Treatment patterns and outcomes for patients with malignant pleural mesothelioma in England in 2013-2017: a nationwide CAS registry analysis from the I-O Optimise initiative

Baas, P.; Daumont, M.J.; Lacoin, L.; Penrod, J.R.; Carroll, R.; Venkatesan, S.; ... ; Snee, M.

Lung Cancer 162 (2021) 185–193

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

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Paul Baas [a], Melinda J. Daumont [b], Laure Lacoin [c], John R. Penrod [d], Robert Carroll [e], Sudhir Venkatesan [f], Harveen Ubhi [f], Alan Calleja [f], Michael Snee [g,*]

[a] Department of Thoracic Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[b] Worldwide Health Economics & Outcomes Research, Bristol Myers Squibb, Braine-L'Alleud, Belgium
[c] Epi-Fit, Bordeaux, France
[d] Worldwide Health Economics & Outcomes Research, Bristol Myers Squibb, Princeton, NJ, USA
[e] Centre for Observational Research and Data Science, Bristol Myers Squibb, Uxbridge, UK
[f] Real World Solutions, IQVIA, London, UK
[g] Leeds Teaching Hospital NHS Trust, Leeds, UK

ARTICLE INFO

Keywords:
Malignant pleural mesothelioma
I-O Optimise
Systemic anticancer therapy
Real-word evidence

ABSTRACT

Objectives: Malignant pleural mesothelioma (MPM) is a rare and aggressive cancer with a poor prognosis and limited treatment options. This study assessed the characteristics, treatment patterns, and outcomes for patients diagnosed with MPM in England.

Materials and methods: As part of I-O Optimise, this retrospective cohort study analyzed data recorded in the Cancer Analysis System in England for all adult patients newly diagnosed with MPM between 2013 and 2017, with follow-up to March 2018 or death, whichever occurred first. Overall survival (OS) was estimated using Kaplan–Meier methods. A Cox regression model was used to describe the impact of sociodemographic and clinical characteristics at diagnosis on OS.

Results: 9458 patients diagnosed with MPM were analyzed. Median age at diagnosis was 75 years; 83.4% were male. Eastern Cooperative Oncology Group performance status (ECOG PS) was 0–1 for 44.5%; 2 for 11.5%; >2 for 9.1%; and missing for 34.9% of patients. TNM stage was missing for 60.4%. A majority of patients had epithelioid histology (36.4%) or not otherwise specified (NOS) MPM (43.3%). After diagnosis, 48.7% of all patients received best supportive care (BSC; no surgery, radiotherapy, SACT); 11.4% received palliative radiotherapy alone; 6.5% underwent surgery; 33.4% received systemic anticancer therapy (SACT) as initial treatment. Platinum plus pemetrexed was the main SACT regimen used in both first and second line. Median OS (8.3 months) varied by histopathology and ranged from 4.3 to 13.3 months for sarcomatoid and epithelioid MPM, respectively. After adjusting for age, sex, and ECOG PS, sarcomatoid, biphasic, and NOS MPM remained significantly associated with worse OS than epithelioid MPM (all $p < 0.001$). Median OS varied from 4.6 to 17.0 months for patients receiving BSC/palliative radiotherapy, and patients receiving surgery, respectively.

Conclusion: Outcomes for patients with MPM in England remain poor. Future studies will investigate the impact of newer therapies on the treatment patterns and survival of MPM patients.

1. Introduction

In a rapidly evolving cancer treatment landscape, there is a need to assess how newer therapies, such as immunotherapies, are impacting real-world patient survival in order to guide future treatment decisions. Establishing a pre-immunotherapy "baseline" helps to accurately monitor and understand changes in patient management and overall survival (OS) as these therapies start to be used clinically. Real-world data are a valuable and complementary source of evidence to clinical trials, and they provide information that can help to assess the use and impact of new therapies in routine clinical practice.

Malignant pleural mesothelioma (MPM) is a rare and aggressive

* Corresponding author.

https://doi.org/10.1016/j.lungcan.2021.11.001
Received 23 June 2021; Received in revised form 30 September 2021; Accepted 2 November 2021
Available online 10 November 2021

cancer originating in the lung pleura; in 2020, there were around 30,900 new cases and 26,300 deaths from MPM globally [1]. In Great Britain, the incidence of MPM in males is around 3.4 per 100,000 of the population [2], and in England, up to 87% of MPM diagnoses have been attributed to occupational asbestos exposure [3–6]. Although products containing asbestos have been banned from use in the UK since 1999 [7,8], the incidence of MPM has increased over the past decade due to a 30–50-year latency period between asbestos exposure and the development of disease [2,9,10]. Non-asbestos risk factors for developing MPM are less common and include ionizing radiation, exposure to erionite, and germline mutations in *BRCA1*-associated tumor protein (BAP1) [11,12].

MPM tumors are heterogeneous, and exist as three main histological subtypes: epithelioid, which is the most common subtype, sarcomatoid, and biphasic (mixed epithelioid and sarcomatoid) [13], with non-epithelioid tumors being associated with a poorer prognosis than epithelioid tumors [14,15]. Although histological subtyping is important for treatment decisions, a high proportion of MPM cases in the UK remain unspecified [16].

Treatment guidelines by the British Thoracic Society (BTS) recommend surgical options to be further examined in the context of clinical trials for patients with MPM and a good prognosis; extra-pleural pneumonectomy (EPP) is not recommended and extended pleurectomy decortication (EPD) is not recommended outside of a clinical trial [7]. The BTS and the European Society for Medical Oncology (ESMO) recommend chemotherapy and/or radiotherapy (RT), but do not make recommendations based on histological subtype [2,7]. Platinum (cisplatin or carboplatin) plus pemetrexed has been shown to cause modest improvements in survival [17], and, in the UK, it is the only systemic anticancer therapy (SACT) regimen reimbursed/funded in unresectable MPM. In Europe, this regimen has been the first-line standard of care (SoC) for patients with good performance status until recently (Eastern Cooperative Oncology Group performance status [ECOG PS] of 0–1) [2]. Guidelines recommend adding bevacizumab to this regimen, where licensed [7], yet this treatment remains unapproved for MPM in most countries, and presents cost or reimbursement challenges [18].

The prognosis for patients with MPM is poor, with a median OS from diagnosis of only 8–14 months [11] and limited available treatment options; this highlights a high unmet need for effective therapies that improve patient outcomes. Recent advances in the diagnosis and understanding of malignant mesotheliomas have led to the development of newer therapies that have potential to improve the prognosis for patients with MPM [19].

As part of I-O Optimise, a multinational research initiative providing insights into the real-world management of thoracic malignancies [20], this study aimed to provide a detailed description of patient characteristics, treatment patterns, and outcomes in terms of OS for patients diagnosed with MPM in England between 2013 and 2017 prior to the approval of immunotherapies, using data recorded in the Cancer Analysis System (CAS) registry.

2. Materials and methods

2.1. Design and data source

This retrospective cohort study was a nationwide population-based analysis using data from the national CAS registry in England, which is under the control of the National Cancer Registration and Analysis System (NCRAS) in Public Health England (PHE). CAS captures data on all cases of cancer that occur in people living in England who receive medical care in the National Health Service (NHS). The CAS registry contains the SACT dataset as well as the Cancer Outcomes and Services Dataset (COSD), and includes detailed information on patient demographics, staging, pathology, and mortality [21]. Data on deaths were extracted from the National Death Registry.

2.2. Ethics

This study was conducted in accordance with International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practice (GPP) and applicable regulatory requirements. The study protocol was approved by the PHE NCRAS. As this was a retrospective study, informed consent was not required from patients. Nevertheless, in the UK, NHS patients may opt out of sharing their data within the CAS database (this is usually less than 1% of all patients).

2.3. Study population

The study included all patients aged ≥18 years in the CAS registry who were newly diagnosed with MPM (International Classification of Disease, 10th revision [ICD-10] code [C45.0]) within the inclusion period (January 1, 2013–December 31, 2017). All patients were followed from their initial diagnosis until the end of the study (March 31, 2018) or death, whichever occurred first. Patients with missing data on age, sex, or NHS number recorded in the CAS registry; any concomitant primary malignancy (except non-metastatic non-melanoma skin cancer; ICD-10 codes C44, C4A); or any SACT treatment received up to 5 years prior to MPM diagnosis were excluded.

2.4. Measures and analyses

Patient characteristics, including age, sex, body mass index (BMI), and ECOG PS, were collected at diagnosis. ECOG PS was also collected at the start of each line of therapy. MPM histology was described based on the following International Classification of Diseases for Oncology (ICD-O)-2 codes: 90503 for mesothelioma not otherwise specified (NOS), 90513 for sarcomatoid mesothelioma, 90523 for epithelioid mesothelioma, and 90533 for biphasic mesothelioma. TNM staging was the best stage reported in the CAS data source at the time of MPM diagnosis. Therefore, strict mapping to a specific TNM staging system is not possible with this variable.

The date of initial diagnosis was extracted from the CAS database. Initial treatment was defined as the first treatment received after diagnosis and any associated treatment within the following 60–120 days (the algorithm used to derive initial treatments is included in the supplementary information). Patients receiving best supportive care (BSC) were defined as those who did not receive any SACT, surgery, or radiotherapy (RT) from diagnosis to death or end of the study period. OPCS Classification of Interventions and Procedures (OPCS-4) codes consistent with potentially curative surgery were selected as follows: E541, total pneumonectomy; T071, decortication of pleura; T072, open excision of lesion of pleura; T078, other specified open excision of pleura; and T079, unspecified open excision of pleura.

A line of therapy (LoT) algorithm was defined considering SACT regimens only. Start of the first LoT was taken as the first SACT regimen received by patients not undergoing surgery (unresected patients) or the first subsequent SACT regimen received among patients undergoing surgery. Any treatment gap of >100 days after the estimated end date of the last cycle was considered as an advance to the next LoT, regardless of whether there was a change in the regimen agent(s). Finally, any introduction of a new SACT treatment (drug not received within 28 days of LoT start) with a gap of ≤100 days was considered as a change in LoT, except for bevacizumab and a change from cisplatin to carboplatin.

Summary statistics were used to describe patient baseline characteristics and initial treatment. Analyses were stratified by mesothelioma histology (epithelioid, sarcomatoid, biphasic, NOS, unknown). OS was estimated using Kaplan–Meier methods, and was defined as time from the index date to the date of death from any cause during the study period. Patients who were alive were censored at the end of the study period. A Cox regression model was used to describe the impact of sociodemographic and clinical characteristics (age, sex, ECOG PS, histology) at diagnosis on OS.

3. Results

3.1. Characteristics of patients diagnosed with MPM

Overall, 9458 patients diagnosed with MPM between January 1, 2013 and December 31, 2017 were included in this study (Table 1). The median (interquartile range [IQR]) age of patients at diagnosis was 75 (69–81) years, and most (83.4%) were male. At diagnosis, 44.5% of all patients had an ECOG PS of 0–1; 11.5% had a PS of 2; and 9.1% had a PS > 2. For around one-third (34.8%) of patients, data on PS were missing; this proportion decreased from 50% in 2013 to 31% in 2017.

A total of 36.4% of patients had epithelioid histology, 9.3% had sarcomatoid, 7.3% had biphasic, and 43.3% had NOS MPM; histology data were unknown or missing (no histology code) for 3.7% of patients. The proportion of female patients with epithelioid MPM was slightly higher (19.4%) than those with non-epithelioid MPM (sarcomatoid, 11.3%; biphasic, 14.3%; NOS, 16.2%). The overall percentage of patients with NOS MPM decreased from 52.5% in 2013 to 36.4% in 2017, while the percentage with unknown or missing histology, although low, increased progressively over the study period, from 0.8% in 2013 to 6.1% in 2017. Patients with NOS MPM tended to be older and were more likely to have a higher or missing ECOG PS than patients with other known histology. Similarly, patients diagnosed with sarcomatoid MPM tended to be older and have a higher ECOG PS than those with epithelioid MPM.

Data on TNM stage at diagnosis were missing for 60.4% of patients over the study period; however, this decreased over time, from 72.7% in 2013 to 51.3% in 2017. Overall, 12.8% of all patients were classified as TNM stage 1–2, 16.1% as stage 3, and 10.7% as stage 4. TNM stage distribution tended to be similar across the different histological subtypes, except that a higher proportion of patients with epithelioid histology were classified as TNM stage 1–2 at diagnosis (39.4%) (Table 1).

3.2. Treatment patterns of patients diagnosed with MPM

3.2.1. Initial treatment

Almost half (48.7%) of all patients diagnosed with MPM over the study period remained untreated (i.e., they received no surgery, RT, or SACT); these patients were considered to have received BSC only. In addition, 11.4% of patients received palliative RT alone (i.e., no SACT and no surgery). The proportion of patients receiving BSC or palliative RT alone varied by histology, with 48.2% of patients with epithelioid MPM; 49.5% with biphasic MPM; 65.2% with sarcomatoid MPM; and 70.0% with NOS MPM receiving BSC only (Fig. 1b). Age and ECOG PS at diagnosis were also associated with the receipt of treatment. Among patients with an ECOG PS of 0–1 at diagnosis, 19.3% of those aged <65 years, 26.7% aged 65–74 years, and 59.1% aged ≥75 years remained untreated or received palliative RT alone. Similarly, most patients with an ECOG PS >2 at diagnosis (over 85%) remained untreated or received palliative RT alone throughout the study period (Fig. 1c).

Overall, 6.5% (n = 617) of patients received surgery (Fig. 1). Of these, 57% (n = 349) underwent a decortication of the pleura (OPCS-4 code T071), 43% (n = 264) an open excision of the pleura (codes T072 [n = 38], T078 [n = 29], T079 [n = 197]), and n<5 a total pneumonectomy (code E541). Among patients who received surgery, 56.6% received at least one SACT regimen during the study period. The proportion of patients who underwent surgery was higher among those with epithelioid and biphasic MPM (10.4% and 10.7%, respectively) than among those with sarcomatoid and NOS MPM (4.0% and 3.3%, respectively) (Fig. 1b).

One-third of patients (34.9%) diagnosed with MPM during the study period received an SACT regimen (i.e., a first LoT) as initial treatment after diagnosis (defined as SACT and no surgery within 120 days after SACT start; or RT and no surgery within 60 days after RT start and SACT at any time): 21.8% of patients received SACT alone and 11.6% also received some RT during the study period (Fig. 1a and Supplementary Table 1). Receipt of a first LoT varied by histological subtype, with 40.8% of patients with epithelioid MPM; 39.1% with biphasic MPM, 29.7% with sarcomatoid MPM, and 26.5% with NOS MPM receiving a first LoT over the study period.

3.2.2. Lines of therapy

Treatment information was available for 3117 of 3159 unresected patients who received a first LoT (Supplementary Table 2). Most

Table 1
Baseline demographic and clinical characteristics of patients diagnosed with MPM between 2013 and 2017 – overall and by histology.

	All (N = 9458)	Epithelioid (N = 3440)	Sarcomatoid (N = 883)	Biphasic (N = 693)	NOS (N = 4093)	Unknown (N = 349)
Age (years)						
Median (IQR)	75 (69–81)	73 (67–79)	75 (69–80)	73 (67–79)	77 (70–83)	77 (72–82)
Min–Max	25–101	25–96	39–94	40–92	27–101	42–96
<65	1189 (12.6)	577 (16.8)	96 (10.9)	103 (14.9)	403 (9.9)	10 (2.9)
65–74	3375 (35.7)	1408 (40.9)	331 (37.5)	298 (43.0)	1250 (30.5)	88 (25.2)
≥75	4894 (51.7)	1455 (42.3)	456 (51.6)	292 (42.1)	2440 (59.6)	251 (71.9)
Sex						
Male	7884 (83.4)	2772 (80.6)	783 (88.7)	594 (85.7)	3430 (83.8)	305 (87.4)
ECOG PS						
0–1	4210 (44.5)	1893 (55.0)	379 (42.9)	372 (53.7)	1423 (34.8)	143 (41.0)
2	1090 (11.5)	364 (10.6)	120 (13.6)	80 (11.5)	473 (11.6)	53 (15.2)
>2	862 (9.1)	171 (5.0)	89 (10.1)	33 (4.8)	533 (13.0)	36 (10.3)
Missing	3296 (34.9)	1012 (29.4)	295 (33.4)	208 (30.0)	1664 (40.7)	117 (33.5)
Histopathology						
Epithelioid	3440 (36.4)					
Sarcomatoid	883 (9.3)					
Biphasic	693 (7.3)					
NOS	4093 (43.3)					
Unknown	349 (3.7)					
TNM stage						
I–IIA	620 (6.6)	288 (8.4)	41 (4.6)	71 (10.2)	220 (5.4)	0 (0.0)
IIB	586 (6.2)	260 (7.6)	66 (7.5)	60 (8.7)	200 (4.9)	0 (0.0)
III	1527 (16.2)	664 (19.3)	191 (21.6)	118 (17.0)	554 (13.5)	0 (0.0)
IV	1011 (10.7)	304 (8.8)	109 (12.3)	60 (8.7)	538 (13.1)	0 (0.0)
Undetermined	5714 (60.4)	1924 (55.9)	476 (53.9)	384 (55.4)	2581 (63.1)	349 (100)

Data are presented as n (%) unless otherwise indicated.
ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; NOS, not otherwise specified.

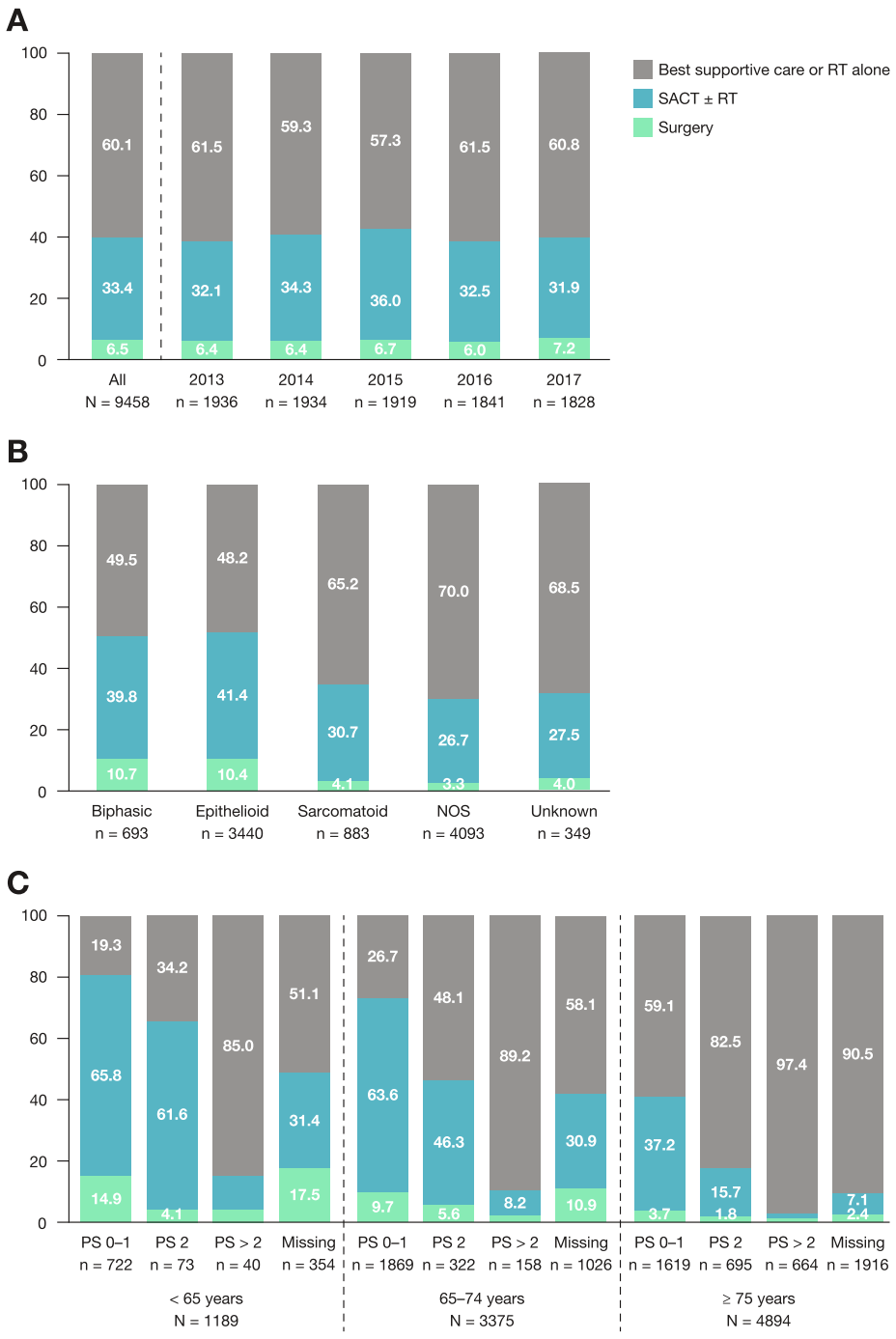

Fig. 1. Initial treatment in patients diagnosed with MPM by date of diagnosis (a), by histology (b) and by age and ECOG PS score (c). BSC, best supportive care; MPM, malignant pleural mesothelioma; RT, radiotherapy; SACT, systemic anticancer therapy.

(90.2%) patients received SoC with platinum plus pemetrexed in first line (Supplementary Fig. 1); of these patients, 60.6% received carboplatin, 37.3% received cisplatin, and 2.1% switched to cisplatin/carboplatin (Supplementary Table 2). Median (IQR) treatment duration for SoC in the first-line setting was 2.1 (0.9–3.4) months. Overall, 58.1% of the patients died during or after receiving a first line and 17.1% were censored alive at the end of the study period during or after receiving a first line. Around one-quarter of patients who received a first line were treated with a second line during the study period (n = 774) (Supplementary Fig. 1 and Table 2).

Of the 774 patients who received a second line, 43.6% were treated with platinum plus pemetrexed, 13.7% received another platinum-based chemotherapy, 24.4% received vinorelbine alone, and 18.9% were included in a clinical trial (Supplementary Table 2). Treatment sequencing for the first three lines of therapy received by patients over the study period is shown in Fig. 2.

3.3. Overall survival of patients diagnosed with MPM

3.3.1. OS, overall and by histology

In the overall MPM population, median OS (IQR) was 8.3 (3.1–17.2) months, with 1-, 2-, and 3-year survival rates (95% confidence interval [CI]) of 38% (37–39), 16% (15–16), and 8% (7–9), respectively (Fig. 3a). Median OS varied by histology, from 4.3 months for patients

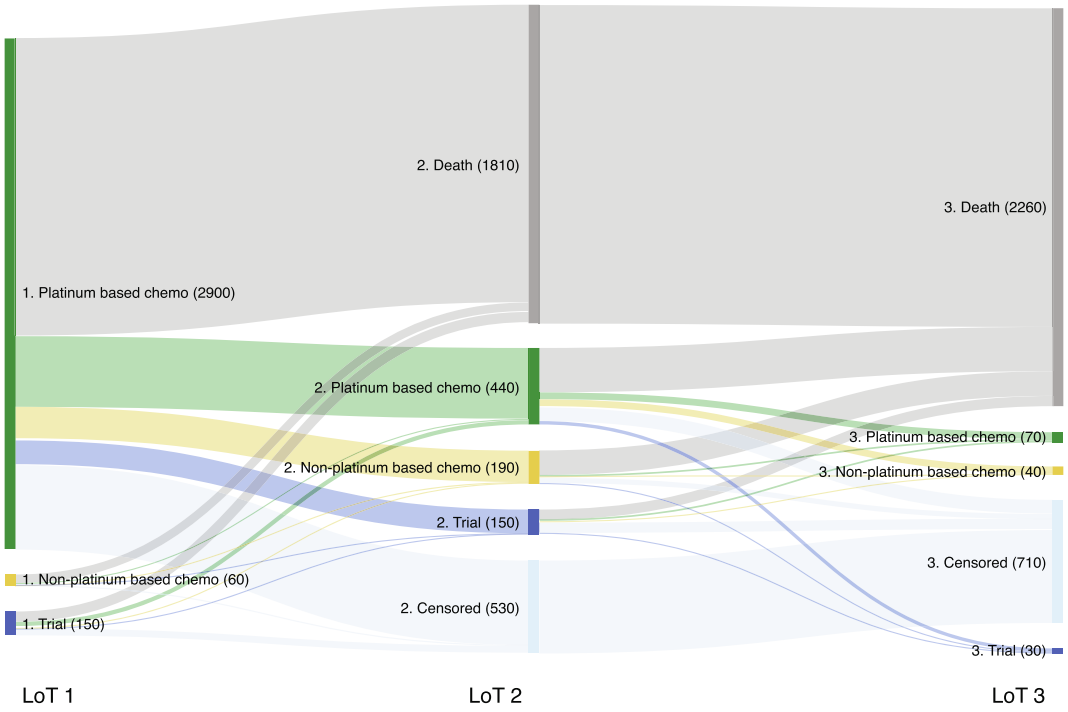

Fig. 2. Treatment sequencing in unresected patient diagnosed with MPM in 2013–2017 receiving a first LoT.[a] LoT, line of therapy; PD1, programmed cell death protein 1; PDL1, programmed death-ligand 1. [a] Results rounded to closest 10 and numbers < 5 masked.

with sarcomatoid MPM to 13.3 months for those with epithelioid MPM (Fig. 3b). One-year OS (95% CI) ranged from 15% (12–17) for patients with sarcomatoid MPM to 54% (53–56) for those with epithelioid MPM. Three-year OS in these subgroups was 2% (1–4) and 12% (11–14), respectively.

3.3.2. Clinical characteristics associated with OS by multivariate model

After adjusting for age, sex, and ECOG PS, sarcomatoid and biphasic MPM remained significantly associated with worse OS than epithelioid MPM (hazard ratio [HR] 1.79 [95% CI: 1.60–2.01] for biphasic MPM and 2.58 [2.31–2.89] for sarcomatoid MPM; both $p < 0.001$) (Fig. 4). NOS MPM was also significantly associated with worse OS compared with epithelioid MPM (HR 1.32 [95% CI: 1.23–1.42]; $p < 0.001$). Other clinical factors significantly associated with worse OS in the multivariate model included higher ECOG PS (HR 1.76 [95% CI: 1.58–1.96] for ECOG PS 2 and HR 2.66 [2.15–3.29] for ECOG PS > 2 vs 0–1; both $p < 0.001$) and older age (HR 1.17 [1.07–1.28] for age 65–74 years vs 18–64 years HR 1.36 [1.23–1.49] for age ≥ 75 years vs 18–64 years; $p < 0.001$). Female sex was significantly associated with a better OS versus male sex (HR 0.87 [0.80–0.96]; $p = 0.0035$).

3.3.3. OS by initial treatment

Median (95% CI) OS varied by the initial treatment received, and was 17.0 (15.2–19.2) months in patients who underwent surgery; 14.0 (13.6–14.4) months in patients treated with SACT ± RT; and 4.6 (4.4–4.9) months in patients receiving BSC or palliative RT alone (Fig. 3c). Although OS was longest for patients who underwent surgery as initial therapy, the 3-year OS (95% CI) was only 19% (16–24). Among inoperable patients who received a first line (SACT ± RT), and those who received BSC or RT alone, the 3-year OS (95% CI) was 11% (10–13) and 5% (4–6), respectively.

3.3.4. OS by line of therapy

Among all inoperable patients receiving a first line, the median (95% CI) OS from the start was 11.2 (10.7–11.7) months (Supplementary Table 2). The median (95% CI) OS for those who received SoC (platinum plus pemetrexed) was 11.3 (10.8–11.8) months overall, and ranged from 5.8 (5.2–6.5) months for patients with sarcomatoid MPM to 13.5 (12.7–14.1) months for those with epithelioid MPM (Supplementary Fig. 2).

In inoperable patients who received a second line, median OS (95% CI) was 8.5 (7.7–9.2) months (Supplementary Table 2), being 11.3 (10.0–12.8) months for patients treated with platinum plus pemetrexed and 5.1 (4.5–6.3) months for patients treated with vinorelbine.

4. Discussion

The results of this nationwide study, using data from the CAS national registry in England from 2013 to 2017, show that the OS of patients diagnosed with MPM remains poor, highlighting the significant unmet needs and difficulty in managing the disease. The demographics of patients with MPM in this study were consistent with the known profile of the disease, with a substantially higher proportion being male and a median age at diagnosis of 75 years [6,8,22–25]. This reflects the higher exposure to occupational asbestos among males, and the long latency period between exposure and disease onset [2,3,26].

The diagnosis of MPM is challenging, and involves radiological, biomarker and pathological investigations [11]. In our study, more than half of all patients had missing TNM data, which may reflect the difficulty in staging MPM in routine clinical practice, and a possible indifference to this factor by treating clinicians. Additionally, most patients in our analysis were aged >75 years, which may have contributed to a preference for a less invasive method of diagnosis. Accurate determination of histopathology is essential for appropriate treatment decision-making and has relevance for prognosis [7,16]. Despite these difficulties, we found that the proportion of patients with confirmed histology increased over the study period and the proportion diagnosed with NOS MPM decreased (from 53% in 2013 to 36% in 2017). Moreover, a better documented histology was seen compared with a previous population-based study in the UK over 2002–2005 (64%) [6]. The proportion of patients with unspecified histology in our study was still far higher than the 10% recommended by the National Mesothelioma

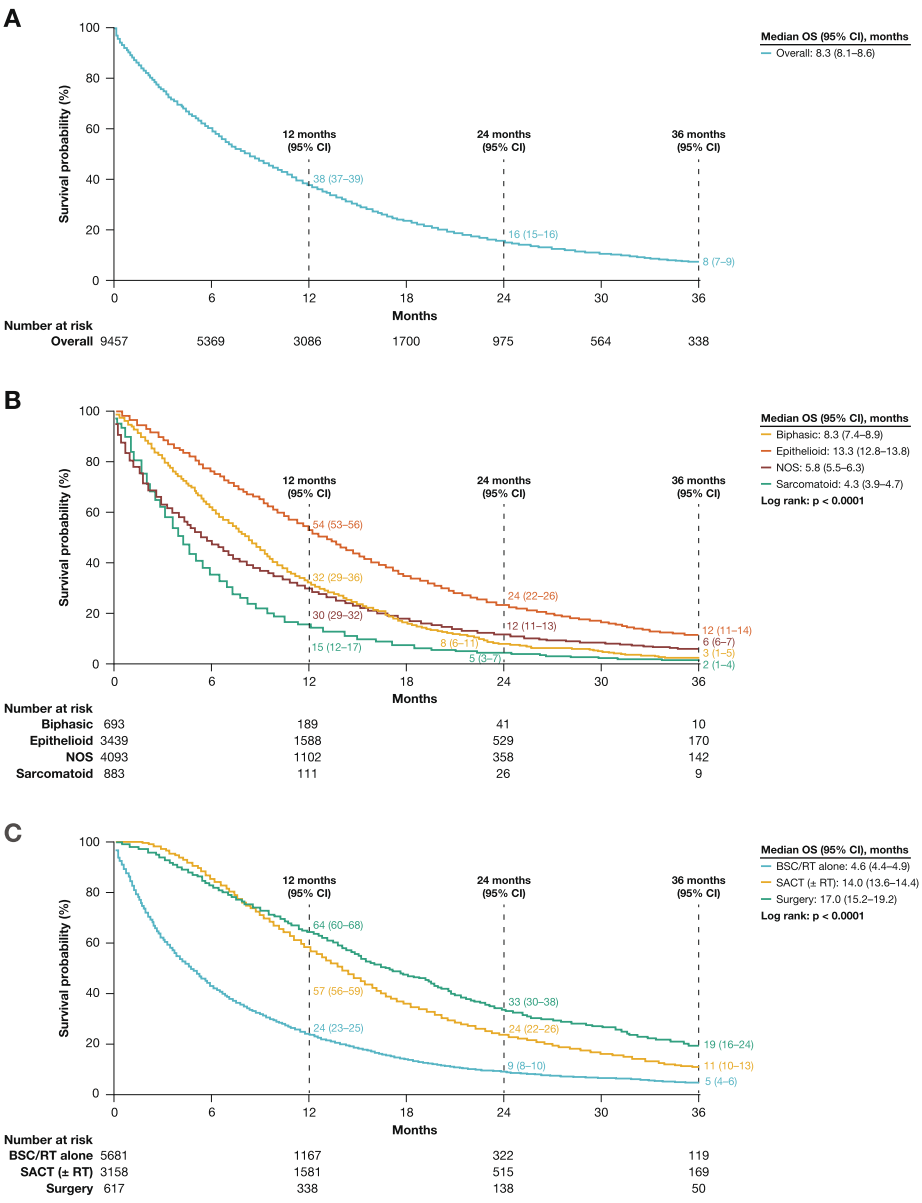

Fig. 3. Overall survival from MPM diagnosis date: overall (a), by histopathology (b), and by initial treatment (c). BSC, best supportive care; CI, confidence interval; MPM, malignant pleural mesothelioma; NOS, not otherwise specified; OS, overall survival; RT, radiotherapy; SACT, systemic anticancer therapy.

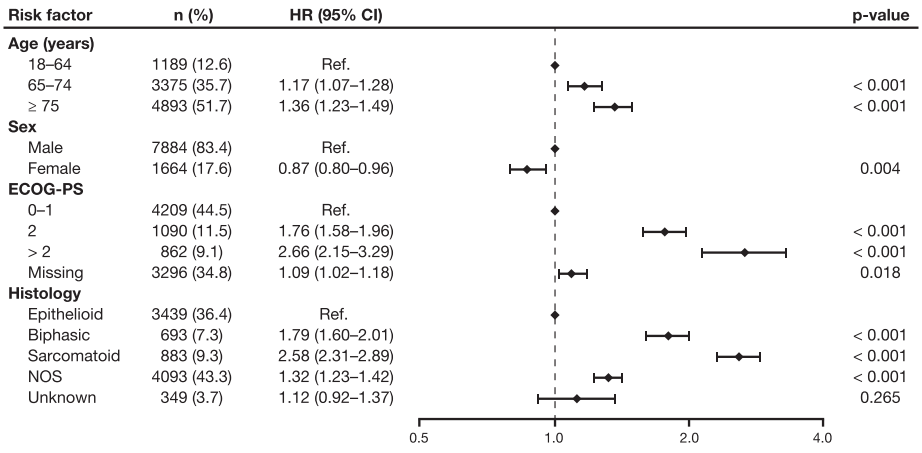

Fig. 4. Clinical characteristics of patients at diagnosis associated with overall survival (multivariate model) (N = 9458). CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; NOS, not otherwise specified.

Audit [16], suggesting that further improvements are needed. Patients with NOS MPM were older and had a higher or missing ECOG PS compared with those with confirmed histology. Most of these patients (70%) received BSC or palliative RT only after diagnosis. Thus, invasive diagnostic procedures, such as biopsy, might have been considered unsuitable for some of these patients, with diagnosis based on clinical-radiological findings without histological or cytological confirmation, as previously reported [22]. In some cases, this may be due to data recording issues in the database rather than pathology not being obtained.

The OS among patients with MPM was poor, at around 8 months in the overall population despite any treatment. This was lower than the median OS of 9.5 months observed over 2007–2011 in England based on an analysis of the National Lung Cancer Audit (NLCA) database [23]; however, that study only included patients with pathologically confirmed MPM. The OS reported for patients with a clinical diagnosis (nonpathological confirmation) in the NLCA database was 6.8 months [23]. Over 2007–2010, the OS for patients with pathologically confirmed MPM was 9.2 months in the Netherlands and 10.7 months in Belgium; correspondingly, the proportion of treated patients was higher in Belgium [23]. Similarly, over 2000–2012, the OS for patients with pathologically confirmed MPM in Finland based on national registry data was 9.7 months [24].

Consistent with previous reports [3,25], sarcomatoid histology was associated with shorter survival compared with biphasic and epithelioid histologies. In the UK, there have been no improvements in OS among patients with confirmed histology since 2008–2012 [22] and similar results were observed over 2004–2012 based on national registry data in Belgium [27]. As expected, non-epithelioid histology, high PS (≥2), male sex, and older age (≥75 years) were found to be independent predictors of shorter OS. This is consistent with previous studies in England, Europe, and the US [5,25,28–31]. Prognostic scoring systems developed by the European Organisation for Research and Treatment of Cancer (EORTC) and Cancer and Leukemia Group B (CALGB) based on clinical characteristics of patient with MPM enrolled in clinical trials include, among other factors, poor PS, non-epithelioid histology, older age, and male sex, as being predictive of poor OS [28,29]. Both the EORTC and CALGB prognostic scoring systems have been validated in real-world cohorts of patients with MPM in the UK [5,32].

Overall, we observed no notable changes in the management of MPM in England between 2013 and 2017. Treatment rates were low, with almost two-thirds of patients receiving BSC or palliative RT alone. Initial treatment varied by age and ECOG PS at baseline, consistent with previous observations and treatment guidelines [2,7]. These results may highlight the difficulties treating elderly patients, as approximately 60% of patients aged ≥75 years with a PS of 0–1 remained untreated. In addition, comorbidities may impact the treatment of these older patients, as well as patient preference and the perceived limited benefit of pleurectomy decortication and platinum-based chemotherapy. Median OS among patients with MPM who received BSC or palliative RT alone was low, at only 4.6 months.

Surgery (mainly decortication or excision of the pleura) was undertaken in 6.5% of patients; however, information on the extent of the intervention was not available. Therefore, some of these patients may not have had a complete resection of the tumor and only received partial pleurectomy. For this reason, our study is unable to evaluate the survival of MPM patients receiving radical surgery (complete resection). Consistent with this potential misclassification, the median OS in our surgery group was slightly lower than that reported in patients who received radical surgery in Belgium (19 and 22 months, respectively; 3-year OS [95% CI] of 19% [16-24] and 27% [17-38], respectively) [27].

One-third of patients received a first line of therapy (i.e., SACT regimen) following the diagnosis of MPM. This is consistent with recent observations from the National Mesothelioma Audit in England and Wales for 2016–2018 [16]. While an increase in the use of chemotherapy after diagnosis (from 19% to 36%) was observed between 2008 and 2012 in England and Wales [33], there were no changes between 2013 and 2017. Based on national registries data covering the period from 2000 to 2012, the proportion of patients with MPM who received chemotherapy was similar in England, the Netherlands, Finland, and Italy at around 40% [23,24,34], but higher in Belgium (60%) [23]. The OS for patients treated with chemotherapy in our study was similar to that observed in Spain, Finland, Belgium, and the Netherlands [23,24,27,31].

In line with treatment recommendations, most patients initiating a first line received SoC with platinum (cisplatin or carboplatin) plus pemetrexed chemotherapy, the only SACT regimen approved for the first-line treatment of MPM in the UK at the time of this study [2,7,35]. Consistent with ESMO and BTS guidelines, the most common regimens used in second-line therapy in this study were SoC with platinum plus pemetrexed, or vinorelbine alone, with 19% of patients treated in a clinical trial [2,7].

This study has several strengths. First, it included a large, unselected real-world population of patients with MPM from clinical practice across England, and thus provides insight into treatment patterns and OS on a national level. Second, this analysis provides detailed clinical data covering all types of treatment. Finally, there is high confidence in the death data present in the dataset; these are obtained by linkage to the Office for National Statistics, which collect information on the date and cause of death from statutory death registration records.

However, this study also had limitations. First, ECOG PS, a key variable for treatment decision-making, was poorly reported in the CAS database and was missing for one-third of the patients, even when restricting to treated patients only. Considering other key variables, TNM staging was missing in 60.4% of patients over the study period, and histology was not otherwise specified in 43.3% of the patients. Thus, only limited conclusions can be reached for these subgroups. Second, data on smoking status, asbestos exposure, other malignancies, and comorbidities are not available in the CAS database. Third, despite the selection of surgical codes that are most likely related to radical surgery, patients may have received surgery with palliative intent. Therefore, the survival in this group may not reflect that in patients who are suitable for radical surgery. Fourth, patients diagnosed in 2017 had a maximum of 15 months of follow-up; therefore, any improvement in treatment outcomes occurring in these patients would not be properly captured in this study. Finally, there is the potential for immortal time bias when reporting OS by treatment received. Patients who received BSC could die at any point after diagnosis. Therefore, care should be taken when making comparisons between treatment groups.

This study is of importance because it allows us to start to compare local and timely developments in diagnosis and therapies between different countries. It identifies the difficulties in diagnosing MPM, confirming histological type and TNM staging. It will help us to define new diagnostic and treatment avenues such as the implementation of combination immuno-oncology therapy in patients with MPM.

In the Phase 3 CheckMate 743 trial, first-line immunotherapy with nivolumab and ipilimumab significantly prolonged OS compared with platinum plus pemetrexed for patients with unresectable MPM [36,37]. Additionally, single agent immunotherapy in second- and later-line has demonstrated promising clinical efficacy in Phase 2 trials of patients with relapsed MPM [18,38,39]. In October 2020, the US Food and Drug Administration approved the use of dual immunotherapy with nivolumab, an anti-PD1 inhibitor, and ipilimumab, an anti-CTLA-4 inhibitor, for the first-line treatment of patients with unresectable MPM [40]. In July 2021, the UK Medicines and Healthcare products Regulatory Agency also approved this dual immunotherapy as first-line treatment for patients with unresectable MPM [41]. Furthermore in 2021, England NHS issued interim treatment guidance during the COVID-19 pandemic, allowing single-agent nivolumab to be used for the treatment of patients with mesothelioma instead of second-line chemotherapy to reduce the risk of immunosuppression [42]. Future studies of the CAS database will investigate the impact of newer therapies, such as immunotherapy, on

the treatment patterns and survival of patients diagnosed with MPM.

Funding

This work was supported by Bristol Myers Squibb. IQVIA received funding from Bristol Myers Squibb to coordinate the data analyses presented in this manuscript.

CRediT authorship contribution statement

Paul Baas: Conceptualization, Methodology, Validation, Writing – review & editing. **Melinda J. Daumont:** Conceptualization, Methodology, Validation, Writing – review & editing. **Laure Lacoin:** Conceptualization, Methodology, Validation, Writing – review & editing. **John R. Penrod:** Conceptualization, Methodology, Validation, Writing – review & editing. **Robert Carroll:** Conceptualization, Methodology, Validation, Writing – review & editing. **Sudhir Venkatesan:** Conceptualization, Methodology, Validation, Writing – review & editing, Formal analysis. **Harveen Ubhi:** Conceptualization, Methodology, Validation, Writing – review & editing. **Alan Calleja:** Conceptualization, Methodology, Validation, Writing – review & editing. **Michael Snee:** Conceptualization, Methodology, Validation, Writing – review & editing.

Declaration of Competing Interest

Paul Baas is consultant for Bristol Myers Squibb (BMS) and has received funding for studies for his institute.

Melinda J. Daumont is an employee of BMS.

Laure Lacoin was contracted (paid) as a consultant by BMS to support the I-O Optimise initiative and is an employee of Epi-Fit.

John R. Penrod is an employee of BMS.

Robert Carroll is an employee of BMS.

Sudhir Venkatesan is an employee of IQVIA.

Harveen Ubhi is an employee of IQVIA.

Alan Calleja is an employee of IQVIA.

Michael Snee is an employee of IQVIA.

Acknowledgements

Professional writing and editorial assistance were provided by Lisa Jolly, PhD, of Parexel, funded by Bristol Myers Squibb.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2021.11.001.

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