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Review

The role of radiation treatment in pleural mesothelioma: Highlights of the 14th International Conference of the International mesothelioma interest group

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ARTICLE INFO

Keywords:

Mesothelioma

Radiation

Palliation

Radiotherapy

ABSTRACT

Radiation remains an important component of mesothelioma treatment in 2018. Its use as a treatment modality continues to evolve as the technology for planning and delivery continues to improve. Use of radiation to improve local control in the involved hemithorax has been a common adjuvant treatment post extrapleural pneumonectomy for many years. Modern treatment options with advanced planning techniques including protons and intensity modulated radiation therapy lead to new potential options for treatment post lung-sparing surgery or in the unresectable setting. Presentations and discussions on the implementation of these strategies for palliation, treatment of oligometastatic recurrence or unresectable disease were the focus of a session dedicated to the role of radiation therapy at the 14th International Conference of the International Mesothelioma Interest Group and are reviewed in this article. Preclinical data to better understand how to integrate radiation and the delivery of novel systemic therapy approached like check point inhibitors are also presented.

1. Introduction

The International Mesothelioma Interest Group (IMIG)'s biennial conference in Ottawa, Canada held a session that addressed the contributions of Radiation Oncology to the treatment of this disease. While the contribution of hemithoracic radiation to the local control of this disease has held much interest, this session explored the application of radiation in other clinical scenarios. The ideas presented around the application of palliative approaches to radiation delivery that improve symptom burden in this disease are being addressed in a randomised trial in the United Kingdom. In a similar vein the idea of using modern radiation techniques of 4D imaging and IMRT, SBRT and protons to improve symptom burden or in cases of oligometastatic disease to try to improve progression-free and overall survival were presented. There is a huge push in the world of thoracic oncology to try to implement strategies where immune oncology agents are integrated into the treatment of disease. Researchers from Western Australia present their

preclinical data about how the addition of checkpoint inhibitors to radiation improves local control. They highlight the need to understand the interactions of radiation and these agents at a mechanistic level to achieve improved survival. Many of these strategies are still at an early level of implementation. This review article provides an overview of the content and discussion at the Radiotherapy session at the 14th International Conference of the International Mesothelioma Group in May 2018.

2. Palliative Radiotherapy in Malignant Pleural Mesothelioma (MPM)

This review presentation addressed the possible roles for radiation in MPM aside from radical dose hemithoracic treatment. The evidence for the use of low dose radiation in preventing chest wall metastases at sites of interventions was evaluated, with reference to updated international guidelines. Pain remains a difficult symptom for the majority

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<https://doi.org/10.1016/j.lungcan.2019.03.023>

Received 23 March 2019; Accepted 24 March 2019

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of MPM patients. The potential of palliative radiotherapy to relieve pain was explored, highlighting recent and ongoing clinical trials SYSTEMS-1 and 2. The UK National Lung Cancer Audit demonstrated that in 2016 only 16.5% UK patients with MPM received any form of radiotherapy treatment [1]. Boutin [2] proposed that prophylactic radiation to the chest wall reduced incidence of tract metastasis from 40% to zero. This was challenged by subsequent randomised trials [3] but with varying practice and guidelines internationally. Two recent large RCTs [4,5] with a combined total of 578 patients and in an era of chemotherapy, have concluded that the risk of metastasis is low (< 10%), that any metastases are rarely painful and that prophylactic radiation does not significantly alter the risk of metastases. The current consensus is that there is no role for prophylactic RT to intervention sites acknowledged in both the BTS and ASCO guidelines of 2018 [6,7].

The complex and problematic pain of MPM impacts hugely on quality of life for patients. Although radiotherapy has an established role in palliation of pain in other malignancies the evidence base in MPM was historically limited to series mainly without prospective validated measures and with inconsistent results. SYSTEMS-1 [8,9] was the largest ever prospective trial of palliative RT in MPM and demonstrated effective pain relief in a subset of patients with short course simple palliative regimen of 20Gy/5. Response rate was 47% in evaluable patients at 5 weeks (35% ITT). The ASCO guidelines 2018 include this study for consideration of RT for pain relief.

3. SYSTEMS-2: A phase II randomised study of radiotherapy dose escalation for pain control in malignant pleural mesothelioma

The design of SYSTEMS-2, a randomised study of radiotherapy dose escalation for pain control in MPM, was presented at IMIG 2018 (Fig. 1). SYSTEMS-2 employs a hypo-fractionated, dose escalated regime (36Gy/6#), that will be compared with the standard dose (20Gy/5#) [10]. The primary endpoint is pain at the radiotherapy site at week 5, assessed using the Brief Pain Inventory (BPI). Secondary endpoints include acute toxicity, radiological response, quality of life and overall survival. Exploratory endpoints include biomarker studies of radiotherapy response.

A total of 112 patients will be recruited from 10 to 20 centres across the United Kingdom. Eligible patients will have a histological or multidisciplinary team diagnosis of MPM, a pain score of $\geq 4/10$ after analgesia optimisation, a performance status 0–2, a contrast-enhanced CT scan within 8 weeks of radiotherapy and a radiotherapy plan compatible with the dose escalated arm prior to randomisation.

To ensure that appropriate sites are targeted, wire markers will be used to delineate sites of pain at planning CT acquisition (Fig. 1). Advanced radiotherapy techniques will be employed to facilitate safe dose escalation. Use of intensity modulated radiotherapy (IMRT) is strongly encouraged, however if this technology is not available at participating sites then 3-D conformal techniques may be used. Dose constraints to organs at risk (OAR) surrounding the PTV should be used to guide radiotherapy planning. If there is concern about the risk of acute

toxicity due to PTV size or OAR dose, the final fraction of the dose escalated arm may be omitted, treating with 30Gy/5 fractions.

Patients will be assessed for their pain score at baseline, at the end of radiotherapy and at weeks 5 and 9. A clinically significant response will be regarded as a fall of ≥ 2 points in the ‘worst pain’ component of the BPI from baseline to week 5.

Radiological response will be assessed with a contrast-enhanced CT scan at week 9. This will be reviewed in conjunction with the radiotherapy plan in order to identify the target volume and response will be reported according to the Modified RECIST Criteria. This will be a centrally-run process, conducted in Glasgow by a single radiologist, blinded to the radiotherapy dose received by the patient.

SYSTEMS-2 is currently open at 10 UK centres, with a further 10 sites in set up. 44 patients are currently registered, with 37 randomised. Satisfactory dose-escalated plans have been achieved for all patients and radiological responses have been noted.

Results will inform the optimal dose and fractionation of palliative radiotherapy in MPM. Radiological data will enable further characterisation of radiation responses and their correlations with clinical outcome. Biomarker studies of radiotherapy response could facilitate the prospective identification of patients who may benefit from radiotherapy (Fig. 2).

4. Stereotactic body radiation therapy (SBRT) as salvage therapy for oligometastasized pleural mesothelioma after curative intent multi-modal therapy

Malignant pleural mesothelioma has a devastating prognosis, even after recent advancements in therapy options in a curative intent multimodality treatment. Though overall survival for MPM patients is positively influenced by multimodal treatment concepts including induction chemotherapy followed by macroscopic complete resection, the main limiting factor is still the high local recurrence pattern in this disease. Pleural and regional relapses are common and sometimes warrant an aggressive local salvage strategy.

In a retrospective series, investigators from Zürich evaluated the feasibility and clinical outcome after local radiotherapy, mostly by stereotactic body radiotherapy (SBRT) for oligometastatic MPM. Data from 12 patients treated with salvage radiotherapy for recurrent MPM following the initial treatment was analyzed with a focus on clinical outcome including treatment related toxicity and survival as well as treatment associated parameters. The radiation treatment delivery was planned with a CT acquired as 4D-CT with retrospective amplitude-based image sorting. If possible, an additional 3D-CT was performed in free breathing to allow for contrast intravenous injection. Gross tumor volume (GTV) was contoured as the visible tumor in the planning CT supplemented by information from FDG-PET or magnetic resonance imaging (MRI) if available. No additional CTV margin was added (i.e. GTV = CTV). The internal target volume (ITV) was generated as a composite GTV from the different amplitude-based reconstructed CT scans complemented by a margin of 5 mm to derive the planning target

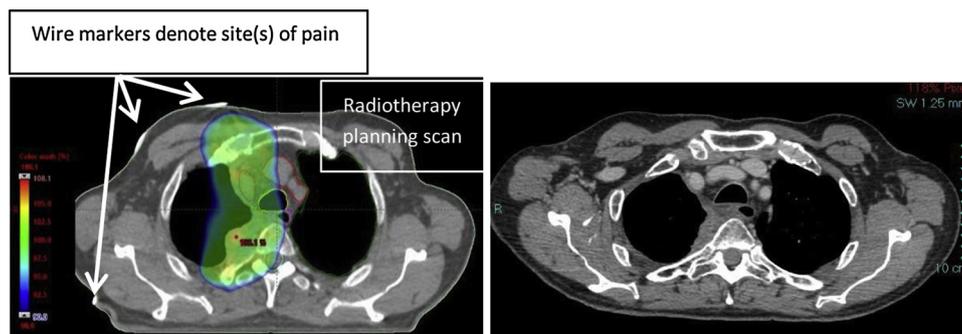


Fig. 1. Wire markers facilitate accurate delivery of IMRT to sites of pain, with radiological responses being achieved at week 9.

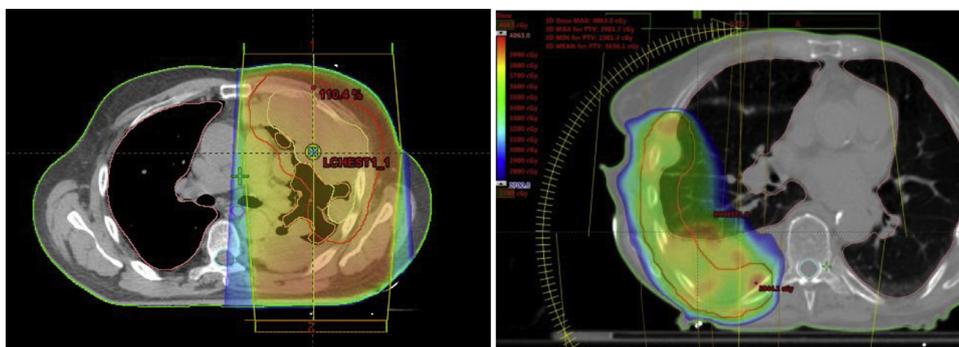


Fig. 2. (a) Simple AP/PA simple RT plan for SYSTEMS I. (b) VMAT/IMRT plan to enable dose escalation for SYSTEMS II.

volume (PTV).

During the time period from 2005 to 2015, 12 patients with ($n = 6$) or without ($n = 6$) initial induction chemotherapy or additional intracavitary chemotherapy ($n = 3$) followed by macroscopic complete resection (MCR) were identified as having received salvage SBRT for oligorecurrent disease with a total of 29 lesions targeted. The median number of lesions treated per patients was 2 (range 1–3). The respective volumes ranged from 0.4 cc to 311 cc (median 6.8 cc). The median single fraction dose was 6.0 Gy (range 2.5 Gy–12.5 Gy) with a median number of fraction of 5 (range 3–15) and a median prescription isodose of 65% (range 65–100%). The median EQD2Gy (2 Gy equivalent dose) was 53.6 Gy (range 37.8 Gy–105.8 Gy).

Crude in-field failure was 7% with a 12 month actuarial local control of 94%. The median progression free survival after SBRT was 11 months (95%CI: 5.6–26.4) and the overall survival at 3 years was 71.3%, while the median OS has not been reached at the time of analysis, as nine patients were still alive at last follow up. Additional courses of SBRT were applied in 7 patients, before widespread metastatic disease developed (median number of SBRT course was 2, range 1–3).

Two patients experienced Grade 3 toxicity. One suffered from a fractured rib located in close proximity to the radiation field (3 fractions with 12.5 Gy fraction dose (65% IDL)). The other patient developed an upper GI hemorrhage during radiotherapy of the mediastinum for a recurrent MPM infiltrating the esophagus. This patient died of massive esophageal bleeding three months after radiotherapy.

To our knowledge, there is no other study, which reports “Stereotactic Body Radiation Therapy (SBRT)” as local treatment in recurrent malignant pleural mesothelioma. SBRT is a safe and locally effective treatment option for recurrent MPM. SBRT provided a very encouraging treated metastases control of 94% at 12 months. Overall, in selected patients with localized and low tumor burden, SBRT may be a promising local ablative therapy to provide effective local control in a short overall treatment time to delay systemic therapy until further disease progression.

5. Understanding the immune response to radiotherapy in a dual tumour model of mesothelioma

Radiotherapy has been shown to increase tumour cell immunogenicity as well as induce an immune response to neoantigens [11]. Even abscopal effects distant from the irradiated tumor have been observed when radiotherapy was combined with immunotherapies (Postow et al., NEJM 2012). However, the exact mechanism and timing of these events is unknown and these observations have not yet been described in mesothelioma models or patients with mesothelioma. Australian investigators developed a bilateral tumour model of subcutaneous mesothelioma in order to study differences between immune responses in irradiated vs non-irradiated tumours within the same host. They used two asbestos derived models of murine mesothelioma (AB1 &

AE17 tumour cell lines in Balb/c and C57BL/6 mice respectively) to examine radiation doses of either 9, 18, or 27Gy, fractionated across 3 days. Only one tumour was irradiated per mouse, sparing the contralateral tumour and creating an experimental model with a non-irradiated tumour site. Radiation was administered to anaesthetized and restrained mice using a CT image (< 10 cGy/min) guided small animal irradiator (X-RAD SmART, 225 kVp, 4.5kW, 0.3mm Cu) to tumours. Tumor growth was monitored and intratumoral immune cells and markers were assessed using 11-parameter flow cytometry. Experiments using anti-PD1, anti-CTLA4, anti-OX40, and anti-TIM3 were performed with radiotherapy in an attempt to further modulate the immune response.

In small-to-medium AB1 tumours (20–50mm²) in BALB/c mice, localized radiotherapy with 18 or 27Gy resulted in reduced tumour growth in all mice when compared to non-irradiated control tumors, whereas a single dose of 9Gy showed no significant effect on tumor growth. Larger tumours (50–80mm²) demonstrated delay in growth followed by a period of tumour shrinkage in the 18 or 27Gy treated groups, although all tumours eventually grew out. Findings were similar using AE17 tumours in C57/BL6 mice. Addition of single agent checkpoint blockade to radiotherapy did not affect secondary tumours synergistically. Finally, preliminary experiments indicated that localized radiotherapy increased the expression of T cell activation and checkpoint markers PD-1, OX40, and TIM-3 on TILs in irradiated, but not in non-irradiated tumours in individual mice.

These data demonstrate a dose and fractionation schedule required to observe an anti-tumour response in these mesothelioma models. Single agent checkpoint blockade therapy does not appear capable of improving secondary tumour outcomes when combined with radiotherapy using the scheduling described here, however increased local tumour control was observed. Changes have been identified in the immune response to radiotherapy in the tumour microenvironment that could inform selection of combination adjunctive immunotherapies, in order to enhance the antitumor effect of radiotherapy in the future.

6. Radiation therapy: radical/salvage approaches

In most pleural mesothelioma patients receiving radiotherapy, the modality is delivered for palliative purposes. However, radiation therapy has also been used in mesothelioma to prevent instrument tract site recurrences [2], as neoadjuvant therapy in select cases prior to extrapleural pneumonectomy [12], as adjuvant hemi-thoracic therapy after extrapleural pneumonectomy [13], and now more recently as adjuvant whole pleural radiotherapy after lung-sparing extended pleurectomy-decortication [14].

As the use of lung-sparing surgery with the intention of achieving a macroscopic total resection for malignant pleural mesothelioma is increasing [15], advanced radiation techniques have become increasingly important to deliver in the adjuvant setting. In fact, intensity-modulated radiation therapy (IMRT) has been implemented safely in a

prospective study and recently reported [14], and it now represents the most commonly used adjuvant technique for mesothelioma treatment [16].

A new concept of using radiation therapy as definitive therapy for malignant pleural mesothelioma was presented to propose an expansion of the use of radiation therapy as salvage therapy after surgical or systemic therapy failures. Patients with local progression of mesothelioma can have significant morbidities, including respiratory compromise, pain, and hemoptysis. Aggressive local therapy can help to control or prevent such symptoms. In patients who have more limited sites of progression after prior therapies, including those with progression or recurrence after surgery or systemic therapy, radiation therapy can effectively salvage patients with ipsilateral thoracic oligoprogressive disease by treating all sites of gross disease recurrence. In such cases of limited progression, radiotherapy may be effectively delivered with stereotactic body radiation therapy (SBRT). When progression is not amenable to SBRT due to the diffuse nature of the disease, disease extent, or location, conventionally fractionated or mildly hypofractionated radiotherapy should be considered, and advanced modalities like IMRT or proton therapy [17] may help to reduce the irradiation dose to nearby organs at risk. In those scenarios more comprehensive radiation therapy, potentially such as hemi-thoracic whole pleural radiotherapy, may be used as more radical and salvage treatment modality.

Although mesothelioma is a relatively radiosensitive tumor [18,19], the use of definitive or aggressive salvage radiotherapy has been limited to date, likely due to concerns of potentially fatal complications when treating large volumes of the lung and heart to high doses. When treating these large volumes, including whole pleural radiotherapy with IMRT or proton therapy, it is recommended that patients are enrolled on prospective clinical trials or treated at high-volume centers of excellence. It is known that patients undergoing definitive surgery for mesothelioma have more favorable outcomes when treated at high-volume centers [20], and given that treatment at high-volume centers is associated with better overall survival following irradiation for locally advanced non-small cell lung cancer [21], radiation oncology expertise for pleural mesothelioma treatment and adherence to strict to dose-volume constraints are imperative. Radiotherapy treatment planning and target delineation for salvage or definitive mesothelioma treatment may be aided by the use of advanced imaging modalities, including PET/CT [22] and MRI [23] imaging.

7. Conclusion

The Radiation Oncology session at the 2018 edition of the IMIG conference demonstrated that radiotherapy is a highly effective treatment modality in MPM even for those patients for whom radical surgery and hemithorax radiation are not an option. SYSTEMS-2 promises better understanding of the possible benefit of dose escalated palliation. The advent of proton therapy and application of SBRT opens the way for more conformal therapy to problematic sites of disease or for local progression/metastases. Further potential research is the combination of radiation, even at low dose, as a primer or adjunct to immunotherapy and finally we need to explore the biology of the abscopal effect of radiation which has now been observed in MPM. The next meeting in 2020 will provide an opportunity to showcase the advancements made on this topic.

Acknowledgements

This paper has been endorsed by the Publication Committee of the International Mesothelioma Interest Group (IMIG)

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