A radiobiological model of metastatic burden reduction for molecular radiotherapy: application to patients with bone metastases

Denis-Bacelar, A. M., Chittenden, S. J., Murray, I., Divoli, A., Ralph McCready, V., Dearnaley, D. P., O'Sullivan, J. M., Johnson, B., & Flux, G. D. (2017). A radiobiological model of metastatic burden reduction for molecular radiotherapy: application to patients with bone metastases. Physics in Medicine and Biology, 62(7), 2859-2870. https://doi.org/10.1088/1361-6560/aa5e6f

Published in:
Physics in Medicine and Biology

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Publisher rights
© 2017 Institute of Physics and Engineering in Medicine. This is an open access article published under a Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution and reproduction in any medium, provided the author and source are cited.

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Open Access
This research has been made openly available by Queen's academics and its Open Research team. We would love to hear how access to this research benefits you. – Share your feedback with us: http://go.qub.ac.uk/oa-feedback
A radiobiological model of metastatic burden reduction for molecular radiotherapy: application to patients with bone metastases

This content has been downloaded from IOPscience. Please scroll down to see the full text.
2017 Phys. Med. Biol. 62 2859
(http://iopscience.iop.org/0031-9155/62/7/2859)

View the table of contents for this issue, or go to the journal homepage for more

Download details:

IP Address: 143.117.193.86
This content was downloaded on 21/04/2017 at 09:26

Please note that terms and conditions apply.

You may also be interested in:

Cancer therapy using bone-seeking isotopes
V J Lewington

Dose escalation for prostate implant
X Allen Li, Jian Z Wang, Robert D Stewart et al.

The impact of prostate edema on tumor control
Zhe (Jay) Chen, Kenneth Roberts, Roy Decker et al.

A mathematical approach for evaluating the influence of dose heterogeneity on TCP for prostate cancer brachytherapy treatment
L Strigari, L C Orlandini, I Andriani et al.

Impact of growth mechanism within the LQ model
H McAneney and S F C O'Rourke

Effect of radiotherapy treatment delays
R M Wyatt, A H Beddoe and R G Dale

Re-186 and Sm-153 dosimetry based on scintigraphic imaging data in skeletal metastasis palliative treatment and Monte Carlo simulation
M Andreou, N Lagopati and M Lyra

The biological effectiveness of TRT based on a whole-body pharmacokinetic model
Joseph J Grudzinski, Wolfgang Tomé, Jamey P Weichert et al.

High brachytherapy doses can counteract hypoxia in cervical cancer—a modelling study
Emely Lindblom, Alexandru Dasu, Catharina Beskow et al.
A radiobiological model of metastatic burden reduction for molecular radiotherapy: application to patients with bone metastases

Ana M Denis-Bacelar, Sarah J Chittenden, Iain Murray, Antigoni Divoli, V Ralph McCready, David P Dearnaley, Joe M O’Sullivan, Bernadette Johnson and Glenn D Flux

1 Joint Department of Physics, The Institute of Cancer Research and The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom
2 Department of Nuclear Medicine, Brighton and Sussex University Hospitals NHS Trust, Brighton, United Kingdom
3 Division of Radiotherapy and Imaging, The Institute of Cancer Research and The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom
4 Centre for Cancer Research and Cell Biology, Queen’s University Belfast, Belfast, United Kingdom

E-mail: ana.denisbacelar@icr.ac.uk

Received 11 November 2016, revised 5 January 2017
Accepted for publication 6 February 2017
Published 14 March 2017

Abstract

Skeletal tumour burden is a biomarker of prognosis and survival in cancer patients. This study proposes a novel method based on the linear quadratic model to predict the reduction in metastatic tumour burden as a function of the absorbed doses delivered from molecular radiotherapy treatments.

The range of absorbed doses necessary to eradicate all the bone lesions and to reduce the metastatic burden was investigated in a cohort of 22 patients with bone metastases from castration-resistant prostate cancer. A metastatic burden reduction curve was generated for each patient, which predicts the reduction in metastatic burden as a function of the patient mean absorbed dose, defined as the mean of all the lesion absorbed doses in any given patient. In the patient cohort studied, the median of the patient mean absorbed dose predicted to reduce the metastatic burden by 50% was 89 Gy (interquartile range: 66–107 Gy).

Original content from this work may be used under the terms of the Creative Commons Attribution 3.0 licence. Any further distribution of this work must maintain attribution to the author(s) and the title of the work, journal citation and DOI.

5 Author to whom any correspondence should be addressed. Joint Department of Physics, The Institute of Cancer Research and The Royal Marsden Hospital NHS FT, London, SM2 5NG, United Kingdom.
83–105 Gy), whilst a median of 183 Gy (interquartile range: 107–247 Gy) was found necessary to eradicate all metastases in a given patient. The absorbed dose required to eradicate all the lesions was strongly correlated with the variability of the absorbed doses delivered to multiple lesions in a given patient (r = 0.98, P < 0.0001). The metastatic burden reduction curves showed a potential large reduction in metastatic burden for a small increase in absorbed dose in 91% of patients.

The results indicate the range of absorbed doses required to potentially obtain a significant survival benefit. The metastatic burden reduction method provides a simple tool that could be used in routine clinical practice for patient selection and to indicate the required administered activity to achieve a predicted patient mean absorbed dose and reduction in metastatic tumour burden.

Keywords: radiobiology, dosimetry, radiopharmaceuticals, bone metastases, prostate cancer, molecular radiotherapy

(Some figures may appear in colour only in the online journal)

Introduction

Bone metastases are a common indicator of distant relapse from various cancers, in particular those arising in the prostate, lung and breast (Mundy 2002). They can lead to complications such as severe pain, pathological fractures and spinal cord compression; which significantly decrease patient quality of life and shorten survival (Coleman 2001). Current treatments for patients with bone metastases are primarily palliative, including the use of analgesics, external beam radiotherapy, bisphosphonates, chemotherapy or molecular radiotherapy with bone-seeking radiopharmaceuticals (Coleman 2001).

Radiation therapy is an effective treatment modality for bone pain palliation and evidence has shown equal pain relief for single and multi-fraction treatments, providing pain relief in up to 80% of patients (Chow et al 2012). The biological effects of radiation in a curative cancer treatment are not as relevant to a palliative setting, as low absorbed doses are used for bone pain palliation in contrast to the higher levels of radiation required for tumour eradication. However, recent treatment advances in stereotactic body radiation therapy (SBRT) have enabled the safe delivery of ablative radiation doses with minimal normal tissue toxicity to patients with low number of metastases and oligometastatic disease (Tree et al 2013, Saluja et al 2016). Molecular radiotherapy with bone-seeking radiopharmaceuticals can also potentially deliver high absorbed doses to the bone lesions cells whilst minimising bone marrow toxicity (Goyal and Antonarakis 2012). A survival benefit has been observed for 89Sr-dichloride following 6 weekly cycles of doxorubicin as compared to chemotherapy alone in patients with metastatic castration-resistant prostate cancer (mCRPC) (Tu et al 2001). More recently, 223Ra-dichloride was shown to improve survival against placebo (Parker et al 2013), introducing a shift in patient management from pain palliation to prolonged survival (Liepe and Shinto 2016). The prospect of further significant improvements in survival is underlined by the limited haematological toxicity resulting from current treatments (Bruland et al 2006, Parker et al 2013) and the practicality of high activity administrations in combination with stem cell transplantation (O’Sullivan et al 2002, O’Sullivan 2006). This indicates the potential for more aggressive administrations if a personalised treatment planning approach is used. Such
treatments require quantification of image data to facilitate patient-specific dosimetry and the
development of models to explain the clinical significance of the calculated absorbed doses.

Available radiobiological models of metastatic control provide the probability of eradicating
all the metastases in a given patient (Bernhardt et al. 2003, 2004). Numerous studies have
shown that the skeletal tumour burden (Soloway et al. 1988, Dennis et al. 2012, Denis-Bacelar
et al. 2017) is closely related to overall survival. Therefore, a more clinically realistic measure
of metastatic control would be to consider the reduction in metastatic burden for any given patient-specific distribution of lesion absorbed doses following radiotherapy. The application of this methodology in clinical practice was assessed using available clinical data from patients with mCRPC, which reveals a new framework within which the potential for prolonged survival and metastatic tumour burden reduction could be explored.

Material and methods

Ionising radiation induces DNA damage mainly via single and double-strand breaks, which
lead to cell death. The linear quadratic (LQ) model is commonly used to describe cell kill
from tissue irradiation (Dale 1985), where the cell survival fraction is given as:

$$SF(D) = e^{-\alpha D - \frac{\beta D^2}{2}}$$

(1)

where $\alpha (\text{Gy}^{-1})$ and $\beta (\text{Gy}^{-2})$ are tissue dependent constants used to describe the probability
of cell death by double-strand breaks and by two consecutive single-strand breaks to occur
respectively. Repopulation effects were not considered.

Considerably lower absorbed dose rates are delivered in molecular radiotherapy as compared
to external beam radiotherapy; therefore the contribution from the quadratic component is
smaller, as many of the single-strand breaks are repaired during irradiation. To account
for the repair of sub-lethal damage from protracted irradiation during a time $T$, the quad-
ratic component of the LQ model is modified by the Lea–Catcheside factor ($G$) (Millar 1991,
Gerweck et al. 2006):

$$G(T) = \frac{2}{D^2} \int_0^T \frac{dD(t)}{dt} \int_0^t \frac{dD(t')} {dt'} e^{-\mu(t-t')},$$

(2)

For molecular radiotherapy, with a mono-exponentially decreasing absorbed dose rate which
is allowed to decay ($T \to \infty$):

$$G(\infty) = \frac{\lambda}{\lambda + \mu},$$

(3)

where $\lambda$ is the effective decay constant which accounts for the physical and biological half-
lives of a given radiopharmaceutical, and $\mu$ is the repair rate constant. Typical sub-lethal damage repair half-times range between 16 min and 3 h (Dale and Carabe-Fernandez 2005).

The biological effective dose (BED) accounts for the effects of the absorbed dose rate and
the radiosensitivity and repair capacity of the considered tissue (Fowler 1989):

$$BED = -\frac{\ln(SF)}{\alpha} = D\left[1 + \frac{\lambda}{\lambda + \mu}\right].$$

(4)

where the $\alpha/\beta$ ratio quantifies the radiosensitivity of a given tissue to changes in fractionation
and $D\lambda$ is the initial absorbed dose rate of the radiopharmaceutical. Typical ratios for tumours
and early-reacting tissues including the bone marrow are 10 Gy, whilst late-responding tissues show ratios of 2–5 Gy (Dale 2004). Prostate cancer is an exception, where most studies indicate low ratios of about 1–5 Gy (Brenner and Hall 1999, Fowler et al 2001, Wang et al 2003, Oliveira et al 2012, Dearnaley et al 2016). An average effective half-life of 62 h was used (Graham et al 1999).

From the LQ model and considering Poisson statistics, the tumour control probability (TCP) expresses the probability of killing all clonogenic cells ($N_0$) in a given bone lesion:

$$TCP = \exp(-N_0 \times SF) = \exp(-\rho_c V \times \exp(-\alpha \text{BED}))),$$

where $\rho_c$ is the clonogenic cell density and $V$ is the tumour volume.

The absorbed doses required to obtain a TCP of 0.95 depend on the radiobiological parameters used, however these are not known for radionuclides and bone lesions from prostate cancer. The results of this study are based on parameters corresponding to prostate cancer cells, with a clonogenic cell density of $3 \times 10^6 \text{cm}^{-3}$, $\alpha/\beta$ of 3.1 Gy, $\alpha$ of 0.15 Gy$^{-1}$ and repair constant $\mu$ of 0.46 h$^{-1}$ (Wang et al 2003).

The metastatic control probability model

The metastatic control probability (MCP) model (Bernhardt et al 2003, 2004), has been previously used in molecular radiotherapy (Elgqvist et al 2010, Walrand et al 2012). In the context of skeletal metastases, it provides the probability of eradicating all the bone lesions in a given patient and it is defined as the product of the $N$ individual lesion TCPs:

$$\text{MCP} = \prod_{i=1}^{N} \text{TCP}.$$  

The metastatic burden reduction model

A new framework for treatment planning is proposed, where the decrease in metastatic tumour burden is predicted as a function of the absorbed doses delivered to multiple bone lesions. If the patient mean absorbed dose (PMAD) is defined as the mean of $N$ lesion absorbed doses in any given patient ($\text{PMAD} = \sum_{i=0}^{N} D_i/N$), the metastatic burden reduction (MBR) following treatment is calculated as:

$$\text{MBR} = \frac{1 - \sum_{i=0}^{N} v_i \times k(D_i)}{V},$$

where $V = \sum_{i=0}^{N} v_i$ is the metastatic burden at baseline calculated as the sum of the volumes for $N$ lesions of volume $v_i$, and $k(D_i) = \begin{cases} 1, & \text{TCP}(D_i) < 0.95 \\ 0, & \text{TCP}(D_i) \geq 0.95 \end{cases}$ is a binary parameter that describes the eradicated ($k = 0$) or non-eradicated ($k = 1$) status of the $i$th lesion for a given lesion absorbed dose $D_i$. The MBR ranges from 0 (no metastases have been eradicated) to 1 (all metastases have been eradicated).

Application to clinical data

Clinical data were obtained from 22 patients with CRPC metastatic to bone treated with a fixed administered activity of 5 GBq of $^{186}$Re-HEDP and with peripheral blood stem cell transplant support during a phase II clinical trial (O’Sullivan 2006). All patients provided
written informed consent to take part in the trials, which were approved by the Royal Marsden NHS Trust and The Institute of Cancer Research Ethics committee. Bone lesion dosimetry and skeletal metastatic tumour burden calculations were performed from quantitative sequential SPECT imaging as part of a previous study (Denis-Bacelar et al. 2017). The delivered patient mean absorbed dose (PMAD_{delivered}) was defined as the mean of the absorbed doses delivered to all lesions in any given patient. The relative distribution of lesion absorbed doses and the lesion volumes were used as the basis for the radiobiology calculations.

Calculations of the TCP were performed under the assumption of uniform absorbed dose distributions within the bone lesion and uniform radiosensitivity and clonogenic density across lesions and patients. The patient mean absorbed dose necessary to eradicate all the bone lesions within a patient (PMAD_{MCP=0.95}) was obtained by iteratively scaling the relative distribution of absorbed doses delivered to the lesions in a given patient by a target dose scaling factor until MCP = 0.95.

To assess the impact of the degree of absorbed dose variability between lesions upon the PMAD_{MCP=0.95}, different measures of variability were considered; including the range, variance, standard deviation, coefficient of variation and the range scaled by the minimum value.

The patient mean absorbed dose at which the metastatic tumour reduction is 100% approaches PMAD_{MCP=0.95}. Metastatic tumour reduction curves were obtained for a range of patient mean absorbed doses derived from scaling the relative distribution of absorbed doses delivered to the lesions for all patients. The patient mean absorbed dose required to decrease the metastatic tumour burden by 50% (PMAD_{MBR=0.5}) was calculated for each patient.

To assess the impact of the cut-off probability on the metastatic control and metastatic burden reduction, the calculations were also performed for values of 0.9 and 0.99. The effect of an $\alpha$ parameter of 0.25 Gy$^{-1}$ to represent metastatic lesions less radio-resistant than prostate cancer cells was also characterised.

**Comparison between predicted and delivered absorbed doses**

The predicted PMAD_{MCP=0.95} and PMAD_{MBR=0.5} values for the 22 patients were compared with the PMAD_{delivered} from 5 GBq of $^{186}$Re-HEDP. Follow-up imaging was not available to determine the actual metastatic burden reduction following treatment.

**Statistical considerations**

Median and interquartile range (IQR) were used to describe continuous variables. Pearson’s correlation coefficients were used to quantify the degree to which two variables are related and regression analysis was used to identify relationships between variables. Two-sided $P$-values below 0.05 were considered significant.

**Results**

**The metastatic control probability model**

A median PMAD_{MCP=0.95} of 183 Gy (IQR: 107–247 Gy) was obtained across the 22 patients. For cut-offs of 0.9 and 0.99 the PMAD median values of 178 Gy (IQR: 104–241 Gy) and 193 Gy (IQR: 113–260 Gy) were obtained respectively. An $\alpha$ parameter of 0.25 Gy$^{-1}$ reduced the PMAD_{MCP=0.95} by 32% on average, with a median of 125 Gy (IQR: 73–169 Gy). Figure 1(a) shows a strong negative correlation and power relationship between the target dose scaling
factor and the minimum lesion absorbed dose \((r = -0.89, P < 0.0001)\). This indicates the strong influence of the minimum absorbed dose in the probability of metastatic control.

From all the measures of absorbed dose variability in a given patient, the best correlation with the PMADMC\(_{0.95}\) was obtained with the range scaled by the minimum absorbed dose \((r = 0.98, P < 0.0001)\), shown in figure 1(b). When the ratio between the maximum and minimum lesion absorbed dose increases by an order of magnitude, the patient mean absorbed dose required to eradicate all the lesions increases more than 300\% (from 49 Gy to 200 Gy for a ratio of 1–10 respectively), highlighting the negative effects of absorbed dose variability between lesions.

The metastatic burden reduction model

The metastatic burden reduction curves for the 22 patients are shown in figure 2. The PMADMBC\(_{0.5}\) was 89 Gy (IQR: 83–105 Gy) across all patients. For cut-offs of 0.9 and 0.99 in the TCP calculation, PMAD median values of 88 Gy (IQR: 81–106 Gy) and 93 Gy (IQR: 89–111 Gy) were obtained respectively. An \(\alpha\) parameter of 0.25 Gy\(^{-1}\) reduced the PMADMC\(_{0.95}\) by 31\% on average, with a median of 61 Gy (IQR: 57–73 Gy). Steep gradients were observed for 20 of the 22 patients, which show the potential for a large increase in metastatic burden reduction for a small increase in the patient mean absorbed dose delivered. Examination of the individual disease distribution for patients 3 and 4, showed that both had the highest variability in lesion absorbed doses within the patient cohort.

Clinical dosimetry

Our previous study found a total of 379 lesions identified in 22 patients with a median of 11 lesions (IQR: 3–25) and 227 ml of metastatic tumour burden (IQR: 81–300 ml) per patient. The median PMAD\(_{\text{delivered}}\) across all patients was 19 Gy (IQR: 14–23 Gy) or 3.72 Gy GBq\(^{-1}\) (IQR: 2.80–4.69 Gy GBq\(^{-1}\)). Further details can be found in Denis-Bacelar et al (2017).

Comparison between predicted and delivered absorbed doses

Table 1 and figure 3 summarize the results obtained for the patient cohort studied. The median PMADMC\(_{0.95}\) was 183 Gy (IQR: 107–247 Gy), the PMADMBC\(_{0.5}\) was 89 Gy (IQR: 83–105 Gy) and the median PMAD\(_{\text{delivered}}\) dose was 19 Gy (IQR: 14–23 Gy).
Discussion

Standard radiobiological models of metastatic control were used to assess the patient-specific absorbed doses required to cure all metastatic bone lesions in 22 patients with CRPC metastatic to bone. A new treatment planning framework was introduced to predict the decrease in metastatic burden as a function of the absorbed doses delivered, which could enable personalised treatment of bone metastases with the aim of prolonged survival.

The results showed a strong correlation between metastatic control probability and the degree of variability of the absorbed doses delivered to multiple lesions, with a median $PMAD_{MCP\rightarrow0.95} = 0.95$ of $183 \text{ Gy}$. A strong correlation between metastatic control probability and minimum lesion absorbed dose was also observed. This indicates the limitations of this model alone for treatment planning, since a metastatic burden reduction, rather than complete eradication of metastases can still be considered a good response to treatment. Application of the newly proposed method to the clinical data showed that a median $PMAD_{MBR\rightarrow0.95} = 0.95$ of $89 \text{ Gy}$ would be required to reduce the metastatic tumour burden by 50% in this patient cohort. The patient-specific metastatic burden control curves showed that 91% of the patients have a steep gradient of the curve, where a large benefit in terms of metastatic burden reduction could be achieved by a small increase in the patient mean absorbed dose. In 50% of patients, the patient mean absorbed doses required to reduce the metastatic burden by half varied by only $21 \text{ Gy}$, whilst differences of $119 \text{ Gy}$ were found necessary to eradicate all the lesions. The metastatic burden control model could be used to identify patients that would benefit more from treatment. For instance, the results for patient 4 suggest that this treatment may not be effective, as it would require very high patient mean absorbed doses to obtain any significant metastatic reduction, which would likely result in myelotoxicity. To reduce the risk of toxicity, treatment could also be planned according to the lesions that for a given administered activity receive high absorbed doses and the lesion(s) with low absorbed doses could be treated with a boost dose of external beam radiotherapy.

The predicted absorbed doses for elimination of metastases and metastatic burden reduction were considerably higher than the calculated delivered absorbed doses. However, a wide range of lesion absorbed doses in patients treated with $^{186}\text{Re}$-HEDP are available in the literature. Israel et al obtained a mean absorbed dose delivered to lesions of $2.1 \text{ Gy GBq}^{-1}$ from $1.532 \text{ GBq}$ (Israel et al
Table 1. The patient mean absorbed doses delivered (PMAD_{delivered}) and predicted to eradicate all the lesions (PMAD_{MCP=0.95}) and to reduce the metastatic tumour burden by 50% (PMAD_{MBR=0.5}) for the 22 patients. Absorbed doses for MCP values of 0.9 and 0.99 and TCP values of 0.9 and 0.99 for the MBR = 0.5 calculation are shown between brackets. Absorbed doses for MCP = 0.95 and MBR = 0.5 with a radiosensitivity parameter \( \alpha \) of 0.25 are shown in the last two columns. Patient no.

| Patient no. | Delivered | MCP = 0.95 | MBR = 0.5 | MCP = 0.95 (\( \alpha = 0.25 \) Gy\(^{-1} \)) | MBR = 0.5 (\( \alpha = 0.25 \) Gy\(^{-1} \)) |
|-------------|-----------|------------|-----------|---------------------------------|---------------------------------|
| 1           | 8         | 88 (85–93) | 80 (79–90) | 60                              | 56                              |
| 2           | 22        | 243 (237–256) | 84 (81–87) | 166                             | 58                              |
| 3           | 15        | 349 (340–367) | 57 (58–64) | 239                             | 42                              |
| 4           | 30        | 559 (545–588) | 499 (486–500) | 383                          | 331                            |
| 5           | 22        | 206 (200–218) | 79 (79–85) | 140                             | 56                              |
| 6           | 11        | 105 (102–111) | 70 (65–72) | 72                              | 48                              |
| 7           | 31        | 295 (287–312) | 84 (81–89) | 201                             | 57                              |
| 8           | 20        | 212 (207–224) | 105 (101–110) | 145                         | 71                              |
| 9           | 25        | 187 (182–198) | 88 (86–93) | 128                             | 60                              |
| 10          | 18        | 100 (97–105) | 87 (84–92) | 68                              | 60                              |
| 11          | 19        | 201 (196–212) | 106 (106–111) | 138                        | 74                              |
| 12          | 15        | 107 (104–113) | 90 (88–91) | 73                              | 59                              |
| 13          | 24        | 144 (140–150) | 132 (129–141) | 99                         | 92                              |
| 14          | 9         | 178 (174–187) | 119 (114–122) | 122                        | 79                              |
| 15          | 23        | 145 (142–153) | 103 (102–109) | 99                         | 72                              |
| 16          | 10        | 90 (88–95) | 88 (88–93) | 62                              | 62                              |
| 17          | 18        | 150 (146–157) | 107 (105–112) | 103                        | 74                              |
| 18          | 25        | 204 (199–216) | 90 (88–95) | 140                             | 62                              |
| 19          | 22        | 301 (293–319) | 81 (80–86) | 205                             | 55                              |
| 20          | 17        | 259 (252–273) | 98 (95–104) | 177                             | 66                              |
| 21          | 16        | 148 (144–155) | 96 (94–99) | 101                             | 66                              |
| 22          | 12        | 90 (88–95) | 83 (84–90) | 62                              | 60                              |

Figure 3. Range of predicted PMAD_{MCP=0.95} and PMAD_{MBR=0.5}, and delivered PMAD_{delivered} for the 22 patients. The median and inter-quartile range is shown.
in close agreement with our results. Higher absorbed doses were obtained by Maxon et al.,
with 33 Gy GBq\(^{-1}\) from 1.225 GBq calculated using whole-body planar imaging (Maxon
et al 1990); and by Andreou et al with 52 Gy GBq\(^{-1}\) from 1.295 GBq (Andreou et al 2010).
Differences in lesion absorbed doses are likely due not only to the challenges associated with
the heterogeneity of uptake of bone-seeking radiopharmaceuticals and the difficulty to calculate
the tumour volume (Bouchet et al 1999, Bouchet and Bolch 1999, Strigari et al 2007), but also
to the lack of standardization of imaging and dosimetry protocols. Nonetheless, the calculations
were based on the relative distribution of absorbed doses delivered to multiple lesions in a given
patient. Therefore the methodology and conclusions drawn from this study are not affected by the
absolute absorbed doses. Absolute dosimetry would be required to fully understand the biological
effects of the radiation doses delivered and tailoring the treatment to individual patients (Pouget
et al 2015). Therefore more efforts are required towards improving the reproducibility and repeat-
ability of the absorbed dose as a biomarker of response in molecular radiotherapy.

This study has some limitations. The relative biological effectiveness (RBE) and radiosensi-
tivity parameters vary for different radionuclides, tissues and activity distributions. The uptake
of radiopharmaceuticals used for bone metastases highly depends on the osteoblastic activity
for bone-seeking agents and is highly heterogeneous at the microscopic scale, particularly for
alpha emitting radionuclides. However the limited resolution of clinical imaging systems only
allows for macroscopic dosimetry and the assumptions of uniform distribution of activity are
often made for bone lesion dosimetry (Liepe et al 2003, Baum et al 2016, Pacilio et al 2016).
The parameters used in the LQ model have been derived from uniformly distributed absorbed
doses delivered by external beam radiotherapy in prostate cancer patients, as these are not avail-
able for mCRPC and \(^{186}\)Re-HEDP. Different radiobiological parameters would have the effect of
shifting the absorbed doses required to produce a given effect to lower or higher values although
the relative positions of the curves would remain constant for all patients. A change in \(\alpha\) from
typical prostate cancer cells (0.15 Gy\(^{-1}\)) to less radio-resistant cells (0.25 Gy\(^{-1}\)) would reduce
the patient mean absorbed dose required to kill all the metastases and half the metastatic tumour
burden by 31–32%. Further clinical studies with pre- and post-therapy imaging would allow the
validation and refinement of the parameters used in metastatic burden reduction model.

The use of bone-seeking radiopharmaceuticals is rapidly increasing. A survival benefit has
been observed in patients treated with \(^{223}\)Ra as compared to placebo and \(^{177}\)Lu-DKFZ-617 PSMA
has been shown to induce remission in a patient with metastatic prostate cancer (Kratochwil et al
2015). Due to the low number of patients treated and the wide range of absorbed doses reported
from fixed and/or weight-based administered activities, absorbed dose response relationships
have not yet been established. Radiation therapy can be an effective treatment for bone pain
relief and 48 Gy in 3 fractions SBRT treatment in patients with multiple oligometastases, have
shown promising long-term disease control (Salama et al 2012). An on-going clinical trial is
investigating the eradication of oligometastases, including bone lesions, in patients with mCRPC
(NCT02685397). Radiation therapy is typically used in symptomatic and late stages of disease.
However, implementation of treatment early in the course of the disease may increase quality
of life and reduce overall metastatic tumour burden; in turn, delaying disease progression and
improving long-term survival. This could be of particular relevance for molecular radiotherapy,
where radiation is targeted to specific molecular sites and toxicity is limited.

Conclusion

The metastatic burden reduction model proposed in this study offers the potential to provide
individualised treatment and could be used as a patient selection tool by relating potential
benefit and toxicity. Metastatic burden reduction curves could be predicted from pre-therapy
imaging or from therapy imaging, which would enable adaptive treatment planning for repeated administrations. This simple tool has the potential to inform patient management by individualising treatment in patients with multiple tumours or metastatic disease undergoing molecular radiotherapy. Future studies of treatment response will allow validation and refinement of the model.

Acknowledgments

This work was supported by CRUK and EPSRC support to the Cancer Imaging Centre at ICR and RMH in association with MRC & Department of Health C1060/A10334, C1060/A16464 and a grant from the National Cancer Institute supported by NIH grant number CA86784-02. We acknowledge NHS funding to the NIHR Biomedical Research Centre at The Royal Marsden Hospital and The Institute of Cancer Research.

Conflict of interest

The authors have no potential conflicts of interest relevant to the subject of this article.

Ethical approval

This article does not contain any studies with animals performed by any of the authors. All patients provided written informed consent to take part in the study, which were approved by the Royal Marsden NHS Foundation Trust and The Institute of Cancer Research Ethics committee.

References

Andreou M, Papanikolos G, Vamvakas G, Kotsakis N and Lyra M 2010 10th IEEE Int. Conf. on Information Technology and Applications in Biomedicine (ITAB) (3–5 November 2010) pp 1–4
Baum R P, Kulkarni H R, Schuchardt C, Singh A, Wirtz M, Wiessalla S, Schottelius M, Mueller D, Klette I and Wester H J 2016 177Lu-labeled prostate-specific membrane antigen radioligand therapy of metastatic castration-resistant prostate cancer: safety and efficacy J. Nucl. Med. 57 1006–13
Bernhardt P, Ahlman H and Forsell-Aronsson E 2003 Model of metastatic growth valuable for radionuclide therapy Med. Phys. 30 3227–32
Bernhardt P, Ahlman H and Forsell-Aronsson E 2004 Modelling of metastatic cure after radionuclide therapy: influence of tumor distribution, cross-irradiation, and variable activity concentration Med. Phys. 31 2628–35
Bouchet L G and Bolch W E 1999 A three-dimensional transport model for determining absorbed fractions of energy for electrons within cortical bone J. Nucl. Med. 40 2115–24
Bouchet L G, Jokisch D W and Bolch W E 1999 A three-dimensional transport model for determining absorbed fractions of energy for electrons within trabecular bone J. Nucl. Med. 40 1947–66
Brenner D J and Hall E J 1999 Fractionation and protraction for radiotherapy of prostate carcinoma Int. J. Radiat. Oncol. Biol. Phys. 43 1095–101
Bruland O S, Nilsson S, Fisher D R and Larsen R H 2006 High-linear energy transfer irradiation targeted to skeletal metastases by the alpha-emitter 223Ra: adjuvant or alternative to conventional modalities? Clin. Cancer Res. 12 6250s–7s
Chow E, Zeng L, Salvo N, Dennis K, Tsao M and Lutz S 2012 Update on the systematic review of palliative radiotherapy trials for bone metastases Clin. Oncol. 24 112–24
Coleman R E 2001 Metastatic bone disease: clinical features, pathophysiology and treatment strategies Cancer Treat. Rev. 27 165–76
Dale R 2004 Use of the linear-quadratic radiobiological model for quantifying kidney response in targeted radiotherapy Cancer Biother. Radiopharm. 19 363–70
Dale R and Carabe-Fernandez A 2005 The radiobiology of conventional radiotherapy and its application to radionuclide therapy Cancer Biother. Radiopharm. 20 47–51
Dale R G 1985 The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy Br. J. Radiol. 58 515–28
Denis-Bacelar A M, Chittenden S J, Dearnaley D P, Divoli A, O’Sullivan J M, McCready V R, Johnson B, Du Y and Flux G D 2017 Phase I/II trials of 186Re-HEDP in metastatic castration resistant prostate cancer: post-hoc analysis of the impact of administered activity and dosimetry on survival Eur. J. Nucl. Med. Mol. Imaging 40 620–9
Dearnaley D et al 2016 Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial Lancet Oncol 17 1047–60
Dennis E R, Jia X, Mezheritsky I S, Stephenson R D, Schoder H, Fox J J, Heller G, Scher H I, Larson S M and Morris M J 2012 Bone scan index: a quantitative treatment response biomarker for castration-resistant metastatic prostate cancer J. Clin. Oncol. 30 519–24
Elgqvist J, Johansson B R, Partheen K and Danielsson A 2010 Tumor cure probability during alpha-RIT of ovarian cancer with different radiation sensitivity Anticancer Res. 30 2545–51
Fowler J, Chappell R and Ritter M 2001 Is alpha/beta for prostate tumors really low? Int. J. Radiat. Oncol. Biol. Phys. 50 1021–31
Fowler J F 1989 The linear-quadratic formula and progress in fractionated radiotherapy Br. J. Radiol. 62 679–94
Gerweck L E, Vijayappa S, Kurimasa A, Ogawa K and Chen D J 2006 Tumor cell radiosensitivity is a major determinant of tumor response to radiation Cancer Res. 66 8352–5
Goyal J and Antonarakis E S 2012 Bone-targeting radiopharmaceuticals for the treatment of prostate cancer with bone metastases Cancer Lett. 323 135–46
Graham M C, Scher H I, Liu G B, Yeh S D, Curley T, Daghighbian F, Goldsmith S J and Larson S M 1999 Rhenium-186-labeled hydroxyethylidene diphosphonate dosimetry and dosing guidelines for the palliation of skeletal metastases from androgen-independent prostate cancer Clin. Cancer Res. 5 1307–18
Israel O, Keidar Z, Rubinov R, Issilevski G, Frenkel A, Kuten A, Betman L, Kolodny G M, Yarnitsky D and Front D 2000 Quantitative bone single-photon emission computed tomography for prediction of pain relief in metastatic bone disease treated with rhenium-186 etidronate J. Clin. Oncol. 18 2747–54
Kratochwil C, Giesel F, Eder M, Afsar-Oromieh A, Benešová M, Mier W, Kopka K and Haberkorn U 2015 177Lu-Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer Eur. J. Nucl. Med. Mol. Imaging 42 987–8
Liepe K, Hiilsic R, Kropp J, Runge R, Knapp F F and Franke W G 2003 Dosimetry of 188Re-hydroxyethylidene diphosphonate in human prostate cancer skeletal metastases J. Nucl. Med. 44 953–60
Liepe K and Shinto A 2016 From palliative therapy to prolongation of survival: 223RaCl2 in the treatment of bone metastases Ther. Adv. Med. Oncol. 8 294–304
Maxon H R 3rd et al 1990 Re-186(Sn) HEDP for treatment of painful osseous metastases: initial clinical experience in 20 patients with hormone-resistant prostate cancer Radiology 176 155–9
Millar W T 1991 Application of the linear-quadratic model with incomplete repair to radionuclide directed therapy Br. J. Radiol. 64 242–51
Mundy G R 2002 Metastasis: metastasis to bone: causes, consequences and therapeutic opportunities Nat. Rev. Cancer 2 584–93
O’Sullivan J M et al 2002 High activity rhenium-186 HEDP with autologous peripheral blood stem cell rescue: a phase I study in progressive hormone refractory prostate cancer metastatic to bone Br. J. Cancer 86 1715–20
O’Sullivan J M et al 2006 A phase 2 study of high-activity 186Re-HEDP with autologous peripheral blood stem cell transplant in progressive hormone-refractory prostate cancer metastatic to bone Eur. J. Nucl. Med. Mol. Imaging 33 1055–61
Oliveira S M, Teixeira N J and Fernandes L 2012 What do we know about the α/β for prostate cancer? Med. Phys. 39 3189–201
Pacilio M et al 2016 Dosimetry of bone metastases in targeted radionuclide therapy with alpha-emitting (223)Ra-dichloride Eur. J. Nucl. Med. Mol. Imaging 43 21–33
Parker C et al 2013 Alpha emitter radium-223 and survival in metastatic prostate cancer New Engl. J. Med. 369 213–23
Pouget J P, Lozza C, Deshayes E, Boudousq V and Navarro-Teulon I 2015 Introduction to radiobiology of targeted radionuclide therapy Front. Med. 2 12
Salama J K et al 2012 Stereotactic body radiotherapy for multisite extracranial oligometastases Cancer 118 2962–70
Saluja R, Cheung P, Zakotynski K and Emmenegger U 2016 Disease volume and distribution as drivers of treatment decisions in metastatic prostate cancer: from chemohormonal therapy to stereotactic ablative radiotherapy of oligometastases Urol. Oncol. 34 225–32
Soloway M S, Hardeman S W, Hickey D, Raymond J, Todd B, Soloway S and Moinuddin M 1988 Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan Cancer 61 195–202
Strigari L, Sciuto R, D’Andrea M, Pasqualoni R, Benassi M and Maini C L 2007 Radiopharmaceutical therapy of bone metastases with 89SrCl₂, 186Re-HEDP and 153Sm-EDTMP: a dosimetric study using Monte Carlo simulation Eur. J. Nucl. Med. Mol. Imaging 34 1031–8
Tree A C, Khoo V S, Ecles R A, Ahmed M, Dearnaley D P, Hawkins M A, Huddart R A, Nutting C M, Ostler P J and van As N J 2013 Stereotactic body radiotherapy for oligometastases Lancet Oncol. 14 e28–37
Tu S-M et al 2001 Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomised phase II trial Lancet 357 336–41
Walrand S, Hanin F-X, Pauwels S and Jamar F 2012 Tumour control probability derived from dose distribution in homogeneous and heterogeneous models: assuming similar pharmacokinetics, 125 Sn–177 Lu is superior to 90 Y–177 Lu in peptide receptor radiotherapy Phys. Med. Biol. 57 4263
Wang J Z, Guerrero M and Li X A 2003 How low is the alpha/beta ratio for prostate cancer? Int. J. Radiat. Oncol. Biol. Phys. 55 194–203