Combined modality treatment in mesothelioma: a systemic literature review with treatment recommendations

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Abstract: In spite of recent progress, malignant pleural mesothelioma (MPM) remains synonymous with poor prognosis. A selected minority (<10%) of patients is eligible for a radical treatment with a combination of systemic chemotherapy (CT) and/or surgery and/or radiotherapy (RT), in an effort to maintain locoregional tumor control after achieving a macroscopically complete resection (MCR). However, as of yet there is no standard of care for this so-called multimodality treatment. As its potential gain is still limited (approximately one year added to overall survival), we must balance its efficacy with its cumulative toxicity. Several combined modality treatment trials are currently ongoing using novel techniques in surgery, RT and/ or CT in an attempt to reduce the morbidity and mortality associated with older multimodality treatment protocols. Guidelines are following suit and are now including or mentioning this treatment option. In this systematic review, we analyze the available data in order to address the following questions: Is combined modality better than single modality? What is the optimal regimen within each modality? What is the optimal sequence of combined modality?

Keywords: Malignant mesothelioma; multimodality treatment; surgery; chemotherapy (CT); radiotherapy (RT)

Introduction

It was first suggested in 1980 that selected patients with malignant pleural mesothelioma (MPM) are to be treated with a combination of different therapeutic modalities, usually surgery, chemotherapy (CT) and radiotherapy (RT), in order to achieve locoregional control and to improve overall outcome (1). Other types of neoplasms that are treated in this manner include lung (2), esophageal (3) and colorectal cancer (4).

As we seem to reach consensus on the necessity of such a multimodality approach or at least on the need for more randomized trials ascertaining its role in the treatment of MPM, there is ongoing debate and research on its individual components and how they should be sequenced. Historically, surgery for MPM consisted of extrapleural pneumonectomy (EPP), which is an en bloc resection of both the parietal and visceral pleurae, the ipsilateral lung as well as pericardium and diaphragm. In the last five years there has been an evolution towards pleurectomy/decortication (P/D), which is a less invasive procedure whereby the parietal and visceral pleurae are removed but lung, pericardium and diaphragm are spared. When diaphragm and pericardium are also resected, this procedure is called an extended P/D (eP/D). Partial pleurectomy is performed to obtain tissue for diagnosis or

to relieve symptoms in a palliative setting but is not part of a multimodality treatment for MPM (5).

In 2003 and 2005, two large scale randomized control trials showed superiority in overall survival time with cisplatin and pemetrexed/raltitrexed over monotherapy with cisplatin, as well as in time to progression and response (6,7). Since then this combination of cytotoxic agents (platinum based plus antifolate) has become the standard of care, as it is the sole treatment with proven benefit on outcome. In 2015, the French MAPS trial showed that the association of bevacizumab, a monoclonal antibody targeting the vascular endothelial growth factor A (VEGF-A), to a cisplatin-pemetrexed backbone improved overall survival in highly selected patients (8).

Concerning radical RT there is an ongoing effort to find the most effective radiation technique that will improve locoregional disease control but will not result in excess radiation pneumonitis. Because of the large surface area of the pleura, the volume with conventional RT is very high, resulting in damage to the underlying lung (in case of P/D) and/or surrounding tissue and organs. Intensity modulated radiotherapy (IMRT) aims at a better dose distribution and hence less toxicity, which is especially important when RT is administered after lung sparing surgery (9).

The 2010 European Respiratory Society (ERS)-European Society of Thoracic Surgeons (ESTS) guidelines, recommend that eligible patients (early stage, preferably epithelioid subtype, satisfactory pulmonary and cardiac status) should be included in prospective randomized control trials evaluating multimodality treatment in experienced centers (10). The 2015 European Society for Medical Oncology (ESMO) guidelines are more restrictive as they conclude that there is insufficient evidence supporting standardized implementation of adjuvant RT in the treatment of MPM, however they do advise against monotherapy with surgery and recommend surgery be part of a multimodality treatment, preferably in a trial setting (11). The 2018 British Thoracic Society (BTS) advise against EPP in any way and against eP/D outside of clinical trials. Based on the results of the MAPS trial, they suggest association of bevacizumab to a platinum-antifolate doublet to improve survival (8,12). The 2018 American Society of Clinical Oncology (ASCO) guidelines state that cytoreductive surgery should ideally be supplemented by RT or (neo)adjuvant CT seeing as surgery alone has not shown to provide adequate disease control. For patients with proven N2 status they only recommend surgery when part of a multimodality treatment, preferably in a trial

setting (13). An overview of the most recent guidelines is listed in *Table 1*.

The purpose of this manuscript is to report the results of a systematic literature search performed on the subject of combined modality treatment in mesothelioma and formulate graded recommendations.

The following clinical questions were raised:

(I)   Is multimodality treatment better than CT alone?
(II)   What is the optimal regimen within each modality?
(III)   What is the optimal sequence of interventions within a combined modality approach?

Methods

This systematic review is part of the revision of the 2010 ERS-ESTS guidelines on mesothelioma by a core group of experts, led by Prof Dr. A Scherpereel. A literature search was performed in November 2016 in the Ovid Medline system by a librarian. The clinical questions were translated in the "PICO" (population, intervention, comparator, outcome) model (14) (*Table 2*). The corresponding search criteria were translated into MeSH terms, and free-text keywords that were searched for in titles, abstracts and name of substances (*Table S1*). Completed search strategies included "P" and "I" criteria, combined with "O" criteria when the number of retrieved citations was too large. Results were limited to articles published from 2009 onwards. Citations were exported from Medline into reference manager databases to allow the removal of duplicates and to facilitate the selection process performed by the reviewers. They were first selected for their eligibility based on the abstract content and language. The remaining articles were evaluated further for inclusion in the current review. The final selection was performed by reading the full publication. Selection was independently done by the four authors and discrepancies were consensually resolved. This search was supplemented by screening the references of the selected articles and a manual selection of literature up to January 2018 by the experts. An evidence level and grade of recommendation was assigned using the SIGN methodology.

Results

We withheld out of 80 abstracts, 35 valid full articles, of which 9 reviews/editorials/comments, 5 guidelines, 9 manuscripts addressing pure surgical issues, 7 population studies, 4 manuscripts on recurrence pattern after combined

Table 1 Overview of current guidelines

Group	Published	Guidelines regarding multimodality treatment in MPM	Grade
ESMO	2015	The first- and second-line treatment of unresectable mesothelioma; patients in good condition should be recommended to join studies in second line	II, A
		RT can be given in an adjuvant setting after surgery or chemo-surgery to reduce the local failure rate. However, no evidence is available for its use as a standard treatment	II, A
		The indications for surgery are; to be part of a multimodality treatment, preferably as part of a study	II, A
		To perform a macroscopic complete resection by means of P/D or EPP	III, C
ERS/ESTS	2010	Pleurectomy/decortication should not be proposed in a curative intent but can be considered in patients to obtain symptom control, especially symptomatic patients with entrapped lung syndrome who cannot benefit from chemical pleurodesis. The VATS approach is preferred	IC
		Radical surgery (EPP) should only be performed in clinical trials, in specialized centres, as part of multimodal treatment	IA
		Radiotherapy should not be performed after pleurectomy or decortication. Post-operative irradiation after EPP should only be proposed in clinical trials, in specialized centres, as a part of multimodal treatment. Patients who are considered candidates for this multimodal approach should be included in a prospective randomized trial in specialized centres	IA
BTS	2018	Do not offer extra-pleural pneumonectomy (EPP) in MPM	B
		Do not offer extended pleurectomy decortication (EPD) outside of a clinical trial	D
		Offer patients with MPM with good PS (WHO 0–1) first line therapy with cisplatin and pemetrexed. Where licensed (not presently in the UK), bevacizumab should be added to this regime. Raltitrexed is an alternative to pemetrexed	A
		Where cisplatin is contraindicated, or has adverse risk, offer carboplatin in combination with pemetrexed. First-line clinical trials are an appropriate option for patients with good PS and are recommended above any other option for second-line treatment, providing the patient is of adequate PS. Do not offer preoperative or postoperative radiotherapy in MPM	A
		Do not offer hemithorax radiotherapy for MPM	D

Table 1 (*continued*)

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Group	Published	Guidelines regarding multimodality treatment in MPM	Grade
ASCO	2018	Given the very limited activity of second-line chemotherapy in patients with mesothelioma, participation in clinical trials is recommended	Type of recommendation: evidence based; evidence quality: intermediate; strength of recommendation: strong
		Maximal surgical cytoreduction as a single modality treatment is generally insufficient; additional antineoplastic treatment (chemotherapy and/or radiation therapy) should be administered. It is recommended that this treatment decision should be made with multidisciplinary input involving thoracic surgeons, pulmonologists, medical and radiation oncologists	Type of recommendation: evidence based; evidence quality: intermediate; strength of recommendation: strong
		Patients with ipsilateral histologically confirmed mediastinal lymph node involvement should only undergo maximal surgical cytoreduction in the context of multimodality therapy (neoadjuvant or adjuvant chemotherapy). Optimally, these patients should be enrolled in clinical trials	Type of recommendation: evidence based; evidence quality: intermediate; strength of recommendation: strong
		A maximal cytoreduction (either lung sparing or non-lung sparing) should only be considered in patients who meet specific preoperative cardiopulmonary functional criteria, have no evidence of extrathoracic disease, and are able to receive multimodality treatment (adjuvant or neoadjuvant)	Type of recommendation: evidence based; evidence quality: intermediate; strength of recommendation: strong
		Since surgical cytoreduction is not expected to yield an R0 resection, it is strongly recommended that multimodality therapy with chemotherapy and/or radiation therapy should be administered	Type of recommendation: evidence based; evidence quality: intermediate; strength of recommendation: strong
		Chemotherapy may be given pre- or postoperatively in the context of multimodality treatment	Type of recommendation: evidence based; evidence quality: low; strength of recommendation: moderate
		In the context of multimodality treatment, four to six cycles of pemetrexed/platinum-based chemotherapy may be administered pre- or postoperatively	Type of recommendation: evidence based; evidence quality: intermediate; strength of recommendation: moderate

Variable	1: CMT > 1T	2: optimal regimen	3: sequencing
Population	'Resectable' mesothelioma	'Resectable' mesothelioma	'Resectable' mesothelioma
Intervention	Bimodality, trimodality	EPP, 3D conformal TRT, cisplatin-pemetrexed	Postoperative
Comparison	Single modality (resection)	e-P/D, IMRT, non-cisplatin-pemetrexed	Pre-operative
Outcome	Outcome, toxicity/complications/mortality/QoL/PROM, compliance, recurrence		

CMT, combined modality treatment; 1T, single modality treatment; EPP, extrapleural pneumonectomy; TRT, thoracic radiotherapy; e-P/D, extended pleurectomy decortication; IMRT, intensity modulated radiotherapy; QoL, quality of life; PROM, patient reported outcome measures.

modality and 1 case report (for grading see *Table S1*). Among these 35 articles, there was 1 observational study on single modality treatment, 1 phase II trial on single modality treatment (CT), 3 randomized phase III trials on single modality treatment (of which 2 on CT and 1 on immunotherapy), there were 12 reports on 2 modalities, of which 3 prospective, non-randomized series, 7 on surgery with CT (of which 2 with intracavitary CT): 1 observational, 1 phase 2 trial, 5 on peri-operative RT of which 1 prospective; 17 reports on 3 modalities among which 1 systematic review, 1 retrospective analysis, 7 phase 2 trials, 2 randomized trials; 7 on PORT; 1 on resection. These were the basis for addressing the three PICO questions.

PICO 1: is multimodality treatment better than CT alone?

Primary endpoint: survival

Two groups have analyzed the pooled mesothelioma data in the National Cancer Database (NCDB), wherein MPM patients' records are collected. Both report that almost half of the patient population received no mesothelioma specific treatment. Saddoughi *et al.* found that the 3 percent of MPM patients who underwent multimodality treatment between 2004–2013 performed better than those treated with CT alone (median overall survival 19.9 *vs.* 11.3 months, respectively) (15). Nelson *et al.* confirmed the use of multimodality treatment in only 8% of seemingly ideal trimodality treatment patients (under 70 years old, stage I through III, epithelioid histology) (16).

Although some reports are in favor of a multimodal approach when it comes to the treatment of MPM, others have shown similar or even better overall survival treating patients with CT alone. The explanation for this lies in the morbidity and mortality associated with EPP.

Hillerdal *et al.* treated a series of patients with MPM with a combination of carboplatin, liposomal doxorubicin and gemcitabine. They found an overall median survival of 13 months. Epithelioid subtypes reached a median survival of 17 months and even 21 months in good performance status patients, comparable with the outcome of patients treated with neoadjuvant CT and EPP, suggesting that treatment with CT alone is equally effective in similarly selected MPM patients (17).

Sharkey *et al.* retrospectively analyzed their database in order to establish the ideal timing for CT in patients treated with EPP and to identify which MPM patients benefit most from (neo)adjuvant CT. Their results showed a median survival from time of diagnosis of 23.3 months in the adjuvant CT group and 23.9 months in the neo-adjuvant group. A scenario wherein no CT was given until disease progression, performed similarly with a median survival of 20.3 months. Those patients with non-epithelioid histology and nodal involvement performed better with true adjuvant CT than when it was delayed (overall survival 15.6 *vs.* 8.2 months and progression free survival 14.9 *vs.* 6.0 months respectively) (18).

The Mesothelioma and Radical Surgery (MARS) trial, which randomized eligible patients after 3 cycles of induction CT to either EPP or postoperative radiotherapy (PORT) versus 3 more cycles of CT without attempt at resection or RT, concluded that the likelihood of a benefit of EPP on the overall survival and quality of life endpoints was small. This futility analysis caused the premature closure of the trial and affected standard practice worldwide (19). Median survival of the EPP group (14.4 months) was low compared to 19.5 months in the no EPP group, but also lower than in other similarly designed historical EPP trials. The start date of the time-to-event analysis—after induction CT—is the most likely explanation

for this comparably low outcome, as in other trials this was calculated from the time CT was started.

Additionally, overall survival reported in the CT arm of the MARS trial is significantly better than that reported in certain multimodality treatment series. Bille *et al.* included 25 patients in a prospective study examining the effects of trimodality treatment and reported a median survival of only 12.8 months (20).

Although intertrial comparisons are hazardous, these results do not strengthen the role of surgery in the treatment of MPM, especially when considering the time patients undergoing a multimodality treatment spend hospitalized after surgery or due to complications of treatment.

The MARS group is currently assessing the feasibility of a study comparing CT alone versus CT and eP/D. Patients will be randomized to either eP/D or no surgery after completing 3 cycles of CT (21).

The addition of RT to surgery has also been studied, with variable results. The SAKK 17/04 trial, a prospective randomized trial, assessed whether adding PORT to a combination of neo-adjuvant CT (cisplatin-pemetrexed) and EPP resulted in a better locoregional relapse-free survival (22). Although they showed a significantly longer local relapse free survival in the RT arm (9.4 *vs.* 7.6 months), the authors were unable to make a convincing case for the addition of PORT to CT and surgery when it comes to median survival seeing as it was similar to the no-RT arm, namely 19.3 *vs.* 20.8 months respectively. The addition of PORT also comes at a price, as there was a radiation related death in the SAKK PORT arm, as opposed to no treatment related mortality in the SAKK no PORT arm.

These findings were similar to those published by a Japanese group performing a feasibility study with a comparable trimodality protocol (CT-EPP-RT) in mesothelioma patients. Median survival in this patient population was 19.9 months and although they met the primary endpoints of achieving a macroscopic complete resection and maintaining an acceptable treatment related mortality, they concluded that the risk-benefit ratio was unsatisfactory. Progression free survival time was 11 months in those wherein a macroscopic complete resection was achieved (23).

It would be premature however to exclude RT from the treatment of MPM altogether based on these results alone. It is plausible that more rigorous patient selection and fine-tuning of the techniques could result in better outcomes and less toxicity. The SAKK trial included patients with extensive disease (proven N2 status) and non-epithelioid type mesotheliomas, both of which are negative prognostic features usually serving as exclusion criteria in this type of trial. The RT regimen in both trials also consisted of hemithoracic RT, which is associated with a high radiation dose and hence high toxicity. EPP was the surgical procedure of choice in both trials, which has a high mortality and is prone to complications. In this light, the results of the JMIG1101 trial, a prospective feasibility study of induction CT followed by P/D will be of particular interest.

A recent systematic review of randomized controlled trials of multimodality treatment in MPM (namely MARS and SAKK trials), concluded that based on this data there is not enough evidence to support standardized implementation of a combined modality treatment, especially given the morbidity and cost associated with these treatment protocols (24).

In conclusion, the current evidence in favor of a combined modality approach is weak and likely subject to different biases. Nevertheless, the rationale is challenging and the best survival data reported were obtained in series combining local and systemic modalities.

Other endpoints

Marulli *et al.* did a retrospective analysis of mesothelioma patients who received neo-adjuvant CT and found that it improved their pulmonary lung function tests and exercise capacity (25). Not only should this affect quality of life, this could also prime patients before surgery, possibly resulting in lower surgery-associated morbidity.

Maintaining a satisfactory physical condition is essential for completing these demanding treatment schedules. Exactly how challenging these therapies are, is revealed in the number of patients completing the treatment protocols, or the time it takes to reach completion versus an optimal preset timeline. In the EORTC 08031 study, a prospective feasibility study assessing multimodality treatment (CT-EPP-PORT) in the treatment of early stage MPM, only 42% of enrolled patients were able to complete the treatment within the preset time frame (26). In the aforementioned SAKK trial, only 36% of patients were able to or agreed to proceed on to RT after undergoing neo-adjuvant CT and EPP (22). So, attrition is high and compliance to treatment becomes an important endpoint. Omitting to report this attrition is common in retrospective series and is the cause for the commonly encountered

Table 3 Type and number of fatal toxicities by treatment group in prospective combined modality treatment trials for MPM

Trial	Treatment protocol	Grade 5 toxicity
EORTC 2010	NA CT + EPP + HTRT	Pulmonary embolism [1], combined lung edema and pneumonia [1], pneumonia [2]
MARS 2011	NA CT + EPP + HTRT vs. CT	Aortic rupture during EPP [1], bronchopneumonia [1], unknown cause [1]
SAKK 2015	NA CT + EPP +/– HTRT	Pneumonitis [1], pulmonary embolism and right heart failure [2], cardiac arrest [1], diaphragmatic patch failure [1], septic multiorgan failure [1]
Bille 2012	NA CT + EPP + HTRT	Aortic rupture during EPP [1], pulmonary embolism [1], pneumonia [1], sepsis [1]
JMIG 0601 trial	NA CT + EPP + HTRT	ARDS [3], cardiac herniation and hemothorax [1]
Minatel 2015 (30)	P/D + IMRT	Pneumonitis [1]
Krug 2009 (31)	NA CT + EPP + HTRT	Pneumonitis [1], bronchopleural fistula [1], sepsis [1]
De Perrot 2009	NA CT + EPP + HTRT	Cardiac herniation [1], cardiac arrhythmia [1], bronchopleural fistula with empyema [1]
De Perrot 2016 SMART	IMRT + EPP +/– CT	Empyema [2], cardiac arrest [1]
Federico 2013	NA CT + EPP + HTRT	Cardiopulmonary [2], empyema [1], cardiac arrest [1], sepsis [2]

NA, neo-adjuvant; CT, chemotherapy; EPP, extrapleural pneumonectomy; HTRT, hemithoracic radiotherapy; IMRT, intensity modulated radiotherapy.

immortality bias in combined mortality series.

Toxicity is systematically underreported thus minimalizing the morbidity associated with multimodality treatment schedules. Toxic or treatment-related deaths are most often the result of complications brought on by surgery or radiation. In the SMART trial (IMRT followed by EPP and CT), de Perrot *et al.* report that 24 out of 62 patients developed a grade 3 or higher toxicity. This number does not account 6 patients with multiple grade 3 or higher toxicities, summing up to 31 the overall number of single serious adverse events in this patient group (27). In their series, Federico *et al.* had to reduce the radiation dosage after two patients died due to radiation related cardiopulmonary complications (28). Even after this dose reduction, the grade 3-4 toxicity incidence remained high at 66.7% of patients. Note that this is again the percentage of patients developing one or more grade 3–4 toxicities, not the number of single serious adverse events.

On occasion, adverse events are reported per treatment modality (e.g., CT related toxicity) instead of an overall number of adverse events (22,23,29). This too can lead to an underestimation of the morbidity inflicted by the entire treatment regimen.

Table 3 shows the toxic deaths reported in the prospective multimodality treatment trials. As these are mostly complications of local treatment, improvements should be made in these areas in order to reduce mortality.

Unfortunately, neither resection nor RT currently results in adequate locoregional disease control. Cao *et al.* pooled the results of all major trimodality treatment trials and found disease relapse to occur most often locally, with an incidence ranging between 4–41% (32).

In conclusion, a combined modality approach leads to accumulated toxicity and mortality which is the main reason for the failure of CMT to show an unequivocal benefit in outcome. Any approach reducing the latter might well result in an improved survival and adoption of CMT.

PICO 2: what is the optimal regimen within each modality?

What is the optimal PORT-technique?

RT of the pleura is understandably challenging as there is a large surface area to irradiate, the shape is complex and there are vital organs and large vascular structures close to the pleura that need to be shielded from radiation as much as possible (33). The evolution towards lung sparing surgical techniques introduces additional difficulty as measures must be taken to avoid radiation pneumonitis or other complications in the spared ipsilateral as well as in the contralateral lung. The most frequently used radiation technique in multimodality treatment protocols for MPM are conventional 3-dimensional conformal RT and intensity modulated RT (IMRT). Conventional 3D hemithoracic

RT has shown to be excessively toxic by Gupta *et al.* and Stahel *et al.* among others, both in the context of lung sparing surgery and after EPP (22,34). IMRT allows for a tailored approach wherein large doses of radiation are administered to the affected pleura and the underlying lung and surrounding tissue are spared (35). Helical tomotherapy or dynamic arc RT combines the precision of the IMRT technology with a megavoltage CT-scan. This allows for daily image-guided adjustments, which creates a more precise application of radiation. The fact that the radiation beam moves around the patient while the table moves through the arc enables irradiation of larger areas in a shorter time period (36). Sylvestre *et al.* applied this technique for MPM in 24 MPM patients after EPP and reported a median disease free survival of 24 months. Two patients died of radiation pneumonitis (36). Krayenbuehl *et al.* compared IMRT and 3D conformal RT in 39 MPM patients after EPP. They found a non-significantly longer median time to relapse in the IMRT group (16.2±3.1 versus 10.9±5.4 months with 3DRT). This did not however result in a longer overall survival (22.3±15.3 months for IMRT and 21.2±9.2 months for 3DCRT), probably because of a higher rate of distant relapse (33). Rimner *et al.* evaluated IMRT after CT and P/D and reported a median progression free survival of 12.4 months and a very promising median overall survival of 23.7 months. There were no treatment related deaths. There were 8 cases (30% of patients) of grade 2–3 pneumonitis which responded well to steroid treatment (35). In conclusion, IMRT techniques are hence likely to be preferable to 3DRT with regards to toxicity.

What is the optimal CT regimen?

The standard CT regimen in multimodality treatment for MPM is a cisplatin-pemetrexed doublet. Pasello *et al.* performed a retrospective analysis of 51 patients who received neoadjuvant CT (pemetrexed plus cisplatin or carboplatin) as part of a multimodality treatment approach for MPM. Although they report a similar median progression free survival outcome in both groups (14.5 months in the carboplatin group versus 13.1 months in the cisplatin group), overall survival was significantly longer in the carboplatin group (25.5 versus 15.2 months in the cisplatin group). The authors attribute this to the patients' characteristics being more favorable in the carboplatin group. When they compared outcomes for only epithelioid-type mesothelioma in both groups, the

difference was not statistically significant (26.9 months in the carboplatin group versus 18.9 months in the cisplatin group, P=0.054). As expected, cisplatin was tolerated more poorly and treatment with cisplatin resulted in higher numbers of anemia, nausea, vomiting and asthenia as opposed to carboplatin-based therapy (37). A Turkish series, in which patients were treated with a pemetrexed-carboplatin doublet similarly showed a better median survival than with a pemetrexed-cisplatin doublet (38).

In conclusion, these reports suggest that carboplatin containing regimens could be equally effective and less toxic and thus preferable in a combined modality approach already hampered by other toxicities.

PICO 3: what is the optimal sequence of combined modality?

Neo-adjuvant vs. adjuvant CT

Advocates for neoadjuvant CT claim a better tolerance, compliance and resectability with this approach (22,26,28,29). In their retrospective series, Sharkey *et al.* however, did not find a difference in overall survival between the adjuvant CT group and the neo-adjuvant CT group (18).

Cao *et al.* reported a median overall survival of 23.1 months in the adjuvant CT group versus 27.8 in the neo-adjuvant CT group (32). Important to note here is that overall survival was estimated from different starting points in the different trials, which undoubtedly affects the entire analysis. Also, the trials assessing adjuvant CT are older than the neo-adjuvant series and -with one exception- all of retrospective nature. The adjuvant CT regimens differed between the trials so comparing them as a group to the more homogenous neo-adjuvant CT trials is presumptuous.

In conclusion, both approaches are defendable. The European Organization for the Research and Treatment of Cancer (EORTC) is currently enrolling (cT1–3 N0–2 M0) patients for its 1205 trial wherein they are randomized to P/D, preceded or followed by 4 cycles of platinum-pemetrexed.

Pre-op vs. post-op RT

Cho *et al.* sought to reduce disease relapse—thought to be caused by tumor soiling during EPP—by implementing a short course of IMRT prior to EPP. Ideally, both a direct tumoricidal effect and a distal immunomodulating or abscopal effect are generated to prevent tumor growth in distant sites. Neoadjuvant RT was well tolerated, without

severe toxicity or mortality. After five years, only one out of 9 patients with epithelioid histology and no N2 involvement had relapsed (39). De Perrot *et al.* confirmed these results in the prospective SMART trial with an encouraging median survival of 36 months.

Discussion

We recognize several flaws in the reporting of combined modality treatment series. As malignant mesothelioma is a relatively rare disease, the volume of patients being treated in any given center is low. A small number of specialized institutions tend to dominate the publications and as a result, the published outcomes do not mirror the real-life outcomes. Recording data in (inter)national registries could help in overcoming this selection bias.

Treatment protocols also tend to be amended and adapted depending on findings during therapy, e.g., PORT is sometimes added based on operative findings. This lack of standardization makes retrospective comparison of different series hazardous.

Aside from this heterogeneity in treatment protocols, there is also the issue of bias in the definition of resectable disease. The availability of experienced surgeons or radiotherapists plays an important role in this interpretation. Patient characteristics such as N2 disease and histological subtypes are also not routinely documented and considering how significant these prognostic factors are, omitting them is casting a bias on the results.

Time-to-event outcomes such as median overall survival and progression free survival, are estimated from different starting points in different trials, making comparison between individual series and trials difficult and confusing.

Retrospective series suffer from immortal time or guarantee time bias. This arises when the analysis includes the time period before or in between treatment(s) as part of follow-up, as is often the case in multimodality treatment trials (40,41). Nelson *et al.* attempted to overcome this by implementing propensity matched analysis when studying the National Cancer Database (42). Vogl pointed out that this analysis is still biased in favor of the multimodality treatment group. A tell-tale sign of this statistical wizardry is the fact that the survival curve of the multimodality treatment group starts out flat. Only the patients that complete the entire treatment protocol are included in the analysis. As they have to be alive to undergo the different treatment modalities any patient who drops out of the trial ahead of completion is not taken into account when analyzing the treatment group. As a result an overestimation will occur favoring the treatment group. Unfortunately, in any disease with a prognosis as dismal as that of malignant mesothelioma, patients will die in between treatment modalities or even before any treatment is given, as such a plateau in the survival graph is inaccurate and misleading (41).

Conclusions & recommendations

Disappointingly, despite previous evidence-based guidelines and recommendations, most patients are still being treated outside of clinical trials. In this review, we found that between 2009 and 2016, only 104 patients were treated in randomized controlled trials. As such, important questions remain unanswered. The role of surgery is still up for debate as even pleurectomy/decortication scores low on the benefit to cost ratio. Novel techniques in RT and CT are promising and should be investigated further, both as monotherapy and as part of combined modality treatment. The optimal sequencing of different modalities has yet to be identified.

Answers to a number of secondary questions have been indirectly obtained from case control series and these issues should therefore not be prioritized for investigation in upcoming trials. Examples are the equivalence of carboplatin to cisplatin when it comes to efficacy, the benefit of adding CT to surgery in improving outcome and the role of advanced precision RT techniques for avoiding toxicity.

We recommend that further reports on multimodality therapy in MPM should unequivocally include an intention-to treat population analysis, report time-to-outcome measurements from day 1 of the first treatment and confer a CONSORT diagram of patient disposition over the different steps of the multimodality protocol.

Furthermore, decisions to step up or down in a combined modality approach should be agreed upon before treatment starts and not ad hoc based on intraoperative or durante treatment findings, obscuring the true effect of each modality.

We emphasize the role of well conducted randomized phase 2 trials including a control group in order to compensate for patient selection bias and to avoid embarking on large phase 3 trials based on immature results in single arm phase 2 trials.

Lastly, it is imperative that good performance patients be referred to high volume expert centers in order to be

considered and proposed for the clinical trials necessary to take forward the issue of multimodality treatment on the outcome in MPM.

Recommendations

(I) There is level 2 evidence that a multimodality treatment consisting of at least macroscopic resection and CT, is superior to either single modality in selected patients with regard to survival, but at the cost of increased treatment related morbidity and mortality. Selected patients should be adequately informed and referred to expert centers in order to be included in either clinical trials or large institutional series (grade of recommendation: D).

(II) There is level 2+ evidence that for PORT, IMRT techniques should be preferred over conventional 3D RT (grade of recommendation: C).

(III) There is level 3 evidence that a carboplatin-based platinum-pemetrexed doublet is non-inferior to a cisplatin based one as a (neo-)adjuvant CT regimen with less toxicity (grade of recommendation: D).

(IV) There is level 2 evidence for neo-adjuvant CT to be preferred over adjuvant CT in a multimodality approach (grade of recommendation: D).

(V) No recommendation can be made regarding the optimal sequencing of RT in a combined modality treatment protocol.

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Footnote

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Table S1 Results of systematic review of literature

Reference	Design	Other type of trial: define in words	Date of publication	Number of patients	Type of intervention (define in words)	Results description according to the endpoint	Attrition bias?	Reporting bias?	Overall
(9)	4	Phase I clinical study	2015	36	(NA chemotherapy) + lung sparing surgery + IMRT or NA chemotherapy + IMRT	Acceptable toxicity	No	No	Better survival in + IMRT group as opposed to IMRT alone
(10)	4	ERS-ESTS Guidelines	2010	–	–	–	–	–	See *Table 2*. To be updated in 2018
(11)	4	ESMO clinical Guidelines	2015	–	–	–	–	–	See *Table 2*
(12)	4	ASCO Guidelines	2018	–	–	–	–	–	See *Table 2*. Conservative position regarding role of surgery and radiotherapy, based on low quality evidence
(13)	4	BTS Guidelines	2018	–	–	–	–	–	See *Table 2*. Strong recommendation to avoid monotherapy with surgery, based on intermediate quality evidence
(15)	1	Not applicable	2017	19,134	–	Best survival outcomes in patients treated with combined modality approach	–	–	Large database analysis supporting implementation of combined modality treatment. 40% of patients did not receive any MPM specific treatment
(16)	1	Not applicable	2017	20,561	–	2.6% of patients received trimodality therapy. Patients treated at an academic centre or who travel >26 miles for treatment were more likely to undergo trimodality therapy. Younger age, satisfactory overall condition and presence of private insurance also increased likelihood of multimodality treatment	–	–	Large database analysis reporting low numbers of patients treated with surgery-based multimodality therapy. Use of combined modality treatment is stable over time
(18)	1	Not applicable	2016	229	True adjuvant therapy *vs.* neo-adjuvant therapy *vs.* therapy reserved until disease progression *vs.* conservative in those unfit for chemotherapy	True adjuvant chemotherapy may be beneficial in those with a poorer prognosis based on cell type and nodal stage	No	Yes	Overall survival similar in all chemotherapy groups, even when calculated from time of diagnosis
(19)	3	Not applicable	2011	112	Chemotherapy followed by EPP and radiotherapy or no EPP	Hazard ratio for overall survival after factor adjustments was 2.75, P=0.016)	No	No	Good quality clinical trial showed high mortality on EPP group
(20)	2	Not applicable	2012	25	EPP, neoadjuvant chemotherapy and adjuvant radiotherapy	18.2 treatment mortality, 81% completed trimodality treatment, median survival of 12.8 months	Yes	No	Moderate case series report with shows similar survival with chemotherapy only
(21)	4	Systematic review	2017	–	Radical surgery and debulking surgery	More RCTs required	–	Yes	Author was co-investigator on the MARS1 trial and is part of ongoing MARS2 trial
(22)	3	Not applicable	2015	151	Neoadjuvant chemotherapy followed by EPP and control/ treatment group of radiotherapy	Median locoregional relapse free survival was 7.6 months in the no radiotherapy group and 9.4 months in the radiotherapy group showing no support use of radiotherapy after chemotherapy + EPP	No	No	Study terminated earlier than expected due to slow accrual. Good quality study showing no clinical benefit of post-surgery radiotherapy and an overall survival of 20 months - less than other retrospective studies
(23)	2	–	2015	42	Induction chemotherapy, EPP and adjuvant radiation	Macroscopic complete resection of 71% and mortality of 9.5%	No	No	Prospective cohort that shows trimodality treatment is feasible in Japan
(24)	4	Systematic review	2018	–	Radical surgery ± radical RT ± photodynamic therapy ± systemic therapy *vs.* each other or *vs.* palliative care	Not enough evidence supporting routine implementation of multimodality treatment	No	No	Systematic review based on two multimodality treatment trials, including the already heavily cited MARS1trial. Limited added benefit
(25)	2	–	2010	36	Neoadjuvant chemotherapy	Significant improvement in FEV1 (0.13±0.30 L; P=0.01), in VO2 peak (1.76±2.91 mL kg^{-1} min^{-1}; P=0.005), in PaO2 at rest (4.76±9.84 mmHg; P=0.03) and in PaO2 at peak exercise (6.26±12.72 mmHg; P=0.04) was detected. Diffusion capacity was increased but non-significantly	No	No	Most significant lung function improvement in patients who showed response to chemotherapy, effect of overall better condition or true chemotherapy effect?
(26)	3	Phase II clinical study- no control group	2010	59	Induction chemotherapy followed by EPP followed by radiotherapy	Trimodality treatment completed in 64.9% of patients. 24 /42.1% patients met success of treatment (primary end point) and median overall survival was 18.4 months	No	No	Good quality clinical study showed that TMT is feasible but did not met the definition of success as per primary endpoint
(27)	4	Phase I/II clinical study	2016	62	IMRT followed by EPP and adjuvant chemotherapy (SMART protocol)	Ongoing phase II study—SMART protocol is feasible and 39% developed 3 + complications, 4.8% developed grade 5 complications and died	No	No	Moderate quality study suggesting a protocol with high complications on a selective population
(28)	4	Phase II clinical study- no control group	2013	56	Chemotherapy followed by EPP followed by radiotherapy	Median event free survival (EFS) was 6.9 months, 33% achieved 1 year EFS and 24% 2 years EFS. Median PFS was 8.6 months and 1 year PFS 40.7%	No	No	Good quality phase II study shows trimodality treatment is feasible in highly selective population
(29)	1	Not applicable	2009	60	Chemotherapy followed by EPP followed by radiotherapy	50% patients completed protocol, 5-year survival 53% of those completed the protocol-median survival of all patients included was 14 months	No	No	High selective population-retrospective study with 6.7% mortality of EPP
(32)	4	Systematic review	2012	16 studies, 744 patients	Radical pleurectomy followed by chemotherapy (Cis-Pem) and radiotherapy	Inconsistent results of long term survival from current studies	No	No	Good quality systematic review shows inconsistent results between prospective/retrospective and 1 randomized trial no allowing definitive conclusions to be drawn for the surgical procedures
(33)	1	Not applicable	2014	39	Postoperative highly conformal versus 3D conformal radiotherapy	Better local control in treatment group, problematic distant relapsing affecting overall survival	No	Yes	The more conformal, the lesser toxicity
(35)	4	Phase II clinical study- no control group	2016	45	Chemotherapy followed by PD followed by hemithoracic intensity modulated pleural radiation therapy (IMPRINT)		Less than 50% of enrolled patients did not undergo surgery	No	Moderate quality clinical study which showed the safety of IMPRINT but not established any clinical use
(36)	1	Not applicable	2011	24	Helical tomotherapy radiotherapy after chemotherapy and EPP or chemotherapy only	HT had comparable toxicity compared to IMRT	No	No	Retrospective study which suggests that HT is safe based on a retrospective study
(37)	1	Not applicable	2012	51	Induction chemotherapy (carboplatin or cisplatin) followed by EPP or PD and radiotherapy	Response rate of 22% (carboplatin) versus 17 (cisplatin). Higher grade 3 anaemia on the carboplatin group	No	No	Moderate quality retrospective study with selection bias not clear conclusions to be drawn
(39)	3	Not applicable	2014	25	IMRT followed by EPP and adjuvant chemotherapy (SMART protocol)	Feasibility study with 25 patients completed trial with no grade 3–5 toxicities	No	No	82% of patients screened were not eligible for the study. Selective population only conclusion that can be drawn is that IMRT followed by EPP is feasible on a selective population
(42)	1	Not applicable	2017	20,561	–	Cancer-directed surgery, chemotherapy, and radiation therapy were associated with improved survival (hazard ratio, 0.77, 0.74, and 0.88, respectively)	No	Yes	Immortal time bias
(30)	2	Not applicable	2015	69	PD or extended P/D, chemotherapy and radiotherapy (IMRT)	OS, PFS and locoregional control no different between groups	No	Not clearly demonstrated results	Moderate quality prospective study showing a high OS post PD and no toxicities post radiotherapy
(31)	4	Phase II clinical study- no control group	2009	77	Chemotherapy followed by EPP followed by radiotherapy	median survival of 16.8 months, 5% of EPP pathological complete response was observed	No	No	Clinical study that showed feasibility of TMT on a selective population
(43)	1	Not applicable	2015	169	Extrapleural pneumonectomy (EPP) and chemotherapy and radiotherapy	75% of patients developed recurrent disease with multimodality treatment	No	Yes	Poor quality retrospective analysis with variabilities on chemotherapy and radiotherapy among patients
(44)	1	Not applicable	2102	530	Extrapleural pneumonectomy and chemotherapy and radiotherapy	Median survival of multimodality group 317 days	No	No	Poor quality retrospective analysis, no control group for comparison, relative risk of death between multimodality treatment and untreated 0.57 and 0.61 respectively
(45)	1	Not applicable	2015	53	Adjuvant radiotherapy following EPP	18.7 months follow up survival	No	Yes	Poor quality retrospective analysis, no control group for comparison, selection bias and no regular reporting of CT scans
(46)	2	Not applicable	2012	25	EPP, neoadjuvant chemotherapy and adjuvant radiotherapy	28% average increase in FVC and 23.9% increase in FEV1	Yes (9 patients excluded)	No	Moderate case series report which shows improvement of FVC/ FEV1 post trimodality treatment with high mortality rates and poor design
(47)	2	Not applicable	2011	102	Radical pleurectomy (RP) followed by chemotherapy (Cis/Pem) and radiotherapy	Surgical morbidity and mortality were 20% and 2.9%. Trimodality mortality was 5.8%	Yes	Yes from the initial 102 patients only 35 included in the analysis and not clear why the rest were not included	Moderate case series showing a lower mortality-morbidity rate with RP
(48)	1	Not applicable	2009	55	Induction chemotherapy, EPP and adjuvant radiation	Overall mortality after EPP 4.3%	Yes	No	Poor quality case series with selection bias, most aggressive cases were excluded from the cohort
(49)	2	Not applicable	2015	24	Intensity modulated radiation therapy after pleurectomy/ decortication (PD) or EPP	IMRT post PD produced high grade toxicity but better overall survival compared to IMRT post EPP	No	Yes-minimal information for the matched control group	Poor quality study
(50)	4	Phase I clinical study	2012	3	EPP followed by hemithoracic IMRT	1 patient had grade 2 complication, 1 developed recurrence	No	No	Phase I feasibility study
(51)	1	Not applicable	2012	41	Chemotherapy followed by EPP followed by radiotherapy	1 year survival was 45% (overall) and patients with trimodality therapy showed significantly better survival rates after 1, 2, 5 years	No	No	Good quality retrospective study suggests that trimodality treatment should be considered in highly selected patients
(52)	3	Not applicable	2011	38	PD and photodynamic therapy	Median progression free survival (PFS) 9.6 months and median survival of 31.7 months	No	No	Retrospective study with selection bias suggesting the safety of lung sparing surgical approach
(53)	1	Not applicable	2009	36	EPP, adjuvant chemotherapy and radiotherapy	Mortality of 11%, PFS was 19 months	No	No	Retrospective study with selection bias, total mortality of 11%
(54)	1	Not applicable	2015	17	Induction chemotherapy, EPP and adjuvant radiation using volumetric modulated arc therapy (VMAT)	1 year overall survival and progression free survival of 43.1% and 55.7 respectively	No	No	Retrospective study which shows suggests that VMAT is safe
(55)	2	Not applicable	2016	210	Registry-no interventions planned	Differences on population treated with MTM compared to chemotherapy or best supportive care	No	No	Registry that shows patients who were treated with MTM were significantly younger, fitter and with better PS
(56)	1	Not applicable	2009	26	Chemotherapy followed by EPP followed by radiotherapy (IMRT)	1 patient died from intracranial hemorrhage, 4 patients had grade 5 toxicities	No	No	Retrospective study focusing on toxicities post radiotherapy
(57)	2	Not applicable	2015	186	Induction chemotherapy followed by EPP	Prognostication score based on database results proposed	No	No	No validation cohort to assess prognostication score-limited use at this stage
(58)	1	Not applicable	2013	103	Hyperthermic intraoperative pleural cisplatin chemotherapy	Patient on treatment group exhibited a significantly longer interval to recurrence (27.1 *vs.* 12.8) and overall survival (35.3 *vs.* 22.8) compared to control	No	No	Poor quality retrospective study with highly heterogenous groups
(59)	2	Not applicable	2015	62	Chemotherapy followed by EPP followed by radiotherapy	Overall survival was 20.4 months, no grade 4 toxicities with radiotherapy	No	No	Retrospective study of moderate quality
(60)	2	Not applicable	2009	83	Chemotherapy followed by EPP (or EPP followed by chemotherapy) followed by radiotherapy	Overall survival of 14.9 months, 4.8% mortality rates	No	No	Retrospective study showed site experience on trimodality treatment

Design: 1= retrospective series; 2= prospective observational cohort; 3 =randomised controlled trial; 4= other. CT, chemotherapy; EPP, extrapleural pneumonectomy; HT, helical tomotherapy; IMRT, intensity modulated radiotherapy; MCR, macroscopic complete resection; NA, neo-adjuvant; OS, overall survival; PD, pleurectomy decortication; PFS, progression free survival; RP, radical pleurectomy.

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