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Impact of centralization of care for malignant peritoneal mesothelioma: A historical cohort study from the Dutch mesothelioma expert centers

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ABSTRACT

Background: Malignant peritoneal mesothelioma (MPM) is a rare and aggressive cancer that has a poor prognosis. An earlier population-based study found that the majority of Dutch patients do not receive anti-cancer treatment. In 2015, Dutch Malignant Mesothelioma care was centralized in two expert centers. We reviewed treatment patterns at these centers, to assess the impact of centralization of MPM care in the Netherlands.

Methods: Data from all patients referred to the Dutch MPM expert centers from 2014 to 2020, were retrospectively collected. Descriptive statistics regarding referrals, patient and tumor characteristics, and treatment patterns were provided. Population-based incidence rates were provided by the Netherlands Cancer Registry.

Results: From 2014 to 2020, 78 patients were referred to the Dutch Mesothelioma expert centers, of whom 32 were female (41%). From 2014 to 2017, 27 patients were referred, whereas 51 patients were referred from 2018 to 2020. This represents about 24% and 61% of the estimated population incidence, respectively. Treatment patterns were comparable between both periods. Between 2014 and 2018, 33% of patients underwent surgery, 44% systemic therapy, and 22% received best supportive care (BSC), while this was 29%, 37%, and 33% respectively from 2018 to 2020.

Conclusion: Centralization of care for patients with MPM resulted in an increase of annual referrals to the Dutch mesothelioma expert centers. While population-based incidence did not change during the study period, the absolute number of patients receiving treatment at our centers did increase. This might be considered a first important step towards better treatment for patients with this fatal disease.

1. Introduction

Malignant peritoneal mesothelioma (MPM) is a rare and aggressive cancer that primarily arises from the peritoneal lining. Comprising about 10–15% of cases, it is the second most common malignant mesothelioma (MM) location, after malignant pleural mesothelioma. Most cases are confined to the abdominal cavity, though a small percentage extends through the diaphragm into the thoracic cavity, or metastasizes to distant lymph nodes [1,2].

Abbreviations: MPM, Malignant Peritoneal Mesothelioma; MM, Malignant Mesothelioma; WDPMP, Well-Differentiated Papillary Mesothelioma of the Peritoneum; CRS, Cytoreductive Surgery; HIPEC, Hyperthermic Intraperitoneal Chemotherapy; PCI, Peritoneal Carcinomatosis Index; PD1, Programmed Cell Death Protein 1.

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Exposure to asbestos is the main risk factor for developing MPM, but other risk factors such as germline BAP1 mutations have recently been identified [3,4]. MPM can be stratified into three main histological subtypes: the epithelioid subtype is the most common (90%) with the best prognosis, while the sarcomatoid and biphasic subtypes comprise about 5% of cases each [5–7]. Well-differentiated papillary mesothelioma (WDPMP) and multicystic peritoneal mesothelioma are other, more rare subtypes, that most often present as indolent tumors and have good prognosis [8,9].

Currently, cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC), is considered to be the best available treatment for a selected group of MPM patients [10–12]. However, most patients are considered ineligible to undergo this major procedure, due to extent of disease, poor prognostic factors or performance status. Another treatment option is systemic chemotherapy with the anti-folate pemetrexed and a platinum derivative (e.g. carboplatin, cisplatin) [13–15]. More recently, several clinical trials have been initiated, exploring the possible use of various immunotherapies [16,17].

Earlier, we explored the incidence, treatment, and survival for patients with MPM in the Netherlands over a period of 25 years up to 2016 [18]. This study demonstrated that survival slightly improved over the years, though it is still poor. However, it also revealed that up to 60% of patients did not receive anti-tumor treatment. We stated that centralization of care for MPM in expert centers could benefit patients as patients would likely receive treatment more often. Centralization of cancer care has previously been demonstrated to increase the treatment rate, and improve survival in other solid tumors [19–21].

Since 2015, there have been two officially acknowledged mesothelioma expert centers in the Netherlands. These are the Erasmus MC Cancer Institute (EMC) in Rotterdam, and the Netherlands Cancer Institute (NKI) in Amsterdam. The aim of this study was to review treatment and survival of patients referred to the two Dutch expert centers in recent years, in relation to centralization of care for patients with MPM in the Netherlands.

2. Methods

2.1. Study design and participants

This retrospective cohort study included all MPM patients who were referred to the two Dutch mesothelioma expert centers from 2014 until 2020. At the Erasmus MC Cancer Institute, a phase 2 clinical trial (MESOPEC), investigating the safety and feasibility of adjuvant dendritic cell based immunotherapy (DCBI) after CRS-HIPEC for patients with MPM, was initiated in 2018 [16]. For the purpose of prompt patient accrual, it was agreed upon within the 'Dutch Peritoneal Oncology Group' (DPOG) to preferentially refer all MPM patients to this center from 2018 onward.

2.2. Data collection and approval

Data were retrospectively obtained from patients' electronic medical records. At the Erasmus MC, patient and tumor characteristics as well as data regarding treatment, treatment response, disease progression and overall survival were collected from patient charts. At the NKI patient and tumor characteristics were provided by the central research department, who performed a search in the Dutch Cancer Registry and original patients charts were reviewed by the local study investigators. The Dutch Personal Records Database was consulted in March 2021 for survival analyses. To describe the impact of centralization on a national level, the number of referrals was compared to the estimated population incidence of MPM, retrieved from the Dutch Cancer Registry (NKR). The NKR provides incidence numbers by identifying cancer patients in the Dutch Pathological Anatomical National Automated Archive (PALGA) and the National Registry of Hospital Discharge Diagnoses.

All data were collected and managed according to the latest European privacy regulations (General Data Protection Regulation (GDPR), EU 2016/679). The study was approved by both the EMC local ethics committee (MEC 2018–1286) and the Dutch NKI-AVL Institutional Review Board (IRBd20-176).

2.3. Statistical analysis

Because the number of referred patients increased upon starting the MESOPEC study, we tabulated characteristics of the study population according to their period of referral (2014–2017 vs 2018–2020). These groups were not statistically compared because of a lack of rationale. Continuous variables were presented as medians with interquartile ranges [IQR]. Categorical variables were shown as absolute numbers with percentages. Overall survival was calculated for all patients from date of diagnosis until death or last date of follow-up. Progression free (PFS) and disease free survival (DFS) were calculated from the start of treatment until progression or last date of follow-up. Comparison of survival between subgroups was not performed due to the large number of confounding factors caused by the retrospective design. To illustrate survival estimates, Kaplan Meier overall survival-curves were created using R version 3.5.1 (http://www.r-project.org). Other figures were also constructed using R. Statistical analyses were performed with Statistical Package for Social Sciences (SPSS) version 25.0.0.1 (IBM corporation, Armonk, NY, USA).

3. Results

3.1. Referrals

Between January 2014 and July 2020, a total of 78 patients with histologically proven MPM were referred to the EMC and NKI. The number of referrals markedly increased after starting the phase II MESOPEC trial, from about 5 to 9 cases per year between 2014 and 2017, to a total of 15, 20 and 16 referrals in 2018, 2019 and 2020 respectively (Fig. 1). National population based incidence did not increase during the study period, with a mean annual incidence of 28.7 cases (95%CI = 18.6–37.0). The proportion of referred patients compared to the population incidence, was 24% between 2014 and 2017, and 61% from 2018 to 2020, a more than two-fold increase.

3.2. Patient characteristics

Fifty-nine percent of patients were male and median age at diagnosis was 62.5 years (IQR 52–69). History of (occupational) asbestos exposure was confirmed for 19 patients (24%), and 55% percent of patients had no history of asbestos exposure. For 22% of patients, history of asbestos exposure could not be retrieved (Table 1).

3.3. Tumor characteristics

Prognostic factors, such as histological subtype, Ki67 index, lymph node metastases and peritoneal cancer index (PCI), a measure for peritoneal disease load, did not show major differences between both periods. Epithelioid histology was the most common subtype (85%), while 5% of patients presented with sarcomatoid histology and another 5% with biphasic histology. WDPMP was diagnosed in 2 patients (3%). For 3% of patients the histology was unknown. One patient was first diagnosed with WDPMP over 20 years ago. After initial surgery, the disease recurred after 15 years.

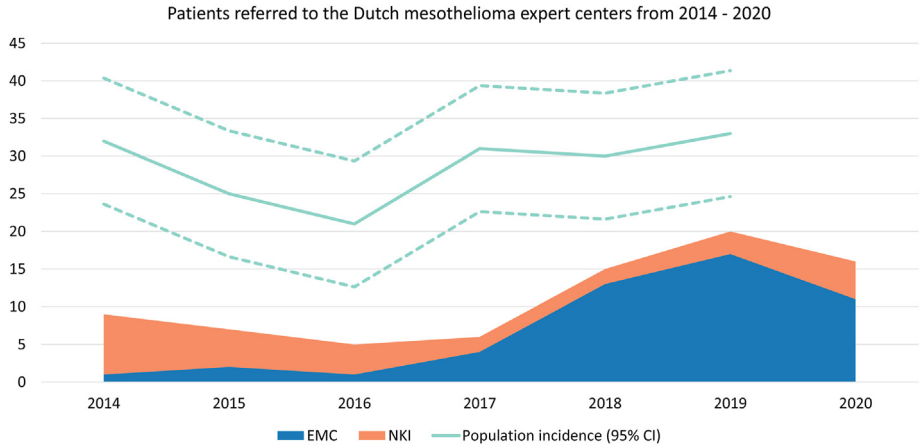

Fig. 1. Annual peritoneal mesothelioma referrals to Dutch mesothelioma expert centers MPM patients referred to the Dutch mesothelioma expert centers from 2014 to 2020. EMC: Erasmus MC Cancer Institute. NKI: Netherlands Cancer Institute.

Table 1
Patient and tumor characteristics.

	Referred from 2014–2017 (n = 27)	Referred from 2018–2020 (n = 51)	Total (n = 78)
Sex			
Female	12 (44)	20 (39)	32 (41)
Male	15 (56)	31 (61)	46 (59)
Age at diagnosis	64 [51.5–68]	62 [52–69]	62.5 [52–69]
Asbestos exposure			
Yes	6 (22)	13 (26)	19 (31)
No	19 (70)	23 (45)	42 (69)
Unknown	2 (7)	15 (29)	17 (22)
Histology			
Epithelioid	22 (81)	44 (86)	66 (85)
Biphasic	0	4 (8)	4 (5)
Papillary	1 (4)	1 (2)	2 (3)
Sarcomatoid	3 (11)	1 (2)	4 (5)
Unknown	1 (4)	1 (2)	2 (3)
Ki67 proliferation index	5 [2–20]	10 [5–20]	8 [5–20]
Unknown	10 (37)	11 (22)	21 (27)
Ki67 high vs. low			
Ki67 < 10%	7 (26)	21 (41)	28 (36)
Ki67 ≥ 10%	10 (37)	19 (37)	29 (37)
Unknown	10 (37)	11 (22)	21 (27)
Peritoneal Cancer Index (PCI)			
Total	34 [21–39]	28 [20–38]	30 [20–39]
Determined by radiology	27 [18–37]	22 [15–28]	22 [16–32]
Determined by Surgery	36 [30–39]	38 [29–39]	38 [29–39]
Lymph node metastases			
Yes	4 (15)	10 (20)	14 (18)
No	21 (78)	41 (80)	62 (79)
Unknown	2 (7)	0	2 (3)
Ascites			
Yes	23 (85)	37 (72)	60 (77)
No	4 (15)	14 (28)	18 (23)
BAP1 germline mutation			
Yes	2 (7)	2 (4)	4 (5)
No	0	8 (16)	8 (10)
Unknown	25 (93)	41 (80)	66 (85)

Categorical variables are provided as number with (percentage). Continuous variables are provided as median with [interquartile range]. Some percentages do not accumulate to 100% due to rounding.

This patient was treated with CRS-HIPEC, after which the disease recurred after 5 years. This time pathological examination showed invasive growth. Therefore the tumor was re-classified as a malignant epithelioid mesothelioma, rather than WDPMP. The patient was again treated with CRS-HIPEC.

Median proliferation index, determined by the percentage of Ki67 positive tumor cells, was 8 [IQR 4–20%]. Median PCI at diagnosis was 30 [IQR 20–39], based on 76 (97.4%) patients for whom PCI was available. Surgically determined PCI was available for 38 (48%) of patients. Median PCI was significantly higher when determined by surgery (i.e. diagnostic laparoscopy or laparotomy), compared to PCI determined by radiology (i.e. CAT scan). Median surgical PCI was 38 [29–39], whereas median radiographic PCI was 22 [16–32] ($p < 0.0001$). Ascites was present in 60 patients (76%). In 14 patients (18%) there were clinically suspected or pathologically confirmed lymph node metastases.

3.4. Treatment

A comprehensive overview of treatment for the entire population, as well as treatment per time period (i.e. 2014-2017 vs. 2018–2020) is provided in Fig. 2 and Fig. 3 respectively. Treatment was first categorized into three main groups: 1. Surgery, 2. Systemic treatment only, and 3. Best supportive care (BSC). Within these categories, subcategories were created illustrating the multimodality of most treatment strategies.

Most patients who received CRS-HIPEC, received some form of systemic therapy as well (79%), either as (neo) adjuvant or second line treatment after recurrence. Completeness of cytoreduction (CC-score) was assessed for 21 of 25 patients (86%) who underwent CRS-HIPEC. In nine patients (36%) complete cytoreduction was achieved (CC-0). Four patients (16%) had residual tumor nodules smaller than 2.5 mm (CC-1). In eight patients (32%), extensive residual disease was present after cytoreduction (CC-3). For five of these CC-3 patients, CRS-HIPEC was indicated for palliation. In the other two patients, the goal was to achieve complete cytoreduction. However, due to extensive small bowel involvement this was not feasible. Median progression free survival (PFS) from CRS-HIPEC was 23.1 months [IQR 5.6-NR months].

CRS-HIPEC was not considered feasible in most patients (70%). Poor performance status or comorbidity (22%) and irresectability of the tumor (30%) were the most common reasons. Biphasic or sarcomatoid histology was considered a contraindication in nine percent of patients (Fig. 2).

In total 40 patients (51%) received systemic chemotherapy at some point during treatment. The vast majority (95%) received pemetrexed combined with a platinum based agent (i.e. cisplatin, carboplatin, oxaliplatin). Median number of chemotherapy cycles was four (IQR 3–5). Median PFS of systemic chemotherapy was 6.2 months [IQR 3.4–22.8] (Table 2).

Anti-PD1 immunotherapy was given to 11 patients (14%), of whom six (55%) received nivolumab, four (36%) received pembrolizumab, and 1 patient (9%) received atezolizumab. One patient received immunotherapy as first line treatment, all others received immunotherapy as second line treatment. The median number of immunotherapy cycles was five (IQR 3–17). Eventually all patients developed disease progression. Median progression free survival after start of anti-PD1 immunotherapy was 3.7 months [IQR 2.1–5.8] (Table 2).

3.5. Survival

The survival of patients referred between 2014-2017 and 2018–2020 was comparable (Fig. 4a). The survival of patients with lymph node metastases was worse compared to patients without positive lymph nodes (HR 2.2 [95% CI: 1.03–3.8], Fig. 4b). Patients with a low ki67 index had better survival (median 58 months) compared to patients with a high ki67 index (median 9.7 months, HR 0.34 [95% CI 0.15–0.76], Fig. 4c).

4. Discussion

The aim of this study was to review the impact of centralization of care for malignant peritoneal mesothelioma (MPM) in the Netherlands. Therefore we reviewed referrals of, and treatment received by patients referred to the Dutch mesothelioma expert centers from 2014 to 2020. Officially, centralization took place in 2015, when both the Dutch Cancer Institute (NKI) and the Erasmus MC Cancer Institute (EMC) were officially accredited as mesothelioma expert centers by the Dutch Federation of University Hospitals (NFU). At first this centralization was mainly focused on pleural mesothelioma and peritoneal mestohelioma cases were mostly referred to one of seven CRS-HIPEC expert centers. However, by initiating a phase-II clinical trial for patients with MPM in 2018, centralization of care became truly effective in The Netherlands. For prompt patient accrual, it was agreed to refer all MPM patients to the Erasmus MC Cancer Institute. This caused a major boost in referrals to this expert center. We found a more than two-fold increase in the percentage of patients being referred to the expert centers, despite of the decreased number of referrals in 2020, likely caused by the COVID-19 pandemic. On the other hand, initiating a clinical trial would not have been possible without centralizing care, which illustrates the synergystic effect of centralization and clinical research with regard to patients being referred to expert centers. This positive feedback mechanism, where centralization

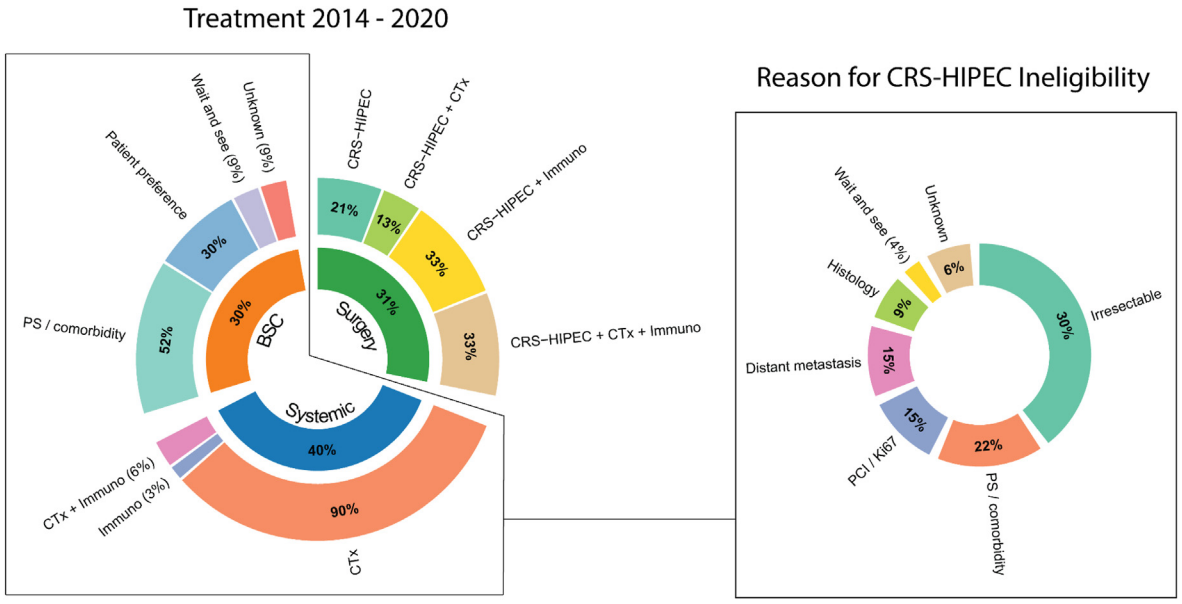

Fig. 2. Overview of treatment for peritoneal mesothelioma at the Dutch mesothelioma expert centers from 2014–2020. BSC: best supportive care. CRS-HIPEC: cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. CTx: systemic chemotherapy. Immuno: systemic immunotherapy. PS: performance score. PCI: peritoneal cancer index.

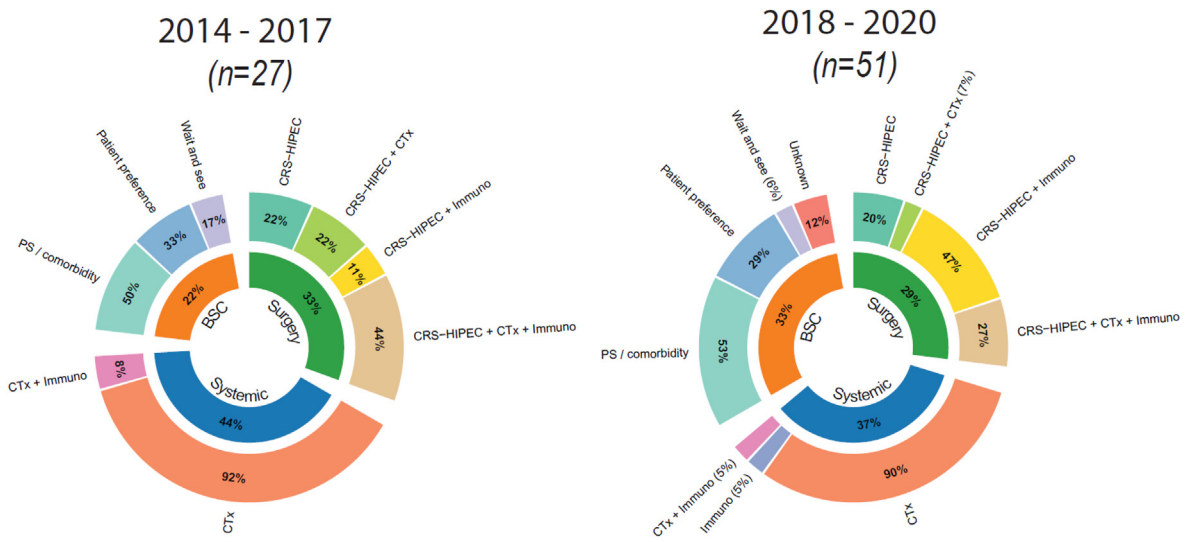

Fig. 3. Overview of treatment for peritoneal mesothelioma at the Dutch mesothelioma expert centers before and after centralization. BSC: best supportive care. CRS-HIPEC: cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. CTx: systemic chemotherapy. Immuno: systemic immunotherapy. PS: performance score.

Table 2
Treatment characteristics.

	N = 78
CCR-score	
CCR-0	9 (36)
CCR-1	4 (16)
CCR-2	0 (0)
CCR-3	8 (32)
Unknown	4 (16)
Palliative intent CRS-HIPEC	
Yes	6 (24)
No	16 (64)
Unknown	3 (12)
CRS-HIPEC median PFS	
Total	23.1 [5.6 – NR]
CCR-0	NR [33.1 – NR]
CCR-1	NR [1 – NR]
CCR-3	5.6 [4.6–16.8]
Type of chemotherapy	
Pemetrexed + Platinum	38 (95)
Gemcitabine + Platinum	2 (5)
Number of chemotherapy cycles	4 [4,5]
Type of anti-PD1 immunotherapy	
Nivolumab	6 (55)
Pembrolizumab	4 (36)
Atezolizumab	1 (9)
Number of immunotherapy cycles	5 [3–17]
Months of PFS from systemic treatment	
Chemotherapy	6.2 [3.4–22.8]
Anti-PD1 immunotherapy	3.7 [2.1–5.8]

Categorical variables are provided as number with (percentage). Continuous variables are provided as median with [interquartile range]. CRS = cytoreductive surgery, HIPEC = hyperthermic intraperitoneal chemotherapy, NR = not reached. Some percentages do not accumulate to 100% due to rounding.

stimulates research and this research stimulates patients being referred and treated, might improve the future management of this disease and might ultimately improve its outcome.

As centralization of care became truly effective in 2018, we studied treatment patterns before and after 2018. We found that treatment patterns at our centers remained comparable between both periods, though logically a slight increase in the proportion of patients receiving best supportive care (BSC) from 22% to 33%, was observed. In an earlier population based study, we found that between 1989 and 2018 there were no trends in MPM incidence, with a median of 0.18 cases per 100.000 person years RESR (revised European standard population rate) [22]. This study also showed that about one third of patients received anti-cancer treatment between 2013 and 2018, while about two-thirds received best supportive care only. Taking into account these steady population incidence rates, and comparing the observations of the current study to earlier observed treatment paterns, it appears that more MPM patients are eligible to undergo anti cancer treatment than earlier thought. Whether this will eventually result in better quality of life or better survival outcome can not be determined by this study. Nonetheless, centralization might be an important first step towards better treatment for MPM patients. Especially as there currently is no consensus on the optimal treatment for MPM. Systemic chemotherapy is the standard of care according to the Dutch mesothelioma guideline. However, in recent years the use of CRS-HIPEC has increased for patients that are considered eligible. The Dutch guideline on mesothelioma treatment is mainly based on studies in pleural mesothelioma that showed a survival benefit of platinum-doublet therapy, and extended access programs for peritoneal mesothelioma patients [13,14]. There are countries however, in which CRS-HIPEC is considered the golden standard, which is mostly based on retrospective series published over a decade ago [12,23,24]. These studies showed that CRS-HIPEC is feasible, and results in good prognosis for a selected group of patients, though the benefit of CRS-HIPEC for MPM patients has never been investigated in randomized trials. A major problem of CRS-HIPEC remains the fact that the majority of MPM patients are not eligible, and recurrence rates are high. Therefore new strategies are being investigated to tackle these problems. Le Roy et al. have investigated the use of bidirectional neoadjuvant chemotherapy (both intraperitoneal and systemic chemotherapy) [25]. They performed CRS-HIPEC in 50% of patients that were first considered ineligible due to extensive disease. Kepenekian et al. explored a similar strategy, but with pressurized intraperitoneal aerosol chemotherapy (PIPAC) combined with systemic chemotherapy [26]. They achieved similar results. To battle early recurrence, Sugarbaker et al. use normothermic intraperitoneal chemotherapy (NIPEC) as an adjuvant treatment. In a recent propensity mathced analysis they observed significantly improved survival for patients receiving NIPEC, with a five year OS rate of 70% [27].

For any treatment that is offered to MPM patients (surgical and/

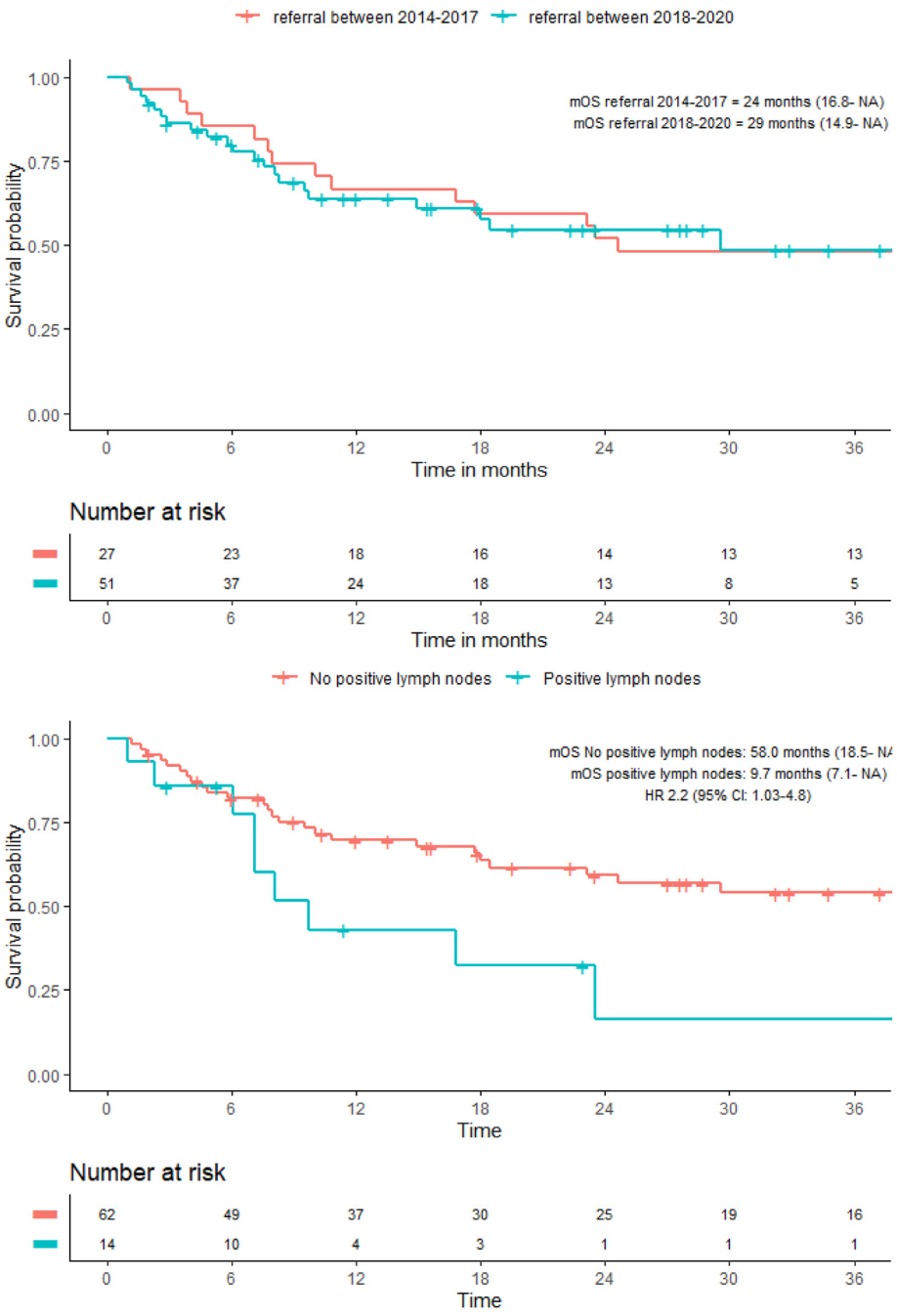

Fig. 4a–c. Kaplan Meyer overall survival curves for patients referred to the Dutch mesothelioma expert centers from 2014–2020 mOS: median overall survival. NA: not applicable. HR: hazard ratio. Ki67: marker of proliferation Ki67.

or systemic), patient selection is of great importance. Especially as both treatments are associated with considerable morbidity. However, selection of MPM patients who are eligible to undergo treatment is complex. Expert multidisciplinary assessment could provide a more tailored treatment plan with consideration for prognostic factors, comorbidity and patients' preferences. Centralization of care will likely improve this process and is considered an important measure to be able to provide high-quality care [28]. The 'Dutch cancer registry' (NKR) recently observed that survival outcomes for rare cancers trail behind on more common malignancies in the Netherlands [29]. They also recommended to centralize expertise for rare cancers and suggested this can lead to improved outcome.

Several prognostic factors have been described in literature that might facilitate selection for treatment. For example, the proliferation index of the tumor, represented by the Ki67 index, has been shown to be associated with OS both in pleural and peritoneal mesothelioma [30–33]. In the current study, patients with a low ki76 index had a better survival (Fig. 4C), though the independent effect could not be assessed in multivariable analysis due to patient and treatment heterogeneity. A recent study by Belderbos et al. investigated the ki67 index in patients with pleural mesothelioma

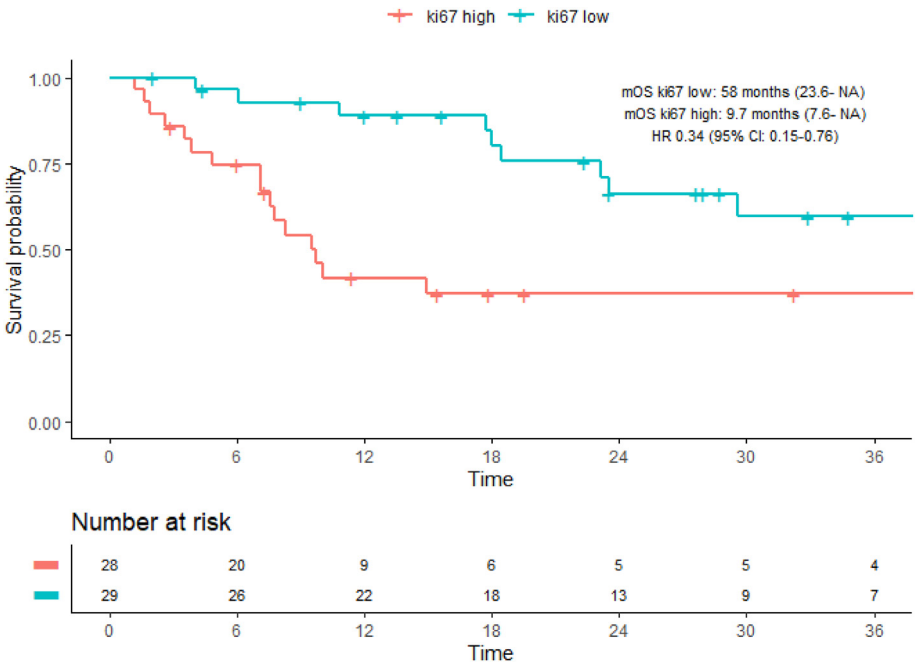

Fig. 4a–c. (*continued*).

[34]. They also found that Ki67 could be utilized as a prognostic marker for patients with pleural mesothelioma undergoing extended pleurectomy/decortication. This is especially useful for identifying patients who are unlikely to benefit from surgery. They used a cut off value of 10% Ki67 positive cells, and found that tumors with Ki67 indexes below 10% resulted in better prognosis after surgery. Kusamura et al. used the same cut off and found a similar outcome for patients with MPM [31].

Other established prognostic factors are tumor histology and lymph node status. Patients with epithelioid MPM show better survival, when compared to patients with biphasic or sarcomatoid histology [6,11,35,36]. The same applies to patients with lymph node metastases. Nodal dissemination has shown to be of great prognostic significance and has been adopted in a proposed TNM classification by Yan et al. [36] In a study by the same author, median survival after CRS-HIPEC for patients with positive lymph nodes was 6 months, and 2-year survival was 0% [37]. Others have shown similar results [1]. Preferably, lymph node status is meticulously assesed for patient selection to prevent futile treatment.

A feature that results in favorable prognosis, is being a carrier of a germline BAP1 mutation. Baumann et al. even showed that patients with a germline BAP1 mutation, have a sevenfold increased long term survival compared to other MPM patients [38]. In our cohort, four patients (5%) were identified as carrier of such a mutation. Patients are not routinely tested for this mutation, but only by indication (such as a history of earlier malignancies or diagnosis at a very young age). The exact frequency of MPM patients that carry this germline mutation is unknown. It could have implications for choice of treatment and therefore it should be subject of further study.

The extent of peritoneal involvement is also of prognostic significance. This is represented by the PCI which varies from 0 – no peritoneal lesions, to 39 – confluent or >5 cm lesions in all regions of the abdomen. For systemic therapy there are no data regarding the extent of disease in relation to survival, while for surgical treatment there is a clear relation between the PCI and survival [11,36]. In our cohort, PCI determined by radiology was significantly lower than PCI determined by surgery. This also has been reported for peritoneal metastases from colorectal cancer [39,40]. Small lesions are not detected by CAT or MRI scans, likely resulting in an underestimation of the true PCI. Therefore, we first performed diagnostic laparoscopy (DLS) in every patient that was considered for CRS-HIPEC.

As with every study there are limitations to the current work. Due to the retrospective data collection, there were missing data for various variables. Therefore it was not possible to perform unbiased comparative analyses between subgroups. For this reason we only provided descriptive statistics. Also, detailed population based treatment data were unavilable. Therefore we could not compare treatment at our centers with the population based treatment patterns, making it difficult to truly assess the impact of centralization. On the other hand, we were able to compare treatment at our centers with population based data that were reviewed earlier, which indicated that more patients undergo treatment when refferred to an expert center. Also, we could only estimate the proportion of referred patients compared to the population incidence, as recent incidence rates were yet unavailable. Moreover, patients diagnosed in a certain year might be referred in the following year, which made it impossible to compare the number of annual referrals with the annual population incidence (which was provided completely anominized). Therefore it can not be fully ruled out that the increased number of patients referred to our centers is caused by an increase of MPM incidence. However, earlier work showed that from 1989 to 2018 MPM incidence in the Netherlands did not significantly change, thereby making this scenario highly unlikely [22].

5. Conclusion

Centralization of care for patients with MPM in The Netherlands has provided the opportunity to perform clinical trials and has resulted in an increase of referrals to the Dutch mesothelioma expert centers. While population-based incidence did not change during the study period, the absolute number of patients receiving treatment at our centers did increase. Whether this will result in better quality of life or prognosis, remains to be determined.

Nonetheless, centralization of care might be considered as a first important step towards better treatment for patients with this fatal disease.

CRediT authorship contribution statement

Job P. van Kooten: Data acquisition, Quality control of data and algorithms, Formal analysis, interpretation, Statistical analysis, Manuscript preparation, Writing – review & editing. **Cornedine J. de Gooijer:** Data acquisition, Quality control of data and algorithms, Formal analysis, interpretation, Statistical analysis, Manuscript preparation, Writing – review & editing. **Jan H. von der Thüsen:** Data acquisition. **Arend G.J. Albers:** Data acquisition. **Max J. Lahaye:** Data acquisition. **Kim Monkhorst:** Data acquisition. **Jacobus A. Burgers:** Manuscript preparation, All authors, Conceptualization, Study design, Writing – review & editing. **Eva V.E. Madsen:** Quality control of data and algorithms, Manuscript preparation.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JB reports reimbursements for his institution (Netherlands Cancer Institute) outside the submitted work from Roche, AstraZeneca and Boehringer Ingelheim. JA reports grants outside the submitted work from Amphera and Roche, ownership interest (including patents) from Amphera, and advisory roles for Amphera, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, MSD and Roche, outside the submitted work. All other authors declare no conflict of interest.

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