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In lung cancer patients where a malignant pleural effusion is found at operation could resection ever still be justified?

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Abstract

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was whether surgery could ever be justified in non-small cell lung cancer patients with an unexpected malignant pleural effusion at surgery. Eight papers were chosen to answer the question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers were tabulated. Study limitations included a lack of retrospective studies, the heterogeneous patient population and various treatments applied. Three papers found that surgery—compared to exploratory thoracotomy—was associated with a survival advantage in cases of minimal pleural disease. One paper showed that the median survival time of 58.8 months in patients with pleural effusion was better than that of patients with more extensive pleural dissemination as pleural nodule (10 months; $P = 0.0001$) or pleural nodule with effusion (19.3 months; $P = 0.019$). Another study showed that pleural effusion patients with N0–1 status had a median survival time more than 5 years longer than patients with similar or more extensive pleural dissemination but with N2–N3 status. A further study showed a better 5-year survival time in patients with pleural effusion, than in patients with pleural nodule (22.9% vs 8.9%, respectively; $P = 0.45$). In two papers, surgery vs exploratory thoracotomy had better survival in cases of N0 status and of complete tumour resection independently of pleural dissemination. Different strategies were employed to obtain freedom from macroscopic residual tumour, including pneumonectomy, lobar resection or, to a lesser extent, pleurectomy in patients having pleural dissemination. Only one paper reported a worse median survival time after pneumonectomy than for more limited resections (12.8 vs 24.1 months, respectively; $P = 0.0018$). In the remaining papers, no comparison between the different resections was made. In all studies except one, surgery was a component of multimodal treatment. Intrapleural chemotherapy was largely applied with systemic adjuvant chemotherapy and/or radiotherapy. The study period and/or year of publication of most papers was 10 years or more, this may explain the different chemotherapy regimens used in the various studies. No current guidelines support surgery over conservative therapy and the identified studies in this review are not strong enough to change this recommendation.

Keywords: Surgery • Non-small cell lung cancer • Malignant pleural effusion

INTRODUCTION

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

THREE-PART QUESTION

In [non-small cell lung cancer (NSCLC) patients with unexpected malignant pleural effusion (MPE)] could [resection] ever be [justified]?

CLINICAL SCENARIO

A 55-year-old patient comes to your practice presenting a resectable NSCLC. During surgery, an unexpected PE is found; a sample is send to the pathology unit for cytology. Despite the tumour looking fully resectable and the N2 nodes being negative on frozen sections, the cytology turns out to be positive. As stipulated by standard protocols, the surgeon decides against resection. The patient undergoes chemo-radiotherapy, surviving 10 months. Considering the poor prognosis, you check the literature to see whether proceeding with the resection could have improved his prognosis.

SEARCH STRATEGY

Medline 1950 to May 2012 using OVID interface [resection] AND [NSCLC.mp OR exp non-small cell lung cancer/] AND [MPE.mp OR exp malignant pleural effusion/].

SEARCH OUTCOME

Forty papers were found using the reported research strategy. Six papers covering patients with malignant pleural nodule

Table 1: Best evidence papers

Author, date & country, journal Study type (level of evidence)	Patient group	Outcomes	Key results					Comments
Okamoto *et al.* (2012) Japan [2]; Eur J Cardiothorac Surg Retrospective single-centre case series (level 3)	Between 1990 and 2007, 73 patients with pleural involvement were evaluated *Subgroups* MPE ($n = 32$) MPN ($n = 41$) Distant metastases (M1b) ($n = 25$) *Surgery* Lobectomy ($n = 73$) Pneumonectomy ($n = 5$) Bilobectomy ($n = 11$) Partial resection resection ($n = 9$) *Other treatment* Intrapleural chemotherapy: 50% Postoperative systemic chemotherapy (mitomycin-C or cisplatin): 33%	MST (months)	Variables M1a/M1b N0–1/N2–3 MPE-N0–1/ MPE-N2–3 MPN-N0–1/ MPN-N2–3 Others/Pn	*n* 73/25 7/39 14/18 20/21 70/3	MST 25.9/8.7 37.7/24.4 75.4/24.4 33.7/24.1 26.1/12.8	*P* 0.014 0.004 0.011 0.15 0.001		M1a resected patients had better survival than M1b patients Among M1a patients, surgery may be indicated for MPE patients with N0–1 status
Ichinose *et al*, (2001) Japan [3]; Surgery Today Retrospective multicentre study (level 3)	Between January 1985 and December 1994, 227 patients were evaluated *Subgroups* MPE ($n = 55$) MPN ($n = 89$) MPE + MPN ($n = 83$) *Surgery* Resection (R) Lobectomy ($n = 139$) Pneumonectomy: ($n = 29$) Limited resection ($n = 25$) Exploratory thoracotomy (ET) ($n = 34$) *Other treatment* Intrapleural chemotherapy (cisplatin; adriamycin; mitomycin): 44% Intrapleural sclerosing agent: 3% Postoperative chemotherapy (platinum based combination): 47% Radiotherapy with or without chemotherapy: 9%	YST (%)	Variables R/ET Ad/oth. pN0/1/2 MRT–/MRS+	*n* 193/34 178/49 58/31/97 155/61	3-YST 29/11 29/16 47/35/14 31/13	5-YST 15/0 14.5/9 28/15/5 18/6	*P* 0.04 0.004 <0.0001 0.001	Surgery is associated with longer survival in case of histology of adenocarcinoma N0 status and freedom from macroscopical residual tumour
Fukuse *et al.* (2001) Japan [4]; Lung Cancer Retrospective single-centre case series (level 3)	From January 1981 to December 1997, 49 patients were evaluated *Subgroups* MPE ($n = 16$) MPN ($n = 17$) MPE + MPN ($n = 16$)	Operative mortality MST (months)			1 patient (2%) MST 37.9/23.2/6.2 58.8/10[a]/19.3[b] 37/15[c]/9.9[d] 23/10.4	 *P* – [a]0.0001; [b]0.019 [c]0.0004; [d]0.011 0.09		Surgery may be indicated in patients with T1-2 primary tumour and with MPE only
			Variables CR/PR/ET MPE/MPN/ MPE + MPN T1/2/3 pN0/N2	*n* 32/7/10 16/17/16 9/28/12 –				

Continued

Table 1: (*Continued*)

Author, date & country, journal Study type (level of evidence)	Patient group	Outcomes	Key results						Comments
	Surgery Complete resection (CR): Lobectomy with/or without PI (*n* = 27) Pleuropneumonectomy (*n* = 5) Partial resection (PR) (*n* = 7) Exploratory thoracotomy (ET) (*n* = 10) *Other treatment* Intrapleural chemotherapy (cisplatin; adriamycin; mitomycin; alone or in combination): 100% Postoperative chemotherapy: 100% (cisplatin in 41%) Adjuvant radiotherapy: 6%	YST (%)		All patients	MPE	MPN	MPE + MPN		
			3-YST	26.7	60	6.3	9.1		
			5-YST	15.7	45	0	0		
Shiba *et al.* (2001) Japan [5]; Ann Thorac Surg Retrospective single-centre case series (level 3)	From 1985 to 1995, 65 patients were valuated *Subgroups* MPE or D0 (*n* = 25) MPN with/or without MPE or D1 (*n* = 40) *Surgery* Lobectomy (L) (*n* = 55) Partial resection (PR) or exploratory thoracotomy (ET) (*n* = 10) In all specimens Ki-67, a tumour proliferative marker was evaluated *Other treatment* Intrapleural chemotherapy (mytomicin-C): 100%	YST (%)	Variables	*n*	5-YST	*P*			Surgery appears to be beneficial in patients with N0 status and low Ki-67 index
			L/PR + ET	55/10	14/0	–			
			D0/D1	25/40	22.9/8.9	0.45			
			Ad/oth.	58/7	13.2/0	0.02			
			N0/N1-2	11/46	46.7/5.8	0.01			
			Ki-67low/ Ki-67high	21/36	28.6/4.1	<0.0001			
Kodama *et al.* (1993) Japan [6]; Cancer Retrospective single-centre case series (level 3)	From April 1985 to December 1991, 31 patients were valuated *Subgroups* MPE: 6 MPN with or without MPE: 25 (7 clinically diagnosed) *Surgery* Pleuropneumonectomy (*n* = 5) Pneumonectomy (*n* = 3) Lobectomy (*n* = 18) Segmentectomy or wedge (*n* = 5) *Other treatment* Intrathoracic chemotherapy (cisplatin) with radio frequency hyperthermia: 100%	MST (months) YST (%)	Variables	*n*	MST	3-YST	5-YST	*P*	Surgery may be indicated in patients with N0 status
			N0–1/N2	14/17	43/16	68.4/22.7	48.7/0	0.01	

Continued

BEST EVIDENCE TOPIC

Table 1: (*Continued*)

Author, date & country, journal Study type (level of evidence)	Patient group	Outcomes	Key results					Comments
Shigemura *et al.* (2003) Japan [7]; Interact CardioVasc Thorac Surg Retrospective single-centre case series (level 3)	Five patients with MPE + MPN were evaluated Four were clinically diagnosed *Surgery* Panpleuropneumonectomy (*n* = 5) *Other treatment* Intrapleural hyperthermic chemotherapy before and after operation (cisplatin): 100% Postoperative systemic chemotherapy: 100%	Operative mortality MST (months)	0% 19 The poorest survival was 8 months (T4N2M0) and the longest was 32 months (T4N0M0)					Multimodality treatment seems to be effective for radical local tumour control in very selected cases
Kimura *et al.* (2010) Japan [8]; Interact CardioVasc Thorac Surg Retrospective single-centre non-consecutive case series (level 3)	From May 2001 to July 2005 and from October 2006 to November 2008, 19 patients with pathologically MPE with/or without MPN were evaluated *Subgroups* Group A (*n* = 7): Intraoperative intrathoracic hyperthermotherapy Group B (*n* = 5): Intraoperative intrathoracic hyperthermo-chemotherapy Group C (*n* = 7): no additional therapy Each patient received chemotherapy after surgery (different regimen) *Surgery* Lobectomy (*n* = 10) Segmentectomy or wedge (*n* = 6) Probe thoracotomy (*n* = 3) all classified in Group A	Operative mortality MST (months) Recurrence of pleural effusion (RPE) (%)	0% Variables MTS RPE	Group A 19.4 0	Group B 41 20	Group C 25 57*	*P* NS *0.02	Intrapleural hyperthermic therapy alone or with chemotherapy might be beneficial in the prevention of pleural effusion
Sawabata *et al.* (2002) Japan [9]; Ann Thorac Surg Retrospective single-centre case series (level 3)	Between 1980 and 1994, 43 patients were evaluated *Subgroups* MPE (*n* = 22) MPN (*n* = 21) *Surgery* Complete resection (CR) (*n* = 11) Incomplete resection (IR) (*n* = 14) Exploratory thoracotomy (ET) (*n* = 18) No chemotherapy	MST (months) YST (%)	Variables CR/IR/ET	*n* 11/14/18	MST 13/34/17	5-YST 9/10/0	*P* –	Surgery is not beneficial

[a]MPN vs MPE.
[b]MPE + MPN vs MPE.
[c]T2 vs T1.
[d]T3 vs T1.
*Group C vs Group A.

(MPN) but not MPE were excluded. Finally, eight papers were identified that provided the most applicable evidence to answer the question. They are presented in Table 1.

RESULTS

Okamoto *et al*. [2] reported 73 patients staged as M1a (32 had MPE and 41 MPN) and 25 as M1b. The median survival time (MST) of resected M1a vs M1b patients was 25.9 vs 8.7 months, respectively, $P < 0.01$. Fifty percent of patients had intrapleural chemotherapy; 33% also received adjuvant chemotherapy. The MST of MPE patients with N0–1 status (75.4 months) was better than of MPE with N2–3 (24.4 months; $P = 0.011$), of MPN with N0–1 (33.7 months) and of MPN with N2–3 (24.1 months). Pneumonectomy had worse MST than lesser resection (12.8 vs 24.1 months, respectively, $P = 0.0018$).

Ichinose *et al*. [3] enrolled 227 patients: 55 had MPE, 89 MPN and 83 MPE = MPN. Resection ($n = 193$) vs exploratory thoracotomy ($n = 34$) had better 3-year survival time (3-YST) (28.8% vs 10.9%, respectively) and 5-year survival time (5-YST) (14.9% vs 0%, respectively; $P = 0.04$). Six modalities of chemotherapy were registered. Histology of adenocarcinoma ($P < 0.028$), N0 status (0.006) and complete resection (0.045) were favourable prognostic factors.

Fukuse *et al*. [4] evaluated 49 patients: 16 presented MPE, 17 MPN and 16 MPN + MPE. Resected patients vs exploratory thoracotomy had a longer survival (37.9 vs 6.2 months, respectively). All patients received intrapleural and adjuvant chemotherapy. The MST of MPE patients (58.8) was better than MPN (10; $P = 0.0001$) and than MPE + MPN (19.3; $P = 0.019$) independently of other factors.

Shiba *et al*. [5] evaluated 65 patients; 25 had MPE (microscopic pleural involvement or D0) and 40 MPN with/or without MPE (macroscopic involvement or D1). A longer 5-YST was found in resected vs exploratory thoracotomy patients (14.3 vs 0%, respectively) and in D0 vs D1 patients (22.9 vs 8.9%, respectively, $P = 0.45$). All patients had only intrapleural chemotherapy. Histology of adenocarcinoma ($P = 0.02$), N0 status ($P = 0.01$) and low Ki-67 expression ($P < 0.0001$) were favourable prognostic factors.

Kodama *et al*. [6] operated on 31 patients with pleural involvement; six had MPE and 25 MPN with/or without MPE. Of these, seven were clinically diagnosed. After surgery, all patients received intrathoracic hyperthermic chemotherapy. N0–N1 vs N2 status had better 3-YST (68.4 vs 22.7%, respectively, $P < 0.01$) and 5-YST (48.7% vs 0%, respectively).

Shigemura *et al*. [7] operated on five patients with MPE with/or without MPN (four clinically diagnosed). All patients received a multimodality treatment with intrapleural hyperthermic chemotherapy and panpleuropneumonectomy. The MST was 19; the poorest survival 8 months (T4N2M0) and the longest 32 months (T4N0M0).

Kimura *et al*. [8] operated on 19 patients with MPE with/or without MPN. Before operation, seven patients received intrapleural hyperthermotherapy (Group A), five intrapleural hyperthermo-chemotherapy (Group B) and seven no additional therapy (Group C). All patients received systemic adjuvant chemotherapy. No survival difference was found between groups; Group C presented an earlier and higher recurrence of PE (57%) than Group B (20%) and Group A (0%; $P = 0.02$).

Sawabata *et al*. [9] found that surgery was not beneficial for MPE patients, also in the absence of pleural dissemination. The MST and 5-YST, respectively, were 13 and 9% for completely resected patients ($n = 11$), 34 and 10% for incompletely resected patients ($n = 14$; $P = 0.3$) and 17 and 0% for exploratory thoracotomy patients ($n = 18$; $P = 0.8$). No patient received adjuvant treatment, which may partially explain the poor prognosis.

CLINICAL BOTTOM LINE

The management of patients with positive cytology of PE is palliative [10]. The limitations of this analysis included the lack of retrospective studies, patient selection bias (enrolling patients with MPE only, patients with MPN and/or MPE + MPN) and various treatments applied. Three papers found that surgery vs exploratory thoracotomy had a survival advantage in cases of minimal pleural disease [2, 4, 5]. One paper showed that MPE patients had a better MST (58.8 months) than MPN (10 months; $P = 0.0001$) and MPE + MPN patients (19.3 months; $P = 0.019$), independently from other factors [4]. Another showed that MPE patients with N0–1 status had an MST longer than patients with similar or more extensive pleural involvement but with N2–N3 status [2]. A further study demonstrated a 5-YST benefit of MPE vs MPN patients (22.9 vs 8.9%; respectively, $P = 0.45$) [5].

In two papers, surgery vs exploratory thoracotomy had better survival in case of N0 status and complete tumour resection [3, 6]; different pleural dissemination was not analysed.

Different strategies, including pneumonectomy and lobar or lesser resection, were employed to obtain freedom from macroscopic residual tumour associated with pleurectomy in patients having pleural dissemination. Only one paper reported a worse MST after pneumonectomy vs more limited resections (12.8 vs 24.1 months; respectively; $P = 0.0018$) [2]. In the remaining papers, no comparison between different resections was attended [3–6, 8]. Only three studies included the operative mortality [4, 7, 8]. In all studies [2–8], with the exception of one [9], surgery was a component of multimodality treatment. Intrapleural chemotherapy was generally applied [2–8], with systemic adjuvant chemotherapy [2–4, 7, 8] and/or radiotherapy [3, 4]. The study period and/or year of publication of most papers was 10 years or more, resulting in different chemotherapy regimens adopted [2–8]. No current guidelines support surgery over conservative therapy and the identified studies in this review are not strong enough to change this recommendation.

Conflict of interest: none declared

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