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AIMS/INTRODUCTION: At University Hospital Galway (UHG) 125-Iodine seeds permanent implantations of the prostate commenced in January 2007. A retrospective study is presented relating spatially defined dose information of the prostate to the occurrence of rectal toxicity.

MATERIALS/METHODS: The study is based on 136 consecutive patients treated with permanent 125I radioactive seeds. The prescription dose was 160Gy. Rectal toxicity was reported as grades of proctitis and haemorrhage, based on the Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Dose-volume histogram (DVH) parameters were derived for defined sectors of the prostate gland and for the rectum, as contoured on the intraoperative ultrasound images in the Variseed 8.0.1 treatment planning system (Varian Medical Systems). The sector analysis was restricted to three prostate sectors, proximal to the rectum. In order to determine if rectal toxicity can be explained by the DVH dosimetry data, a binary logistic regression model has been applied with the categorical response variables proctitis ‘yes/no’ and haemorrhage ‘yes/no’. Explanatory variable selection was performed by stepwise removing variables that prove non-significant (p>0.05).

RESULTS: In the cohort of 136 patients, 30 patients (22%) presented with proctitis and 10 patients (7%) presented with treatment related haemorrhage. The highest grade observed was Grade 3. The median follow up time was 55 months. A preliminary statistical analysis for a subset of 41 patients showed that the prostate dose parameter D10% (sector 7) is the sole variable that significantly (p=0.022) affects the probability of occurrence of proctitis. No such dependency could be found for the occurrence of haemorrhage.

CONCLUSION: The probability of contracting proctitis exceeds 20% with D10% (sector 7) > 320 Gy. This parameter can be monitored during implantation and the procedure be modified as necessary. The analysis will be extended to 136 patients.
AIMS/INTRODUCTION: Following the work of Bashar et al, the purpose of this study was to develop our own site specific nomograms for predicting the number of I125 seeds required for Prostate Brachytherapy using the bestfit approach and machine learning methods.

MATERIALS/METHODS: A dataset of 247 patients was compiled and retrospectively analyzed for development of the nomograms. The dataset was randomized and subdivided into training (148), cross validation (50) and testing (49) sets.

The current method of calculating seed requirements is based on Bashar’s equation, where the prostate volume and seed strength are input to give an estimate of seeds needed for implant, and an additional 10% are then added.

The correlation between the pre-needle volume, as determined from ultrasound, and the total implanted activity was calculated on the training dataset using a bestfit with an upper confidence interval of 95%. This bestfit was used to derive the equivalent of Bashar’s equation for our own center. The use of various Machine Learning techniques was also assessed as a possible means of seed number prediction. The overall performance was measured in terms of the Mean Square Error (MSE) of the prediction models as measured against the known test dataset seed numbers. The entire process was repeated 50 times with a different randomization each time and the MSEs averaged.

RESULTS: All the nomograms demonstrated a similar performance, with MSEs ranging from between 40 and 50 with a Neural Network method of Machine Learning achieving the lowest MSE.

CONCLUSION: With further development, the use of site-specific nomograms demonstrates the potential for a reduction in treatment costs, as well as reducing the burden associated with storage/disposal of excess seeds. Machine Learning may also provide a means of correcting for the variations observed in prostate shape not accounted for with the bestfit approach.
AIMS/INTRODUCTION: The aim of the study was to investigate the application of machine learning techniques to intra-operative implant dosimetry data for prediction of rectal dose classes determined 30 days post implant.

MATERIALS/METHODS: A retrospective analysis of brachytherapy implant data was carried out on the 300 patients that underwent permanent I-125 brachytherapy for low-risk prostate cancer. For each patient, the dose received by 2cm$^3$ of the rectum (D2cc) at day 30 was defined as belonging to 1 of 3 classes, Low <=80 Gy, <80 Gy Medium <=100 Gy, and High >100Gy. The original dataset (301) of all intra-operative dose measurements was reduced using software to a selection of 10 best performing predictors and sub-divided into two datasets, one for training (226) and the remainder for testing (75). Machine learning techniques, developed in Weka and Matlab software environments, were trained on this refined dataset to make predictions of rectal dose classification at day 30. The performance of a technique on the testing dataset was assessed in terms of its true and false positive rates, precision, recall, F-Measure and Receiver Operator Curve Area based on a 10-fold cross validation procedure.

RESULTS: The Radial Basis Function Network demonstrated the best performance with an overall accuracy of 80%, and the weighted averages of True Positive = 80%, False Positive = 21%, Precision = 79%, Recall = 80%, F-Measure = 78% and ROC Area = 0.89.

CONCLUSION: While Machine Learning methods demonstrated high performance in classification of the Low and High classes, the Medium class proved to be ill defined on the basis of the training data, resulting in ROCs of between 0.55 and 0.76 for various techniques. Redefining class thresholds and retaining only High and Low groups with uncertainties attached to each prediction may be the most clinically useful potential application of such a classification system.
AIMS/INTRODUCTION: To assess the feasibility of using prostate brachytherapy equipment for Magnetic Resonance/Ultrasound (MR/US) fusion-guided prostate biopsy.

METHOD: We recently introduced the Oncentra Seeds (OS) planning system for delivering LDR prostate brachytherapy. The software is designed to handle multiple image sets and has tools for image registration and fusion. We wish to use this functionality to introduce MR/US fusion-guided biopsy, before doing so the following tests were performed:

1. A review of the software (OS) handling of MR images was performed with a number of clinical MR datasets. From this the preferred MR acquisition parameters were established.
2. A prostate phantom study was performed to check the image registration accuracy of the software.

RESULTS:

1. Image quality of the MR images in OS is equivalent to that seen in Sectra PACS for the acquisition plane. OS reconstructs a 3D dataset from this which appears blurry with the standard MR prostate protocols. As a result, the slice width and spacing of the MR sequence should be reduced or acquisitions in the sagittal and coronal plane utilised.
2. OS assumes the primary acquisition angle of the imported MR image set is axial.
3. Multiple datasets can be imported but only two can be registered and fused.
4. The secondary dataset adopts the slice width of the primary dataset if the primary dataset has a smaller step size.
5. The manual image registration tools are flexible and enable accurate registration of MR and US contours with +/-2mm variation.
6. The image registration is not stored with the dataset to refer back to.

CONCLUSION:

1. This study supports the use of brachytherapy planning software (OS) in MR/US fusion guided prostate biopsies.
2. The results have been used to establish a safe protocol from which a service can be established.
AIMS/INTRODUCTION: An optical fibre sensor for monitoring low dose radiation is presented. The sensor is based on a scintillation material coated optical fibre, which emits visible light when exposed to low level ionising radiation. The incident level of ionising radiation can be determined by analysing the observed emission spectra.

MATERIALS/METHODS: A PMMA (polymethyl methacrylate) based plastic optical fibre is coated with radiation sensitive inorganic scintillators that fluoresce when exposed to ionising radiation. The emitted signal penetrates the fibre and propagates along the fibre where it is remotely monitored using a Photon Counter. Three major scintillation materials such as terbium-doped gadolinium oxysulfide(Gd2O2S:Tb, Gadox) and thallium-doped cesium iodide(CsI:Tl) and cerium-doped lutetium oxyorthosilicate(Lu2SiO5:Ce) were used. The optical fibre sensor is constructed by drilling a 0.5mm with an approx depth within fibre and coating the end with the mentioned phosphors. A 1 metre PMMA plastic optical fibre (POF) of 1mm core diameter is prepared.

RESULTS: The optical fibre sensor was initially tested for its response to 6.3mCi and 5.43mCi of Iodine 125 within SI HDR 1000 Well Chamber, three phosphors were analyzed for their respected response. During irradiation the sensor demonstrates a stable response and then returns to its original off state when the radiation is removed. The sensor was then tested at repeated radiation doses of 6.3mCi and 5.43mCi to test for the stability of the optical fibre sensor at repeated exposures.

CONCLUSION: This work presents the ongoing development and characterisation of an optical fibre sensor suitable for use in brachytherapy applications. The optical fibre set-up allows for real-time monitoring of the radiation, for improved patient safety. Further work is also ongoing to investigate the use of the probe in brachytherapy with the utilization of the urinary catheter to monitor urethra dose and also placement along the transperineal ultrasound probe to monitor rectal wall dose.
To investigate contemporary rates of variation in the biopsy Gleason grading in prostate cancer, between local and central pathologists, based on central review of the pathological slides from Seed and Hormone for Intermediate-risk Prostate Cancer (SHIP) 0804, a phase III, multicenter, randomized, controlled study. From April 2008 to May 2011, 18 Japanese institutions participated. All H&E slides were reviewed independently, without clinical information, and a tumor grade was assigned according to the modified Gleason grading system proposed by the International Society of Urological Pathology (ISUP). Prostate biopsy specimens of 642 cases were available for evaluation. An exact concordance rate of Gleason score (GS) between local and central pathologists was determined to be 65.3%; with the under-grading and over-grading of grades to be 14.6% and 20.1%, respectively. The central review resulted in numbers of tumor-bearing cores reassigned in 99 of 616 cases in which such information by the local pathologists was available (16.1%). Discordance in biopsy Gleason grading was still found in one third of the cases in the SHIP0804 study. This information is valuable in extrapolating the diagnostic error range in contemporary clinical studies conducted without central pathological review.

published elsewhere: Pathology International 2015
PURPOSE: Our Institution has performed >2500 LDR I125 brachytherapy implants since 1999. The first one thousand patients were treated with a two stage pre-planned stranded I125 brachytherapy technique as popularised by the Seattle group. In 2009 we developed a one stage real-time implant technique using stranded seeds around the periphery of the gland and loose seeds within the centre. The positions of the loose seeds are planned intra-operatively to achieve target dosimetry. This technique has been termed 4D Brachytherapy.

METHODS: We present the outcomes of 350 consecutive patients from both cohorts, after our learning curve in the brachytherapy technique, to compare the dosimetry and clinical outcomes. Data retrieved from a prospectively collected database. The two stage cohort dated from February 2002 to September 2004 and the 4D group from June 2009 to October 2011.

RESULTS: There was no significant difference in cancer demographics between the two groups regarding PSA, Stage and prostate volume, those receiving EBRT and brachytherapy boost and those receiving hormones. There was a significant improvement in the post implant dosimetry and toxicity for 4D Brachytherapy over the standard 2 Stage technique.

Prostate D90(%) range for 4D 105.1 ± 6.9 vs 103.4 ±13.1. Rectal V100(%) 4D 0.7 ± 6.7 vs 1.6 ± 1.0. Urethral V150(%) 4D 4.0 ± 6.7 vs 9.8 ± 9.6, all p<0.05.

98% of 4D patients achieved D90 target of 90 to 120% of target dose vs 75%, 4D 99% achieved a Prostate V150< 65% vs 83.1. Mean IPSS change from baseline at 1 year was 0.9 for 4D vs 2.3. Mean Urinary QOL change form baseline at 1 year 4D 1.2 vs 1.7. All results p<0.05.

CONCLUSION: We demonstrate improved dosimetry across all parameters irrespective of prostate size, and improvement in urinary toxicity. The procedure takes no longer than the 2 stage technique.

*published_elsewhere: ASTRO 2015*
PURPOSE: Focal therapy offers the potential of functional preservation whilst treating clinically significant cancer and sparing unaffected tissue. We present an interim analysis of a Hemi-Ablative Prostate Brachytherapy (HAPpy) study, a phase 2S trial using LDR I-125 implantation targeting the half of the gland containing the disease.

METHODS: 34 Low risk patients (Gleason score 7, PSA<15, <T2bN0M0) with unilateral disease confirmed on multi-parametric MRI (mp-MRI) and trans-perineal biopsy template are being recruited. Primary outcomes are serial assessment of IPSS, urinary quality of life and bowel symptoms. Secondary outcomes are tumour control with serial PSA measurement and repeat mp-MRI and template biopsy after 2 years. Controls are taken from a prospectively collected database and matched for stage, prostate volume and PSA.

A modification of the 4D Brachytherapy technique was employed, utilizing stranded seeds around the periphery of the hemi-gland and loose seeds centrally, in a one-stage real-time procedure. Controls were treated by a standard 4D brachytherapy technique.

RESULTS: 15 patients were treated from 30/1/13 to 11/12/14. Median age 68 (54-79). Prostate volume mean 44.7cc (32.9-62.2). PSA mean 7.8ng/ml (5.0-12.0). No significant differences seen with control group (independent T test). Target dose to the hemi-prostate 145Gy.

Porsotate D90(%) HAPpy 104.0 ± 8.4, control 108.0 ± 6.9 (N/S), Prostate V100 coverage HAPpy 91.7 ± 3.9 vs 93.7 (p<0.05).

Urethra D30(Gy) HAPpy 151 ± 22 vs 174.2 ± 15, Rectal D2cc (Gy) HAPpy 53.4 ± 8.3 Vs 96.9 ± 21.1, both p<0.05.

Maximum IPSS change from baseline HAPpy 3.5 vs 9 control, Urinary QOL maximum change 0.5 vs 2.0, max change in bowel symptoms 1.0 vs 2.0, all p<0.05.

CONCLUSION: Acceptable dosimetry is achievable treating half the gland with a consequent reduction in hot spots in organs at risk. Patients report less toxicity compared with whole gland treatment both in urinary and bowel symptoms.

published elsewhere: ASTRO 2015

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*St Luke’s Cancer Centre, Royal Surrey County Hospital, Guildford
INTRODUCTION: PBOS and large prostates have been considered contraindications to permanent prostate brachytherapy implant (PPB) on the basis of likely toxicity and technical difficulties although their effects on oncological control have not been previously reported. This study determined the effect of PBOS and prostate size on oncological outcomes in patients undergoing PPB.

METHODS: Patients undergoing monotherapy PPB for low to intermediate risk prostate cancer between 2003-2013 were assessed. Primary outcome was biochemical recurrence free survival (BRFS) defined by PSA rise >2ng/ml above nadir. Secondary outcomes were the incidence of toxicity according to the Radiation Therapy Oncology Group toxicity grading, salvage therapy and PSA nadir. Univariate Kaplan-Meier, multivariate cox proportional hazards and logistic regression analyses were conducted.

RESULTS: The study identified 407 patients including 76(19%) with PBOS, which consisted of TURP(n=72), Holep(n=4), HoLAP(n=1) and Millens prostatectomy(n=1). Prostate sizes ranged between 12.5-91.28cm³. Median interval between PBOS and PPB was 7.6months, with 74% undergoing PPB within 12months. Median follow up time was 43 months and mean D90 was 171(±13)Gy. No significant difference in actuarial BRFS was detected between those with and without PBOS. Favourable BRFS was observed in larger prostate volumes (p=0.02). Multivariate analysis of pre-treatment variables showed large prostate volume as the only independent predictor of BRFS (p=0.026). Independent predictors of BRFS post treatment were prostate volume (HR=0.50, p=0.024), PSA nadir (p=0.003) and time to nadir (p<0.001). High PSA was a pre- and post-operative predictor of grade III toxicity (HR=1.26, p=0.01).

CONCLUSION: Large prostate size is an independent predictor of favourable BRFS after PPB. History of PBOS did not affect BRFS nor increase the incidence of grade III toxicity and hence is not a reason to deny PPB.
PURPOSE: It is controversial whether brachytherapy for prostate cancer will increase the risk of subsequent bladder cancer. Some studies reported that the incidence of bladder cancer after brachytherapy were the same as in the general population, but the clinical characteristics tended to be higher grade and stage, and a few cases with prostatic and bladder sarcoma after radiation or brachytherapy were reported. This study was designed to assess the clinical characteristics of the patient with bladder cancer after 125-iodine brachytherapy with or without external beam radiotherapy (EBRT) for prostate cancer.

MATERIALS AND METHODS: Between 2003 and 2014, 1204 patients diagnosed of localized prostate cancer were treated with brachytherapy (with or without EBRT) at The Jikei University Hospital. We reviewed our records among 1204 patients to identify the patients who had a diagnosis of bladder cancer after brachytherapy. Patient age, date of brachytherapy, date of diagnosis of bladder cancer, symptoms, cancer site at bladder, final pathology, definitive therapy, and disease status were collected.

RESULTS: Of the 1204 patients, nine patients (0.7%) had bladder cancer with a median interval of 41.8 months after brachytherapy. Most common symptom at initial diagnosis of bladder cancer after brachytherapy was asymptomatic macro-hematuria. Four of those nine bladder cancer patients had high grade. Two of those four patients had been performed laparoscopic radical cystectomy. One patient had inflammatory myofibroblastic tumor(IMT) with sarcomatoid differentiation. Unfortunately, those who had been operated died because of aggressive progression of bladder cancer within a year after surgery.

CONCLUSIONS: Clinical characteristics of bladder cancer after brachytherapy tend to be higher grade and stage in our brachytherapy series. In particular, sarcomatous tumor like our case may occur after radiation or brachytherapy. Patients with prostate cancer who are treated with brachytherapy should be monitored more carefully for earlier detection of subsequent bladder cancer.
INTRODUCTION: Comparative studies of prostate brachytherapy and radical prostatectomy for organ-confined prostate cancer have previously demonstrated similar PSA recurrence-free survival between the two treatment modalities. Here, overall survival (OS) is compared in patients with low-to-intermediate risk prostate cancer undergoing either low-dose rate prostate brachytherapy (PB) or robotic-assisted radical prostatectomy (RARP).

METHODS: The study cohort comprised 1869 patients with organ-confined prostate cancer treated at a single UK centre between 2003-2013 with either PB or RARP. Patients were excluded if PSA>20ng/ml, total Gleason score ≥8, clinically stage T3, had prior prostate cancer treatment, or planned adjuvant radiotherapy. Data on pre-treatment PSA, biopsy-derived Gleason score, age, race, prostate volume, treatment date, Charlson co-morbidity score, mode of initial diagnostic biopsy (transrectal or transperineal), treatment date, and dosimetric parameters were collected via the Electronic Patients Records system. Socio-economic score was calculated from the patients’ addresses. Overall survival data were derived from the Cancer Registry. Statistical methods included Kaplan-Meier and Cox proportional hazards analyses.

RESULTS: A total of 1392 patients satisfied the inclusion criteria. Median followup time was 48.2mths. Actuarial overall survival for PB (n=408) vs RP (n=984) at 48 and 96mths were 97.5% and 98.4%, and 87.8% and 91.1% respectively (p=0.25). Multivariate analysis identified modified Charlson co-morbidity score (p<0.001) and age (p<0.05) as independent predictors of OS. Mode of treatment, mode of initial diagnostic biopsy, and other covariates did not independently predict OS.

CONCLUSION: Overall survival differences were not observed between PB and radical prostatectomy in this retrospective study. Pre-treatment comorbidity and age were independent predictors of overall survival.