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Short Communication

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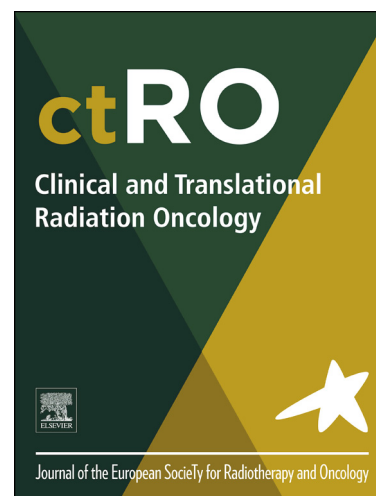
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SYSTEMS-2: A randomised phase II study of radiotherapy dose escalation for pain control in malignant pleural mesothelioma

M. Ashton^{*1,2}, N. O'Rourke², N. Macleod², B. Laird³, J. Stobo⁴, C. Kelly⁴, L. Alexander⁴, K. Franks⁵, K. Moore², S. Currie², R. Valentine², A.J. Chalmers^{1,2}

¹University of Glasgow; ²Beatson West of Scotland Cancer Centre, Glasgow; ³Edinburgh Cancer Centre; ⁴Cancer Research UK Clinical Trials Unit, Institute of Cancer Sciences, University of Glasgow, Glasgow; ⁵St James' Institute of Oncology, Leeds

*Corresponding author: Dr Miranda Ashton, Beatson West of Scotland Cancer Centre, 1053 Great Western Road, Glasgow. G12 0YN
Email: miranda.ashton@glasgow.ac.uk

Summary

SYSTEMS-2 is a randomised study of radiotherapy dose escalation for pain control in 112 patients with malignant pleural mesothelioma (MPM). Standard palliative (20Gy/5#) or dose escalated treatment (36Gy/6#) will be delivered using advanced radiotherapy techniques and pain responses will be compared at week 5. Data will guide optimal palliative radiotherapy in MPM.

Introduction

Malignant pleural mesothelioma (MPM) is a rare, aggressive cancer with a dismal prognosis. [1] As there are no curative options, management focuses on palliation. Pain is the most common symptom. [2, 3] It is typically dull and diffuse and worsens throughout the course of the disease. [4] Aetiology is multifactorial, often including neuropathic and bone related components which can be difficult to control, and patients are often on a variety of analgesics with inadequate relief. [5]

Radiotherapy for pain control is recommended by the British Thoracic Society as a component of standard care. [4] Nevertheless, a systematic review conducted in 2014 revealed that only Level 3 evidence was available to support this practice and highlighted the need for robust and accurate symptom response data. [6] We therefore conducted the SYSTEMS study, a multicentre, single arm phase II study of conventional dose palliative radiotherapy in MPM (20Gy in 5#), delivered using parallel opposing beams. The first prospective study to use validated outcome measures to assess pain in MPM, SYSTEMS recruited 40 patients over 18 months and reported clinically significant pain responses 5 weeks after radiotherapy in one third of patients, with minimal toxicity. [7]

We hypothesised that a higher radiation dose would achieve clinically meaningful pain responses in a greater proportion of patients and might extend analgesia duration. We will test this hypothesis in SYSTEMS-2, which will compare the effects of dose escalated and standard dose radiotherapy on pain control in MPM patients. Recognising that dose escalation might increase toxicity, which could negate any palliative benefit of the treatment, we will utilise advanced radiotherapy delivery

techniques, predominantly intensity modulated radiotherapy (IMRT), to facilitate dose escalation to tumour volumes whilst maintaining acceptable doses to normal tissues.

Responses to radiotherapy doses can be predicted using the α/β ratio of the tumour. Whilst there are little data on which to estimate the α/β ratio of MPM, its relatively low proliferation rate, mesenchymal origin and apparent radioresistance are suggestive of a low α/β value. [7] For this reason, and to allow palliative treatment to be delivered succinctly, a hypofractionated regime of 36Gy in 6 fractions over 2 weeks has been selected for the dose escalation arm of SYSTEMS-2.

Methods/Study Design

SYSTEMS-2 was developed through multidisciplinary collaboration between the Beatson West of Scotland Cancer Centre, Edinburgh Cancer Research Centre and the Cancer Research UK Clinical Trials Unit Glasgow. The study is sponsored by NHS Greater Glasgow and Clyde and the University of Glasgow (GN13ON388). Ethical approval was granted from the National Research Ethics Committee on 19th January 2016 (REC number 15/SS/0225). The study complies with Research Governance Framework for Health and Community Care, the British Good Clinical Practice regulations and the Declaration of Helsinki. The study is registered on the publically available ISRCTN database and is badged by the National Institute for Health Research.

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SYSTEMS-2 is a randomised, phase II, multicentre trial comparing two hypofractionated schedules of radiotherapy for pain control in MPM: dose escalated (36Gy in 6 fractions over 2 weeks) and standard (20Gy in 5 fractions over 1 week). 112 patients in whom radiotherapy is clinically indicated for MPM associated pain will be enrolled.

Inclusion criteria:

- Histological/MDT diagnosis of MPM
- Performance status 0-2 (ECOG)
- Predicted life expectancy >12 weeks
- Contrast enhanced CT scan within 8 weeks of starting radiotherapy
- Worst pain score $\geq 4/10$ after analgesia optimisation
- Ability to provide written informed consent
- Willingness to comply with study procedures
- Radiotherapy plan compatible with the dose escalated arm prior to randomisation

Exclusion criteria:

- Patients receiving anti-cancer therapy within 4 weeks of study entry or who are planned for anti-cancer therapy within 6 weeks of radiotherapy

- Prior radiotherapy where there is concern that the proposed treatment volume would overlap with a previously irradiated area. This does not include patients who have received superficial photon or electron therapy to drain sites
- Psychotic disorders/cognitive impairment
- Co-existing lung tumours
- Pregnant/breastfeeding
- Patients of child-bearing potential, unwilling to use 2 effective methods of contraception.

Study objectives and endpoints

Primary objective: to establish whether dose escalated, hypofractionated radiotherapy increases the proportion of MPM patients experiencing a clinically significant improvement in pain at the site of radiotherapy at week 5, compared with standard radiotherapy. Pain will be assessed using the Brief Pain Inventory (BPI). A responder will be any patient who has at least a 2 point drop in the 'worst pain score' component of the BPI, from baseline to week 5.

Secondary objectives:

1. Acute toxicity (end of the radiotherapy and weeks 5 and 9)
2. Overall BPI score and BPI components of average pain, intensity subscale and functional interference subscale (weeks 5 and 9)
3. Radiological response (week 9)
4. Overall survival (OS)
5. Quality of life (QoL) at weeks 5 and 9 (assessed by EORTC QLQ-C30 and LC13).

Exploratory endpoints will include change in strong opioid use, health related QOL at week 9 and translational biomarker studies.

In order to allow the effects of the radiotherapy to be determined accurately, patients must have their analgesia optimised prior to randomisation and if necessary should be reviewed by their local palliative care team.

Radiotherapy details

Radio-opaque markers should be used to demarcate painful sites at the time of CT acquisition. (Figure 1)

IMRT is recommended for radiotherapy planning and delivery; however, if this technology is unavailable, 3D conformal techniques are acceptable. The clinical target volume (CTV) will be outlined on each slice and should include the area(s) demarcated by wire markers. If there is neuropathic pain, the relevant nerve root should be included. The planning target volume (PTV) will be formed by adding a 1-2cm margin around the CTV. Relevant organs at risk (OARs) should be outlined on each CT slice, depending on tumour position. (Table 1)

While IMRT provides an effective way of manipulating dose distribution, the inverse planning process may allow dose to be 'dumped' in regions with no maximum specified dose. Therefore, OARs must be outlined and allocated an appropriate constraint.

There are few data to support OAR dose constraints for hypofractionated regimes, particularly in the palliative setting. However, relevant data is available for stereotactic ablative radiotherapy, where large doses are delivered in small numbers of fractions to limited volumes, often with radical intent. [8, 9] These data have been used to guide development of dose constraints for SYSTEMS-2. (Table 1)

PTV coverage should not be compromised unless there are clinical concerns that dose(s) to OAR(s) would cause unacceptable acute toxicity. In situations where dose constraints cannot be met, it is acceptable to reduce the total dose to 30Gy in 5 fractions over 2 weeks.

Dose will be prescribed using an isocentric technique. Plans should be normalised with 100% prescription to the target volume median dose in accordance with ICRU83. Centres unable to prescribe to the median dose can alternatively prescribe to the mean dose. Anticipated PTV coverage parameters are shown in Table 1.

To prevent bias in treatment planning and target volume delineation, radiotherapy planning will occur before randomisation. All patients will initially be planned for the dose escalated arm and any patient randomised to standard treatment will be re-planned prior to the first fraction. Any patient for whom a dose-escalated plan is not achievable will be ineligible.

Radiotherapy quality assurance will be implemented by the National Radiotherapy Trials QA Group.

Acute radiation toxicities should be managed with supportive medicines as per local policy. Timings and dosages of all analgesics should be recorded. In the event of a pleuritic pain flare, a short course of high dose steroids is advised.

Follow up

The follow up schedule is shown in Figure 2. After 26 weeks, 2 monthly survival assessments will be conducted by the recruiting centre.

Central radiological review will be led by a Glasgow based consultant radiologist, blinded to the delivered radiotherapy dose. Appropriate target lesions will be selected on the basis of the baseline CT and radiotherapy plan. Response at week 9 will be reported to Modified RECIST criteria.

Safety reporting

All Adverse Events (AE) must be recorded in full and include the event nature, start and stop dates, severity (graded to CTCAEv4), seriousness and relationship to radiotherapy.

As the safety profile of radiotherapy is well known, only events that meet the criteria of a Serious Adverse Event (SAE), are directly related to the administration of radiotherapy and are not listed as expected side effects of radiotherapy (Table 2) require reporting as SAEs.

Translational Research

Patients will be asked to consent to the collection and use of surplus archived formalin-fixed paraffin embedded tumour tissue from their original diagnostic biopsy and to the prospective collection of blood samples at 3 time-points throughout the trial.

Statistical Analysis

The study is designed to detect an absolute increase of 20% in the proportion of responders at week 5 on dose escalated radiotherapy compared to standard radiotherapy from 40% (SYSTEMS [7] response rate) to 60%. This requires 112 patients, 56 per arm (comparison of proportions, 90% power, 20% 1-sided level of statistical significance; equivalent to 80% power, 10% level of statistical significance).

- Primary efficacy analysis

The benefit of radiotherapy will be assessed by comparing the proportion of responders at 5 weeks between the treatment arms using an adjusted logistic regression model.

- Secondary efficacy analysis

Analysis of pain response scores and subscales at weeks 5 and 9 and radiological response at week 9 will use the same approach as the primary efficacy analysis. OS will be compared between the study arms using an adjusted Cox model. A Kaplan-Meier curve will illustrate the relative OS. AUC techniques will be employed to analyse QoL data.

- Safety analysis

The worst recorded toxicity grade for each patient will be summarised by study arm and compared using the Mann-Whitney U test.

- Interim analysis

The study data will be reviewed annually by an independent data monitoring committee. There will be a formal assessment of futility at 50 % recruitment. The 3-outcome design [10] will determine whether a phase III study is warranted.

Discussion

Management of MPM associated pain can be complex and often requires a multidisciplinary approach. While chemotherapy is associated with modest survival benefit, there is no evidence that it is helpful for pain. [11] Similarly, while surgical procedures can alleviate symptoms such as breathlessness, post thoracotomy pain is common and often difficult to manage. [12] Percutaneous

cervical cordotomy appears to be beneficial in selected patients, [13] but is not widely available and there is no prospective randomised evidence to support its role in MPM.

Palliative radiotherapy can be beneficial for a variety of cancer associated symptoms, particularly bone pain. [14] While MPM is generally regarded as radioresistant, palliative doses have long been used to alleviate pain. Nevertheless, the majority of evidence behind this practice is of poor quality, [6] and the SYSTEMS study provides the only robust evidence that palliative radiotherapy is clinically beneficial in a substantial proportion of MPM patients. [7] The question of whether dose escalation can improve response rates and prolong pain control has been difficult to address because 2-dimensional techniques are ill-suited to delivering high radiotherapy doses to the thoracic cavity. However, recent advances in radiotherapy planning and delivery have enabled dose escalation while maintaining acceptable dose constraints to normal tissues.

We anticipate that SYSTEMS-2 will provide robust and accurate symptom response data for palliative radiotherapy in MPM and help to establish the optimal dose and fractionation in this setting. Radiological data will enable further characterisation of radiation responses and their correlations with clinical outcome. Furthermore, the associated sample collection will create a unique bioresource for future translational research into mesothelioma-specific predictive and response biomarkers, which are urgently required.

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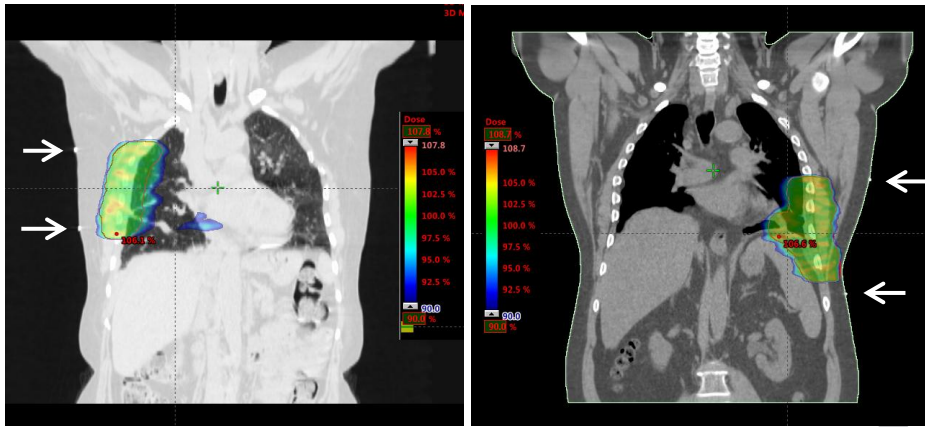
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Figure 1. Wire markers denoting the site of pain to aid radiotherapy planning



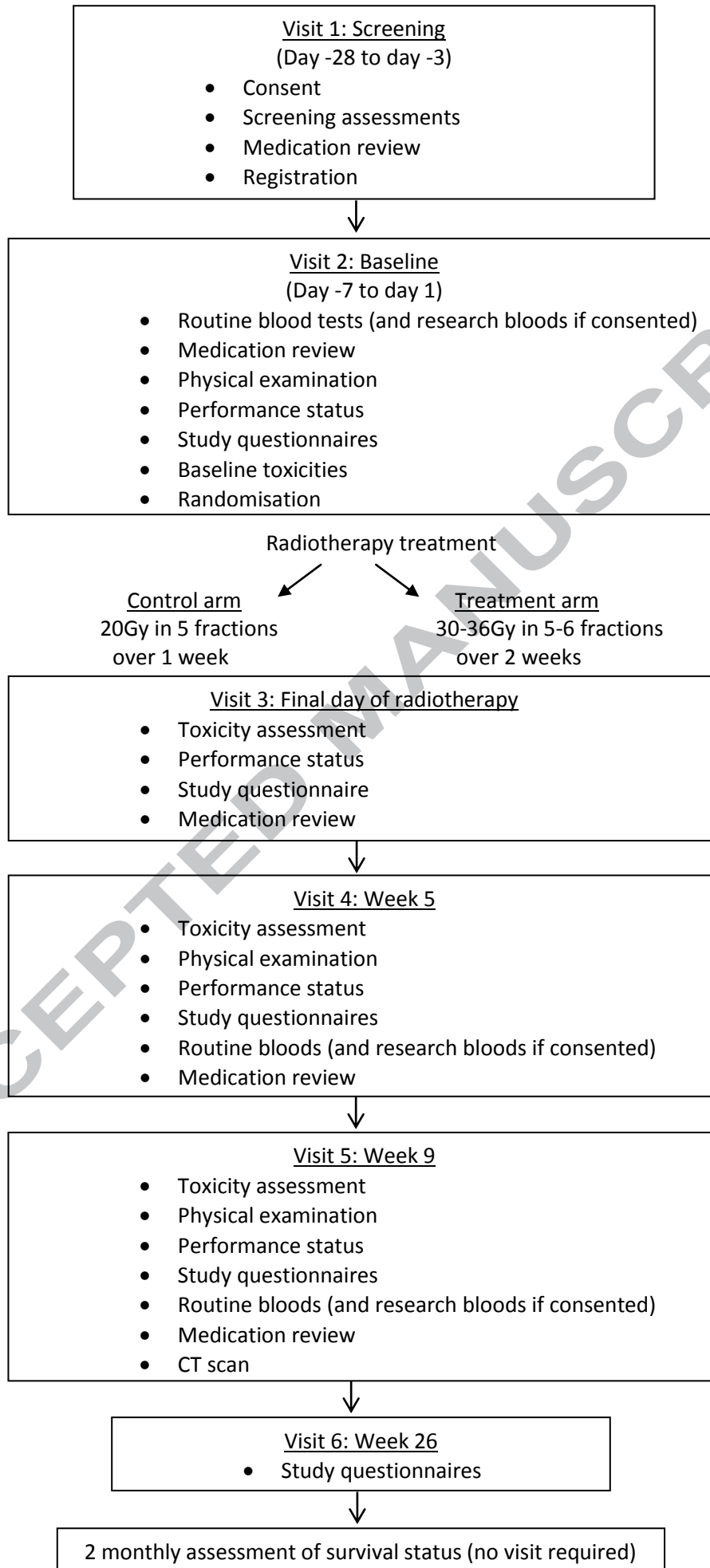


Figure 2: Schedule of events

Table 1. Dose constraints for SYSTEMS-2

Structure	Constraint	Maximum dose	Indication for delineation
OARs			
Contralateral lung	<5%	V20 Gy	Any tumour position
	<50%	V10 Gy	
	<70%	V5 Gy	
Oesophagus	Dmax (0.5 cc)	30 Gy	Any tumour position
Spinal canal	Dmax (0.5 cc)	27 Gy	Any tumour position
Trachea and proximal bronchus	Dmax (0.5 cc)	36 Gy	Any tumour position
Heart	Dmax (0.5 cc)	36 Gy	Any tumour position
Liver	Mean Liver Dose	16 Gy	Low lying right sided tumours where >700cc of liver scanned
Kidneys (individual and combined)	Mean kidney dose	10 Gy	Low lying tumours
If solitary kidney or if one kidney mean dose >10Gy	<45%	V10 Gy	Low lying tumours
Stomach	Dmax (0.5 cc)	30 Gy	Low lying left sided tumours
Great Vessels	Dmax (0.5 cc)	36 Gy	Any tumour position
Small bowel	Dmax (0.5 cc)	30 Gy	Low lying tumours
Ipsilateral Brachial Plexus	Dmax (0.5 cc)	36 Gy	PTV above T2
Large bowel	Dmax (0.5cc)	30 Gy	Low lying tumours
PTV			
Minimum	D98%	>95%	
Median	D50%	100%	
Maximum	D2%	<107%	

Table 2. Expected side effects of radiotherapy

Pulmonary haemorrhage	Pneumonitis
Oesophageal candidiasis	Dermatitis radiation
Anaemia	Pulmonary fistula
White blood cell decreased	Carbon monoxide diffusing capacity decreased
Neutrophil count decreased	Forced expiratory volume decreased
Nausea	Vital capacity abnormal
Vomiting	Cardiac toxicity (pericardial disease or myocardial infarction)
Constipation	Spinal cord toxicity
Fatigue	Late oesophageal stricture
Febrile neutropenia	Late radiation fibrosis
Neutropenic sepsis	RT induced rib fracture
Lung infection	Late malignancy within the radiation field
Oesophagitis	Pleuritic pain flare

- A randomised phase II trial of radiotherapy dose escalation for pain control in MPM
- Comparison of 2 hypofractionated regimes (20Gy/5# and 36Gy/6#)
- Highly conformal radiotherapy techniques used to aid safe dose escalation
- Primary outcome: pain control at week 5 at radiotherapy site
- Secondary endpoints: acute toxicity, radiological response, quality of life
- Recruitment target: 112 patients from 10-15 UK centres

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