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# Is surgical resection of primary tumour superior to exploratory thoracotomy without resection in treating lung cancer patients with unexpected pleural metastasis detected during operation?

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## Summary

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was 'In lung cancer patients with unexpected pleural metastasis detected during operation, is surgical resection of primary tumour superior to exploratory thoracotomy without resection in improving long-term survival?'. Altogether, 1443 papers were found using the reported search, of which 1 meta-analysis and 10 retrospective observational cohort studies represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers were tabulated. One meta-analysis and 9 cohort studies found that surgical resection of the primary tumour, on the discovery of pleural metastases, yielded a better overall survival than exploratory thoracotomy alone, while 1 cohort study showed no difference. Six studies found that main tumour resection was an independent favourable prognostic factor for overall survival in lung cancer patients with unexpected pleural metastasis detected during operation, while 3 cohort studies also showed improved progression-free survival over exploratory thoracotomy. Therefore, we conclude that surgical resection of the primary tumour is superior to exploratory thoracotomy in treating lung cancer patients with unexpected pleural metastasis detected during operation.

**Keywords:** Lung cancer • Pleural metastasis • Intraoperatively detected • Surgical resection

## INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the ICVTS [1].

## THREE-PART QUESTION

In [lung cancer patients with unexpected pleural metastasis detected during operation] is [surgical resection of primary tumour] superior to [exploratory thoracotomy without resection in improving long-term survival]?

## CLINICAL SCENARIO

A 69-year-old male patient with clinical early-stage lung cancer without evidence of metastasis on preoperative staging investigations was taken to surgery in your clinic. However, during the operation, pleural metastatic nodules (pM1a disease) were discovered. Whether surgical resection of the primary lung cancer should continue, or the operation abandoned, was immediately discussed at the table. The planned lung resection was

completed, but you resolved to check the literature to assure yourself you made the right decision.

## SEARCH STRATEGY

We searched MEDLINE by using the PubMed interface from 1950 to August 2019 with the following search terms: (lung cancer[Title/Abstract] OR lung carcinoma[Title/Abstract] OR lung tumour[Title/Abstract] OR lung neoplasm[Title/Abstract] OR lung adenocarcinoma[Title/Abstract] OR lung squamous cell carcinoma[Title/Abstract]) AND (malignant pleural disease OR pleural metastasis OR pleural metastases OR pleural spread OR pleural seeding OR pleural dissemination OR pleural nodule OR carcinomatous pleuritis) AND (surgery OR surgical OR resection OR lobectomy OR sublobar resection OR pneumonectomy).

## SEARCH OUTCOME

A total of 1443 papers were found using the reported search terms from MEDLINE. From these papers, 1 meta-analysis and 10

**Table 1:** Best evidence papers

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Ichinose <i>et al.</i> (2000), Surg Today, Japan [2]  Cohort study (level 3)	227 NSCLC patients from 1985 to 1994 from the Japanese Clinical Oncology group  Surgical resection group: 193 patients  Lobectomy/pneumonectomy/limited resection: 139/29/25  Exploratory group: 34 patients  Reason for exploratory thoracotomy: NA	Follow-up	NA	
		3-Year OS rate	Surgical resection group: 28.8% Exploratory group: 10.9% ( $P = 0.047$ )	
		5-Year OS rate	Surgical resection group: 14.9% Exploratory group: 0% ( $P = 0.047$ )	
		Prognostic factors	Histology, cN stage and residual tumour	
Fukuse <i>et al.</i> (2001), Lung Cancer, Japan [3]  Cohort study (level 3)	49 NSCLC patients from 1981 to 1997 from Otsu Red-Cross Hospital  Surgical resection group: 39 patients  Lobectomy/pneumonectomy/limited resection: 27/5/7  Exploratory group: 10 patients  Reason for exploratory thoracotomy: NA	Follow-up	Mean: 60 months	Limited sample size
		Median OS	Surgical resection group: Lobectomy: 37.8 months Limited resection: 23.2 months Exploratory group: 6.2 months	
		Prognostic factors	Pleural dissemination and tumour invasion	
		Exploratory group: 10 patients		
Sawabata <i>et al.</i> (2002), Ann Thorac Surg, Japan [4]  Cohort study (level 3)	43 NSCLC patients from 1980 to 1994 from Japan National Chest Hospital Study Group for Lung Cancer  Surgical resection group: 25 patients  Complete resection/incomplete resection: 11/14  Exploratory group: 18 patients  Reason for exploratory thoracotomy: pleural dissemination or unresectable	Follow-up	>5 Years	Surgical resection might decrease local relapse
		5-Year OS rate	Surgical resection group: Complete resection: 9% Incomplete resection: 10%  Exploratory group: 0% ( $P > 0.05$ )	Limited sample size
		Median OS	Surgical resection group: Complete resection: 13 months Incomplete resection: 34 months  Exploratory group: 17 months ( $P > 0.05$ )	
		Local relapse	Surgical resection group: Complete resection: 2/11 Incomplete resection: 2/14  Exploratory group: 5/18	
		Exploratory group: 18 patients		
Mordant <i>et al.</i> (2011), Eur J Cardiothorac Surg, France [5]  Cohort study (level 3)	70 NSCLC patients from 1983 to 2006 from Georges Pompidou European Hospital  Surgical resection group: 32 patients  Lobectomy/pneumonectomy: 23/9  Exploratory group: 38 patients	Follow-up	Mean: 72.8 months	Relatively high peri-operative risk
		Morbidity rate	Surgical resection group: 34% Exploratory group: 0%	
		Mortality rate	Surgical resection group: 16% Exploratory group: 0%	
		5-Year OS rate	Surgical resection group: 16% Exploratory group: 0%	
		Median OS	Surgical resection group: 15 months Exploratory group: 13 months	

Continued

Table 1: Continued

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
	Reason for exploratory thoracotomy: diffuse unresectable pleural dissemination	Death from cancer	Surgical resection group: 57% Exploratory group: 93%	
Wang <i>et al.</i> (2011), J Surg Res, China [6]  Cohort study (level 3)	138 NSCLC patients from 1990 to 2008 from Taipei Veterans General Hospital  Surgical resection group: 90 patients  Standard resection/limited resection: 60/30  Exploratory group: 48 patients  Reason for exploratory thoracotomy: surgeon's preference	Follow-up  3-Year OS rate  5-Year OS rate  Prognostic factors	Median: 19.9 months  Surgical resection group: 34.2% Exploratory group: 13.2% ( $P < 0.001$ )  Surgical resection group: 23.0% Exploratory group: 5.3% ( $P < 0.001$ )  Main tumour resection: HR 3.066 (95% CI 2.038–4.612) and pN stage	
Ren <i>et al.</i> (2015), Interact CardioVasc Thorac Surg, China [7]  Cohort study (level 3)	83 NSCLC patients from 2005 to 2013 from Shanghai Pulmonary Hospital  Surgical resection group: 62 patients  Lobectomy/bilobectomy/limited resection: 43/11/8  Exploratory group: 21 patients  Reason for exploratory thoracotomy: surgeon's preference	Follow-up  3-Year OS rate  Median OS  Prognostic factors	Median: 34 months  Surgical resection group: 45.8% Exploratory group: 11.8% ( $P = 0.001$ )  Surgical resection group: 37.3 months Lobectomy: 35.0 months Limited resection: 37.1 months  Exploratory group: 17.4 months ( $P = 0.001$ )  Main tumour resection: HR 3.678 (95% CI 1.308–10.347), pleural effusion, histology and N stage	
Yun <i>et al.</i> (2018), Thorac Cardiovasc Surg, Korea [8]  Cohort study (level 3)	78 NSCLC patients from 2000 to 2011 from Seoul Asian Medical Center  Surgical resection group: 36 patients  Lobectomy/pneumonectomy/limited resection: 21/3/12  Exploratory group: 42 patients  Reason for exploratory thoracotomy: diffuse unresectable pleural dissemination	Follow-up  3-Year OS rate  5-Year OS rate  Median OS  3-Year local PFS rate  3-Year regional PFS rate  Prognostic factors	Mean: 28.7 months  Surgical resection group: 66.7% Exploratory group: 41.1% ( $P = 0.012$ )  Surgical resection group: 42.7% Exploratory group: 15.2% ( $P = 0.012$ )  Surgical resection group: 52 months Exploratory group: 33 months ( $P = 0.012$ )  Surgical resection group: 71.3% Exploratory group: 12.6% ( $P < 0.001$ )  Surgical resection group: 17.6% Exploratory group: 0% ( $P = 0.03$ )  Main tumour resection: HR 0.472 (95% CI 0.266–0.837)	Surgical resection improved both OS and loco-regional PFS
Xu <i>et al.</i> (2016), J Thorac Dis, China [9]  Meta-analysis (level 1)	9 cohort studies with 861 NSCLC patients (only 5 studies were pooled for survival analysis)  Surgical resection group: 245 patients	Follow-up  OS  Prognostic factors	NA  Surgical resection group versus exploratory group: HR 0.443; 95% CI 0.344–0.571; $P < 0.001$  Main tumour resection, gender and N stage	

Continued

Table 1: Continued

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
	Exploratory group: 167 patients  Reason for exploratory thoracotomy: NA			
Li <i>et al.</i> (2017), J Thorac Dis, China [10]  Cohort study (level 3)	110 NSCLC patients from 2006 to 2015 from Peking University Cancer Hospital  Surgical resection group: 62 patients  Lobectomy/limited resection: 18/44  Exploratory group: 48 patients  Reason for exploratory thoracotomy: NA	Follow-up  3-Year OS rate  5-Year OS rate  Median OS	NA  Surgical resection group: 69.4% Exploratory group: 41.7% ( $P = 0.037$ )  Surgical resection group: 31.7% Exploratory group: 19.5% ( $P = 0.037$ )  Surgical resection group: 49.0 months Exploratory group: 29.4 months ( $P = 0.037$ )	
Li <i>et al.</i> (2018), J Thorac Cardiovasc Surg, China [11]  Cohort study (level 3)	43 NSCLC patients from 2006 to 2014 from National Taiwan University Hospital  Surgical resection group: 30 patients  Lobectomy/limited resection: 13/17  Exploratory group: 13 patients  Reason for exploratory thoracotomy: surgeon's preference	Follow-up  Morbidity rate  Mortality rate  3-Year OS rate  Median OS  3-Year PFS rate  Median PFS time  Prognostic factors	Mean: 28 months  Surgical resection group: 6.7% Exploratory group: 7.7%  Surgical resection group: 0% Exploratory group: 0%  Surgical resection group: 82.9% Exploratory group: 38.5% ( $P = 0.013$ )  Surgical resection group: 64 months Exploratory group: 35 months ( $P = 0.013$ )  Surgical resection group: 44.5% Exploratory group: 0% ( $P = 0.009$ )  Surgical resection group: 35 months Exploratory group: 19 months ( $P = 0.009$ )  Main tumour resection: OS: HR 0.239 (95% CI 0.066–0.873); PFS: HR 0.340 (95% CI 0.134–0.861)	Surgical resection improved both OS and PFS  Limited sample size
Chiang <i>et al.</i> (2018), Oncotarget, China [12]  Cohort study (level 3)	134 NSCLC patients from 1990 to 2012 from Taipei Veterans General Hospital  Surgical resection group: 87 patients  Lobectomy/limited resection: 58/29  Exploratory group: 47 patients  Reason for exploratory thoracotomy: surgeon's preference	Follow-up  Median OS  Prognostic factors	NA  Surgical resection group: 35.3 months Exploratory group: 17.0 months ( $P < 0.001$ )  Main tumour resection: HR 0.484 (95% CI 0.273–0.859) and postoperative epidermal growth factor receptor-tyrosine kinase inhibitor use	

CI: confidence interval; HR: hazard ratio; NA: not available; NSCLC: non-small-cell lung cancer; OS: overall survival; PFS: progression-free survival.

retrospective observational cohort studies comparing surgical resection of the primary tumour with exploratory thoracotomy without resection of the primary tumour were identified, which provided the best evidence to answer the question. These are presented in Table 1.

## RESULTS

Ichinose *et al.* [2] explored the role of surgical resection of the primary tumour in treating lung cancer patients with unexpected pleural metastasis detected during operation by comparing the survival of patients receiving surgical resection and that of patients receiving exploratory thoracotomy without resection of the primary tumour. They included a total of 227 patients who had no pleural metastasis on preoperative radiographic examination but were pathologically confirmed with pleural metastasis (pM1a) intraoperatively (193 patients receiving surgical resection and 34 patients receiving exploratory thoracotomy). They found that the surgical resection group yielded a significantly higher 3-year (28.8% vs 10.9%) and 5-year (14.9% vs 0%) overall survival (OS) rate than the exploratory group ( $P=0.047$ ). Moreover, freedom from macroscopic residual tumour after surgical resection was found to be an independent favourable prognostic factor for those patients [hazard ratio (HR) 0.680, 95% confidence interval (CI) 0.466–0.992;  $P=0.045$ ]. Fukuse *et al.* [3] found that the median OS of the patients receiving lobectomy, limited resection and exploratory thoracotomy was 37.8, 23.2 and 6.2 months, respectively. Sawabata *et al.* [4] found that the 5-year OS rate of the patients receiving complete resection, incomplete resection and exploratory thoracotomy was 9%, 10% and 0%, respectively and the median OS of those patients was 13, 34 and 17 months, respectively ( $P>0.05$ ). However, the local relapse rate of pleural metastasis was numerically higher in patients receiving exploratory thoracotomy (27.8%) than those receiving complete resection (18.2%) and incomplete resection (14.3%). Mordant *et al.* [5] found that the surgical resection group had a high rate of post-operative morbidity (34%) and mortality (16%) but it yielded a 5-year OS rate of 16% while there was no patient living beyond 5 years in the exploratory group even though the median OS of the 2 groups was similar. Moreover, there were more deaths from cancer in the exploratory group than in the surgical resection group (93% vs 57%). Wang *et al.* [6] also found that the surgical resection group yielded a significantly higher 3-year (34.2% vs 13.2%) and 5-year (23.0% vs 5.3%) OS rate than the exploratory group ( $P<0.001$ ). In addition, main tumour resection was found to be an independent favourable prognostic factor for those patients (HR 3.066, 95% CI 2.038–4.612;  $P<0.001$ ). Similarly, Ren *et al.* [7] also found that the surgical resection group yielded a significantly higher 3-year (34.2% vs 13.2%) OS rate and longer median OS (37.3 vs 17.4 months) than the exploratory group ( $P=0.001$ ) and main tumour resection was also found to be an independent favourable prognostic factor for those patients (HR 3.678, 95% CI 1.308–10.347;  $P=0.014$ ). Yun *et al.* [8] also found that the surgical resection group yielded a significantly higher 3-year (66.7% vs 41.1%) and 5-year (42.7% vs 15.2%) OS rate as well as longer median OS (52 vs 33 months) than the exploratory group ( $P=0.012$ ). Moreover, the surgical resection group also yielded a significantly higher 3-year local (71.3% vs 12.6%,  $P<0.001$ ) and regional (17.6% vs 0%,  $P=0.03$ ) progression-free survival (PFS) rate than the exploratory group. Furthermore, the

main tumour resection was again found to be an independent favourable prognostic factor for those patients (HR 0.472, 95% CI 0.266–0.837;  $P=0.01$ ). In 2016, a meta-analysis by Xu *et al.* [9] included 5 of the above cohort studies [4–8] for survival analysis and found that the surgical resection group yielded a significantly better OS than the exploratory group (HR 0.443; 95% CI 0.344–0.571;  $P<0.001$ ).

Recently, Li *et al.* [10] in their study included 32 patients receiving surgical resection and 38 patients receiving exploratory thoracotomy. Again, they found that the surgical resection group yielded a significantly higher 3-year (69.4% vs 41.7%) and 5-year (31.7% vs 19.5%) OS rate as well as longer median OS (49.0 vs 29.4 months) than the exploratory group ( $P=0.037$ ). Another study by Li *et al.* [11] found that there was no significant difference in morbidity and mortality between the surgical resection group and the exploratory group, but the surgical resection group yielded a significantly high 3-year OS rate (82.9% vs 38.5%) as well as longer median OS (64 vs 35 months) than the exploratory group ( $P=0.013$ ). Moreover, the surgical resection group yielded a significantly higher 3-year PFS rate (44.5% vs 0%) as well as longer median PFS time (35 vs 19 months) than the exploratory group ( $P=0.009$ ). Furthermore, main tumour resection was confirmed to be an independent favourable prognostic factor of OS (HR 0.239, 95% CI 0.066–0.873;  $P=0.03$ ) and PFS (HR 0.340, 95% CI 0.134–0.861;  $P=0.023$ ) for those patients. Chiang *et al.* [12] also found that the surgical resection group yielded a significantly longer median OS (35.3 vs 17.0 months) than the exploratory group ( $P<0.001$ ) and main tumour resection was also found to be an independent favourable prognostic factor in those patients (HR 0.484, 95% CI 0.273–0.859;  $P=0.013$ ).

## CLINICAL BOTTOM LINE

The available evidence showed that in lung cancer patients with unexpected pleural metastasis detected during operation, surgical resection of the primary tumour yields better OS and PFS than exploratory thoracotomy alone, and is an independent favourable prognostic factor for these patients. We conclude that surgical resection of the primary tumour is superior to exploratory thoracotomy in treating lung cancer patients with unexpected pleural metastasis detected during operation.

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**Conflict of interest:** none declared.

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