The delineation of intraprostatic boost regions for radiotherapy using multimodality imaging

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ABSTRACT

Dose-escalation to the prostate improves tumour control but at the expense of increased rectal toxicity. Modern imaging can be used to detect the most common site of recurrence, the intraprostatic lesion (IPL), which has led to the concept of focussing dose-escalation to the IPL in order to improve the therapeutic ratio. Imaging must be able to detect lesions with adequate sensitivity and specificity to accurately delineate the IPL. This information must be carefully integrated into the radiotherapy planning process to ensure the dose is targeted to the IPL. This review will consider the role and challenges of multi-parametric MRI (mp-MRI) and positron emission tomography computed tomography (PET-CT) in delineating a tumour boost to be delivered by external beam radiotherapy (EBRT).

KEYWORDS

Prostate cancer, intraprostatic lesion, dose-escalation, boost, MRI, PET-CT

Background – the rationale behind the intraprostatic boost

Dose-escalation

Increasing the dose to the prostate during radical radiotherapy (RT) has consistently shown improvement in biochemical control [1-6]. A meta-analysis showed that the postulated improvement in biochemical control rate at five years was an increase of 19.2% in high-risk patients between the dose ranges of 70-80Gy [3]. However, dose-escalation to the whole prostate is associated with an increase in bladder and rectal toxicity [4-7].

Patterns of recurrence

Although prostate cancer tends to be multifocal, histopathology from prostatectomy specimens commonly reveals a larger focus or intraprostatic lesion (IPL), also referred to as the dominant intraprostatic lesion (DIL). Local recurrence following radical radiotherapy largely occurs at the site of the IPL [8-10]. Cellini et al reported on 12 patients who had an intraprostatic recurrence, following EBRT and androgen deprivation therapy (ADT) [8]. For all 12 patients, clinical examination and imaging findings showed recurrence was at the site of the primary tumour. Pucar et al reviewed pathology from salvage radical prostatectomy in 9 patients with locally recurrent disease [9]. Visual comparison of pathology, together with pre- and post-RT magnetic resonance imaging (MRI) showed that all significant recurrent lesions occurred at the site of the primary tumour.

Therefore a higher dose to the IPL may reduce biochemical prostate-specific antigen (PSA) failure and it is suggested that improving local control may translate into a reduction in distant metastases [11].

Improved therapeutic ratio

The demonstration of disease recurrence within the DIL has led to the proposal of boosting this region, whilst maintaining a standard dose to the rest of the prostate, in order to improve the therapeutic ratio [12]. The boost dose needs to be at least 80-90Gy in 2 Gray fractions, to reach the top of the tumour control probability (TCP) curve [3, 5]. The aim of treatment would be to increase the TCP without increasing the normal tissue complication probability (NTCP) for the bladder and rectum.

Multifocality

Prostatectomy specimens reveal the multifocality of prostate cancer [13] and when more than one tumour is identified on imaging, boosting several dominant nodules is technically possible [14]. The significance of smaller, incidental tumours however, is unclear. Noguchi et al reported that the secondary tumours identified following radical prostatectomy did not predict for biochemical failure [15]. In a disease where we know some low risk cancers can safely be observed [16, 17], stratification systems have been produced which help to determine intraprostatic disease which can be considered insignificant on template-mapping biopsy procedures [18]. This is an important concept to consider when discussing IPL boost.

Dose Painting

Focal therapies to an IPL include the different techniques of external beam radiotherapy (EBRT), brachytherapy, high intensity focused ultrasound (HIFU) or cryotherapy. With radiotherapy techniques such as intensity modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT), more complex dose distributions are possible, allowing an increase in dose to a particular volume, whilst limiting the dose to the organs at risk (OAR.) To deliver this dose accurately and improve the therapeutic ratio, prostate movement needs to be accounted for by image-guided radiotherapy (IGRT). The boost may be delivered sequentially, following standard treatment to the prostate, or as a simultaneous integrated boost (SIB). The optimal boost dose and radiotherapy planning method is unclear- this is beyond the scope of this review and will not be debated here. Most studies to date have used static field IMRT [14, 19-23]. Planning studies have also assessed VMAT [24-26] and SBRT techniques [27, 28]. Figure 1 shows an example of an IPL boost plan for Cyberknife delivered SBRT.

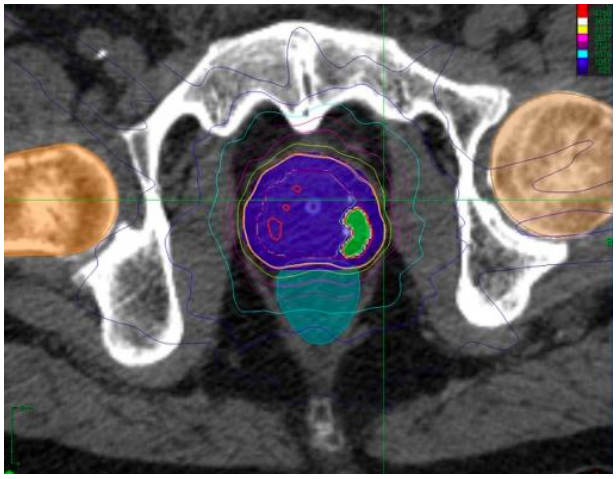

Figure 1. An example of an IPL boost delivered using Cyberknife within the SPARC trial (NCT02145494). Purple shading represents prostate planning target volume (PTV), green shading represents IPL boost

Also unclear is which groups of patients would benefit from an intraprostatic boost. Given the excellent control rates seen from studies such as the CHHiP trial [29], it may be that only higher risk patients will benefit from an intraprostatic boost.

Identification of IPL

Although imaging techniques have previously been reviewed for detection of an IPL, whether an image is sufficient to accurately define the tumour boundary is a separate question. An accurate IPL boost involves several stages, from optimal imaging, accurately transferring this information to the planning CT, correct identification and delineation of the lesion, and then delivering the radiotherapy as intended.

In this article, we will be looking at the use of imaging when delineating a boost for EBRT modalities, specifically concentrating on multiparametric MRI (mp-MRI) and positron emission tomography (PET). For each of these, we consider the limitations, practicalities and challenges of IPL delineation under the following sections

- Type of imaging
- Limitations and challenges of imaging
- Histopathological correlation of contours for boost techniques
- Feasibility of boost delivery
- Integration of imaging during radiotherapy

MR IMAGING

There are clear benefits for the addition of MRI when contouring the prostate as a whole, with the improved soft tissue contrast providing better definition of the prostate boundary and subsequent reduced inter-observer variability [30-33].

Multiparametric Imaging

The accuracy of MRI in staging prostate cancer has been extensively studied. Conventional MRI consists of anatomical T2 weighted images (T2W) with prostate cancer exhibiting low T2 signal intensity. Multiparametric MRI (mp-MRI) includes functional data from dynamic contrast-enhanced (DCE), MR spectroscopy (MRS) and/or diffusion weighted imaging (DWI), which can all provide additional information on the tumour to improve the sensitivity and specificity of tumour detection [34-39].

DCE-MRI acquires images whilst contrast is administered and therefore provides information on the perfusion and vascular permeability of a tumour. DWI assesses the motion of water molecules, with tumours showing a restricted diffusion due to increased cellularity. This restriction of diffusion is expressed as the apparent diffusion coefficient (ADC) and has been found to be a predictor of the aggressiveness of a prostate cancer [40, 41]. MRS is a form of metabolic imaging that detects prostate cancer due to the lower levels of intracellular citrate and higher levels of choline compared to benign prostate tissue. There is increased sensitivity for detection of prostate cancer with the addition of MRS [36], however spatial resolution is poor, limiting accurate tumour delineation.

Combining modalities improves the sensitivity compared to T2W images alone [37-39]. Pooled results from studies using the combination of T2W, DWI and DCE-MRI show a sensitivity of 0.74 (95% CI, 0.66–0.81) with specificity of 0.88 (95% CI, 0.82–0.92) [42]. Of the three multiparametric modalities (DWI, MRS and DCE), two appear to be sufficient for maximal sensitivity and adding in the third modality may not be of additional benefit [43]. Current recommendations suggest the use of two functional MRI techniques in addition to standard T2 weighted images [44]. Figure 2 shows an IPL on mp-MRI and PET imaging with an IMRT plan depicting the boost dose for the DELINEATE trial (UKCRN ID 10309).

Figure 2a

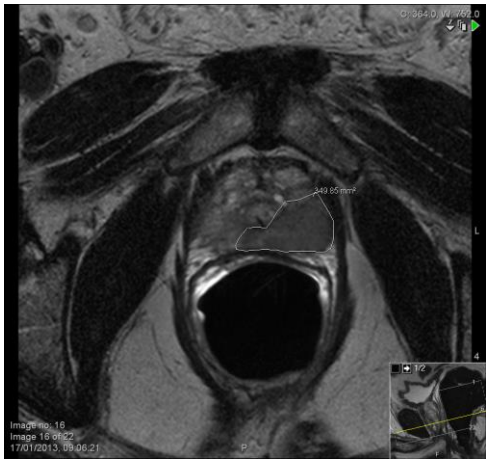

Figure 2b

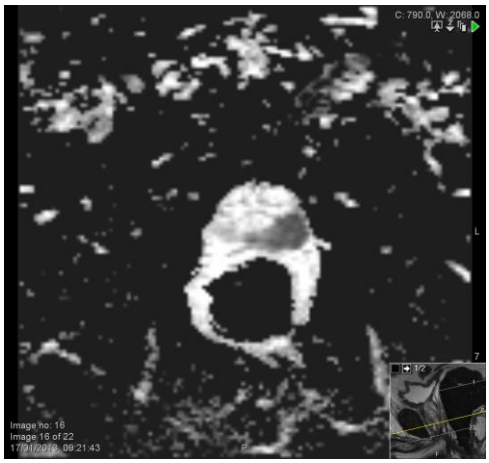

Figure 2c

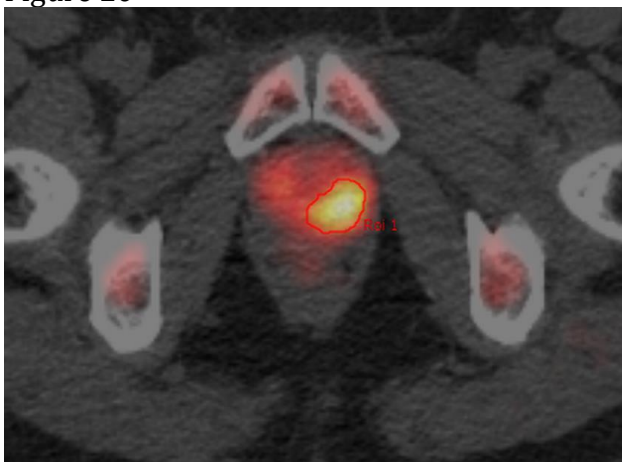

Figure 2d

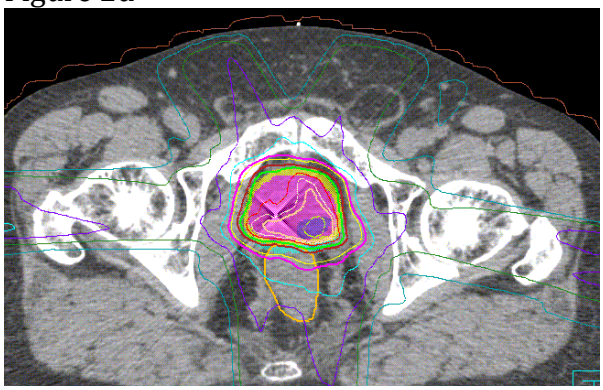

Figure 2- An IMRT delivered IPL boost to a left sided tumour with corresponding MRI and PET-CT imaging. Figure 2a) T2W imaging. Figure 2b) DW-MRI. Figure 2c) PET-CT imaging. Figure 2d) IMRT delivered boost in the context of the DELINEATE study- pink shading represents prostate CTV, yellow shading represents prostate PTV, purple shading represents IPL boost.

Limitations and Challenges of MRI for delineation of IPL

Accuracy

The reported accuracy of MR imaging for IPL delineation is variable and dependent on a number of imaging factors as well as tumour characteristics. Technical factors include field strength, b values (which assess the strength of the gradients for DWI), signal- to-noise ratio and whether an endorectal coil (ERC) is used. The latter improves the spatial resolution and has been found to improve the sensitivity, specificity and staging accuracy of prostate cancer [45] but the presence of the coil causes distortion of the prostate, which limits its use in planning radiotherapy.

Low signal on T2W can be seen with prostatitis, haemorrhage, post radiotherapy change and scarring, and distinguishing these from tumour nodules can be challenging.

MRI is limited in the detection of small volume tumours e.g. $<0.5cm^3$ [46], particularly those of lower Gleason score. This is due to histological characteristics of the tumour focus, such as the ratio of malignant epithelium-to-stroma, which are inherently different in lesions picked up on MRI compared to those that are not detected [47, 48].

Interobserver Variability

The delineated shape and size of the IPL should be consistent, aiming to minimise inter- and intraobserver variability. Steenbergen et al compared the delineated tumours using mp-MRI from six teams from three different centres [49]. These were compared to the histological findings from prostatectomy to assess the accuracy of tumour delineation and interobserver variability. Using the combination of T2W, DWI and DCE images, 18 out of 20 dominant lesions were detected by all groups. However, parts of the dominant lesion were missed and 66 out of 69 satellite lesions were undetected. As discussed previously, the clinical significance of these satellite lesions, most of which were smaller than $0.4cm^3$, is unclear [15]. Although this data is consistent with the high sensitivity of detecting tumours with mp-MRI, there was discrepancy of the shape and size of the dominant lesion to be boosted. This may have an impact on local control if the dose to the remaining prostate were to be reduced, or focal therapy techniques used in isolation. However, overall there was good agreement (kappa statistic of 0.61) between observers.

Image Interpretation

The variation and discrepancy in IPL delineation is a significant limitation in allowing accurate radiotherapy boost and subsequent introduction to routine practice. There are scoring systems to allow a more standardised method of reporting, such as the PI-RADS score [44, 50] but the experience of the reporting radiologist remains important. A significant hurdle can be combining the information from multiparametric datasets. A comparison of the IPL delineation from DWI and DCE-MRI [51] showed a large variation in the overlap with particularly poor agreement in certain patients. This adds to the uncertainty of the IPL volume, with the same group suggesting a pathologically validated statistical model to predict the risk of tumour presence on a voxel level [52].

Computer aided delineation techniques such as this and others [53, 54] use quantitative features from images to assess whether each voxel is classified as tumour or normal tissue. Further validation is required but these programmes could help to reduce uncertainty in delineation and reduce interobserver variation [55].

Effect of Androgen Deprivation Therapy

The timing of the imaging to be used for definition of the boost is particularly relevant in prostate cancer. Dominant nodules may be easily defined on initial diagnostic imaging, however most patients then receive ADT, which decreases the size of the IPL, and reduces tumour conspicuity [56]. Imaging for DIL delineation for radiotherapy planning could therefore be acquired prior to starting ADT with immediate irradiation, thus necessitating a change in the treatment paradigm. Alternatively, the information from pre-ADT imaging can be 'mapped' onto post-ADT imaging using deformable registration techniques. Additionally, it is unknown whether the optimal target is in fact the pre- or post-ADT lesion. The latter would require further investigation into the effect of ADT on mp-MRI images and may become clearer when the exact benefits of an IPL boost are confirmed.

Histopathological Correlation of Contours with MRI

The gold standard of any imaging technique is correlation with histopathology, however accurate comparison with imaging is extremely challenging. Even with studies comparing imaged IPLs with 'whole-mount prostate' reference histology there are certain limitations such as shrinkage of tissue during fixation and co-registration errors, which may be introduced when aligning histopathology specimens to the equivalent imaging slice. To reduce the impact of such errors one group have used individualised MRI-based custom moulds to aid accurate co-registration of the specimens following prostatectomy [57].

Variability of tumour volume estimation

Data shows a positive correlation between the tumour volume derived from histopathology and the MRI defined volume, with the accuracy of MRI estimation improving with a higher tumour volume [46, 58]. However, even for lesions greater than 0.5cm^3, there is still variability [46]. Coakley et al found the MRI defined tumour volume ranged from 3% to 433% of the actual volume on histopathology [46]. However, this study looked at any Gleason grade of tumour in the specimen and as discussed above, Gleason grade 3+3 may be less distinct on MRI.

Several studies show tumour volume may be under- rather than overestimated on MRI [59-62]. One such study comparing the volume seen on MRI compared to histology in 50 tumours [59], showed underestimation by mp-MRI with the volume being lower by a mean of 47% compared to histopathology. Interestingly, this group found that the underestimation was worse for lesions with a high Gleason score [59, 62], which has the potential to severely impact the outcome for these patients.

Consideration of margins required to cover tumour

Groenendaal et al found that the use of mp-MRI for IPL delineation gave a tumour coverage of 44-89% of the corresponding lesion on whole mount histopathology [60]. The addition of a margin of two voxels (approximately 5mm) improved coverage to 85% or more. Similar results for the margin required have been suggested by other studies. Anwar et al identified prostate foci using MRS and subsequently contoured these lesions using T2W images in patients about to undergo prostatectomy (mp-MRI was not used) [61]. When compared to whole mount histopathology, they found that in order to cover the 'MRI undercall' (i.e. the areas underestimated by the readers) that expansion by 5mm at the non-capsular margin would cover 95% of the actual tumour volume.

A similar study comparing MRI contouring to histopathology concluded that a 9mm margin would be adequate to cover all 46 tumours analysed [62]. This differed from the studies above by looking at which margin would be required to cover the entire tumour. The authors suggested 9mm as the non-capsular margin and 3mm for the capsular margin, to take into account extraprostatic extension. However, the maximum Hausdorff Distance (HD), looking at the difference between the MR delineated lesion and histology, was significantly greater for high grade lesions. It must be considered that the 9mm margin suggested, included coverage of Gleason 6 tumours (10/46 lesions). Margins could therefore be stratified based on tumour characteristics, especially as in the absence of de-escalation to the whole prostate gland, coverage of low risk disease is not the objective. For example the same study showed that a smaller margin of 5mm covered 73.9% of tumours, 7mm covered 93.5% of tumours.

From a radiotherapy planning point of view, these studies indicate an intraprostatic margin of 5mm around the MRI defined IPL would be suitable [60, 61]. A further factor to be considered is the administration of ADT, which would shrink the IPL and surrounding prostate, so a smaller margin may subsequently be appropriate.

Feasibility of MRI-defined boost delivery - theoretical

There have been a number of planning studies estimating the TCP, NTCP and investigating the factors that would make an IPL boost feasible. These are outlined in Table 1.

Table 1: Planning Studies delivering a boost to an MRI defined IPL

REFERENCE	PATIENTS	IMAGING TECHNIQUES	RADIOTHERAPY TREATMENT	FINDINGS
Van Lin (2006) [63, 64]	n=5	1.5T MRI with ERC T2W, MRS, DCE MR and CT fusion using fiducials IPL delineation by radiologist	Step and shoot IMRT with SIB <u>Plan 1 (boost to IPL):</u> Prostate + 7mm 70Gy/35f IPL + 5mm 90Gy/35f <u>Plan 2 (no boost to IPL):</u> Prostate + 7mm 78Gy/39f	In 5/5 patients, increased therapeutic ratio with boost plan due to a reduction in rectal NTCP with maintained TCP
Housri (2011) [64]	n=42 overall n=24 had visible IPL	MRI with ERC T2W, DCE, ADC, MRS Treatment planning MR without ERC in 14/24 patients with IPL. Manual transfer of MRI information	Step and shoot IMRT with SIB Prostate + 9mm (5mm post) 75.6Gy/42f IPL + 3mm 151.2Gy/42f Dose escalation to 151.2Gy achieved in 12/24 and between 94.5Gy-136.1Gy in 9/24	SIB infeasible lesions less than 4.2mm from rectum SIB more feasible with greater hip-hip width >37.22cm
Ost (2011) [24]	n=12	T2W and/or MRS MR and CT fusion	Step and shoot IMRT (3,5,7 field) compared to VMAT Prostate + 4mm $D_{50} \geq$ 78Gy IPL + 0mm $D_{50} \geq$85Gy	SIB feasible with 5,7 field IMRT and VMAT VMAT superior to IMRT for rectal volumes receiving 20-50Gy
Tree (2013) [28]	n=15	T2W MR and CT fusion IPL delineation by oncologist and radiologist	SBRT with SIB Planned for both Cyberknife and RapidArc IPL + 0mm 47.5Gy/5f Prostate + 5mm (3mm post) 36.25Gy/5f	Boost feasible with both treatment methods If margins increased to 8mm (5mm post) 37/75 compared to 11/75 of constraints missed
Riches (2014) [65]	n=23 overall n=20 had visible IPL	1.5T MRI with ERC T2W, MRS, DCE (pre-ADT) MR and CT fusion using fiducials	Step and shoot IMRT IPL + 2mm 82Gy/37f Prostate + 3mm (0mm post) 74Gy	TCP significantly higher in boost plan Rectal NTCP significantly lower in boost plan
Murray (2014) [26]	n=10	1.5T MRI T2W, DWI, DCE IPL delineation by radiologist MR and CT fusion	VMAT Prostate + 6mm 42.7Gy/7f (alternate days) IPL + 4mm, prescription dose increased by 5% increments starting at 115% Plans with proximal SV 32.4-36.5Gy/7f	For prostate alone plus boost-median SIB 53.4Gy/7f (125%) Rectal NTCP increased with IPL boost
Feng (2015) [66]	n=14 n=7 planned (smaller IPL)	1.5T MRI T2W IPL delineation by radiologist	VMAT (dual arc) Prostate + 5mm (3mm post) 36.25Gy/5f IPL + 3mm 47.5Gy/5f	SIB feasible in all 7 patients Standard rigid registration not clinically acceptable

The largest of these was published by Housri et al. Nine-field IMRT plans were designed with the aim of delivering a total dose of 151.2Gy to the IPL without violating dose constraints [64]. This was possible in 12 out of 24 patients and in particular, they reported the distance between the IPL and rectum was predictive of whether high dose radiation could be delivered to the IPL, with a plan being infeasible with a distance of less than 4.2mm from the IPL to the rectum.

Riches et al. planned IMRT at a dose of 74Gy to the whole prostate with an additional 8Gy SIB in twenty patients with an IPL identified using mp-MRI [65]. A planned boost was feasible in all patients whilst meeting dose constraints. Radiobiological modelling suggested a significant improvement for the TCP in the boosted plans with a significantly lower rectal NTCP for the boosted plan. This finding has also been reported in other studies [25, 63] and may be due to the redistribution of dose, including hotspots, when a boost is planned.

Feasibility of MRI-defined boost delivery – clinical

Acknowledging the limitations described above, and with the aspiration that MR imaging will continue to increase its accuracy in delineating IPLs, several investigators have assessed the practicalities of delivering radiotherapy with focal dose-escalation. There have been several studies confirming that an MRI-planned radiotherapy boost is practically feasible, can be delivered within dose constraints and is possible without an increase in acute toxicity. These are summarised in Table 2.

The studies in Table 2 have generally shown that an IPL can be selectively dose-escalated with no obvious toxicity penalty. Further randomised studies are needed to confirm this hypothesis.

Table 2: **Clinical studies delivering a boost to an IPL.** Abbreviations: CRT conformal radiotherapy; EORTC European Organization for Research and Treatment of Cancer; GU genitourinary; GI gastrointestinal; L/I/H Percentage of patients in Low/Intermediate/ High risk groups; QoL Quality of Life; RTOG Radiation Therapy Oncology Group.

REFERENCE	PATIENTS	IMAGING	RADIOTHERAPY TREATMENT	SUMMARY OF TOXICITY
De Meerleer (2005) [19]	n=15 ADT 87% L/I/H: not specified	1.5T MRI with ERC T2W 9/15 patients had ERC	Step and shoot IMRT with SIB Verification with daily ultrasound Prostate + 7-10mm 74Gy IPL +0mm dose 80Gy	Long term follow up not specified Acute: (RTOG) GI- 20% Gr2, 0% Gr3 GU- 40% Gr2, 7% Gr3
Singh (2007) [14]	n=3 ADT not specified L/I/H: not specified	3T MRI with ERC T2W, MRS, DCE MR and CT fusion using fiducials	Step and shoot IMRT with SIB Fiducials Prostate + 7mm 75.6Gy/42f IPL +3mm dose 94.5Gy/42f	Follow up at 18, 6 and 3 months 2/3 patients Gr2 acute GU (RTOG) 1/3 patients Gr1 acute GI All symptoms resolved at 3 months
Fonteyne (2008) [67]	n=230 overall n=118 had SIB ADT 98% L/I/H: 2/40/58%	1.5T MRI with ERC T2W, MRS (in 49%) MR and CT fusion	Step and shoot IMRT with daily ultrasound verification Prostate + 4mm dose 78Gy/38f IPL + 8mm dose 80Gy/38f	Median follow up 12 months No increase in acute toxicity with SIB (RTOG)
Miralbell (2010) [27]	n=50 ADT 66% L/I/H: 10/24/66%	MRI with ERC T2W and DCE MR and CT fusion (endorectal balloon used for planning CT)	Sequential hypofractionated boost, infrared markers. Prostate dose 64-64.4Gy 28/50 patients 50.4Gy/28f to pelvic nodes 21/50 patients 2f of 5-7Gy boost 29/50 patients received 2f of 8Gy boost	Late (at 5 years): (RTOG) GI- 10% Gr2, 10% Gr3 GU- 12% Gr2, 0% Gr3
Ippolito (2012) [68]	n=40 ADT 100% L/I/H: 10/42/48%	1.5T MRI with ERC	Step and shoot IMRT with SIB Prostate + 10mm 72Gy/40f IPL + 5mm 80Gy/40f	Median follow up 19 months Late: (RTOG/EORTC) GI- 5% Gr2, 2.5% Gr3 GU- 5% Gr2, 2.5% Gr4
Aluwini (2013) [69]	n=50 (n=14 had SIB) ADT 0% L/I/H: 60/40/0%	1.5T MRI (no ERC) T2W MR and CT fusion using fiducials and foley catheter	SBRT SIB in patients with visible tumour Prostate + 3mm 38Gy/4f (daily) IPL up to 44Gy/4f (daily)	Late (at 24 months): (RTOG/EORTC) GI- 3% Gr2 GI, 0% Gr3 GU- 10% Gr2 GU, 6% Gr3 GU No difference in toxicity with SIB
Pinkawa (2012) [70, 71]	n=67 (n=46 had SIB)ADT 17% L/I/H: not specified	18F-Choline PET-CT IPL defined by tumour to background ratio of >2.0	Prostate + 4-8mm 76Gy/38f IPL + 4mm (3mm post) 80Gy/38f Verification with daily ultrasound	Median follow up 19 months No significant difference in QoL with addition of SIB
Wong (2011) [23]	n=71 overall n=51 scans positive ADT 24% L/I/H: 44/42/14%	Indium-111-capromab pendetide imaging Co-registration with planning scan	Step and shoot IMRT Verification with daily ultrasound Prostate + 6mm 75.6Gy/42f IPL + 0mm 82Gy/42f	Median follow up 66 months Late: (Mayo modification of RTOG) GI- 21% Gr2, 0% Gr3 GU- 39% Gr2, 4% Gr3, 1% Gr4 (haematuria)

Integration of imaging

Optimal boost delineation requires imaging to be carefully integrated into the planning process [65, 72]. At present, a radiotherapy planning CT provides the electron density data required for dose calculation and hence any additional boost imaging needs to be precisely co-registered with the planning CT to allow fidelity of the boost volume transcription. Even if imaging were to have 100% accuracy, if it is not precisely co-registered into the radiotherapy planning pathway, the IPL will not be faithfully represented.

At present, the optimal method for incorporating the information from MRI, is to 'fuse' the CT and MRI dataset. Although this process can be performed manually, software provides deformation algorithms to aid this complicated process, these programmes differ in the steps used to match the images and the degree of flexibility. Given the variability in rectal and bladder volumes and movement of the prostate, as expected, deformable image registration (DIR) is more accurate than rigid techniques [73]. Image registration can introduce a systematic anatomical error although the presence of gold seeds improves this process [72, 74]. Additional complications include MRI artefacts, limitations with the geometric fidelity of MRI and the distortion of the prostate seen when an ERC is used, all of which make accurate delineation of an IPL challenging. The discrepancy introduced by these MRI factors should be limited where possible, for example an endorectal balloon (ERB) can be used for the planning scan and throughout treatment to compensate for the ERC [63] but may not be practical.

The ease of image registration is also dependent on whether the patient was scanned in the radiotherapy treatment position for the secondary image set (in this case MRI) with identical immobilisation including knee wedges, foot stocks and with the same bladder filling protocol and rectal preparation.

If fusion is not possible, images are reviewed side by side to delineate the boost area, known as 'visual cognitive fusion'. This will add a further uncertainty to this process although this manual transfer method has been used in planning studies [19, 64].

Implementation of tumour dose-escalation

Adequate margins must be added to take into account co-registration and delineation errors plus motion during the treatment course (intra- and interfraction motion). Even taking into account the margin required to cover the IPL adequately, given the discrepancy seen with delineation as discussed earlier, the optimal intraprostatic margin for the boost is unclear and is dependent on the mode of delivery with some studies using a 0mm margin and relying on a relatively shallow dose fall off within the prostate CTV [19, 23, 24, 28]. Treatment must be delivered accurately with the use of in-room IGRT, with fiducial markers as the current gold standard.

Although the studies detailed here confirm the feasibility of delivering focal dose- escalation, with the potential for increased tumour control with decreased NTCP, additional information is needed. Prospective clinical trials such as the Phase III randomised controlled trial FLAME [75], HEIGHT (clinicaltrials.gov NCT01411332) and the Phase II DELINEATE (UKCRN ID 10309) and SPARC trials (clinical trials.gov NCT02145494) will provide the vital information on clinical outcome, toxicity and feasibility of boosting to decide whether focal dose escalation should become standard practice.

PET-CT IMAGING

Acquisition of Images

PET-CT is a form of molecular imaging, requiring injection of a radio-labelled tracer which accumulates based on tissue characteristics. For prostate cancer, differences in choline metabolism have been most frequently exploited for PET imaging. In particular, research has focused on [^{11}C] and [^{18}F] labelled choline derivatives, taking advantage of the increased turnover of choline in prostate cancer, which is required for phospholipids in the cell membrane. Although ^{11}C-Choline PET-CT has the advantage of non-urinary excretion, it has a short half life (20 minutes) and requires an onsite cyclotron, which limits it usage. ^{11}C-acetate has also been explored, however seems less favourable [76]. There are further investigations into other radiotracers including those targeting prostate-specific membrane antigen (PSMA), the synthetic amino acid analogue anti-1-amino-3-F18-fluorocyclobutane-1-carboxylic acid (FACBC) and F-18-fluoro-5α-dihydrotestosterone (FDHT) which targets the androgen receptor.
PET imaging is not routinely obtained for patients being treated for prostate cancer, although is increasingly used to enhance staging in locally advanced or relapsed disease.

Limitations and Challenges of PET-CT

There have been several studies assessing the role of PET-CT in defining IPLs in prostate cancer, the majority of these use ^{11}C- or ^{18}F-Choline [77-81]. For example, a study with ^{11}C-Choline PET-CT showed a sensitivity of 66% and specificity of 81% [77]. However, the uptake of lesions can be variable and the studies are limited by conflicting results and small sample sizes. As a result, there continue to be concerns over the use of PET-CT in radiotherapy planning [82]. As with MRI, false positives can be seen with prostatitis and inflammation secondary to biopsy or treatment [77]. Van den Bergh et al reported that when multiparametric MRI is used, there is no additional benefit of PET-CT [83], with the accuracy of detecting lesions dependent on the SUV used.

Image interpretation

There are two main methods that have been used for identifying the target in prostate cancer with PET-CT; manual interpretation of the images or the use of automated threshold techniques. The latter has the benefit of defining a target volume without observer bias and therefore maintaining consistency. However, there are a number of factors that will alter the SUV and therefore IPL volume

including inhomogeneity within an IPL, lesion size and motion artefact [84]. Using an absolute SUV value to define the target volume does not take into account the variable background activity of the prostate. Therefore, the two main threshold methods are using a tumour-to-background ratio or percentage of the maximum SUV (SUV_{max}). Values have been derived from histopathological studies and are discussed further below.

Spatial resolution

PET-CT has limited spatial resolution, being unable to detect lesions smaller than 5mm. The SUV_{max} of smaller tumours is less than that of larger ones [81]. The partial-volume effect (PVE) leads to smaller lesions either being lost or appearing larger (and therefore encompassing normal tissues) but dimmer [85].

Histopathological correlation of delineation using PET-CT

Variability of studies

The accuracy of IPL delineation using PET-CT has been assessed by studies using histopathological correlation. Sensitivity and specificity can vary significantly depending on whether studies use voxel, segments or whole prostate level of analysis as the area of interest. Studies also vary depending on the patient population, the standardised uptake value (SUV) threshold used and the acquisition of images. As noted earlier, there are limitations of these histopathological studies, which must be considered when interpreting results. Amongst the issues to be considered are the accuracy and type of pathology (biopsy or whole mount specimens), the optimal timing of the imaging following tracer injection, and the most appropriate segmentation or thresholding level for defining the IPL.

Timing of PET Imaging

Kwee et al analysed the change in maximum SUV (SUV_{max}) in malignant and benign areas in prostate cancer using additional delayed scanning at one hour [78]. SUV_{max} for malignant areas increased from the initial to delayed scan whereas the mean SUV_{max} for benign areas decreased. The difference between areas marked as 'dominant malignant' and 'probably benign' was only statistically significant on delayed imaging with the mean malignant-to-benign ratio increasing from 1.4 on the initial images to 1.8 on the delayed images. The additional challenge of using delayed imaging with this modality however, is that ^{18}F-Choline is renally excreted with accumulation of radioactivity within the bladder, which can complicate image interpretation of the prostate base.

Methods for IPL delineation

A mean tumour-to-background ratio of approximately 2 has been identified in several studies as a method for IPL delineation [77, 78, 81] and was used by Pinkawa et al for delineation of a clinically delivered boost volume [70]. In this study, definition of the IPL was based on a slightly increased tumour to background ratio of >2 in order to increase specificity, although this would lead to a decreased sensitivity with smaller tumours excluded.

An autocontour method based on 60% of the maximum SUV (SUV_{60}) has been reported by several groups as having the best correlation with histopathology

[79, 80, 86]. However, in these studies, the SUV_{60} was not found to be significantly better when compared to the other threshold contours [80, 86]. It is also unclear as to which correlation indices are best to compare contours and whether the dice similarity co-efficient (DSC) and Youden Index (YI) adequately assess the clinical significance of overlap. Therefore, although SUV_{60} had the highest correlation indices (as per DSC and YI), this requires prospective clinical validation before implementation.
As the percentage of SUV_{max} threshold increases, specificity increases but sensitivity decreases as used by Pinkawa et al to increase the specificity for dose-escalation [20].

Comparison of PET-CT with MRI for delineation accuracy
Chang et al [86] used reference contours defined from prostatectomy pathology in 21 patients to compare the accuracy of manual contours from ^{11}C- Choline PET-CT to manual contours using DW-MRI. They found that PET-CT had significantly better correlation to the reference contours compared to T2W/DW-MRI. A limitation of this study however, was that multiparametric sequences of DCE-MRI or MRS were not included, as per the Barentz recommendations [44] therefore the comparison did not include the optimal set of MR images. This group also found, as previously shown [79, 80], that the SUV_{60} had the best correlation to the reference contours and in fact performed significantly better compared to manual delineation by a radiologist using the PET-CT.

Feasibility of Boost Delivery using specific tracers

There have been several studies investigating the feasibility of delivering a dose-escalated boost to the delineated IPL using various specific PET tracers. The clinical study by Pinkawa is outlined in Table 2, with planning studies summarised in Table 3.

Table 3: Planning studies delivering a boost to a PET-CT defined IPL

REFERENCE	PATIENTS	IMAGING TECHNIQUES	RADIOTHERAPY TREATMENT	FINDINGS
Kuang (2015) [25]	n=30	18F-Choline PET/CT Boost defined by 60% and 70% of SUV_{max} threshold (labelled $IDL_{SUV60\%}$ and $IDL_{SUV70\%}$ respectively)	VMAT <u>Plan1:</u> Prostate + 3-6mm 79Gy/39f <u>Plan 2:</u> Prostate + 3-6mm 79Gy/39f $IDL_{SUV60\%}$ + 3-6mm 100Gy/39f $IDL_{SUV70\%}$ + 3-6mm 105Gy/39f	SIB feasible in all patients TCP significantly higher in boost plan Slightly lower rectal NTCP in boost plan
Seppala (2009) [22]	n=12	11C-Acetate PET/CT Co-registration with planning scan SUV of 2.0 used for IPL delineation	Step and shoot IMRT <u>Plan 1:</u> Prostate + 6mm 77.9Gy/41f <u>Plan 2:</u> Prostate + 6mm 72.2Gy/41f IPL + 6mm 77.9Gy-90Gy/41f	TCP increased for all boost plans Average dose of 82.1Gy to IPL gave the highest probability of uncomplicated control
Chang (2012) [21]	n=8	11C-Choline PET/CT Co-registration with planning scan Boost defined by 60% and 70% of SUV_{max} threshold (labelled $SUV_{60\%}$ and $SUV_{70\%}$ respectively)	Step and shoot IMRT <u>Plan 1 (standard):</u> Prostate + 6mm 78Gy/39f <u>Plan 2 (boost plan):</u> Prostate + 6mm 78Gy/39f IPL ($SUV_{60\%}$) + 6mm 84Gy/39f IPL ($SUV_{70\%}$) + 6mm 90Gy/39f <u>Plan 3 (boost plan, de-escalation to prostate):</u> Prostate + 6mm 72Gy/39f IPL ($SUV_{60\%}$) + 6mm 84Gy/39f IPL ($SUV_{70\%}$) + 6mm 90Gy/39f	SIB feasible in all patients TCP significantly higher for both boost plans compared to standard plan No significant difference in TCP comparing boost plans 2 and 3 No significant difference in rectal NTCP for all three plans

^{11}C- Choline PET-CT

Chang et al [21] generated IMRT plans for 8 patients using the contouring methods described above [80] to deliver two boost doses within a single plan. $PLAN_{78-90}$ delivered 78Gy, 84Gy and 90Gy and $PLAN_{72-90}$ delivered 72Gy, 84Gy and 90Gy to the whole prostate, $SUV_{60\%}$ and $SUV_{70\%}$ respectively. All plans were feasible whilst meeting dose constraints, with the rectal NTCP being non-significantly lower in the boost plan. Both boost plans had a significantly higher TCP for the PET defined volume (TCP_{PET}) and the prostatectomy specimen defined volume (TCP_{path}) compared to the standard plan where 78Gy was planned to the whole prostate alone. However, the risk of de-escalating the non-DIL prostate was demonstrated for one of the patients where the TCP_{path} was lower in the $PLAN_{72-90}$ boost plan compared to $PLAN_{78}$. Overall, using the histopathology from prostatectomy, they were able to demonstrate increased population TCP with this method. .

^{18}F-choline PET-CT

Kuang et al concluded ^{18}F-choline PET-CT can be used to localise a boost volume for VMAT plans [25]. Using a similar method to Chang, radiotherapy plans had a two dose level boost of 105Gy defined using the 70% of the SUV_{max} threshold (labelled $IDL_{SUV70\%}$) 'nested' inside a larger boost of 100Gy defined by 60% of the SUV_{max} (labelled $IDL_{SUV60\%)}$ with the aim of delivering the higher dose to the area of greater tumour specificity, whilst maintaining a dose of 79 Gy to the whole gland. They reported a higher TCP and a slightly lower rectal NTCP with the addition of a boost compared to a plan delivering 79Gy alone to the prostate.

^{11}C-acetate PET-CT

^{11}C-acetate PET-CT was used by Seppala et al to define the IPL using an absolute SUV of 2.0 in a planning study of 12 patients [22]. They similarly confirmed an improved TCP with IMRT plans delivering a SIB up to 90Gy, without increasing the NTCP. However, a meta-analysis has concluded that ^{11}C-acetate should not be used for IPL localisation due to poor sensitivity and specificity [76].

Just as for MRI planning, the higher TCP seen with dose-escalation to the IPL is on the assumption that the imaging perfectly defines the target. Dose modelling has demonstrated that any additional benefit in TCP due to a SIB will be dependent on the sensitivity of imaging [87].

Integration of Imaging

With combined PET-CT images, the process of image registration is simpler compared to that needed for CT-MRI fusion. However, the PET imaging component is acquired in several phases so there will still be some discrepancy with bladder and bowel filling and prostate position. PET-CT images are obtained without the distortion from ERC discussed previously and can be used in patients with contraindication to MRI.

Implementation of Tumour Dose-escalation

The importance of accurate delivery with IGRT has already been discussed. The optimal technique for tumour segmentation and delineation with PET-CT is not yet clear. Further investigation and validation of proposed methods such as tumour to background and SUV_{60} is required with rigorous histopathological assessments and robust follow up of outcomes. An expansion margin may be additionally required to cover the IPL adequately, similar to those described above for MRI [60-62].

OTHER IMAGING

An Indium-111-capromab pendetide scan (ProstaScint) uses an FDA-approved monoclonal antibody to target upregulated prostate-specific membrane antigen (PSMA) receptors on prostate cancer cells. This tracer shows much promise in both the staging of de novo prostate cancer and in detecting recurrent disease. It has been used in a prospective trial to localise an IMRT planned boost (see Table 2) [23]. Results including biochemical control and toxicity were reported as favourable but further studies are needed to confirm the accuracy of localisation. The study used a prostate/muscle ratio of signal intensity 3:1, but similar to the choline studies, the optimal threshold for contouring would need further investigation. There are conflicting results on the reliability of localising prostate cancer [88, 89] however research continues into other agents that target PSMA.

FUTURE PERSPECTIVE

Combining imaging modalities

A combination of imaging may be helpful, which would optimally use one modality with high sensitivity and a second with high specificity. Imaging techniques are constantly evolving and refinements in MR or PET technique may increase our confidence in IPL delineation. Combining several modalities may further increase the fidelity of our contouring.

Patient stratification

The studies discussed here have demonstrated the technical feasibility of dose-escalation to an IPL but follow up is required from randomised prospective trials to determine the benefit and effect on toxicity. There is significant heterogeneity in prostate cancers, which will complicate the decision as to whether a boost is required and the appropriate dose to be used. Tumours of the same size can have a different risk of relapse dependent on tumour biology and other pathological predictive factors [90]. Ideally, utilising information from a combination of sources including imaging, pathology and biomarkers will allow stratification of patients to reflect the heterogeneity of tumours in the radiotherapy dose distribution. The use of hypoxic markers can be considered for dose-escalation combined with prognostic markers for personalised radiotherapy.

In addition, imaging patients during a radiotherapy course for an early response assessment may predict those likely to fail biochemically, identifying patients who would benefit from further dose-escalation. This escalation could then be given using adaptive radiotherapy to the existing plan or as a hypofractionated boost at the end of treatment. Further research is ongoing to search for such imaging biomarkers.

Differential Dose

Rather than having a single dose to the entire IPL, several planning studies discussed here have demonstrated how more than one boost dose can be delivered to the IPL using PET-CT [21, 25]. This can maintain the maximum dose within the area of higher specificity, whilst having a fall off for the dose closer to organs at risk. The same approach could be used with mpMRI, based on guidelines for the interpretation of MR imaging [44] or validated models which predict tumour presence [52]. This model by Groenendaal et al for example suggests three levels; a GTV, a high-risk CTV and low-risk CTV (i.e. standard prostate dose) based on high, intermediate and low tumour probability respectively. Alternatively a multiple dose level approach could be considered when imaging is used to identify a sub-volume of more aggressive or radio-resistant disease within the IPL.

MRI workflow

MR currently is the preferred modality for boost delineation. As there are some limitations of image registration with CT, an MRI only workflow would eliminate this systemic error. Planning using MRI images alone has its own challenges, including the lack of electron density information required for dose calculations and distortion, however there are several methods described and being developed for this such as 'pseudo' or 'synthetic' CT [91, 92].
IGRT improves accuracy of radiotherapy delivery, but most commonly used methods, such as CBCT and gold seeds do not take into account intra-fraction movement, which contributes to the margin to be added and impacts the therapeutic ratio. Imaging during treatment further improves the accuracy of treatment, allowing gating or adaptation. Development of combinations of a linear accelerator or cobalt machine with on board MRI imaging [93, 94] may further improve inter- and intra-fraction imaging. Furthermore, acquisition of MR images during treatment may mean the boost regions could be directly visualised during beam delivery, increasing accuracy, calculation of delivered dose and facilitating adaptive planning strategies.

What is the objective of imaging a dominant lesion?

Prostate cancer comprises a wide spectrum of disease, ranging from what could be considered a variant of normal ageing (organ confined Gleason 6 disease) to a life-limiting aggressive disease. Current stratification is inadequate to identify patients who would most benefit from dose-escalated local treatment. For those with low to low-intermediate risk disease, conventional doses are sufficient to cure the vast majority of patients and a boost is unlikely to be required. For those

with intermediate or high risk disease, a boost to the IPL may increase TCP with little or no effect on toxicity. In this case, the optimal imaging modality may not need to be sensitive to low risk Gleason 6 disease, which will be adequately treated with conventional dose. A deficit of the current literature is the lack of understanding of the correlation between imaging findings with high risk pathology only. In addition, mpMRI and PET imaging have not been robustly compared, to help determine the optimal imaging modality for IPL delineation.

If the identification of the IPL is a prelude to de-escalating or even not treating the rest of the prostate gland, then there is still some way to go before we can be confident that our chosen imaging modality identifies all intra-prostatic disease or indeed that which requires treatment.

CONCLUSION

Dose-escalation to an MRI or PET-CT defined IPL is theoretically feasible, but further studies are needed to confirm the optimal imaging techniques which will faithfully represent the IPL in the radiotherapy planning process. Early clinical data suggest acceptable toxicity when DIL boosts are delivered with sophisticated radiotherapy techniques and state-of-the-art IGRT. Prospective clinical data is required to confirm which patient groups would benefit and to quantify any improvement in the therapeutic index.

EXECUTIVE SUMMARY

Rationale behind intraprostatic boost

- Dose-escalation to the whole prostate improves biochemical control but at the expense of increased toxicity
- Local recurrence occurs at the site of the primary tumour, therefore a boost to the IPL may improve the therapeutic ratio

MRI for IPL delineation

- Although mp-MRI improves the accuracy of tumour detection, there are a number of limitations including a mismatch between different MRI techniques, false positive findings and the effect of ADT on imaging
- The interpretation of MR images is operator and training dependent and prone to interobserver variation, even in the presence of published scoring systems
- Histopathological correlation studies indicate that IPL volumes delineated by MRI tend to underestimate the true tumour volume, with studies suggesting a margin of 5-9mm to cover the 'undercall'
- Clinical and planning studies have shown that a boost to an IPL is feasible, with acceptable levels of toxicity and the potential to improve the TCP
- The IPL must be accurately transferred through the radiotherapy planning process by using the fusion of images, and treatment must be delivered using high quality IGRT

PET-CT for IPL delineation

- PET-CT can be used for tumour delineation but sensitivity and specificity is variable, with fewer studies confirming histopathological correlation

- Image interpretation is variable; IPL delineation can be manual or automated, with methods used to define the IPL based on a percentage of the SUV_{max} or a tumour to background ratio
- The limited clinical and planning studies indicate that a boost is feasible to a PET-CT defined IPL, with the possibility of using differing SUV thresholds to varying dose levels
- The IPL must be faithfully represented throughout the planning process and treatment delivered accurately with IGRT

Future Perspectives

- Data is needed from prospective trials to confirm the benefits of delivering a boost to the IPL and to confirm the best imaging, contouring methods, boost dose and radiotherapy techniques
- A combination of imaging, pathology and biomarkers could be used to stratify patients and individualise treatment to identify those patients who will benefit from focal dose-escalation

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