BRIEF REPORT

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Feasibility and safety of extended pleurectomy/decortication for malignant pleural mesothelioma. A single group experience

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Abstract

Surgery is part of a multimodal therapeutic approach to malignant pleural mesothelioma (MPM) although its real beneficial effect is still controversial. The optimal precise sequence of treatments within the trimodality is unclear, and should be decided upon a multidisciplinary consensus for each individual patient. Here, we analyzed the perioperative data of 19 MPM patients who underwent extended pleurectomy/decortication (EPD) with curative intent. The mean age at diagnosis was 67 years; 11 males and eight females. Ten patients were diagnosed with MPM via medical thoracoscopy (MT), and nine via video-assisted thoracoscopic surgery (VATS). The vast majority of cases harbored epitheliod forms. We compared neoadjuvant chemotherapy (NCT) followed by surgery (11 cases) versus surgery followed by adjuvant chemotherapy (ACT, 8 cases) within a 3-year period. All patients had extended pleurectomy/decortication and none had an extended pneumonectomy. Analysis of survival curves suggested that the short-term outcomes are better with upfront EDP followed by ACT if compared to EDP preceded by NCT. Although limited, the data highlighted the safety and feasibility of EPD, with manageable postoperative complications and no major burden for the patients.

KEYWORDS
malignant pleural mesothelioma, pleurectomy, multidisciplinary

INTRODUCTION

The management of malignant pleural mesothelioma (MPM) consists of a multidisciplinary approach with chemotherapy, surgery, and radiotherapy in selected cases.[1–3]

Although the multimodal treatment scheme for MPM has been uniformly accepted, the sequence of the different treatment modalities has not yet been standardized. The Interdisciplinary Group on Thoracic Neoplasms (GINT) in our Institution discuss treatment strategy case by case, opting either for neoadjuvant chemotherapy followed by extended pleurectomy/decortication EPD (NCT/EPD) or oppositely for EPD followed by adjuvant chemotherapy (EPD/ACT) with or without radiotherapy. The aim of this study was to retrospectively analyze and compare the perioperative data and short-term outcomes of our patients undergoing NCT/EPD versus EPD/ACT.

METHODS

Patient identification, selection, and data analysis

We retrospectively analyzed a consecutive series of MPM patients who underwent EPD with curative intent from July 2019 to July 2021 in the Thoracic Surgery Unit at the IRCCS Fondazione Policlinico San Matteo. Within 3 years of the study, overall we evaluated 52 novel diagnoses; of these 19 entered the present project, whereas the remaining 43 patients harbored advanced disease. Each case was evaluated and discussed by a multidisciplinary team, based on the AIOM (Associazione Italiana di Oncologia Medica—Linee Guida AIOM 2019 Mesotelioma pleurico) and NCCN (National Comprehensive Cancer Network, website at Guidelines Detail (nccn.org]) guidelines and the local PDTA (Percorso Diagnostico Terapeutico e Assistenziale – Territorial Diagnostic, Therapeutic and Assistance Planning) for MPM, active since 2014 and defined within the Provincial Oncology Intercompany Department (DIPO) of Pavia.[3] It is clearly recommended by the national and international guidelines that MPM patients susceptible to multimodal approaches encompassing surgery, should be referred to specialized centers and evaluated by multidisciplinary teams to assess the best optimal treatment sequence in a personalized manner.

For each case, data were collected from the anamnestic records, outpatient reports, operative reports and discharge letters of the Thoracic Surgery Unit and the outpatient clinic of asbestos–related diseases at IRCCS Policlinico San Matteo and are summarized in Tables 1 and 2. Inclusive criteria for surgery is detailed in Table 3.

The treatment goal with surgery is to achieve macroscopic complete resection (MCR), defined as the removal of all grossly visible and palpable tumor in the affected hemithorax. For this purpose, the main surgical options are either extrapleural pneumonectomy (EPP) or extended pleurectomy/decortication (EPD). EPP is defined as the en bloc resection of the lung with the visceral and parietal pleura, with or without affected diaphragm and/or pericardial resection. EPP was found to have a higher perioperative morbidity and mortality in comparison to EPD, while the overall survival difference was negligible.[4] For this reason and for personal experience, in our center the operation of choice for surgical candidates is EPD, which is defined as a lung-sparing procedure consisting of the parietal and visceral pleurae exeresis, including the diaphragm and /or the pericardium. Currently in the UK, the MARS 2 study is comparing effectiveness of EPD versus no surgery for treatment of MPM testing the hypothesis that surgery and chemotherapy is superior to chemotherapy alone with respect to overall survival.[5] In our center, EPD is performed via open lateral thoracotomy, possibly muscle-sparing, to allow an increased field of view and maneuver during decortication. In this way, MCR is prioritized over mini-invasiveness which would be guaranteed with an approach by video-assisted thoracoscopy (VATS). However, a hybrid approach may be preferred by employing the thoracoscope in a later phase of EPD, when the thoracic cavity has been cleared and most of the pleurae has been resected: this may provide a thorough exploration of the entire cavity with an increased image resolution to identify eventual remaining affected pleura. The diagnostic work-up in all patients consisted of a chest x-ray (CXR) followed by CT scan together with an exhaustive environmental and occupational history of asbestos-exposure. Typical imaging features in CXR include a unilateral pleural effusion, pleural mass, and varying degrees or pleural thickening. Other characteristic features include reduced volume of the involved lung, lymphadenopathy in the mediastinum, destruction of a rib due to local invasion and, most commonly, shifting of the mediastinum.[6,7] Although these features are indicative, and CXR is the recommended first-line evaluation, CT has diagnostic, categorical and prognostic importance. CT features that are suggestive of MPM are similar to those in CXR but are greater in number and detail, allowing the allocation of patients to either medical thoracoscopy (MT) or VATS for definitive diagnosis of MPM. These two procedures have several similarities and differences and require sampling pleural biopsies for histological definitive diagnosis of MPM. In our center, MT is performed by interventional pulmonologists: the patient is spontaneously breathing under moderate sedation with local anesthesia and only one entry port is required. VATS is performed by thoracic surgeons: in this case, the patient is placed under general anesthesia and is then intubated in the operating room (OR), with a bilumen tube in case single-lung ventilation is required.[8] One or two 1 cm incisions are used for the entry ports. VATS is required when the affected hemithorax is expected to have several adherences with fibrous bands and/or multiple loculated effusions that would be otherwise difficult to remove via MT.[8] After MT/VATS all patients receive talc pleurodesis to manage malignant pleural effusions. MT and VATS also play an important role in the decision-making process as to whether to refer the patient for either upfront surgery first or proceed with induction

chemotherapy. Simultaneously with diagnostic pleural biopsies, they allow the degree of affected pleura to be identified macroscopically. The direct visualization of the macroscopic pleural involvement may assist in patient selection: a low macroscopic disease burden may result in a higher chance of maximum cytoreduction, while on the other hand a high disease burden may result in increased difficulty to reach MCR with EPD. In particular, the involvement of the lung fissures is generally a contraindication from the surgical point of view to perform decortication. Second, MT/VATS at the time of pleural biopsies offers another vital insight for MPM management: the feasibility of pleural resection for biopsies. The easier the bioptic samples are resected, the higher the chance to reach MCR; while a pleura that is tenacious to be resected

T A B L E 1 Description of the population cohort analyzed for each cohort

PARAMETER	NCT/EPD ($n = 11$)	EPD/ACT ($n = 8$)
Age at diagnosis (years)		
• Mean (IQR)	67 (60–72)	67 (63–71)
Gender		
• Male	6	5
• Female	5	3
Cigarette smoking habit		
• None	7	5
• Past smoker	3	2
• Current smoker	1	1
Absestos exposure		
• None	4	3
• Environmental	6	4
• Occupational	1	1
Diagnostic procedure for pleural biopsy		
• MT	5	4
• VATS	6	4
Macroscopic pleural involvement at MT/VATS		
• Parietal only	3	4
• P. + diaphragmatic	3	2
• P. + D. + visceral	5	2
Definitive histology		
• Epithelioid	10	7
• Sarcomatoid	0	0
• Biphasic	1	1
Weeks from VMT/VATS to surgery		
• Mean (IQR)	26 (19–31)	6 (4–7)
Hemoglobin concentration (g)		
• Preoperative (IQR)	12.5 (11.3-13.5)	13.3(13.0-13.5)
• Postoperative (IQR)	10.4 (9.4–10.9)	11.3(10.4–12)
Postoperative course and complications		
• Persistent air leak	1	2
• Anemia	9	4

(Continues)

T A B L E 1 (Continued)

PARAMETER	NCT/EPD ($n = 11$)	EPD/ACT ($n = 8$)
• Mean pRBCs§ sack	2.2	1.2
• ICU observation	3	1
Postoperative hospital stay (days)		
• Mean (IQR)	11 (9–10)	14 (6–16)
Pleural thickness (mm) at surgical specimen		
• Visceral	4.3	3.1
• Over cutpoint (5 mm)	3	1
• Parietal	5.8	4.3
• Over cutpoint (5 mm)	6	2
• Diaphragmatic	4.5	4.4
• Over cutpoint (5 mm)	4	3

Inclusion criteria for determining patients suitable for surgery include: (i) age ≥ 18 years (ii) the absence of mediastinal lymph node (N) involvement; (iii) absence of the involvement of the mediastinal pleural layer and of pericardium; (iv) tumor extension >50% of pleura surface evaluated during thoracoscopy; (v) any previous pleurodesis or talcade procedures; together with general positive evaluation assessed by: ECOG performance status 0–2; adequate respiratory function on clinical assessment; left ventricular ejection fraction (LVEF) ≥ 50% as determined by echocardiogram; ability to give informed consent prior to any screening procedures being performed and be capability of complying with the protocol and its requirements; routine hematological and biochemical indices within the normal ranges; life expectancy ≥3 months. D, diaphragmatic; ICU, intensive care unit; IQR, interquantile range; MT, medical thoracoscopy; P, parietal; RBC, red blood cells; VATS, video-assisted thoracoscopic surgery.

and offers increased resistance for biopsies may be a contraindication to perform EPD before chemotherapy, predicting a possible complex decortication and an unsatisfactory MCR. These aspects, together with the presurgical parameters such as performance status, no cardiovascular or pulmonary risks, are evaluated and discussed during GINT to refer the patient for proper treatment sequence evaluating the possibility of an upfront surgery rather than an induction chemotherapy potentially followed by surgery. In detail accurate oncological and functional preoperative staging includes: (1) The absence of mediastinal lymph node (N) involvement investigated by imaging (computed tomography [CT] scan, positron emission tomography [PET]) and if necessary, by tissue aspirate through endobronchial ultrasound; (2) absence of the involvement of the mediastinal pleural layer and of pericardium; and (3) tumor extension >50% of pleura surface evaluated during diagnostic thoracoscopy.

Basic descriptive analysis was assessed in the study population. It should be noted that in the case of countable data, the patients were classified into two groups and if the number was low, a binomial test was used. However, as a general rule, binomial distribution should not be applied to observations from a simple random sample (SRS) unless the population size is at least 10 times larger than the sample size. Thus, descriptive statistics could not be performed in the cohort analyzed (11 vs. 8 cases), although samples were coherent wth already literature and epidemiologic known data. Kaplan–Meier curves for DFS and OS each cohort

TABLE 2 Systemic therapy regimen administration and clinical outcome

Systemic therapy	NCT/EPD (n = 11)	EPD/ACT (n = 8)
First-line regimen		
• Cisplatin + pemetrexed	11	7
• Carboplatin + gemcitabine	0	1
Second-line regimen		
• Gemcitabine	4	2
• Vinorelbine	1	0
• None	5	5
Third-line regimen		
• Vinorelbine	2	1
• Gemcitabine	1	0
• None	7	7
Parameter	**NCT/EPD (n = 11)**	**EPD/ACT (n = 8)**
Disease status after NCT		
• Stable disease	7	/
• Regression	3	/
• Progression	1	/
Disease status after surgery		
• Progression/recurrence at 3 months	8	1
• Disease-free at 3 months	3	7
• Progression/recurrence at 6 months	8	3
• Disease-free at 6 months	3	5

TABLE 3 Inclusion criteria for determining patients suitable for surgery

Inclusive surgical criteria
Age ≥ 18 years;
ECOG performance status 0–1;
Adequate respiratory function on clinical assessment
Left ventricular ejection fraction (LVEF) ≥ 50% as determined by echocardiogram
Able to give informed consent prior to any screening procedures being performed and be capable of complying with the protocol and its requirements
Hematological and biochemical indices within the ranges shown below: • Hemoglobin (Hb) ≥ 9 g/dl (transfusion to achieve this allowed); • Neutrophils ≥ 1500/µl; • Platelet count ≥ 100 000/µl; • AST or ALT ≤2.5 × ULN; • Alkaline phosphatase ≤5 × ULN; • Serum bilirubin ≤1.5 × ULN;
Life expectancy of at least 3 months

have been obtained through MedCalc software for each cohort.

RESULTS

Clinical features of the cohort analyzed

We identified and selected 19 patients who underwent EPD with curative intent from July 2019 to July 2021: 11 patients (57.89%) were referred to the neoadjuvant chemotherapy +- EPD treatment scheme (NCT/EPD), while eight patients (42.11%) were referred to the upfront EPD + adjuvant chemotherapy treatment scheme (EPD/ACT). Table 2 shows the epidemiological, clinical, and significant data for each cohort. Of the 19 patients, eight (42%) were female and 11 (58%) were male; median age at diagnosis was 67.07 years. The median age at which patients were assessed for possible surgery was 67.2 years. Clinical conditions were similar after surgery and only one patient had a worse state with ECOG 2. The clinical signs and symptoms observed in most cases were dyspnea and chest pain, associated with dry cough; one patient was completely asymptomatic. Imaging findings at diagnosis were, for all patients, massive pleural effusion at the initial chest x-ray. The side of interest by the onset of the disease was equally distributed as the right

hemithorax was involved in 10 patients (53%) and the other nine of the left one. The macroscopic thoracoscopic appearance was limited to the parietal pleura in seven (37%) cases, involving concomitantly the parietal and diaphragmatic pleura in five (26%) cases, whereas in the remaining seven (37%) cases a diffuse involvement of the parietal, visceral and diaphragmatic layers was reported. Average levels of preoperative hemoglobin were 12.8 g/dl, whereas after surgery 10.4 g/dl (average variation of 2.03 g/dl).

Clinical outcomes

Only four (21%) out of the 19 patients required Intensive Care Unit observation after surgery. No major postoperative complications were observed: anemia occurred in 14 (74%) patients and three (16%) patients who presented with persistent air leak after surgery. Overall, the average hospital stay after surgery was 12.6 days. All data are described in detail in Table 1. All the patients had epithelioid histology at the time of MT/VATS pleural biopsies. However, one (5%) patient for each cohort was diagnosed as biphasic at the pathological analysis of the surgical specimen after EPD. We calculated the average weeks passed from MT/VATS to EPD in the two cohorts: for NCT/EPD was 26 (IQR: 19–31), whereas for EPD/ACT was 6 weeks (IQR: 4–7). These time intervals are explained by two main processes: (1) 1–2 weeks for the histopathological diagnosis, and obviously (2) the chemotherapy cycles which delays surgery inevitably for the NCT/EPD. The agents administered as systemic therapy for each cohort are shown in detail in Table 2. All the patients received chemotherapy as first-line treatment, either preceding or following surgery. The first-line chemotherapeutic regimen (both neoadjuvant and adjuvant) administration was cisplatin + pemetrexed in 18 (95%) patients for three cycles and in patients with stable disease three more cycles.
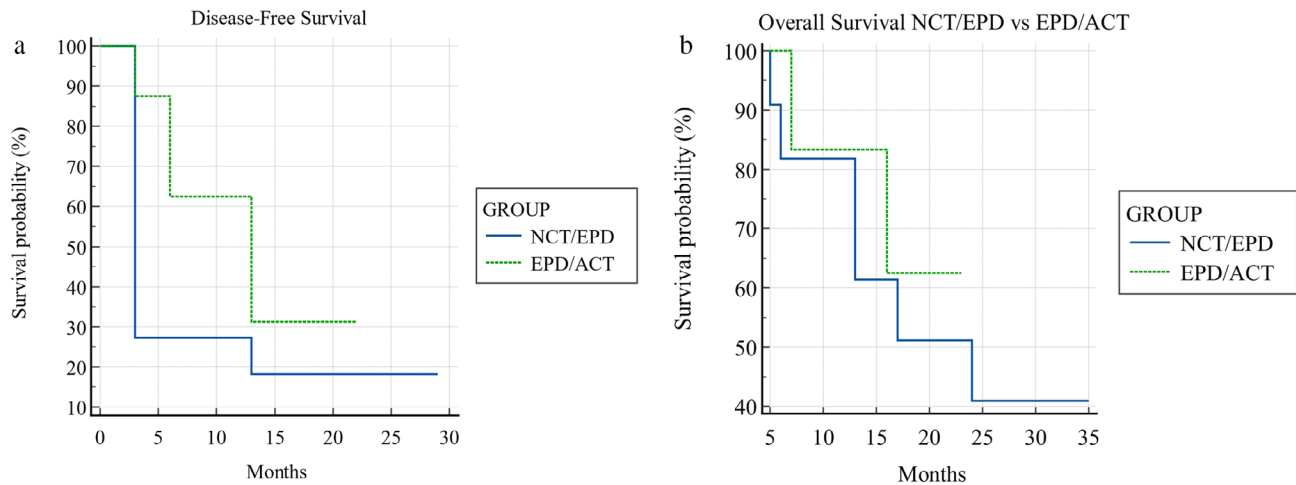
FIGURE 1 Kaplan–Meier curves for DFS and OS in the two cohorts analyzed

Only one (5%) patient received carboplatin + gemcitabine regimen as first-line therapy. The second-line chemotherapy agent mainly employed was gemcitabine for both groups, while the third-line agent was mainly vinorelbine. Table 3 shows in detail the disease status before and after surgery in each cohort. For the NCT/EPD cohort, we analyzed the disease status after NCT based on the restaging CT scan before surgery: seven (37%) patients showed stable disease, three (16%) patients showed regression of the disease while only one (5%) showed minimal progression before surgery consisting of a small percentage of size increase of the known pleural plaques. This patient underwent surgery regardless of disease progression thanks to an extremely high PS, absence of comorbidities and young age. We then moved to analyze disease-free survival (DFS) of the patients at the first and second CT scan after surgery, at 3 and 6 months, respectively. In the NCT/EPD group, eight (42%) patients showed progression or recurrence of the disease 3 months after surgery at the first restaging CT scan. Exclusively, the three (16%) patients showing regression after NCT were those who did not progress after the first and second restaging CT scan. At the time of this study, two (10.5%) patients were still disease-free with a PFS of 17 and 26 months, while one (5%) showed recurrence at the 13th month. In the EPD/ACT group, seven (37%) patients were disease-free at the first restaging CT scan 3 months after surgery, while only one (5%) patient showed recurrence. The latter died 7 months after surgery due to cancer recurrence. Among the remaining seven patients, two (28%) progressed after 6 months at the second CT scan after surgery, while five (72%) patients were disease-free. At the time of this study, only one (20%) out of the five patients showed disease recurrence (13 months after surgery). Kaplan–Meier estimates for each cohort disease-free survival are illustrated in Figure 1a. Median DFS for the entire cohort was 6 months (95% confidence interval [CI]: 3–13). The EPD/ACT patients had a higher median DFS (median 13 months; 95% [CI]: 3–13) than NCT/EPD patients (median 3 months; 95%

[CI]: 3–13) ($p = 0.13$). Kaplan–Meier estimates for each cohort overall survival are illustrated in Figure 1b. Median overall survival (OS) was 22.3 months (95% [CI]: 16.5–28.1). For NCT/EPD, the mean OS was 20.6 months (95% CI: 13.6–27.6), whereas for EPD/NCT 18.9 months (95% CI: 14.0–23. 8) ($p = 0.44$).

DISCUSSION

The preliminary findings of this study allow us to draw some conclusions that may help in the case-by-case discussion to determine which patients are suitable for surgery either preceding or following chemotherapy. First, the diagnostic method for pleural biopsy was not a criterion for treatment sequence selection. The patients were equally directed to surgery regardless of the biopsy approach that was performed by pulmonologists in cases of MT, whereas directly by the thoracic surgeons in case of VATS according to an efficient multidisciplinary collaboration. Second, the perioperative data confirmed the feasibility of EPD in both groups as a result of the low postoperative morbidity and nil mortality. Nevertheless, the two cohorts showed some differences in the postoperative course. For instance, hemoglobin variation before and after surgery was about 2 g/dl for both groups: this data reflects the nature of EPD consisting of bloody pleural stripping and decortication. However NCT/EPD patients showed an increased tendency to anemia in the following days: 81.2% of patients required hemotransfusions compared to 50% that underwent upfront decortication. Moreover, three patients NCT/EPD versus one patient EPD/ACT were admitted to the ICU directly from the OR after surgery. Persistent air leak occurred in 16% of cases (one case in the NCT/EPD group versus two cases in the EPD/ACT group) and resulted in prolonged chest tube stay and invariably to longer hospitalization (from 24 to 33 days). For this reason, the average hospitalization length after surgery was slightly longer in the EPD/ACT group

(14 days vs. 11 days). Third, as short-term outcomes we investigated disease-free and overall survival at 3 and 6 months after surgery. In the NCT/EPD cohort, only 16% of patients showing regression at restaging CT scan after neoadjuvant chemotherapy did not show progression/ recurrence at 3 and 6 months after surgery. Unfortunately, all the patients with stable disease after NCT showed progression/recurrence at 3 months after surgery and needed subsequent second-line chemotherapy. In the EPD/ACT cohort, seven patients remained disease-free at 3 months and five patients at 6 months after decortication: of these, five received adjuvant chemotherapy one month following surgery, while it was received by two patients 3 months after surgery. The survival curves for DFS of these preliminary data suggest that the short-term outcomes for DFS are better with upfront EDP followed by ACT compared to EDP preceded by NCT. Analogously, OS curves suggest a better survival in the former group.

Overall the study findings suggest an increased feasibility of EPD preceding chemotherapy rather than following it, since it is associated with lower postoperative morbidity and associated better short-term outcomes. In particular (1) corrected average postoperative stay was slightly lower in EPD/ACT, (2) anemia was significantly lower in patients undergoing upfront EPD with reduced pRBCs required, (3) and significantly less patients required postoperative ICU monitoring. Furthermore, DFS and OS curves seem to be improved in patient undergoing immediate decortication. However, it should be noted that this study has several limitations. First, the sample size cannot guarantee statistical significance for most of the data. Moreover, the cases analyzed are coherent essentially to epithelioid histology and no conclusion can be found on mixed or sarcomatoid MPMs. Second, the retrospectivity itself may influence the outcome of these preliminary data, either favoring or disfavoring each cohort. Further investigation and studies are thus needed. In this perspective, the NCT02436733 study, still ongoing, is a multicenter, randomized, noncomparative phase II trial which aims to evaluate the most advantageous approach in early stage MPM, by comparing immediate surgery followed by three cycles of chemotherapy versus three cycles of chemotherapy followed by P/D, for nonprogressing patients (website at www.clinicaltrial.gov). Although patients in both cohorts progress, the differences in the chemotherapy schedule used after first-line therapy do not allow the identification of the most efficient regimens. Moreover, none of the patients evaluated underwent radiotherapy (RT) treatment, and therefore no conclusions can be drawn regarding a full multimodal approach towards early stage disease. The analysis of a small series (17 cases) reported by Vicidomini et al. suggested that two cycles of induction chemotherapy, followed by PD and postoperative RT 3–6 weeks seemed to be feasible with a median OS of about 32 months.[9] The role of RT is supposed to acquire greater relevance into the next future multimodal regimens due to both novel techniques and abscopal interaction with immunotherapy,[10–12] which is now going to play a significant role against MPM.[13–15]

Although limited, our fundings highlight a rationale for local therapeutic delivery after a starting surgical approach with the aim, on one hand, of acting on the immunoinflammatory pathways which drive MPM progression[16,17] and, on the other hand, of limiting the systemic toxicities of chemo- and immunotherapy.[18–22]

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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REFERENCES
1. Popat S, Baas P, Faivre-Finn C, Girard N, Nicholson AG, Nowak AK, et al. Malignant pleural mesothelioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(2):129–42. https://doi.org/10.1016/j.annonc.2021.11.005
2. Bilancia R, Nardini M, Waller DA. Extended pleurectomy decortication: the current role. Transl Lung Cancer Res. 2018;7(5):556–61. https://doi.org/10.21037/tlcr.2018.06.07
3. Saracino L, Bortolotto C, Tomaselli S, Fraolini E, Bosio M, Accordino G, et al. Integrating data from multidisciplinary Management of Malignant Pleural Mesothelioma: a cohort study. BMC Cancer. 2021;21(1):762. https://doi.org/10.1186/s12885-021-08532-x
4. Cao C, Tian D, Park J, Allan J, Pataky KA, Yan TD. A systematic review and meta-analysis of surgical treatments for malignant pleural mesothelioma. Lung Cancer. 2014 Feb;83(2):240–5. https://doi.org/10.1016/j.lungcan.2013.11.026
5. Warnock C, Lord K, Taylor B, Tod A. Patient experiences of participation in a radical thoracic surgical trial: findings from the mesothelioma and radical surgery trial 2 (MARS 2). Trials. 2019;20(1):598. https://doi.org/10.1186/s13063-019-3692-x
6. Wang ZJ, Reddy GP, Gotway MB, Higgins CB, Jablons DM, Ramaswamy M, et al. Malignant pleural mesothelioma: evaluation with CT, MR imaging, and PET. Radiographics. 2004;24(1):105–19. https://doi.org/10.1148/rg.241035058
7. Cardinale L, Ardissone F, Gned D, Sverzellati N, Piacibello E, Veltri A. Diagnostic imaging and workup of malignant pleural mesothelioma. Acta Biomed. 2017;88(2):134–42. https://doi.org/10.23750/abm.v88i2.5558
8. Shojaee S, Lee HJ. Thoracoscopy: medical versus surgical-in the management of pleural diseases. J Thorac Dis. 2015;7(Suppl 4):S339–51. https://doi.org/10.3978/j.issn.2072-1439.2015.11.66
9. Vicidomini G, Della Corte CM, Noro A, Di Liello R, Cappabianca S, Fiorelli A, et al. A Trimodality, four-step treatment including chemotherapy, pleurectomy/decortication and radiotherapy in early-stage malignant pleural mesothelioma: a single-institution retrospective case series study. Cancers. 2021;14(1):142. https://doi.org/10.3390/cancers14010142
10. Alley EW, Katz SI, Cengel KA, Simone CB 2nd. Immunotherapy and radiation therapy for malignant pleural mesothelioma. Transl Lung Cancer Res. 2017;6(2):212–9. https://doi.org/10.21037/tlcr.2017.04.01
11. Barsky AR, Cengel KA, Katz SI, Sterman DH, Simone CB 2nd. First-ever Abscopal effect after palliative radiotherapy and immuno-gene therapy for malignant pleural mesothelioma. Cureus. 2019;11(2):e4102. https://doi.org/10.7759/cureus.4102
12. Mampuya WA, Bouchaab H, Schaefer N, Kinj R, La Rosa S, Letovanec I, et al. Abscopal effect in a patient with malignant pleural

mesothelioma treated with palliative radiotherapy and pembrolizumab. Clin Transl Radiat Oncol. 2021 Jan 1;27:85–8. https://doi.org/10.1016/j.ctro.2020.12.006

13. Grégoire M. What's the place of immunotherapy in malignant mesothelioma treatments? Cell Adhes Migr. 2010, 1;4:153–61. https://doi.org/10.4161/cam.4.1.11361

14. Gray SG, Mutti L. Immunotherapy for mesothelioma: a critical review of current clinical trials and future perspectives. Transl Lung Cancer Res. 2020;9(Suppl 1):S100–19. https://doi.org/10.21037/tlcr.2019.11.23

15. Ceresoli GL, Bonomi M, Sauta MG. Immune checkpoint inhibitors in malignant pleural mesothelioma: promises and challenges. Expert Rev Anticancer Ther. 2016 Jul;16(7):673–5. https://doi.org/10.1080/14737140.2016.1191951

16. Bograd AJ, Suzuki K, Vertes E, Colovos C, Morales EA, Sadelain M, et al. Immune responses and immunotherapeutic interventions in malignant pleural mesothelioma. Cancer Immunol Immunother. 2011;60(11):1509–27. https://doi.org/10.1007/s00262-011-1103-6

17. Abbott DM, Bortolotto C, Benvenuti S, Lancia A, Filippi AR, Stella GM. Malignant pleural mesothelioma: genetic and microenviromental heterogeneity as an unexpected Reading frame and therapeutic challenge. Cancers. 2020;12(5):1186. https://doi.org/10.3390/cancers12051186

18. Lisini D, Lettieri S, Nava S, Accordino G, Frigerio S, Bortolotto C, et al. Local therapies and modulation of tumor surrounding stroma in malignant pleural mesothelioma: a translational approach. Int J Mol Sci. 2021;22(16):9014. https://doi.org/10.3390/ijms22169014

19. Choi AY, Singh A, Wang D, Pittala K, Hoang CD. Current state of pleural-directed adjuncts against malignant pleural mesothelioma. Front Oncol. 2022;12:886430. https://doi.org/10.3389/fonc.2022.886430

20. Cova E, Pandolfi L, Colombo M, Frangipane V, Inghilleri S, Morosini M, et al. Pemetrexed-loaded nanoparticles targeted to malignant pleural mesothelioma cells: an in vitro study. Int J Nanomed. 2019;14:773–85. https://doi.org/10.2147/IJN.S186344

21. Chan WH, Sugarbaker DJ, Burt BM. Intraoperative adjuncts for malignant pleural mesothelioma. Transl Lung Cancer Res. 2017;6(3):285–94. https://doi.org/10.21037/tlcr.2017.05.04

22. Bertoglio P, Aprile V, Ambrogi MC, Mussi A, Lucchi M. The role of intracavitary therapies in the treatment of malignant pleural mesothelioma. J Thorac Dis. 2018;10(Suppl 2):S293–7. https://doi.org/10.21037/jtd.2017.10.165