PREDICT: Prostate – a Novel Individualised Prognostic Model for Non-metastatic Prostate Cancer with the Potential to Reduce Overtreatment of Lower-risk Disease

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Purpose: To develop an individualised prognostic model for non-metastatic prostate cancer (PCa) that contextualises PCa-specific mortality (PCSM) against other cause mortality, and estimates the survival benefit of treatment and to assess the potential impact of the model on clinician decision-making.
Methods: Using records from the UK National Cancer Registration and Analysis Service, data were collated for 10 089 men diagnosed with PCa between 2000 and 2010 in eastern England. Median follow-up was 9.8 years with 3829 deaths (1202 PCa-specific). Data were randomly split 70:30 into model development and validation cohorts. Separate multivariable models were built for 15-year PCSM and non-prostate cancer mortality (NPCM) using fractional polynomials. Discrimination and calibration were assessed by Harrell's C-index and chi-squared goodness-of-fit, respectively, within the UK validation cohort and an independent Singaporean dataset of 2546 men. An online clinician survey using hypothetical vignettes was developed using Qualtrics® software and distributed to professionals in urology and oncology.
Results: A multivariable model called 'PREDICT: Prostate' was constructed combining age, PSA, histological grade, biopsy core involvement, stage and primary treatment type, which were each independent prognostic factors for PCSM; and age and comorbidity, which were prognostic for NPCM. The model demonstrated good discrimination with C-index 0.83 (95%CI: 0.80–0.85) and 0.86 (95%CI: 0.83–0.89) for 15-year PCSM and 0.75 (95%CI: 0.74–0.77) and 0.77 (95%CI: 0.74–0.79) for overall mortality in the UK and Singapore validation cohorts, respectively. This outperformed currently endorsed international risk-stratification criteria ($P < 0.001$). Among 142 survey respondents (63.4% urologists), there was a trend towards lower rates of recommendation for treatment in men with favourable prognosis when PREDICT: Prostate estimates were shown.
Conclusion: PREDICT: Prostate is the first truly individualised multivariable PCa prognostic model built from baseline diagnostic information and the first to model potential treatment benefit on survival. The eventual web-tool should aid in patient counselling and treatment decision-making.

Exploring the Value of a Pre-trial Outlining Exercise in the POPS Trial, which Evaluated the Localising Device ProSpare in Prostate Bed Radiotherapy

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Purpose: ProSpare is a self-insertable, single use rectal obturator designed as a daily image-guidance tool for prostate and prostate bed radiotherapy. It helps to stabilise the rectum, prostate bed and seminal vesicles [1]. We evaluated the impact of the POPS pre-trial quality assurance outlining exercise and the use of ProSpare on the reproducibility of prostate bed outlining.
Methods: POPS is a randomised phase II trial comparing prostate bed radiotherapy with/without ProSpare. The study design requires that all participating consultants complete a pre-trial outlining exercise both with and without ProSpare [2]. If contouring did not adequately follow RTOG guidelines [3] the outlining exercise was repeated after personalised feedback. The gold standard outline was developed by a specialist uro-radiologist with the chief investigator. 12 investigators from 11 centres contributed to the exercise. We measured the variability between each contour set and the gold standard using the Dice Similarity Coefficient (DSC). A DSC $\geq$ 0.7 indicates good agreement [4]. DSC was calculated for each set of contours in both ProSpare and non-ProSpare groups.
Results: In the initial outlining exercise, the median DSC was 0.84 (range 0.61–0.90). 4 investigators repeated outlining with ProSpare and 7 without ProSpare. For these 11 contours the median DSC improved from 0.78 to 0.90. For the initial outlines the median DSC was similar in the Prospare groups (0.85) and the non-ProSpare groups (0.82). 8 of the 11 cases re-contoured had a DSC of more than 0.7.
Conclusion: This study highlights clinician variability in contouring for prostate bed radiotherapy. Centralised audit and review has been shown to improve reproducibility. Outlining had a similar consistency in ProSpare and non-ProSpare groups.
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Palliative Radiotherapy to Bladder Cancer – Futile or Utile?

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Purpose: To investigate the efficacy of palliative pelvic radiotherapy (RT) for patients with advanced bladder cancer and identify factors associated with futile treatment.
Methods: Retrospective data were collected for bladder cancer patients receiving palliative pelvic RT between 2013 and 2017. Patients were stratified and overall survival (OS) was analysed. Patients were followed up at approximately 6 weeks after RT. Death before, during or within 6 weeks of treatment was considered as a marker of receiving futile treatment.
Results: 134 patients were planned to receive palliative pelvic RT. Median age was 78 years (53–95 years). Majority had transitional cell carcinoma (89.6%) and advanced stage (stage III, IV and recurrent disease; 90%). The main indications were local control (39%), haemostasis (33%) and pain control (22%). Most common radiotherapy regimens were 20 Gy/5 fractions (38%), 21 Gy/3 fractions (36%) and 30 Gy/10 fractions (27%). About 45% of patients were of poor performance status (ECOG 3 or 4) and had significant co-morbidities (ACE-27 score 2 or 3). The median OS after last fraction of RT was 95 days (2–1042 days). 30% ($n = 40$) of patients died within 6 weeks after receiving palliative RT. More than half ($n = 73$) reported their outcomes during clinic or telephone follow-up with median follow-up time of 48 days (14–113 days). 31% ($n = 42$) of patients reported no improvement of symptoms. Patients of better performance status (ECOG 0–2) survived significantly longer than those with worse performance status [151 days (108–193 days) versus 45 days (19–70 days), $P = 0.000071$]. Otherwise, there were no significance differences between median OS with high co-morbidity, advanced stage, age or radiotherapy regimen.
Conclusion: A third of patients either did not complete RT or died within 6 weeks of treatment. Patients might not have achieved maximal benefit or suffered side-effects during this time, making this a futile treatment. Patient selection and comprehensive assessment are crucial in preventing ineffective treatment.

Multidisciplinary Inter-observer Variation using Magnetic Resonance Imaging (MRI) for Muscle Invasive Bladder Cancer (MIBC) Radiotherapy Target Definition

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Purpose: Multi-parametric MRI has established high diagnostic performance in evaluating MIBC compared with CT [1]. However, radiotherapy planning is reliant on CT data. Improving soft tissue definition should make visualisation of key target areas easier, allowing greater accuracy and reproducibility in volume delineation. However, experience of MRI in radiotherapy planning is limited. This study aims to establish the inter-observer variability of target volume definition for bladder radiotherapy using MRI prior to any education/consensus meeting.
Methods: MRI scans of 3 patients with MIBC were contoured by 8 members of the bladder cancer MDT (4 clinical oncologists, 2 radiologists, 2 radiotherapy radiographers). Participants were given case vignettes and guidance on GTV and CTV definitions, but were not coached on MRI interpretation. Participants were blinded to each other's volumes. GTV and CTV contours were completed on T2- and outer bladder wall (oBW) contours completed on T1-weighted imaging; diffusion-weighted images were available for reference. Once all contours were completed a Simultaneous Truth and Performance Level Estimate (STAPLE) was created for each structure set to facilitate inter-observer comparisons. Tests for variability were carried out using ADMIRE research version v2.0 (Elekta AB, Stockholm, Sweden).
Results: In total, 72 contours were completed. The median DICE coefficients for GTV, CTV and oBW were 0.78 (IQR 0.69–0.84), 0.94 (IQR 0.74–0.95) and 0.95 (IQR 0.94–0.96), respectively. The median Cohen Kappa was 0.75 (IQR 0.67–0.81), 0.91 (IQR 0.90–0.92) and 0.92 (IQR 0.90–0.93), respectively, and the median Hausdorff distance was 10.20 (IQR 6.98–16.4), 8.55 (IQR 6.52–11.16) and 7.80 (IQR 6.71–10.19), respectively.
Conclusion: MRI target volume definition shows good concordance between bladder MDT experts. Greatest variance was seen for GTV delineation. Ongoing work will involve developing MRI-based radiotherapy consensus contouring guidance for MIBC.

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Re-planning Bladder Cancer Radiotherapy: Should we be Moving to Adaptive Radiotherapy?

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Purpose: Variation in organ shape and position significantly compromises target coverage despite typically large margins for bladder radiotherapy [1]. Adaptive radiotherapy (ART) strategies can be employed to reduce normal tissue dose and therefore toxicity [2]. With the increased time burden for bladder PTV revision mid-treatment we sought to identify the indications for re-plan and assess bladder size and position interfractional changes compared with planned volume, to identify whether ART introduction would be beneficial.
Methods: This retrospective study collected data on the last 5 radical bladder RT patients. Reasons for re-plan were collected. Bladder volumes were contoured on daily cone beam CTs (CBCTs) and verified by a second reviewer. Subsequent daily bladder volume and interfractional translational shift data were analysed. The selected patients were also audited as compared with London Cancer Bladder Radiotherapy guidelines [3] for comparing timing of radiotherapy from decision to treat and completion of baseline investigations prior to radiotherapy treatment initiation.
Results: 5 patients underwent radical radiotherapy for bladder cancer with stages between T2a and T4 disease. All were treated using volumetric modulated arc therapy with daily CBCT and soft tissue match. 3/5 patients were re-planned: 2 due to changes in CTV position falling out of original PTV and 1 due to increasing CTV not covered by original PTV. 2/5 had conventional fractionation (66 Gy in 33 fractions) and 3/5 were hypofractionated (55 Gy in 20 fractions) and did not receive concurrent chemotherapy due to comorbidities. Large interfractional treated bladder volume variations existed (largest variation 168.5 ± 26 ml).
Conclusion: High re-plan rates support the transition to adaptive strategies. However, large intra-patient variations in bladder volume and translational shifts in this small study reinforce the importance of proper bladder preparation.

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Immunogenic Effects of Radiotherapy for Bladder Cancer

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Purpose: Radiotherapy (RT) is an important part of the management of many patients with bladder cancer (BC), albeit with radical or palliative intent [1]. As well as directly cytotoxic effects, RT can exert immunogenic changes in the tumour microenvironment [2]. RT may cause tumour cells to undergo 'immunogenic cell death' and upregulation of cell-surface proteins in the tumour microenvironment leading to tumour-specific immune responses [3]. We aim to determine if RT exerts immunostimulatory effects in murine bladder cancer cell lines. We also developed a murine orthotopic tumour model more characteristic of *de novo* human tumours [4,5] to determine immunogenic changes occurring *in vivo*.
Methods: A murine vaccination study was employed to determine immunogenicity of cell death after RT. Western blotting and flow cytometry determined immune phenotypic changes in response to RT *in vitro*. To generate an orthotopic model of murine BC, MBT2 cells were inoculated intravesically into C3H/Hen mice. Ultrasound monitoring was used to measure tumour growth.
Results: Mice inoculated with BC cells irradiated with a single fraction of 16 Gy prior to implantation demonstrated a survival advantage after subsequent re-challenge with viable cells. RT led to upregulation of immunostimulatory surface proteins ICAM1 ± CD80, MHC I and Fas but not calreticulin or HMGB1, in a dose- and time-dependent manner after treatment in MB49 or MBT2 cells *in vitro*. Bladder tumours were visible on ultrasound 10–15 days after inoculation and showed reproducible growth with a >80% take rate.
Conclusion: RT induces immunogenic effects on murine BC cells, including upregulation of various tumour cell surface proteins. Future work will evaluate the importance of these changes for efficacy of RT. Successful generation of an orthotopic model of murine BC will allow determination of RT-induced immune changes within a representative tumour microenvironment. This information may help determine therapeutic strategies to enhance the efficacy of RT for patients with BC.

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