Ⅲ.　研究成果の刊行に関する一覧表

＜研究成果の刊行に関する一覧表＞

【 書　籍 】

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
藤本伸一	悪性胸膜中皮腫	福井次矢、高木誠、小室一成	今日の治療指針－私はこう治療している―2024 年版	医学書院	東京	2024	307-308
宮藤遥子、藤本伸一	中皮腫の治療	松野吉宏、鍋島一樹編	腫瘍病理鑑別診断アトラス「縦隔腫瘍・胸膜腫瘍　第 2 版」第 4 部臨床との連携	文光堂	東京	2022	307-310

【 雑　誌 】

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Hasegawa S, Shintani Y, Takuwa T, Aoe K, Kato K, Fujimoto N, Hida Y, Morise M, Moriya Y, Morohoshi T, Suzuki H, Chida M, Endo S, Kadokura M, Okumura M, Hattori S, Date H, Yoshino I.	Nationwide prospective registry database of patients with newly diagnosed untreated pleural mesothelioma in Japan.	Cancer Sci.	115(2)	507-528	2024
武口哲也、藤本伸一	中皮腫における薬物治療の現況と今後の展望	週刊医学のあゆみ	289(3)	207-208	2024
Fujimoto N.	Spare the lung: surgical treatment approach for malignant pleural mesothelioma.	Transl Lung Cancer Res.	12(2)	197-199	2023
Tanaka T, Asakura S, Hisamatsu K, Fujimoto N.	Thrombocytopenia as an immune-related adverse event in malignant pleural mesothelioma: a case report.	TO Clin Res Rep.	3(7)	100351. doi: 10.1016/j.jtocrr.2022.100351.	2022

＜研究成果の刊行に関する一覧表＞

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Nagamatsu Y, Sakyo Y, Barroga E, Koni R, Natori Y, Miyashita M.	Bereaved Family Members' Perspectives of Good Death and Quality of End-of-Life Care for Malignant Pleural Mesothelioma Patients: A Cross-Sectional Study.	J Clin Med.	11(9)	2541. doi: 10.3390/jcm11092541.	2022
Nagamatsu Y, Sakyo Y, Barroga E, Koni R, Natori Y, Miyashita M.	Depression and Complicated Grief, and Associated Factors, of Bereaved Family Members of Patients Who Died of Malignant Pleural Mesothelioma in Japan.	J Clin Med.	11(12)	3380. doi: 10.3390/jcm11123380.	2022
原尚史, 藤本伸一	1. 診断総論 (2) 胸膜中皮腫の診断総論	日本臨牀	80 (増刊号 8):	176-180	2022
Miyamoto Y, Kozuki T, Aoe K, Wada S, Harada D, Yoshida M, Sakurai J, Hotta K, Fujimoto N.	JME-001 phase II trial of first-line combination chemotherapy with cisplatin, pemetrexed, and nivolumab for unresectable malignant pleural mesothelioma.	J ImmunoTherapy Cancer	9(10)	e003288 doi: 10.1136/jitc-2021-003288.	2021

Ⅳ.　研究成果の刊行物・別刷

者に事前に説明するとともに，継続してそれらの症状がないかフォローする．
・トラメチニブは，冷蔵庫（2～8℃）で保管するよう説明する．ダブラフェニブ，トラメチニブはボトルでの払い出しであり，1回内服量について事前に説明する．
・テポチニブ，セルペルカチニブ，ソトラシブの特定されたリスクとして，間質性肺疾患や肺機能障害が報告されている．
・エヌトレクチニブは，小児に投与する場合は週5日投与および週3日投与のときがある．患者本人だけでなく家族にも説明する．
（下線部：RMP-重要な特定されたリスク）

エビデンス・文献

悪性胸膜中皮腫

malignant pleural mesothelioma

藤本伸一　労働者健康安全機構岡山労災病院・腫瘍内科部長

頻度　あまりみない
GL 肺癌診療ガイドライン 2022 年版―悪性胸膜中皮腫・胸腺腫瘍含む

治療のポイント

- 切除可能と判断される症例には外科療法に術前あるいは術後の化学療法，さらに胸膜肺全摘術施行例には術後の片側胸郭照射を加えた集学的治療を検討する．
- 切除不能例に対しては，免疫チェックポイント阻害薬の併用療法，あるいはシスプラチン＋ペメトレキセド併用化学療法を行う．
- 診断，治療とも専門性が高く，経験を有する外科医，内科医，放射線科医，病理医などによる合議が必要である．

病態と診断

A 病態

- 悪性胸膜中皮腫は，壁側胸膜から生じる，腫瘍細胞が中皮細胞由来または中皮細胞への分化を示す悪性腫瘍である．
- 過去のアスベスト曝露に起因することが多く，わが国においても全体の約8割の症例において，職業あるいは住環境などによるアスベスト曝露との関連が示唆されている．
- 過去のアスベスト曝露から30～40年の潜伏期間ののちに発症することが多く，70歳前後に好発し，男女比はほぼ4：1である．
- 直近のデータでは，本邦では年間約1,800人が発症し，約1,600人が死亡している．
- 胸水貯留による息切れ，咳にて発症することが多く，発熱，胸痛，食欲低下，体重減少を伴うことも多い．

B 診断

- 胸部X線あるいはCTにて胸水貯留や不整な胸膜肥厚を認める．典型例では胸膜腫瘤あるいは腫瘍性胸膜肥厚を認めるが，明らかに悪性病変を示唆するような腫瘤を認めなくても，特に縦隔側の胸膜に不整な肥厚像を認める場合は積極的に胸膜中皮腫を疑う必要がある．
- 胸水を認める場合，胸腔穿刺により胸水を採取するが，胸水細胞診のみでは診断確定に至らない場合が多い．セルブロックを用い後述する免疫染色を組み合わせることで診断率が高まる．
- 胸水中のヒアルロン酸値が高値を呈する場合，胸膜中皮腫が強く疑われるが，診断感度は高くない．
- 可能な限り全身麻酔下での胸腔鏡検査により胸膜生検を行い，免疫染色を用いて病理的に診断する．
- 免疫染色において，単一で診断できるマーカーはないため，複数の陽性マーカーと陰性マーカーを組み合わせて診断する．陽性マーカーとしてカルレチニン，WT-1，D2-40，AE1/AE3，CAM 5.2など，陰性マーカーとしてCEA，claudin-4，TTF-1，Napsin Aなどが用いられる．これらを組織亜型，鑑別すべき疾患に応じて選択する必要がある．
- *p16*のホモ接合性の欠失は診断に有用であり，関連する*BAP1*あるいは*MTAP*の消失も診断に有用である．

治療方針

肉眼的な完全切除が可能と判断される全身状態が良好な上皮様症例に対しては，手術に術前あるいは術後の化学療法を組み合わせた集学的治療が行われる．手術療法は，以前は胸膜肺全摘術が主であったが，近年は肺を温存する胸膜剝皮術が主流となっている．胸膜剝皮術後の放射線療法は肺臓炎のリスクが高く，臨床試験以外では勧められない．

切除不能と判断される症例に対しては以下の薬物療法が選択される．

A 1次治療

Rx 処方例　下記のいずれかを用いる．

1) ニボルマブ（オプジーボ）注　1回360 mg　1日1回　3週ごと，または1回240 mg　1日1回　2週ごと＋
イピリムマブ（ヤーボイ）注　1回1 mg/kg　1日1回　6週ごと
点滴静注（病勢悪化まで2年間を上限に継続）
2) シスプラチン（ランダ）注　1回75 mg/m^2　1日1回＋
ペメトレキセド（アリムタ）注　1回500 mg/

m^2　1日1回
点滴静注　3週ごとに4〜6コース行う

Ⓑ 2次治療

℞ 処方例　下記のいずれかを用いる．

1) ニボルマブ（オプジーボ）注　1回480 mg　1日1回　4週ごと，または1回240 mg　1日1回　2週ごと　点滴静注（病勢悪化まで継続）
2) ゲムシタビン（ジェムザール）注　1回1,000 mg/m^2　第1，8，15日　点滴静注　4週ごと（病勢悪化まで継続）保外
3) ビノレルビン（ナベルビン）注　1回25 mg/m^2　第1，8日　点滴静注　3週ごと（病勢悪化まで継続）保外

1次治療でペメトレキセドが投与されていない症例に対しては，2次治療としてペメトレキセドとプラチナ製剤の併用療法を考慮する．

▶専門医へのコンサルト

- 原因不明な胸水を認める場合，特に過去のアスベスト曝露歴がある場合は積極的に胸膜中皮腫を疑い，胸腔鏡検査などによる胸膜生検を考慮する必要がある．
- 病理診断やその後の治療方針の決定は内科医，外科医，放射線科医を含め集学的に行われる必要があり，それらの経験を有する専門施設へのコンサルトが望ましい．

▶患者説明のポイント

- 原因不明な胸水を認める場合は，過去のアスベスト曝露歴について詳細に問診する．胸膜中皮腫が疑われる場合は専門施設による精密検査を勧める．
- 悪性胸膜中皮腫と診断された場合，職業性石綿曝露歴があれば労災保険における補償，また労災保険の補償対象とならない場合は石綿健康被害救済法に基づく救済制度の対象となるため，適切に情報提供をする必要がある．

▶看護・介護のポイント

- 予後不良で治療の選択肢が限られ，また早期から痛み，呼吸困難などの症状を伴う．身体的な痛みに加えアスベスト曝露に関連する心理的・社会的な苦痛により不眠，うつなどが起こりやすい．疼痛管理やカウンセリングなど，多方面からのケアが重要である．

縦隔腫瘍

mediastinal tumor

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頻度　あまりみない

GL 肺癌診療ガイドライン2022年版―悪性胸膜中皮腫・胸腺腫瘍含む

治療のポイント

- 縦隔内に発生する原発性腫瘍のうち，胸腺，リンパ節，神経，心膜，縦隔胸膜，迷入甲状腺，迷入副甲状腺，脂肪組織から発生する縦隔内の腫瘍や嚢胞性病変を総称して縦隔腫瘍とよぶ．甲状腺腫瘍の縦隔内進展は縦隔腫瘍に含める．また，気管支，食道，心膜から発生する嚢胞は新生物ではないが，慣例的に縦隔腫瘍に含められる．発生臓器，発症年齢，良悪性，病理学的診断の点で多様な腫瘍が包含される．
- 原発臓器の種類と悪性度によって，外科治療，薬物療法，放射線治療，およびこれらの組み合わせの治療が選択される．治療方針を決定するために，生検による病理診断が必要になることがある．
- 最も頻度の高い疾患は胸腺上皮性腫瘍である．胸腺上皮性腫瘍には正岡病期分類とUICCによるTNM病期分類があり，病期診断によって治療法を決定する．

病態と診断

Ⓐ 病態

- 主な疾患は胸腺上皮性腫瘍，胸腺胚細胞性腫瘍，神経原性腫瘍，リンパ系腫瘍，脂肪腫，嚢腫である．日本胸部外科学会の集計によると，2018年の1年間に本邦の749施設において手術を施行された縦隔腫瘍5,361例のなかで，胸腺腫が2,098例（39.1%）で最も多く，その次は気管支原性嚢腫などの先天性嚢腫1,224例（22.8%）であった．
- 小児の縦隔腫瘍は有症状が多く，悪性腫瘍が多い．成人では人間ドックのCTにより無症状で発見されることや，傍腫瘍症候群の合併で発見されることが多い．
- 胸腺腫には，重症筋無力症，赤芽球癆，低ガンマグロブリン血症（Good症候群）などの自己免疫疾患が合併することが知られている．
- 胸腺カルチノイドは多発性内分泌腫瘍症候群（MEN：multiple endocrine neoplasia）I型として発症することがある．クッシング症候群を合併することもある．
- 悪性腫瘍や巨大な腫瘍では，呼吸器系，循環器系，神経系，食道系への浸潤や圧迫による症状が出現する．上大静脈の閉塞による頭頸部の浮腫（上大静脈症候群）や気道の狭窄には，緊急の処置を必要とすることがある．

Ⓑ 診断

- 胸部CTにより腫瘍の局在（上縦隔，前縦隔，中縦隔，後縦隔）を決定する．
- 悪性胚細胞性腫瘍ではHCG，AFP，CEAが，リンパ腫では可溶性インターロイキン2受容体

Ⅲ．中皮腫の治療

はじめに

悪性胸膜中皮腫 malignant pleural mesothelioma（MPM）は壁側胸膜の中皮細胞に発生する予後不良な悪性腫瘍である．中皮腫の患者数は，かつての石綿の使用により世界的には現在でも増加傾向にある．本邦では，経済成長に伴い1970年から90年代にかけて大量の石綿が輸入されてきた．2012年にすべての石綿の使用が禁止されたが，過去の石綿曝露から中皮腫発症までの潜伏期間を考慮すると，今後の本邦における中皮腫の発生ピークは2030年頃と予測されている．また現在でも規制前の建築物の老朽化に伴う解体作業において飛散する石綿に曝露する可能性がある．

MPMの治療には外科治療，放射線治療，薬物治療がある．切除可能例には外科治療，切除不能例には薬物治療を中心に治療計画が立てられる．

1．外科治療

全身状態が良好で手術によって肉眼的完全切除 macroscopic complete resection（MCR）が達成できると考えられる症例は手術適応となる．ただしMPMは手術単独で予後を改善させるエビデンスはなく，手術は術前あるいは術後の化学療法等を含めた集学的治療の一環として施行される．MPMの手術では，壁側胸膜と周囲組織との切除マージンが存在しないため，R0切除（病理学的断端陰性）は不可能であり，R1切除（病理学的断端遺残陽性）を目指すこととなる．MCRを達成するための術式には，胸膜肺全摘術 extrapleural pneumonectomy（EPP）と胸膜切除/肺剝皮術 pleurectomy/decortication（P/D）の2種類がある．EPPは，壁側胸膜，臓側胸膜，一側肺，横隔膜，心膜を一塊に切除する拡大術式であり，P/Dは壁側胸膜，臓側胸膜のみを切除し，肺を温存する縮小術式である．

EPPとP/Dのいずれを選択すべきかについてはいまだ結論には至っていない．EPPとP/Dを直接比較した前向き試験は存在しないが，複数の後方視的解析によると両者の生存率に有意差は認められない．手術死亡率に関しては，P/D群が2.9％に対して，EPP群は6.8％と有意に高く，手術合併症発生率においても，P/D群が27.9％に対して，EPP群は62.0％であり，安全性の面ではEPPよりP/Dが優れる[1]．どちらの術式を選択すべきかについては，病変の分布，PS（performance status），予測される術後の呼吸機能等の患者それぞれの背景と，外科医や施設の技術や経験によって検討されるべきと考えられている[2]．

切除可能なMPMに対して，術前または術後のいずれかにおいて集学的治療の一環として化学療法が検討される．術前，術後のどちらに周術期化学療法を行うべきかについてはそれぞれにメリット，デメリットがあり結論に至っていない．

2．薬物治療

非手術適応症例や再発例では，薬物治療が治療の主体となる．

これまでMPMの薬物治療においては，ペメトレ

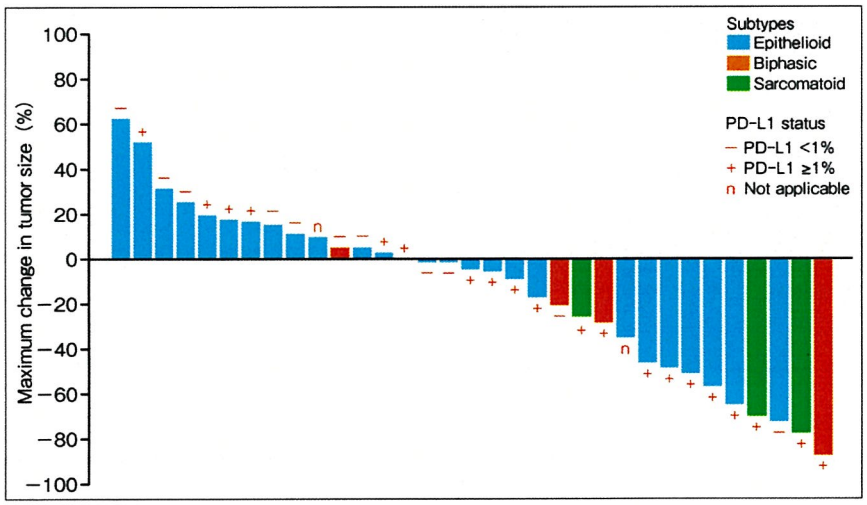


図1 | MERIT試験における各症例の腫瘍径の最大変化率
組織型を色別に，またPD-L1発現状況を−，+，nにて表示している．（文献5より）

キセドpemetrexed（PEM）とシスプラチンcisplatin（CDDP）の併用化学療法が，2003年に大規模臨床試験により有用性が報告されて以来唯一の標準化学療法として使用されてきた[3]．また実臨床ではCDDPが使用しにくい症例も多く，その場合はカルボプラチンcarboplatin（CBDCA）とPEMの併用療法が用いられている．これらのプラチナ製剤併用薬物治療は，一般的に3週間隔で計6コースの投与が推奨される．75歳以上の高齢者においても全身状態が良好であれば，これらの化学療法が選択される．

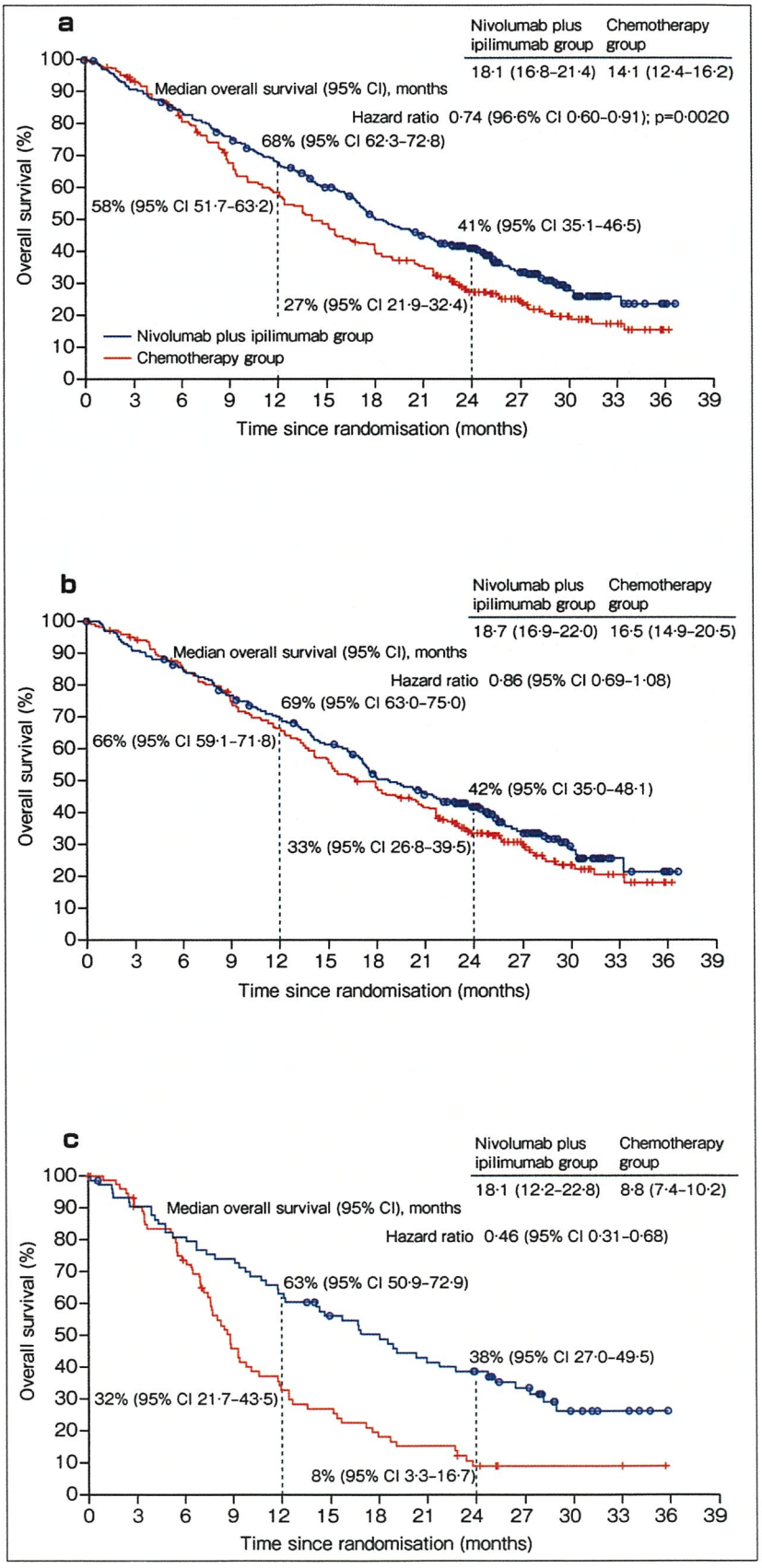
二次治療以降は選択肢が限られる．二次治療以降で使用される殺細胞性抗がん剤としては，ビノレルビン単剤，ゲムシタビン単剤が用いられることが多く，ビノレルビンとゲムシタビンの併用療法も選択肢となる[4]．PEM既治療例であっても一次治療を病勢進行のない状態で終了していた場合には，PEM単剤の再投与も選択肢の一つとなる．

CDDPとPEMの併用療法が標準的初回化学療法に位置づけられて以降10年以上にわたり，MPMの化学療法において目覚ましい進歩は認められなかった．しかし，2014年に本邦で免疫チェックポイント阻害薬が上市され次々に適応疾患が広がることとなった．ニボルマブは，ヒト型抗ヒトPD-1モノクローナル抗体であり，T細胞に存在するPD-1とがん細胞に存在するPD-1リガンド（PD-L1およびPD-L2）の結合を阻害することで，がん細胞によって不応となっていた抗原特異的T細胞を再活性化させ，抗腫瘍効果を発揮する．MPMにおいても，国内で既治療例を対象とした多施設共同第二相試験（MERIT試験）が行われ，34例中10例に部分奏効が得られ（奏効率29.4%）（**図1**），全生存期間中央値は17.3ヵ月と良好な結果が示された[5]．本試験をもとにニボルマブは，2018年8月に「がん化学療法後に増悪した切除不能な進行・再発の」MPMに対し承認された．MERIT試験では少数例ではあるがこれまであらゆる治療において抵抗性を示してきた肉腫型にも奏効例がみられ，朗報となった．

ニボルマブは，別の免疫チェックポイント阻害薬であるイピリムマブと併用することでMPMの初回治療においても有用性が報告されている．イピリムマブは，ヒト型抗ヒトCTLA-4モノクローナル抗体であり，CTLA-4とそのリガンドである抗原提示細胞上のCD80およびCD86分子との結合を阻害することにより，抗原特異的T細胞の増殖，再活性化を行い，抗腫瘍効果を発揮する．イピリムマブとニボルマブの併用療法をこれまでの標準化学療法であるCDDPまたはCBDCAとPEMの併用療法と比較する第Ⅲ相試験（CheckMate743試験）が行われ，全生存期間の中央値は，ニボルマブとイピリムマブ併用療法群で18.1ヵ月，化学療法群では14.1ヵ月であり，イピリムマブとニボルマブの併用療法群において有意に延長していた[6]（**図2a**）．また，イピリムマブとニボルマブの併用療法における全生存期間の中央値は非上皮型で18.1ヵ月，上皮型で18.7ヵ月であり，組織型で違いは認められなかったが，化学療法群の全生存期間の中央値は非上皮型で8.8ヵ月，上皮型では16.5ヵ月と組織型により違いがあり，非上皮型においてイピリムマブとニボルマブの併用療法の優位性が際立つ結果であった（**図2b, c**）．これらの結果に基づき，2021年5月にイピリムマブとニボル

図2 | CheckMate743試験における全生存期間

l survival in all randomised patients. a：無作為割り付けされた全患者，b：上皮型患者，c：非上皮型患者．（文献6より）



マブの併用療法は，切除不能な進行・再発のMPMの一次治療として追加承認された．

3．胸膜中皮腫の治療と組織型

外科治療を受けた上皮型，二相型，肉腫型患者の生存期間中央値は，それぞれ19ヵ月，12ヵ月，4ヵ月であり，上皮型および二相型では外科治療が予後良好因子であった[7]．EPP施行例の予後因子に関するシステマティックレビューでも，非上皮型であることは有意な予後不良因子とされており，一部の早期症例を除き肉腫型症例に外科治療は推奨されない．二相型中皮腫においては，上皮型コンポーネントの割合が独立した予後予測因子とされており，外科治療を検討する際の重要な材料である[8]．

薬物治療においては，これまでの限られた選択肢のなかでは組織型により薬剤の選択が変わることはなかった．前述のCheck Mate743試験を受けてイピリムマブとニボルマブの併用療法が標準治療となると思われるが，上皮型では両群の全生存期間の違いが明らかでないため，免疫チェックポイント阻害薬特有の有害事象が懸念されるような症例では引き続きプラチナ製剤＋PEM併用化学療法も選択されうる．今後は薬物治療の選択においても，組織型は重要なファクターとなる．

（宮藤遥子，藤本伸一）

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ORIGINAL ARTICLE

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Nationwide prospective registry database of patients with newly diagnosed untreated pleural mesothelioma in Japan

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Abstract

Due to the scarcity of large-sized prospective databases, the Japanese Joint Committee for Lung Cancer Registry conducted a nationwide prospective registry for newly diagnosed and untreated pleural mesothelioma. All new cases diagnosed pathologically as any subtype of pleural mesothelioma in Japan during the period between April 1, 2017, to March 31, 2019, were included before treatment. Data on survival were collected in April 2021. The eligible 346 patients (285 men [82.3%]; 61 women [17.7%]; median age, 71.0 years [range, 44–88]) were included for analysis. Among these patients, 138 (39.9%) underwent surgery, 164 (47.4%) underwent

Abbreviations: AJCC, American Joint Commission on Cancer; BSC, best supportive care; CI, confidence intervals; EPP, extrapleural pneumonectomy; ET, exploratory thoracotomy; FDG-PET, fluorodeoxyglucose-positron emission tomography; IASLC, International Association for the Study of Lung Cancer; IMIG, International Mesothelioma Interest Group; IQR, interquartile range; JJCLCR, the Japanese Joint Committee for Lung Cancer Registry; MCR, macroscopic complete resection; MTT, maximum tumor thickness; NOS, not otherwise specified; OS, overall survival; P/D, pleurectomy/decortication.; PFS, progression-free survival; PM, pleural mesothelioma; PP, partial pleurectomy; PS, performance status; RT, radiation therapy; STLT, sum of three-level thickness; SUV, standardized uptake value; UICC, Union for International Cancer Control.

non-surgical therapy, and the remaining 44 (12.7%) underwent best supportive care. The median overall survival for all 346 patients was 19.0 months. Survival rates at 1, 2, and 3 years for all patients were, 62.8%, 42.3%, and 26.5%, respectively. Median overall survival was significantly different among patients undergoing surgery, non-surgical treatment, and best supportive care (32.2 months vs. 14.0 months vs. 3.8 months, $p < 0.001$). The median overall survival of patients undergoing pleurectomy/decortication and extrapleural pneumonectomy was 41.8 months and 25.0 months, respectively. Macroscopic complete resection resulted in longer overall survival than R2 resection and partial pleurectomy/exploratory thoracotomy (41.8 months vs. 32.2 months vs. 16.8 months, $p < 0.001$). Tumor shape, maximum tumor thickness, and sum of three level thickness were significant prognostic factors. The data in the prospective database would serve as a valuable reference for clinical practice and further studies for pleural mesothelioma.

KEYWORDS
chemotherapy, database, pleural mesothelioma, staging system, surgery

1 | INTRODUCTION

Pleural mesothelioma (PM) is an aggressive cancer caused by exposure to asbestos. Although many developed countries have banned the use of asbestos, middle- and low-income countries continue to utilize asbestos.[1] The estimated number of global mesothelioma deaths is currently up to 38,000 per year and increasing.[2]

The largest database of PM is the International Association for the Study of Lung Cancer (IASLC) database. The IASLC, in collaboration with the International Mesothelioma Interest Group (IMIG), developed its first international database in 2009[3,4] to update the IMIG staging system introduced in 1994.[5] The staging systems based on the first and second IASLC databases were accepted in the seventh and eighth editions of the Union for International Cancer Control UICC/American Joint Commission on Cancer (AJCC) manuals, respectively.[3,6–8]

The majority of the large number of available retrospective nationwide databases[9–15] are used for epidemiological purposes, while few have complete data on patient treatment, clinical courses, and patient outcomes. Retrospective studies focused on patient prognosis factors,[9,16–22] but only a few were prospective, multicenter studies.[23,24] These limitations lead to difficulties in decision-making regarding treatment strategies for newly diagnosed/untreated PM patients.

Therefore, in our study, we conducted a nationwide prospective registry of newly diagnosed, untreated PM. To the best of our knowledge, this is the first nationwide prospective registry. This study was conducted as the ninth project of the Japanese Joint Committee for Lung Cancer Registry (JJCLCR).[25] JJCLCR has contributed to the establishment of the staging system of lung cancer through several nationwide registries,[26–30] including a prospective one.[29]

The main study aims were to clarify the following issues in newly diagnosed/untreated PM patients in Japan: current status of surgical and non-surgical treatment; surgery completion rate, mortality and morbidity and survival for all patients undergoing surgical intervention; macroscopic complete resection (MCR) as the goal of curative-intent surgery; tumor shape, tumor thickness, and the sum of three-level thickness (STLT) as possible prognostic factors; and feature and prognostic power of the seventh and eighth staging systems.

2 | PATIENTS AND METHODS

2.1 | Study setting

The JJCLCR conducted a prospective observational cohort study enrolling patients first diagnosed with PM between April 1, 2017, and March 31, 2019, in Japan.

The study protocol is described in Supplementary File S1.[25]

2.2 | Inclusion criteria

All patients newly diagnosed according to pathological (including cytology) findings including any subtype of PM in Japan between April 1, 2017, and March 31, 2019, were included. Patients were not given any treatment before registration.

2.3 | Variables

The case report form is shown in Supplementary File S2.[25] The following data were collected and analyzed: (i) demographic characteristics including date of registration, sex, and date of birth; (ii) preoperative status including Eastern Cooperative Oncology Group performance status (PS), preoperative comorbidities (e.g., asbestos exposure and smoking), laboratory values (including tumor markers), radiological findings (tumor shape, tumor thickness, and maximum

standardized uptake value of the pleura on fluorodeoxyglucose-positron emission tomography), and respiratory function tests; (iii) details of diagnosis (e.g., date of diagnosis, diagnostic method, immunohistochemical evaluation results, histologic type, and clinical stage based on both seventh and eighth AJCC/UICC staging systems); (iv) surgical treatments, including induction therapy, surgical interventions, combined resection, status of residual tumor, and postoperative morbidity; (v) postoperative pathological diagnosis and stage based on both seventh and eighth AJCC/UICC staging systems; (vi) chemotherapy regimen; (vii) radiotherapy characteristics, including irradiated sites and type of radiation therapy (RT); and (viii) follow-up data including date of last follow-up, vital signs and symptoms during last follow- up, and date and location of initial relapse.

2.4 | Definitions

2.4.1 | Radiological examination

Localized PM was defined according to Allen's criteria.[31] All the cases were classified into three categories according to the radiological appearance of the tumor: minimal, nodular, or rindlike.[8] Tumor thickness was measured in accordance with the IASLC report.[8] Briefly, measurements of tumor thickness perpendicular to the chest wall or mediastinum on axial imaging were made, representing the upper, middle, and lower third of the hemithorax.[8]

2.4.2 | Diagnosis at registration

In the cases where PM was diagnosed by only cytology, the date of diagnosis was recorded as the date of thoracentesis. In cases where biopsy was performed, the date of diagnosis was the date of biopsy regardless of precedent cytological diagnosis.

2.4.3 | Final diagnosis

In non-surgical cases, diagnosis at registration was the final diagnosis. In surgical cases, the final diagnosis was the diagnosis based on the surgical specimen collected and the date of the final diagnosis was the date of surgery.

2.4.4 | Surgical nomenclature

Surgical nomenclature was defined according to the IASCL/IMIG consensus report.[32]

In this study, MCR was divided into two subgroups: R0-1 was defined as the absence of microscopic tumor cells at the surgical margin, while R1 was defined as microscopic residual tumor cells confirmed at the surgical margin. R2 resection was defined as completion of surgery with macroscopic residual disease. Because both partial pleurectomy (PP) and exploratory thoracotomy (ET) were indicated as incomplete surgery, they were merged into a PP/ET group.

2.5 | Assessments of survival and relapse

Overall survival (OS) was defined as the period from the date of diagnosis at registration to death. Progression-free survival (PFS), defined as the period from surgery to disease progression or death, was calculated in patients who underwent surgery with MCR. Relapse pattern was defined according to Kostron et al.[33]

2.6 | Enrollment and study periods

Patients were enrolled from April 1, 2017, to March 31, 2019.

The study period was between April 1, 2017, and March 31, 2026.

2.7 | Ethics Statement

This study was approved by the institutional review board of Osaka University Hospital, where the registry office is located, on October 11, 2016 (approval number 16038). The registry and the study using the registered data were approved by each institutional review board of all participating institutions. Written informed consent was obtained from all study participants.

This study was registered at the UMIN Clinical Trials Registry as UMIN 000024664 (http://www.umin.ac.jp/ctr/index.htm). This study adhered to the ethical guidelines for epidemiologic studies published jointly by the Japan Ministry of Science, Culture, and Education and the Japan Ministry of Health, Labor, and Welfare on June 17, 2002, and revised on February 28, 2017.

2.8 | Data collection and data analysis

The methods of data management have been previously described.[25] Briefly, patient data were retrieved from the JJCLCR website using a USB drive with a coded institution-individual serial key. Data on survival were collected in April 2021.

2.8.1 | Statistical analysis

Patients' characteristics were summarized with median, interquartile range (IQR) and range (minimum, maximum) for continuous variables and frequencies for categorical variables. For summary statistics, two-tailed 95% confidence intervals (CI) were presented. Survival functions were estimated using the Kaplan–Meier method and their 95% CIs were calculated by using the Greenwood variance with the complementary log–log transformation. Comparisons among

multiple groups were made using the log-rank test, which is referred to as the omnibus test. For ordinal groups, the log-rank test with the linear scores attached was used, referred to as the trend test. Differences between survival functions were evaluated using the log-rank method. Statistical analyses were performed after excluding cases with missing values for relevant variables. No multiplicity adjustment was applied and a *p*-value of less than 0.05 was considered statistically significant. The SAS version 9.4 (SAS Institute, Cary, NC) and R version 4.1.2 (R Core Team; https://www.R-project.org/) were used for statistical analyses. To draw the graphs for the Kaplan–Meier estimates, the *survminer* package for R was used.

3 | RESULTS

3.1 | Clinical characteristics of patients

Between April 1, 2017, and March 31, 2019, a total of 348 cases of PM were registered from 54 institutions. One duplicate case and another case with multiple missing values were removed. The remaining 346 cases were included for analysis (Figure 1).

The clinical characteristics of the 346 patients are shown in Table 1. The median age was 71.0 years (range, 44–88 years). The cohort included 285 men (82.3%) and 61 women (17.7%). Most patients (93.7%) had a good PS score (0 or 1). Asbestos exposure was detected in 67.1% of the patients, and 73.2% of patients were current/former smokers.

3.2 | Diagnosis and pathological findings

Diagnosis at registration was made using biopsy specimens in 97.4% of patietns (337/346) and cell blocks in 2.6% (9/346) (Table 1; Figure 2). Methods of biopsy included open surgery (2.1%, 7/337), video-assisted thoracoscopy under general anesthesia (74.5%, 251/337), thoracoscopy under local anesthesia (11.3%, 38/337), needle biopsy (8.9%, 30/337), and others (3.3%, 11/337). Histological subtype at registration comprised epithelioid (71.5%, 241/337), biphasic (9.5%, 32/337), sarcomatoid (17.8%, 60/337), and not otherwise specified (NOS, 1.2%, 4/337) categories.

Postoperative pathological analysis of surgical specimens was performed in all 138 surgical cases. Diagnosis at registration was made using cell block specimens in six patients, which turned out to be epithelioid ($n = 5$) and biphasic ($n = 1$) subtypes defined during postoperative analysis. In the remaining 132 cases, diagnosis at registration was made using biopsy specimens. We observed and corrected a discrepancy between preoperative and postoperative subtype diagnostics in 8.7% of patients (12/132) as follows: epithelioid to biphasic ($n = 5$), epithelioid to sarcomatoid ($n = 3$), biphasic to epithelioid ($n = 1$), biphasic to sarcomatoid ($n = 1$), biphasic to NOS ($n = 1$), and sarcomatoid to epithelioid ($n = 1$). Consequently, the final diagnosis of 343 patients who underwent biopsy and/or surgery was epithelioid (70.0%, 240/343), biphasic (10.2%, 35/343), sarcomatoid (18.4%, 63/343), and NOS (1.5%, 5/343).

3.3 | Radiological findings

Computed tomography scans and tumor thickness measurements were performed in all cases: 38 (11.0%) localized PM and 299 (89.0%) diffuse PM. Patients were classified as having minimal ($n = 68$, 19.7%), nodular ($n = 96$, 27.7%), and rind-like ($n = 178$, 51.4%) tumors (Table 2). The median maximum tumor thickness (MTT) and the STLT were 11 mm (IQR: 5.0–21.0) and 22 mm (IQR: 11.0–39.0), respectively.

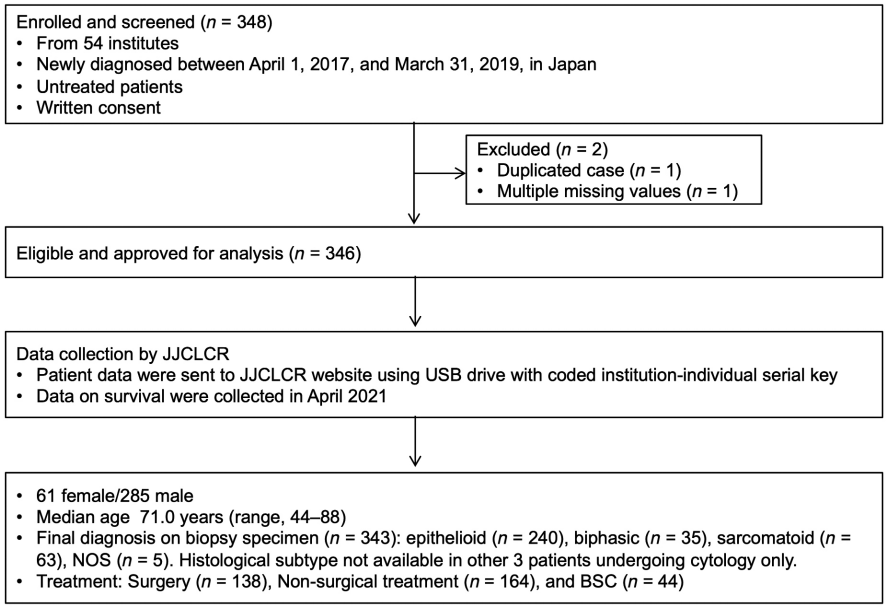


FIGURE 1 CONSORT diagram. Between April 1, 2017, and March 31, 2019, a total of 348 cases of pleural mesothelioma (PM) were registered from 54 institutions. One duplicate case and another case with multiple missing values were removed. The remaining 346 cases were included for analysis. BSC, best supportive care; JJCLCR, Japanese Joint Committee for Lung Cancer Registry; NOS, not otherwise specified.

TABLE 1 Patient's clinical characteristics.

Characteristic	Total ($n = 346$)	Surgery ($n = 138$)	Non-surgical Tx ($n = 164$)	BSC ($n = 44$)
Sex — Number (%)				
Female	61 (17.6)	21 (15.2)	33 (20.1)	7 (15.9)
Male	285 (82.4)	117 (84.8)	131 (79.9)	37 (84.1)
Age — Number (%)				
40–49	5 (1.4)	1 (0.7)	4 (2.4)	0 (0.0)
50–59	27 (7.8)	13 (9.4)	10 (6.1)	4 (9.1)
60–69	114 (32.9)	66 (47.8)	44 (26.8)	4 (9.1)
70–79	154 (44.5)	51 (37.0)	85 (51.8)	18 (40.9)
80–89	46 (13.3)	7 (5.1)	21 (12.8)	18 (40.9)
Age				
Total number	346	138	164	44
Median	71.0	68.5	73.0	78.0
Range	44–88	44–88	45–88	51–88
IQR	66.0–77.0	64.0–73.0	67.0–78.0	71.0–82.0
PS — Number (%)				
0	185 (53.5)	103 (74.6)	69 (42.1)	13 (29.5)
1	139 (40.2)	33 (23.9)	89 (54.3)	17 (38.6)
2	16 (4.6)	1 (0.7)	6 (3.7)	9 (20.5)
3	4 (1.2)	0 (0.0)	0 (0.0)	4 (9.1)
4	2 (0.6)	1 (0.7)	0 (0.0)	1 (2.3)
Asbestos exposure — Number (%)				
Yes	232 (67.1)	94 (68.1)	107 (65.2)	31 (70.5)
No	71 (20.5)	26 (18.8)	36 (22.0)	9 (20.5)
Unknown	43 (12.4)	18 (13.0)	21 (12.8)	4 (9.1)
Smoking — Number (%)				
Never	91 (26.3)	29 (21.0)	46 (28.0)	16 (36.4)
Former	231 (66.8)	95 (68.8)	110 (67.1)	26 (59.1)
Current	22 (6.4)	13 (9.4)	7 (4.3)	2 (4.5)
Unknown	2 (0.6)	1 (0.7)	1 (0.6)	0 (0.7)
Laterality — Number (%)				
Right	209 (60.4)	74 (53.6)	109 (66.5)	26 (59.1)
Left	137 (39.6)	64 (46.4)	55 (33.5)	18 (40.9)
Histology at registration— Number (%)				
Epithelioid	241 (69.7)	112 (81.2)	106 (64.6)	23 (52.3)
Biphasic	32 (9.2)	9 (6.5)	17 (10.4)	6 (13.6)
Sarcomatoid	60 (17.3)	11 (8.0)	36 (22.0)	13 (29.5)
NOS	4 (1.2)	0 (0.0)	2 (1.2)	2 (4.5)
NA (cytology only)	9 (2.6)	6 (4.3)	3 (1.8)	0 (0.0)
Final histology— Number (%)				
Epithelioid	240 (69.4)	111 (80.4)	106 (64.6)	23 (52.3)
Biphasic	35 (10.1)	12 (8.7)	17 (10.4)	6 (13.6)
Sarcomatoid	63 (18.2)	14 (10.1)	36 (22.0)	13 (29.5)
NOS	5 (1.4)	1 (0.7)	2 (1.2)	2 (4.5)
NA (cytology only)	3 (0.9)	0 (0.0)	3 (1.8)	0 (0.0)

Abbreviations: BSC, best supportive care; IQR, interquartile range; NA, not available; NOS, not otherwise specified; Tx, treatment.

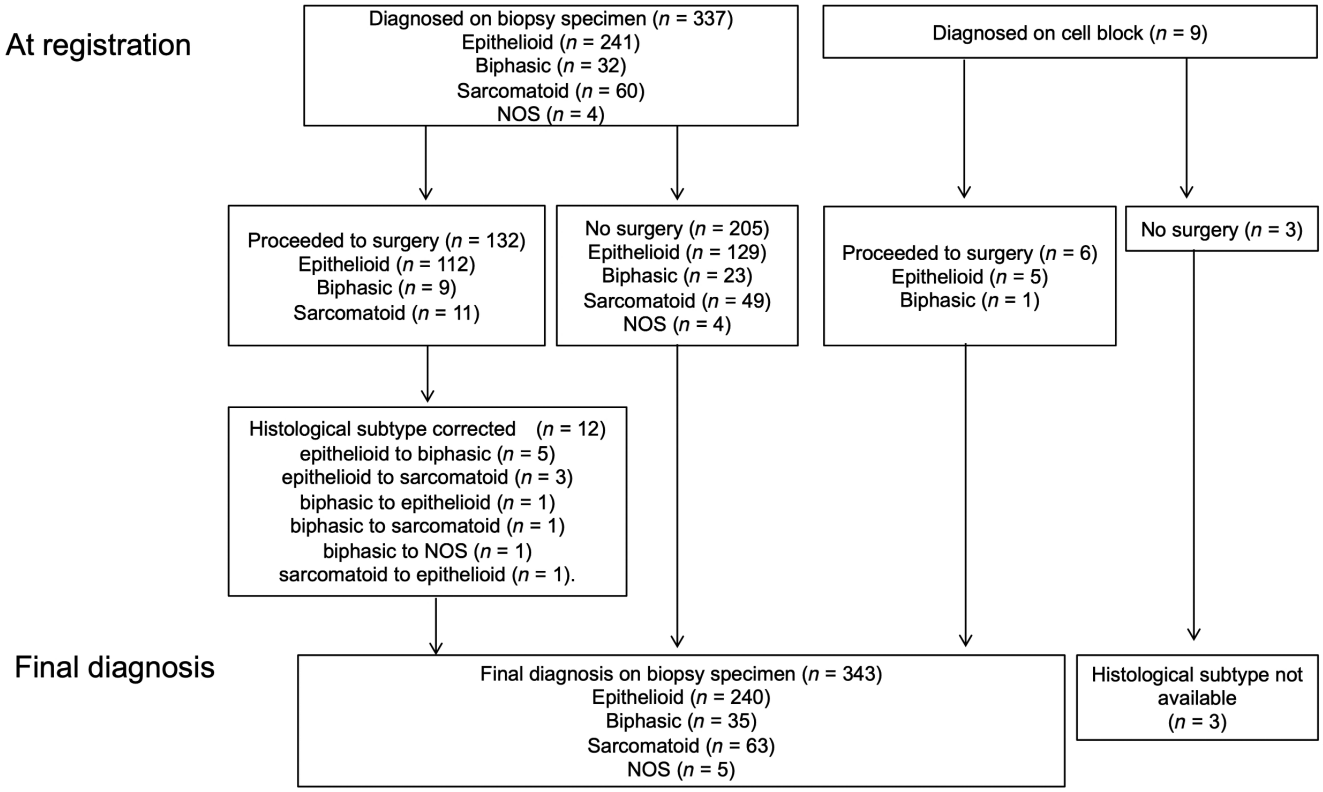


FIGURE 2 Pathological diagnosis at registration and final diagnosis. Pathological diagnosis at registration and final diagnosis are shown. We observed and corrected a discrepancy between preoperative and postoperative subtype diagnostics in 8.7% (12/132). NOS, not otherwise specified.

TABLE 2 Radiological findings.

Characteristic	Total (*n* = 346)	Surgery (*n* = 138)	Non-surgical Tx (*n* = 164)	BSC (*n* = 44)
Diffuse/local — Number (%)				
Diffuse	299 (86.4)	122 (88.4)	136 (82.9)	41 (93.2)
Localized	38 (11.0)	10 (7.2)	25 (15.2)	3 (6.8)
No data	9 (2.6)	6 (4.3)	3 (1.8)	0 (0.0)
Tumor shape — Number (%)				
Minimal	68 (19.7)	32 (23.2)	29 (17.7)	7 (15.9)
Nodular	96 (27.7)	33 (23.9)	49 (29.9)	14 (31.8)
Rind-like	178 (51.4)	71 (51.4)	86 (52.4)	21 (47.7)
Missing data	4 (1.2)	2 (1.4)	0 (0.0)	2 (4.5)
Maximum thickness				
Total number	346	138	164	44
Median (IQR)	11.0 (5.0–21.0)	8.0 (4.0–17.0)	14.0 (7.0–25.0)	12.0 (7.5–18.5)
Range	0–89	0–77	0–89	0–80
Sum of three level thickness				
Total number	346	138	164	44
Median (IQR)	22.0 (11.0–39.0)	18.0 (8.0–31.0)	29.0 (13.0–46.0)	26.5 (15.0–39.5)
Range	0–232	0–154	0–232	0–118
Maximum SUV on FDG-PET				
Total number	234	97	106	31
Median (IQR)	5.8 (3.4–9.6)	4.4 (2.7–7.4)	7.6 (4.0–11.2)	6.5 (3.3–9.5)
Range	0–32	0–23	0–32	0–18

Abbreviations: BSC, best supportive care; FDG-PET, fluorodeoxyglucose-positron emission tomography; IQR, interquartile range; SUV, standardized uptake value; Tx, treatment.

3.4 | Clinical and pathological stages

Clinical stages were defined for all patients. Similarly, for patients undergoing surgery, their pathological stages were determined according to both the seventh and eighth versions of TNM staging systems (Tables 3–5). Stage distribution in the seventh and eighth versions of the staging system is shown in Figure 3. Assessment of the discrepancy between clinical and pathological stages according to the version seventh staging system revealed the following: 54.3% (75/138) unchanged, 39.9% (55/138) upstaged, and 6.5% (9/138) down-staged cancer cases. In contrast, according to the version eighth staging system, the results were as follows: 42.8% (59/138) unchanged, 52.2% (72/138) upstaged, and 5.1% (7/138) down-staged cancer cases.

TABLE 3 Clinical stages according to seventh and eighth TNM staging systems.

Characteristic	Total ($n=346$)	Surgery ($n=138$)	Non-surgical Tx ($n=164$)	BSC ($n=44$)
T (version 7) — Number (%)				
T0, T1a	89 (25.7)	56 (40.6)	25 (15.2)	8 (18.2)
T1b	30 (8.7)	9 (6.5)	18 (11.0)	3 (6.8)
T2	54 (15.6)	29 (21.0)	23 (14.0)	2 (4.5)
T3	104 (30.1)	41 (29.7)	47 (28.7)	16 (36.4)
T4	69 (19.9)	3 (2.2)	51 (31.1)	15 (34.1)
N (version 7) — Number (%)				
N0	267 (77.2)	123 (89.1)	111 (67.7)	33 (75.0)
N1	12 (3.5)	4 (2.9)	7 (4.3)	1 (2.3)
N2	52 (15.0)	11 (8.0)	35 (21.3)	6 (13.6)
N3	15 (4.3)	0 (0.0)	11 (6.7)	4 (9.1)
M (version 7) — Number (%)				
M0	326 (94.2)	137 (99.3)	150 (91.5)	39 (88.6)
M1	20 (5.8)	1 (0.7)	14 (8.5)	5 (11.4)
Stage (version 7) — Number (%)				
Stage I	118 (34.1)	64 (46.4)	43 (26.2)	11 (25.0)
Stage II	41 (11.8)	25 (18.1)	16 (9.8)	0 (0.0)
Stage III	108 (31.2)	45 (32.6)	48 (29.3)	15 (34.1)
Stage IV	79 (22.8)	4 (2.9)	57 (34.8)	18 (40.9)
T (version 8) — Number (%)				
T0, T1	148 (42.8)	80 (58.0)	57 (34.8)	11 (25.0)
T2	25 (7.2)	14 (10.1)	9 (5.5)	2 (4.5)
T3	104 (30.1)	41 (29.7)	47 (28.7)	16 (36.4)
T4	69 (19.9)	3 (2.2)	51 (31.1)	15 (34.1)
N (version 8) — Number (%)				
N0	267 (77.2)	123 (89.1)	111 (67.7)	33 (75.0)
N1	64 (18.5)	15 (10.9)	42 (25.6)	7 (15.9)
N2	15 (4.3)	0 (0.0)	11 (6.7)	4 (9.1)
M (version 8) — Number (%)				
M0	326 (94.2)	137 (99.3)	150 (91.5)	39 (88.6)
M1	20 (5.8)	1 (0.7)	14 (8.5)	5 (11.4)
Stage (version 8) — Number (%)				
Stage IA	142 (41.0)	77 (55.8)	54 (32.9)	11 (25.0)
Stage IB	87 (25.1)	44 (31.9)	31 (18.9)	12 (27.3)
Stage II	12 (3.5)	5 (3.6)	6 (3.7)	1 (2.3)
Stage IIIA	26 (7.5)	8 (5.8)	16 (9.8)	2 (4.5)
Stage IIIB	59 (17.1)	3 (2.2)	43 (26.2)	13 (29.5)
Stage IV	20 (5.8)	1 (0.7)	14 (8.5)	5 (11.4)

Abbreviations: BSC, best supportive care; Tx, treatment; ver., version.

TABLE 4 Clinical stages for surgical cases by seventh and eighth TNM staging systems.

Characteristic	Total ($n=138$)	EPP ($n=26$)	P/D ($n=83$)	PP/ET ($n=26$)	Other surgery ($n=3$)
T (version 7) — Number (%)					
T0, T1a	56 (40.6)	8 (30.8)	44 (53.0)	4 (15.4)	0 (0.0)
T1b	9 (6.5)	1 (3.8)	7 (8.4)	1 (3.8)	0 (0.0)
T2	29 (21.0)	7 (26.9)	14 (16.9)	6 (23.1)	2 (66.7)
T3	41 (29.7)	9 (34.6)	18 (21.7)	13 (50.0)	1 (33.3)
T4	3 (2.2)	1 (3.8)	0 (0.0)	2 (7.7)	0 (0.0)
N (version 7) — Number (%)					
N0	123 (89.1)	25 (96.2)	75 (90.4)	20 (76.9)	3 (100.0)
N1	4 (2.9)	0 (0.0)	4 (4.8)	0 (0.0)	0 (0.0)
N2	11 (8.0)	1 (3.8)	4 (4.8)	6 (23.1)	0 (0.0)
M (version 7) — Number (%)					
M0	137 (99.3)	26 (100.0)	83 (100.0)	25 (96.2)	3 (100.0)
M1	1 (0.7)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)
Stage (version 7) — Number (%)					
Stage I	64 (46.4)	9 (34.6)	50 (60.2)	5 (19.2)	0 (0.0)
Stage II	25 (18.1)	7 (26.9)	10 (12.0)	6 (23.1)	2 (66.7)
Stage III	45 (32.6)	9 (34.6)	23 (27.7)	12 (46.2)	1 (33.3)
Stage IV	4 (2.9)	1 (3.8)	0 (0.0)	3 (11.5)	0 (0.0)
T (version 8) — Number (%)					
T0, T1	80 (58.0)	14 (53.8)	59 (71.1)	7 (26.9)	0 (0.0)
T2	14 (10.1)	2 (7.7)	6 (7.2)	4 (15.4)	2 (66.7)
T3	41 (29.7)	9 (34.6)	18 (21.7)	13 (50.0)	1 (33.3)
T4	3 (2.2)	1 (3.8)	0 (0.0)	2 (7.7)	0 (0.0)
N (version 8) — Number (%)					
N0	123 (89.1)	25 (96.2)	75 (90.4)	20 (76.9)	3 (100.0)
N1	15 (10.9)	1 (3.8)	8 (9.6)	6 (23.1)	0 (0.0)
M (version 8) — Number (%)					
M0	137 (99.3)	26 (100.0)	83 (100.0)	25 (96.2)	3 (100.0)
M1	1 (0.7)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)
Stage (version 8) — Number (%)					
Stage IA	77 (55.8)	14 (53.8)	56 (67.5)	7 (26.9)	0 (0.0)
Stage IB	44 (31.9)	10 (38.5)	19 (22.9)	12 (46.2)	3 (100.0)
Stage II	5 (3.6)	0 (0.0)	5 (6.0)	0 (0.0)	0 (0.0)
Stage IIIA	8 (5.8)	1 (3.8)	3 (3.6)	4 (15.4)	0 (0.0)
Stage IIIB	3 (2.2)	1 (3.8)	0 (0.0)	2 (7.7)	0 (0.0)
Stage IV	1 (0.7)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)

Abbreviations: EPP, extrapleural pneumonectomy; P/D, pleurectomy/decortication; PP/ET, patrial pleurectomy/exploratory thoracotomy; ver., version.

3.5 | Treatment distribution

Among the enrolled 346 patients, 138 (39.9%) underwent surgery, 164 (47.4) underwent non-surgical therapy (i.e., chemotherapy with or without radiation therapy), and the remaining 44 (12.7%) underwent BSC.

3.5.1 | Surgical treatment

One hundred and thirty-eight patients underwent surgery in 35 experienced centers. Of 138 surgeries, 81 (58.7%) were performed in three high-volume centers. Surgical technique consisted of extrapleural pneumonectomy (EPP, $n=26$), pleurectomy/

TABLE 5 Pathological stages for surgical cases by seventh and eighth TNM staging systems.

Characteristic	Total ($n=138$)	EPP ($n=26$)	P/D ($n=83$)	PP/ET ($n=26$)	Other surgery ($n=3$)
T (version 7) — Number (%)					
T0, T1a	17 (12.3)	2 (7.7)	12 (14.5)	3 (11.5)	0 (0.0)
T1b	9 (6.5)	0 (0.0)	7 (8.4)	2 (7.7)	0 (0.0)
T2	30 (21.7)	11 (42.3)	16 (19.3)	2 (7.7)	1 (33.3)
T3	61 (44.2)	11 (42.3)	41 (49.4)	7 (26.9)	2 (66.7)
T4	21 (15.2)	2 (7.7)	7 (8.4)	12 (46.2)	0 (0.0)
N (version 7) — Number (%)					
N0	107 (77.5)	20 (76.9)	62 (74.7)	22 (84.6)	3 (100.0)
N1	4 (2.9)	1 (3.8)	2 (2.4)	1 (3.8)	0 (0.0)
N2	26 (18.8)	5 (19.2)	18 (21.7)	3 (11.5)	0 (0.0)
N3	1 (0.7)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
M (version 7) — Number (%)					
M0	137 (99.3)	26 (100.0)	83 (100.0)	25 (96.2)	3 (100.0)
M1	1 (0.7)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)
Stage (version 7) — Number (%)					
Stage1	26 (18.8)	2 (7.7)	19 (22.9)	5 (19.2)	0 (0.0)
Stage2	25 (18.1)	8 (30.8)	14 (16.9)	2 (7.7)	1 (33.3)
Stage3	64 (46.4)	14 (53.8)	42 (50.6)	6 (23.1)	2 (66.7)
Stage4	23 (16.7)	2 (7.7)	8 (9.6)	13 (50.0)	0 (0.0)
T (version 8) — Number (%)					
T0, T1	35 (25.4)	5 (19.2)	25 (30.1)	5 (19.2)	0 (0.0)
T2	21 (15.2)	8 (30.8)	10 (12.0)	2 (7.7)	1 (33.3)
T3	61 (44.2)	11 (42.3)	41 (49.4)	7 (26.9)	2 (66.7)
T4	21 (15.2)	2 (7.7)	7 (8.4)	12 (46.2)	0 (0.0)
N (version 8) — Number (%)					
N0	107 (77.5)	20 (76.9)	62 (74.7)	22 (84.6)	3 (100.0)
N1	30 (21.7)	6 (23.1)	20 (24.1)	4 (15.4)	0 (0.0)
N2	1 (0.7)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
M (version 8) — Number (%)					
M0	137 (99.3)	26 (100.0)	83 (100.0)	25 (96.2)	3 (100.0)
M1	1 (0.7)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)
Stage (version 8) — Number (%)					
Stage IA	32 (23.2)	4 (15.4)	23 (27.7)	5 (19.2)	0 (0.0)
Stage IB	59 (42.8)	14 (53.8)	35 (42.2)	7 (26.9)	3 (100.0)
Stage II	5 (3.6)	3 (11.5)	2 (2.4)	0 (0.0)	0 (0.0)
Stage IIIA	19 (13.8)	3 (11.5)	15 (18.1)	1 (3.8)	0 (0.0)
Stage IIIB	22 (15.9)	2 (7.7)	8 (9.6)	12 (46.2)	0 (0.0)
Stage IV	1 (0.7)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)

Abbreviations: EPP, extrapleural pneumonectomy; P/D, pleurectomy/decortication; PP/ET, patrial pleurectomy/exploratory thoracotomy; ver., version.

decortication (P/D, $n=83$), PP/ET ($n=26$), and other surgeries ($n=3$) (Tables 6 and 7). Surgery alone and surgery as part of a multimodality treatment with chemotherapy and/or radiation therapy were conducted in 29 and 109 patients, respectively. The median age of patients who underwent surgical intervention was 68.5 years (IQR: 64.0–73.0). The median value of operation time and blood loss were 406.5 min (IQR: 282.5–509.5) and 1210 g (IQR: 613.8–1855.8). The resection statuses were R0-1 ($n=41$), R1 ($n=55$), and R2 ($n=42$), respectively, and MCR (R0-1 and R1) was achieved in 69.6% (96/138). Data analysis indicated that 30- and 90-day postoperative deaths were 0.7% (1/138, PP/ET group) and 4.3% (6/138, EPP: 1, P/D: 2, PP/ET: 3). The causes within the

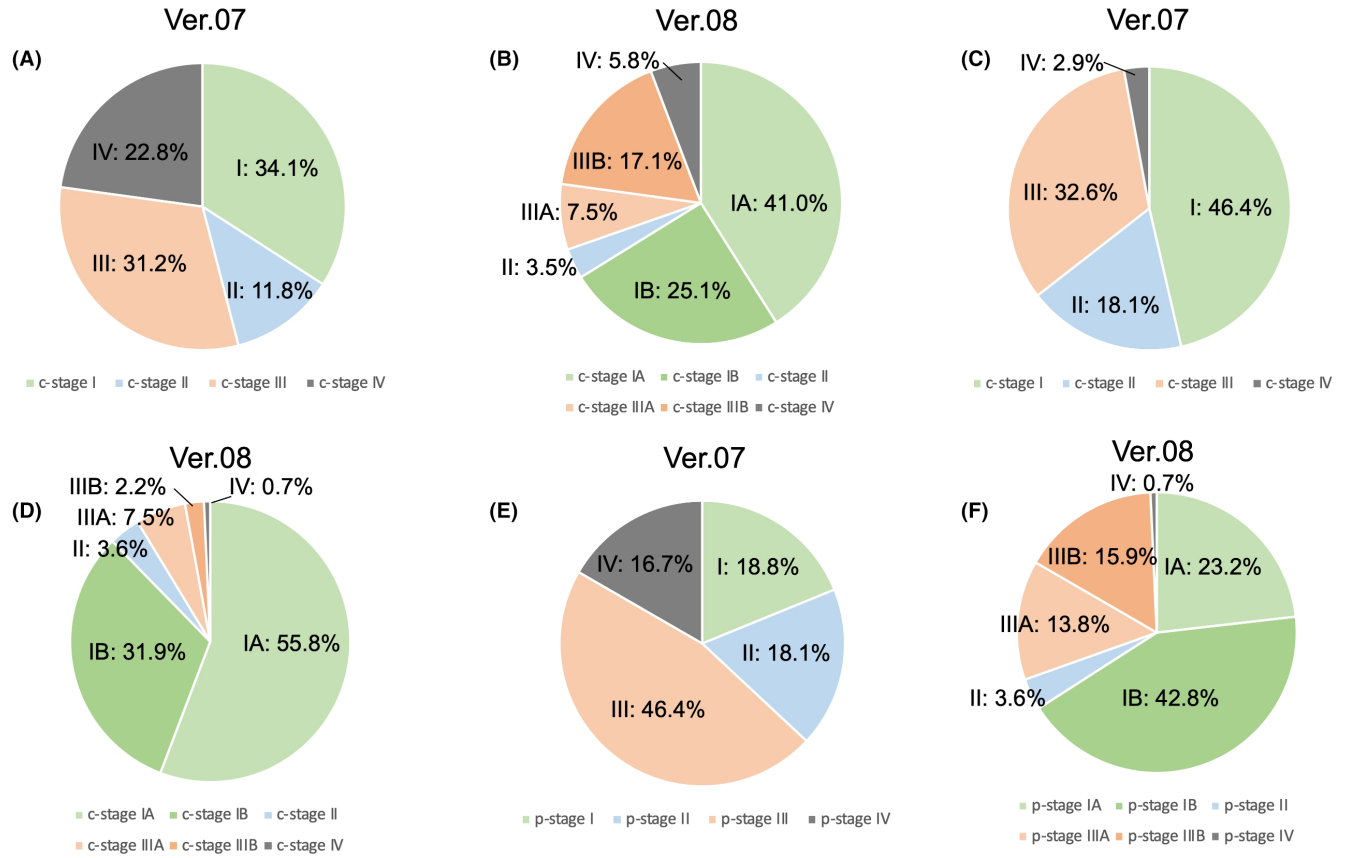


FIGURE 3 Stage distribution in seventh and eighth TNM staging systems. Distributions of clinical stages for all cases are shown in Figure 2A,B, respectively. There were 34.3% of c-stage I and 31.2% of c-stage III patients according to the version 7 staging system (A), and 66.1% cases were classified as c-stage I in the version 8 staging system (B). In surgical cases, 46.4% and 87.7% of cases were classified as c-stage I by version 7 and version 8 staging systems, respectively (C, D). Distributions of pathological stages for surgical cases are shown in Figure 2E,F: There were 46.4% of p-stage III according to the version 7 staging system (E) and 66.0% of p-stage I patients according to the version 8 staging system (F).

90-day mortality range were diagnosed with interstitial pneumonia (two patients) and mesothelioma progression (four patients). Of the 37 patients with localized PM, 10 underwent surgery: P/D ($n=7$), PP ($n=2$), and other surgery ($n=1$). Of these 10 patients, four underwent R0-1 resection, another four underwent R1 resection, and two underwent R2 resection.

3.5.2 | Non-surgical treatment

First-line treatment in 164 patients undergoing non-surgical treatment consisted of concurrent chemoradiotherapy (4.3%, $n=7$), cisplatin plus pemetrexed (51.2%, $n=84$), carboplatin plus pemetrexed (28.7%, $n=47$), pemetrexed alone (6.7, $n=11$), and others (9.1%, $n=15$) (Table 8). Of the 164 patients, 67.7% ($n=111$) and 17.7% ($n=29$) underwent second- and third-line treatment, respectively. A total of 43 patients underwent RT. Post-EPP hemithoracic RT was performed in 21 patients (45–54 Gy, dose unknown in 1). One patient underwent focal adjuvant RT after R2 resection of P/D. Eight patients underwent RT for postoperative recurrence.

3.6 | Survival analysis

Among 346 patients, 242 patients died during the follow-up period. The median follow-up period for the 104 surviving patients was 945.5 days (range, 1–1480 days). At the time of data collection in April 2021, 229 patients died of PM, 13 died of other diseases (seven with PM, six without PM), 85 were alive with PM, and 19 were alive without PM. Median OS was 19.0 months (95% CI: 15.4–22.3). Survival rates at 1, 2, and 3 years for all patients were 62.8% (95% CI: 57.4%–67.6%), 42.3% (95% CI: 37.0%–47.5%), and 26.5% (95% CI: 21.3%–31.9%), respectively (Figure 4A).

In the surgery group, median OS was 32.2 months. In non-surgical treatment group, OS was 14.0 months, while in the BSC group, OS was only 3.8 months. Survival rates at 1, 2, and 3 years in the surgery group were 81.8%, 61.3%, and 41.9%, respectively. Survival rates at 1, 2, and 3 years in non-surgical treatment group were 56.5%, 32.3%, and 17.2%, respectively. Finally, the survival rates in BSC group were 22.9%, 17.8%, and 11.4%, respectively (Figure 4B). These results show significant differences in OS among three groups.

Median OS after multimodality therapy ($n=109$) was significantly longer than that in the surgery alone group ($n=29$): 34.6 months vs.

TABLE 6 Surgical treatments.

	Case No
EPP	26
EPP alone	2
EPP + AC	1
EPP + RT	8
EPP + RT + AC	2
NAC + EPP	2
NAC + EPP + RT	11
P/D	83
P/D alone	13
P/D + AC	18
NAC + P/D	31
NAC + P/D + AC	20
NAC + P/D + RT + AC	1
PP/ET	26
PP/ET alone	12
NAC + PP/ET	14
Other surgery	3
Other surgery alone	2
Other surgery + AC	1
Total	138

Abbreviations: AC, adjuvant chemotherapy; EPP, extrapleural pneumonectomy; ET, exploratory thoracotomy; NAC, neoadjuvant chemotherapy; P/D, pleurectomy/decortication; PP, partial pleurectomy; RT, radiation therapy.

21.0 months (HR = 0.53) (Figure 4C). Median OS by surgical technique is shown in Figure 4D: 25.0 months for EPP, 41.8 months for P/D, and 17.5 months for PP/ET. Survival time of P/D, not EPP, was significantly longer than that for PP/ET.

Median OS for R1 resection, R2 resection, and PP/ET were 39.5 months, 32.2 months, and 16.8 months, respectively (Figure 4E). Median OS for R0-1 group was undefined. There was no significant difference in OS time between R0-1 and R1 groups. Median OS time for the MCR group (R0-1 plus R1) was 41.8 months, which was significantly longer than that for R2 resection and PP/ET (Figure 4F).

The trend of survival in each clinical stage is shown in Table 9A and Figure 5A,B. A significant difference in survival between stage groups was observed using both seventh and eighth staging systems. The survival rates at each pathological stage are shown in Table 9B. No differences in survival rates were observed using the seventh staging system ($p = 0.080$; Figure 5C). A significant difference was observed for pathological stages using the eighth staging system approach ($p = 0.005$; Figure 5D).

The median OS for minimal ($n = 68$), nodular ($n = 96$), and rindlike ($n = 178$) tumor shape groups were 26.7, 21.3, and 15.0 months, respectively (Figure 6A). The survival time in minimal and nodular groups was significantly longer than that in the rindlike group ($p = 0.007$, $p = 0.029$ respectively). The median OS time (27.0 months) was significantly longer in the MTT < 5.1 mm group ($n = 91$) than that in the MTT ≥ 5.1 mm group ($n = 255$) (15.5 months) ($p = 0.013$) (Figure 6B). The median OS time (26.3 months) for the STLT < 13 mm group ($n = 101$) was significantly longer than that for the 13 ≤ STLT < 60 mm group ($n = 203$) (15.5 months) ($p = 0.022$) and the STLT ≥ 60 mm group ($n = 42$) (12.0 months) ($p = 0.008$) (Figure 6C).

3.7 | Relapse after macroscopic complete resection

Relapse occurred in 74 (77.1%) of the 96 MCR patients and resulted in PM-related death ($n = 36$), death due to other causes with PM ($n = 1$), and survival with PM ($n = 37$). Among 22 patients without recurrence, four died of other causes, while 18 survived. Relapse pattern was described in 71 of 74 relapsed patients. Initial relapse sites were local only in 53 (74.6%), distant only in eight (11.3%), and both in 10 (14.1%) (Table 10). Distant only metastasis was observed in 27.8% (5/18) of EPP patients and 5.9% (3/51) of P/D patients.

The PFS time was calculated in 93 of the 96 MCR cases, excluding three cases without detailed relapse information. Median PFS and survival rates at 1, 2, and 3 years for 93 MCR patients were 16.6 months, 73.1%, 29.3%, and 19.1%, respectively (Figure 7A). Median PFS and PFS rates at 1, 2, and 3 years were 13.6 months and 63.6%, 13.6%, and 13.6% for EPP patients ($n = 22$), and 19.4 months and 76.2%, 34.4%, and 20.7% for P/D patients ($n = 68$), respectively (Figure 7B).

4 | DISCUSSION

The JJLCRC generated several nationwide registries to establish the international staging system of lung cancer.[27,29,30] This study is the first investigation and analysis of a PM registry by JJLCRC. Like previous JJLCRC registries[26–30] this study provides reliable and critical information with few excluded cases and missing values of clinical data. According to the annual report of the Japanese Ministry of Health, Labor, and Welfares,[34] 1555 and 1512 deaths were associated with PM in 2017 and 2018, respectively. According to the National Clinical Database of Japan, 622 curative-intent surgeries for PM were performed between January 2014 and December 2017.[35] Thus, this study represents approximately 10% of all PM cases and 50% of surgical cases in Japan during the study period.

With the nationwide enrollment prospectively, the present study has provided critical information on PM treatment. We found that median OS time for non-surgical treatment groups and BSC groups were 14.0 months and 3.8 months, respectively. These results were in line with a large-scale retrospective study in the United States.[36] This study revealed that prognosis for unresectable PM remains poor. Furthermore, our study provided the surgery completion rate, MCR rate, mortality/morbidity rate, and postoperative survival rate of all patients undergoing surgery, which had been lacking in the literature. Surgery incompletion

TABLE 7 Clinical characteristics of patients with PM surgery.

Characteristic	Total (*n* = 138)	EPP (*n* = 26)	P/D (*n* = 83)	PP/ET (*n* = 26)	Other surgery (*n* = 3)
Gender — Number (%)					
Female	21 (15.2)	4 (15.4)	10 (12.0)	6 (23.1)	1 (33.3)
Male	117 (84.8)	22 (84.6)	73 (88.0)	20 (76.9)	2 (66.7)
Age — Number (%)					
40–49	1 (0.7)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
50–59	13 (9.4)	4 (15.4)	9 (10.8)	0 (0.0)	0 (0.0)
60–69	66 (47.8)	11 (42.3)	43 (51.8)	11 (42.3)	1 (33.3)
70–79	51 (37.0)	9 (34.6)	27 (32.5)	13 (50.0)	2 (66.7)
80–89	7 (5.1)	1 (3.8)	4 (4.8)	2 (7.7)	0 (0.0)
Total number	138	26	83	26	3
Median (IQR)	68.5 (64.0–73.0)	68.0 (62.0–71.0)	68.0 (64.0–73.0)	71.0 (65.0–75.0)	73.0 (67.0–78.0)
Range	44–88	44–80	55–80	60–88	67–78
Completeness of resection— Number (%)					
R0-1	41 (29.7)	10 (38.5)	30 (36.1)	0 (0.0)	1 (33.3)
R1	55 (39.9)	12 (46.2)	41 (49.4)	1 (3.8)[a]	1 (33.3)
R2	42 (30.4)	4 (15.4)	12 (14.5)	25 (96.2)	1 (33.3)
Surgical time (min.)					
Median (IQR)	406.5 (280.0–510.0)	393.0 (357.0–487.0)	466.0 (372.0–554.0)	175.5 (90.0–233.0)	274.0 (222.0–290.0)
Range	30–885	177–705	68–885	30–544	222–290
Blood loss (gram)					
Median (IQR)	1210.0 (610.0–1861.0)	1186.0 (870.0–1700.0)	1450.0 (860.0–2160.0)	290.0 (34.0–740.0)	270.0 (120.0–670.0)
Range	1–25205	300–8036	5–25205	1–4530	120–670

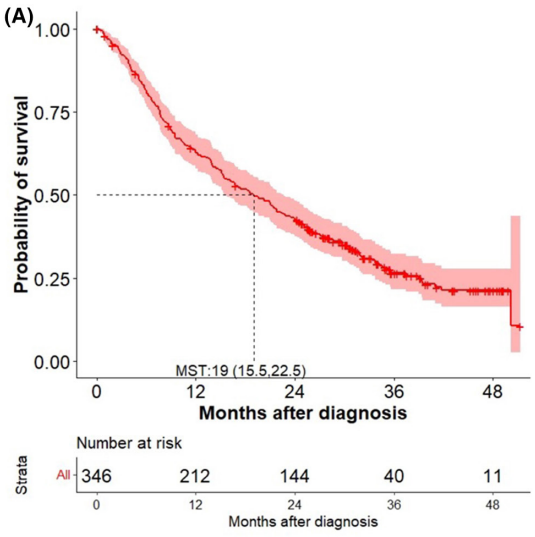
Abbreviations: EPP, extrapleural pneumonectomy; ET, exploratory thoracotomy; IQR, interquartile range; P/D, pleurectomy/decortication; PM, pleural mesothelioma; PP, partial pleurectomy.

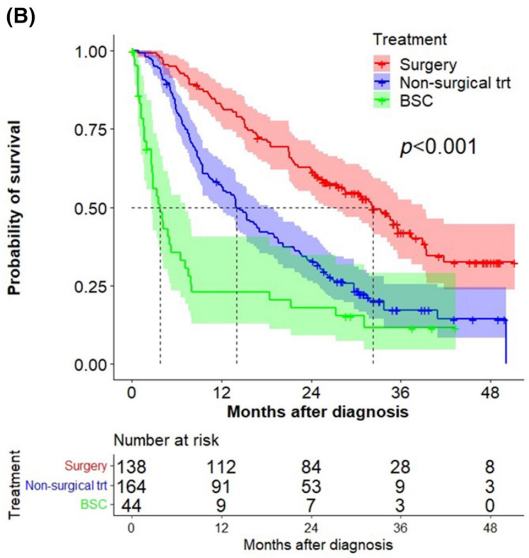
[a]Localized mesothelioma.

TABLE 8 Non-surgical treatment.

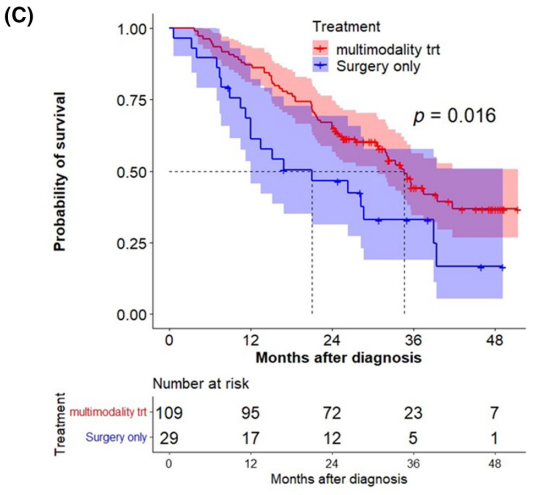
First-line Tx (*n* = 164)	Second-line Tx (*n* = 111)	Third-line Tx (*n* = 29)
Chemoradiotherapy (*n* = 7)		
CDDP+PEM (*n* = 84)	CDDP+PEM (*n* = 2)	BSC (*n* = 2)
	CBDCA+PEM (*n* = 8)	Others (*n* = 2), BSC (*n* = 6)
	PEM (*n* = 5)	Others (*n* = 2), RT (*n* = 1), BSC (*n* = 2)
	Others (*n* = 45)	CDDP+PEM (*n* = 1), PEM (*n* = 1), Others (*n* = 4), RT (*n* = 1), BSC (*n* = 38)
	RT (*n* = 1)	Others (*n* = 1)
	BSC (*n* = 23)	
CBDCA+PEM (*n* = 47)	CBDCA+PEM (*n* = 3)	Others (*n* = 1), BSC (*n* = 2)
	PEM (*n* = 1)	BSC (*n* = 1)
	Others (*n* = 19)	CBDCA+PEM (*n* = 1), PEM (*n* = 2), Others (*n* = 2), BSC (*n* = 14)
	RT (*n* = 2)	Others (*n* = 1), BSC (*n* = 1)
	BSC (*n* = 22)	
PEM (*n*=11)	Others (*n* = 5)	Others (*n* = 1), BSC (*n* = 4)
	BSC (*n* = 6)	
Others (*n*=15)	CDDP+PEM (*n* = 3)	Others (*n* = 3)
	CBDCA+PEM (*n* = 2)	Others (*n* = 1), BSC (*n* = 1)
	PEM (*n* = 1)	BSC (*n* = 1)
	Others (*n* = 7)	CBDCA+PEM (*n* = 1), Others (*n* = 2), RT (*n* = 1), BSC (*n* = 3)
	BSC (*n* = 2)	

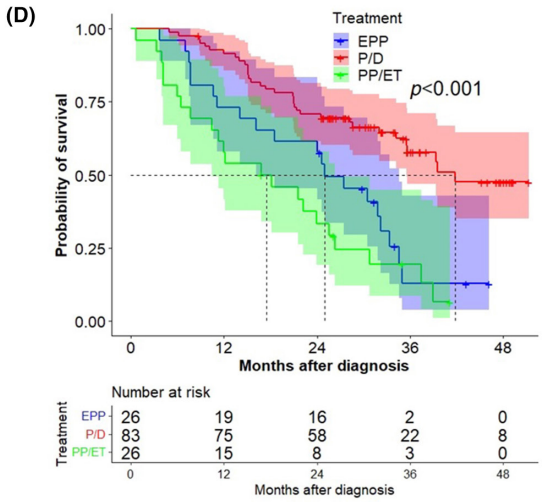
Abbreviations: BSC, best supportive care; CBDCA, carboplatin; CDDP, cisplatin; PEM, pemetrexed; RT, radiation therapy; Tx, treatment.





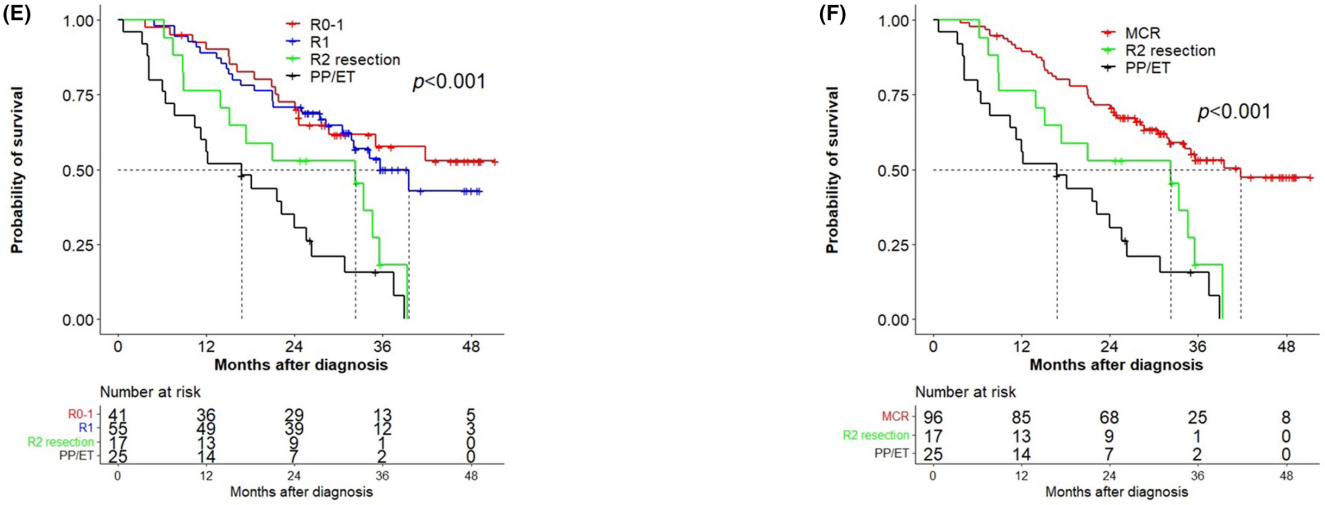
		Number	Survival Probability			MST	HR	
group	n	of event	1 year	2 year	3 year	(95%CI)	(95%CI)	*p*-value
Total	346	242	0.628 (0.574,0.676)	0.423 (0.370,0.475)	0.265 (0.213,0.319)	19.03 (15.37,22.27)		< 0.001 (omnibus)
Surgery	138	77	0.818 (0.743,0.873)	0.613 (0.525,0.688)	0.419 (0.325,0.510)	32.23 (25.60,37.47)	0.22 (0.15, 0.33)	< 0.001
Non-surgical Tx	164	130	0.565 (0.485,0.637)	0.323 (0.252,0.395)	0.172 (0.110,0.245)	14.03 (11.47,17.07)	0.48 (0.33, 0.69)	< 0.001
BSC	44	35	0.229 (0.114,0.367)	0.178 (0.078,0.310)	0.114 (0.036,0.243)	3.80 (2.63,6.53)	1 (reference)	





		Number	Survival Probability			MST	HR	
group	n	of event	1 year	2 year	3 year	(95%CI)	(95%CI)	*p*-value
Total	138	77	0.818 (0.743,0.873)	0.613 (0.525,0.688)	0.419 (0.325,0.510)	32.23 (25.60,37.47)		
Multimodality treatment	109	57	0.872 (0.793,0.922)	0.651 (0.554,0.733)	0.441 (0.333,0.544)	34.60 (30.53,41.77)	0.53 (0.32, 0.89)	0.016
Surgery alone	29	20	0.613 (0.410,0.764)	0.466 (0.276,0.636)	0.329 (0.158,0.512)	20.97 (11.27,38.97)	reference	0.016 (omnibus)
EPP	26	20	0.731 (0.517,0.862)	0.577 (0.368,0.739)	0.127 (0.024,0.319)	25.00 (14.03,32.23)	0.67 (0.37, 1.24)	0.203
P/D	83	34	0.915 (0.830,0.959)	0.708 (0.596,0.793)	0.578 (0.448,0.687)	41.77 (35.57,.)	0.27 (0.16, 0.46)	< 0.001
PP/ET	26	22	0.577 (0.368,0.739)	0.333 (0.162,0.515)	0.194 (0.065,0.374)	17.48 (7.67,25.60)	reference	< 0.001 (omnibus)
Other surgery	3	1		0.667 (0.054,0.945)	0.667 (0.054,0.945)	.(20.97,.)	NE	

FIGURE 4 (Continues)



		Number	Survival Probability			MST	HR	
group	n	of event	1 year	2 year	3 year	(95%CI)	(95%CI)	*p*-value
R0-1	41	17	0.901 (0.758,0.962)	0.701(0.534,0.818)	0.576(0.398,0.719)	.(24.60,.)	reference	< 0.001(omnibus)
R1	55	25	0.891 (0.773,0.949)	0.709(0.570,0.811)	0.500(0.341,0.640)	39.50 (30.53,.)	1.20(0.65, 2.24)	0.559
R2 resection	17	13	0.765 (0.488,0.904)	0.529(0.276,0.730)	0.182(0.032,0.430)	32.23 (8.90,35.57)	2.59(1.24, 5.40)	0.011
PP/ET	25	22	0.560 (0.348,0.727)	0.305(0.139,0.491)	0.157(0.043,0.337)	16.83 (7.67,23.93)	4.39(2.29, 8.41)	< 0.001
MCR	96	42	0.895 (0.814,0.942)	0.706 (0.603,0.786)	0.532 (0.415,0.637)	41.77 (31.80,.)	reference	< 0.001 (omnibus)
R2 resection	17	13	0.765 (0.488,0.904)	0.529 (0.276,0.730)	0.182 (0.032,0.430)	32.23 (8.90,35.57)	2.32 (1.24, 4.36)	0.009
PP/ET	25	22	0.560 (0.348,0.727)	0.305 (0.139,0.491)	0.157 (0.043,0.337)	16.83 (7.67,23.93)	3.93 (2.32, 6.67)	< 0.001

FIGURE 4 Overall survival (OS). (A) Median OS and survival rates at 1, 2, and 3 years for all patients were 19.0 months and 62.8%, 42.3%, and 26.5%, respectively. (B) Median OS and survival rates at 1, 2, and 3 years were 32.2 months and 81.8%, 61.3%, and 41.9%, respectively, for the surgery group; at 14.0 months and 56.5%, 32.3%, and 17.2%, respectively, for the non-surgical treatment group; and at 3.8 months, 22.9%, 17.8%, and 11.4% for the BSC group, respectively. (C) Median OS for multimodality therapy ($n = 109$) was significantly longer than surgery alone ($n = 29$): 34.6 months vs. 21.0 months. (D) Median OS by surgical technique were 25.0 months for EPP, 41.8 months for P/D, and 17.5 months for PP/ET. There was a significant difference in OS between P/D and PP/ET. (E) Median OS for R0-1, R1, and R2 resection and PP/ET groups were undefined, 39.5 months, 32.2 months, and 16.8 months. OS for R0-1 and R1 resections were significantly longer for those of R2 resection and PP/ET. There was no significant difference in OS between R0-1 and R1. (F) The median OS for the MCR group was 41.8 months and was significantly longer than those for R2 resection and PP/ET. BSC, best supportive care; EPP, extrapleural pneumonectomy; MCR, macroscopic complete resection; OS, overall survival; P/D, pleurectomy/decortication; PP/ET, patrial pleurectomy/exploratory thoracotomy; Tx, treatment.

rate (i.e., ET/PP) in this study was 18.8%, similar to the result of a previous single-center retrospective study.[37] However, the found rate was relatively high compared to the data from previous prospective studies.[38–42] The relatively high surgery incompletion rate in this study might have reflected that some of participating surgeons were not sufficiently experienced. The ambiguity of surgical nomenclature might also serve as a possible explanation of our findings. Since the distinction of R2 resection, PP, and ET in surgery-intended cases is not clearly described in the consensus paper,[32] surgery incompletion rate might vary according to the surgeon's definition.

The median OS time (32.2 months) for all surgical cases in the present study was longer than that in previous prospective studies (up to 24.4 months).[38,39,43–47] The recent small-scale phase II clinical trial reported an intent-to-treat basis survival of 41.4 months.[42] The present study demonstrated that the postoperative survival for all surgical cases was extending over 30 months.

This study reconfirmed that MCR is a reasonable goal for PM surgery. Since any type of curative-intent surgery for PM provides R1 resection, MCR has become a surgical goal.[48,49] However, some experts were critical of the reliability of MCR, which was subject to the surgeon's discretion.[50] This study revealed that the survival of the MCR group was significantly longer than those of the R2 resection and ET/PP groups. During the planning phase of this study, we hypothesized that a part of MCR surgery might be more radical than the rest. Thus, we divided MCR into two subcategories: R0-1 and

TABLE 9 Overall survival by clinical and pathological stages.

(A) Overall survival by clinical staging								
			1-yr survival, %	2-yr survival, %	3-yr survival, %	MST, mo	HR	*p*-value
	n	Event	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
T (version 7)								
T0 T1a T1b	119	73	0.771 (0.684, 0.837)	0.581 (0.487, 0.665)	0.334 (0.237, 0.433)	27.00 (21.83, 33.37)	Reference	<0.001 (trend)
T2	54	41	0.778 (0.642, 0.867)	0.407 (0.277, 0.534)	0.258 (0.141, 0.392)	21.03 (15.53, 28.23)	1.29 (0.88, 1.89)	0.196
T3	104	68	0.559 (0.458, 0.649)	0.402 (0.307, 0.496)	0.322 (0.228, 0.420)	18.13 (10.47, 24.03)	1.30 (0.93, 1.81)	0.122
T4	69	60	0.356 (0.244, 0.470)	0.186 (0.103, 0.288)	0.042 (0.005, 0.154)	8.00 (6.57, 11.93)	2.88 (2.03, 4.07)	<0.001
N (version 7)								
No	267	178	0.686 (0.626, 0.738)	0.476 (0.414, 0.534)	0.299 (0.238, 0.362)	21.83 (18.13, 26.23)	Reference	<0.001 (omnibus)
N1-3	79	64	0.427 (0.316, 0.534)	0.240 (0.151, 0.341)	0.147 (0.071, 0.248)	8.87 (6.73, 15.30)	1.83 (1.37, 2.44)	<0.001
M (ver.7)								
Mo	326	227	0.640 (0.585, 0.690)	0.435 (0.380, 0.489)	0.267 (0.214, 0.323)	19.63 (15.77, 22.80)	Reference	0.143 (omnibus)
M1	20	15	0.421 (0.204, 0.625)	0.211 (0.066, 0.410)	0.211 (0.066, 0.410)	11.57 (4.03, 23.93)	1.48 (0.88, 2.49)	0.143
Stage (ver.7)								
Stage I	118	73	0.769 (0.682, 0.835)	0.578 (0.482, 0.662)	0.331 (0.235, 0.430)	27.00 (21.83, 33.37)	Reference	<0.001 (trend)
Stage II	41	31	0.829 (0.675, 0.915)	0.439 (0.286, 0.582)	0.243 (0.114, 0.399)	21.60 (15.53, 32.23)	1.22 (0.80, 1.86)	0.351
Stage III	108	71	0.585 (0.486, 0.672)	0.406 (0.312, 0.497)	0.325 (0.230, 0.422)	18.53 (11.27, 24.03)	1.28 (0.92, 1.77)	0.144
Stage IV	79	67	0.362 (0.257, 0.469)	0.201 (0.120, 0.298)	0.097 (0.038, 0.188)	7.87 (6.60, 11.57)	2.59 (1.86, 3.62)	<0.001
T (ver.8)								
T0-1	148	94	0.782 (0.706, 0.841)	0.562 (0.477, 0.638)	0.319 (0.234, 0.406)	26.73 (21.77, 31.17)	Reference	<0.001 (trend)
T2	25	20	0.720 (0.501, 0.855)	0.320 (0.152, 0.502)	0.240 (0.082, 0.444)	18.43 (12.20, 35.00)	1.44 (0.89, 2.34)	0.137
T3	104	68	0.559 (0.458, 0.649)	0.402 (0.307, 0.496)	0.322 (0.228, 0.420)	18.13 (10.47, 24.03)	1.26 (0.92, 1.72)	0.145
T4	69	60	0.356 (0.244, 0.470)	0.186 (0.103, 0.288)	0.042 (0.005, 0.154)	8.00 (6.57, 11.93)	2.80 (2.01, 3.89)	<0.001
N (ver.8)								
N0	267	178	0.686 (0.626, 0.738)	0.476 (0.414, 0.534)	0.299 (0.238, 0.362)	21.83 (18.13, 26.23)	Reference	<0.001 (omnibus)
N1-3	79	64	0.427 (0.316, 0.534)	0.240 (0.151, 0.341)	0.147 (0.071, 0.248)	8.87 (6.73, 15.30)	1.83 (1.37, 2.44)	<0.001
M (ver.8)								
M0	326	227	0.640 (0.585, 0.690)	0.435 (0.380, 0.489)	0.267 (0.214, 0.323)	19.63 (15.77, 22.80)	Reference	0.143 (omnibus)
M1	20	15	0.421 (0.204, 0.625)	0.211 (0.066, 0.410)	0.211 (0.066, 0.410)	11.57 (4.03, 23.93)	1.48 (0.88, 2.49)	0.143
Stage (version 8)								
Stage IA	142	90	0.787 (0.710, 0.846)	0.571 (0.485, 0.649)	0.320 (0.233, 0.409)	27.00 (21.83, 31.80)	Reference	<0.001 (omnibus)
Stage IB, II	99	65	0.629 (0.525, 0.717)	0.402 (0.305, 0.498)	0.337 (0.238, 0.439)	18.13 (12.23, 22.50)	1.22 (0.88, 1.67)	0.23
Stage IIIA-IV	105	87	0.407 (0.312, 0.500)	0.238 (0.161, 0.324)	0.115 (0.055, 0.200)	8.87 (7.13, 11.97)	2.26 (1.68, 3.04)	<0.001

(Continues)

TABLE 9 (Continued)

(B) Overall survival by pathological stage								
	n	Event	1-year survival, % (95% CI)	2-year survival, % (95% CI)	3-year survival, % (95% CI)	MST, mo (95% CI)	HR (95% CI)	*p*-value
T (version 7)								
T0T1aT1b	26	9	0.921 (0.721, 0.980)	0.757 (0.537, 0.883)	0.580 (0.336, 0.762)	(26.30, NE)	Reference	0.013 (trend)
T2	30	15	0.867 (0.683, 0.948)	0.733 (0.537, 0.857)	0.442 (0.241, 0.626)	32.23 (27.50, NE)	1.39 (0.61, 3.19)	0.431
T3	61	38	0.820 (0.698, 0.896)	0.525 (0.393, 0.641)	0.349 (0.215, 0.487)	24.60 (20.97, 35.63)	2.04 (0.99, 4.22)	0.055
T4	21	15	0.619 (0.381, 0.788)	0.524 (0.297, 0.709)	0.393 (0.179, 0.602)	32.03 (10.47, 38.97)	2.45 (1.07, 5.60)	0.034
N (version 7)								
No	107	55	0.840 (0.756, 0.898)	0.631 (0.532, 0.715)	0.470 (0.360, 0.572)	35.57 (26.30, 39.50)	Reference	0.125 (omnibus)
N1-3	31	22	0.742 (0.550, 0.862)	0.548 (0.360, 0.703)	0.269 (0.118, 0.446)	25.60 (17.43, 34.60)	1.47 (0.90, 2.42)	0.125
M (ver.7)								
Mo	137	76	0.817 (0.741, 0.872)	0.617 (0.530, 0.693)	0.422 (0.327, 0.513)	32.23 (25.60, 37.47)	Reference	0.454 (omnibus)
M1	1	1		0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	23.93 (NE, NE)	2.13 (0.29, 15.38)	0.454
Stage (ver.7)								
Stage I	26	9	0.921 (0.721, 0.980)	0.757 (0.537, 0.883)	0.580 (0.336, 0.762)	NE (26.30, NE)	Reference	0.080 (trend)
Stage II	25	11	0.880 (0.673, 0.960)	0.760 (0.542, 0.884)	0.539 (0.320, 0.715)	NE (27.50, NE)	1.22 (0.51, 2.95)	0.657
Stage III	64	40	0.828 (0.711, 0.901)	0.547 (0.418, 0.659)	0.340 (0.211, 0.474)	25.60 (20.97, 35.57)	2.00 (0.97, 4.12)	0.061
Stage IV	23	17	0.609 (0.383, 0.774)	0.478 (0.268, 0.661)	0.359 (0.163, 0.560)	23.93 (10.47, 38.97)	2.62 (1.17, 5.89)	0.02
T (ver.8)								
T0-1	35	12	0.942 (0.787, 0.985)	0.762 (0.580, 0.873)	0.597 (0.392, 0.752)	NE (30.80, NE)	Reference	0.007 (trend)
T2	21	12	0.810 (0.569, 0.924)	0.714 (0.472, 0.860)	0.337 (0.113, 0.580)	30.53 (21.83, NE)	2.02 (0.91, 4.51)	0.086
T3	61	38	0.820 (0.698, 0.896)	0.525 (0.393, 0.641)	0.349 (0.215, 0.487)	24.60 (20.97, 35.63)	2.24 (1.17, 4.30)	0.015
T4	21	15	0.619 (0.381, 0.788)	0.524 (0.297, 0.709)	0.393 (0.179, 0.602)	32.03 (10.47, 38.97)	2.69 (1.26, 5.75)	0.011
N (ver.8)								
N0	107	55	0.840 (0.756, 0.898)	0.631 (0.532, 0.715)	0.470 (0.360, 0.572)	35.57 (26.30, 39.50)	Reference	0.125 (omnibus)
N1-3	31	22	0.742 (0.550, 0.862)	0.548 (0.360, 0.703)	0.269 (0.118, 0.446)	25.60 (17.43, 34.60)	1.47 (0.90, 2.42)	0.125
M (ver.8)								
M0	137	76	0.817 (0.741, 0.872)	0.617 (0.530, 0.693)	0.422 (0.327, 0.513)	32.23 (25.60, 37.47)	Reference	0.454 (omnibus)
M1	1	1		0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	23.93 (NA, NE)	2.13 (0.29, 15.38)	0.454
Stage (version 8)								
Stage IA	32	10	0.936 (0.769, 0.984)	0.772 (0.581, 0.885)	0.637 (0.422, 0.790)	NE (30.80, NE)	Reference	0.005 (trend)
Stage IB, II	64	37	0.828 (0.711, 0.901)	0.594 (0.463, 0.702)	0.363 (0.226, 0.501)	30.53 (20.97, 39.50)	2.22 (1.10, 4.46)	0.026
Stage IIIA-IV	42	30	0.714 (0.552, 0.826)	0.524 (0.364, 0.661)	0.343 (0.195, 0.496)	25.07 (18.53, 35.00)	2.82 (1.38, 5.77)	0.005

Abbreviations: HR, hazard ration; MST, median survival time; NE, not evaluable.

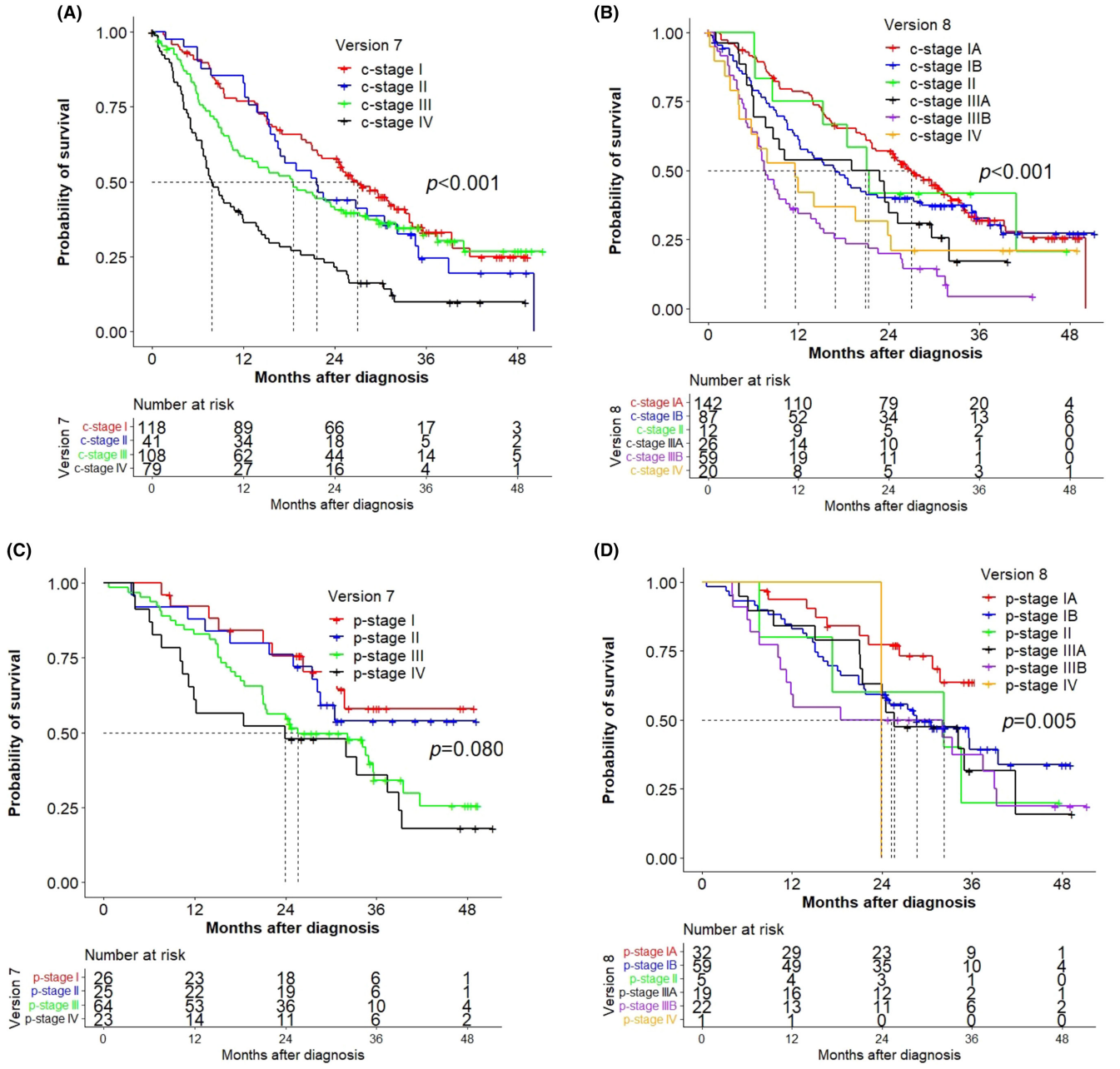


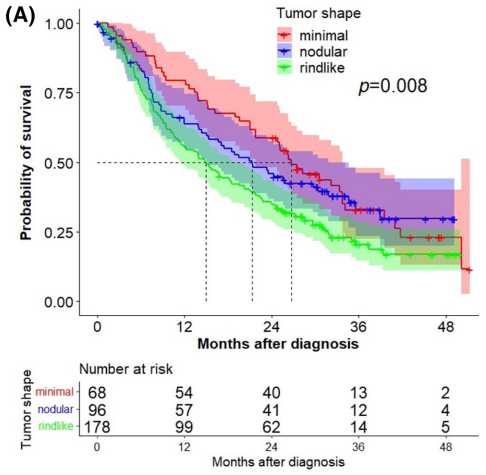
FIGURE 5 Overall survival by clinical and pathological stages. (A, B) A significant survival difference between clinical stage groups was observed in both seventh (A) and eighth (B) staging systems. (C) There was not a significant survival difference at the seventh version pathological stages. (D) A significant survival difference was observed at the eighth version pathological stages.

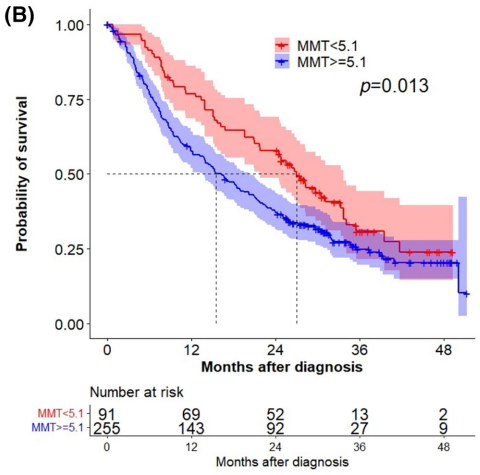
R1. However, R0-1 and R1 groups had similar survival rates. Thus, the results confirmed that MCR is a reliable and practical goal of PM surgery.

In the present study, P/D, not EPP, showed a significantly longer survival than PP/ET. Because this study may contain patient selection bias, including conversion from P/D to EPP,[40] it is not appropriate to draw any conclusion on the comparison of different surgical techniques. However, the results of this study might suggest that we should be cautious in indicating surgical intervention for EPP.

Our study confirmed the prognostic power of both tumor shape and tumor thickness that had been found in the previous IASLC registry.[8] The reliability of MTT and STLT was previously confirmed by single-center studies.[51,52] To the best of our knowledge, this study was the first to validate that tumor shape is a reliable prognostic variable. Since tumor shape and thickness are readily accessible to practicians, they are promising candidates for the next T descriptors.

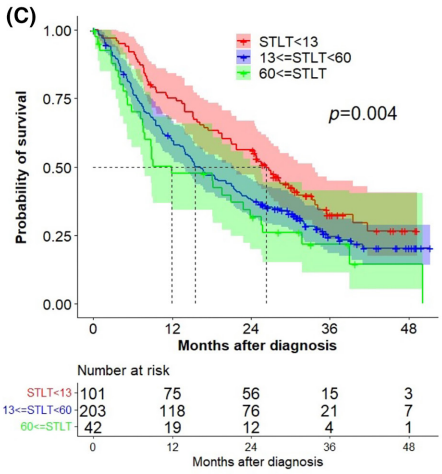
We verified and compared the prognostic power using the seventh and eighth versions of the TNM staging system. Approximately two-thirds of patients were categorized as c- and p-stage I in the eighth TNM staging system. The results of the present study concur with previously reported data of a retrospective study that validated





		Number	Survival Probability			MST	HR	
Tumor shape	n	of event	1 year	2 year	3 year	(95%CI)	(95%CI)	*p*-value
minimal	68	46	0.794 (0.677,0.873)	0.588 (0.462,0.694)	0.328 (0.209,0.451)	26.73 (21.03,33.77)	0.63 (0.45, 0.88)	0.007
nodular	96	58	0.639 (0.531,0.728)	0.448 (0.344,0.547)	0.329 (0.222,0.440)	21.33 (14.40,30.40)	0.71 (0.52, 0.97)	0.029
rindlike	178	136	0.556 (0.480,0.626)	0.347 (0.278,0.417)	0.204 (0.141,0.276)	14.97 (11.27,18.43)	reference	0.008 (omnibus)
data lacking	4	2	0.750 (0.128,0.961)	0.375 (0.011,0.808)	0.375 (0.011,0.808)	15.13 (0.80,..)	NE	

		Number	Survival Probability			MST	HR	
MTT	n	of event	1 year	2 year	3 year	(95%CI)	(95%CI)	*p*-value
< 5.1 mm	91	58	0.768 (0.667,0.842)	0.579 (0.471,0.673)	0.308 (0.202,0.420)	27.00 (21.03,33.37)	reference	0.013 (omnibus)
≥ 5.1 mm	255	184	0.577 (0.513,0.635)	0.366 (0.306,0.426)	0.249 (0.191,0.310)	15.53 (13.23,19.53)	1.46 (1.08, 1.96)	0.013



		Number	Survival Probability			MST	HR	
STLT	n	of event	1 year	2 year	3 year	(95%CI)	(95%CI)	*p*-value
< 13 mm	101	64	0.752 (0.655,0.825)	0.561 (0.459,0.652)	0.324 (0.224,0.429)	26.30 (19.63,31.17)	reference	0.004 (trend)
≥ 13, < 60 mm	203	146	0.596 (0.524,0.660)	0.373 (0.307,0.440)	0.244 (0.179,0.313)	15.53 (13.70,21.10)	1.41 (1.05, 1.89)	0.022
≥ 60 mm	42	32	0.476 (0.316,0.619)	0.317 (0.180,0.464)	0.216 (0.097,0.366)	11.97 (7.47,22.80)	1.77 (1.16, 2.72)	0.008

FIGURE 6 Overall survival (OS) by tumor shape and tumor thickness. (A) Median overall survival for minimal ($n = 68$), nodular ($n = 96$), and rind-like ($n = 178$) groups were 26.7, 21.3, and 15.0 months, respectively. Survivals for minimal and nodular groups were significantly longer than for the rind-like group. (B) Median OS was significantly longer in the MTT <5.1 mm group ($n = 91$) than that in the MTT ≥5.1 mm group ($n = 255$): 27.0 months vs. 15.5 months. (C) The median OS for the STLT <13 mm group ($n = 101$) was significantly longer than those for the 13 ≤ STLT <60 mm group ($n = 203$) and the STLT ≥60 mm group ($n = 42$): 26.3 months vs. 15.5 months and 12.0 months, respectively. MTT, maximum tumor thickness; OS, overall survival; STLT, sum of three-level thickness.

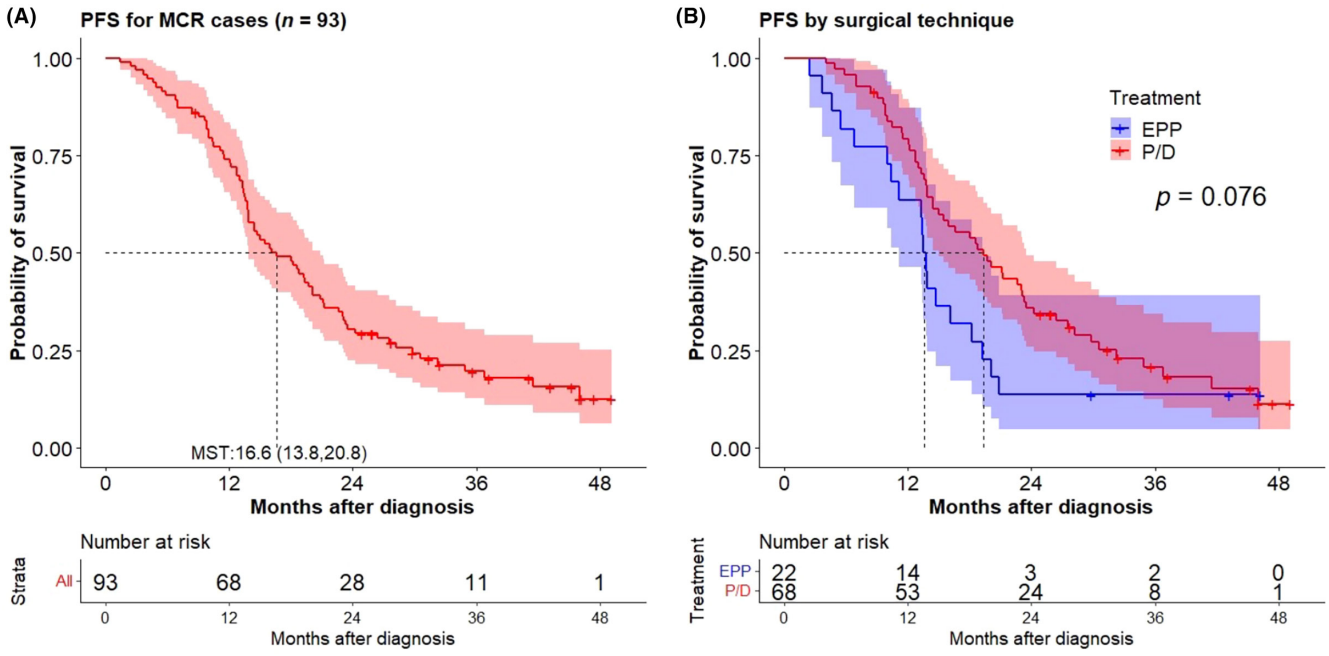
the sixth and eighth TNM staging system using the surveillance, epidemiology, and end results (SEER) database.[53] This study revealed the "bulky stage I" issue of the eighth version as a task for the ninth version of the TNM staging system.

This study has some limitations. First, there may be sampling bias because this study did not collect all the Japanese PM cases during the study period. This study might have not reflected the real-world situation in Japan because the majority of the participating institutions were academic centers or large hospitals. Second, the results of this study might not directly translate to other countries because of differences in racial composition, cultural habits, and medical systems.[54] Complimentary periodic medical checkups

TABLE 10 Relapse pattern and sites.

Relapse pattern	Relapse site (local)		Relapse site (distant)	
	Site	No (EPP/PD/Other)	Site	No (EPP/PD/Other)
Local only ($n=53$)	Total	53 (11/40/2)		
	Ipsilateral chest wall	45 (9/34/2)		
	Ipsilateral diaphragm	1 (1/0/0)		
	Ipsilateral mediastinal LN	11 (0/11/0)		
	Ipsilateral axillar/supraclavicular LN	2 (1/1/0)		
	Pericardium	4 (3/1/0)		
Distant only ($n=8$)			Total	8 (5/3/0)
			Contralateral chest wall	3 (2/1/0)
	Abdomen			2 (2/0/0)
	Contralateral LN			1 (1/0/0)
	Intrapulmonary			3 (1/2/0)
Local + distant ($n=10$)	Total	10 (2/8/0)		
	Ipsilateral chest wall	6 (2/4/0)	Contralateral chest wall	1 (0/1/0)
	Ipsilateral diaphragm	1 (0/1/0)	Abdomen	1 (0/1/0)
	Ipsilateral mediastinal LN	4 (0/4/0)	Contralateral LN	1 (1/0/0)
	Ipsilateral axillar/supraclavicular LN	1 (1/0/0)	Intrapulmonary	8 (2/6/0)
	Pericardium	1 (0/1/0)		

Abbreviation: EPP, extrapleural pneumonectomy; LN, lymph node; P/D, pleurectomy/decortication.



		Number	Progression-free Survival Probability			MST	HR	
	n	of event	1 year	2 year	3 year	(95%CI)	(95%CI)	p-value
Total	93	75	0.719 (0.615,0.799)	0.294 (0.205,0.389)	0.197 (0.119,0.289)	16.63 (13.83,20.10)		
EPP	22	19	0.636 (0.403,0.799)	0.136 (0.034,0.309)	0.136 (0.034,0.309)	13.62 (10.03,18.20)	1.61 (0.95, 2.73)	0.076
P/D	68	54	0.762 (0.642,0.847)	0.344 (0.233,0.457)	0.207 (0.114,0.320)	19.37 (14.47,23.33)	reference	0.076 (omnibus)
PP/ET	1	0				.(.,.)	NE	
Other surgery	2	2	0.000 (0.000,0.000)	0.000 (0.000,0.000)	0.000 (0.000,0.000)	2.15 (1.43,2.87)	NE	

FIGURE 7 (Legend on next page)

FIGURE 7 Progression-free survival. (A) Median PFS and survival rates at 1, 2, and 3 years for MCR patients ($n=93$) were 16.6 months and 73.1%, 29.3%, and 19.1%, respectively. (B) Median PFS and PFS rates at 1, 2, and 3 years were 13.6 months and 63.6%, 13.6%, and 13.6% for EPP patients ($n=22$), and 19.4 months and 76.2%, 34.4%, and 20.7% for P/D patients ($n=68$), respectively. EPP, extrapleural pneumonectomy; MCR, macroscopic complete resection; P/D: pleurectomy/decortication; PFS, progression-free survival.

for high-risk populations and complimentary medical interventions for patients with PM are available in Japan. Third, nivolumab treatment was not considered in the questionnaire of the case report form because registration of this study was started in April 2017, a year before the approval of nivolumab in Japan. Although most of the chemotherapeutic agents listed as "others" were presumed to be nivolumab, this cannot be verified. It is also presumed that nivolumab had an additional effect on the prognosis of both surgical and non-surgical cases.

AUTHOR CONTRIBUTIONS

Seiki Hasegawa: Conceptualization; investigation; methodology; project administration; validation; writing – original draft; writing – review and editing. **Yasushi Shintani:** Data curation; validation; writing – original draft; writing – review and editing. **Teruhisa Takuwa:** Investigation; writing – original draft. **Keisuke Aoe:** Investigation. **Katsuya Kato:** Investigation. **Nobukazu Fujimoto:** Investigation. **Yasuhiro Hida:** Investigation. **Masahiro Morise:** Investigation. **Yasumitsu Moriya:** Investigation. **Takao Morohoshi:** Investigation. **Hidemi Suzuki:** Investigation; project administration. **Masayuki Chida:** Investigation. **Shunsuke Endo:** Data curation. **Mitsutaka Kadokura:** Investigation. **Meinoshin Okumura:** Funding acquisition; supervision. **Satoshi Hattori:** Data curation; formal analysis; visualization; writing – original draft. **Hiroshi Date:** Funding acquisition; supervision. **Ichiro Yoshino:** Funding acquisition; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

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ETHICS STATEMENT

This study was approved by the institutional review board of Osaka University Hospital, where the registry office is located, on October 11, 2016 (approval number 16038). The registry and the study using the registered data were approved by each institutional review board of all participating institutions.

Informed consent statement: This study complied with the Declaration of Helsinki. Written informed consent was obtained from all study participants.

This study adhered to the ethical guidelines for epidemiologic studies published jointly by the Japan Ministry of Science, Culture, and Education and the Japan Ministry of Health, Labor, and Welfare on June 17, 2002, and revised on February 28, 2017.

Clinical Trial Registration: UMIN 000024664.

Animal Studies: N/A.

DATA AVAILABILITY STATEMENT

Under Japan's Personal Information Protection Law (Amended version in 2022), it is obligatory to obtain re-consent from research participants when providing data to a third-party. Since it is impossible to obtain consent again from the research participants, we cannot provide the data.

DISCLAIMER

The findings and conclusions of this study are those of the authors and do not necessarily represent the views of the Japanese Joint Committee for Lung Cancer Registry or its participating medical associations.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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TOPICS

呼吸器内科学

中皮腫における薬物治療の現況と今後の展望

Treatment of asbestos-related diseases：the current status and future perspectives of systemic treatment for mesothelioma

石綿と中皮腫

石綿（アスベスト）関連疾患には中皮腫や肺癌，良性石綿胸水，びまん性胸膜肥厚などがあるが，そのなかでも中皮腫は治療方法が限られており，予後も不良な疾患である．中皮腫は胸膜，腹膜，心膜，精巣鞘膜の中皮細胞から発生する悪性腫瘍であり，胸膜が80～85%，腹膜が10～15%，その他が1%以下とされる．中皮腫の約80%において何らかの石綿曝露との関連が明らかになっているが[1]，明らかな石綿曝露歴がなくとも発症している報告[2]や，遺伝的な素因も明らかになってきている．厚生労働省の発表[3]では令和4年の中皮腫による死亡者数は1,554名で令和3年の1,635名よりも減少しているものの，1995年の500人からは年々増加傾向であること，日本における発生ピークは2030年頃とされていることから，今後も患者数が増加することが予想され，さらなる治療開発が望まれている．

本稿では石綿関連疾患のうち，主に胸膜中皮腫に対する薬物治療の現況と今後の展望について述べる．

胸膜中皮腫の治療

胸膜中皮腫は組織型により上皮様・肉腫様・二相性に分類される．治療選択のアルゴリズムを示す（**図1**）．

上皮様症例の場合，Ⅰ～ⅢA期で肉眼的完全切除が得られると考えられる症例は外科的切除（耐術能に応じて胸膜切除/肺剝皮術あるいは胸膜肺全摘術）の適応となるが，解剖学的に切除マージンの確保が困難であり，病理学的な断端陰性ではなく肉眼的完全切除を目指すこととなるため再発の頻度が高く，術前あるいは術後の化学療法（シスプラチン，ペメトレキセド併用療法）が推奨される．また胸膜肺全摘術後には再発予防のため補助放射線治療を行うことがある．二相性症例についても同様の検討を行うが，上皮様症例に比べると外科的切除の適応についてより慎重である必要がある．肉腫様症例については予後が著しく不良であるため外科的切除は原則として推奨されていない．

肉腫様症例や切除不能例，術後再発例に対しては薬物療法が行われるが，2007年にシスプラチン，ペメトレキセド併用療法が承認されて以降，長らく新規治療薬の承認がなかった．しかし近年の免疫チェックポイント阻害薬の登場に伴い，抗PD-1抗体薬であるニボルマブ単剤療法がわが国における臨床第Ⅱ相試験（MERIT試験）[5]の結果に基づき二次治療以降のレジメンとして2018年に承認された．また，ニボルマブと抗CTLA-4抗体薬であるイピリムマブとの併用療法が，国際第Ⅲ相試験（CheckMate743試験）[6]において標準化学療法であるシスプラチン，ペメトレキセド併用療法に対し全生存期間を延長させることが示され，2021年に一次治療として承

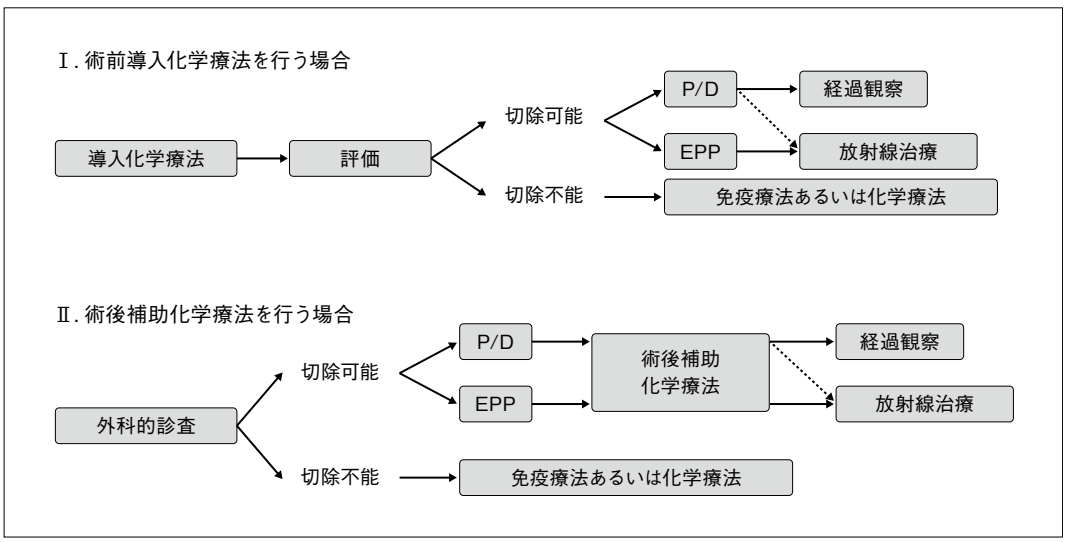

図1　胸膜中皮腫の診療アルゴリズム[4]

認された．特にこれまで治療抵抗性であった非上皮様症例においてハザード比 0.46（95％信頼区間：0.31-0.68）と著明な全生存期間の延長効果が認められており，これらの症例に対する治療成績の改善が期待される．

一方で免疫チェックポイント阻害薬については，特にその併用において従前とは異なったさまざまな免疫関連有害事象が出現する．非小細胞肺癌に対する国内第Ⅲ相試験（JCOG2007 試験）で，化学療法とニボルマブ，イピリムマブの併用療法において，予期していた範囲を超える治療関連死亡（治療との因果関係を否定できない死亡）が報告された[7]．治療選択肢が限られる胸膜中皮腫においてはニボルマブとイピリムマブ併用療法が有望な標準療法であることに疑いはないものの，有害事象には細心の注意を払いながら治療を進める必要がある．

その他の中皮腫に対する薬物療法

胸膜以外の中皮腫に対しては頻度が少ないこともあり標準治療として定まったものはなく，薬物療法については胸膜中皮腫に準じた治療が行われてきた．しかしわが国で行われた医師主導治験（VIOLA 試験）の結果に基づき，2023 年 11 月にニボルマブ単剤での治療が胸膜を除く中皮腫に対しはじめて国内承認され，使用可能となっている[8]．

今後の展望

胸膜中皮腫，その他の中皮腫に対し上述のような新規薬剤が登場しているものの，いまだ治療選択肢が限られているのが現状である．胸膜中皮腫に対しては一次治療としてデュルバルマブと標準化学療法の併用[9]や，二次治療以降の治療としてペムブロリズマブ，レンバチニブの併用療法[10]やペムブロリズマブ単剤治療[11,12]の試験結果が報告されている．ペムブロリズマブについてはプラチナ，ペメトレキセド併用化学療法と併用することで全生存期間を延長させることが報告されており[13]，新たな治療選択肢となることが期待される．またプラチナ，ペメトレキセド併用化学療法へのベバシズマブの上乗せについては有効性が示されており[14]，診療ガイドライン[4]にも記載があるものの保険償還されておらず注意が必要である．また新規の免疫チェックポイント阻害薬と化学療法の併用についても臨床試験が進行中である．

免疫チェックポイント阻害薬をはじめとする新規薬剤の登場により，多くの癌種で予後の改善が認められており，中皮腫においても今後のさらなる治療の発展が期待される．

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Editorial

Spare the lung: surgical treatment approach for malignant pleural mesothelioma

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Comment on: Klotz LV, Hoffmann H, Shah R, *et al.* Multimodal therapy of epithelioid pleural mesothelioma: improved survival by changing the surgical treatment approach. Transl Lung Cancer Res 2022;11:2230-42.

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In a recent study published on *Translational Lung Cancer Research*, Klotz and colleagues report the results of their retrospective analyses, where they compared treatment outcomes among patients diagnosed with epithelioid malignant pleural mesothelioma (MPM) (1). They compared survival of three patient cohorts: one was treated with an extrapleural pneumonectomy (EPP); one was treated with an extended pleurectomy/decortication (EPD) combined with hyperthermic intrathoracic chemoperfusion (HITOC) and adjuvant chemotherapy; and one was treated with chemotherapy alone. They demonstrated that the median overall survival (OS) was significantly longer in the EPD/HITOC cohort than in the EPP and chemotherapy cohorts. In addition, their multivariate analysis showed that EPD/HITOC was significantly associated with improved OS. Based on these findings, they concluded that a less radical lung-sparing surgery, EPD, should be performed in patients with epithelioid MPM.

MPM is strongly associated with past asbestos exposure, and its incidence has continued to increase in many developing countries. Surgical resection is applied to patients in the earlier stages of the disease. However, a tumor resection with wide microscopically negative margins is not feasible in MPM, due to the surrounding vital structures. The aim of a surgical resection for MPM is to remove the entire macroscopic tumor from the hemithorax. A macroscopic complete resection can be achieved with both an EPP and a PD. However, it remains controversial which is the more appropriate procedure. Although an EPP was traditionally the technique of choice, perioperative mortality and morbidity were significantly lower with an EPD than with an EPP. A systematic review showed that OS was comparable between those treated with an EPP and those treated with an EPD (2). Those results were further supported in a meta-analysis (3). In addition, the EPP is generally more deleterious than an EPD, in terms of quality of life for the patient (4). Based on those reports, the recent European Society of Medical Oncology Clinical Practice Guidelines considered a lung-sparing EPD the first-choice surgical procedure (5). However, an EPP could also be offered to highly selected patients in high-volume centers. Due to the lack of a direct comparison between these two surgical modalities, the superiority of an EPD has not been established.

Klotz and colleagues analyzed the outcomes of patients with epithelioid MPM treated with a multimodal approach during the last 2 decades in a single high-volume center in Germany. They changed their surgical approach between 2012 and 2013, from an EPP-based multimodal treatment to an EPD/HITOC treatment. Many institutions around the world have similarly changed their surgical policies, based on a randomized feasibility study that compared EPP and no-EPP treatments (6).

In the Klotz study, the median OS of the EPD/HITOC, EPP, and chemotherapy cohorts were 38.1, 24.0, and 15.8 months, respectively. These median OS were

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consistent with those reported previously. Better survival was significantly associated with good performance status, a younger age, and negative lymph node status. The perioperative morbidity rate was significantly higher in the EPP cohort (36.2%) than in the EPD/HITOC cohort (18%). The strength of the study was that the results of different surgical approaches were compared in a high-volume institution. This real-world data might support a less radical lung-sparing technique as the first-choice surgical procedure for epithelioid MPM. It seems quite natural that survival was worst in the chemotherapy cohort, because those patients had unresectable, advanced disease.

Of note, the study by Klotz and colleagues had some limitations. The main limitations were the retrospective study design and the limited number of selected patients. Moreover, the EPD/HITOC cohort contained more patients and better performance status, compared to the EPP cohort. Second, as the authors described, due to the time difference, potential improvements in perioperative management and recent advancements in treating tumor recurrence might have influenced the improved OS in the EPD/HITOC cohort. Third, the role of an HITOC adjunct to surgery for MPM has not been established. The objective of the HITOC is to eradicate the remaining cancer cells. To date, improvements in recurrence-free survival and OS have been observed in a retrospective single-center analysis (7). However, the efficacy of HITOC has not been demonstrated in a prospective trial.

In the future, the lung-sparing EPD will be a standard surgical approach for resectable MPM, based on the above-mentioned retrospective studies, including the meta-analyses. The current report by Klotz and colleagues also supported the efficacy of EPD and demonstrated that it could maintain the patient's quality of life. Nevertheless, many problems remain to be resolved concerning the surgical approach for MPM. First, there is no clear evidence on the impact of EPD on extended OS in patients with MPM. The evidence may be provided by the MARS2 trial, which will prospectively compare the extent of survival improvement between EPD and non-surgical therapy (8). Another major outstanding issue is whether systemic chemotherapy should be delivered in a neoadjuvant or adjuvant setting. Some clues to this issue might come from a randomized phase II trial that aims to compare the effect of neoadjuvant and adjuvant chemotherapy in combination with surgery in MPM (9). Furthermore, the exact role of HITOC should be clarified in a prospective clinical trial.

We sincerely hope that, through prospective clinical trials and grounded real-world data, an optimal clinical approach will be established for patients with MPM.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CASE REPORT

Thrombocytopenia as an Immune-Related Adverse Event in Malignant Pleural Mesothelioma: A Case Report

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ABSTRACT

A 69-year-old man presented with a pulmonary opacity at a regular medical check-up. He had been exposed to asbestos in a chemical fiber manufacturing setting. Result of positron emission tomography with computed tomography (CT) revealed fluorodeoxyglucose accumulations along the right pleura in areas with multiple nodules and irregular pleural thickening. On the basis of analysis of a CT-guided needle biopsy result, he had been diagnosed with having epithelioid malignant pleural mesothelioma. He received neoadjuvant chemotherapy, and subsequently, a pleurectomy and decortication. After 6 months, malignant pleural mesothelioma recurred with multiple tumors in the pleural cavity. Nivolumab was administered as salvage immunotherapy. A CT scan result revealed marked tumor reduction; however, his platelet count was low (8000/μL), and he was diagnosed with having nivolumab-induced immune thrombocytopenia. Oral prednisone and thrombopoietin receptor agonist were delivered, and the platelet count improved; therefore, a sustained cycle of nivolumab was resumed. This case revealed that nivolumab could be readministered for continued antitumor effects, with careful management of immune-related adverse events.

Keywords: Mesothelioma; Nivolumab; Thrombocytopenia; Thrombopoietin receptor agonist; Case report

Introduction

Malignant pleural mesothelioma (MPM) is a rare malignant disease that occurs in the pleura, peritoneum, and less often, in other sites. Asbestos exposure is considered the main cause of MPM.

Nivolumab is an antibody that acts as an immune checkpoint inhibitor (ICI) by targeting the programmed death-1. Nivolumab was approved for patients with recurrent MPM in Japan in 2018, based on results from a phase 2 trial.[1] ICIs cause various immune-related adverse events (irAEs). Here, we describe a patient with MPM who developed severe thrombocytopenia during treatment with nivolumab.

Case Presentation

A 69-year-old man presented with a pulmonary opacity on a chest radiograph at a regular medical check-up. He had been exposed to asbestos for 3 years, while working in a chemical fiber manufacturing setting, and he had a history of smoking (20 cigarettes/d) for 18 years from the age of 20 years. In addition, he had been

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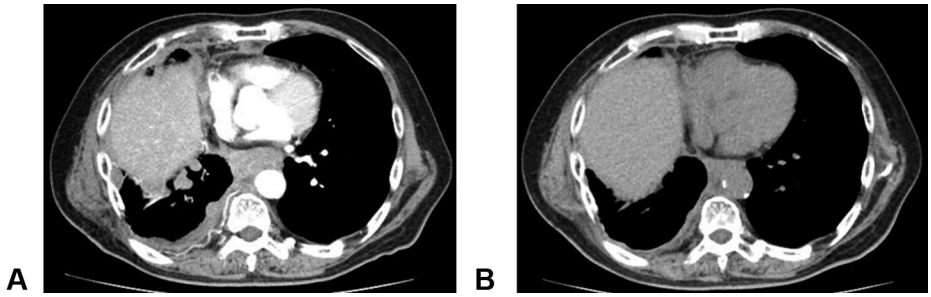

Figure 1. CT images of the chest reveal nivolumab treatment of recurrent MPM. (*A*) At 6 months postsurgery, multiple tumors are present in the pleural cavity, which suggest MPM recurrence. (*B*) CT images after four administrations of nivolumab reveal marked improvement in recurrent MPM tumors. CT, computed tomography; MPM, malignant peritoneal mesothelioma.

diagnosed with having type 2 diabetes mellitus at the age of 59 years.

Result of a positron emission tomography–computed tomography (CT) analysis revealed fluorodeoxyglucose accumulations along the right pleura, in areas with multiple nodules and irregular pleural thickening. On the basis of a CT-guided needle biopsy analysis, he had been diagnosed with having epithelioid MPM. Clinical staging revealed a TNM stage of T3N0M0 (Union for International Cancer Control TNM Classification of Malignant Tumors, seventh edition). The patient received three cycles of neoadjuvant chemotherapy (cisplatin and pemetrexed), and subsequently, underwent a pleurectomy with decortication. At 6 months postsurgery, MPM recurrence was detected, when multiple tumors were found in the pleural cavity (Fig. 1*A*). Nivolumab (240 mg/d) was administered as salvage immunotherapy, every 2 weeks. After four cycles, a CT scan result revealed marked tumor reduction (Fig. 1*B*).

After the ninth cycle, during a routine check-up, thrombocytopenia was detected (platelet count: 8000/μL) without anemia or leukopenia. Consequently, nivolumab administration was stopped. The thrombocytopenia was not associated with bleeding complications. A bone marrow biopsy result revealed no megakaryocytic abnormalities or chromosomal aberrations. The platelet-associated immunoglobulin G (PA-IgG) level was elevated (197 ng/10^7 cells). Antiplatelet antibodies were negative. Result of the serum test for hepatitis B c-antibody, hepatitis C antibody, *Helicobacter pylori* antibody, human T-cell lymphotropic virus type I antibody, and human immunodeficiency virus antibody was negative. On the basis of these examinations, the patient was diagnosed with having nivolumab-induced immune thrombocytopenia (ITP). Oral prednisone at 0.5 mg/kg/d was delivered to treat the ITP, and the platelet count improved on day 3 (50,000/μL). A thrombopoietin receptor (TPO-R) agonist was also delivered as the prednisone was tapered off. The platelet count improved to 200,000/μL on day 24 (Fig. 2). At 3 months after the onset of ITP, a 10th cycle of sustained nivolumab was resumed with the consent of the patient.

At the 14th cycle of nivolumab administration, there were no reappearance of ITP and no exacerbation of MPM.

Discussion

For the past several years, studies have revealed the efficacy of ICIs in various types of malignancies. Nevertheless, studies have also reported that ICIs cause a variety of irAEs.[2] Hematological irAEs are relatively rare; when all grades are considered, they occur at a rate of approximately 3.6% (the grade 3–4 rate is estimated at approximately 0.7%).[3] The occurrence of hematological irAEs was reported to increase with programmed death-1 and programmed death-ligand 1 antibody administration, compared with CTLA-4 antibody administration. In one review, among 63 patients treated with ICIs, nine patients died and 18 patients experienced ITP complications.[3] According to a previous observational study, there were 35 patients with hematologic irAEs including nine patients with ITP among 948 screened patients,[4] and median time to onset of ITP was 10.1 weeks. Only one case of nivolumab-induced ITP in MPM has been reported to date, in which ITP developed 16 weeks after the first administration of nivolumab.[5] ITP also

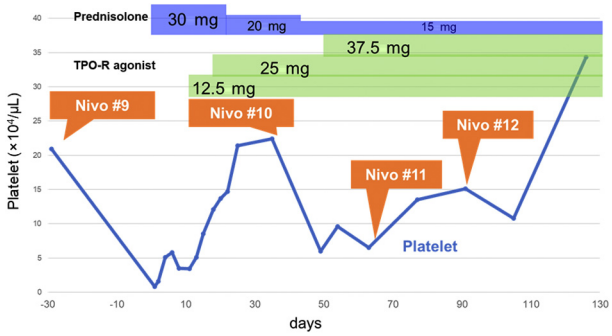

Figure 2. Clinical course of the case. #, number of the administration; Nivo, nivolumab; TPO-R, thrombopoietin receptor.

developed 16 weeks after the first administration of nivolumab in the current case.

In the current case, thrombocytopenia was likely caused by PA-IgG antibodies produced by activated lymphocytes. The elevated PA-IgG level and the negative finding for antiplatelet antibodies supported the notion that ITP had caused thrombocytopenia. It is generally known that steroids have an inhibitory effect on ICIs; consequently, they are often administered to treat ITP. Other treatment options include intravenous immunoglobulins, TPO-R, and other immunosuppressive therapies, such as azathioprine and rituximab.[5–7]

In the present case, we started treatment with steroids. In addition, we used TPO-R in a combinational therapy. We aimed avoiding to deliver steroids at high doses for a long term, because the patient had type 2 diabetes. We also aimed to readminister and continue nivolumab treatment because nivolumab had produced a remarkable antitumor effect. In fact, MPM exacerbation occurred during withdrawal of nivolumab in a previous reported case with nivolumab-induced thrombocytopenia.[5] We could resume nivolumab therapy after the ITP resolved without detectable MPM aggravation in the current case. The decision to resume ICI therapy after resolution of toxicity is challenging. A patient's tumor response status is an important factor in deciding whether to resume ICI. According to American Society of Clinical Oncology guideline, for some patients with a rapid resolution of certain moderate-to-severe irAEs after corticosteroid use, resumption of ICI may be less precarious.[7] We aimed to resume and continue nivolumab treatment because nivolumab had produced a remarkable antitumor effect.

A previous study revealed that nivolumab had clinical effectiveness as a second-line therapy for an unselected population of patients with mesothelioma.[8] More recently, nivolumab was approved as a first-line therapy for MPM in combination with ipilimumab.[9] Thus, in future, nivolumab will play a more prominent role in MPM treatment strategies. According to a recent report, nivolumab displayed more antitumor efficacy in patients with irAEs than in patients without irAEs.[10] We need to manage irAEs appropriately, particularly in MPM treatments, where the treatment options remain limited, compared with other types of malignancies.

Conclusions

We described a patient with MPM who developed an irAE of severe thrombocytopenia. We successfully treated nivolumab-induced ITP with steroids and TPO-R. The current case revealed that nivolumab could be readministered and continued as an MPM treatment, with careful management of irAEs.

CRediT Authorship Contribution Statement

Takaaki Tanaka: Conceptualization, Investigation, Writing—original draft preparation.

Shoji Asakura: Investigation.

Kazuya Hisamatsu: Writing—review and editing.

Nobukazu Fujimoto: Investigation, Supervision.

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Bereaved Family Members' Perspectives of Good Death and Quality of End-of-Life Care for Malignant Pleural Mesothelioma Patients: A Cross-Sectional Study

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Abstract: Objective: This study investigated whether malignant pleural mesothelioma (MPM) patients achieved good deaths and good quality of end-of-life care compared with other cancer patients from the perspective of bereaved family members in Japan. Methods: This cross-sectional study was part of a larger study on the achievement of good deaths of MPM patients and the bereavement of their family members. Bereaved family members of MPM patients in Japan (n = 72) were surveyed. The Good Death Inventory (GDI) was used to assess the achievement of good death. The short version of the Care Evaluation Scale (CES) version 2 was used to assess the quality of end-of-life care. The GDI and CES scores of MPM patients were compared with those of a Japanese cancer population from a previous study. Results: MPM patients failed to achieve good deaths. Only 12.5% of the MPM patients were free from physical pain. The GDI scores of most of the MPM patients were significantly lower than those of the Japanese cancer population. The CES scores indicated a significantly poorer quality of end-of-life care for the MPM patients than the Japanese cancer population. The total GDI and CES scores were correlated (r = 0.55). Conclusions: The quality of end-of-life care for MPM patients remains poor. Moreover, MPM patients do not achieve good deaths from the perspective of their bereaved family members.

Keywords: mesothelioma; asbestos; rare lung disease; palliative care; good death; quality of care

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1. Introduction

Malignant pleural mesothelioma (MPM) is a rare fatal malignancy caused mainly by asbestos [1]. The number of people with MPM who die each year in Japan is about 1550, and that number is growing [2]. It is estimated that Japan will have 66,000–100,000 deaths from mesothelioma between the years 2003 and 2050 [3,4]. The median survival from the time of diagnosis in Japan is 7.9 months [5]. MPM causes a series of debilitating physical symptoms, such as chest pain, dyspnea, fatigue, anorexia, insomnia, constipation, and sweating [6–11]. Psychological issues, such as uncertainty, lack of control [12], memory problems, difficulties in concentrating, feeling that problems cannot be solved [13], depression, anxiety, fear, and isolation [8], all negatively affect the quality of life of MPM patients. Finally, there is additional psychological distress for victims of the asbestos industry [14]. Suffering from asbestos-related disease causes fear of premature death [15]. MPM patients in Japan reportedly suffer from physical and psychological distress [16], and their quality of life is impaired [9].

Lamentably, the quality of life of MPM patients in the terminal stage, particularly their achievements of good deaths and good quality of end-of-life care, has been scarcely

researched and thus remains poorly understood. Unfortunately, there are barriers to conducting research on MPM patients in their terminal stage. These include their small population, and the short lengths of time between disease diagnosis, debilitation, and death. Moreover, conducting research on terminally ill patients imposes unnecessary burdens on them. Therefore, many studies are conducted with bereaved family members [13,17–20] to evaluate the patients' achievements of good deaths and the quality of their end-of-life care.

This study aimed to investigate whether MPM patients achieved good deaths and good quality of end-of-life care compared with other cancer patients in Japan from the perspective of bereaved family members. The data for the other cancer patients in Japan were taken from a previous study [21].

2. Methods

2.1. Study Design, Participants, and Setting

This study used a cross-sectional survey design to examine the achievements of good death and good quality of end-of-life care for MPM patients from the perspective of bereaved family members.

The inclusion criteria for bereaved family members were as follows: (1) had lost a loved one to MPM, (2) had a loved one who had been diagnosed with MPM after 2008 when the first evidence-based chemotherapy succeeded in prolonging the survival of MPM patients, and (3) could respond to a self-administered questionnaire written in Japanese. The exclusion criterion was a bereaved family member who had experienced a loss within six months. This research is part of a larger study which also investigated the complicated grief of the bereaved family members of MPM patients. According to the previous study, the diagnosis of complicated grief should be made at least six months after the death of a family member [22].

A request for cooperation was sent to the advocacy group of the Japan Association of Mesothelioma and Asbestos-Related Disease Victims and their Families. The association has 15 branches across Japan and works with approximately 700 victims of asbestos-related diseases and their families. The association sent the informed consent information and questionnaires to 109 bereaved family members in November 2016. Those agreeing to participate returned the completed questionnaires via postal mail by March 2017.

2.2. Outcomes

The primary outcomes were the achievements of a good death and good quality of end-of-life care for MPM patients. The secondary outcome was the presence of the common symptoms of MPM.

2.3. Instruments

2.3.1. Information of Patients and Bereaved Family Members

The following information was provided by the bereaved family members about the deceased patients: sex, age at diagnosis, survival and received treatments, receipt of two types of insurance compensation benefits, and place of death.

The information about the bereaved family members included the following: age, relationship to the patient, time of bereavement, experience of end-of-life discussion with the patient, timing of patient's death, financial impact of patient's MPM on family, and level of anger toward asbestos. The bereaved family members were also asked about their satisfaction with care on diagnosis, when the patient became critical, and when the patient died.

2.3.2. Good Death Inventory

Achievement of good death was measured using the Good Death Inventory (GDI), which had internal consistency (α = 0.74–0.95) and acceptable test–retest reliability (intra-class correlation coefficient = 0.38–0.72) [17]. The GDI was validated to evaluate the achievement of good death from the perspective of bereaved family members in Japan [17]. The GDI has 18 items consisting of 10 core items and 8 optional items, and is answered using a seven-point

Likert scale (1 = absolutely disagree, 7 = absolutely agree). The possible scores range from 18 to 126, and a high score indicates the achievement of a good death.

2.3.3. Care Evaluation Scale

The short version of the Care Evaluation Scale (CES) version 2 (Cronbach's $\alpha = 0.96$) was used to evaluate the quality of end-of-life care in Japan [23]. The CES consists of 10 items. The bereaved family members answered using a six-point Likert scale (1 = highly disagree, 6 = highly agree). A high total CES score indicates a good quality of end-of-life care.

2.3.4. Symptoms

The presence of the common symptoms of MPM, namely, pain, dyspnea, anorexia, fatigue, anxiety, dysphagia, constipation, nausea, insomnia, edema, and palpitation, was asked with respect to two time points. These time points were (1) at the end of chemotherapy (only for the bereaved family members of patients who received chemotherapy—i.e., when chemotherapy was stopped, being no longer effective), and (2) at the final critical stage (i.e., when the patient entered the critical stage). The bereaved family members checked the items of symptoms the MPM patients experienced. These two time points enabled the comparison of the present results with previous results that reported on the care needs of patients because of their severe symptoms [16].

2.4. Missing Data

Mean imputation was conducted for the missing data of GDI and CES scores according to the instructions for the tools.

2.5. Comparison of Study Data

A nationwide project to evaluate hospice and palliative care in Japan was previously conducted by Miyashita et al. and reported as the Japan Hospice and Palliative care Evaluation (J-HOPE) study [21]. This project evaluated the end-of-life care of cancer patients from the perspective of bereaved family members in nationwide designated cancer centers, inpatient palliative care units (PCUs), and home hospices. The study focused on care satisfaction, the structure and process of care, and the achievement of a good death. This previous study compared the data according to the last place of care. Data from this previous study were provided to us by Dr. Miyashita, who is a co-author of the present study. There were 8398 questionnaire responses from family members that were analyzed by Miyashita et al. [24].

2.6. Statistical Analysis

The scores of each scale were calculated using a previously reported scoring procedure [17,23]. The scores of the measurement tool items in GDI and CES were totaled and compared with those of cancer patients in the J-HOPE study [21]. The GDI and CES mean scores in the J-HOPE study [21] were calculated according to the place of death and compared with the GDI and CES mean scores in the present study. The achievements of good death (measured using GDI) and good quality of end-of-life care (measured using CES) scores in the present MPM study and the previous J-HOPE study were compared using the binominal test. The GDI and CES total scores in the present MPM study and the previous J-HOPE study were compared using a one-sample *t*-test.

The correlations between the GDI and the CES were examined. Thereafter, the GDI scores and the patients' and bereaved participants' information were examined. Sex, receiving treatments, approval for compensation, experience of end-of-life discussion with patients, and satisfaction of care were treated as dichotomous variables. Finally, the coefficients and their 95% confidence intervals estimated by multiple regression analysis were used to assess the correlations between the GDI and CES scores and the clinical social factors. A *p*-value of < 0.05 was considered to indicate a statistically significant difference. Statistical analysis was performed using SPSS version 27.

2.7. Ethical Consideration

This study was approved by the Research Ethics Committee of St. Luke's International University (16-A035). It was conducted based on the ethical principles of avoiding harm, voluntary participation, anonymity, and the protection of privacy and personal information.

3. Results

Of the 109 questionnaires distributed to the bereaved family members through the related victims and family advocacy group, 74 (67.9%) were completed and returned via postal mail by the end of March 2017. Two bereaved family member respondents who had experienced a loss within the last six months were excluded. Thus, a total of 72 questionnaires were analyzed.

3.1. Characteristics of Malignant Pleural Mesothelioma Patients and Bereaved Family Members

As shown in Table 1, 81.9% of the deceased MPM patients were men, and their mean age at diagnosis was 66.9 years. The treatment modalities they received were chemotherapy (70.8%), palliative care (56.9%), and surgery (19.4%). A large minority (48.6%) died in the respiratory ward, followed by the PCU or hospice (33.3%). Only 13.9% died at home. The mean survival time was 14.5 months from the time of diagnosis. The majority of the bereaved family members (72.2%) was spouses of the MPM patients, and the mean bereavement time was 45.2 months.

Table 1. Comparison of the characteristics of malignant pleural mesothelioma patients and cancer patients, and their bereaved participants.

Disease			**MPM**		**Cancer ***					
					Place of Death					
			***n* = 72**		**Designated Cancer Center (*n* = 2794)**		**Palliative Care Unit (*n* = 5312)**		**Home Hospice (*n* = 292)**	
Patients			***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Sex	Men		59	81.9	1820	65.1	2906	54.7	181	62
	Women		13	18.1	973	34.8	2364	44.5	111	38
Primary cancer site	Pleura **		72	100	-	-	-	-	-	-
	Lung		0	0	688	24.6	1246	23.5	63	21.6
	Stomach		0	0	395	14.1	635	12	36	12.3
	Colorectum/rectum		0	0	260	9.3	651	12.3	54	18.5
	Liver		0	0	279	10	281	5.3	18	6.2
	Gall bladder/bile duct		0	0	165	5.9	201	3.8	14	4.8
	Pancreas		0	0	243	8.7	398	7.5	18	6.2
	Esophagus		0	0	112	4	184	3.5	8	2.7
	Breast		0	0	83	3	266	5	8	2.7
	Others		-	-	513	18.4	1389	26.2	69	23.7
Source of asbestos exposure	Occupation		49	68.1						
	Neighboring factory		17	23.6						
	School		1	1.4						
	Family		1	1.4						
	Unknown		4	5.4						
Treatment (includes multiple treatments)	Surgery		14	19.4						
		Extrapleural pneumonectomy	12	16.7						
		Pleurectomy decoration	2	2.8						
	Chemotherapy		51	70.8						
	Radiotherapy		15	20.8						
	Palliative care		41	56.9						
Compensated (some had both types)	Workmen's accident compensation insurance		47	65.3						
	Asbestos-related health damage relief system		56	77.8						
Place of death	Respiratory ward		35	48.6						
	Palliative care unit/hospice		24	33.3						
	Home		10	13.9						
	Other		3	4.2						
Age at diagnosis (years)		Range: 36–92	Mean ± SD	66.9 ± 9.6	69.8 ± 11.5		70.9 ± 12.1		71.8 ± 13.0	
Survival (months)		0.5–69		14.5 ± 14.1						
Bereaved family members			***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Sex	Men		15	20.8	825	29.5	1694	31.9	60	20.6
	Women		57	79.2	1696	60.7	3556	67.1	228	78.1
Relationship with patient	Spouse		52	72.2	1535	54.9	2506	47.2	165	56.5
	Child		20	17.8	672	24.1	1809	34.1	78	26.7
	Son/daughter-in-law		0	0	181	6.5	353	6.7	34	11.6
	Parent		0	0	49	1.8	100	1.9	4	1.4
	Sibling		0	0	56	2	310	5.8	6	2.1
	Others		0	0	32	1.2	188	3.5	4	1.4
Experience of end-of-life discussion with patient	Yes		27	37.5						
	No		44	61.1						
Timing of patient's death	Much sooner than expected		31	43.1						
	Sooner than expected		25	34.7						
	Moderate		9	12.5						
	Later than expected		5	6.9						
	Much later than expected		2	2.8						

Table 1. *Cont.*

Disease				MPM		Cancer *					
						Place of Death					
				n = 72		Designated Cancer Center (*n* = 2794)		Palliative Care Unit (*n* = 5312)		Home Hospice (*n* = 292)	
Patients				*n*	%	*n*	%	*n*	%	*n*	%
Satisfaction with care on diagnosis	Satisfied			29	40.3						
	Not satisfied			43	59.7						
When patient became critical	Satisfied			31	38.9						
	Not satisfied			41	61.1						
When patient died	Satisfied			47	65.3						
	Not satisfied			25	34.7						
Financial impact of patient's MPM on family	Significant impact			12	16.7						
	Some impact			15	20.8						
	Moderate impact			20	27.8						
	Minor impact			15	20.8						
	No impact			10	13.9						
Level of anger toward asbestos	Very angry			56	77.8						
	Angry			11	15.3						
	Moderately angry			4	5.6						
	Slightly angry			1	1.4						
	Not angry at all			0	0						
Age (in years)		Range:	32–82	Mean ± SD	62.5 ± 12.2	60.4 ± 12.5		59.3 ± 12.8		60.6 ± 12.1	
Time since bereavement (months)			9–110		45.2 ± 27.2	12.4 ± 3.5		11.8 ± 3.7		12.2 ± 6.6	

* Cited from the J-HOPE study (reference [21]). ** Pleural mesothelioma was classified as "Others" in the J-HOPE study. MPM = malignant pleural mesothelioma.

3.2. Achievement of Good Death

The obtained data revealed that MPM patients failed to achieve good deaths. The mean total GDI score of the MPM patients was 61.9 ± 15.7, which was significantly lower than the 81.1 of the J-HOPE cancer patients. Figure 1 shows the comparison of the percentage scores of MPM patients and J-HOPE cancer patients for the GDI items for the achievement of good death. The lowest percentages of achievement by the MPM patients in the 10 core items of the GDI were for the items "being free from physical distress" (12.5%) followed by "feeling that life is completed" (18.1%) and "having some pleasure in daily life" (27.8%). The binominal test showed that the percentages regarding the achievement of a good death in the MPM patients were significantly lower than those in the J-HOPE cancer patients in all items, except for the following four items: "being independent in daily activities", "knowing what to expect about the future condition", "living in calm circumstances", and "supported by religion". The greatest gaps in the achievement of good death between the MPM patients and the J-HOPE cancer patients were for "being free from physical distress", which was true for 12.5% of the MPM patients compared with 64.7% of the J-HOPE cancer patients, followed by "not exposing one's physical and mental weakness to family", "dying a natural death", and "feeling life is completed".

3.3. Quality of End-of-Life Care

The total scores of CES in the MPM patients and the J-HOPE cancer patients were significantly different, as shown in Figure 2. The mean total score of CES in the MPM patients was 70.3 ± 16.0, which was significantly lower than the 75.8 in the J-HOPE cancer patients. The binominal test showed that all the scores of the CES items indicated a significantly poorer quality of end-of-life care in the MPM patients than in the J-HOPE cancer patients except in the items "cost", "coordination and consistency", and "explanation to family by physician".

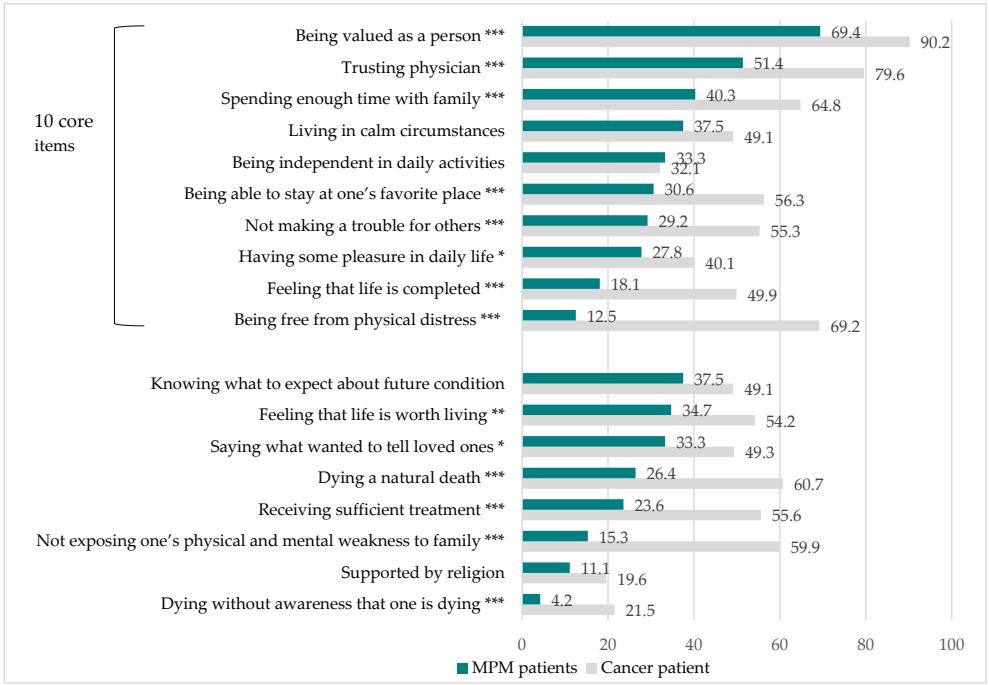

Figure 1. Comparison of the percentages of MPM patients and J-HOPE cancer patients concerning GDI items for the achievement of a good death. Sum of "somewhat agree", "agree", and "absolutely agree" responses. Data of cancer patients were from the J-HOPE national survey of Japanese cancer patients (reference [21]). Weighted means of GDI scores in general cancer patients in Japan (reference [21]) were calculated according to the place of death. Core and optional items were established by factor analysis (reference [17]). * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$.

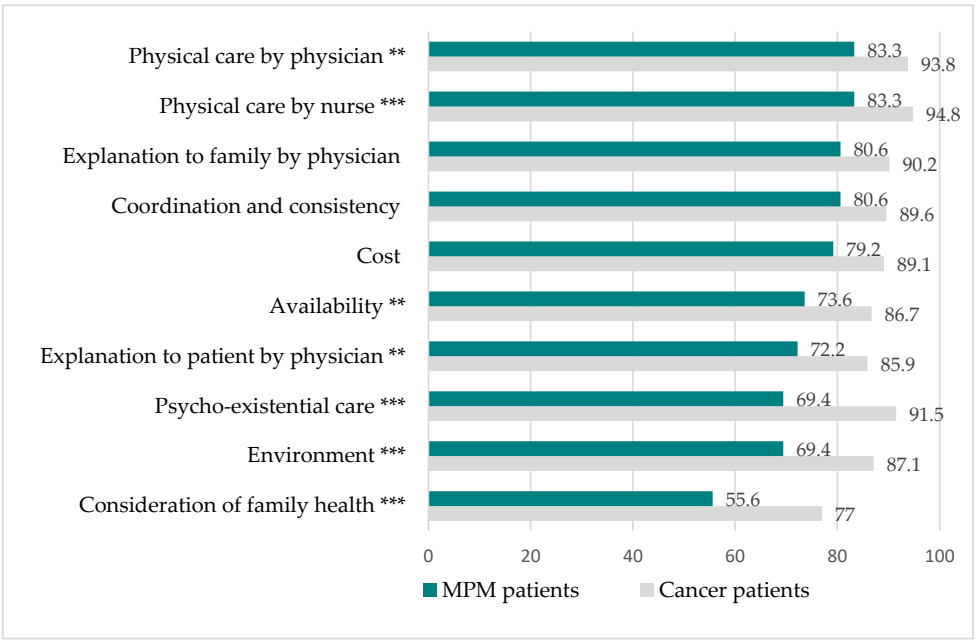

Figure 2. Comparison of the percentages of MPM and J-HOPE cancer patients with regard to CES items for achieving good quality end-of-life care. Sum of "somewhat agree", "agree", and "absolutely agree". The weighted means of CES scores in general cancer patients in Japan were calculated according to the place of death. Data are from the J-HOPE study (Reference [21]). ** $p < 0.005$, *** $p < 0.001$.

3.4. Symptoms

The percentages of MPM patients who experienced symptoms at the end of chemotherapy are shown in Figure 3, and the same percentages at the final critical stage are shown in Figure 4. More than half of the MPM patients experienced pain, dyspnea, anorexia, and anxiety at the end of chemotherapy. When the MPM patients reached the final critical stage, symptoms such as fatigue and dysphasia followed.

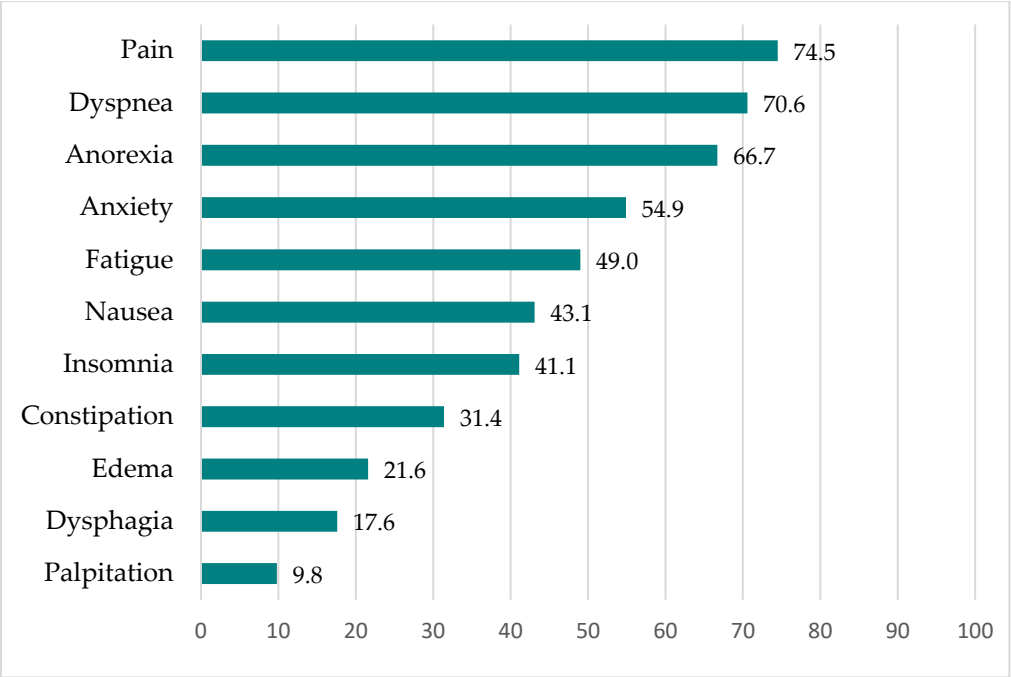

Figure 3. Percentages of MPM patients experiencing symptoms at the end of chemotherapy (n = 51).

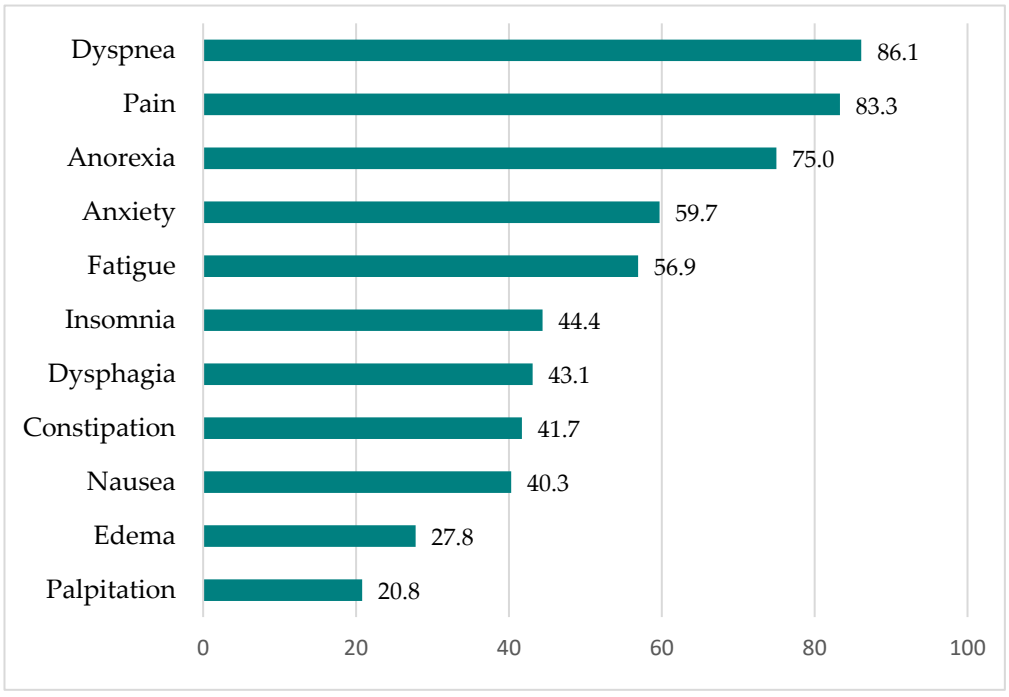

Figure 4. Percentages of MPM patients experiencing symptoms at the final critical stage (n = 72).

3.5. Factors Associated with a Good Death

The GDI and CES total scores were significantly associated (correlation coefficient $\rho = 0.554$, $p = 0.0001$), indicating that the patients who received better end-of-life care were more likely to achieve good deaths. The multiple regression analysis results are shown in Table 2.

Table 2. Multiple regression model predicting good death ($n = 72$).

Dependent Variable: GDI Total Score (F = 9.098, $p = 0.0001$, Adjusted $R^2 = 0.260$)						
Model	**B**	**SE**	**β**	**t**	**95% CI**	***p*-Value**
Constant	41.724	4.769		8.794	32.202–51.246	0.001
Satisfied with care received when patient became critical	11.597	3.278	0.370	3.538	5.053–18.141	0.001
Female bereaved family member	11.061	4.028	0.284	2.746	3.018–19.103	0.008
Patient died later than expected	3.270	1.556	0.220	2.102	0.164–6.376	0.039

Abbreviations: F, overall F-test for regression; R^2, correlation of determination; B, unstandardized coefficient; SE, standard error; β, standardized coefficient (beta); t, independent-sample *t* test; CI, confidence interval. Note: The variables included were as follows: patient's age on diagnosis; sex of patient; survival; whether the patient received certified workmen's accident compensation insurance; whether the patient was certified for asbestos-related health damage relief system; whether the patient received surgery; whether the patient received chemotherapy; whether the patient received palliative care; age of bereaved family member; sex of bereaved family member; timing of patient's death; bereaved family members' level of anger toward asbestos; the financial impact of the patient's MPM on the family; whether bereaved family members were satisfied with the care received on diagnosis; whether bereaved family members were satisfied with the care received when the patient became critical; whether family members were satisfied with the care received at the point of death; the relationship of patient and bereaved family members; and whether family members had an end-of-life discussion with the patient.

The final regression model for predicting good death showed that higher GDI scores were significantly related to the surveyed family member being female, the patient dying later than expected, and satisfaction with care when the patient became critical.

3.6. Factors Associated with Quality of End-of-Life Care

The final regression model for predicting good death (Table 3) showed that higher CES scores were significantly related to the following: satisfied with the care received when the patient died, and Received chemotherapy.

Table 3. Multiple regression model predicting quality end-of-life care ($n = 72$).

Dependent Variable: CES Total Score (F = 34.558, $p = 0.0001$, Adjusted $R^2 = 0.493$)						
Model	**B**	**SE**	**β**	**t**	**95% CI**	***p*-Value**
Constant	30.545	1.807		16.907	26.939–34.152	0.001
Satisfied with the care received when the patient died	13.272	1.727	0.664	7.683	9.824–16.720	0.001
Received chemotherapy	4.048	1.832	0.191	2.209	0.391–7.705	0.031

Abbreviations: same as Table 2. Note: same as Table 2.

4. Discussion

In this study, we described the extent to which Japanese MPM patients achieved good deaths and their good quality of end-of-life care. The findings were compared with those of a large cohort of Japanese cancer patients from the J-HOPE study [21].

The present results demonstrate a lack of good deaths among MPM patients. The three main findings of this study are as follows: (1) there was a remarkable lack of good deaths among the MPM patients; (2) there was an enormous burden of symptoms in the MPM patients; and (3) the quality of end-of-life care in the MPM patients was poorer than that in the J-HOPE cancer patients. The CES score was correlated with the GDI score, consistent with the findings of Miyashita et al. [17]. The final regression model showed that a higher GDI score was significantly related to the surveyed family member being

female, the patient dying later than expected, and satisfaction with the care received when the MPM patient became critical.

4.1. Poor Achievement of Good Death

This study showed an extreme lack of good deaths among the MPM patients. The lowest score from among the 10 GDI core items was for the item "being free from physical distress" (12.5%), which was significantly lower than the 62.9% score for the Japanese cancer population [21]. Symptom management is difficult in MPM patients, possibly because (1) MPM progresses rapidly and causes a variety of severe symptoms [6,9,25,26]; and (2) MPM results in anger and negative feelings of injustice [7,14,16], which tend to complicate the patient's physiological distress more than other malignancies. Additionally, MPM has the potential to cause spiritual pain. Some studies have advocated care to ease the spiritual pain of MPM patients [27,28].

Only 18.1% of the MPM patients in the present study had the "feeling that life is completed", which was significantly lower than the figure of 49.9% among the cancer population [21]. The possible reasons are as follows: (1) In this current study, the mean age of diagnosis was 66.9 years, and the mean survival time was only 14.5 months. The patients died relatively young, and they had very little time to complete their lives and face their deaths. (2) As the cause of MPM was asbestos and not one's own doing, the patient may have felt that death from MPM was unfair.

For patients with MPM, "Dying without awareness that one is dying" (4.2%) was, for the most part, not possible. Patients were told at the time of their diagnosis that their disease was incurable [7].

Only 11.1% of the MPM patients felt "supported by religion"; however, this percentage was not significantly different from the 19.6% of the cancer population [21]. As Ando et al. [29] reported, religious care is not very common in Japan.

The multiple regression analysis showed that the family member surveyed being female, the patient dying later than expected, and satisfaction with care when the patient became critically ill were related to the GDI score. It is not clear why the family member surveyed being female was related to a higher GDI score. One possibility is that a higher number of Japanese females do not work and focus on caregiving; however, we did not ask about the jobs of the bereaved family members. It is necessary to investigate the relationship between the gender of the family member and the achievement of a good death. Carr [30] reported that the interval between the onset of terminal illness and death provided opportunities for people to plan their end-of-life care. However, an MPM diagnosis leaves a much shorter time for patients than in most cases, especially for those who died sooner than expected, reducing their capacity to prepare for good deaths.

The satisfaction with care when patients become critical is related to the achievement of a good death, which is consistent with the findings in the "Good Death" study by Miyashita et al. [17]. For patients with MPM to achieve a good death, preparation for the acute exacerbation of the disease and the implementation of physical, psychological, and spiritual care in a timely manner are crucial.

4.2. Heavy Symptom Burden

The present results show that the MPM patients experienced various kinds of symptoms. As shown in other published studies [6,9,25,26,31], pain, dyspnea, anorexia, and fatigue were the major symptoms exhibited by the MPM patients. The major symptoms of MPM patients are similar to the major symptoms of lung cancer patients, with a high prevalence of pain, fatigue, dyspnea, anorexia, and anxiety [6,32]. An important outcome of the present study was that it revealed the high prevalence of the various symptoms of MPM patients at the end of chemotherapy. For symptom management in MPM, several studies have recommended the introduction of palliative care in the early stages of MPM [26,33]. Unfortunately, similarly to cancer patients [34], MPM patients often refuse palliative care because of their denial of the fatal nature of the disease. They are thus unwilling to end

their anticancer treatment and enter palliative care. Advanced care planning is encouraged; however, this is challenging for MPM patients, who have short prognoses. Horne et al. reported that discussions about end-of-life care planning following the disclosure of a terminal prognosis caused a feeling of abandonment [35].

4.3. Poor Quality of End-of-Life Care

The present results show a poor quality of end-of-life care for MPM patients in Japan and significantly worse care than for other cancer patients. The possible reasons for this poor quality of end-of-life care could be (1) the limited availability of treatment for MPM, which has recently improved in Japan [36]; and (2) the health providers' lack of knowledge and skills regarding the treatment and care of MPM patients [8]. As the multiple regression analysis showed that "Satisfaction with the care received when the patient died" and "Received chemotherapy" were related to the CES score, improvements in end-of-life care are recommended through (1) the assurance of quality care on the death bed, and (2) the provision of continuous end-of-life care to patients who do not receive chemotherapy.

4.4. Implications for Care and Further Research

The MPM patients experienced various symptoms at the end of chemotherapy and when they entered the final critical stage. Medical professionals need to understand that MPM patients develop various symptoms in the early stages of the disease, even when treated with chemotherapy. Thus, medical professionals need to inform MPM patients regarding the possible symptoms that they will encounter and advise them on how to prepare, which may be challenging for patients. To support MPM patients at this difficult time, transition care is crucial. The care for MPM patients must include (1) symptom management from the earliest stage; (2) care for psychological, social, and spiritual pain; and (3) care for their families as provided by a multidisciplinary team, consisting of a patient and family advocacy group, and a lawyer [10,27,28].

4.5. Limitations

This study has some limitations. First, not all of the bereaved family members of the deceased MPM patients were contacted, as Japan has no registration system for MPM patients. Therefore, this study had a small sample. Second, as the participants were members of the advocacy group, it is uncertain whether the results are representative of the general population of bereaved family members of deceased MPM patients. The patients and family advocacy group, with their network of medical staff and hospitals, may have represented bereaved family members who are less distressed by the care their loved ones receive, thus representing a biased group. Third, the mean number of months of bereavement was 45.2; therefore, the participants may have had recall bias or forgotten key factors. Finally, this study was a cross-sectional study, and therefore, no causal relationships were established. To overcome the limitations regarding representativeness, it is necessary to conduct census surveys based on an MPM registration system, as this will allow representative random samplings.

5. Conclusions

This cross-sectional study revealed the remarkably rare achievement of a good death among MPM patients in Japan. The MPM patients experienced an enormous burden from their symptoms and were seldom free of physical distress. Another challenge faced by MPM patients in the achievement of a good death was the sense of life completion, which was difficult for patients with MPM caused by asbestos. The quality of end-of-life care of MPM patients was poorer than that of other cancer patients. The GDI score of the MPM patients was closely correlated with their CES score. Further research and interventions are urgently required, aimed at achieving a good death for MPM patients by providing quality continuous care, including (1) symptom management from the earliest stage; (2) care for

psychological, social, and spiritual pain; and (3) care for their families as provided by a multidisciplinary team.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of St. Luke's International University (16-A035).

Informed Consent Statement: This research was conducted based on the ethical principles of avoiding harm, voluntary participation, anonymity, and the protection of privacy and personal information. The purpose, procedures, and confidentiality of the study were explained in written format. The participants were informed that nonparticipation would not disadvantage them. Answering the questionnaire and sending it to the authors was regarded as written informed consent to participate in the study. Informed consent was obtained from all the subjects for the publication of their details.

Data Availability Statement: The datasets generated and analyzed from this study are not publicly available to protect the anonymity of the participants but are available from the corresponding author, Yasuko Nagamatsu, upon reasonable request.

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Depression and Complicated Grief, and Associated Factors, of Bereaved Family Members of Patients Who Died of Malignant Pleural Mesothelioma in Japan

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Abstract: Objectives: we investigated the prevalence and associated factors of depression and complicated grief (CG) among bereaved family members of malignant pleural mesothelioma (MPM) patients in Japan. Methods: Bereaved family members of MPM patients (n = 72) were surveyed. The Japanese version of the Patient Health Questionnaire-9 (PHQ-9) and the Japanese version of the Brief Grief Questionnaire (BGQ) were used to assess depression and complicated grief (CG), respectively. Socio-economic factors, anger toward asbestos, care satisfaction, achievement of good death, and quality of end-of-life care were assessed in relation to depression and CG. Results: In the family members of MPM patients, the frequencies of depression and CG were 19.4% and 15.3%, respectively. The bereaved family members who were not compensated by the asbestos-related health-damage relief system (p = 0.018) and who felt the financial impacts of the patient's MPM on the family (p = 0.006) had a higher likelihood of depression. The bereaved family members who were not satisfied with the care given when the patient became critical (p = 0.034), who were not compensated by the asbestos-related health-damage relief system (p = 0.020), who felt the financial impact of the patient's MPM on the family (p = 0.016), and whose deceased relative underwent surgery (p = 0.030) had a higher likelihood of CG. Conclusions: For bereaved family members of MPM patients, routine screening for depression and CG and the provision of grief care are suggested. In addition, for family members of MPM patients, financial support, including the promotion of the asbestos-related health-damage relief system, and improved care for patients who undergo surgery and when patients become critical, are recommended.

Keywords: mesothelioma; grief; depression; complicated grief; asbestos; bereaved; family

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1. Introduction

Grief is a natural response to bereavement. The pain from grief usually eases gradually, and the bereaved eventually establish a new life without the deceased. However, some people experience ongoing poor psychological wellbeing, including depression and complicated grief (CG). CG is characterized by intense grief that lasts longer than usual and causes impairment in daily functioning [1]. It is important to be aware of the circumstances in which individuals may become more vulnerable to CG. One study in Japan found that CG occurred in 2.4% of the general population, and almost 25% when subclinical CG was included [2]. The prevalence of CG in bereaved family members of cancer patients was 14% [3]. The risk factors include place of death, inadequate social support, the family having difficulty accepting death, dissatisfaction with palliative care, perceived preparedness [4], and financial problems after death [1,5]. Additionally, a violent loss of life, such as

suicidal death [6], death by terrorism [7], and homicide [8], is associated with a higher rate of CG. Other bereavement-related mental impairments, such as depression, may appear along with CG; however, they are considered independent, distinct entities [9].

Malignant pleural mesothelioma (MPM) is a rare, fatal malignancy caused by asbestos decades after the initial exposure [10]. Japan banned asbestos in 2006 and tightened regulations in 2012 [11]. People develop MPM not only by occupational exposure, but also by environmental exposure. An increased, scandalizing mortality ratio of mesothelioma in both sexes has been observed in Amagasaki city, which was the location of the major asbestos factories in Japan [12]. Occupational-oriented MPM is compensated by workmen's accident compensation insurance, and environment-oriented MPM is compensated by the asbestos-related health-damage relief system [13]. The number of annual deaths caused by MPM in Japan is about 1600, and this number has been growing [14].

The survival period after the diagnosis of MPM is as short as 7–15 months [15–18]. MPM causes a series of debilitating symptoms [19,20], various emotional and psychological problems [21], and additional distress associated with legal procedures for compensation [22]. Furthermore, the family members of MPM patients are at risk of depression due to the impact of diagnosis [23] and may experience impaired emotional functioning [22] and caregiving burdens [24], which are risk factors for CG [1].

People with MPM reportedly receive little information about their disease, have a sense that their needs are ignored, and feel angry at their country and the employer responsible for their fatal disease [25], which impairs their quality of life [26]. This indicates that bereaved family members of MPM patients experience significant psychological distress. However, little is known about the psychological distress of the bereaved family members of MPM patients.

In this study, we aimed to investigate the prevalence and associated factors of depression and CG among the bereaved family members of MPM patients in Japan. The present study is part of a larger study on the quality of life of the bereaved family members of MPM patients.

2. Methods

2.1. Study Design, Participants, and Setting

A cross-sectional survey design was chosen to examine the prevalence and associated factors of depression and CG among the bereaved family members of MPM patients.

The inclusion criteria were people who (1) had lost a family member to MPM, (2) had a family member who had been diagnosed with MPM after 2008, when the first evidence-based chemotherapy succeeded in prolonging the survival of MPM patients, and (3) could answer a self-administered questionnaire written in Japanese. The exclusion criteria included bereaved family members who lost a family member within six months, as, according to a previous study, the diagnosis of CG should be made at least six months after the death of a family member [27]. This research is part of a larger study investigating the bereaved family members of MPM patients. The participants in this study were identical to the participants of a previously published study that investigated the achievement of a good death and quality of end-of-life care of MPM patients from the perspective of bereaved family members [28].

A request for cooperation was sent to the advocacy group of the Japan Association of Mesothelioma and Asbestos-Related Disease Victims and their Families. The association has 15 branches across Japan and works with approximately 700 victims of asbestos-related diseases and their families. The association generated the list of eligible bereaved family members according to the criteria and sent a set of the informed consent information and questionnaires to 109 eligible bereaved family members in November 2016. Those who agreed to participate returned the completed questionnaires via postal mail by March 2017.

2.2. Outcomes

The primary outcome was the prevalence of depression in bereaved family members of MPM patients. The secondary outcome was the prevalence of complicated grief in bereaved family members of MPM patients.

2.3. Instruments

2.3.1. Information of the Patients and Bereaved Family Members

The following information was provided by the bereaved family members about the deceased patients: sex, age at diagnosis, survival, received treatments, and place of death. The receipts of two types of insurance compensation benefits were also obtained.

The information on the bereaved family members included the following: age, relationship to the patient, time of bereavement, experience of end-of-life discussion with the patient, timing of patient's death, financial impact of patient's MPM on family, and level of anger toward asbestos. The bereaved family members were also asked about their satisfaction with care upon diagnosis, when the patient became critical, and when the patient died.

2.3.2. Depression

Depression was evaluated using the Japanese version of the Patient Health Questionnaire-9 (PHQ-9). The original PHQ-9 was developed to screen for depression, and its validity has been proven in several studies [29,30]. The PHQ-9 consists of nine items and is answered using a four-point Likert scale (0 = not at all, 1 = several days, 2 = more than half the days, 3 = nearly every day). PHQ-9 scores of 10 and over represented moderate to severe depression [31]. The meta-analysis by Manea et al. showed the sensitivity and specificity values of the PHQ-9 cutoff of $\geq$10 compared to semi-structured interviews are 0.88 and 0.86. The original PHQ-9 was translated into Japanese and validated with a Japanese population [32].

2.3.3. Complicated Grief (CG)

CG was evaluated using the Japanese version of the Brief Grief Questionnaire (BGQ) [33], a validated Japanese version of the original BGQ developed by Shear [7] consisting of five items on CG to screen for CG. The items were answered using a three-point Likert scale (0 = not at all, 1 = somewhat, 2 = a lot), and the possible scores range from 0 to 10. A total score of 8 or higher on the BGQ indicates CG, between 5 and 7 implies probable CG, 5 or higher implies possible CG, and less than 5 denotes absence of CG [7]. In this study, bereaved family members who scored 9 or higher were considered to have CG.

2.3.4. Achievement of Good Death (GDI)

The achievement of good death was assessed using the Good Death Inventory (GDI), which has been validated to evaluate the achievement of a good death from the perspective of bereaved family members [34]. The GDI consists of 18 items and is answered using a seven-point Likert scale (1 = absolutely disagree, 7 = absolutely agree). A high score suggests the achievement of good death.

2.3.5. Quality of End-of-Life Care (CES)

The quality of end-of-life care was assessed by the short version of the Care Evaluation Scale (CES) [35]. The CES consists of 10 items. The bereaved family members answered using a six-point Likert scale (1 = highly disagree, 6 = highly agree). A higher score indicates better quality end-of-life care.

2.3.6. Missing Data

Mean imputation was conducted for the missing data of the PHQ9, BGQ, GDI, and CES scores, according to the instructions for the tools.

2.4. Statistical Analysis

The scores of each scale were calculated under a scoring procedure. The scores of each item of the measurement scales (i.e., PHQ-9, BGQ, GDI, CES) were summed and used as the scale score.

First, we examined the presence of correlations between the total scores of the PHQ-9, BGQ, GDI, and CES. Then, the scores of the PHQ-9 and BGQ were examined with clinical social factors such as age and sex of patient and family member, survival, treatments received, place of death, approved compensations, experience of end-of-life discussion, satisfaction with care, financial impact of MPM on the family, timing of patient's death, and level of anger towards asbestos (Supplementary Table S1).

Finally, we used the odds ratio and 95% confidence intervals (d) in binominal logistic regression analysis to assess the correlations between depression (PHQ-9 score was equal to or more than 10) and complicated grief (BGQ score was equal to or more than 8) and the clinical social factors. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 27.

2.5. Ethical Considerations

This study was approved by the Research Ethics Committee of St. Luke's International University (16-A035). It was conducted based on the ethical principles of avoiding harm, voluntary participation, anonymity, and the protection of privacy and personal information.

3. Results

Of the 109 questionnaires distributed to the bereaved family members through the association, 74 (67.9%) were completed and returned. Two respondents who had experienced a loss within the past six months were excluded. Finally, a total of 72 questionnaires were subjected to analysis.

3.1. Characteristics of Malignant Pleural Mesothelioma Patients and Bereaved Family Members

As shown in Table 1, 81.9% of the deceased MPM patients were men, and their mean age at diagnosis was 66.9 years. The treatment modalities they received were chemotherapy (70.8%), palliative care (56.9%), and surgery (19.4%). A large minority (48.6%) died in the respiratory ward, followed by the PCU or hospice (33.3%). Only 13.9% died at home. The mean survival time was 14.5 months from the time of diagnosis. The majority of the bereaved family members (72.2%) were spouses of the MPM patients, and the mean bereavement time was 45.2 months.

Table 1. Characteristics of malignant pleural mesothelioma patients and their participating bereaved family members (n = 72).

Patients			***n***	**%**
Sex	Men		59	81.9
	Women		13	18.1
Source of asbestos exposure	Occupation		49	68.1
	Neighboring factory		17	23.6
	School		1	1.4
	Family		1	1.4
	Unknown		4	5.4
Treatment	Surgery		14	19.4
(includes multiple treatments)		Extrapleural pneumonectomy	12	16.7
		Pleurectomy decoration	2	2.8

Table 1. *Cont.*

Patients			***n***	**%**
	Chemotherapy		51	70.8
	Radiotherapy		15	20.8
	Palliative care		41	56.9
Compensation	Worker's accident compensation insurance		47	65.3
(some had both types)	Asbestos-related health-damage relief system		56	77.8
Place of death	Respiratory ward		35	48.6
	Palliative care unit/hospice		24	33.3
	Home		10	13.9
	Other		3	4.2
Age at diagnosis (years)	Range:	36–92	Mean ± SD	66.9 ± 9.6
Survival (months)		0.5–69		14.5 ± 14.1
Bereaved family members			***n***	**%**
Sex	Men		15	20.8
	Women		57	79.2
Relationship with patient	Spouse		52	72.2
	Child		20	17.8
Experience of end-of-life	Yes		27	37.5
discussion with patient	No		44	61.1
Timing of patient's death	Much sooner than expected		31	43.1
	Sooner than expected		25	34.7
	Moderate		9	12.5
	Later than expected		5	6.9
	Much later than expected		2	2.8
Satisfaction with care:	Satisfied		29	40.3
On diagnosis	Not satisfied		43	59.7
When patient became critical	Satisfied		31	38.9
	Not satisfied		41	61.1
When patient died	Satisfied		47	65.3
	Not satisfied		25	34.7
Financial impact of patient's	Significant impact		12	16.7
MPM on family	Some impact		15	20.8
	Moderate impact		20	27.8
	Minor impact		15	20.8
	No impact		10	13.9
Level of anger toward asbestos	Very angry		56	77.8
	Angry		11	15.3
	Moderately angry		4	5.6
	Slightly angry		1	1.4
	Not angry at all		0	0
Age (in years)	Range:	32–82	Mean ± SD	62.5 ± 12.2
Time since bereavement (months)		9–110		45.2 ± 27.2

3.2. Depression and Complicated Grief and among Bereaved Family Members

Of the 72 participants, 19.4% of the bereaved family members were screened as having moderate to severe depression. Based on the BGQ score, 15.3% suffered from CG and 56.9% exhibited probable CG. In total, 72.2% of the bereaved family members were categorized into possible CG (PCG). Two bereaved family members (2.8%) suffered from both depression and CG (Figure 1).

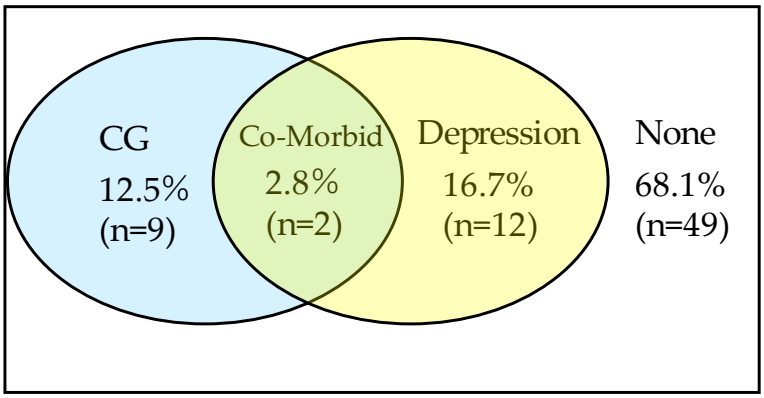

Figure 1. Percentage of complicated grief (CG) and depression in the bereaved family members.

3.3. Correlation between the Total Scores of the PHQ-9, BGQ, GDI, and CES

The PHQ-9 score was significantly correlated with the BGQ score (r = 0.481, $p = 0.000$) but not with the GDI or CES scores. The BHQ score was significantly correlated with GDI (r = −0.403, $p = 0.000$), however, was not correlated with CES.

3.4. Factors Associated with Depression

The results of the binomial logistic regression analysis of depression are shown in Table 2. The bereaved family members who were not compensated by the asbestos-related health-damage relief system and who suffered a financial impact from the patient's MPM had a higher risk of depression.

Table 2. Binominal logistic regression model predicting depression ($n = 72$).

Variable	Estimated Odds Ratio	95% CI	*p*-Value
Family financially impacted by patient's MPM	2.569	1.316–5.015	0.006
Not compensated by the asbestos-related health-damage relief system	7.334	1.401–38.374	0.018

Model chi-square = 12.641, d = 1, $p = 0.002$, $R^2 = 0.263$. Dependent variables: 1: PHQ-9 score is equal to or more than 10, 0: PHQ-9 score is less than 10.

3.5. Factors Associated with BGQ Total Score

The results of the binominal logistic regression analysis for CG (BGQ score is equal to or more than 8) are shown in Table 3. The bereaved family members of deceased MPM patients who received surgery, whose households were financially impacted by MPM, who were not compensated by the asbestos-related health-damage relief system, and who were not satisfied with the care given when the patient became critical, were more likely to develop CG.

Table 3. Binominal logistic regression model predicting CG ($n = 72$).

Variable	Estimated Odds Ratio	95% CI	*p*-Value
Family financially impacted by patient's MPM	3.278	1.250–8.596	0.016
Not compensated by the asbestos-related health-damage relief system	19.210	1.609–229.392	0.020
Received surgery	11.301	1.256–101.649	0.030
Not satisfied with the care given when the patient became critical	13.626	1.213–153.009	0.034

Model chi-square = 22.206, d = 4, $p = 0.001$, $R^2 = 0.471$. Dependent variables: 1: BGQ score is equal to or more than 8, 0: BGQ score is less than 8.

4. Discussion

This cross-sectional study demonstrated the prevalence of depression and CG among the bereaved family members of deceased MPM patients in Japan. The results showed: (1) the BGQ score and the PHQ-9 score were associated with GDI score; (2) depression and CG rarely occur at the same time in MPM; (3) financial impact and lack of compensation from the asbestos-related health-damage relief system are related to depression and CG; and (4) dissatisfaction with care when the patient became critical and received surgery are related to CG.

The rates of depression (19.4%) among family members of MPM patients were slightly higher, but almost at the same level, as reported for bereaved family members of other cancer patients, i.e., 15.5–17% [3,36]. Regarding CG, the rate of CG (BGQ $\geq$ 8) was 15.3%, which was higher than the 0.7–2.5% in the Japanese general population [2,37] and at the same level as the other cancer population (10.9–14%) [3,36] and cardio-vascular disease patients (14%) [38]. It was lower than the 61% for traffic accidents [39]. The possible CG (BGQ > 5) was 72.2%, which was higher than the Japanese general population at 2.5–22.7% [2,37] and the population of other cancers population at 55% [40]. The possible reasons for the high PCG in MPM are poor achievement of good death of the patient, unpreparedness and unacceptance of loss, and strenuous legal hurdles to claiming compensation for bereaved family members, who are often not compensated before the patient dies. A previous study showed some items of the GDI are related to CG [3]. In MPM, the GDI score was significantly poorer than in the wider cancer population [28]. Previous studies have also reported that advanced preparations for the loss [4] and acceptance of death [41] are associated with lower risks of bereavement-related complications. Unfortunately, MPM patients and their families generally have difficulty accepting the disease and facing death because MPM is caused by asbestos, and could have been avoided [25].

Another characteristic of grief in MPM is the low comorbidity of depression and CG. Only 2.8% of our sample had depression and CG at the same time. A systematic review by Komischke-Konnerg [42] estimated the co-occurrence of prolonged grief disorder and depression at 63%. The reason for the lack of co-morbid CG and depression in MPM is unclear, but the results of this study indicate that CG and depression are more distinguishable in MPM. A previous study reported that CG and depression can be considered as different forms of disorder, even though some of their symptoms overlap [43]. This may be related to the cause of distress. Ball et al. [44] reported that causes of psychological distress may differ in MPM and lung cancer because (1) MPM has a worse outlook than lung cancer, (2) there is additional stress due to legal and financial matters even after loss in MPM, and (3) MPM patients experience distress and blame a third party for the development of the disease.

The factors relating to depression and CG in MPM indicate that a lack of support impairs the quality of life of MPM patients, and, eventually, bereaved family members develop psychological distress; however, further research is necessary to prove this. Another important finding was that, in MPM, the financial impact on the household and the lack of compensation from the asbestos-related health-damage relief system related to both depression and CG. This finding supported previous studies reporting financial status as a factor related to depression [5] and CG [45] in the cancer population. Worker's accident compensation insurance is more generous, but only available for occupational MPM. The current study showed that lack of compensation by the asbestos-related health-damage relief system that covers all MPM patients is associated with CG. However, financial impacts and lack of compensation from the asbestos-related health-damage relief system were independent related factors, meaning that even a recipient of compensation from the asbestos-related health-damage relief system may experience financial impacts. The results indicate that the compensation from the asbestos-related health-damage relief system may have a positive effect on bereaved family members, not only financially but also through easing the pain of victims. Further research is needed to clarify the effect of compensa-

tion on the bereaved family members of MPM patients, including whether compensation relieves the financial burden of affected families.

CG had additional related factors, such as patients undergoing surgery and dissatisfaction with care when the patient became critical. This finding suggests that the provision of quality care for MPM patients and their family before the patient's death may be useful to prevent CG. The targeted points of care are when patients receive surgery and when the patient becomes critical. It is not clear how surgery is related to CG. The possible reasons may be complications [46], a reduction in lung volume after surgery [47], and reduced quality of life from pain [48]. As international guidelines recommend, surgery should be executed by skilled surgeons in high-volume centers, and should be considered only in a multimodality treatment plan for selected patients [49]. Other factors that have been reported to be associated with CG, such as the bereaved family member being female and the spouse of the deceased [50] and place of death [43], showed no significant association in the present study.

4.1. Implications of Care

Given the high prevalence of PCG in the current study, we recommend routine screening of depression and CG for bereaved family members of MPM patients. For those who have depression and CG, sufficient treatment must be provided by a specialist. Reportedly effective treatments should be considered, such as antidepressants for depression [51], and counseling [52] and cognitive behavioral therapy [53–55] for CG.

Care and social support obtained from a good support network were protective against depression and CG [42,56]. The recommended means highlighted in this study to support bereaved family members who suffer from depression and CG are financial support, including the promotion of the asbestos-related health-damage relief system; improvement in care for MPM patients, especially those who undergo surgery; and improvement in care when patients become critical.

4.2. Implications for Further Research

A future study to clarify the mechanisms of depression and CG among the bereaved family members of deceased MPM patients using multisite research across countries is recommended, as the number of family members of patients with MPM is limited in a single country. There is also a need to examine more psychosocial factors, such as posttraumatic stress disorder [57], pre-existing mental impairment [3], preparedness for death [58], and sense making [6]. Furthermore, the financial problems of MPM patients' households and CG among bereaved family members of patients who undergo surgery need to be clarified to improve the quality of life of patients, and to prevent CG associated with MPM.

4.3. Representativeness of the General Population of Bereaved Family Members of MPM Patients

This study had a small convenience sample, as access to bereaved family members was limited because Japan has no registration system for people with MPM. Additionally, the bereaved family members assessed in this study were members of an advocacy group, so our results may not be representative of the general population of bereaved family members of deceased MPM patients. However, the characteristics of the patients of this study were similar to those in a previous study on MPM patients [26] and deceased MPM patients [16]. The majority were male [28] and over sixty years old. Around 20% underwent surgery [16], 70–80% received chemotherapy [28], around 20–30% received radiotherapy, and around 40% received palliative care. However, in this study, survival was 14.5 months, which is longer than average [16]. Furthermore, more patients in this study were compensated by the workmen's accident compensation insurance (65%) and the asbestos-related health-damage relief system (78%) than previous studies (56% and 46%) [26].

4.4. Limitations

This study has some limitations. First, as we mentioned above, we had a small convenience sample. Second, the bereaved family members may have demonstrated recall bias because the mean duration of bereavement was 45 months. Finally, this study was a cross-sectional study. The results were based on self-report data, and no clinical interviews were conducted. We believe that loss of life caused by asbestos contributes greatly to the development of CG. To prove this hypothesis, more extensive studies with a larger number of participants are required. Specifically, a longitudinal study is warranted to develop an optimal support and care program.

5. Conclusions

The rates of depression and CG of bereaved family members of MPM patients were the same as for cancer and cardio-vascular disease and higher than in the general population but lower than it is for those affected by traffic accidents. PCG occurred more in MPM than in cancer. For bereaved family members, routine screening for depression and CG and the provision of grief care are recommended. In MPM, financial impacts and a lack of compensation from the asbestos-related health-damage relief system relates to both depression and CG, along with dissatisfaction with the care received when the patient becomes critical and undergoes surgery. These results suggest the importance of financial support for MPM patients and their family members, including the promotion of the asbestos-related health-damage relief system; improved care, especially for patients undergoing surgery; and improved care when patients become critical.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11123380/s1, Table S1: Bivariate analysis of PHQ-9 and BQG scores with clinical social factors.

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Informed Consent Statement: This research was conducted based on the ethical principles of avoiding harm, voluntary participation, anonymity, and the protection of privacy and personal information. The purpose, procedures, and confidentiality of the study were explained in written format. The participants were informed that nonparticipation would not disadvantage them. Answering the questionnaire and sending it to the researchers was regarded as written informed consent to participate in the study. Informed consent was obtained from all the subjects for the publication of their details.

Data Availability Statement: The datasets generated and analyzed from this study are not publicly available to protect the anonymity of the participants, but are available from the corresponding author, Yasuko Nagamatsu, upon reasonable request.

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IV. 診　　断

診断総論

胸膜中皮腫の診断総論

Diagnosis of pleural mesothelioma

原　尚史[1]　　藤本伸一[2]

Key words：胸膜中皮腫，アスベスト，胸膜疾患，mesothelioma

はじめに

中皮腫は体腔表面を覆う漿膜のうち，胸膜，心膜，腹膜，精巣漿膜に存在する中皮細胞から発生する，比較的まれで予後不良な悪性腫瘍である(1年生存率42.8%，5年生存率4.9%[1])．そのうち，胸膜中皮腫が約80%を占め，主な発症原因としてアスベスト(石綿)の吸入曝露が考えられており[2]，本邦では1980年代半ばまで使用されていた．アスベスト曝露開始から発症までの潜伏期間は25～50年で，米国などではすでに中皮腫の発生率は減少しているが，本邦における胸膜中皮腫の発症のピークは2030年ごろと予想され，死亡者数も今なお増加傾向にある．ほとんどの患者が発症時には進行期であり，早期に確実な診断を行い治療につなげることが重要である．

1. 胸膜中皮腫の診断アプローチ

発症は60代を中心に50～70代が多い．自覚症状として，多くの患者が胸痛，呼吸困難，咳嗽，発熱，体重減少，倦怠感などの非特異的な症状を徐々に呈する．診断の数カ月以上前から症状が進行することがある一方で，無症状で他疾患の治療中や健診で偶発的に胸水貯留などの胸部異常陰影を指摘され発見につながる場合もある．胸膜中皮腫の約80%に胸水がみられるが，胸水そのものは一般臨床で広くみられる非特異的な所見であり，胸水をみた場合には必ずアスベスト曝露の病歴を確認し，胸膜中皮腫を鑑別に挙げなければならない．中皮腫は石綿肺に比して低濃度のアスベスト曝露でも経時的に発症リスクが増大することから，職業性曝露(アスベストを用いた断熱作業，建物や船舶，車両の解体補修など)のみならず，非職業性曝露(アスベスト労働者の同居家族，アスベスト関連工場周辺の近隣環境曝露など)を含めた詳細な問診が必要となる．患者によってはアスベスト曝露歴を自覚していない場合があるが，画像所見などから疑わしい場合は改めて問診に立ち返って職業歴や住環境などを再確認する．

胸水または不整な胸膜肥厚およびアスベスト曝露歴のある患者の呼吸器症状をみた場合，胸膜中皮腫を疑って診断を進める．主なアプローチとして，CTを含む画像診断，胸水穿刺，胸膜

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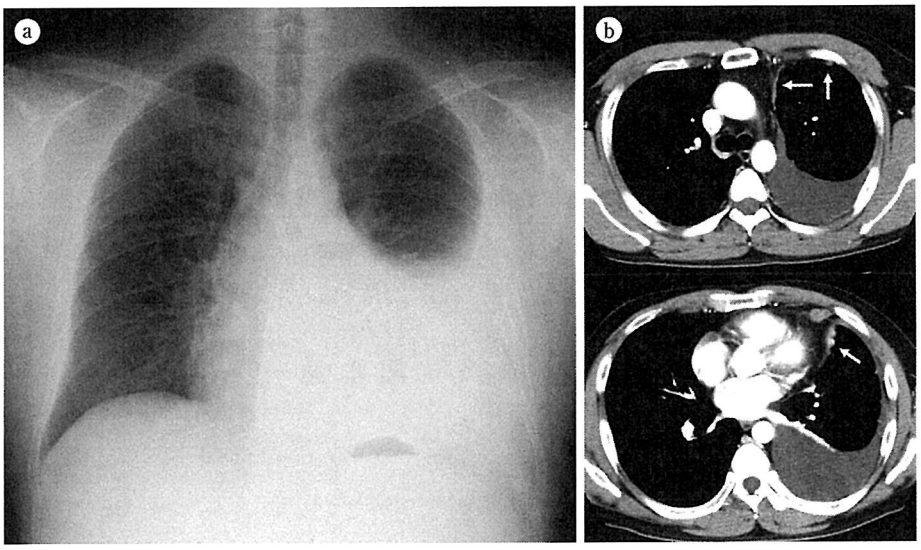

生検が挙げられるが，単一の検査法のみでは中皮腫の診断は難しく，確定診断には組織診断において複数の免疫組織化学的な検査が必須[3]であることから，最終的に十分な量の組織採取を行った上で総合的な判断が求められる．また，胸膜中皮腫の治療は組織分類と病期分類を基に判断するため，その点においても組織診断は特に重要といえる．

1）画像診断

胸部写真，CT，MRI，PETが用いられるが，他の石綿関連疾患や肺癌などの他の悪性腫瘍の胸膜播種との鑑別は困難であることも多い．一般的にみられる中皮腫の画像診断所見は非特異的な所見であり，すなわち，胸水貯留，胸膜肥厚，胸膜の腫瘤形成といった所見は，いずれも中皮腫以外の癌性胸膜炎でもみられるため，早期診断を難しくしている．一方，胸膜生検に踏み切るための判断材料，病期診断および治療効果判定，中皮腫を疑う症例の経過観察においては画像診断の果たす役割は非常に大きいといえる．

a. 胸部写真

単純撮影では片側性の胸水貯留，進行例では胸膜肥厚や胸膜腫瘤，不整を伴う片側性のびまん性胸膜肥厚像を指摘できる場合がある．胸水を伴わず限局的な胸膜腫瘤形成を認めるような例であっても，経過中に胸水が貯留することが多いといわれているが，早期の場合，胸水は自然に増減を繰り返すことがあり，慎重に経過をみる必要がある（**図 1-a**）．

b. CT

アスベスト曝露の所見として，胸膜プラークや石灰化を伴うこともあるが，典型的なCT像としては広範なびまん性環状全周性の胸膜肥厚，結節状の胸膜肥厚，厚さ1 cmを超える胸膜肥厚，縦隔胸膜の肥厚がみられる．これらの所見が多いほど悪性病変がより疑われるとされる[4]が，感度はそれぞれ50%前後であり，これらの所見がみられないからといって中皮腫を否定することはできず，中皮腫以外の肺癌その他の悪性腫瘍の播種病変との鑑別は難しい（**図 1-b**）．

禁忌がなければ造影剤を使用し，肥厚部分に造影増強効果がみられることを確認することが望ましく，胸部～骨盤部までを含む撮像範囲で腹膜病変の有無を含め評価する必要がある．

c. MRI，FDG-PET

病期診断におけるTNM分類（**表 1，2**）を決定する目的で，大血管や胸壁，縦隔臓器および

表 1 胸膜中皮腫の UICC-TNM 分類 Ver. 8

T-原発巣
- T1：同側胸膜(胸膜または臓側胸膜)に腫瘍が限局(縦隔胸膜，横隔膜を含む)
- T2：同側胸膜(壁側または臓側胸膜)に腫瘍があり，以下のいずれかが認められる
  - 横隔膜筋層浸潤
  - 肺実質浸潤
- T3：同側胸膜(壁側または臓側胸膜)に腫瘍があり，以下のいずれかが認められる
  - 胸内筋膜浸潤
  - 縦隔脂肪織浸潤
  - 壁側軟部組織の孤発性腫瘍
  - 非貫通性心膜浸潤
- T4：同側胸膜(壁側または臓側胸膜)に腫瘍があり，以下のいずれかが認められる
  - 胸壁への浸潤(肋骨破壊の有無は問わない)
  - 経横隔膜的腹膜浸潤
  - 対側胸膜浸潤
  - 縦隔臓器浸潤(食道，気管，心臓，大血管)
  - 脊椎，神経孔，脊髄への浸潤
  - 貫通性心膜浸潤(心嚢液の有無は問わない)

N-リンパ節
- N0：所属リンパ節転移なし
- N1：同側胸腔内リンパ節転移(肺門，気管支周囲，気管支分岐部，内胸など)
- N2：対側胸腔内リンパ節，同側または対側鎖骨上窩リンパ節転移

M-遠隔転移
- M0：遠隔転移なし
- M1：遠隔転移あり

[肺癌診療ガイドライン―悪性胸膜中皮腫・胸腺腫瘍含む 2021 年版(特定非営利活動法人 日本肺癌学会 編)，金原出版，2021．(https://www.haigan.gr.jp/guideline/2021/2/0/210200000200.html)より許諾を得て転載]

横隔膜の病変について浸潤の有無を確認するために組織分解能に優れる MRI を行うことがあるが，多くの場合は FDG-PET が病期診断に最も有用とされる[5]．特に外科的切除が可能かどうかを検証するためのモダリティとしては，CT や MRI 単独よりも PET-CT が有用であったとする報告があり，可能な限り胸膜中皮腫と診断した全症例において施行が推奨される．

また，胸膜中皮腫は中枢神経転移を来しにくいことから，ASCO(American Society of Clinical Oncology)ガイドライン[3]では神経症状を認めなければ頭部造影 MRI は必須ではないとされており，本邦においても全症例ルーチンでの施行は推奨されないが，外科治療を検討する症例においてはその限りではなく，施行を検討してよい．

2) 胸水へのアプローチ

初期の胸膜中皮腫では腫瘍性胸膜肥厚や腫瘤病変を伴わず，胸水貯留のみを呈することがあるため，アスベスト曝露に関連した胸水をみた場合は必ず精査を行う必要がある．

表 2 胸膜中皮腫の病期分類(UICC-TNM 分類 Ver. 8)

	N0	N1	N2
T1	Stage IA	Stage II	Stage IIIB
T2	Stage IB		
T3		Stage IIIA	
T4	Stage IIIB		
M	Stage IV		

[肺癌診療ガイドライン―悪性胸膜中皮腫・胸腺腫瘍含む 2021 年版(特定非営利活動法人 日本肺癌学会 編)，金原出版，2021．(https://www.haigan.gr.jp/guideline/2021/2/0/210200000200.html)より許諾を得て転載]

エコーガイド下に胸腔穿刺を行い，胸水の性状を確認し細胞診を提出する．胸水は通常滲出性で，その他の生化学所見は他の良性胸膜疾患との鑑別に有用である．胸水 pH については胸膜中皮腫が平均 7.22±0.06 と他の悪性腫瘍の

7.33±0.01 と比較して低かったという報告[6]がある.

細胞診については陽性率が30%未満という報告[7]があり，陰性であっても中皮腫を否定できない．一方，特に胸水細胞診のセルブロック検体において，免疫染色によるBAP1 lossなど補助アッセイの使用により組織と同等の診断率を得られるという知見が近年示されており[8]，診断率は向上しつつある．

また，胸水中マーカーとしてはヒアルロン酸がカットオフ値100,000 ng/mL以上で感度44%，特異度95.6%[9]（保険未収載）であり，高値であれば診断価値が高いが，低値であっても中皮腫である症例が多いことには留意しなければならない．可溶性メソテリン関連ペプチド（SMRP）は感度67%，特異度98%[10]とヒアルロン酸と同等の有用性といえる．通常，胸水中CEAは上昇しない[11]ため，高値であれば胸膜中皮腫は否定的である．

3）胸膜生検

胸膜中皮腫の確定診断には免疫組織化学染色を含む組織診断が必須であり，そのために胸膜生検は最も重要な検査といえる．胸膜生検の方法としては，経皮的針生検（盲目的または超音波，CTガイド下生検），局所麻酔下胸膜生検，全身麻酔下の外科的胸膜生検（胸腔鏡または開胸）といった選択肢があるが，2021年版本邦ガイドライン[12]においては，全身麻酔下の外科的胸膜生検が推奨されている（推奨の強さ1）．非開胸の生検での診断率が約40%であったのに対し，胸腔鏡補助下手術（VATS）による生検での診断率は98%であったとの報告[7]による．

胸腔鏡の内腔所見は隆起型と肥厚型に分けられ，隆起型の場合は肉眼的な観察によりCTなどの画像では早期発見が難しい微小な病変を見いだすことができる場合もある．一方，肥厚型病変の場合は肉眼的に病変部が判別しづらく，全層性の生検を複数箇所から行うなど工夫が必要になる．

2. 鑑別診断

良性疾患としては，アスベスト関連疾患として胸膜プラーク，びまん性胸膜肥厚，良性石綿胸水が挙げられ，その他にも一般的な感染性疾患としての細菌性胸膜炎，膿胸などが鑑別に挙がる．腫瘍性疾患においては，後述の上皮型および二相型中皮腫との鑑別として原発性肺癌（特に腺癌）やその他臓器原発の悪性腫瘍の胸膜播種が，肉腫型中皮腫との鑑別として滑膜肉腫や血管肉腫などが挙げられる．胸水生化学所見や画像所見，組織診断がこれら疾患との鑑別の手掛かりとなるが，個々の検査のみでは除外診断が難しい場合があり，総合的な判断が求められる．

3. 胸膜中皮腫の組織型

ほとんどの胸膜中皮腫は上皮型，肉腫型およびその両方の成分がみられる二相型の3つの組織学的サブタイプに分けられる．2021年のWHO組織分類の改訂により，中皮腫（mesothelioma）のカテゴリは全て悪性中皮腫を指すこととなり[13]，あえて悪性を付ける必要はなくなった．

それぞれのタイプにおいて，広範囲の形態学的特徴が存在する場合と存在しない場合があり，多くの場合，形態だけで診断を確立することは難しいため，詳細な評価のために免疫組織化学染色が用いられる．International Mesothelioma Interest Groupでは中皮腫の診断確定のため2種類の陽性マーカーと2種類の陰性マーカーのパネルを使用することを推奨しており[14]，本邦においても他の癌腫との鑑別のため同様の抗体を用いた検討が推奨されている．中皮腫の陽性マーカーとしてはカルレチニン，D2-40，WT-1などがあり，他の癌腫でみられるCEA，TTF-1，Napsin A，Ber-EP4などが陰性マーカーとして用いられる．組織診断の詳細については他稿に譲る．

また，肉腫型および二相型は上皮型に比べ予後が悪いことが知られており，あるデータベー

スにおいては上皮型，二相型，肉腫型の組織型を有する患者の生存期間中央値はそれぞれ 19，13，8 カ月であった[15]．

おわりに

胸膜中皮腫はまれな疾患であるが，胸水貯留と呼吸器症状という比較的日常診療で遭遇しやすい臨床像を呈する．特にアスベスト曝露に関連する病歴のある胸水をみた際には本疾患を疑い，適切な精査を行って診断・治療に結び付けることが重要である．

なお，中皮腫はアスベストによる健康被害に関連する社会保障制度の対象疾病であり，中皮腫と診断されれば労災保険や石綿健康被害救済法に基づく給付を受けられる．また，中皮腫を発症する前であっても，過去にアスベストを使用した業務に従事した事実と一定の所見があれば，都道府県労働局に申請することで石綿健康管理手帳の交付を受けられ，定期的に無料で検診を受けられるため，患者に各種申請を行うよう勧める必要がある．

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JME-001 phase II trial of first-line combination chemotherapy with cisplatin, pemetrexed, and nivolumab for unresectable malignant pleural mesothelioma

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ABSTRACT

Background JME-001 is a phase II trial assessing the efficacy and safety of cisplatin, pemetrexed, and nivolumab as first-line therapy in malignant pleural mesothelioma (MPM).

Patients and methods Patients with untreated, unresectable MPM with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1 were included. The primary endpoint is the centrally reviewed objective response rate. The secondary endpoints include (1) response rate assessed by investigators, (2) disease control rate, (3) overall survival, (4) progression-free survival, (5) duration of response, and (6) time to response. Safety and adverse events will also be evaluated. Cisplatin (75 mg/m^2), pemetrexed (500 mg/m^2), and nivolumab (360 mg/body) were administered intravenously every 3 weeks with a total of 4–6 cycles. If patients did not progress during the combination phase, maintenance therapy with nivolumab was administered until disease progression or unacceptable toxicity. Tissue samples were required and collected for programmed death ligand 1 analysis.

Results Eighteen patients (mean age 69.2 years, 15 men) were enrolled between January 2018 and May 2019. The ECOG PS was 0 in 3 patients and 1 in 15 patients. Fourteen (77.8%; 95% CI 52.4% to 93.6%) patients had an objective response. The disease control rate was 94.4% (95% CI 72.7% to 99.9%). Fourteen (77.8%) patients had partial response (PR), three had stable disease, and one was not evaluable. Tumor shrinkage was observed in 10/14 (71.4%) patients with epithelioid, and 2/2 (100%) patients with sarcomatoid or biphasic histological subtype had PR. Ten (55.6%) patients experienced grade 3 or worse adverse events, including disorder of metabolism or nutrition (33.3%), loss of appetite (27.8%), anemia (16.7%), and hyponatremia (11.1%). No treatment-related deaths occurred.

Conclusions The safety and efficacy of this study strongly support a definitive trial of this combination.

Trial registration number UMIN000030892.

INTRODUCTION

Malignant pleural mesothelioma (MPM) is an aggressive tumor that arises from mesothelial-lined surfaces and has a poor survival rate.[1] The industrial use of asbestos has been banned in Japan since 2006, but the incidence of MPM is expected to continue to increase for the next few decades due to past usage of asbestos.[2] Treatment of MPM is challenging. Most cases are diagnosed at an advanced stage and treated with systemic chemotherapy. Combination chemotherapy with cisplatin and pemetrexed is the standard treatment regimen; however, the median overall survival (OS) is only about 12 months.[3] Recently, the addition of bevacizumab was shown to improve OS when added to cisplatin and pemetrexed in the treatment of unresectable MPM.[4] However, the prolongation of OS was less than 3 months and it can only be administered to bevacizumab-eligible patients. Therefore, cisplatin and pemetrexed is still considered the standard treatment regimen and additional treatment options are urgently needed.

Immune checkpoint inhibitors (ICIs), such as programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T lymphocyte associated protein-4 (CTLA-4), have revolutionized cancer treatment. Nivolumab is a human monoclonal antibody that targets the PD-1 cluster of differentiation 279 cell surface membrane receptor. Binding of PD-1 to its ligands, PD-L1 and PD-L2, results in the downregulation of lymphocyte activation. Nivolumab inhibits the interaction between PD-1 and its ligands, promotes immune responses, and triggers antitumor activity and has already been approved in Japan for multiple types of cancer, including malignant melanoma, non-small cell lung cancer, and gastric cancer. Mesothelioma carcinogenesis occurs on the background

of the chronic inflammatory responses to asbestos, and the tumor microenvironment is composed of pro-inflammatory cytokines, growth factors, endothelial cells, stromal cells, and immune cells.[5] Thus, there is a strong biological rationale to use ICIs in MPM. A phase II trial has demonstrated a favorable response to nivolumab in previously treated MPM.[6] Based on the results, nivolumab has been approved for patients with MPM that is refractory or intolerable to platinum/pemetrexed chemotherapy.

A recent report indicated that platinum drugs enhance the effector immune response through modulation of PD-L1.[7] These encouraging results may extend to the first-line treatment of MPM with the hope of enhancing the antitumor response, particularly when used in combination with the current standard chemotherapy. Unfortunately, no prospective clinical trial is being conducted to evaluate the combination of nivolumab and cisplatin/pemetrexed. Therefore, we launched the current trial to assess combination chemotherapy with cisplatin, pemetrexed, and nivolumab for MPM.

MATERIALS AND METHODS

Study design and patients

JME-001 is a single-arm, prospective, non-randomized, non-comparative, open label, multicenter, phase II trial conducted from January 1, 2018, to November 30, 2019 (data cut-off date), at four centers in Japan. All patients who met the inclusion and exclusion criteria (online supplemental tables 1 and 2) were invited for screening. Eligible patients were ≥20 years old with histologically confirmed, untreated, unresectable advanced MPM and had ≥1 measurable lesion(s) as defined in the modified Response Evaluation Criteria in Solid Tumors V.1.1 (mRECIST)[8] for mesothelioma and confirmed by imaging within 14 days prior to enrollment. Eligible patients also had to have tumor tissue samples available for the analysis of PD-L1 expression and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Main exclusion criteria were severe hypersensitivity reactions to any other drug, including antibody products; concurrent autoimmune disease or a history of chronic or recurrent autoimmune disease; multiple primary cancers; brain metastases; current or history of interstitial lung disease or pulmonary fibrosis diagnosed based on imaging or clinical findings; or previous treatment with nivolumab, anti-PD-1 antibody, anti-PD-L1 or PD-L2, or any other therapeutic antibodies or pharmacotherapies for T-cell regulation.

Procedures

Treatment comprised two sequential phases: the combination phase and the maintenance phase. In the combination phase, cisplatin (75 mg/m^2), pemetrexed (500 mg/m^2), and nivolumab (360 mg/body) were administered intravenously. Nivolumab was kindly provided by Ono Pharmaceutical. This treatment was mandated to repeat every 3 weeks for a total of 4–6 cycles. If there was no progression of MPM during the combination phase, maintenance therapy with nivolumab was administered until disease progression, unacceptable toxicity, or the patient's condition met the withdrawal criteria.

Both cisplatin and pemetrexed are usually administered every 3 weeks. Under the consideration of practical utility and dose intensity, we planned to administer nivolumab every 3 weeks at the dose of 360 mg/body. Patients underwent tumor imaging by CT or MRI every three cycles. Target lesion diameters were measured, and the tumor response was assessed according to mRECIST criteria.

PD-L1 expression was analyzed in a central laboratory (Cancer Genetics, New Jersey, USA) using archival tumor tissue samples with 28–8 antibody (Dako, California). One or more formalin-fixed, paraffin-embedded (FFPE) blocks of tumor tissue samples collected by core needle biopsy, excisional biopsy, or incisional biopsy of ≥5 FFPE unstained slide samples (serial tissue sections) were analyzed for PD-L1 status. Each sample was required to contain ≥100 evaluable tumor cells. PD-L1-positive was defined as membranous staining in ≥1% of tumor cells. Samples were classified as not evaluable (NE) if the biological conditions of the sample rendered the stained cell membranes difficult to assess, even if the samples otherwise met the evaluation criteria.

Outcomes

This study assessed the efficacy and safety of first-line combination therapy with cisplatin, pemetrexed, and nivolumab for advanced or metastatic MPM. The primary endpoint was the centrally assessed objective response according to mRECIST. The objective response rate (ORR) was defined as the proportion of patients whose best overall response was a complete response (CR) or partial response (PR). The secondary endpoints included efficacy evaluated by the (1) response rate assessed by investigators, (2) disease control rate, (3) OS, (4) progression-free survival (PFS), (5) response duration, and (6) time to response. Safety and adverse events were also evaluated.

The OS was defined as the duration from study registration until the date of death from any cause. PFS was defined as the time from registration to first progressive disease (PD) or death from any cause, whichever is earlier. The disease control rate was the percentage of patients whose best overall response was CR, PR, or stable disease (SD).

Adverse events (AEs) and treatment-related AEs (TRAEs) were monitored throughout the study period and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, V.4.0. Quality of life (QOL) was evaluated using the EuroQol 5 Dimension Japanese edition[9] and the Lung Cancer Symptom Scale for Mesothelioma.[10] QOL was evaluated at each treatment visit according to the treatment schedule before the administration of agents.

Statistical analysis

The trial size was set as 18 due to feasibility. If we assume that 6–12 patients would have a response, the response rate would be 33.3%–66.7%. In this case, the estimate accuracy indicates that the range between the point estimate of the response rate and the lower confidence limit (two-sided 95% confidence coefficient based on exact test) would be 18%–22%.

The statistical analysis was conducted based on predetermined statistical analysis plan. The efficacy and safety-related endpoints were analyzed with full and safety analysis sets, respectively. The patient characteristics, the numbers of treatment cycles and dose reductions, duration of treatment, the relative dose intensity and trial continue/discontinue condition with the reasons were summarized. The centrally reviewed ORR (primary endpoint), investigator-assessed ORR and the disease control rate (included in the secondary endpoints) were estimated with 95% CI. Response rate per histological subtypes and PD-L1 expression status were also calculated. The other secondary endpoints; OS, PFS, duration of response, and time to response were analyzed based on the Kaplan-Meier product limit approach. The best reduction percentage and the change in the sum of target lesions from baseline in each patient were graphed (waterfall and spider plots). The frequency of AEs and TRAEs were summarized with the grade. The summary statistics of the QOL scale/score difference between time points was calculated.

Role of the funding source

The funding source was not involved in the study design, the collection, analysis, and interpretation of data, writing the report, or in the decision to submit the paper for publication.

RESULTS

Eighteen patients were enrolled between January 2018 and May 2019 (table 1). Four patients (22.2%) continued treatment, and 14 (77.8%) discontinued treatment until data cut-off (November 30, 2019). The reasons for discontinuation included PD (n=8, 44.4%), development of a grade 3 or greater infusion reaction (n=1, 5.6%), and continuation of treatment judged as inappropriate by the principal investigator (n=3, 16.7%). One patient withdrew consent to the treatment after the first cycle of induction chemotherapy. All 18 patients were included in both the full and safety analysis sets. Median follow-up was 15.2 (range 6.9–19.4) months.

Patients received an average of 4.8 (range 2–6) cycles of induction triplet chemotherapy. Nine patients (50.0%) received four cycles and eight patients (44.4%) received six cycles. The average number of dose reductions was 0 for nivolumab, 0.3 (range 0–1) for pemetrexed, and 0.3 (range 0–1) for cisplatin. The relative dose intensity in combination phase was 93.5% (range 75.0%–100.0%) for nivolumab, 89.4% (range 60.9%–101.3%) for pemetrexed, and 90.1% (range 63.8%–101.1%) for cisplatin. The average number of nivolumab total cycles was 10.9 (range 2–26). The average total duration of treatment was 7.5 (range 0.7–18.7) months.

Table 1 Patient characteristics (N=18)

Characteristic	Value
Median age, years (range)	69 (64–78)
Male/female	15 (83) / 3 (17)
ECOG PS, 0/1	3 (17) / 15 (83)
Histological subtype	
Epithelioid	14 (77.8)
Sarcomatoid	2 (11.1)
Biphasic	2 (11.1)
TNM classification	
T1N0M0	2 (11.1)
T1N2M0	1 (5.6)
T2N0M0	1 (5.6)
T3N0M0	6 (33.3)
T3N2M0	1 (5.6)
T4N0M0	3 (16.7)
T4N1M0	1 (5.6)
T4N2M0	2 (11.1)
T4N2M1	1 (5.6)
Stage	
I	8 (44.4)
II	0 (0.0)
III	9 (50)
IV	1 (5.6)
PD-L1 expression	
<1%	1 (5.6)
≥1%	17 (94.4)

Values are n (%) unless otherwise noted.
ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; PS, performance status; TNM, tumor, node, metastases.

The best percentage reduction and the change in the sum of target lesions in each patient are shown in figure 1. Fourteen (77.8%; 95% CI, 52.4% to 93.6%) patients had an objective response by central assessment (table 2), which was consistent with the investigator-assessed objective response. Regarding best overall response, 14 patients had a PR. The responses and disease control rate are given in table 2. Tumor shrinkage was observed in all histological subtypes, in 10/14 (71.4%) patients with epithelioid, and the four patients with non-epithelioid disease had a PR. The three remaining patients with epithelioid had SD and one remaining patient with epithelioid was NE. Tumor shrinkage was observed regardless of PD-L1 status and occurred in 13/17 (76.5%) patients with PD-L1

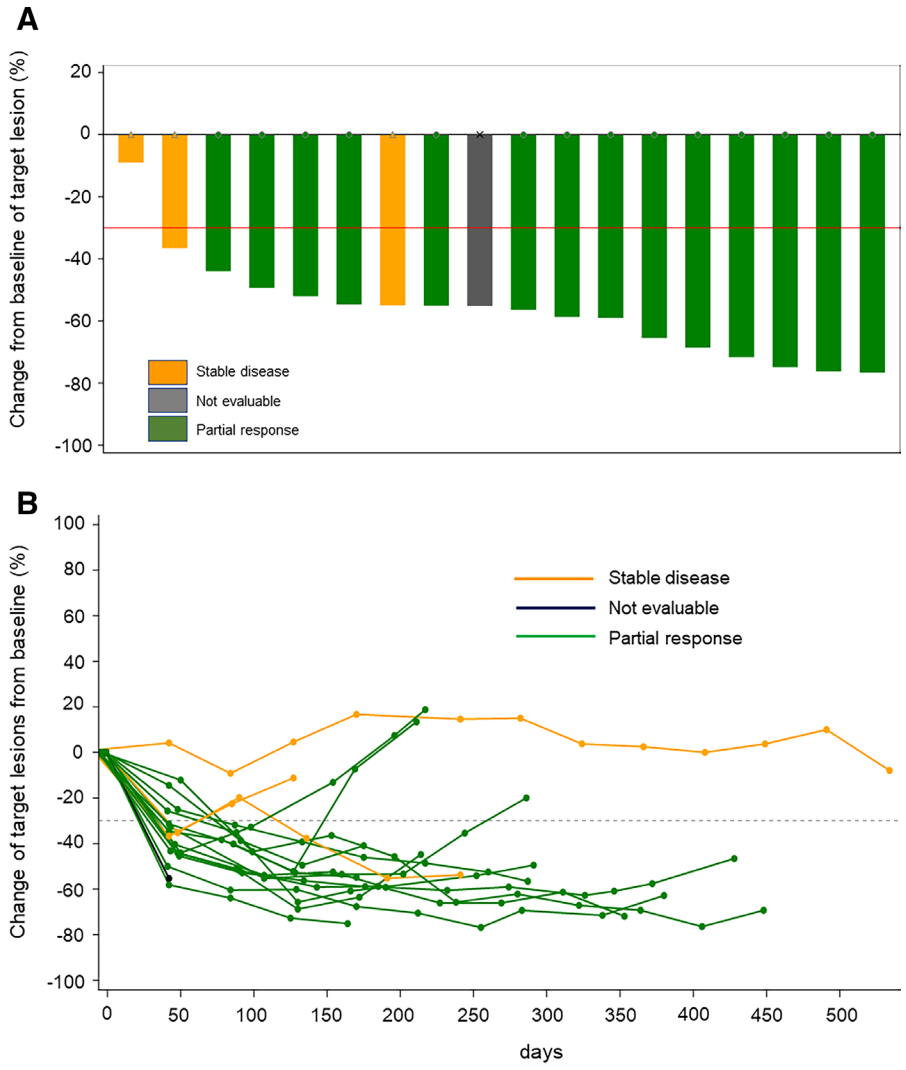

Figure 1 The best reduction percentage (A) and the change in the of sum of target lesions (B) in each patient.

expression ≥1% and 1/1 (100%) patients with PD-L1 expression <1%.

At data cut-off, three patients (16.7%) had an ongoing response. The median response duration was 6.7 months (95% CI 4.21 to not reached), with median time to response of 1.54 (range 1.4–3.3) months. The median reduction in target lesions from baseline (depth of response) was 55.9% (IQR 52.2%–68.8%).

Table 2 Response and disease control rates

	No. of patients	%
Response		
CR	0	0
PR	14	77.8
SD	3	16.7
PD	0	0
NE	1	5.6
Response rate (95% CI)		77.8 (52.4 to 93.6)
Disease control rate (95% CI)		94.4 (72.7 to 99.9)

CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

The Kaplan-Meier curve for PFS, determined by blinded independent central review, is shown in online supplemental figure 1A. At the time of data cut-off, 11 (61.1%) events had occurred, and 7 (38.9%) cases were censored. All 11 events were PD, and there was no death before disease progression. Median PFS was 8.02 months (95% CI 5.59 to 14.06). The 6-month and 12-month PFS rate was 69.0% (95% CI 40.8% to 85.8%) and 40.3% (95% CI 16.2% to 63.5%), respectively. The Kaplan-Meier curve for OS is shown in online supplemental figure 1B. At the time of data cut-off, 2 (11.1%) events had occurred, and 16 (88.9%) cases were censored. Median OS was 20.8 months. The 6-month and 12-month overall survival rate was 100% (95% CI 100.0% to 100.0%) and 92.3% (95% CI 56.6% to 98.9%), respectively.

All 18 patients experienced AEs, but no treatment-related death was recorded. All-cause AEs occurring in ≥10% of patients are shown in table 3. Ten (55.6%) patients experienced grade 3 or greater AEs, including disorder of metabolism or nutrition, loss of appetite,

Table 3 Adverse events

Event	Grade 1	Grade 2	Grade 3	Grade 4	Unknown	Total	Grade ≥3
Nausea	7 (38.9)	4 (22.2)	1 (5.6)	–	–	12 (66.7)	1 (5.6)
Appetite loss	2 (11.1)	4 (22.2)	5 (27.8)	–	–	11 (61.1)	5 (27.8)
Hiccup	4 (22.2)	7 (38.9)	–	–	–	11 (61.1)	–
Constipation	4 (22.2)	5 (27.8)	–	–	–	9 (50.0)	–
Rush	3 (16.7)	4 (22.2)	–	–	–	7 (38.9)	–
Anemia	–	4 (22.2)	3 (16.7)	–	–	7 (38.9)	3 (16.7)
Fatigue	2 (11.1)	4 (22.2)	–	–	–	6 (33.3)	–
Nasopharyngitis	3 (16.7)	2 (11.1)	–	–	–	5 (27.8)	–
Insomnia	4 (22.2)	1 (5.6)				5 (27.8)	–
Neutropenia	–	5 (27.8)	–	–	–	5 (27.8)	–
Diarrhea	1 (5.6)	3 (16.7)	–	–	–	4 (22.2)	–
Fever	4 (22.2)	–	–	–	–	4 (22.2)	–
Peripheral neuropathy	2 (11.1)	1 (5.6)	1 (5.6)		–	4 (22.2)	1 (5.6)
Leukopenia	–	3 (16.7)	1 (5.6)	–	–	4 (22.2)	1 (5.6)
Mucositis	–	3 (16.7)	–	–	–	3 (16.7)	–
Pneumonia	–	2 (11.1)	1 (5.6)	–	–	3 (16.7)	1 (5.6)
Dysgeusia	1 (5.6)	1 (5.6)	–	–	1 (5.6)	3 (16.7)	–
Hearing impairment	2 (11.1)	1 (5.6)	–	–	–	3 (16.7)	–
Abdominal discomfort	1 (5.6)	1 (5.6)	–	–	–	2 (11.1)	–
Angular cheilitis	1 (5.6)	1 (5.6)	–	–	–	2 (11.1)	–
Hyponatremia	–	–	1 (5.6)	1 (5.6)	–	2 (11.1)	2 (11.1)
Muscle pain	1 (5.6)	1 (5.6)	–	–	–	2 (11.1)	–
Back pain	–	1 (5.6)	1 (5.6)	–	–	2 (11.1)	1 (5.6)

Values are n (%).

anemia, hyponatremia, leukopenia, lymphocytopenia, increased serum alanine aminotransferase, increased serum aspartate aminotransferase, pneumonia, nausea, colitis, diverticulitis, dental pulpitis, pulmonary embolism, peripheral neuropathy, and back pain. Two patients (11.1%) experienced peripheral neuropathy during nivolumab maintenance treatment, leading to treatment discontinuation.

The mean (±SD) difference in the health visual analog scale based on the start of the induction treatment was −5.6±24.2 mm (range −65 to 30) at the start of nivolumab maintenance treatment and 0.5±23.3 mm (range −40 to 30) at the end of the treatment. The mean (±SD) difference in the index score based on the start of the induction treatment was 0.0185±0.1389 (range −0.319 to 0.292) at the start of nivolumab maintenance treatment and −0.0166±0.1912 (−0.364 to 0.292) at the end of the treatment. The mean (±SD) difference in the total visual analog scale based on the start of the induction treatment was −0.01±13.57 mm (−21.1 to 28.1) at the start of nivolumab maintenance treatment and −2.11±21.38 mm (−41.3 to 36.0) at the end of the treatment.

DISCUSSION

To the best of our knowledge, this study is the first clinical trial to evaluate the effect of combining nivolumab and platinum-based chemotherapy for the treatment of advanced MPM. The combination of an ICI and cytotoxic chemotherapy is a rapidly evolving area of interest in cancer treatment. Cytotoxic agents, including platinum, could modulate the immune response through PD-1/PD-L1 inhibition by enhancing the potential immunogenic effect.[11–13] Combination regimens that include a PD-1 or PD-L1 inhibitor have led to prolonged OS in small cell lung cancer[14] and non-small cell lung cancer.[15] Previous reports have also shown that cytotoxic agents can induce immune-stimulating properties in mesothelioma cell models.[16 17]

Nivolumab is currently administered at a dose of 240 mg/body biweekly in clinical practice based on recent clinical trials.[6 18] However, combination chemotherapy with cisplatin and pemetrexed is administered every 3 weeks. In the current study, nivolumab was administered every 3 weeks at a dose of 360 mg/body based on a recent report that the combination of nivolumab (10 mg/kg) and pemetrexed/cisplatin every 3 weeks has

an acceptable toxicity profile and encouraging antitumor activity in patients with advanced non-small cell lung cancer.[19]

We set a centrally assessed ORR according to mRECIST as the primary endpoint. A modification of the RECIST criteria has specifically addressed the difficulties measuring and assessing changes in tumor bulk in MPM. In addition, the mRECIST criteria have successfully distinguished between responders and non-responders for the parameters of OS,[20] demonstrating its ability as an appropriate endpoint, particularly in phase II studies. The combination of nivolumab and cisplatin/pemetrexed has demonstrated a notable ORR of 77.8%. This is the highest ORR reported thus far in chemotherapy for MPM. Moreover, all participants demonstrated tumor shrinkage. One of the most remarkable aspects of the participants in the current study was a high tumor proportion score for PD-L1 expression. PD-L1 is expressed in a substantial proportion of MPM and is associated with poor survival.[21] The association of PD-L1 expression in mesothelioma cells and the response to anti-PD-1 inhibitors are still controversial. PD-L1 positivity was not correlated with outcome in one trial,[22] but increased ORR and prolonged survival was observed in patients with PD-L1-positive patients in another study.[6] Nivolumab plus ipilimumab combination therapy exhibited higher ORR in patients with PD-L1-positive MPM compared with that in patients with PD-L1-negative MPM.[23] In another study, PD-L1 expression was not only associated with the increase of ORR but also associated with the improvement in PFS and OS when treated with a combination of nivolumab plus ipilimumab.[24] These results indicate that PD-L1 expression could be a reliable biomarker for ICI response. The high PD-L1 expression may contribute to the favorable response in the current study. The AE profile in the current study was consistent with what is expected when combining cisplatin and pemetrexed with nivolumab. The addition of nivolumab did not appear to increase the frequency or severity of AEs associated with chemotherapy with cisplatin and pemetrexed.

Recently, a multicenter phase II study was conducted in Australia[25] in 55 patients with untreated MPM who received cisplatin, pemetrexed, and durvalumab for a maximum of six cycles, followed by durvalumab maintenance for up to 12 months. The primary endpoint, 6-month PFS, was 57%, and the ORR and disease control rate were 48% and 87%, respectively. Based on these favorable results, a multicenter trial is planned to randomize participants for cisplatin and pemetrexed with or without durvalumab. More recently, an international randomized phase III trial evaluated the combination of ipilimumab, a CTLA-4 inhibitor, and nivolumab versus standard first-line platinum-pemetrexed chemotherapy in treatment-naïve patients with untreated, unresectable MPM.[26] The primary endpoint of OS was met with a 4-month prolongation in median OS in those who received nivolumab–ipilimumab compared with those who received platinum–pemetrexed chemotherapy. These findings led to the recent approval of nivolumab plus ipilimumab in the USA for first-line treatment of unresectable MPM. The combination of nivolumab and ipilimumab would be a new standard first-line treatment, but some problems still remain. One of the problems is a rapid drop-off in PFS in patients receiving nivolumab plus ipilimumab. Similar results have been shown in clinical trials of non-small cell lung cancer, which has shown improvement in OS and PFS.[27] A recent study of non-small cell lung cancer that ipilimumab plus nivolumab with two cycles cytotoxic chemotherapy demonstrated an improvement in the rapid drop-off of PFS and OS.[28] These results support the further clinical development of the ICI-chemotherapy combination in first-line treatment of MPM.

The main limitation of the current study is its single-arm, non-comparative design. In addition, we included a few participants without tumor PD-L1 expression. Survival analyses are immature because most of the participants were censored at the time of data cut-off. The trial size was determined based not on statistical power, but on our ability to accrue patient. However, the estimated lower limit of the ORR in the current study was 52.4%, which is higher than the ORRs reported in previous studies of front-line cisplatin/pemetrexed combination chemotherapy.

In conclusion, the combination of cisplatin, pemetrexed, and nivolumab demonstrated sufficient activity and safety as first-line therapy in unresectable MPM. We think that adding nivolumab to cisplatin/pemetrexed would be a treatment option for patients with advanced MPM, though the efficacy and safety should be examined in a definitive randomized study.

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Ethics approval JME-001 was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines in Japan. The study protocol was reviewed and approved by the institutional review board of each site before study initiation. All patients provided written informed consent.

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Data availability statement Data are available upon reasonable request. The patients' de-identified clinical data may be made available to other investigators after approval by the institutional review board. Requests should be directed to the corresponding author.

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