Review Article

Treatment-associated quality of life in patients with malignant pleural mesothelioma

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Abstract: The symptomatic burden of malignant pleural mesothelioma (MPM) remains unsurmountable due to not only the insidious nature of its development and abrupt nature of progression, but also due to our relatively limited capabilities to treat it or even slow down its progress and the associated toll such a disease has on an individual's overall quality of life (QoL). The majority of cases are linked to occupational asbestos exposure and arise after a latency period of up to 40 years. Overall survival (OS) drastically varies across studies and treatments, with pooled analyses approximating 13 months post-diagnosis median survival and 10% 5-year survival. As a result of its very grim prognosis and significant deterioration in QoL, treatment strategies began to incorporate the effects of a particular treatment on a patient's QoL. Treatment is often multimodal and consists of surgery, chemotherapy, and radiotherapy (RT). Recent investigations have utilized standardized QoL measurement tools, such as the Lung Cancer Symptom Scale for mesothelioma (LCSS-Meso) and the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30), to make studies more comparable so treatments and their effects can be better understood and expanded on. Overall, surgery remains the mainstay of therapy with recent studies finding pleurectomy and decortication leads to improved QoL when compared to extrapleural pneumonectomy (EPP). Chemotherapy and immunotherapy are the most rapidly advancing segment of trimodality therapy due to technological advances which have improved development, synthesis, administration, and efficacy. RT's impact on QoL continues to be debated despite its significant palliative potential due to a high risk of radiation toxicity even after approach, dose, and timing modifications. Given the complexities in MPM treatment, understanding the standardized data generated by these questionnaires and investigating their generalizability in assessing patient QoL will be crucial in the advancement of MPM treatment.

Keywords: Malignant pleural mesothelioma (MPM); quality of life (QoL); surgery; chemotherapy; radiotherapy (RT)

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Introduction

Malignant pleural mesothelioma (MPM) is notorious for its aggressive nature and poor prognosis (1,2). MPM was first associated with asbestos exposure in 1960 by Wagner *et al.* with recent studies estimating 70% of cases occurring in patients with occupational exposures (3,4). MPM patients typically present with dyspnea, weight loss, fatigue, and/or non-pleuritic chest pain with decreased breath sounds at the lung bases on exam. Eventual development of a scoliosis towards the side of the lesion occurs during late-stage disease. As a result, patients inevitably experience considerable debilitation and significant detriments to quality of life (QoL).

Diagnosing MPM poses several challenges. Beyond identifying characteristic symptoms and asbestos exposure, a 10–30-year latency period between asbestos exposure and symptomatic presentation delays diagnosis to late in the disease course when the malignancy is no longer resectable, resulting in reduced post-diagnosis overall survival (OS) (5). Median survival varies widely based upon MPM subtype and ranges from 18–29 months with an estimated 20% 5-year survival (6-11).

MPM treatment depends on initial staging, histological subtype, and patient operability (12). Treatment goals focus on median survival and symptomatic burden reduction rather than on more advanced outcome measures, such as remission rates, due to MPM's aggressive nature, heterogeneity, indolent tendencies, and predilection for older patients, all of which complicate treatment and contribute to a shorter median survival time and lower 5-year survival (13-15). In conjunction with the discordance surrounding treatments and therapies, treatment-associated QoL has become a larger focus of MPM research (16-19).

This review discusses MPM and the changes in QoL associated with its treatment.

Assessing QoL in MPM

QoL in MPM has been reported since the 1990s, however, the use of different questionnaires, metrics, endpoints, and evaluation strategies led to increased inter-study heterogeneity and unvalidated methodologies obfuscated comparisons (20-23). In 2004, Hollen *et al.* developed the first widely-used instrument for formally assessing QoL in MPM patients by modifying the Lung Cancer Symptom Scale for mesothelioma (LCSS-Meso) (24). The LCSS-Meso demonstrated good internal consistency for the eight-item measure (alpha =0.86) and reasonable five-item observer consistency (alpha =0.66), a high degree of convergence between patient and observer forms (r=0.57), and well-supported validity through the prediction of survival time, time to progression, and tumor response rate which, along with the total LCSS-Meso score, demonstrated statistically significant predictability (P<0.005) (25). Nowak *et al.* evaluated the practicality of utilizing the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) and Lung Cancer Module (QLQ-LC13) and found them to be both practical and valid through the demonstration of a strong relationship between patient survival and a baseline composite pain score derived from both the QLQ-C30 and QLQ-LC13 (P=0.02) (26). Similarly, the Functional Assessment of Cancer Therapy-Lung (FACT-L), another patient-reported outcome measure (PROM) originally modified for lung cancer was validated for mesothelioma through factor analysis (27-29). The FACT-L has also been found to be sensitive to changes in performance status (PS) over time (P=0.03) (27).

In 2009, the Food and Drug Administration (FDA) published guidelines for the development of purpose-specific PROMs for use during clinical trials to support medical product labeling with a strong recommendation to include direct input from the intended patient population in the PROMs' development (30). This prompted Williams *et al.* to adapt the MD Anderson Symptom Inventory for use in patients with MPM (MDASI-MPM) with direct patient input through 20 qualitative MPM patient interviews regarding experiences of disease, treatment, and overall burden (31). In a follow-up study, Mendoza *et al.* found the MDASI-MPM had good internal consistency and reliability as estimated by the high Cronbach coefficient alpha values computed at both baseline and during treatment (all >0.88 and 0.91, respectively) (32). Mendoza *et al.* also demonstrated the validity of the MDASI-MPM through the strong correlation observed between MDASI-MPM subscales and LCSS-Meso scores (P<0.001 and r>0.70 for all comparisons) (32). Nevertheless, as an inherent consequence of these tools' recent developments and relative rarity of MPM, the transition from questionnaire development to publication of results in sizeable prospective studies has only recently begun.

The impact of surgery on QoL in MPM

The earliest documented surgery for mesothelioma was a

right thoracotomy tumor resection performed by Ehrenhaft *et al.* on November 23, 1927 on a 25-year-old female who eventually passed on April 22, 1928 due to a postoperative empyema (33). Subsequent attempts by others produced similarly grim results until 1976 when Butchart *et al.* reported extrapleural pneumonectomy (EPP) significantly increased OS in epithelial type MPM 6 months post-operatively relative to mixed epithelial and mesenchymal (P<0.01) and 12 months post-operatively relative to all patients with stage 1 tumors (P<0.05) and type A MPM tumors at 2 years post-operatively relative to all patients of epithelial type (P<0.05) (34-38). However, Butchart *et al.* also reported 31% operative mortality and subsequent studies were unable to corroborate the survival benefits published by Butchart *et al.* (34,39-42). The discordance in observations is attributed to MPM's low incidence rates, small sample sizes, high selection bias, surgical approach, varying inclusion/exclusion criteria, inadequate independent variable isolation, the aggressive nature of MPM dissuading patients from undergoing standard of care rather than potentially efficacious treatment, etc. (39,43,44).

As QoL became a more central focus, palliative interventions, such as pleurectomy/decortication (PD), garnered attention for their efficacy, safety, and potential utility in treatment. Indeed, in their investigation of PD for palliation in 100 mesothelioma patients (44% subtotal and 56% total PD), Soysal *et al.* found 100% of patients with dyspnea and cough and 85% of patients with chest pain at baseline experienced marked symptomatic improvement post-operatively and 96% of pleural fluid accumulations became controlled, resulting in a 17-month median survival with 99% of patients returning to their daily lives after discharge (45).

The role of surgery as the mainstay of treatment for mesothelioma was repeatedly corroborated by various groups (42,46-48). In 1999, Sugarbaker *et al.* published results on 183 MPM patients treated from 1980 to 1997 with trimodal therapy (EPP with adjuvant chemoradiation therapy) showcasing a median follow-up of 13 months, 38% survival at 2 years, 15% survival at 5 years, and median survival of 19 months (48). Through univariate analysis, Sugarbaker *et al.* identified three prognostic variables associated with improved survival; epithelial cell type (52% 2-year survival, 21% 5-year survival, and 26-month median survival, P=0.0001), negative resection margins (44% 2-year survival, 25% 5-year survival, and 23-month median survival, P=0.02), and negative extrapleural nodes (42% 2-year survival, 17% 5-year survival, and 21-month median survival, P=0.004) with the 31 patients with all 3 variables demonstrating superior survival (68% 2-year survival, 46% 5-year survival, and 51-month median survival, P=0.013) (48). Cox proportional hazard modeling estimated an increased risk of death for nonepithelial cell type [odds ratio (OR) =3.0; 95% confidence interval (CI): 2.0–4.5; P<0.0001], positive resection margins (OR =1.7; 95% CI: 1.2–2.6; P<0.0082), and positive extrapleural nodes (OR =2.0; 95% CI: 1.3–3.2; P<0.0026) (48). Similarly, In their study of 302 patients treated between 1989 and 1998, Aziz *et al.* found the 191 patients treated only through palliative care had an average survival of 8.9 months, the 60 patients treated only surgically had an average survival of 13 or 14 months (EPP *vs.* PD, respectively), and the 51 patients treated with adjunctive intrapleural and systemic post-operative chemotherapy averaged a 35-month survival (46). Weder *et al.* investigated the utility of neoadjuvant chemotherapy followed by EPP and assessed QoL using the Rotterdam Symptom Checklist (RSCL). In their study of 61 MPM patients, 45 were operable and underwent EPP following neoadjuvant chemotherapy which resulted in 37 achieving R0 or R1 and eight achieving R2 with a median survival of 19.8 months for all 61 patients and 23 months for the surgical patients while maintaining QoL (47). Overall, Weder *et al.* not only demonstrated the viability of neoadjuvant chemotherapy followed by EPP in improving survival, but also provided a standardized metric which showcased patients' QoL was maintainable despite undergoing radical surgery (47).

In their multi-center, phase II clinical trial, Ribi *et al.* assessed standard *vs.* individualized [Schedule for the Evaluation of Quality of Life-Direct Weighting (SEIQoL-DW)] QoL measurement tools in 61 MPM patients undergoing trimodal therapy with neoadjuvant chemotherapy, EPP, and adjuvant radiation therapy (49). Ribi *et al.* concluded that, despite a moderate correlation, the two instruments are not interchangeable and RSCL is favorable for MPM as it provides information related to disease course and treatment whereas SEIQoL-DW's patient-nominated and weighted QoL domains make its results less generalizable (49). The data collected by Ribi *et al.* increased skepticism for EPP in MPM as it was a phase II clinical trial that employed two QoL tools that both demonstrated stable QoL throughout chemotherapy only to be followed by immediate, clinically significant deterioration in QoL following EPP, mild interval improvement, and overall lower-than-baseline scores by the end of the study, indicating deterioration was likely a long-term effect of surgery (49). Schipper *et al.*

found EPP (n=73) resulted in a significantly longer median survival (16.0 months) than subtotal PD [n=34; 8.1 months; hazard ratio (HR) =1.62; P=0.04], exploration only (n=22; 6.8 months; HR =1.97; P=0.01), or biopsy alone (n=146; 9.2 months; HR =1.51; P=0.02) while total PD (n=10) had the longest, albeit clinically insignificant, median survival (17.2 months; HR =0.74; P=0.50) with lower mortality and major complication (0% and 20%, respectively) rate than EPP (8.2% and 50.7%, respectively) (50). Flores *et al.* analyzed outcomes of 663 MPM patients who either underwent EPP or PD between 1990 and 2006 and found PD resulted in significantly longer median survival (16 *vs.* 12 months, P<0.001) with multivariate analysis demonstrating an EPP-to-PD HR of 1.4 (P<0.001) after controlling for stage, histology, gender, and multimodality therapy (51).

Rena and Casadio reported on a group of 77 MPM patients who underwent EPP (n=40) or PD (n=37) as part of a trimodal regimen with platinum-based chemotherapy and external beam radiation of the entire hemithorax for the EPP cohort (45–60 Gy) and of the surgical incisions for the PD cohort (21 Gy) (52). Twenty-five/40 (62%) EPP patients had major post-operative complications with 2/40 (5%) EPP patients dying within 14 days of surgery and median post-operative hospitalization of 9 days while 9/37 (24%, P=0.002) PD patients experienced major post-operative complications with 0 (0%) deaths and 7-day median post-operative hospitalization (52). Rena and Casadio also found PD patients had an insignificantly longer median survival than EPP patients (25 *vs.* 20 months, P=0.98) in addition to a significantly longer median residual time to death after recurrence detection (14 *vs.* 9 months, P=0.001) (52). QoL measurements per EORTC QLQ-C30 showed no significance difference between surgical interventions at baseline and patients only reported mild to moderate dyspnea with minimal cough and pain, however, patients in the PD cohort had significantly better QoL in 5/7 parameters measured 6 and 12 months after surgery (52).

In the Mesothelioma and Radical Surgery (MARS) feasibility study, Treasure *et al.* evaluated clinical outcomes and QoL of patients undergoing EPP *vs.* patients not undergoing EPP (53). After adjusting for sex, histological subtype, stage, and age, the HR for OS between patients assigned to EPP and no EPP was 2.75 (95% CI: 1.21–6.26; P=0.016) (53). Additionally, QoL assessment via EORTC QLQ-C30 and QLQ-LC13 demonstrated no significant difference between the two cohorts, with overall study findings suggesting not only does EPP offer no survival benefit or QoL improvement, but also it possibly harms patients (53).

The safety and tolerability of PD have been further corroborated in several studies with recent efforts investigating its utility in subpopulations of MPM patients in order to more optimally stratify surgical candidates likely to benefit (18,54-57). Recent studies investigated the association between PS and surgical impact on QoL (16,55,58). Mollberg *et al.* conducted a prospectively investigated study on the impact of radical PD (removal of parietal and visceral pleura, dissection in fissures and resection of hemidiaphragm with prosthetic reconstruction, partial or total pericardiectomy, and excision of previous surgical tracts in skin and subcutaneous tissue) on QoL in PS 0 MPM patients (n=16, 57.1%) *vs.* PS 1 (n=12, 42.9%) using EORTC QLQ-C30 up to 9 months after surgery (16). PS 1 patients had significantly worse scores in global health QoL (P=0.049), physical function (P=0.009), and role function (P=0.018) as well as worse overall symptomatic burden such as fatigue (P=0.027), pain (P=0.012), dyspnea (P=0.004), appetite loss (P=0.002), and financial difficulties (P<0.001) at baseline when compared to PS 0 patients (16). However, PS 1 patients also had significant improvement in global QoL (+19.4, P=0.038) and fatigue (–21.3, P=0.050) at 5–6 months relative to baseline whereas the PS 0 cohort experienced no significant changes (16). A similar trend was observed at 8–9 months; PS 0 patients had only improved in fatigue (–21.2, P=0.026) relative to baseline while PS 1 patients reported improvements in global QoL (24.2, P=0.009), dyspnea (–13.1, P=0.048), and appetite loss (28.6, P=0.050), suggesting PD does not negatively impact QoL in asymptomatic patients and can provide significant improvement in QoL in patients with high symptomatic burden (16).

Burkholder *et al.* examined the association between changes in QoL and pulmonary function tests (PFTs) after extended PD (EPD) (55). QoL was assessed with the EORTC QLQ-C30 pre-operatively and up to 8 months post-operatively and PFTs were obtained prior to surgery and 5–7 months post-operatively and compared according to baseline PS (55). 36 patients were enrolled, 17 PS 0 and 19 who were either PS 1 or 2 at baseline which translated to PS 1 and 2 patients at baseline having significantly worse global health QoL, physical and role functioning, and symptomatic burden (all P<0.05) (55). Results showed EPD did not improve overall QoL and negatively impacted forced vital capacity (P=0.001), forced expiratory volume

in 1 second (P=0.002), total lung capacity (P=0.0006), and diffusion capacity for carbon monoxide (P=0.003) in PS 0 patients (minimally symptomatic at baseline). However, in PS 1 or 2 patients (symptomatic at baseline), EPD significantly improved global health QoL, all functional domains, and symptom burden as early as 4 months with continued progression at 7–8 months but did not affect pulmonary function, suggesting the improved QoL may have been due to preserved pulmonary function (55).

Subsequent study documenting longer post-operative periods corroborated improvements in QoL of PS 1 and 2 patients following PD in addition to finding non-epithelioid histology with larger tumoral burden and worse QoL at baseline experienced QoL improvement following PD (58). These results suggested, in addition to extending life and improving QoL for patients with favorable characteristics, PD also improves QoL for patients with unfavorable characteristics (58). Thus, despite PD not improving survival in patients with non-epithelioid histology and high tumoral burden, the significant improvement in QoL PD offers justifies a reassessment of surgical candidacy exclusion criteria (58).

A meta-analysis conducted by Magouliotis *et al.* of 18 studies evaluating long-term outcomes of PD and EPP from 1980 to 2022 documenting 4,852 MPM patients revealed EPP (n=2,156) resulted in significantly higher 30-day mortality (OR =2.70; 95% CI: 1.3–6.01; P=0.009) and shorter median survival when compared to PD (n=2,696; weighted mean difference =–4.55; 95% CI: –6.05 to –3.04; P<0.001) (59).

The impact of chemotherapy on QoL in MPM

Twenty mg of nitrogen mustard was instilled into a 30-year-old male's thoracotomy tube in four daily installments with each instillation followed by, "*…the patient [being] rolled back and forth to ensure dispersal of the drug*" was the first chemotherapy regimen prescribed for MPM in 1960 (60). The patient was evaluated for more than a year, and at last follow-up, "*…his appetite was excellent and he was exercising with barbells to increase his strength*" (60). Subsequent trials implementing nitrogen gas did not pan out, and by 1980, the arsenal of chemotherapeutics trialed as adjuvant therapies for MPM grew to include methotrexate, vincristine, cyclophosphamide, doxorubicin, mitomycin C, hydroxyurea, platinum, actinomycin D, 5-fluorouracil, and radioactive gold (^{198}Au), however, none yielded positive results and all patients had nausea, vomiting, and alopecia with 78% of patients dying as a direct complication of local disease despite aggressive chemotherapy (61,62). Ensuing single-agent chemotherapy studies typically demonstrated a response rate <20% (63-67). Regimens using combination chemotherapy yielded similarly grim results (68-73).

In 1992, a phase II study of 21 patients with tumor-node-metastasis stage III or IV MPM using cisplatin and gemcitabine by Byrne *et al.* demonstrated a 47.6% response rate (n=10) with 9/10 responders and 3/9 non-responders reporting symptomatic improvement (OS =41 weeks) (74). However, the inoperability of these patients, advanced state of disease, small sample size, and lack of formal change-in-symptomatic-burden measurement made comparison of treatment efficacy relative to other regimens infeasible (74). These findings (74) was corroborated by the same group in a follow-up 2002 phase II study (21) with the addition of QoL and PFTs on 52 patients. Median survival was 17.3 months with 17 patients (33%) demonstrating partial response, 31 patients (60%) having stable disease, and 4 patients (7%) experiencing disease progression (21). No significant changes were observed in FVC, however, when stratified according to response to therapy, responders experienced significant improvement in FVC compared to baseline (P=0.002) (21). Likewise, QoL did not change significantly from baseline unless stratified by response, in which case responders demonstrated a significant improvement in EORTC QLQ-C30 global QoL (P=0.006) during chemotherapy that failed to persist after cessation (21).

Steele *et al.* conducted a phase II study of 29 patients with MPM stages I–IV using vinorelbine assessing pre- and post-treatment QoL using the RSCL (20). Regarding psychological well-being, lung cancer symptoms, other physical symptoms, and activity, RSCL scoring showed 60%, 50%, 50%, and 0% of patients, respectively, reported improvements after completing three cycles of vinorelbine while 30%, 30%, 50%, and 60%, respectively, reported worsening with an overall median survival of 10.6 months after treatment initiation (20).

A landmark phase III study by Vogelzang *et al.* assessed the utility of pemetrexed with cisplatin *vs.* cisplatin alone in 456 patients and found pemetrexed with cisplatin yielded a median survival of 12.1 *vs.* 9.3 months for cisplatin alone (P=0.020) (75). The combination arm also had a significantly longer median time to progression than the cisplatin alone group (5.7 *vs.* 3.9 months, P=0.001) in addition to a significantly higher response rate (41.3% *vs.* 16.7%, P<0.0001) (75). The combination regimen was also

improved with the addition of folic acid and vitamin B12 which lead to a significant reduction in toxicities of the combination regimen (75).

In an international, randomized phase III study of cisplatin with or without raltitrexed, Bottomley *et al.* implemented the EORTC QLQ-C30 to assess treatment-related symptoms and QoL in 250 patients and found the combination arm to be superior with regard to OS with a mean and 1-year survival of 11.4 (95% CI: 10.1–15) and 46% *vs.* 8.8 months (95% CI: 7.8–10.8) and 40%, respectively (P=0.048) (76). Both groups demonstrated similar reductions in QoL relative to a reference population at baseline with a significant increase in fatigue in both groups (P=0.010) and a clinically significant improvement in dyspnea (P≤0.001) without clinically meaningful differences in other QoL aspects or symptom burden by the study's endpoint, suggesting treatment did not overall further hinder QoL and may have stabilized progression of symptoms (76).

Muers *et al.* conducted a randomized trial on 409 patients on the impact of chemotherapy consisting of either mitomycin, vinblastine, and cisplatin (MVP) or vinorelbine on survival and QoL in patients treated via active symptom control (ASC); i.e., holistic care involving regular specialist follow-up, structured assessments of physical, psychological, and social health. and treatments such as palliative radiotherapy (RT) (77). Results demonstrated no significant survival for chemotherapy plus ASC compared to ASC alone (P=0.29). When each chemotherapy regimen plus ASC was compared to ASC-alone independently, results showed vinorelbine plus ASC had an insignificantly longer OS when compared to ASC alone (P=0.08; HR =0.80; 95% CI: 0.62–1.02) by approximately 2 months (7.6 *vs.* 9.6 months) (77).

Lang-Lazdunski *et al.* prospectively studied the utility of hyperthermic pleural lavage in 36 patients undergoing multimodality therapy consisting of PD followed by hyperthermic pleural lavage, prophylactic RT, and adjuvant chemotherapy between 2004 and 2010 (78). Intraoperative pleural lavage was done using 5–6 L of 40–41 ℃ water mixed with 10% povidone-iodine and allowed to bathe the lungs for 5 minutes 3 times, RT consisted 21 Gy in 3 fractions at 4–6 weeks, and chemotherapy consisted of gemcitabine and cisplatin up until 2007 and pemetrexed and cisplatin onwards (78). Median survival was 24 months (95% CI: 18.5–29.4) with 91.7% 1-year survival and 61% 2-year survival (78). An expanded study was conducted by the same group corroborated these findings (54).

Buikhuisen *et al.* conducted an open-label, multicenter, randomized phase III study assessing thalidomide's antiangiogenic effects in hindering MPM's spread after first-line chemotherapy (NVALT 5) (79). No benefit was observed in the thalidomide group when compared to ASC in regard to physician-reported disease progression, patient deaths, or median time to progression (79).

Arnold *et al.* prospectively evaluated chemotherapy's impact on QoL using results from the multicenter SWAMP trial in which 73 MPM patients were split into 58 patients treated with pemetrexed and cisplatin/carboplatin and 15 who received best supportive care (BSC) (80). QoL was evaluated via EuroQoL 5-Dimension Scale Questionnaire (EQ-5D), EORTC QLQ-C30, and EORTC QLQ-LC13. The chemotherapy group experienced maintenance of QoL while BSC resulted in worsening dyspnea, pain, and overall QoL (P=0.006) as measured via EQ-5D (80). However, when evaluated using the arguably more patient population-appropriate EORTC QLQ-C30 and QLQ-LC13, both groups experienced significant worsening in global health, physical function, and fatigue while only the chemotherapy group experienced significantly worsening social function, nausea, vomiting, alopecia, and sore mouth while the BSC group experienced worsening dyspnea and arm pain only (all P<0.01) (80). Patients with non-epithelioid histological subtype treated with chemotherapy also experienced a significant worsening in overall QoL even when evaluated using the EQ-5D (80). Furthermore, the chemotherapy group was overall younger (median ages of 69 *vs.* 78 years) and had a larger proportion of PS 0 patients (29% *vs.* 13%), both factors repeatedly shown to be not only prognostic of outcomes, such as survival and tolerance of therapy, but in the case of PS, one of three main clinical factors (PS, histological subtype, and tumor size) in MPM management with PS of 2 often used as an exclusion criterion (12,39,43,81-83).

The impact of immunotherapy on QoL in MPM

Nowak *et al.* conducted DREAM, a recent multicenter, single-arm, phase II trial investigating combination cisplatin, pemetrexed, and durvalumab, an anti-PD-L1 antibody, in 54 patients with a primary endpoint of progression-free survival (PFS) at 6 months (84). Thirty-one out of 54 patients (57%; 95% CI: 44–70%) met the primary endpoint with an overall median PFS of 6.9 months (95% CI: 5.5–9.0) by modified Response Evaluation Criteria in Solid Tumors (mRECIST) and median OS of 18.4 months (95% CI: 13.1–24.8) (84).

In CheckMate 743, an open-label, randomized, phase III study across 103 hospitals and 21 countries, Baas *et al.* assessed the utility of nivolumab plus ipilimumab in previously untreated, histologically confirmed, unresectable MPM (11). Six hundred and five ultimately eligible patients were randomized to nivolumab plus ipilimumab (n=303) or standard of care chemotherapy (n=302) consisting of platinum and pemetrexed plus cisplatin or carboplatin (11). Interim analysis in April of 2020 demonstrated significantly longer median survival in the nivolumab plus ipilimumab than in the chemotherapy group [18.1 (95% CI: 16.8–21.4) *vs.* 14.1 months (95% CI: 12.4–16.2), P=0.0020] (11). Subsequently, nivolumab plus ipilimumab was approved by the FDA for use in MPM patients in October of 2020 (11).

Scherpereel *et al.* reported on QoL using LCSS-Meso and EQ-5D data collected during CheckMate 743 and found that, although trends towards improvement were seen in the nivolumab plus ipilimumab group and deteriorations in the chemotherapy group, these did not meet clinically meaningful or relevant thresholds (85). However, Scherpereel *et al.* did not include all questionnaire values collected throughout the study in their analysis of LCSS-Meso data for either group and censored up to 10% of responses in the LCSS-Meso analysis provided in their manuscript when cross-referenced to data provided in *Tab. 2* of their supplementary data (85). Response rates for EQ-5D were not provided (85). The fragility of the study's findings suggests poor robustness and the discrepancies between the data selectively presented or withheld and conclusions presented suggest potential censoring. Recently, Meirson *et al.* assessed the effectiveness of the Mesothelioma Cisplatin Pemetrexed Study (MPS), the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS), and CheckMate743 and found no statistical difference between the three studies in addition to a survival-inferred fragility index in the intention-to-treat (ITT) populations as low as 0.22% of sample size in MPS, –0.45% of sample size in MAPS, and 0.99% of sample size in CheckMate743. Additionally, Meirson *et al.* found significant differential censoring in the ITT population of CheckMate743 favoring the control group through calculation of the reverse restricted mean survival time difference [0.56 (95% CI: 0.18–0.94), P=0.004, RMST-D—the area bound by two Kaplan-Meier curves which reflects absolute change in survival] (86).

The impact of RT on QoL in MPM

Although the application of RT for MPM started as early as 1956, its effects were largely found to be toxic and injurious which defaulted its use to palliative therapy (87-89). Over time, studies found RT was well-tolerated in smaller doses which resulted in its incorporation into trimodality therapy (40,90,91).

In a randomized trial investigating RT in preventing entry tract metastasis following invasive diagnostic procedures in MPM, Boutin *et al.* randomized 40 consecutive patients into two equal groups of RT (three daily doses of 7 Gy, equivalent to 45 Gy over 4.5 weeks) 10–15 days after thoracoscopy or no RT (NORT) (92). Results none of the RT-treated patients developed entry tract metastases while 8 (40%) of the NORT group did (P<0.001) (92). In their phase II study on the effects of RT in the form of 20 daily doses of 2 Gy for 5 days a week (40 Gy in 4 weeks), Lindén *et al.* evaluated 47 patients who underwent RT with subsequent offering of chemotherapy with doxorubicin and cyclophosphamide to those aged ≤70 years and with good PS (16 patients) (93). Three out of the 47 total study patients had a partial response (one from RT-only and two from RT plus chemotherapy), resulting in a total study population median survival of 7 months, RT-only median survival of 6 months, and RT plus chemotherapy median survival of 13 months (93). Hundred percent of total study patients developed radiation-induced fibrosis of the irradiated lung within 6 months after termination of RT and 23.4% developed acute radiation pneumonitis (RP) with fever, shortness of breath, malaise, and overall deterioration of condition requiring prolonged corticosteroid treatments (93). Additionally, 41 out of 47 patients experienced significant decreases in mean Karnofsky PS (KPS) and body weight (P<0.005 for both) and significant increases in pain (P<0.05) 1 month after radiation and continuously decreasing KPS after 6 months for those who survived (P<0.0005) (93).

In their retrospective review of 174 patients ultimately eligible for RT, de Graaf-Strukowska *et al.* found a higher response rate (50% *vs.* 39%) and fewer in-field recurrences at dosages greater than 4 Gy (91 patients) compared to patients who received less (73 patients) which showcased the potential of RT in improving QoL in patients with MPM (94).

Rusch *et al.* conducted a prospective phase II study between 1995 and 1998 to investigate the feasibility and effect on local recurrence and OS in patients undergoing radical resection followed by adjuvant high-dose hemithoracic radiation (HDHRT) (90). Between 1995 and 1998, 88 patients (73 males) were enrolled with adjuvant RT of 54 Gy administered to 57 patients who either

underwent EPP (54) or PD (3) which was well-tolerated with only one late esophageal fistula as grade 3 or higher complication (90). Median survival was 17 months with stratification revealing a significantly longer median survival for patients with stages I or II than for patients with stages III or IV (33.8 and 10 months, P=0.04) (90).

In the 2011 MARS randomized feasibility study, Treasure *et al.* found that five out of the eight patients who received radical RT had complications with three having severe (grades 3 or 4) fatigue, one having pain, two having pneumonitis or dyspnea, one developing ascites, and one developing paraplegia 42 days after completion of RT (53).

The delivery of RT continued to evolve with the goal of reducing the rate of locoregional treatment failure and recurrence through intensity-modulated radiation therapy (IMRT) via conforming radiation doses to tight target volumes and potentially reducing tissue toxicity (95). In their trial of 100 consecutive patients that underwent EPP, 63 received IMRT at a median dose of 45 Gy and no chemotherapy (95). Median OS for all patients was 10.2 months while the survival for IMRT-treated patients was 14.2 months with 13% of IMRT-treated patients having local or regional recurrence (95). In a follow-up study, Gomez *et al.* studied 136 consecutive patients who underwent EPP with planned adjuvant IMRT between 2001 and 2011 (96). Eighty-six patients ultimately underwent EPP followed by hemithoracic IMRT which resulted in a median OS of 14.7 months and toxicity rates of grades 3 or higher occurring in skin (n=15, 17.4%), gastrointestinal (n=14, 16.3%), lung (n=10, 11.6%), and heart (2.3%) and grades of 5 occurring in five patients (pulmonary toxicity, 100%) (96). Locoregional recurrence-free survival was 88% and 71% at years 1 and 2, respectively, while distant metastasis-free survival rates were 55% and 40% at 1 and 2 years, respectively (96). However, when Rimner *et al.* studied the impact of IMRT in 67 MPM patients treated with definitive or adjuvant hemithoracic IMRT, the median time to in-field local failure was 10 months after the end of RT with 43 patients (64%) experiencing in-field local failures (97). Thirty-two of these 43 patients (74%) experienced failures at sites of previous gross disease, suggesting macroscopic complete resection (MCR) remains critical (97). Rimner *et al.* conducted a phase II trial implementing IMRT evaluating the incidence of grade 3 or greater RP. Forty-five patients were recruited and 27 ultimately underwent IMRT with two patients developing grade 3 or greater RP with 30%, 36%, and 33% experiencing, partial response, stable disease, and disease progression, respectively (98).

Shaikh *et al.* analyzed 209 MPM patients who underwent PD with adjuvant RT to compare IMRT to conventional RT (CONV) (99). The 78 patients who underwent IMRT demonstrated a significantly longer median OS when compared to the 131 patients who underwent CONV (20.2 *vs.* 12.3 months, P=0.001) (99). However, the IMRT patients had significant higher rates of epithelioid histology (86% *vs.* 59%, P<0.0001), significantly larger proportion of patients with KPS scores above 80 (50% *vs.* 31%, P=0.008), and significantly higher rates of chemotherapy treatment (89.7% *vs.* 11.5%, P<0.0001) (99). Further muddying the water, the CONV group had a significantly smaller proportion of patients with advanced pathological stage (49% *vs.* 76%, P=0.0001) in addition to a significantly smaller proportion of its cohort above the age of 64 years (45% *vs.* 65%, P=0.006) (99). After multivariate analysis, results showed KPS >80% (P=0.009), epithelioid histology (P=0.002), MCR (P=0.02), and chemotherapy (P=0.02) remained significantly associated with longer OS (99).

MacLeod *et al.* conducted a prospective, multicenter phase II study investigating the utility of RT for the treatment of pain in MPM with 20 Gy in five daily doses with a primary endpoint of pain at RT site at 5 weeks and secondary endpoints of QoL, shortness of breath, fatigue, mood, toxicity, and radiological response (100). Findings showed 14 out of 40 (35%) patients experienced clinically meaningful improvement in pain 5 weeks after completion of RT based on ITT analysis with five of the patients reporting complete resolution of pain, however, no improvement in QoL or any other endpoint was observed (100).

Future perspectives on QoL in MPM

Given the heterogeneity of prior studies in assessing outcomes, measuring QoL, patient population/selection, surgical approach, and chemo-, immune-, and radiotherapeutic regimens, among others, efforts have shifted to bring homogeneity to the study of MPM.

From a surgical standpoint, most experts agree that EPP should not be done for MPM and highly favor PD, however, thus far, no randomized controlled trial (RCT) has been completed that has explicitly evaluated the efficacy of pleurectomy decortication itself. The closest trial was MesoVATS, conducted by Rintoul *et al.*, which evaluated video-assisted thoracoscopic partial PD rather than EPD and thus not comparable as the two

approaches have different aims (101). Currently, MARS 2 is an ongoing RCT evaluating the efficacy of PD plus chemotherapy relative to chemotherapy alone in respect to OS with secondary outcomes of health-related QoL, PFS, and adverse events, among others, all while taking into account surgical consistency, patient treatment pathways, QoL measurements (using EORTC QLQ-C30 and EuroQol EQ-5D-5L periodically for 24 months), and chemotherapeutic regimen.

Newer approaches of radiation therapy are being explored in a phase III RCT evaluating the utility of Intensity-Modulated Pleural Radiation Therapy (IMPRINT)/IMRT in patients undergoing PD and chemotherapy with platinum and pemetrexed given the improved safety profile of IMRT implemented by Rimner *et al.* in their phase II study published in 2016.

The ongoing phase IIa MiST trial is personalizing treatment for MPM in patients that have already undergone chemotherapeutic treatment with disease progression or in which disease has relapsed using prospective molecular profiling of tumor suppressors BAP1, BRCA1, and p16ink4A and an immune checkpoint inhibitor PD-L1. The four arms are composed of: (I) rucaparib, a PARP inhibitor, for BAP1 inactivated/BRCA negative; (II) abemaciclib, a CDK4/6 inhibitor, for p16ink4a negative; (III) pembrolizumab, a PD-1 inhibitor, and bemcentinib, an AXL kinase inhibitor, for patients without biomarker specification; and (IV) atezolizumab (anti-PD-L1) and avastin (anti-VEGF) for PD-L1 positive (102). So far, arms 1–3 have met the primary endpoint of disease control at 12 weeks. Results of arm 4 have yet to be published (102-105).

Conclusions

MPM is an insidious disease that inevitably becomes aggressive and unforgiving with an invariably grim prognosis. Surgery remains the mainstay of therapy with major advancements made in surgical approach utilized favoring PD given its superiority in terms of post-operative complications, survival, and QoL when compared to EPP. Surgery has also been found to provide opportunities such as intracavitary administration of medications and solutions which have produced significant and consistent improvements in patient QoL. Chemotherapy and immunotherapy seem to be the most rapidly advancing segment of trimodality therapy in part due to significant technological advances which have allowed for improvements in development, synthesis, and targeting, however, their current, relative superiority and impact remain topics of debate due to the overtly complex and variable physiology of mesothelioma. Nevertheless, recent studies have demonstrated promising results for chemo- and immunotherapeutics used in conjunction with surgery in terms of median survival, symptomatic burden, such as dyspnea and pain, and overall QoL. RT currently appears to be the modality in which a breakthrough has yet to be made given the high risk of radiation toxicity that continues to exist despite different approaches, doses, and timing. Nevertheless, RT's role in the treatment of mesothelioma should not be mitigated given the significant palliative potential it holds for pain. Thus, while current treatments and therapies remain far from ideal, progress throughout the last few decades has been promising and seems to be significantly increasing in pace. The development of standardized QoL measurement tools established a foundation upon which treatment regimens can now be compared and refined which has resulted in significant improvements in not only PFS or OS, but also QoL.

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