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FOCUS ON

PET-guided prostate cancer radiotherapy: technological innovations for dose delivery optimisation

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I hope that our contributions, among other developments, will be used by many to reduce suffering, improve our health and extend the productivity and fulfilment of our lives. Equally important, I hope that the new biological insights will yield a better understanding of ourselves as human beings and of our relationship to our environment, so that we may become better stewards of a fragile Earth [1].

Mario R. Capecchi

The key to optimal prostate cancer treatment is accurate tumour characterisation and staging. Indeed, while localised primary tumours can be treated with radical prostatectomy, metastatic tumours usually demand a systemic therapeutic regimen. As pointed out by Picchio et al. [2], molecular imaging techniques, such as PET, may be helpful in treatment planning in these patients and PET/CT, in particular, is useful in different steps: (1) tumour characterisation and staging followed by the selection of the most appropriate primary approach; (2) re-staging, and the choice of second-line therapies to target possible sites of recurrence; and (3) disease course and treatment efficacy monitoring.

Since the most commonly used PET tracer, ^{18}F-fluorodeoxyglucose (FDG), shows limitations in the imaging of prostate cancer patients, alternative PET tracers have been proposed for use in this population, giving promising results. Several PET tracers have been developed and successfully applied in the primary detection and staging of prostate cancer; these include ^{11}C-choline, ^{18}F-choline and ^{11}C-acetate. Information on sites of possible recurrence is crucial to the development of an effective therapeutic approach, and ^{11}C-choline imaging is now an established clinical procedure for the non-invasive re-staging of prostate cancer patients presenting raised prostate-specific antigen (PSA) levels after radical treatment. Although the role of PET and PET/CT as a monitoring strategy in prostate cancer has yet to be clarified, the use of PET tracers in therapy planning is a growing research area that has already found its way to the clinic.

In a very recent study, Park et al. used histological data gathered from human prostate cancer patients to validate an automated computer algorithm used for computing target volumes [3]. Various prostate imaging modalities were employed: T2-weighted 3-T magnetic resonance imaging (MRI) and ^{11}C-choline PET imaging were used in vivo, while the ex vivo imaging modalities included 3-T MRI, histology, and block face photos of the prostate specimen. A novel registration method based on mutual information and thin-plate splines was applied to all the modalities. When PET images are obtained with co-registered histology sections, it is possible to perform voxel-by-voxel

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comparisons between PET and histology. Sixteen patients with primary tumour volumes ranging from 1.2 to 12.6 cm^3 were tested. Due to the low spatial resolution of PET, only the four cases with tumours >4 cm^3 were included in the study. Application of a threshold value corresponding to 60% of the ^{11}C-choline maximum standardised uptake value in the tumour resulted in the highest volume overlap between the outlined volume on PET and histology. Medial axis distances between the volume defined on PET and histology showed a mean error of 7.7±5.2 mm. The authors maintain that this is a proof-of-concept study demonstrating for the first time that histology-guided thresholding on PET can delineate tumour volumes in real human prostate cancer.

The same group set out to assess whether ^{11}C-choline PET/CT imaging is able to identify high-risk primary adenocarcinoma of the prostate [4], performing both ^{11}C-choline PET/CT and transpelvic MRI in 14 patients with untreated localised primary adenocarcinoma of the prostate who underwent radical prostatectomy as a form of primary monotherapy within 14 days of the in vivo imaging procedures. To ensure accurate co-registration of whole-mount histology with in vivo images, additional ex vivo MRI of the prostatectomy specimen was performed. Nonlinear three-dimensional image deformations were used for registrations of PET/CT, MRI, and histology. Volumes of interest from tumour and benign tissue were defined on the basis of histology and were transferred into co-registered ^{11}C-choline PET/CT volumes to calculate the mean (T_{mean}/B) and maximum (T_{max}/B) ratio of tumour to benign prostate background. On the basis of MIB-1/Ki-67 expression in tumour tissues represented on a tissue microarray, it was assessed whether ^{11}C-choline uptake correlated with local Gleason score and tumour proliferation. Histology confirmed 42 tumour nodules with Gleason scores between 3+2 and 4+4, with volumes ranging from 0.03 to 12.6 cm^3. T_{mean}/B ($p<0.01$) and T_{max}/B ($p<0.001$) ratios were significantly increased in high Gleason score (>or = 4+3) lesions versus 3+4 and lower disease but failed to distinguish between 3+4 disease versus 3+3 and lower. T_{mean}/B and T_{max}/B ratios were significantly increased in tumours with an MIB-1/Ki-67 labelling index greater than or equal to 5% ($p<0.01$). These preliminary data derived from the use of tumour to benign prostate background ratios showed that ^{11}C-choline imaging preferentially identified aggressive primary prostate cancer.

Wang et al., using various PET image segmentation techniques, instead evaluated the contribution of ^{18}F-choline PET/CT in the delineation of gross tumour volume (GTV) in 17 patients with local-only recurrent prostate cancer (median = 5.7 years) after initial irradiation [5]. Following injection of 300 MBq of ^{18}F-fluorocholine, dynamic PET frames (3 min each) were reconstructed from the list-mode acquisition. Five PET image segmentation techniques were used to delineate the ^{18}F-choline-based GTVs: manual delineation of contours by radiation oncologists and nuclear medicine physicians (GTV_{man}), fixed thresholds (40% and 50%) of the maximum signal intensity ($GTV_{40\%}$ and $GTV_{50\%}$), signal-to-background-ratio-based adaptive thresholding (GTV_{SBR}), and a region-growing algorithm (GTV_{RG}). Geographical mismatches between GTVs were also assessed using overlap analysis. Inter-observer variability for manual delineation of GTVs was high but not statistically significant ($p=0.459$). The authors found that semi-automated segmentation techniques for ^{18}F-choline PET-guided GTV delineation resulted in substantially higher GTVs than with manual delineation and suggested that the former might therefore replace the latter in the evaluation of recurrent prostate cancer for partial prostate re-irradiation.

Weber et al. also considered patients with recurrent prostate cancer after radiation therapy, in this case in a treatment planning comparison study in which RapidArc volumetric modulated arc therapy (RA) was compared with photon intensity modulation (IMRT) and proton intensity modulation (IMPT) radiation techniques [6]. Plans for RA, IMRT and IMPT were optimised for seven patients. The prescribed radiation dose was 56 Gy in 14 fractions. Recurrent GTV was defined on ^{18}F-fluorocholine PET/CT scans. The plans aimed to cover at least 95% of the planning target volume with a dose >50.4 Gy. A maximum dose (D_{Max}) of 61.6 Gy could be delivered to 5% of the GTV. For the urethra, the D_{Max} was limited to 37 Gy while the rectal D_{Median} was <17 Gy. The results were analysed using dose–volume histogram and conformity index (CI_{90}) parameters. The authors found that tumour coverage was better with RA than with IMRT. The proportions of rectal and urethral volumes receiving intermediate doses (35 Gy) were significantly lower with RA and IMPT than with IMRT. CI_{90} was 1.3±0.1 for photons and 1.6±0.2 for protons. The integral dose for all photon techniques was about a factor of three higher than that recorded for IMPT. The authors concluded that RA and IMPT showed improvements in conformal avoidance compared with fixed-beam IMRT in seven patients with recurrent prostate cancer and that IMPT showed further sparing of organs at risk.

Pinkawa et al. conducted a study assessing the impact of dose escalation with an ^{18}F-choline PET/CT defined simultaneous integrated boost (IB), evaluating the dose distribution and changes in the equivalent uniform dose (EUD) [7]. PET/CT was performed in 12 consecutive patients for treatment planning purposes. An intraprostatic lesion was defined by a tumour-to-background uptake value ratio >2. The dose escalation was restricted to the intraprostatic lesion. Two comparisons were performed: whole-prostate irradiation to 76 Gy ± boost to 80 Gy (C1) and whole-prostate irradiation to 66.6 Gy ± boost to 83.25 Gy

(C2). On the basis of their results, the authors concluded that the use of an IB in the treatment planning protocol permits individually adapted dose escalation and that the therapeutic ratio can be improved by a considerable dose escalation to the macroscopic tumour, with only minor EUD changes to the bladder and rectum.

The issue of dose escalation was also considered recently by Seppälä et al., who submitted 12 men with intracapsular prostate carcinoma to ^{11}C-acetate PET/CT imaging in order to demonstrate the theoretical feasibility of the modality in delineating malignant intraprostatic lesions (IPLs) [8]. The data obtained were used to delineate the biologically defined target volume (BTV) and six dynamic IMRT plans were generated for each patient: a standard IMRT (sIMRT) plan with a 77.9 Gy dose to the PTV (prostate gland with a 6-mm margin) and a simultaneous integrated boost IMRT [SIB(IMRT)] plan to deliver 77.9 Gy, 81 Gy, 84 Gy, 87 Gy and 90 Gy doses to the BTV and 72 Gy to the rest of the PTV. Tumour control probabilities (TCPs) and normal tissue complication probabilities (NTCPs) for bladder and rectum were calculated and compared between the treatment plans. [^{11}C]Acetate was used to delineate the IPLs of all 12 patients. In every patient the TCP was increased with SIB(IMRT), without increasing the NTCPs of the bladder or rectum. The probability of uncomplicated control (PUC) was increased on average by 28% with the SIB(IMRT) treatment plans. The highest PUC was achieved with an average dose of 82.1 Gy to the BTV. The results of this study indicate that ^{11}C-acetate can be used to define IPLs. When it is used in combination with SIB(IMRT) the defined areas can theoretically be treated with ultra-high doses without increasing the treatment toxicity. These findings call for the formal validation of ^{11}C-acetate PET for biological dose planning in prostate cancer.

Anti-1-amino-3-F-18 fluorocyclobutane-1-carboxylic acid (FACBC) is a novel radiotracer that may be useful in PET/CT studies for visualising prostate cancer. Jani et al. recently explored the potential impact of FACBC on treatment planning in a prostate cancer patient submitted to radiation treatment [9]. In this case, the FACBC scan, obtained as part of a pilot study, was registered with the PET/CT, which required a simple translation. Deformable image registration of the PET/CT with the planning CT then allowed the FACBC-defined gross tumour volume (GTV_{FACBC}) to be projected into the planning CT. An IMRT plan not including GTV_{FACBC} (with a final dose of 81.0 Gy) was generated (plan A), as was an IMRT plan including the GTV_{FACBC} (with a final dose of 86.4 Gy) (plan B). Target coverage and normal-tissue dose–volume histogram (DVH) endpoints were tabulated. The results obtained in this test case suggest that it is feasible to use FACBC to guide IMRT and highlight the role of deformable image registration of PET/CT with planning CT. According to the authors, they provide a starting point for future studies on the incorporation of FACBC into treatment planning.

Hsi et al. performed a total of 50 PET/CT imaging studies on ten prostate cancer patients immediately after daily proton therapy treatment in an attempt to verify the proton beam path in vivo on the basis of proton-activated positron emission distributions [10]. The PET/CT and planning CT were registered by matching the pelvic bones, and the beam path of the delivered protons (PET-defined beam path) was defined in vivo by the positron emission distribution seen only within the pelvic bones. Because of the need for patient position correction at each fraction, the marker-defined beam path, determined by the centroids of implanted markers seen in the post-treatment (post-Tx) CT, is used for the planned beam path. Angular variation and discordance between the PET- and marker-defined paths were derived to investigate the intrafraction prostate motion. For studies with large discordance, the relative location between the centroid and pelvic bones seen in the post-Tx CT was examined. The PET/CT studies were categorised to distinguish between prostate motion occurring before and after beam delivery. The post-PET/CT was acquired after PET imaging to investigate prostate motion due to physiological changes during the extended PET acquisition. The finding of low angular variation indicated that patient roll was minimal within the immobilisation device. Thirty of the 50 studies with small discordance (good cases) showed consistent alignment between the field edges and the positron emission distributions from the entrance to the distal edge. Of the remaining 20 studies, showing large discordance, 13 studies, referred to as motion-after-Tx cases, also showed large misalignment between the field edge and the positron emission distribution in lipomatous tissues around the prostate. These motion-after-Tx cases were patients with large changes in the volume of rectal gas between the post-Tx and the post-PET CTs. The final seven studies, referred to as position-error cases, had large discordance but no misalignment. The position-error cases were ones showing a large discrepancy in the relative location of the centroid and pelvic bones as seen on post-Tx CT and recorded X-ray radiographs. The authors conclude that systematic analyses of proton-activated positron emission distributions provide patient-specific information on prostate motion (sigmaM) and patient position variability (sigmap) during daily proton beam delivery. The finding of minimal displacement variations in the good cases (less than 2 mm) indicates that population-based values of sigmap and sigmaM are valid in the majority of cases. However, a small proportion of PET/CT studies (approximately 14%) with −4 mm displacement variations may require different margins. As pointed out by the authors, these data are useful in establishing patient-specific planning target volume margins.

Conclusions

Over the past decade PET imaging has evolved rapidly from a pure research tool into a methodology of enormous clinical potential [11]. FDG-PET is currently the probe most widely used in cancer diagnosis and staging, in the assessment of tumour response to treatment, and in radiation therapy planning, as metabolic changes generally precede the change in tumour size, which is the more conventionally measured parameter. Data validating the efficacy of FDG imaging and many other tracers in a wide variety of malignant tumours have accumulated rapidly over the past 10 years, with sensitivity and specificity values often in the high 90 percentile range. As a result, PET/CT, able to obviate the need for further evaluation, as well as guide further diagnostic procedures and assist in treatment planning in a considerable number of patients, has had a significant impact on the clinical management of cases.

In addition to this, the past two decades have seen remarkable progress in radiation therapy technologies. As a result it is now possible to plan highly conformal radiation dose distributions through the use of sophisticated beam targeting techniques such as IMRT using tomotherapy, volumetric modulated arc therapy, and many other promising technologies for sculpted three-dimensional dose distribution. Meanwhile, molecular imaging-guided radiation therapy depends on the use of advanced imaging technologies which, improving the definition of tumour target volumes, make it possible to relate absorbed dose information to image-based patient representations.

The application of PET/CT imaging to radiation therapy planning is an open field in which there is much work still to be done, including the exploration of the various image processing aspects, such as the segmentation of medical images for the purpose of defining target volumes. Indeed, many of the techniques are still in the experimental stage and not yet widely implemented in clinical settings [12].

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