Purpose: To evaluate the significance of fractionated administration of thalidomide combined with γ-ray irradiation in terms of local tumor response and lung metastatic potential, referring to the response of intratumor quiescent (Q) cells.

Materials/methods: B16-BL6 melanoma tumor-bearing C57BL/6 mice were continuously given 5-bromo-2'-deoxyuridine (BrdU) to label all proliferating (P) cells. The tumor-bearing mice then received γ-ray irradiation after thalidomide treatment through a single or 2 consecutive daily intraarterial administrations up to a total dose of 400 mg/kg in combination with an acute hypoxia-releasing agent (nicotinamide, 1,000 mg/kg, intraperitoneally administered) or mild temperature hyperthermia (MTH, 40 centigrade for 60 minutes). Immediately after the irradiation, cells from some tumors were isolated and incubated with a cytokinesis blocker. The responses of the Q and total (P + Q) cell populations were assessed based on the frequency of micronuclei using immunofluorescence staining for BrdU. In other tumor-bearing mice, 17 days after irradiation, macroscopic lung metastases were enumerated.

Results: Thalidomide raised the sensitivity of the total cell population more remarkably than Q cells in both single and daily administrations. Daily administration of thalidomide elevated the sensitivity of both the total and Q cell populations, but especially the total cell population, compared with single administration. Daily administration, especially combined with MTH, decreased the number of lung metastases.

Conclusions: Daily fractionated administration of thalidomide in combination with γ-ray irradiation was thought to be more promising than single administration because of its potential to enhance local tumor response and repress lung metastatic potential.

Keywords: Quiescent cell; Lung metastasis: Thalidomide

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The Malthus Project - updated predictions of national radiotherapy demand to 2030
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Purpose: The Malthus model is an evidence based simulation of radiotherapy demand in England, which was designed to estimate radiotherapy utilisation at local and national level, in order to assist in planning of radiotherapy services. The model utilised cancer registration data from the national cancer registration service, together with predictions of population growth from the Office of National Statistics, and cancer incidence projections. We present the results of an updated model that utilises the latest population projection estimates, and cancer incidence data.

Materials and Methods: Base data on cancer registration was provided by the National Cancer Intelligence Network, broken down by disease site, local Clinical Commissioning Groups (CCGs), age and sex. Equivalent population data was sourced from the Office for National Statistics. These two datasets were combined with data from 2,000 evidence-based clinical decisions, covering 22 different cancer sites. Clinical practice was peer-reviewed by over 100 British oncologists and at a national forum. An updated cancer incidence projection model and population projection model were also used to enable annual demand predictions up to 2035.

Results: The Malthus model estimates that the access rate for radiotherapy in England in 2015 should be 40.5% with a fraction burden of approximately 47,500 fractions per million population. To highlight how different regions within a country can be, Table 1 displays two regions and the England average for comparison. The predicted demand for radiotherapy is also increasing for England. Over the next few year the predicted fractions per million will increase by 0.9% per year, this will increase to 1% per year in 2020 and is expected to hit 1.1% per year by 2026.

Table 1. Fractions per Million for the ‘Big 4’ for England and two different regions.

<table>
<thead>
<tr>
<th>Region</th>
<th>All Sites</th>
<th>Breast</th>
<th>Lung</th>
<th>Prostate</th>
<th>H&amp;N</th>
</tr>
</thead>
<tbody>
<tr>
<td>England</td>
<td>47200</td>
<td>12520</td>
<td>5900</td>
<td>31100</td>
<td>4200</td>
</tr>
<tr>
<td>Dorset</td>
<td>6900</td>
<td>1700</td>
<td>6000</td>
<td>22600</td>
<td>5300</td>
</tr>
<tr>
<td>Tower Hamlets</td>
<td>5400</td>
<td>3400</td>
<td>3400</td>
<td>3400</td>
<td>3400</td>
</tr>
</tbody>
</table>

Conclusions: The Malthus model with updated cancer incidence data suggests a radiotherapy utilisation rate of 40.5%, with a predicted annual increase of fractions per million of around 1% per year. Whilst the observed rates of radiotherapy utilisation still lag behind the model’s predictions, the observed activity increases in England (from the Radiotherapy Data Set) over the last 3 years exceed the rate of rise in predicted demand. Customised simulations for individual regions, such as what Malthus can do, allows local cancer profiles to be taken into account for more accurate current and future demand predictions. The customisability also allows for simulations looking at the impact of new technology, such as MRI Linac and Proton therapy, and data from other countries can be incorporated as well.

Keywords: Health Service Research, Demand Prediction

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Progress with MRI-linac image-guided radiation dose imaging
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Purpose: MRI-linacs will enable 4D image-guided radiotherapy and require accurate MR visible and compatible dosimeter systems for verification.

Methods: Motion-tracking utilising a MagicPlate (M512) silicon array dosimeter capable of high resolution dosimetry (Petasecca, 2015) (figure 1a,b), has been modified for purpose of MR imaging during dynamic detector-tracking (i.e. so named ‘MR guided dynamic dosimaging’). The detector was tested for MRI-safety and functionality without irradiation in a 1T fringe field of 3T Siemens Skyra MRI. As solid water can not be visualised on MRI a tissue-equivalent, gel-water phantom (CIRS® Computerized Imaging Reference Systems Inc. VA, USA), providing signal for detector and fiducial visualisation, was utilised to enable MR imaging (fast spin echo sequence).

Results: MR images of a non-powered detector system demonstrated detector visualization (see figure 1c). Detector movements approximating breathing were also acquired during dynamic MRI acquisition (fast gradient echo), showing that fiducial markers could be visualised when placed on a passive device and tracked. The detector functioned at the 1T bore entry position to simulate the magnetic field of our impending MR linac whilst a water phantom was imaged simultaneously at the mid-bore 3T position, with noise (see figure 1d) seen due to detector RF interference being reduced by aluminium foil shielding of the device and cables (figure 1e).

Conclusions: The current MRI-guided dynamic dosimaging set-up has been demonstrated to be successful in detector visualisation and tracking with a non-powered detector. Noise reduction has been achieved with the detector in operational mode. A MRI-compatible motion platform will be paired with M512. These measurements will be compared to acquisition in MRI-linac magnetic fields on the MRI-linac device being installed at the Ingham Institute in Australia.

Keywords: Health Service Research, Demand Prediction

References: Radiotherapy, MRI-linac, dosimetry
152 Plerixafor Improves Local Control and Reduces Metastases in Cervical Cancer Treated with Radiotherapy and Chemotherapy

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Purpose: There is an important need to improve the effectiveness of radio-chemotherapy (RTCT) for cervical cancer. These tumors recruit myeloid cells from the bone marrow via the CXCL12/CXCR4 pathway, which in turn influence vascular function and radiotherapy response. The objective of this study was to explore combined treatment with Plerixafor (a CXCL12/CXCR4 inhibitor) and standard RTCT on primary tumor control and the development of metastases, using orthotopic primary xenografts derived directly from patients with cervical cancer.

Materials/Methods: Two primary cervix xenografts (OCICx13 and OCICx20) were grown in the cervices of immune deficient mice. These tumor models have been shown to mirror the clinical and biological behavior of cervical cancer in patients. To simulate clinical treatment, image-guided radiotherapy (30 Gy in 15 daily fractions) and concurrent weekly cisplatin (4 mg/kg) were administered, with or without Plerixafor (5 mg/kg/day). The primary endpoints were tumor growth delay, the frequency of lymph node metastases and animal survival. Chemokine expression and neutrophil recruitment were evaluated by immunohistochemistry. Acute gut toxicity was assessed using the crypt cell assay. Blood and normal organs were examined for late toxicity.

Results: The combination of RTCT and Plerixafor produced substantial tumor growth delay, reduced metastases and improved survival compared to standard RTCT alone in patient-derived xenograft models. There was a reduction in chemokine signaling (CXCL12/CXCR4) and myeloid cell infiltration (GCSF, CD11b) with combination treatment compared to RTCT alone. There was no effect of Plerixafor on acute GI toxicity, nor were there changes in blood counts or organ morphology to indicate increased late hematological or normal tissue toxicity.

Conclusion: This preclinical study demonstrates that the addition of Plerixafor to standard RTCT for cervical cancer improves local tumor control and reduced metastases with no increase in toxicity. Plerixafor is commercially available for other indications, which will facilitate translation of these findings to phase I/II clinical studies.

Keywords: Cervical cancer, radiotherapy, Plerixafor, CXCL12, myeloid cells

153 Optimization of prostate cancer irradiation: from technology to fractionation

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Curative 3D standard external beam radiotherapy (EBRT) for prostate cancer has been able to improve disease control with dose escalation during the last 15 years though against the token of significant toxicity. Exploring changes in fractionation, doses-distribution optimization with modulated RT, and reducing CTV-PTV safety margins due to off- or on-line imaging before or during irradiation, may be alternatives worth to be implemented in order to reach the highest possible toxicity-free cure rates. Accurate imaging helping to better define the irradiation target/s (e.g., multiparametric MRI, PET-CT/MRI, SPECT); modulated EBRT optimizing the dose distribution; and image guided RT (e.g., kV imaging, CBCT, fiducial markers, transponders, endorectal balloons, recto-prostatic spacers) controlling for patient repositioning and organ motion are presently available allowing the implementation of high precision treatment techniques. Biomatematical modeling has helped to better understand the very special dose-response relationships of EBRT on prostate cancer concerning fractionation sensitivity (low α/β value), overall treatment time (tumor cell repopulation kinetics), and fraction delivery time (potential biological effective dose modifier). All these factors are rather suggestive that prostate cancer patients, especially those with low- or intermediate-risk disease, can be better treated with “more” dose/fraction, “less” number of fractions, and a “shorter” time protraction and delivery time per fraction. Two opposed modalities conceived to deliver large doses in few fractions are either stereotactic body RT (SBRT) or high-dose rate brachytherapy (HDR-BT) given alone or as a boost. The latter procedure may be limited by dose inhomogeneities and geographical misses. Even a small underdosage of the target or a heterogeneous dose-rate delivery may have a negative influence on outcome. This seems to be especially determinant for tumors with very low α/β values as it is the case for prostate cancer. Thus, SBRT may be theoretically more advantageous because the radiobiological reliability of a homogeneous dose distribution compared to HDR-BT, besides being less invasive and probably less costly.

154 Evaluation of the DNA damage induced by 60 MeV proton irradiation by cytogenetic and molecular methods

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Proton radiotherapy provides a promising and emerging treatment approach for cancer patients. However, understanding of the differences in terms of DNA damage and cell proliferation post-proton irradiation is relatively poor. The purpose of this study was to evaluate DNA damage induced by proton beams using various cytogenetic and molecular methods.