Strategies for Image-guided Proton Therapy of Cancer

a report by
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During the past half century, an ongoing technological revolution in cancer imaging and radiation treatment has taken us ever closer to the goal of treating localised tumours without harming normal tissues. In his visionary 1946 paper,[1] Harvard physicist Robert Wilson suggested that energetic protons could provide a nearly ideal form of radiotherapy. What makes protons the preferred particle type for radiotherapy is their inverted dose profile, called the Bragg peak, in combination with the ability to place the Bragg peak at any depth in the patient, to spread out the peak to cover larger volumes and to have zero dose behind the most distal peak position. In 1989, Dr Wilson visited the first clinical proton treatment centre at Loma Linda University Medical Center in California, which was about to begin its clinical operations (the first patient was treated in October 1990). The reasons more than 40 years elapsed between his original idea to its full technical and practical realisation were manifold, but the lack of adequate image guidance, in both treatment planning and treatment itself, played a key role.

Computed tomography (CT) utilising kilovolt (kV) X-rays was not developed until the early 1970s. For the first time this imaging modality provided 3D information about tumour location and at the same time about the electron density distribution required to perform 3D dose calculations. Therefore, it was a natural choice to develop CT-based radiation treatment planning. Magnetic resonance imaging (MRI) entered the treatment planning scene about 10 years later and provided further details with respect to the geographical relationship between tumour and normal tissues, providing much higher spatial and contrast resolution than X-ray CT. It took another 15 years before positron emission tomography (PET), in particular its combination with X-ray CT, became available for radiation treatment planning and added another dimension to the ability to see tumours and to distinguish them from normal tissue, based on differential metabolism. For conformal radiation modalities such as proton therapy, imaging technology is equally important in guiding the delivery of radiation therapy. Image-guided radiation therapy (IGRT), respiratory gating and related technological advances are about to enter the treatment room in many radiotherapy facilities. The idea behind this is that modern imaging can help not only to detect and outline tumours during treatment planning, but also to ensure that the dose delivered to the tumour in the treatment room is accurate and precise.

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Current Role of Image Guidance in Proton Treatment Planning

Treatment Planning Volumes

Most patients coming to a proton-radiotherapy centre for consultation have been diagnosed with localised, non-metastatic organ cancer, such as prostate or lung cancer, and seek proton therapy as their definitive therapy. In other instances, patients have received surgery as their first-line treatment and require post-operative radiation due to known residual tumour or suspected microscopic disease. Lastly, it is not uncommon to see previously irradiated patients who have failed their initial radiotherapy and reached tolerance dose in nearby organs or vital structures. In any of these cases, accurate imaging-based definition of treatment volumes is crucial. Standard radiation planning volumes, previously defined for photon therapy by the International Commission on Radiation Units and Measurements (ICRU),[2,3] are also suitable for proton therapy. The ICRU planning volumes are: the gross tumour volume (GTV), including macroscopic tumours visible in imaging studies; the clinical target volume (CTV), containing suspected subclinical malignant disease; and the planning target volume (PTV), which expands GTV or CTV by a margin accounting for geometric uncertainties, including set-up errors and internal organ motion.

Utilising modern computerised treatment planning systems, planning volumes together with organs at risk (OARs) are outlined by the radiation oncologist using a CT image set through the region of interest. Common practices of planning volume definition depend on the clinical site and tumour entity. For example, in radiotherapy of cancer of the prostate, the GTV is defined as the entire prostate gland (see *Figure 1*). This is due to the current inability to distinguish malignant tissue ('true GTV') from normal gland tissue. Unless there is suspicion of microscopic extension into regional pelvic lymph nodes, the CTV is practically identical to the GTV in this case.

Imaging Modalities Used for Proton Treatment Planning

CT is a requirement for treatment planning in proton therapy because it provides the electron density distribution required for dose and range calculations. Once the planning volumes have been outlined, two to four proton treatment beams are selected for each volume and their dose distributions are calculated and optimised. The accuracy of the conversion of CT Hounsfield numbers to electron-density values relative to water is a critical parameter in proton radiotherapy because inaccurate values will result either in overdosing of normal tissues or underdosing of tumour, depending on whether the calculated range of the proton beam is over- or underestimated. The demand for conformal target definition grows with increasing conformality of the radiation modality. While photon therapy has gradually evolved from non-conformal treatments with large field margins and relatively low doses to highly conformal,

high-dose, intensity-modulated radiation therapy (IMRT), proton therapy was a high-dose conformal radiation modality from the outset. Therefore, the need to integrate other imaging modalities into the planning volume definition process was obvious. MRI plays an important and still-increasing role in proton treatment planning. Different MRI acquisition techniques are available, which allow better differentiation between malignant and healthy soft tissue than with CT. Thin-cut, zero-gap MRI acquisitions make it possible to provide a continuous 3D data set that can be reformatted in any plane and co-registered or fused with the planning CT data set.[4,5] Examples of proton treatment protocols where MRI is routinely used for planning volume definition include high-grade gliomas – allowing differentiation between tumour GTV and oedema CTV; brain metastases (see *Figure 2*); and arteriovenous malformations treated with stereotactic proton radiosurgery.

PET and single photon emission computed tomography (SPECT) are the latest additions to imaging technology supporting the definition of planning volumes for proton therapy. F-18 fluoro-deoxyglucose (FDG) is the most commonly used tracer in oncological imaging because many tumour cells have an increased glucose metabolism compared with normal tissue cells. FDG-PET can be particularly useful in proton treatment planning for lung cancer, allowing the radiation oncologist to distinguish between tumour and scar or atelectatic lung tissue or to exclude advanced stages with multiple positive mediastinal lymph nodes.[6,7] On the other hand, FDG-PET has no role in prostate cancer, which rarely shows FDG uptake. A good tracer specific to prostate cancer is currently lacking. In addition to PET, SPECT can potentially be useful in differentiating cancer from normal tissue. Its application in radiation oncology is not yet widespread and, to the author's knowledge, no active proton treatment centre is currently using this modality for proton treatment planning.

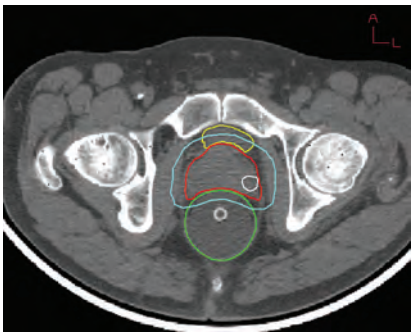
Virtual Treatment Simulation

In traditional radiation therapy, patients were simulated on a therapy simulator, a machine equipped with a treatment couch and a fluoroscopic X-ray unit mounted on an isocentric arm. This process was never implemented in proton therapy. Nowadays, as has always been the case in photon IMRT, a virtual proton treatment simulation is performed with the treatment planning system using the virtual 3D representation of the patient in the CT image set. This requires that the CT scanner dedicated to radiation treatment planning be equipped with a flat table-top simulating the treatment table, and the CT acquisition incorporates the same immobilisation devices used during treatment. During virtual simulation, the treatment planning software calculates simulated X-ray images, called digitally reconstructed radiographs (DRRs), based on CT attenuation values. DRRs closely match the X-rays that will later be taken in the treatment room for the alignment verification process.

The Current Role of Image Guidance in the Proton Treatment Room

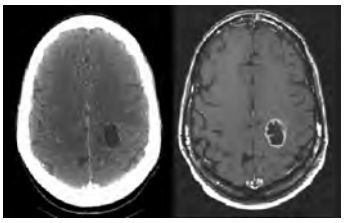
The role of image guidance in proton therapy does not end with completion of the treatment planning process. Image guidance in proton treatment delivery is equally important. Rather than traditional alignment techniques, which were based on alignment of skin marks placed on the patient's body during treatment simulation with treatment-room lasers, more accurate alignment and verification techniques had to be developed for proton therapy. In current proton-treatment centres, kV X-ray sources are integrated in the proton beam lines, allowing the physician to take diagnostic-quality X-rays for alignment verification before each treatment.

Figure 1: Planning Volumes for a Patient with Cancer of the Prostate Undergoing Proton Therapy



True but unknown GTV (white), assumed GTV and CTV (red), PTV (blue), OARs: rectum (green) and bladder (yellow).

Figure 2: Magnetic Resonance Imaging Co-registered with a Planning Computed Tomography Scan in a Patient with Brain Metastasis Undergoing Proton Radiosurgery



These images are compared with the DRRs produced during virtual treatment simulation and corrective moves are performed as required. Modern image registration techniques, based on the comparison of bony landmarks or implanted markers, which are routinely used for stereotactic proton-radiosurgery patients, aid the technician and physician in the treatment room in this process. Alignment with an accuracy and reproducibility of 1–3mm is possible and usually takes five to 10 minutes per treatment beam, depending on treatment site and technique (see *Figure 3*).

Future Role of Image Guidance in Proton Treatment Planning

Recent Developments in Magnetic Resonance Imaging

MRI will play an increasing role in the proton treatment planning process. Prostate cancer may be taken as an example. Endorectal MRI of the prostate is a high-resolution technique that is helpful in evaluating extent of tumour within the prostate and possible extensions through the capsule.[8] Moreover, magnetic resonance spectroscopy (MRS) is likely to play an increasing role in proton treatment planning for prostate cancer because it can help differentiate cancerous areas of low T_2 intensity, seen on endorectal MR images of the prostate, from benign nodular areas that are often found in benign prostatic hyperplasia.[9]

Molecular Imaging

Molecular imaging techniques are currently being developed and will play an increasing role in identifying the extent of tumours, both in the organ of origin and in lymph nodes and potential metastatic sites.[10] Most of these techniques will employ either PET or SPECT in combination with CT and/or MRI. In addition to conventional PET tracers such as FDG, which are not specific for tumour tissues, molecular markers need to be developed that lead to specific uptake in tumour tissues or mark specific characteristics of tumours in order to identify regions of higher

Figure 3: Digital Alignment Verification of a Prostate Cancer Patient

The actual patient digital radiograph (right screen) is compared with the DRR (left screen) and corrective moves are determined by registering landmarks defined by the radiotherapist.

radioresistance and/or malignancy. Molecular imaging will not only be useful for more accurate pre-therapeutic definition of planning volumes, but will also help to monitor the response of cancer during or after treatment.[11] SPECT imaging with capromab pendetide – a ^{111}In-labelled antibody against prostate-specific membrane antigen (PSMA), a glycoprotein that is upregulated in prostate adenocarcinoma – may be seen as a prototype for molecular imaging of prostate cancer. Recently, it has been suggested that one can use SPECT fused with treatment planning CT for definition and selectively boost cancerous lesions in the prostate with brachytherapy or external radiation.[12]

Future Role of Image Guidance in the Treatment Room

Dose Verification

With increasing conformality and complexity of proton dose distributions, more emphasis needs to be placed on quality control. Imaging of 3D proton dose distributions, either in phantoms or, more importantly, in the patient, will need to be implemented in order to verify and record the delivered dose distribution. An exciting possibility is to image the dose delivered by protons with an integrated online PET system. Radioactive oxygen (^{15}O), activated by the proton beam inside the patient, is the most abundant positron-emitting isotope produced during proton therapy and can be used for online 3D dose verification.[13] In a recent article, Nishio et al.[14] reported on the performance of a high-resolution (2mm full width at half maximum) online PET system monitoring the spatial distribution of the activity from positron-emitting nuclei. Using different proton energies, a change of the activity–distribution range could be resolved in a gelatinous water phantom with a resolution of about 2mm. Further, it was demonstrated that the proton-irradiated volume in a rabbit could be imaged.

3D and 4D Volumetric Imaging and Respiratory Gating

Recently developed technology for photon IGRT,[15] which is currently implemented in larger photon treatment centres, is also likely to be implemented in the proton treatment room. The use of 4D CT imaging as the basis for respiratory-gated proton therapy will probably become standard practice in the future. Respiratory-gated CT images are mostly free of motion artifacts and are, therefore, inherently more accurate.[16] Moreover, they allow treatment planning for a specific phase of the breathing cycle, typically near the end of the exhale. Using the same type of respiratory gating for CT imaging and during treatment delivery, a proton beam synchronised with the respiratory phase can be delivered, freezing the motion of the tumour in time. Proton CT is a relatively unrecognised imaging modality that can be performed with protons of sufficiently high energy. Typical maximum proton energies delivered by clinical proton accelerators – 230–250 million electron volts (MeV) – have a range of 35–40cm in water; protons of this energy are sufficiently energetic to penetrate most patients and can be utilised for imaging. The conceptual design of a proton CT scanner has been described recently.[17] With cone-beam geometry and proton-scanning beam technology, a full set of 3D volumetric electron density information over a length of 30cm could be obtained with a single revolution of the proton gantry. However, proton CT reconstruction is not trivial due to multiple Coulomb scattering of protons inside the object; new reconstruction techniques and hardware acceleration technology will be required.

Clinical Treatment Strategies Based on Image Guidance

Great potential exists for applying new imaging and image-guidance technologies in proton therapy, which should lead not only to more accurate tumour volume definition and proton dose delivery but also to novel treatment strategies. These will have to be developed in close collaboration among radiation oncologists defining the goals of radiotherapy; medical physicists responsible for selection, implementation and quality control of imaging and image-guidance techniques; and the vendors of new technologies. Clinical treatment strategies utilising new imaging technologies for treatment planning, IGRT and respiratory gating will lead to better definition of the GTV, higher accuracy and, consequently, higher doses and smaller numbers of dose fractions for boosting the GTV. Furthermore, it should be possible to separate CTV and GTV in tumour sites such as prostate cancer where currently no distinction is possible. ■

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