Original Article

Thoracoscopic pulmonary resection combined with real-time image-guided percutaneous ablation for multiple pulmonary nodules: a novel surgical approach and literature review

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Background: Due to the widespread use of computed tomography (CT) screening and advances in diagnostic techniques, an increasing number of patients with multiple pulmonary nodules are being detected and pathologically diagnosed as synchronous multiple primary lung cancers (sMPLC). It has become a new challenge to treat multiple pulmonary nodules and obtain a favorable prognosis while minimizing the perioperative risk for patients. The purpose of this study was to summarize the preliminary experience with a hybrid surgery combining pulmonary resection and ablation for the treatment of sMPLC and to discuss the feasibility of this novel procedure with a literature review.

Methods: This is a retrospective non-randomized controlled study. From January 1, 2022 to July 1, 2023, four patients underwent hybrid surgery combining thoracoscopic pulmonary resection and percutaneous pulmonary ablation for multiple pulmonary nodules. Patients were followed up at 3, 6 and 12 months postoperatively and the last follow-up was on November 30, 2023. Clinical characteristics, perioperative outcomes, pulmonary function recovery and oncologic prognosis were recorded. Meanwhile we did a literature review of studies on hybridized pulmonary surgery for the treatment of multiple pulmonary nodules.

Results: All the four patients were female, aged 52 to 70 years, and had no severe cardiopulmonary dysfunction on preoperative examination. Hybrid surgery of simultaneous pulmonary resection and ablation were performed in these patients to treat 2 to 4 pulmonary nodules, assisted by intraoperative real-time guide of C-arm X-ray machine. The operation time was from 155 to 240 minutes, and intraoperative blood loss was from 50 to 200 mL. Postoperative hospital stay was 2 to 7 days, thoracic drainage duration was 2 to 6 days, and pleural drainage volume was 300–1,770 mL. One patient presented with a bronchopleural fistula due to pulmonary ablation; the fistula was identified and sutured during thoracoscopic surgery and the patient recovered well. No postoperative 90-day complications occurred. After 3 months postoperatively, performance status scores for these patients recovered to 80 to 100. No tumor recurrence or metastasis was detected during the follow-up period.

Conclusions: Hybrid procedures combining minimally invasive pulmonary resection with ablation are particularly suitable for the simultaneous treatment of sMPLC. Patients had less loss of pulmonary function, fewer perioperative complications, and favorable oncologic prognosis. Hybrid surgery is expected to be a better treatment option for patients with sMPLC.

Keywords: Synchronous multiple primary lung cancers (sMPLC); percutaneous microwave ablation; hybrid surgery; novel surgical strategy

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Introduction

Background

Lung cancer is the most deadly malignancy due to its high morbidity and mortality. In recent years, with the widespread use of high-resolution computed tomography (CT) screening and advances in diagnostic techniques in pulmonary examination, the early detection of small pulmonary nodules has been effectively promoted. Meanwhile, the detection rate of multiple pulmonary nodules is continuously increasing, and their radiologic features are mostly characterized as ground-glass nodules (GGNs) or partially solid nodules (PSNs). A large proportion of patients are finally pathologically diagnosed with synchronous multiple primary lung cancers (sMPLC). The detection rate of sMPLC is 0.2–8% in general population (1), and 2.6–7.9% in patients who were treated with operations to cure lung cancer (2-4). sMPLC generally develops in an inert manner with rare lymph nodes and distant metastases, which offers a favorable prognosis for patients treated with radical surgery (5,6).

Highlight box

Key findings

- We demonstrate a new surgical treatment strategy capable of removing as many lung lesions as possible in patients with multiple primary lung cancers to improve long-term prognosis, while minimizing perioperative risks and impact on lung function.

What is known and what is new?

- It has become a new challenge to treat multiple pulmonary nodules and obtain a favorable prognosis while minimizing the perioperative risk for patients. Traditional surgical treatment can effectively improve long-term prognosis, but it has high requirements for patients' physical conditions and has a great impact on patients' postoperative lung function. In contrast, ablation therapy has less impact on patients' lung function, but the long-term prognosis remains to be tested.
- Followed by our hybrid procedure, thoracoscopic surgery was performed to remove the higher-risk major lesions and microwave ablation to remove as many suspicious minor lesions as possible in patients with synchronous multiple primary lung cancers (sMPLC). With this approach, we minimize the impact of surgery on cardiopulmonary function and improve the long-term prognosis of the patients at the same time.

What is the implication, and what should change now?

- Currently, the number of patients with sMPLC is gradually increasing. To treat multiple primary lung cancers with the traditional strategies of treating single lung nodule is not a good choice, and new strategies of hybrid surgical procedure to treat sMPLC are still seldomly reported. We expect that we can make an approach to improve the current treatment status based on this attempt.

Rationale and knowledge gap

However, developing a suitable radical surgical strategy for sMPLC patients is challenging. First, conventional surgical strategy requires multiple pulmonary resections and has high impact on cardiopulmonary function, and therefore requires patients to have good cardiopulmonary function. Secondly, the risk of perioperative complications after multiple wedge resections, segmentectomies, or lobectomies is significantly higher. Thirdly, in elderly patients, especially those with severe comorbidities such as chronic obstructive pulmonary disease, coronary artery disease, and cerebrovascular disease, multiple pulmonary resections may be life-threatening. Therefore, for sMPLC patients with high surgical risk, the current common surgical strategy is to treat only the major nodules with higher risk in the first surgery, while the other part of the nodules will require a second-stage surgery, or only clinical follow-up, which means that it is not possible to cure all the nodules in a single operation.

In recent years, pulmonary ablation has provided a new option for the treatment of sMPLC. The advantages of pulmonary ablation include being more minimally invasive, having less impact on cardiopulmonary function, and being more suitable for patients of advanced age and worse organ function. Currently, commonly used ablation approaches include percutaneous image-guided pulmonary ablation and electromagnetic navigation bronchoscopy-guided ablation.

However, there are obvious shortcomings: uncertain tumor efficacy, leading to an increased rate of local recurrence if ablation is incomplete; difficulty in systematic sampling of lymph nodes; possible increased rate of distant metastasis; and difficulty in treating multiple pulmonary lesions in a single procedure.

Objective

Patients with multiple pulmonary nodules often face the challenge that while some of the larger nodules are suitable for surgical resection and lymph node dissection, some of the micro-nodules are suitable for ablation, and that a combination of the two procedures would be preferable. We believe that this hybrid surgery combines the advantages of both procedures while avoiding their limitations, providing a better option for the treatment of sMPLC. In this study, we report four cases in which thoracoscopic pulmonary resection and percutaneous pulmonary ablation were combined to treat sMPLC, describe the surgical methods and review the literatures. We present this article in accordance with the PROCESS reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1986/rc) (7).

Methods

Patients selection

This is a retrospective non-randomized controlled study. From January 1, 2022 to July 1, 2023, four patients underwent hybrid surgery combining thoracoscopic pulmonary resection and percutaneous pulmonary ablation for multiple pulmonary nodules was managed in our hospital (teaching hospital and top-level general hospital in China). Patients were selected if they had two or more nodules with diameter of 0.5 cm or greater in unilateral or bilateral lungs based on chest computed tomography (CT), and these nodules were considered as suspicious primary lung cancer with imaging follow-up. In addition, all patients had no prior history of malignancy and no signs of lymph node and distant metastasis according to imaging evaluation. We reviewed and presented these patients with a follow-up cycle of three months or more. The last follow-up time was November 30, 2023. All patients were required to complete a preoperative cardiopulmonary evaluation, including pulmonary function tests, electrocardiograms, and echocardiograms to ensure that there were no contraindications to surgery. Imaging of common metastatic sites was also required to ensure that the indications for surgery are clear. If the patients had a history of smoking, they would be required to quit smoking for at least two weeks prior to surgery.

Surgical technique and literature review

We used a hybridized surgical strategy to treat patients with sMPLC (shown in *Figure 1*). All procedures were performed in our hybrid operation room (*Figure 1A*). In simultaneous surgery, percutaneous microwave ablation of lower-risk lung lesions was performed with the help of intraoperative localization under real-time guide by a C-arm X-ray machine (the Discovery IGS 7 angiography system, GE) (*Figure 1B*), which could bring extremely high-quality C-arm CT imaging, followed by thoracoscopic lobectomy or segmental resection to remove the main lesion. With the aid of thoracoscopic visualization of the ablation site, we could minimize ablation-related complications. Patients in all operations were under combined intravenous and inhalation general anesthesia with single-lumen tube using bronchial blocker to maintain single-lung ventilation. If multiple high-risk nodules were present, staged surgery based on this procedure may also be performed.

Both single-utility port video-assisted thoracoscopic lung surgery and percutaneous microwave ablation are routinely performed at our center (*Figure 1C*,*1D*). And an advanced way to localize small peripheral pulmonary nodules for surgical resection was reported by our center (8). The attending surgeons have more than 10 years of experience in specialized thoracic surgery and a senior professional title. All operators used a standardized surgical approach, and all data were observed and recorded by specialized personnel. The study was approved by the Institutional Ethics Committee of Beijing Hospital (No. 2022BJYYEC-318-02). The study was conducted in accordance with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients. This research was registered in Research Registry with unique identifying number (UIN) of researchregistry9808.

Follow-up and efficacy evaluation

Clinical characteristics such as location of nodules, operation duration, parameters of ablation, intraoperative blood loss, postoperative thoracic drainage volume, postoperative hospitalization and etc. were recorded. After discharge, all the patients were followed up. Follow-up and efficacy evaluation including complications and postoperative 90-day mortality were recorded based on the definitions of General Thoracic Surgery Database of the Society of Thoracic Surgeons (9). Chest CT, abdominal ultrasound and blood tumor markers were reviewed at postoperative 3, 6 and 12 months. Cranial magnetic resonance imaging (MRI) and whole-body bone scan was reviewed annually or when corresponding symptoms appeared. Follow-up time

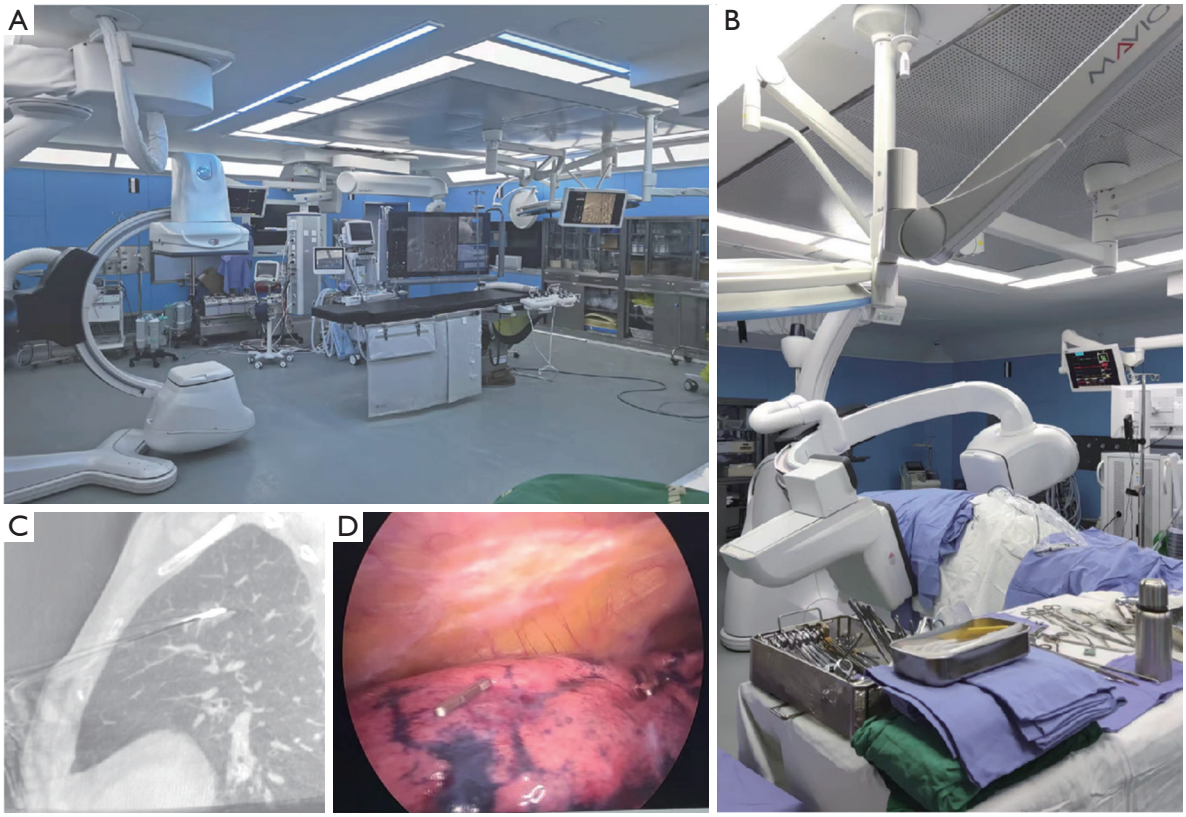

Figure 1 Hybrid operation room and procedures. (A) Hybrid operation room in our hospital. (B) C-arm X-ray machine (the Discovery IGS 7 angiography system, GE) which was used for supporting intraoperative localization procedures in our cases. Meanwhile, this machine was also used for localizing small nodules in VATS. (C) One of CT images of chest which were taken by our C-arm X-ray machine in our ablation procedures to help adjusting the location of microwave ablation needle. (D) In our previous research, an advanced way to localize small peripheral pulmonary nodules for surgical resection was reported (8). This figure shows that a titanium clip (Ethicon endo-surgery 1 ligaclip extra ligating clip cartridge 6 M titanium clips LT 300) was clipped at the visceral pleura under VATS observation to localize small peripheral pulmonary nodule with the help of baseline scan and preoperative CT imaging which was taken by our C-arm X-ray machine in the surgery. VATS, video-assistant thoracic surgery; CT, computed tomography.

and survival time was calculated from the date of surgery. Meanwhile, complete pulmonary function test and ability to perform daily activities were evaluated and recorded. For pathologically confirmed lung cancer, tumor stage was determined according to 8th edition of American Joint Committee on Cancer/Union for International Cancer Control TNM (tumor, node, metastasis) staging system (10).

Literature review

We reviewed the relevant reports on hybrid surgery and new treatment strategies related with surgery for multiple pulmonary nodules in PubMed and China-National-Knowledge-Internet (CNKI) as reference. The term "multiple pulmonary nodules", "multiple lung nodules", "multiple primary lung cancer", and "multiple primary lung carcinoma" combined with "novel strategy", "ablation", "combined" and "combination" were searched in PubMed and Chinese literature database. The literature search formula is "(((((novel strategy[Title/Abstract]) OR (ablation[Title/Abstract])) OR (combined[Title/Abstract])) OR (combination[Title/Abstract])) AND ((((((pulmonary nodules[Title/Abstract]) OR (lung nodules[Title/Abstract])) OR (pulmonary tumors[Title/Abstract])) OR (pulmonary cancer[Title/Abstract])) OR (primary lung cancer[Title/Abstract])) OR (primary lung carcinoma[Title/Abstract]))) AND ((resection[Title/Abstract]) OR (surgery[Title/Abstract]))". And the search formula of CNKI was

"(pulmonary/lung nodules + primary lung cancer/carcinoma)*(novel strategy + ablation + combination + hybrid)*(pulmonary/lung resection + surgery)".

Results

Patients' information

All four patients were female, aged 52 to 70 years. Preoperative examination did not reveal severe cardiopulmonary dysfunction. Two-stage hybrid surgery was performed for one patient who had four simultaneous multiple primary pulmonary nodules and single-stage procedures for another three patients who had two simultaneous multiple primary pulmonary nodules. One patient presented with a bronchopleural fistula due to pulmonary ablation; the fistula was identified and sutured during thoracoscopic surgery and the patient recovered well. The operation time was from 155 to 240 minutes in hybrid procedures and intraoperative blood loss was from 50 to 200 mL. All patients were diagnosed as primary lung cancer based on post-surgery pathological findings with stage Ia1 to Ia2. The patients had 2–7 days postoperative hospital stay with indwelling chest drains for 2–6 days, and total drainage ranging from 300 to 1,770 mL. No postoperative 90-day complications occurred in all patients. During postoperative follow-up, some patients had mild decreased exercise tolerance and Performance Status (PS) scores were from 80 to 100, but no respiratory complaints. Chest CT and other tests showed no tumor recurrence or metastasis. All clinical characteristics and follow-up information are summarized in *Table 1*.

The first patient (all procedures were shown in *Figure 2*), a 65-year-old female, who was found to have pulmonary nodules on physical examination. CT scan showed three pulmonary nodules with diameters greater than 0.6 cm (*Figure 2A*). Nodule 1 was a pure GGN located in the anterior segment of left upper lobe with a maximum diameter of 0.7 cm. Nodule 2 was a mixed GGN with a consolidation tumor ratio (CTR) of less than 0.5, located in the apical posterior segment of left upper lobe with a maximum diameter of 1.2 cm. Nodule 3 was a mixed GGN with a CTR greater than 0.5, located in the anterior basal segment of right lower lobe, with a maximum diameter of 1.2 cm. Nodule 4 was a micronodule located in posterior basal segment of right lower lobe with a maximum diameter of 0.5 cm. She was diagnosed as coronary heart disease at half years ago and treated with coronary angiography and percutaneous coronary intervention. After assessment, nodule 2 was identified as the major lesion, and we performed a two-stage surgery to eliminate all four nodules. At first stage, microwave ablation was operated from two directions to eliminate nodule 1 (*Figure 2B*), and then a subsegmentectomy was operated to eliminate nodule 2. The second stage surgery was performed two months later to eliminate nodule 3 and 4 by segmentectomy and subsegmentectomy (*Figure 2C*).

The second patient (all procedures were shown in *Figure 3*), a 70-year-old female, who was found two pulmonary nodules on chest CT (*Figure 3A*). Nodule 1 was a mixed GGN with a CTR less than 0.5 located in the anterior segment of left upper lobe with maximum diameter of 1.5 cm. Nodule 2 was located in the posterior basal segment of left lower lobe with maximum diameter of 1.1 cm, and it's also a mixed GGN but had higher density compared with module 1. The patient was diagnosed as hypertension (grade 2) for 10 years and blood pressure was stable under oral medication treatment. Microwave ablation was performed to eliminate the nodule 1 (*Figure 3B*) and left lower lobectomy to remove nodule 2. In particular, a bronchopleural fistula located in the upper lobe due to percutaneous microwave ablation was identified during thoracoscopic surgery (*Figure 3C*) and repaired with sutures.

The third patient, a 53-year-old female, pulmonary nodules were detected by chest CT during regular physical examination. Nodule 1 was a mixed GGN adjacent to the segmental hilum of right upper lobe with a maximum diameter of 0.7 cm. Nodule 2 was a mixed GGN with a CTR of less than 0.5 located in the right middle lobe with a maximum diameter of 2.1 cm. Microwave ablation was performed to eliminate the nodule 1 and lobectomy of right middle lobe was performed to resect nodule 2.

The fourth patient, a 52-year-old female, pulmonary nodules were detected by chest CT during regular physical examination. Nodule 1 was a pure GGN located in the apical segment of right upper lobe with a maximum diameter of 0.8 cm. Nodule 2 was a mixed GGN located in the dorsal segment of right lower lobe with a maximum diameter of 1.7 cm. Microwave ablation was performed to eliminate the nodule 1 and segmentectomy of right dorsal segment was performed to resect nodule 2.

Literature review

Up to March 25th, 2024, a total of 526 literatures published in PubMed were retrieved. Literatures published in English

Table 1 Clinical characteristics and perioperative outcomes of patients with hybrid surgery

Case number	Age (years)	No. of lung nodules	Location	Pre-					Anesthesia	Ablation	Ablation power and time	Resection	Other operations	Time of surgery (min)	Blood loss in surgery (mL)	Pathological results	Tumor stage	Post-surgery									
				ECG	LVEF	Measure/ estimated FEV1 (%)	FEV1/ FVC (%)	Measure/ estimated DLCO (%)										Days in hospital post-surgery	Days with drain tube	Total drain volume (mL)	Complication	Barthel index[a]	PS score[b]	Measured/ estimated FEV1	FEV1/ FVC (%)	Measure/ estimated DLCO (%)	Follow-up
Case 1	65	4	n1: LS_3, n2: LS_{1+2}, n3: RS_8, n4: RS_{10}						Combined intravenous and inhalation general anesthesia with single-lumen tube using bronchial blocker to maintain single-lung ventilation																	No recurrence post-operative 12 months
Stage 1				Abnormal ST-T	70%	72.3 (1.53/2.12)	75.08	81.2 (5.85/7.21)		n1	40 W 5 min + 30 W 3 min	n2: LS_{1+2a}	–	240	50	n2: infiltrating adenocarcinoma	n2: pT1bN0 (Ia2)	3	2	300	Tolerable wound pain	100/70	–	67.6 (1.43/2.12)	75.03	73.6 (5.38/7.21)	
Stage 2				–	–	–	–	–		–	–	n3 and n4: RS_{8+9} and part RS_{10}	–	136	100	n3 & n4: moderately & well differentiated infiltrating adenocarcinoma	n3: pT1bN0 (Ia2), n4: pT1aN0 (Ia1)	4	3	650	Tolerable wound pain	–	90	–	–	–	
Case 2	70	2	n1: LS_3, n2: LS_{10}	Normal	65%	113.3 (1.87/1.65)	73.74	81.3 (5.09/6.26)		n1	40 W 6 min + 40 W 5 min	n2: left lower lobectomy	–	310	40	n2: invasive adenocarcinoma	n2: pT1aN0 (Ia1)	7	6	1,770	Pneumothorax, tolerable wound pain	100/80	80	89 (1.76/1.97)	62.73	–	No recurrence post-operative 6 months
Case 3	53	2	n1: RUL, n2: RML	Normal	–	118.7 (3.45/2.91)	78.34	83.9 (7.40/8.81)		n1	40 W 6 min	n2: right middle lobectomy	n1: percutaneous pulmonary puncture biopsy	330	200	n2: invasive adenocarcinoma	n2: pT1bN0 (Ia2)	7	5	1,250	Tolerable wound pain	100/80	100	101 (2.62/2.59)	82.74	–	No recurrence post-operative 3 months
Case 4	52	2	n1: RS_1, n2: RS_6	Nonspecific T-wave changes	–	82.6 (2.10/2.54)	70.53	87.8 (7.06/8.05)		n1	40 W 9 min	n2: RS_6	–	155	50	n2: moderately differentiated infiltrating adenocarcinoma	n2: pT1bN0 (Ia2)	2	2	400	Tolerable wound pain	100/80	90	–	–	–	No recurrence post-operative

[a], scores of Barthel index is assessed by patients' charge nurse on the day of admission and the day before discharge; [b], performance status score was assessed by charge surgeon at 3 months postoperatively in patients using Karnofsky index. LSx, section x in left lobes ('x' instead of number); RSx, section x in right lobes ('x' instead of number); n, nodule; RUL, right upper lobe; RML, right middle lobe; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide; W, watt; PS, performance status.

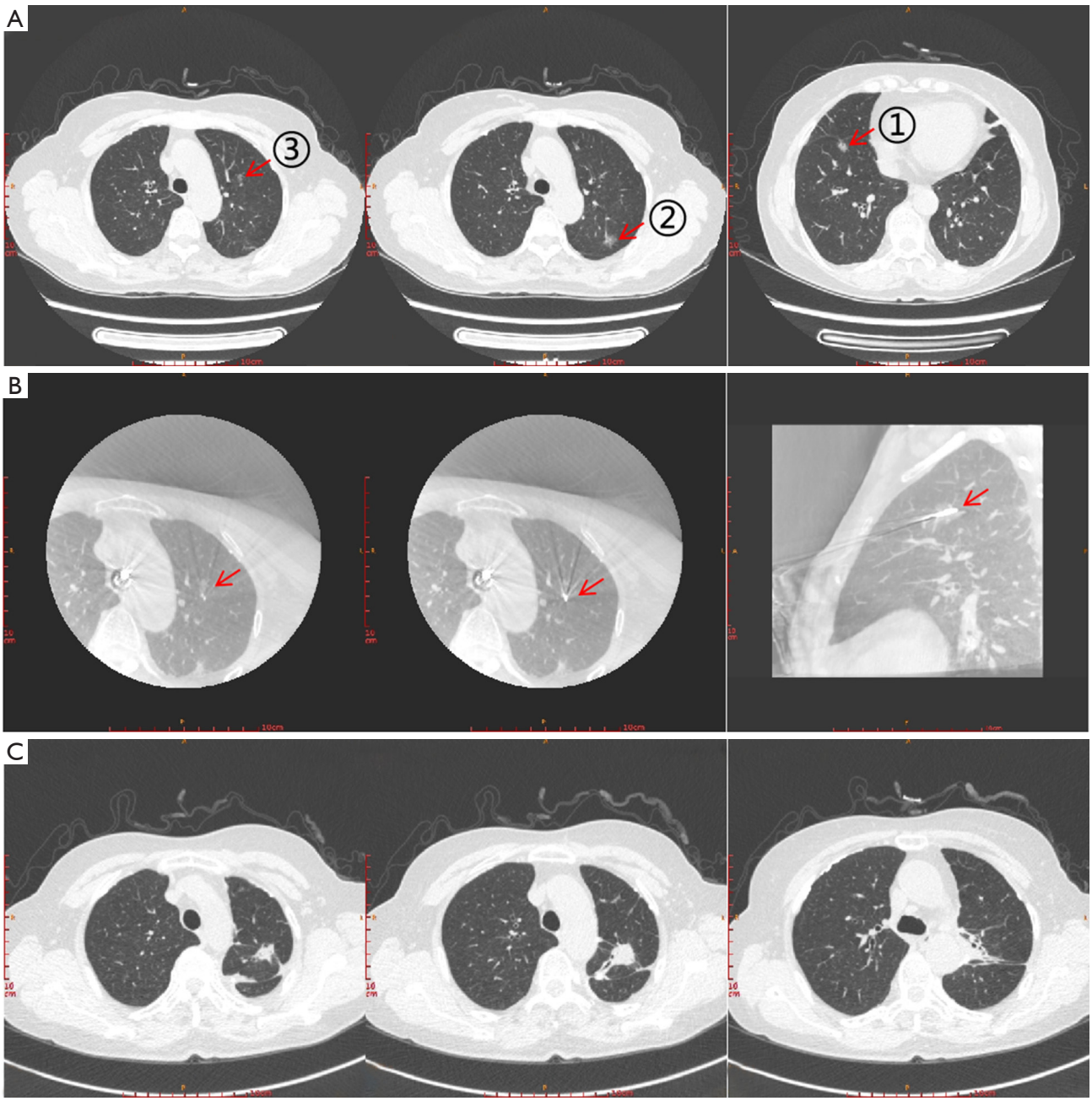

Figure 2 Images of chest CT scanning in case 1. (A) Pre-surgery scanning showed nodule 1 to 3 (n1 to n3, red arrows, marked as ①②③). Nodule 1 is a pure GGN and located in the anterior segment of left upper lobe, with maximum diameter of 0.7 cm. Nodule 2 is also a mixed GGN with maximum diameter of 1.2 cm, which located in the apicoposterior segment of left upper lobe. Nodule 3 is a mixed GGN located in the anterior basal segment of right lower lobe, with maximum diameter of 1.2 cm. (B) Images of intraoperative localization of n1 under real-time guide by a C-arm X-ray. This nodule was treated by microwave ablation with the help of intraoperative localization under real-time guide by a C-arm X-ray machine. Red arrows show the position of the ablation needle tip. (C) CT images of two months after first-stage surgery. In this surgery, nodule 1 was treated by microwave ablation and nodule 3 was treated with segmentectomy of LS_{1+2a}. CT, computed tomography; GGN, ground glass nodule.

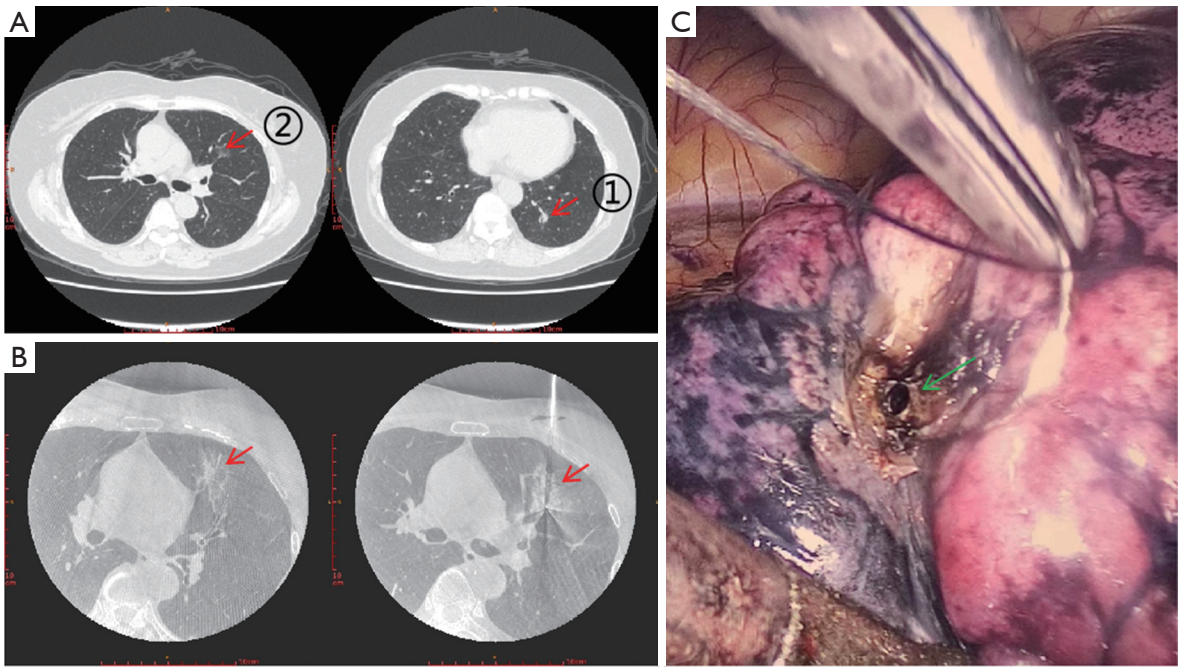

Figure 3 Images of chest CT scanning and surgery in case 2. (A) Pre-surgery scanning of nodule 1 and 2 (red arrows, marked as ① and ②). Nodule 1 is a mixed GGN and located in the anterior segment of left upper lobe with biggest diameter of 1.5 cm. Nodule 2 is a mixed GGN and located in the posterior basal segment of left lower lobe with biggest diameter of 1.1 cm. Nodule 2 was treated by lobectomy of left lower lobe. (B) Images of intraoperative localization of nodule 1 under real-time guide by a C-arm X-ray. This nodule was treated by microwave ablation with intraoperative localization under real-time guide of a C-arm X-ray machine. Red arrows show the position of the ablation needle tip. (C) An ablation-induced bronchopleural fistula (green arrow) was identified during the thoracoscopic procedure and was repaired with sutures, and favorable postoperative recovery was obtained. CT, computed tomography; GGN, ground glass nodule.

and Chinese related to hybrid surgery or combination treatment strategies of surgery and any other non-traditional invasive procedures, either single stage or multiple stages, were collected. Three representative articles presented novel surgical strategy combining traditional pulmonary resection with lung ablation with supporting of different clinical technique (11-13). And one article presented a case of endobronchial brachytherapy for post-surgery lung cancer patient (14). Meanwhile, we are glad for finding an enlightening article from Chinese researchers which summarized "Surgery + X" strategy for patients with sMPLC (15). Patients' characteristic, surgical method, perioperative treatment, recurrence pattern, and survival data reported in these studies were summarized in *Table 2*. We also found a noteworthy case report of a 78-year-old female who developed four heterochronous pulmonary nodules after left upper lobectomy for primary lung cancer, and radiofrequency ablation was used to control the tumor for 9 years, but unfortunately, we could not include this study because it was written in Japanese (16).

Meanwhile, we used CNKI, which is the most widely used Chinese literature database to search related literatures. Sixty-nine publications were categorized under the topic "multiple primary lung cancers", but there were no results that fit the purpose of our study.

Discussion

In recent years, sMPLC have become increasingly common in clinical practice, and have a good prognosis after surgical removal of all lesions, with lobectomy, segmental resection, and wedge resection being the most commonly used radical resection approaches. The 5-year survival rate of sMPLC after radical resection could be up to 70% (17), and the 5-year survival rate of those with tumor diameters less than 0.8 cm could be up to 100% (18). The location, size and CTR of the pulmonary nodule are key factors in the thoracic surgeon's choice of surgical approach.

Table 2 Literature review

No.	Author	Tittle	Year of publication	Journal	No. of cases	Patient characteristics	Operation choice	Hybrid surgery	Surgery stages	No. of nodules	Number of nodules under resection	Operative time	Blood loss in surgery (mL)	Pathology	Days in hospital post operation	Thoracic drainage tube removed	Drain volume (mL)	Complications	Prognosis
1	Sano Y, Kanazawa S, Mimura H, *et al.*	A novel strategy for treatment of metastatic pulmonary tumors: radiofrequency ablation in conjunction with surgery (13)	2008	*J Thorac Oncol*	3	55 to 67 years old; all males; all had a past history of cancer	Radiofrequency ablation + partial resection & lobectomy	Yes	1	6, not mentioned and 6 respectively	5, many nodules in the same lobe and 5 respectively	Not mentioned	Not mentioned	Metastatic pulmonary tumors	Not mentioned	Not mentioned	Not mentioned	None	Alive at 4-year, 20 months and 18 months postoperative follow-up respectively
2	Jiang N, Zhang L, Hao Y, *et al.*	Combination of electromagnetic navigation bronchoscopy-guided microwave ablation and thoracoscopic resection: an alternative for treatment of multiple pulmonary nodules (11)	2020	*Thorac Cancer*	1	47-year-old female, 5 lesions	Microwave ablation + wedge resection & segment resection	Yes	1	5	4 in left lung	Not mentioned	Not mentioned	Right upper lobe & left upper lobe lesion: adenocarcinoma in situ; left lower lobe lesion: minimally invasive adenocarcinoma; lingular segment: chronic inflammation	4	2nd day post-surgery	120	None	3 months follow-up: recover well and no recurrence
3	Harrison OJ, Sarvananthan S, Tamburrini A, *et al.*	Image-guided combined ablation and resection in thoracic surgery for the treatment of multiple pulmonary metastases: a preliminary case series (12)	2021	*JTCVS Tech*	4	40 to 66 years old; 3 males and 1 female; all had a past history of cancer	Percutaneous microwave ablation + wire-assisted wedge resection	Yes	1 for 3 patients and 2 for 1 patient	4 nodules for 1 patient and 2 nodules for 3 patients	2 for patients with 4 nodules and 1 for patients with 2 nodules	51 to 210 minutes	For all patients <10 mL	All confirmed as metastatic disease	Mostly 2–3 days, one stayed 6 days	Not mentioned	Not mentioned	2 intraoperative pneumothorax	3 to 24 months follow-up: recover well and no recurrence
4	Omori K, Nomoto Y, Kawamura T, *et al.*	Endobronchial brachytherapy combined with surgical procedure for synchronous multiple primary lung cancer: a case report (14)	2021	*Thorac Cancer*	1	72-year-old male, 3 lesions	External irradiation + endobronchial brachytherapy followed by surgery	No	1 followed by irradiation	3 (one of them was removed by surgery)	1 in surgery procedure	Not mentioned	Not mentioned	Squamous cell carcinoma in all lesions	Not mentioned	Not mentioned	Not mentioned	None	28 months follow-up: recover well and no recurrence
5	Zhou D, Yao T, Huang X, *et al.*	Real-world comprehensive diagnosis and "Surgery + X" treatment strategy of early-stage synchronous multiple primary lung cancer (15)	2023	*Cancer Med*	465	26–78 years old, 134 males and 331 females, 2 or more lesions	A single- or two-stage surgery was performed to remove the primary and coexisting lesions. Then ablation, SBRT, and EGFR TKIs treatment, were applied to treat the high-risk residual lesions	No	1 or 2 followed by other treatment	–	–	Not mentioned	Not mentioned	All confirmed as sMPLC, and most of the lesions were invasive adenocarcinoma (52.1%, 624/1,198) and MIA (26.8%, 321/1,198)	3.2±4.3 days in average in surgery procedure	2.4±3.9 days in average in surgery procedure	Not mentioned	Pulmonary infection, air leakage, atrial fibrillation, deep vein thrombosis, and incision fat colliquation in surgery procedure	In 31.6 months (19.5–90.6 months) median follow-up period: 11 patients (1.1%) who experienced tumor recurrence or distant metastases, and 6 (1.3%) died at the end of the follow-up course

SBRT, stereotactic body radiation therapy; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; sMPLC, synchronous multiple primary lung cancers; MIA, minimally invasive adenocarcinoma.

Theoretically, resection of all pulmonary lesions in a single surgical procedure for patients with sMPLC would provide the best oncologic prognosis.

However, in patients with multiple pulmonary nodules, balancing the extent of pulmonary resection with loss of pulmonary function and perioperative risk is very important and also very difficult. In patients undergoing lobectomy/sublobar resection (segmental resection and wedge resection), we have found data suggesting a great loss of lung function. As reported, forced vital capacity (FVC) predicted decreased by 23.3%/17.0%, 12.3%/6.4%, and 8.5%/4.1% at 2 weeks, 6 months, and 1 year after surgery from preoperative baseline, respectively, whereas forced expiratory volume in the first second (FEV1) predicted decreased by 21.7%/15.5%, 11.6%/6.0%, and 8.4%/4.0%, respectively, from preoperative baseline (19). Diffusing capacity for carbon monoxide (DLCO) predicted at 6 months and 1 year after surgery in patients with lobectomy/sublobar resection decreased by 14.4%/7.1% and 13.4%/7.3% from preoperative baseline, respectively (19). Obviously, based on the above data, there would be more loss of pulmonary function after unilateral or bilateral multiple pulmonary resections, longer operative time, more severe pain, and a higher incidence of postoperative complications (20). Therefore, surgical treatment of sMPLC is also accompanied by relatively high risks. As reported in the literature, there was no significant difference in 5-year overall survival rate and 5-year disease-free survival rate between lobectomy and sublobar resection to treat sMPLC; the incidence of postoperative complications (40.8% *vs.* 16.3%, P=0.007) and postoperative hospital stay (11.22 *vs.* 9.27 days, P=0.049) in the two treatment groups were less favorable (21). How to balance the long-term efficacy and surgical trauma associated with extensive pulmonary resection has become an urgent issue in the management of multiple pulmonary nodules, especially in elderly patients with significantly reduced organ function. To reduce the postoperative risk of sMPLC, medical centers have adopted the surgical strategy of resecting the major lesion and then resecting the minor lesion at an elective stage, or following up the minor lesion and waiting for it to develop and then performing surgery. However, the shortcomings of the above-mentioned treatment modalities are the potential for tumor progression while waiting for reoperation and follow-up, as well as increased medical costs. Therefore, it is particularly important and urgent for patients with sMPLC to develop a novel surgical strategy that treats all lesions while minimizing surgical trauma.

In recent years, as an alternative treatment to pulmonary resection, pulmonary ablation has become an effective treatment for early-stage lung cancer, especially for high-risk patients with advanced age, poor cardiopulmonary function, accompanied by a variety of comorbidities, and inability to tolerate extensive pulmonary resection (22,23). The significant advantages of pulmonary ablation include significantly less surgical trauma, minimal impact on pulmonary function, easier anesthesia and perioperative management, and the ability to treat bilateral multiple lesions simultaneously. A meta-analysis showed no significant difference in 1- to 5-year overall survival between surgery and pulmonary ablation for stage I non-small cell lung cancer (NSCLC), with a 5-year overall survival rate of 41% after ablation (24). However, according to American national cancer database, the prognosis for patients with sMPLC after pulmonary ablation remains unsatisfactory, with 5-year overall survival rates ranging from 24.6% to 37% (22,25-27). A review summarized 6 studies of pulmonary ablation for early-stage lung cancer showed 5-year overall survival rates ranging from 16% to 68% (28). Possible reasons for poor prognosis include residual tumor due to incomplete pulmonary ablation, lack of lymph node dissection, underestimated tumor staging, and insufficient adjuvant therapy. On the other hand, the discrepancies in data present in these literatures may be due to a variety of reasons such as bias due to sample selection, poor control of ablation indications, and inaccurate staging. However, at least part of the literature suggests that there is no difference in the long-term efficacy of ablation and pneumonectomy in the treatment of stage I lung cancer. Of course, this conclusion remains controversial and it remains to be confirmed by future studies with larger samples. Thus, the indications for pulmonary ablation and the selection of suitable patients are very important.

Meanwhile, a study that enrolled 3,344 patients showed that common complications associated with pulmonary ablation included pneumothorax (38.4%), pneumonia (5.7%), pleural effusion (4.0%), lung collapse (4.0%), hemoptysis (3.9%), respiratory failure (3.5%), and pulmonary edema (0.3%) (29). Bronchopleural fistula as a more serious postoperative complication of pulmonary ablation may lead to poor prognosis or even death of the patient, however its incidence is not high, about 0.5–1% (30,31). Therefore, how to improve the above deficiencies of pulmonary ablation to make it suitable for the treatment of sMPLC has become an important issue.

The solution at our center is to combine pulmonary resection and ablation in a single surgical procedure, taking into account the patient's age, cardiopulmonary function, and the clinical characteristics of each pulmonary nodule to design an individualized surgical plan, therefore named as hybrid surgery. Thoracoscopic pulmonary resection with lymph node dissection is preferred for major lesions, which are usually have larger diameter, higher density and shorter tumor doubling time, also for lesions with special location such as subpleural nodules. Percutaneous pulmonary ablation is preferred for minor lesions and nodules that are deeply located and difficult to be removed locally. The advantages of this hybrid surgery are as follows. First, hybrid surgery helps to treat synchronous multiple pulmonary nodules while preserving pulmonary function as much as possible. Especially when the nodule is located in the junction zone of a lung segment, the required combined segmentectomy or lobectomy is challenging and high-risk, whereas pulmonary ablation can be very effective in managing such nodule. Second, intraoperative real-time scanning with a C-arm X-ray machine provides extremely high-quality tomographic images, ensures precise localization of each pulmonary nodule, and thus improves both resection and ablation success rates. Third, ablation-related complications can be monitored and managed during the thoracoscopic procedure. Fourthly, intrapulmonary and mediastinal lymph nodes dissection via thoracoscopic surgery can well compensate for the inaccurate N staging caused by ablation alone, and adequate tissue and more accurate pathologic stage can better guide postoperative adjuvant therapy. Benefiting from the above advantages, hybrid surgery may improve both short-term and long-term outcomes of patients with sMPLC.

As medical technology advances, the treatment options for lung nodules become more diverse. However, there has never been a uniform protocol on how to treat multiple primary lung nodules precisely. We believe that certain principles need to be followed when performing surgical treatment. First, the surgical indications should be careful, and over-treatment of pure ground glass density nodules with sub-centimeter diameter is inappropriate. Meanwhile, the patient's relevant medical history and follow-up situation should be considered comprehensively to provide the necessary treatment with minimal trauma. For patients with surgical indications, lung ablation is a good choice to eliminate the hidden risk and protect the cardiopulmonary function of the patient at the same time. Secondly, for the higher risk of mixed density and solid lung nodules, we believe that the traditional surgical treatment strategy including lobectomy, segmentectomy, sub-segmentectomy and wedge resection should still be used with a more definite long-term prognosis. Finally, the surgical plan should be individualized, and the patient's underlying physical condition should be taken into account fully while grasping the indications of the surgery. Surgery without indications and excessive surgical scope should be avoided. For patients with multiple primary lung nodules who has to be treated with surgery, our procedure has advantages compared with traditional strategy (simultaneous or staged multiple lung resections) in less loss of pulmonary function, good perioperative safety, less financial burden of hospitalization and the prospect of a favorable long-term prognosis.

To date, similar therapeutic strategy which combined wedge resection and microwave ablation has been applied by surgeons to treat patients with lung metastases from malignant tumors (12), but have not yet been reported for the treatment of sMPLC. Although this novel surgical strategy may become a superior treatment option for sMPLC, there is still a lack of data on its feasibility, safety, and oncologic efficacy. First, the indications for pulmonary ablation remain to be defined, and there are no convincing criteria on how to select surgical resection or ablation based on the clinical and imaging features of pulmonary nodule. Second, for tiny GGNs in the lungs, how to accurately, rapidly, and noninvasively localize the target lesion during the operation remains a challenge. Third, how to design the hybrid surgery remains to be explored, such as the sequence of resection and ablation, avoiding mutual interference between the two procedures, and the prevention and management of ablation-related complications. Therefore, clinical studies are urgently needed to assess the feasibility and efficacy of this hybridized surgical strategy.

Conclusions

Hybrid surgery, which flexibly combines pulmonary resection with ablation, is expected to be a better option for the treatment of patients with sMPLC due to less invasiveness, less loss of pulmonary function, good perioperative safety, and the prospect of a favorable long-term prognosis. Of course, data related to its long-term prognosis and rate of complications remain to be studied in clinical studies with larger samples.

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Footnote

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