsy group (34.7% *vs.* 15.9%,  $P=0.016$ ). PTR only played a significant prognostic role in patients who received systemic treatment (5-year OS 40.0% *vs.* 17.2%,  $P=0.009$ ).

Besides these single-center retrospective studies, in 2016, Xu *et al.* (28) reported a meta-analysis reviewed nine retrospective studies with a total number of 861 unexpected pM1a patients to compare the survival benefit between exploration and PTR. The result showed PTR was a significant favorable predicted factor (HR =0.443; 95% CI: 0.344–0.571;  $P<0.001$ ). Female and lower N stage were also suggested to be beneficial prognostic factor. A most recent meta-analysis reported by Deng *et al.* (29) in 2020 included several newly published studies and drew a simple conclusion. These two meta-analyses were the strongest data supporting PTR superior to exploratory surgery for patients with unexpected pleural metastasis detected during operation till now.

### ***For cM1a patients***

Only a few studies concentrated on PTR for cM1a NSCLC

patients. Several retrospective studies included M1a patients diagnosed both preoperatively and intraoperatively. Iida *et al.* (30) demonstrated that the 5-year OS of 256 patients with pleural carcinomatosis who had received PTR was 33.1% in a multicenter questionnaire survey of JCOG. Best stage nodal status ( $P=0.002$ ) and complete macroscopic resection ( $P=0.013$ ) were independent predictors of survival. In 2015, Liu *et al.* (31) retrospectively analyzed the effectiveness of PTR in 80 M1a patients (including nine contralateral lung nodules) and found that the 5-year OS reached 31%. These researches indicated that selected clinical M1a patients can still benefit from PTR combined with appropriate systemic treatment, suggesting that surgery can be used as a part of comprehensive multimodal treatment. Unfortunately, the sample sizes were limited, and no patients received genetic testing or targeted therapy.

The opening of public databases helped solve the limitation of sample size. In 2016, using the SEER database, Ren *et al.* (32) found that the prognosis of NSCLC patients with ipsilateral MPE after PTR may be better than expected (MST: 20 *vs.* 7 months,  $P<0.001$ ). Nevertheless, patients with pleural nodules and pericardial effusion were excluded from the study. Recently, we further analyzed 5,513 pM1a patients from the SEER database, among which 309 patients underwent PTR (33). Surgery was associated with improved OS in the entire cohort and surgery-recommended cohort, both before and after 1:3 propensity score matching (PSM). The multivariable analysis suggested that PTR was an independent favorable prognostic factor for both OS (HR: 0.56, 95% CI: 0.48–0.54,  $P<0.001$ ) and lung-cancer specific survival (SHR: 0.60, 95% CI: 0.51–0.70,  $P<0.001$ ). Further subgroup analysis showed that except for patients with pericardial effusion ( $P=0.065$ ) or N3 disease ( $P=0.17$ ), PTR was independently associated with prolonged survival in all subgroups (33). These studies are summarized in *Table 2*.

### ***Surgery for patients with different genetic mutations***

In the last 10 years, targeted therapy, such as TKIs for EGFR or anaplastic lymphoma kinase (ALK), significantly improved the survival of driver-oncogene positive stage IV NSCLC patients (35). According to previous literatures, adenocarcinoma is the most common histology subtype in pM1a patients, with a prevalence of 64% to 90.9% (15,17–25,27,30,31,33,34). Thus, pM1a patients are likely to benefit from targeted therapy. Li *et al.* (26) reported an extremely good survival of lung adenocarcinoma patients with unexpected pleural seeding undergoing PTR (MST:

**Table 1** Surgical outcomes in NSCLC patients with unexpected pleural metastasis

Studies	Patient number (PTR/biopsy only)	Inclusion criteria	Ade, %	Surgical method (VATS/thoracotomy), n	OS (PTR/biopsy only)	Neoadjuvant treatment, %	Intrathoracic chemotherapy, %	Adjuvant treatment, %	MST (PTR/biopsy only), mo	Significant prognostic factors
Ichinose (15), 2000	227 (193/34)	Carcinomatous Pleuritis found at thoracotomy	78	0/193	3-year OS 28.8%/10.9%; 5-year OS 14.9%/0%	NA	47	56.8 (chemotherapy)	NA	PTR
Ichinose (16), 2001	100 (100/0)	Carcinomatous pleuritis of minimal disease	74	0/100	3-year OS 31.8%; 5-year OS 22.8%	NA	47	57 (chemotherapy)	20.6	Patients underwent PTR showed a good prognosis
Fukuse (18), 2001	49 (39/10)	MPE detected on thoracotomy	73.5	0/49	NA (only reported OS of the whole cohort)	0	100	100 (chemotherapy); 6 (radiotherapy)	23.2–37.8/6.2	PTR in T1–2 without pleural dissemination
Sawabata (17), 2002	43 (25/11)	Minor MPE detected on thoracotomy	88.4	0/43	5-year OS 9–10%/0%	NA	NA	NA	13–34/17	None (PTR is not beneficial for survival)
Wang (19), 2011	138 (90/48)	Unexpected pleural metastasis	79.7	0/138	3-year OS 34.2%/13.2%; 5-year OS 23%/5.3%	5.1	NA	NA	NA	PTR; N 0/1 status
Mordant (20), 2011	70 (32/38)	Unexpected pleural metastasis	65.6	0/32	5-year OS 16.3%/0%	NA	NA	84.3 (chemotherapy)	15/13	None
Okamoto (21), 2012	73 (73/0)	Unexpected pleural metastasis	84.9	0/73	3-year OS 41.4%; 5-year OS 23.7%	NA	NA	NA	25.9	N0–1
Go (22), 2015	25 (25/0)	Unexpected pleural metastasis	64	0/25	5-year OS 22.2%	NA	80	60	18	PTR; N0 status
Yun (23), 2018	78 (36/42)	Unexpected pleural metastasis	87.2	0/78	3-year OS 66.7%/41.1%; 5-year OS 42.7%/15.2%	3.8	NA	91 (chemotherapy); 59 (targeted therapy); 14 (radiotherapy)	52/33	PTR

**Table 1** (continued)

Table 1 (continued)

Studies	Patient number (PTR/biopsy only)	Inclusion criteria	Ade, % thoracotomy)	Surgical n	OS (PTR/biopsy only)	Neoadjuvant treatment, %	Intrathoracic chemotherapy, %	Adjuvant treatment, %	MST (PTR/biopsy only), mo	Significant prognostic factors
Ren (24), 2016	83 (62/21)	Unexpected pleural metastasis	65	19/64	3-year OS 45.8%/11.8%	0	NA	63.9 (chemotherapy); 10.8 (targeted therapy)	35/17	PTR; adenocarcinoma; dry pleural dissemination
Li (25), 2017	110 (62/48)	Unexpected pleural metastasis	90.9	0/110	3-year OS 69.4%/41.7%; 5-year OS 31.7%/19.5%	11.8	NA	NA	49.0/29.4	PTR
Li (26), 2018	43 (30/13)	Unexpected pleural metastasis	100	42/1	3-year OS 82.9%/38.5%	20.9	0	48.8 (chemotherapy); 67.4 (targeted therapy); 16.3 (radiotherapy)	64/35	PTR
Park (27), 2020	130 (40/90)	Unexpected pleural metastasis	83.8	NA	3-year OS 69.4%/41.7%; 5-year OS 34.7%/15.9%	NA	NA	73.8 (chemotherapy); 55.4 (targeted therapy)	NA	PTR; systemic treatment; low N stage; adenocarcinoma

NSCLC, non-small cell lung cancer; PTR, primary tumor resection; Ade, adenocarcinoma; VATS, video-assisted thoracoscopic surgery; OS, overall survival; MST, median survival time; MPE, malignant pleural effusion; NA, not available.

**Table 2** Surgical outcomes in pM1a patients (without dividing preoperative or intraoperative M1a)

Studies	Patient number (PTR/biopsy only), n	cM0/cM1	Inclusion criteria	Ade, %	EGFR-TKIs, %	OS (PTR/biopsy only)	Neoadjuvant treatment, %	Adjuvant treatment, %	MST (PTR/biopsy only), mo	Significant prognostic factors
Hanagiri (34), 2012 <sup>†</sup>	17 (17/0)	13/4	Stage IV NSCLC	NA	NA	5-year OS 25.3%	NA	NA	NA	NA
Iida (30), 2015	313 (256/57)	232/81	NSCLC patients with pleural carcinomatosis	77.5	NA	5-year OS 33.1%	3.8	57.5 (chemotherapy); 6 (radiotherapy)	23.2–37.8/6.2	ECOG performance status; N status; absence of gross residual tumor
Liu (31), 2015 <sup>‡</sup>	80 (80/0)	NA	M1a patients	68.8	0	5-year OS 31.2%	NA	82.5 (chemotherapy)	34.3	Smoking status; adjuvant treatment
Ren (32), 2016	2,217 (128/2,089)	NA	MPE	50	NA	NA	NA	NA	20/7	PTR
Li (33), 2019	5,513 (309/5,204)	NA	pM1a	71.6	NA	5-year OS 9–10%/0%	NA	NA	20/8	PTR

<sup>†</sup>, This study included 36 patients undergoing surgical resection for stage IV NSCLC, of which 17 patients compared with pleural dissemination. So some data was not available for individual M1a patients. <sup>‡</sup>, this study included also included nine patients with contralateral lung nodules. PTR, primary tumor resection; Ade, adenocarcinoma; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; OS, overall survival; MST, median survival time; NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; NA, not available; MPE, malignant pleural effusion.

64 months). One important reason for the inspiring result was their good use of EGFR-TKIs (76%). However, do we still need to perform PTR among EGFR mutation-positive patients who can have excellent survival with only EGFR-TKIs therapy? Since previous studies had demonstrated that tumor heterogeneity played an important role in acquired resistance of EGFR/ALK-TKIs (36), could PTR reduce tumor burden and heterogeneity to enhance the effect of targeted therapy? Whether PTR is beneficial for different driver oncogene-status patients is an interesting unanswered question.

Our recent study tried to answer it. We included 105 pM1a patients treated in our department between 2006 and 2016, of which 70 patients received genetic testing. Fifty-five patients were positive for driver-oncogene mutations, while the other 50 patients with oncogenes unknown/negative. A total of 54 patients received targeted therapy (except for one patient with ROS1 arrangement refused targeted therapy). In the targeted therapy subgroup, PTR did not prolong OS (MST: 57.1 vs. 50.4 months, P=0.840).

However, in the non-targeted therapy group, PTR significantly prolonged survival (MST: 39.8 vs. 14.2 months, P=0.002) (37). This single-center retrospective study suggested PTR conferred a better outcome in M1a patients who were not candidates for targeted therapy. However, the evidence is still insufficient, and further researches are needed to solve this question. It may also be one of the future research directions in this field.

At present, there are several problems in the researches of PTR for pM1a patients: (I) most studies were retrospective studies with limited sample size, providing not strong enough evidence to change the routine clinical practice; (II) the criteria of appropriate pM1a patients for PTR are still unclear. Although previous studies provided some favorable prognostic factors for pM1a patients performed PTR, it is still difficult to generalize them to all pM1a patients for the circumscribed conclusions; (III) there are few studies regard to the most appropriate surgical resection extension under the multimodal treatment model. Surgeons are still confused about

whether to perform lobectomy or sublobar resection with unexpected pleural metastasis detected during operation. Future larger sample prospective clinical trials are still needed to solve the above questions.

### HITHOC for M1a NSCLC patients

Traditional symptomatic treatment for pleural dissemination includes thoracentesis, thoracic drainage, pleural fixation and so on. Effective control of pleural effusion in MPE patients treated by these therapies was about 82–100% according to the previous literature (38,39). Mainly disadvantages of these treatments were high rate of effusion recurrence and complications. Thoracic hyperthermic perfusion therapy was an emerging technology that used physical methods to heat the perfusion fluid and pour it into the thoracic cavity. This technique could keep the thoracic cavity at a certain temperature and persist for a while, achieving the effect of killing tumor cells and preventing MPE (40). Adding platinum or other chemotherapeutics to the hyperthermic perfusion can enhance the therapeutic effect. This was called HITHOC. The mechanism of HITHOC consist reducing the activity of malignant cells by hyperphysiological temperature and exposing tumor cell to high concentrations of chemotherapeutics (41).

Treating NSCLC patients with MPE were one of the important applications of HITHOC. Several studies reported the result of HITHOC using in M1a patients. In 2017, Hu *et al.* (42) reported a retrospective study involved 54 cases of pM1a patients with MPE. HITHOC was performed under VATS, and pleural biopsies were performed both before and after treatment. All patients received complete response of pleural effusion. Apoptosis of malignant tissue can be microscopically detected after HITHOC. Further follow-up showed good prognosis, with an MST of 21.7 months and 1-year survival rate of 74.1%. Zhou *et al.* (43) conducted a systematic review and meta-analysis comparing the survival of MPE patients between HITHOC group and non-HITHOC group. The results showed that HITHOC significantly prolonged survival of patients with MPE (Hedges  $g=0.763$ ,  $P<0.001$ ). However, the specific rate of NSCLC was unclear. A most recent prospective randomized trial reported by Kleontas *et al.* (44) evaluated the survival difference between HITHOC and talc pleurodesis for NSCLC patients with ipsilateral MPE. They included 20 patients for each group, and no significant difference was found between two groups (MST: 8 *vs.* 9 months,  $P=0.843$ ). This study suggested both HITHOC and talc pleurodesis were equally effective and

safe options. The above studies all supported that HITHOC as an effective treatment for pM1a patients with MPE.

HITHOC under VATS can combine cytoreduction, hyperthermia, and chemotherapy, achieving the purpose of diagnosis and treatment at the same time. Thoracic surgeons sometimes see a direct invasion of the parietal pleura but sometimes they see intraoperatively disseminated nodules on the parietal and mediastinal pleura which can vary from 3,4 to more than 20. When there is a direct invasion and a few disseminated nodules, the decision to proceed with surgery is easy; on the opposite, it is more difficult when there are many disseminated nodules on parietal and mediastinal pleura, or with subsequent MPE. In this circumstances, we prefer to go ahead with the operation if the patient is suitable for HITHOC procedure.

Therefore, some thoracic surgeons tried to compare whether PTR under VATS plus HITHOC can bring more survival benefits to pM1a patients. Yi *et al.* (45) reported a retrospective study that involved 33 pM1a patients (22 cases of cM1a and 11 cases of cM0). Twenty-three cases of the whole cohort underwent HITHOC after PTR, while the other ten patients only underwent PTR. The results showed that the OS of the HITHOC group was significantly longer than that of the PTR alone group (5-year OS 38.6% *vs.* 37.5%,  $P=0.045$ ). In 2019, a systematic review reported by Migliore *et al.* (46) shown favorable outcomes for N0–1 NSCLC patients with MPE undergoing PTR plus HITHOC, with an MST of 18 months and 2-year OS of 28.5%. These studies suggested that PTR combined with HITHOC can be an effective surgical intervention for selected pM1a patients to improve the quality of life and prolong life expectancy. Studies about HITHOC for pM1a patients were listed in *Table 3*.

Taken together of those previous studies, we would like to propose a surgical therapeutic strategy for M1a NSCLC patients as follows. (I) For cM0 but pathological staging pM1a patients, which means “unexpected” pleural dissemination during surgery, surgeons should try to resect the main tumor to prolong patients’ survival and harvest enough tissue for gene testing. (II) For clinical staging pM1a patients, such as MPE confirmed by cytopathology, surgical intervention should be carefully included as an important option of multimodal therapy regimens, especially for patients with negative driver mutations and lymph node-negative (37). (III) The surgery would only be considered in operable patients, and should be relatively contraindicated for patients with N2/N3 metastasis or malignant pericardial effusion because of the poor survival after PTR (33). (IV) To

**Table 3** Effect of HITHOC for pM1a patients

Studies	Patient number	Inclusion criteria	Subgroups	Recurrence rate of effusion, %	OS, %	MST, mo
Kimura (40), 2010	19	pM1a NSCLC patients	PTR + IIH, n=7	0	NA	Not reach
			PTR + HITHOC, n=5	20	NA	41
			PTR only, n=7	NA (median pleural-free survival time 3 months)	NA	25
Yi (45), 2016	33	pM1a NSCLC patients	PTR + HITHOC, n=23	NA	3-year OS 38.6%	NA
			PTR only, n=10	NA	3-year OS 37.5%	NA
Hu (42), 2017	54	pM1a NSCLC patients	HITHOC, n=54	NA	1-year OS 74.1%	21.7
Feng (41), 2018	80	MPE	HITHOC, n=80	28.7	1-year OS 82.5%; 2-year OS 23.8%	16.8
Kleontas (44), 2019 <sup>†</sup>	40	NSCLC patients with ipsilateral MPE	HITHOC, n=20	NA	NA	8
			Talc pleurodesis, n=20	NA	NA	9
Migliore (46), 2019 <sup>‡</sup>	21	NSCLC patients with N0–1 and MPE	PTR + HITHOC, n=21	NA	1-year OS 62%; 2-year OS 28.5%	18

<sup>†</sup>, this study contained 65 NSCLC patients; <sup>‡</sup>, this study was a systematic review. HITHOC, hyperthermic intrathoracic chemotherapy; IIH, intraoperative intrathoracic hyperthermotherapy; OS, overall survival; MST, median survival time; MPE, malignant pleural effusion; PTR, primary tumor resection; NA, not available.

make patients receive systemic therapy sooner, thoracic surgeons should consider the VATS technique superior to thoracotomy. Sublobar resection or lobectomy may be superior to pneumonectomy with a similar survival benefit but fewer complications (33). (V) Apart from the resection of primary tumor, intrathoracic hyperthermotherapy or hyperthermo-chemotherapy should also be considered to prevent MPE and improve the quality of life of pM1a patients with malignant pleural dissemination (46).

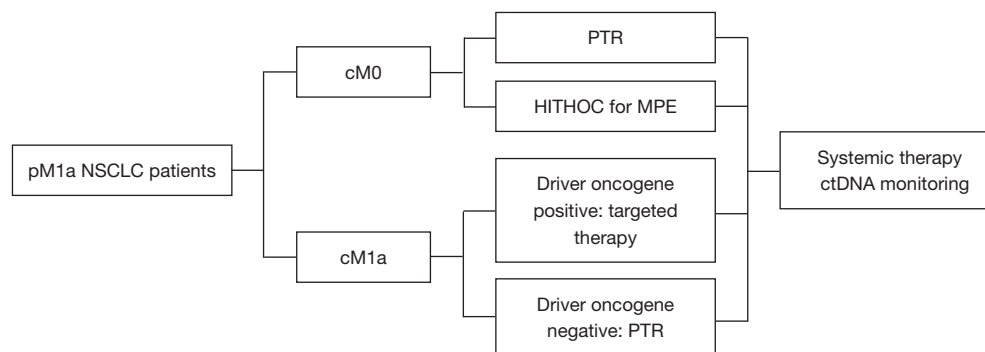
### Management of post-surgery pM1a NSCLC patients

Although most studies recommended systemic treatment after PTR, such as chemotherapy, targeted therapy, and immune therapy, some investigators proposed a wait-and-see treatment strategy due to the observation of gradual progression in some pM1a patients (12). Chen *et al.* (12) retrospectively studied 131 pM1a patients with a diagnosis of special pleural dissemination lesions after PTR. The patients who received chemotherapy or targeted therapy after the wait-and-see strategy showed better OS than for those who received systematic therapy immediately (not reached *vs.* 41.7 months, HR: 0.45, 95% CI: 0.23–0.88, P=0.019). The whole-exome sequencing analysis of

the ten patients with dramatic progression and 13 patients with gradual progression showed that low genomic instability index was significantly associated with better PFS (P=0.016) (12). This study demonstrated that significant heterogeneity of disease progression exists within pM1a patients. The wait-and-see strategy could be considered for special pM1a patients with gradual progression.

The critical issues of the appropriate treatment strategy selection for post-surgery pM1a patients are finding out patients with rapidly progressive diseases. Particularly, the traditional radiological examinations, such as chest CT and PET-CT, could not evaluate tumor burden well due to the loss of evaluable lesions after main tumor resection. Recently, circulating tumor DNA (ctDNA), namely short DNA fragments shed by tumor cells from multiple tumor regions, has been proven capable of accurately assessing minimal residual disease (MRD) and identifying patients who might be at higher risk of relapse (47). Recently, we prospectively studied perioperative dynamic changes of ctDNA (DYNAMIC) and revealed that the median ctDNA half-life was only 35.0 minutes (48,49). The recurrence-free survival of patients with detectable and undetectable ctDNA concentrations on the third day after R0 resection was 278 and 637 days, respectively (P=0.002) (49). Longitudinal





**Figure 1** Management of pM1a patients. NSCLC, non-small cell lung cancer; cM0, clinical stage M0; cM1a, clinical stage M1a; PTR, primary tumor resection; HITHOC, hyperthermic intrathoracic chemotherapy; MPE, malignant pleural effusion; ctDNA, circulating tumor DNA.

ctDNA monitoring showed that the ctDNA changes were correlated with treatment response well and predicted disease progression accurately (49). ctDNA monitoring could be applied to guide the appropriate treatment strategy selection for pM1a patients in the future, especially for patients received main tumor resection. Hence, we conducted an open-label, multicenter, prospective, observational study in which advanced NSCLC patients will be recruited and longitudinal changes in ctDNA levels with changes in radiology will be assessed in order to determine the clinical utility of ctDNA monitoring (50). The study is still in progress, and we hope its result can provide more guidance for treatment strategies development and dynamic monitoring of pM1a patients. Surgical therapeutic strategy and post-surgery management of pM1a patients are summarized as *Figure 1*.

## Conclusions

Overall, NSCLC patients with ipsilateral pleural dissemination have a poor prognosis, and there is still no uniform therapy model for these patients. By reviewing the previous studies, we proposed the treatment of pM1a patients in different clinical scenarios. We suggested that surgery could be used in multimodal therapy for carefully selected pM1a patients. HITHOC can work as an effective symptomatic treatment for MPE caused by NSCLC. The development of genetic testing and ctDNA monitoring might make personalized treatment and follow-up possible in the future. However, previous studies on M1a are mostly retrospective, with certain bias and limited sample sizes. Such concerns should be considered in future multi-

institutional randomized controlled studies.

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*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.

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