

# Feasibility of functional imaging for brachytherapy

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## Abstract

This review summarizes the current understanding of the feasibility of functional imaging for brachytherapy. In following subsections the role of ultrasound, power doppler imaging, positron emission tomography, magnetic resonance imaging, dynamic dose calculation and targeted brachytherapy is analyzed. The combination of functional imaging with the new tools for intraoperative dose calculation and optimization opens new and exciting times in brachytherapy. New optimized protocols are needed and should be tested in controlled trials, to demonstrate an advantage of such a new paradigm.

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**Key words:** functional imaging, ultrasound, Doppler, PET, MRI, targeted brachytherapy.

## Introduction

Brachytherapy can be considered the ultimate conformal therapy in the armamentarium of radiation therapy techniques. It implements sophisticated tools for applicator placement, dose optimization and delivery, but its inherent physical characteristics (internal sources, rapid fall-off of the dose and gradient generation at the edge of target volumes) causes brachytherapy to become self-optimized by nature. No other conformal therapy (except maybe proton therapy) can achieve the degree of conformation and low integral doses to the rest of the anatomy. Since many years brachytherapy has played a major role in the treatment of cancer. It has been used, combined with external beam radiotherapy in the treatment of gynecologic malignancies with good results. Prostate brachytherapy has open a new era in organ and function conservation and became the most prominent example of highly conformal therapies. The use of brachytherapy in breast cancer has contributed to the change of paradigm in breast conserving therapies for early stage low risk breast cancer. Finally, the use of intraoperative brachytherapy approaches will contribute in the following years to more radical surgical results.

In the last forty years a considerable effort was made to understand the relationships between delivered dose, dose rate and irradiated volume. By the late seventies it became clear that low dose rate brachytherapy was an optimal treatment in a variety of tumours, including head and neck and breast [1]. This created the basis of the clinical radiobiology, applied to optimize treatments with radiotherapy. Brachytherapy can exploit the properties of the tissues it interacts with to improve

the therapeutic ratio, creating special conditions depending on the technological solution used. Every modality (low-dose-rate, high-dose-rate, pulsed-dose-rate, permanent implantation) creates a different dose-rate condition, and the mechanisms involved at the molecular level are probably different. The knowledge of the tissue kinetics parameters can lead to optimized brachytherapy treatments with more antitumoral effect without excess of normal tissue toxicity.

Modern brachytherapy relies on the paradigm built around the triad dose-volume-fraction. With the advent of CT-based dose planning a more detailed knowledge of this relationship was possible. However this knowledge was only partial due to the poor resolution of CT for target volume delineation when applicators are in place and the lack of temporal information of organ motion, very important in brachytherapy due the marked gradients involved in dose delivery. On the other hand, clinical results with different dose rates (or doses per fraction) and modeling studies set the basis for the knowledge of the basic rules for tissue response to ionizing radiation. Moreover, in the last five years, technological advances in radiology and nuclear medicine gave us more understanding of the topography and metabolism of tumors, and a new dimension to optimize radiation therapy, including brachytherapy. Genomics, on the other side, opens the possibility to know individual tumor characteristics, and to personalize radiation therapy to the patient. All those developments are leading to a change in the paradigm, forcing us to revisit our concepts and to adapt to the new circumstances.

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## Intraoperative imaging and dose calculation in brachytherapy

Intraoperative dynamic dose calculation (IDDC) represents a paradigm shift in dose prescription and specification and source delivery for brachytherapy. Initially this concept was devised to permanent seed implantation [2]. It mirrors the IGRT paradigm in EBRT in that an intended prescription dose is adaptively matched to a changing 3D target volume, or selectively “sculpted” to paint the different functional volumes. This process of matching may result in alteration of a previously accepted isodose distribution at any time, until the end of the procedure when a satisfactory dose distribution is achieved. Several workflows have been outlined for intraoperative dynamic dose calculation in the field of permanent seed implantation [3, 4]. The general scheme performing IDDC consists of three steps: first, at some point during the implant, coordinates of implanted vectors are identified. Second, vector images are projected onto the reference frame of the intraoperative images for planning; and finally the plan is reoptimized. To accomplish this objective, precise imaging, dose planning and in-vivo dosimetry will be needed.

Intraoperative imaging increases the complexity of treatment planning and dose delivery in brachytherapy. It also increases the precision requirement for target volume localization and for securing geometrical precision before and during irradiation. Different technologies are available for clinical use, including pure intraoperative TRUS based tracking, TRUS-fluoroscopy fusion, intraoperative MR and intraoperative cone-beam CT. TRUS provides adequate imaging of the soft tissue anatomy but it does not allow for robust localization of the implanted vectors. Various researchers have tried to use TRUS to segment the seeds in permanent prostate brachytherapy [5-7]. Fluoroscopy can be used in combination with TRUS to create a reliable method for intraoperative applicator capture and dosimetry optimization. Combining their images by spatial co-registration (fusion) offers the potential for a practical intraoperative dosimetric assessment. TRUS offers the ability to identify the soft tissues (prostate, gynecological relapses), and fluoroscopy can provide the data needed to perform three-dimensional (3D) applicator reconstruction.

Flat-panel based cone-beam computed tomography (CBCT) is a strong candidate technology for intraoperative imaging in image-guided procedures such as brachytherapy [8, 9]. CBCT uses a two-dimensional detector to produce a CT reconstruction from a single rotation of a point source. The soft-tissue imaging performance and potential navigational utility have been investigated by several authors both in pre-clinical and in clinical situation. In image-guided permanent seed implantation, soft-tissue imaging performance and seed detection could satisfy the imaging and navigation requirements. Other implant strategies can be assisted by CBCT. The demonstrated soft-tissue visibility, excellent spatial resolution, low imaging dose, and convenient form factor make C-arm based cone-beam CT a powerful new technology for image-guidance applications, including brachytherapy, vertebroplasty and neurosurgery.

Magnetic resonance imaging (MRI) can overcome some of the limitations inherent to TRUS and CBCT. MRI offers a three-dimensional dataset, arbitrary multiplanar reconstruction and better soft-tissue resolution with good correlation with TRUS-based evaluations and pathologic findings, making it an attractive image modality for brachytherapy dosimetry [10-17]. Different experiences using MRI have been reported, including prostate seed implantation and gynecologic malignancies [18-20].

## Functional imaging for brachytherapy

Over the last few years, the use of molecular imaging, particularly the use of 18F-FDG based PET, has become increasingly popular in oncology, opening a new dimension to management for patients with cancer [21]. The potential role of functional imaging in radiation oncology can be broadly divided into four main areas [22]. First, functional imaging is emerging as a powerful technique in radiation treatment planning assisting in target delineation [23]. Second, functional imaging would help in the modulation of the dose to the target volume (dose painting by numbers). Third, assessing radiobiological processes during and after radiotherapy, term referred to as “radiodynamics”. Finally, functional imaging can be utilized for in vivo predictive testing and in the assessment of response to radiation therapy.

Recent advances now allow highly specific and sensitive detection of cellular and molecular events non-invasively. The diagnostic imaging for radiation oncology aims to map in three dimensions the distribution of a tumor, tissue, or functional feature, and to provide information about the clinical response of tumors or healthy tissues to radiotherapy [24]. In solid tumors, the aim is to provide images of phenotypic or microenvironmental characteristics known to affect the clinical response. Most research has been done to detect tumor burden and clonogen density, tumor hypoxia or proliferation. New markers will allow to probe specific genetic pathways relevant to radiation therapy.

In the new paradigm (dose-guided brachytherapy), imaging is used to know the coordinates of the tumor cells, and to guide applicator insertion to the correct position. To map cancer cells, a number of new image modalities have been developed in the last years: PET, MRI-MRS and power doppler US imaging are among them. All those image modalities give twofold information: morphological in one side and metabolic in the other. Combining the two different aspects it is possible to define areas where it is likely that tumor burden is present, or certain hypoxic areas, or areas of repopulation or intrinsic radiosensitivity load. Those areas are supposed to be liable to be boosted by high-precision modalities. In this setting, brachytherapy will offer the intrinsic advantages already mentioned. The rapid fall-off of the dose would serve to precisely sculpt dose around these sub-volumes. This process is known as dose-painting, as we can paint the different dose levels we want to achieve within the target volume. Correlation studies with pathologic specimens are needed to check for spatial and temporal stability.

Imaging is also required for precise deposition of the prescribed dose. Beyond CT-based 3D planning and US needle guidance for prostate implantation there is a brand new field of "dose guidance" in which the brachytherapist could see in real time the relationship between the planned dose, the applicator and the anatomical volumes of interest. Different tools can be used (CT, MRI, US), every one adapted to different clinical situations. Ultrasound is very suitable in the circumstances where brachytherapy is performed. It can be intraoperative, it is fast, no radiation exposure to the staff, it is cheap and would allow direct visualization of the applicator and the intended dose overlaying together with anatomical and functional information. The new paradigm in brachytherapy relies on the new image modalities for tumor mapping and dose guidance, and brachytherapy will obtain a clear advantage from this modalities that could translate in better treatments, more conformal to the target volume, more dose-intensive, and less toxic to the surrounding tissues.

### Magnetic resonance imaging

Magnetic resonance imaging (MRI) provides numerous techniques for image-based surrogates of different functional pathways: angiogenesis (perfusion MRI), metabolism (MR spectroscopy), tissue at risk and tumor cellularity (diffusion weighted imaging), and motion (4D MRI) [25]. Contrast-enhanced dynamic MRI provides information about tissue perfusion, visualising differences between tissues in the behaviour of a gadolinium-based contrast medium. It has been applied to many different tumors, such as cancers of the breast, prostate, cervix, rectum and liver, as well as gliomas, pulmonary nodules and multiple myeloma. From signal intensity time curves descriptive parameters such as lag time, amplitude, slope and area under the curve (wash-out) can be calculated. They are determined by perfusion and flow and related to microvascular density and permeability. Blood oxygen level-dependent (BOLD) MRI can depict clinically significant prostate tumor hypoxia. Co-registration studies shown a significant correlation between pimonidazole immunostaining of coregistered histological sections and the value of MR relaxivity parameter  $R(2)^*$  [26].

MR spectroscopy (MRS) can provide metabolic information about tumour cells and the surrounding tissue. Shifts in the distribution of certain metabolites provide important hints towards both differential diagnosis and the tumor biological behaviour. MRS appears to be a promising modality for prostate cancer radiotherapy planning. MRS can well distinguish cancer dominant regions from the normal prostate tissue within the prostate gland based on the depletion of citrate relative to choline and creatine. In addition, cancer-positive voxels detected by 3D MRS study can be precisely overlaid on the corresponding MR images, which provides morphological imaging of the lesions. This information can be loaded in the planning of transperineal seed implantation [27, 28].

### Positron emission tomography

FDG-PET (18F-fluoro-deoxyglucose positron emission tomography) is an established imaging technique,

developed 30 years ago. FDG is an analogue of glucose, which is taken up into cells by Glut-1 receptors, which are over-expressed in tumor cells. Intracellularly, the FDG is phosphorylated by hexokinase with the metabolite retained in the cell. It is by this mechanism that tumour cells retain FDG. The radiolabel can be detected and usually demonstrates a high uptake in tumour relative to normal tissue [29]. Although FDG uptake is not tumor specific, FDG-PET is a very useful tool in oncology, with its use spreading in the last few years. Positron emission tomography has been explored by some authors for planning brachytherapy in cervix cancer [30-33]. Feasibility of using PET images for treatment planning was demonstrated with a phantom study showing acceptable reconstruction accuracy. Despite the limited number of patients included in these studies, the authors conclude that PET-based treatment planning allowed for improved coverage to the planning target volume in cervix cancer endocavitary brachytherapy.

### Functional ultrasound

Future developments using functional ultrasound (power doppler imaging, elastography) could bring functional imaging into the operating room. Those imaging techniques should have far-reaching therapeutically implications in some tumor localizations, like prostate and cervix cancer. Optimized dose distributions can be obtained intraoperatively using dynamic dose calculations.

Neo-microvasculature is an essential requirement in the progression of prostatic carcinoma. A progressive increase in the microvessel density (MVD) has been shown by immunohistochemical staining as prostate cancer progresses through various pathological stages. It has been reported that MVD is an important prognostic marker, and is an independent predictor of pathological stage and of the malignant potential of prostatic carcinoma [34]. The use of vascular imaging for detecting neo-vascularity is a rational choice, since it has been demonstrated that tumors larger than 1 mm<sup>2</sup> in area must recruit new blood vessels to grow larger [35]. This neovascularity is expected to give rise to detectable flow using the power Doppler principle. Tumor vascularity can be quantified in power Doppler images by computing the color pixel density (CPD), which is equal to the percentage of image voxels within a region of interest that exhibit detectable flow. Nakanouchi *et al.* [36] reported a clinical study revealing correlation between the degree of blood flow signals on PDI and the microvascular density as determined in radical prostatectomy specimens.

With the advent and the fast evolution of the ultrasound contrast agents a new horizon for Doppler imaging can be foreseen [37]. Sonocontrast agents increase the echoes obtained from the arterial blood with a factor of 3-20, and so the efficacy of Doppler examination. Contrast enhanced ultrasound examinations are reported to improve the detection of malignancies within the prostate, suggesting that perfusion based imaging techniques have the potential to improve the detection of the intraprostatic dominant cancer lesions. Three-dimensional contrast enhanced power Doppler techniques appear to improve

the detection of prostate cancer and have the potential to visualize lesions with increased microvessel density [38].

This semiquantitative evaluation of blood flow signals in prostate cancer lesions, as evaluated by PDI might be of clinical use when planning prostate brachytherapy. However, up to date, no clinical results have been presented using this imaging approach.

### Targeted brachytherapy

Taking the classic concepts of dose-rate and volume effect, modern brachytherapy moves to personalized treatments, using predictive assays and detailed functional information of the tumor to model response of the individual patient to the given treatment. As we already mentioned above, functional imaging gives a picture of the tumor biology, allowing dose delivery to be much more adapted to the actual tumor. Dose prescription will be individualized, with different dose levels to the whole target volume and the different sub-volumes, including the dominant lesion or the more radio-resistant hypoxic regions. Predictive assays are very useful tools to model the behaviour of different tumors based on their individual genetic profiling. Microarray technology has been exploited for its predictive ability in disease development, clinical outcome and prognosis-based treatment. Microarrays have been used in to discriminate which patients treated with brachytherapy for head and neck tumors would need prophylactic neck dissection as part of their treatment [39]. However, predictive assays for local relapse after surgery or radiation therapy are lacking, but needed to personalize local treatments (giving different dose levels to good and poor responders, adding bio-modulators or other local strategies).

Targeted brachytherapy is a new integrative paradigm, where the goal is to improve therapeutic ratio through the integration of detailed information of the tumor coordinates and genetic profiling and precise delivery of the prescribed dose using image guidance. Some of the modules described above are already available. Dose guidance is available in some commercial systems. Technology for intraoperative functional imaging is already available (US power doppler, and elastography). Other modules are under development or still experimental. The work in progress is promising and the whole paradigm could be a reality in a few years.

### Conclusions

In conclusion, the combination of functional imaging with the new tools for intraoperative dose calculation and optimization opens new and exciting times in brachytherapy. New optimized protocols are needed and should be tested in controlled trials, to demonstrate an advantage of such a new paradigm.

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