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The Role of Radical Radiotherapy in the Management of Malignant Pleural Mesothelioma: A Systematic Review

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Introduction

Malignant pleural mesothelioma (MPM) is an aggressive and refractory disease with a prognosis of 6–8 months without treatment. It is a rare cancer which is insidious in its early stages and does not lend itself to accurate radiological interpretation for either staging or response assessment. The long latency period and its association with asbestos exposure means that this disease is most frequently seen in a cohort of older patients with additional co-morbidities, thereby making aggressive treatments more challenging to deliver. MPM has proved resistant to a number of therapeutic strategies and the absence of robust, randomised studies in this area has resulted in a lack of consensus on the 'optimal' radical treatment strategy.

The intention of this systematic review is to assess the role of radical radiotherapy in this disease. The use of radiotherapy in MPM has traditionally fallen into 3 categories: to reduce the risk of local metastasis at intervention sites; for palliation of pain; and as part of a tri-modality approach with curative intent in conjunction with surgery and chemotherapy. The use of radiotherapy in a prophylactic capacity is now falling out of favour following a number of negative trials, including a recently published randomised study of 203 patients. [1–3] Robust evidence supporting the use of palliative radiotherapy in MPM was seen in a prospective phase II study, where a standard dose of 20Gy given over 5 fractions was seen to have a clinically significant effect on pain in one third of patients. [4]

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The most aggressive therapy offered to patients with MPM is the trimodality approach of chemotherapy, surgery and radiotherapy. The rationale for radiotherapy in this setting is to 'sterilise' the post-operative volume in an attempt to prevent recurrent local disease. However, the complex shape of the pleura and the dose restrictions necessitated by the close proximity of neighbouring radiosensitive structures renders the safe delivery of high dose radiotherapy in this setting very challenging. Traditional radiotherapy delivery techniques have been found to be unfeasible, with high rates of toxicity and low rates of local control. Nevertheless, recent developments in radiotherapy planning and delivery have revolutionised our ability to dose escalate treatment to the post-operative clinical target volume, whilst keeping doses to normal tissues at an acceptable level.

These developments have come at a time when the surgical landscape of this disease is also changing. The traditional approach of extrapleural pneumonectomy (EPP) is an aggressive and technically difficult operation which aims to remove all macroscopic disease, including the underlying lung. Significant post-operative morbidity has been reported for this technique, even in experienced centres [5–7], but the first and only randomised trial to assess EPP was the Mesothelioma and Radical Surgery (MARS) feasibility study of 50 patients, which concluded that a larger study would not be viable because of the high mortality associated with the procedure. [8] This outcome prompted significant debate and disagreement, since this feasibility study was neither designed nor powered to assess the outcome of surgery versus no surgery. Nevertheless, EPP has now largely fallen out of favour, and the option of pleurectomy/decortication (PD) has become more popular for patients with operable disease. Data from a multicentre non-randomised study of 663 patients suggests that this less radical approach, which leaves the underlying lung intact, is associated not only with lower rates of intraoperative mortality (7% for EPP compared to 4% for PD), but also with a survival benefit (median overall survival of 12 months for EPP compared to 16 months for PD, $p < 0.001$). [9] More recently, a survival meta-analysis of 2903 patients concluded that EPP was associated with significantly higher short-term mortality rates than PD (percent mortality meta estimate: 4.5% vs 1.7%; $p < 0.05$). [10] The shift away from EPP towards PD has presented a further challenge for the radiation oncologist in that the post-surgical delivery of high dose radiotherapy to the hemithorax now needs to be achieved in the context of two intact, radiosensitive lungs.

The aim of this report is to review the recent advances which have taken place in radiotherapy planning and delivery techniques, and to ascertain how these developments have impacted on the feasibility of using photon-based high-dose radiotherapy with radical intent in mesothelioma.

Methods and Results

Relevant articles were found by searching three electronic databases: Embase, MEDLINE (1946 to present) and PubMed. The search terms 'mesothelioma' and 'radiotherapy' were used in full and truncated formats, and no limits were applied. Relevant articles were also identified through hand-searching. An overview of the search is shown in Figure 1. A more detailed description of the literature search, including details of articles which were subsequently excluded from the review, is given in Appendix 1.

A total of 249 articles were reviewed in detail. The nature of these articles is shown in Table 1.

Literature Review

RADIOTHERAPY IN THE CONTEXT OF EPP

The traditional aim of surgery for MPM has been to achieve macroscopic complete resection (MCR), however, this goal is made very challenging by the infiltrative growth pattern of MPM which often involves the fissures and surrounding thoracic structures. Neoadjuvant chemotherapy is often given with the aim of down staging the tumour and increasing the likelihood of a MCR, but local disease recurrence remains a considerable clinical problem. [11–13] Therefore, even though MPM is classically regarded as a radioresistant tumour, post-operative hemithoracic radiotherapy for local control has been an integral part of the treatment approach for decades. [11, 14, 15]

In the context of EPP, delivery of adjuvant radiotherapy is facilitated by the removal of the ipsilateral lung and the subsequent elimination of its dose-constraint. Despite this relative advantage, the remaining target volume for treatment is large and complex, with a number of critical, dose-limiting organs within or adjacent to it.

Conventional radiotherapy techniques following EPP—The complexity of the post-EPP target volume and the obstacle of dose escalation without excessive toxicity has rendered the application of conventional 2D techniques largely obsolete. A number of groups have attempted to find an elegant solution to this problem and a variety of techniques are described in the literature, all of which aim to achieve more selective isodose distributions to the target volume using a 2D or 3D approach, whilst limiting doses to organs at risk.

One such ‘tissue sparing’ approach has been described by investigators at Brigham and Women’s Hospital and the Dana-Farber Cancer Institute. This technique, known as the moderate-dose photon technique (MDRT) utilises parallel opposing photon fields to deliver 30Gy in 1.5Gy fractions to the hemithorax and 40Gy to the mediastinum. Any areas with post-operative positive margins or positive nodes are subsequently boosted to 54Gy using various beam angles. A pattern of failure analysis for this technique following EPP and adjuvant chemotherapy suggested that while treatment related toxicities were acceptable, local failure rates were high at 35%. Furthermore, clusters of disease recurrence at the chest/abdominal junction and retroperitoneal nodes indicated that doses delivered by this technique were insufficient to control the disease. [11]

Another commonly referenced strategy is a combined photon-electron technique, initially described by investigators at Memorial Sloan Kettering in the 1980s. [14] In 2001, Rusch *et al.* used this technique to deliver dose escalated adjuvant radiotherapy in a phase II study incorporating 57 patients, 94.7% of whom had undergone EPP. [16] Parallel opposed photon fields deliver a dose of 41.4 Gy to the hemithorax and mediastinum, following which the spinal cord is blocked and the dose is increased to 54 Gy. Customised blocks shield the liver, stomach, heart and kidney while an electron boost is used to escalate dose to organs under

the blocked areas. This technique permits delivery of an appropriately high dose of radiotherapy to areas of disease without excessive doses to the underlying normal structures. [17] Data from Rusch *et al.* suggests that this approach was well tolerated, with median survival of 33.8 months reported in early stage disease, compared to 10 months in stage III or IV disease ($p=0.04$). Local control was achieved in 90% of cases and the pattern of recurrence appeared to change, with distant metastases noted in 64.8% of the 54 patients who underwent EPP and radiotherapy. [16] A subsequent analysis of 35 patients from the same institute reported local recurrence rates of 37%, predominantly in the inferior regions of the radiotherapy field. This area, which includes diaphragmatic insertion and pleural reflections at the level of L2 is traditionally the most challenging area in which to achieve dose homogeneity. [17] Other publications have also raised concerns over target dose inhomogeneity, with retrospective reports of disease recurrence noting that the majority occurred at match lines or under the shielding blocks. [18]

A retrospective study comparing MDRT with the matched photon/electron technique to 54Gy concluded that radiotherapy technique was not predictive of local or distant failure or of overall survival, but did note that the higher dose was associated with a lower incidence of in-field recurrence. [19]

Intensity Modulated Radiotherapy (IMRT) following EPP—The suggestion that dose escalation may be associated with better disease control in MPM has encouraged the use of more sophisticated radiotherapy techniques which allow dose to be delivered to the tumour with more accuracy. IMRT refers to an advanced radiotherapy delivery technique which increases the conformity of radiation delivery to the complex target volume and in the context of MPM, can achieve a dose distribution across the pleural surface which is more uniform than could be accomplished with conventional 2- or 3-D techniques. [20] Boosts to areas at high risk of disease relapse can be integrated into the treatment plan and delivered simultaneously rather than at the end of treatment. Furthermore, challenges to dose delivery associated with the large field sizes encountered in MPM have been largely overcome by leaf-sequencing algorithms. [21]

A drawback of IMRT is the ‘dose bathing effect’, in which low doses of radiation are necessarily deposited in normal tissues as the gantry rotates around the patient. The potential magnitude of this effect in a post-EPP setting was identified in planning studies comparing dosimetry achieved with IMRT to that achieved using conventional techniques. [22, 23] While IMRT could achieve greater dose homogeneity across the target volume, it consistently delivered higher doses to organs at risk, in particular the contralateral (remaining) lung. In one study, the volume of contralateral lung receiving 20Gy (V20) was increased by 7.2% ($p<0.01$). [23]

MD Anderson was one of the first centres to publish data describing outcomes for IMRT after EPP. Doses to the CTV were 45–50Gy with boosts to 60Gy to areas of clinical concern or positive margins. Target coverage was good (average 97% of CTV received target dose) and normal tissue constraints were met. Early data from 28 patients was very encouraging: 100% local control rates within the treated volumes at 9 months. [24]

Despite initial encouraging data, enthusiasm for IMRT after EPP declined following the publication of toxicity data from 3 large institutions between 2006 and 2008 (Table 2). [25–27] While potential confounders were proposed to explain the high incidence of fatal pneumonitis reported by the Dana-Faber Cancer Institute (higher total dose of radiotherapy and the administration of intraoperative cisplatin), a consistent theme was the correlation of pulmonary toxicity with dose to the single remaining lung. The volume of contralateral lung receiving 5Gy (V5) and the mean lung dose (MLD) have both been linked with the development of pneumonitis but only V20 has been demonstrated to have a statistically significant predictive association. [27] Data from these and other studies have informed recommended dose volume constraints in the post-EPP setting (Table 3). [25, 27–29]

Following the publication of their toxicity data, researchers at the Dana-Faber Cancer Institute described a ‘restricted field’ IMRT technique which reportedly provides excellent target volume coverage within normal tissue dose constraints and greatly improves results for V5, V20 and MLD compared to standard IMRT. [30]

Significant advances in patient imaging, including the advent of 4D CT scanning which allows any respiratory motion of the target volume to be accounted for during the radiotherapy planning process, has increased the accuracy of treatment delivery, thereby reducing the likelihood of geographical misses and toxicity. Several studies have reported the use of FDG PET to assess the extent of disease, and co-registration of these images with the planning CT and MRI have significantly reduced target volume size [31] and facilitated safe dose escalation to areas of clinical concern. [32–34]

These technical advances, combined with the identification of reliable dosimetric predictors of toxicity, has led to increased uptake of post-EPP IMRT particularly in high-volume centres, where encouraging rates of local control have been reported. A prospective study from MD Anderson describe outcomes from 100 patients undergoing EPP, 63 of whom subsequently received IMRT to the postoperative volume at a dose of 45–50Gy in 25 daily fractions (median dose 45Gy), boosted to 60Gy in areas at high risk of recurrence. [35] IMRT was associated with improved median survival: 14.2 months in irradiated patients versus 10.2 months in the overall cohort. This increased to 28 months in patients with node-negative disease and epithelioid histology. Local or regional relapse was seen in 13% of the irradiated cohort, although only 5% experienced recurrence inside the radiation field. Distant recurrences were seen in 54% of patients treated with EPP and IMRT, and 44% of those undergoing EPP only, strongly suggesting a rationale for the incorporation of systemic treatment.

In 2013, the same institution published retrospective data for 86 patients treated with post-operative IMRT to the same dose and fractionation. [29] Chemotherapy was incorporated for 29 patients. Results suggested that IMRT was associated with encouraging rates of locoregional recurrence free survival (88% at year 1; 71% at year 2), with distant recurrence remaining the predominant pattern of failure (45% of the cohort by 1 year). The need for further dose escalation was implied by the observation that 57% of patients with locally recurrent disease had multiple sites of relapse within their radiotherapy field. Nevertheless, the high incidence of significant skin and gastrointestinal toxicity, in addition to the fatal

pulmonary toxicity rate of 5.81%, highlights the challenges associated with attempts to achieve further dose escalation with this technique.

IMRT was employed in the only randomised study of radiotherapy in the treatment of MPM to date, which was conducted by Stahel *et al* and published in December 2015. [36] This multicentre, phase II study involving 14 hospitals across 3 countries was conducted in two parts. In the first, eligible patients were treated with 3 cycles of neoadjuvant chemotherapy (cisplatin/pemetrexed) and EPP. In the second part, patients who had achieved a macroscopic complete resection were randomised on a 1:1 basis to either receive radiotherapy or not. Radiotherapy was delivered by IMRT or 3D conformal techniques, depending on the technologies available at the participating centres, at a dose of 45–46Gy in either 1.75, 1.8 or 2Gy fractions. Areas at high risk for local relapse were boosted to 55.9–57.6Gy. The primary endpoint for the second part of the trial was locoregional relapse-free survival (analysed on an intention to treat basis). A total of 54 patients were recruited to the second part of the study, with 27 patients starting radiotherapy and 25 patients completing the course. The difference in relapse-free survival between the group who received radiotherapy (9.4 months; 95% CI 6.5–11.9) and those who did not (7.6 months; 95% CI 4.5–10.7) was not statistically significant and was deemed to provide inadequate support for the routine use of hemithoracic radiotherapy in this setting.

These data have subsequently come under intense scrutiny, given the potential impact on clinical practice. In a letter to The Lancet, Rimner *et al* argued that the trial was underpowered for its primary outcome measure due to slow patient accrual and substantial patient dropout. In addition, they criticised the heterogenous nature of the radiotherapy planning, the lack of central review and highlighted that the absence of any dosimetry data makes interpretation of the toxicities difficult. They concluded that the study should be viewed as inconclusive rather than negative. [37]

Highly conformal radiotherapy following EPP—Volumetric modulated arc radiotherapy (VMAT) and helical tomotherapy (HT) are progressively more advanced methods of IMRT which theoretically facilitate more precise dose delivery to the tumour with increased sparing of normal tissues, potentially allowing further dose escalation in the difficult post-operative setting.

The dosimetry achieved with IMRT, VMAT and HT in a post-EPP setting have been compared in planning studies. (Table 4) Equivalent dose homogeneity and PTV coverage is achievable with IMRT and VMAT, but VMAT plans are generally associated with improved sparing of organs at risk and can be delivered more rapidly, using fewer monitor units. [38, 39] These data indicate that VMAT may be more suited to the treatment of mesothelioma patients, in whom target volumes are often large and where reduced intra-fraction patient and organ motion would have a significant impact. [40] A study comparing HT to IMRT reported significantly superior target coverage and dose homogeneity for HT. In addition, the mean dose to the contralateral lung could be lowered to less than 5Gy with HT. [41]

The efficacy and safety of VMAT in the post-EPP setting was assessed prospectively in a study of 15 patients at Hiroshima University Hospital. [42] A dose of 54Gy was delivered to

the post-surgical volume in 30 fractions. PTV coverage was acceptable with adequate conformity and dose homogeneity and contralateral lung constraints were met in all patients, but dose constraints were difficult to achieve for liver and heart in right and left sided disease respectively. Toxicity was similar to that seen for IMRT with a 20% incidence of grade 3 pneumonitis but with no grade 4 or 5 toxicities. Rates of local control at one year were reported to be significantly worse in patients with non-epithelioid histology compared to their epithelioid counterparts (non-epithelioid: 0% (95% CI 0%); epithelioid: 83.3% (95% CI 53.5–100%); $P=0.0011$).

Clinical outcomes following adjuvant HT post-EPP were reported by 2 French institutions in 2011. [43] A cohort of 24 patients received adjuvant radiotherapy at a dose of 50Gy to the surgical cavity and 57Gy to areas of clinical concern as identified by FDG-PET. Excellent dosimetry was achieved (median D2 of 105% and median D98 of 98%) with acceptable levels of toxicity (8% rate of both grade 3 and grade 5 radiation pneumonitis). [44] Despite limited follow up (average period of follow up 7 months after radiotherapy), local recurrence was seen in just 8% of patients. Subsequent data in 2013 reported 1 and 2 year overall survival rates of 65% and 36% respectively. [45]

Although VMAT and HT are potentially able to provide a dosimetric and clinical benefit over IMRT, there is currently no prospective evidence to suggest superiority of one rotational technique over the other.

Selection bias—Much of the outcome data of radiotherapy following EPP is derived from surgical series assessing feasibility of the trimodality strategy. A seminal paper published by Sugarbaker *et al* in 1996 reports on a series of patients who underwent neoadjuvant chemotherapy, EPP and hemithoracic radiotherapy at a dose of 30Gy, with boosts of 50–55Gy to areas at high risk of relapse. Survival rates of 45% at 2 years and 22% at 5 years are reported and a subset of patients with epithelioid histology and node-negative disease were identified, in whom 2 and 5 year survival rates were 74% and 39% respectively. [15] Table 5 summarises data from five multicentre studies (including three phase II trials), which assessed efficacy and feasibility of the trimodality approach. [46–50] A variety of radiotherapy techniques were used and median overall survival rates of between 15.5 and 19.9 months are reported, with several studies noting an increase in median survival for patients completing EPP [46, 48, 49] and a further survival benefit in patients completing radiotherapy. [47–49]

It is difficult to draw firm conclusions from the data generated within these studies because of the lack of control groups and randomisation. Patients eligible for EPP are often highly selected at the outset, and tumours amenable to surgical intervention and subsequent post-operative radiotherapy may have had less aggressive underlying biology than their counterparts; this, rather than their oncological treatment, might be responsible for the favourable outcomes reported in these studies. Nevertheless, the outcomes reported for patients completing trimodality treatment by Krug *et al* [48] and Van Schil *et al* [47] compare more favourably than those reported by Stahel *et al*, [36] (29.1, 33 and 19.3 months respectively), suggesting inherent differences in patient selection between these multi-institutional phase II studies.

Despite the challenges associated with interpreting survival data from studies with inherent selection bias, outcomes following post-operative radiotherapy across this cohort do appear to be positively affected by the application of techniques which permit dose escalation. Whilst there is a lack of robust comparative studies between radiotherapy techniques, retrospective data arising from different treatment modalities over time demonstrate substantial differences in local recurrence rates after EPP patients treated with IMRT compared to conventional radiotherapy with parallel opposing fields (14.3% compared to 41.7%; $p=0.03$) and longer times to disease recurrence following IMRT (12 months versus 7 months; $p=0.19$). [51] Furthermore, a matched pair analysis of post-EPP outcomes achieved with adjuvant 3D radiotherapy and highly conformal techniques (IMRT or VMAT) concluded that the probability of local control is increased with IMRT/VMAT through improved target coverage. [52]

RADIOTHERAPY IN THE CONTEXT OF TWO INTACT LUNGS

The inherent biases associated with outcome data generated in the context of EPP may be less pronounced in the context of lung sparing surgery, since patients referred for this intervention generally have more advanced disease and may be less fit than those considered for EPP.

Conventional radiotherapy techniques following PD—The challenge of delivering radical doses of radiotherapy to the pleura whilst sparing the underlying lung is pushing the boundaries of radiotherapy technology. The redundancy of traditional radiotherapy techniques for this purpose has been demonstrated in a number of studies attempting to deliver definitive radiotherapy for disease control using either 2D or 3D methods. Data suggests that although this practice may have palliative benefits, it confers no survival advantage and is often linked with high incidences of radiation pneumonitis. [53–58] Attempts to use the photon/electron technique to increase target volume conformity and facilitate dose escalation post-pleurectomy were shown to have disappointing local control rates (42% at 1 year) and a high incidence of grade 3–4 toxicities. [59]

IMRT following PD—Much of the data assessing the outcome of IMRT with 2 intact radiosensitive lungs has been generated at Memorial Sloan Kettering. This centre used FDG-PET-CT fusion to aid target delineation in patient cohorts with primarily stage III or IV disease following either PD or no surgery. Retrospective data from 36 patients who received pleural IMRT at a median dose of 46.8Gy (range 41.4Gy–50.4Gy) following PD (56%) or no surgery (44%), reported acceptable levels of toxicity (20% incidence of grade 3 or worse acute pneumonitis including 1 death) and median survival of 26 months (95% CI: 8–NR) in surgical patients, compared to 17 months (95% CI: 11–24) in the unresected cohort. [60]

A subsequent retrospective ‘patterns of failure’ analysis published by the same institution, considered 67 patients treated with definitive or adjuvant hemithoracic IMRT at a median dose of 46.8Gy. Neoadjuvant chemotherapy had been given to 76% of the cohort. Local recurrence remained the predominant challenge, with a 2 year local failure rate of 74%, occurring primarily at sites of previous gross disease and highlighting the importance of complete macroscopic resection. Nevertheless, median survival was 24 months in this

cohort, 76% of whom had stage III or IV disease and 37% of whom did not undergo any surgical resection. Furthermore, IMRT after PD was associated with a significantly longer time to local and distant failure than definitive pleural IMRT. [61]

The safety of IMRT following chemotherapy and PD was assessed prospectively in a two-centre phase II study in which 50.4Gy was delivered in 28 fractions. Planning was performed using 4DCT simulation and FDG-PET scans and the primary endpoint was the incidence of grade 3 or worse pneumonitis. The cohort included 45 patients with advanced disease, mainly stage III or IV. A total of 27 patients commenced radiotherapy (median dose 46.8Gy; range 28.8Gy–50.4Gy) and were assessable for the primary endpoint. Final data suggested that this approach was safe and associated with just 2 cases of grade 3 radiation pneumonitis and no grade 4 or 5 toxicities. Local recurrence was the predominant pattern of failure, most often in areas of previous bulk disease. [62]

Data from this work at Memorial Sloan Kettering has facilitated the generation and publication of recommended dose constraints for pleural IMRT in the post PD setting. [63] (Table 3)

Highly conformal radiotherapy following PD—The significant challenge of planning and delivering radical radiotherapy following a lung sparing procedure has encouraged the use of highly conformal techniques. Dosimetric comparisons of IMRT and VMAT have been performed in this setting. [63, 64] A planning study of 20 patients (left sided disease, n=10; right sided disease, n=10) demonstrated that with careful consideration of arc arrangement, both techniques can produce acceptable plans with adequate PTV coverage. Nevertheless, VMAT was able to spare critical organs more effectively than IMRT and was again associated with a shorter treatment time and a requirement for fewer monitor units. [63] (Table 4)

VMAT has been compared with HT in a pilot study performed on a single patient post-pleurectomy. Homogenous PTV coverage and adequate compliance with dose constraints was achieved with both techniques, but HT reduced doses to the contralateral lung (V20, V10, V5: 0%, 2.3%, 17.1% for HT compared to 0%, 14.8%, 65.8% for VMAT). [65] Nevertheless, only limited conclusions can be drawn from a single case report.

Minatel *et al* have published a series of studies prospectively assessing the safety and efficacy of dose-escalated pleural radiotherapy delivered by HT following lung sparing procedures. [66–68] Daily image guidance aided the accurate delivery of 50Gy in 25 fractions to the PTV, while areas of FDG avidity were simultaneously boosted to 60Gy. Early safety data from a prospective study of 28 patients who had undergone PD (71%) or biopsy only (29%) were encouraging, with no fatal respiratory toxicities, and only 7% of the cohort developing grade 3 pneumonitis within 5 months of treatment, the incidence of which strongly correlated with contralateral lung V5. [66] This study was the first to suggest a critical role for contralateral lung dosimetry in patients in whom both lungs were intact.

Long term follow up data was presented for 20 patients, of whom 60% had stage III or IV disease, 95% had received chemotherapy and all had undergone PD. Median overall survival

and progression free survival were 33 and 29 months respectively and while median loco-regional control was not reached, estimates at 2 and 3 years were 68% and 59% respectively. The predominant pattern of failure was distant, with 35% of patients developing metastatic disease as their first site of failure and only 15% having an isolated loco-regional recurrence. No grade 5 toxicities were reported. These results are amongst the best reported for this approach, and are comparable to those achieved for patients completing all treatments within phase II studies of the trimodality approach encompassing EPP. They may perhaps reflect the superior dosimetry achieved with HT, the value of dose escalation in areas of bulky disease and the importance of combining radiotherapy with a cytoreductive intervention. [67]

PRE-OPERATIVE RADIOTHERAPY

Some of the most encouraging data have arisen from a novel radiotherapeutic approach at Princess Margaret Hospital whereby a short accelerated course of neoadjuvant IMRT is delivered prior to EPP. [69] The rationale for this technique is to sterilize the tumour bed with the aim of preventing seeding during surgery. A dose of 25Gy in 5 fractions is delivered to the entire ipsilateral hemithorax over 1 week with a concomitant boost of 5Gy to the gross tumour volume and tract sites. Surgery, specifically an EPP, takes place within 1 week of the radiotherapy. The timing of this is critical, since any delay in removal of the lung would render the patient at significant risk of potentially fatal radiation pneumonitis. Adjuvant chemotherapy is offered to any patients found to have mediastinal nodal disease on postoperative pathology however, only 41% of eligible patients were able to tolerate this additional treatment.

Results of a non-randomised, phase I/II feasibility study incorporating 25 patients with T1–T3, N0, M0 disease were encouraging with no grade 3–5 IMRT-related toxicities and a peri-operative mortality rate of zero. Surgical staging revealed stage III or IV disease in 96% of the cohort and after a median follow up of 23 months, cumulative overall survival was 58% at 3 years. Those with epithelioid histology survived significantly longer (84% at 3 years) than those with biphasic disease. [70] Longer term phase II data from 62 patients, 94% of whom had stage III or IV disease, indicate excellent outcomes in patients with the epithelioid subtype: median overall survival was 51 months and disease free survival 47 months in this group. [69] These outstanding results are likely testament to the surgical skills of de Perrot and colleagues in their management of MPM and the quality of peri- and post-operative care delivered in this high-volume centre of excellence. Although they have not yet been replicated in any other centre, these data strongly suggest that there may still be a role for EPP in carefully selected patients.

DISCUSSION

The lack of progress in MPM treatment over recent years is illustrated by the results of a large retrospective Italian study on survival of MPM patients treated with combinations of chemotherapy, radiotherapy and surgery between 1982 and 2006. [56] Median survival was calculated over 2 separate timelines: 1982–2000 and 2001–2006, and reported as 310 and 340 days respectively. Despite this apparent stagnation, recently published retrospective data from 209 patients treated at a single institution between 1974 and 2015 found improved

overall survival in patients treated with modern trimodality therapy (PD, chemotherapy and pleural IMRT) compared to those treated with PD and conventional radiotherapy alone (median overall survival 20.2 months and 12.3 months respectively; $p < 0.001$). [71] Notwithstanding the limitations of a retrospective analysis and the impact of developments in radiation oncology, surgery and medical oncology over that time, this data does suggest that we are starting to make progress, or at least that we are increasingly able to select appropriate patients for treatment.

The pace of therapeutic advances in MPM can be partially explained by the paucity of good quality data on which to base clinical decisions, as identified in this literature review.

A large proportion of the literature in this area consists of retrospective reviews of single centre practices. In addition to the inherent biases associated with this type of data, many of the studies were further limited by small numbers of patients and insufficient reporting on the technical aspects of radiotherapy planning, delivery or dosimetry. There was variance within and between data sets, particularly with regard to chemotherapy regime and administration, choice of surgical approach, and radiotherapy techniques, which often changed even within a single cohort if it encompassed data collected over a number of years. Furthermore, reporting of important outcomes such as median overall survival varied, with some studies quoting time from diagnosis and others quoting survival from the start or end of treatments. This made comparisons of retrospective datasets very difficult.

A number of conference abstracts were identified which provided insight into current research, but these reports are subject to less robust peer review procedures than journal articles and information on radiotherapy techniques, dosimetry and toxicities was often limited.

A number of non-randomised prospective studies were reviewed. The inclusion of a variety of disease stages and histological subtypes made comparisons across such an inhomogeneous patient group very challenging, however, stratification of patients according to various clinical features did identify certain prognostic factors which showed consistency between studies. Many studies reported on different radiotherapy regimes or techniques over time, but patient numbers were often insufficient to allow meaningful comparison.

Several multicentre phase II studies have been published in recent years. Data from these trials tend to be more reliable as the patient populations were more homogenous and there was less variation in radiotherapy technique and chemotherapy administration. In addition, centres taking part in multicentre studies are more likely to be high-volume centres of excellence with more experience in technically challenging surgical and radiotherapy procedures. Nevertheless, non-randomised studies are inherently prone to selection bias, as typified by the exclusion of patients who were ineligible for surgery. The potential extent of this bias was addressed in a retrospective review of patients referred for trimodality treatment. [72] The authors reported that median and 1 year survival figures for patients who underwent EPP did not differ significantly from those who were referred for the procedure but did not go ahead (20.4 versus 20.7 months and 76% versus 78%, respectively $p = \text{NS}$). The challenge of recruiting patients to a trial of 'treatment' versus 'no treatment' has clearly

been demonstrated in the MARS study, [8] but the suggestion in this publication that patients did better without surgical intervention is indicative of an underlying inherent bias in many of the non-randomised studies that we currently rely on to make clinical decisions.

The difficulty of recruiting patients with MPM into randomised clinical trials of radical treatment is evidenced by the fact that only two such studies have been undertaken to date, and the validity of the outcomes of both have been challenged by the surgical and oncological communities. [37, 73] It is tempting to conclude that underpowered randomised studies are actually detrimental to the clinical evidence base.

Current international guidelines for the use of radiotherapy in MPM are summarised in Table 6 [74, 75] and mesothelioma-specific radiotherapy trials in progress are outlined in Table 7. These include two Phase II studies and just one randomised controlled trial assessing radiotherapy in the palliative setting.

The future role of radiotherapy in MPM remains unclear, however, the accumulation of encouraging phase II data is difficult to ignore. The dramatic advances in radiotherapy planning and delivery which have taken place in recent years have allowed this treatment modality to be offered to patients in whom a pneumonectomy is not feasible. The less complete surgical resection associated with this technique strengthens the case for adjuvant radiotherapy as a means of achieving tumour control in the ipsilateral hemithorax. The requirement for accurate target delineation, normal tissue sparing and homogenous dosimetry has therefore become increasingly important, [61] not just because of the challenge of safely delivering radiotherapy in the presence of the two underlying radiosensitive lungs, but also because of their inherent movement during the respiratory cycle. Despite these difficulties, recent studies indicate that extended survival may be achievable in these patients for whom, until recently, only palliation was considered appropriate.

Whilst recruitment to randomised clinical trials is difficult in this patient population, the community should strive to design and deliver high quality, multicentre clinical trials, in order to generate a strong evidence base. In order to do this, clear guidance is required in terms of both patient selection and radiotherapy protocols. Accurate and reproducible target volume and normal tissue delineation, dose and fractionation, normal tissue constraints, quality assurance protocols, treatment planning and equipment, treatment verification and assessment of toxicity are all essential.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Overview of the literature search

Table 1

Categorisation of articles reviewed in detail

Type of study	Number of papers
<i>Retrospective case series</i>	
Radiotherapy alone	2
Radiotherapy and surgery	11
Radiotherapy and chemotherapy	1
Radiotherapy, surgery and chemotherapy	52
<i>Retrospective single centre case reports</i>	
Radiotherapy alone	2
Radiotherapy and surgery	0
Radiotherapy and chemotherapy	1
Radiotherapy, surgery and chemotherapy	4
<i>Prospective studies</i>	
Radiotherapy alone	1 (single centre)
Radiotherapy and surgery	6 (all single centre)
Radiotherapy and chemotherapy	4 (all single centre)
Radiotherapy, surgery and chemotherapy	46 (14 multicentre studies)
Letters to the editor	15
Systematic reviews	4
Reviews of the role of radiotherapy in MPM	21
Reviews of management of MPM	26
Technical studies/ radiotherapy planning studies	53

Table 2

Toxicity data for IMRT following EPP

Centre	MD Anderson	Dana-Faber Institute/ Brigham & Women's Hosp	Duke University Medical Centre
Publication date	2007 [27]	2006 [25]	2008 [26]
Nb patients	63	13	13
Median dose to γ CTV/ β PTV	45 or 50Gy/25#	54Gy/30#	45Gy (39.6–55)/25#
Boost	60Gy	60Gy	55–60Gy
Chemotherapy regime	Cisplatin/Pemetrexed (3), Erlotinib (1), Cisplatin Analogue (1)	Cisplatin/Pemetrexed (13) Intraoperative heated Cisplatin (12)	Cisplatin/Pemetrexed (12)
Planning	CT	CT/PET fusion	PET-CT (62%) 4D CT
IMRT technique	Step and shoot	Sliding window	Sliding window
OARs			
Contralateral lung ϵ V20	< 20%	< 20%	<10%
MLD	<8.5Gy	<15Gy	<8Gy
Liver V30	<30%	<33%	<40%
		Mean <31Gy	Mean <30Gy
Contralateral kidney	V15 <20%	V15 <20%	Max dose <5Gy
Heart	V45Gy <50%	V45 <30%; V50 <20%	Mean dose <22Gy
Spinal cord	V45Gy <10%; V50Gy =0	V45Gy <10%; V50Gy =0	Max dose <45Gy
Oesophagus	V55Gy <30%	V55Gy <30%	Max dose <50–55Gy
Small bowel	Not specified	Not specified	Max dose <45Gy
Stomach	Not specified	Not specified	Max dose <45Gy
Mean V20	4.9%	15.2%	3.93%
Mean MLD	8.3Gy	13.8Gy	8.07Gy
Fatal pulmonary toxicity rate	6/63 (9.5%)	6/13 (46%)	1/13 (7.7%)
Median dosimetry with vs. without fatal pulmonary toxicity	V20 (%) 9.8 vs 3.6 (p=0.002)	V20 (%) 17.6 vs. 10.9 (p = 0.08)	V20 (%) 7 vs. 4 (p = NS)
	MLD (Gy) 10.2 vs 7.6 (p=0.013)	MLD (Gy) 15.2 vs 12.9 (p=0.07)	MLD (Gy) 11 v.s 8 (p = NS)

 γ CTV: Clinical target volume β PTV: Planning target volume ϵ V_x: volume of organ receiving xGy (%)

MLD: Mean lung dose

Table 3

Recommended dose-volume constraints in the post-EPP and post-PD setting

Structure	Parameter	Objective post EPP	Objective post PD
Contralateral lung	MLD	* <8 Gy	$\bar{T}$ 8Gy
	V5	+ <60%	$\bar{T}$ <25%
	V10	γ <50%	Not specified
	V20	$\mathcal{L}$ <7%	$\bar{T}$ 7%
Oesophagus	V50	* < 50%	Not specified
	Mean dose	* <34 Gy	$\bar{T}$ 34Gy
	Dmax	γ <66Gy	Not specified
Heart	V30	* 45%	$\bar{T}$ 50%
	Mean dose	* <26 Gy	$\bar{T}$ 30Gy
Spinal cord	Dmax	* <45 Gy	$\bar{T}$ 50 Gy
Liver	V30	* 40%	$\bar{T}$ 50%
	Mean dose	* <30 Gy	$\bar{T}$ 31Gy
Contralateral kidney	Dose to 2/3	* <30 Gy	Not specified
	V18	Not specified	r 33%
Ipsilateral kidney	V18	Not included as OAR	$\bar{T}$ 50%
Stomach (not PTV)	Mean dose	Not included as OAR	$\bar{T}$ 30Gy
Bowel	D0.5%	Not included as OAR	$\bar{T}$ 50Gy

* Taken from Gomez *et al* [29] γ Taken from Kristensen *et al* [28]+ Taken from Allen *et al* [25] $\mathcal{L}$ Taken from Rice *et al* [27] $\bar{T}$ Taken from Dumane *et al* 2016 [63] r Taken from Dumane *et al* 2012 [64]

Table 4
Dosimetry data for planning studies comparing IMRT with VMAT and HT in post EPP and post PD settings

Author	Scorsetti [38]	Sterzing [41]	Dumane [63]	
Date	2010	2008	2016	
Surgical setting	Post EPP	Post EPP	Post PD	
Nb of patients	6	10	20	
Dose to PTV	54Gy	54Gy	50.4Gy	
Techniques/ P value	VMAT Rapid arc	HT (high IMF)	VMAT 2 arcs LL range	IMRT (Sliding window) 9 Coplanar beams Beam angle 200° range
Beam energy	15mV	6mV	6mV	6mV
MU to deliver 2Gy/#	734 +/-82	Not detailed	1000 (average)	3000 (average)
Treatment time (min)	3.7 +/-0.3	19.7 +/-3.2	5 (average)	15 (average)
PTV coverage V _{95%}	93.5 +/-3.4	96.42 +/-0.76	<0.0001	94
CI 95	1.1 +/-0.1	1.13 +/-0.07	ns	1.5 +/-0.2
				0.16
Doses to OARS				
Contralateral lung V5	47.9 +/-7.4	37.6 +/-6.92	<0.0001	32.9 +/-15.7
Contralateral lung V20	0.4 +/-0.4	0.09 +/-0.13	<0.0001	0.2 +/-0.5
Contralateral MLD	5.6 +/-0.7	4.85 +/-0.33	<0.0001	4.7 +/-1.3
Spinal cord				5.1 +/-1.1
Dmean		14.69 +/-3.59	ns	
D1%				
Dmax	38.6 +/-2.1	39.7 +/-2.5	0.5	
Liver				
Dmean [#]		39.52 +/-3.89	ns	45.3 +/-4.7
Dmean [†]				45.2 +/-4.1
Dmean	14.7 +/-8.1	16.6 +/-8.1	0.04	
Oesophagus Heart				
Dmean	26.8 +/-6.1	30.9 +/-7.9	0.03	
Dmean	24.6 +/-8.5	29.1 +/-6.0	0.02	
Dmean [#]				
Dmean [†]				

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IMF: intensity modulation factor; CI95: ratio between the patient volume and the PTV volume receiving more than 95% of the prescribed dose
V95%: percentage of target volume receiving more than 95% of the prescribed dose; Dmean: Mean dose to organ in Gy (#P: Right sided disease; †: Left sided disease)
LL: Lung Limit range (defined by most medial anterior and posterior edges of the contralateral lung)

Data from 5 multicentre studies assessing the efficacy and feasibility of trimodality treatment

Table 5

Author	Federico [50]	Hasegawa [49]	Krug [48]	Weder [46]	Van Schil [47]
Date of publication	2013	2016	2009	2007	2010
Type of study	Phase II	Prospective feasibility	Phase II	Prospective	Phase II
Number of patients	54	42	77	61	59
Stage of disease	T1-3, N0-2	T0-3, N0-2	T1-3, N0-2	T1-3, N0-2	cT1-3, N0-1
Induction chemo	Cisplatin 75mg/m ² Pemetrexed 500mg/m ² x3	Cisplatin 60mg/m ² Pemetrexed 500mg/m ² x3	Cisplatin 75mg/m ² Pemetrexed 500mg/m ² x4	Cisplatin 80mg/m ² Gemcitabine 1000mg/m ² x3	Cisplatin 75mg/m ² Pemetrexed 500mg/m ² x3
Type of surgery	EPP	EPP	EPP	EPP	EPP
Planned radiotherapy dose	54Gy (30 x 1.8Gy) Protocol amendment: 50.4Gy (28 x 1.8Gy)	54Gy (30 x 1.8Gy)	54Gy (30 x 1.8Gy)	Macroscopic disease: 60Gy (30 x 2Gy) High risk areas: 50Gy (25 x 2Gy)	54Gy (30 x 1.8Gy)
Median radiotherapy dose	50.4Gy (21.6 – 54Gy)	Not reported	45.9Gy (0.28 – 60Gy)	Not reported	54.0Gy (43.2 – 54.0)
Radiotherapy technique	Not specified	3D conformal with matched photon/electrons	Matched photon/electrons IMRT	Not specified	3D conformal IMRT
Median OS	15.5 mths (95% CI: 11 – NA)	19.9 mths (95% CI: 14.2 – 27.3)	16.8 mths (95% CI: 13.6 – 23.2)	19.8mths (95% CI: 14.6 – 24.5)	18.4mths (95% CI: 15.6 – 32.9)
Number completing TMT	22 (40.7%)	17 (40.5%)	40 (51.9%)	36 (59%)	37 (62.7%)
Median survival for patients completing chemo and EPP	Not recorded	22.7 mths	21.9 mths (16.8 – 29.1)	23 mths (95% CI: 16.6 – 32.9)	Not recorded
Median survival for Patients completing TMT	Not recorded	39.4 mths	29.1 mths	Not recorded	33 mths
Conclusion	Feasible approach Manageable toxicity profile in carefully selected cohort	Risk:benefit ratio not sufficient to recommend treatment	Feasible approach associated with reasonable long term survival rate	Feasible approach with no increase in psychological distress	Feasible approach but not achievable in protocol timeframe Insufficient data to support use out-with institutions with high levels of expertise

Table 6

Current international guidelines for the use of radiotherapy in MPM

Guidelines for the diagnosis and treatment of malignant pleural mesothelioma, JTD 2013 [74]	
<u>Recommendation</u>	<u>Grade of recommendation</u>
Mesothelioma is sensitive to moderately high radiation doses and radiotherapy is advocated for palliation of symptomatic tumour masses arising from the pleural cavity or metastases in other locations	C
For doses greater than 50 Gy, advanced radiotherapy technologies with strict constraints for contralateral lung doses are recommended to avoid excessive toxicity	C
The administration of prophylactic radiotherapy following pleural interventions in patients with mesothelioma has no significant effect on changing the disease course and is not recommended	C
ESMO Clinical Practice Guidelines 2015 [75]	
<u>Recommendation</u>	<u>Grade of recommendation</u>
Consider radiotherapy for palliation of pain related to tumour growth	A
The use of RT to prevent growth in drainage tracts is not proved to be useful	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	A
When postoperative RT is applied, strict constraints must be adhered to in order to avoid toxicity to neighbouring organs, and special, tissue sparing, techniques should be used	A

Table 7

Radiotherapy trials in progress for MPM

Study name	Neoadjuvant Accelerated Hypofractionated Radiation Therapy Immediately Prior to Radical Pleurectomy/Decortication for Malignant Pleural Mesothelioma: A Pilot Study	Pilot Study of the Feasibility of Intrapleural Photodynamic Therapy in a Multimodal Treatment Combining Extended Pleurectomy/Decortication, Adjuvant Chemotherapy and Prophylactic Radiotherapy in Patients With Malignant Pleural Mesothelioma	Chemotherapy Followed by Surgery and Neoadjuvant Hemithoracic Intensity Modified Radiation Therapy (IMRT) for Patients With Malignant Pleural Mesothelioma	SYSTEMS-2: A Randomised Phase II trial of standard versus dose escalated radiotherapy in the treatment of pain in malignant pleural mesothelioma
Phase	Early Phase 1	Phase II	Observational	Phase II
Primary outcome	To determine the feasibility and toxicity (both acute and chronic) of accelerated hypofractionated neoadjuvant helical intensity modulated radiation therapy prior to pleurectomy/decortication for malignant pleural mesothelioma	Number of Patients having the full multimodal treatment without unacceptable and unexpected toxicities (grade 3)	Survival status upon review of patients every 6 months	Establish whether dose escalated, hypo-fractionated radiotherapy (36 Gy in 6#) increases the proportion of MPM patients experiencing a clinically significant improvement in pain (at treatment site) at 5 weeks compared with standard radiotherapy (20 Gy in 5#)
Opened	September 2015	January 2016	November 2015	August 2016
Est completion date	January 2018	November 2017	December 2018	August 2018
Recruitment target	10 patients	6 patients	200 patients	112 patients
Location	USA	France	USA	UK