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EDITORIAL

Modern brachytherapy

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Brachytherapy can be considered the ultimate conformal therapy in the armamentarium of radiation therapy techniques. It implements sophisticated tools for applicator placement and dose optimization, and delivery, but its inherent physical characteristics (internal sources, rapid dose falloff, 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.

Brachytherapy has a prominent role within oncological therapeutics. It can be used either as exclusive treatment or in combination with external-beam radiotherapy, for radical treatments with curative intent, combined with surgery (preoperatively, intraoperatively, or postoperatively), or in a palliative setting. Brachytherapy presents the ideal conditions to test combination schedules with radiosensitizing drugs or other molecules with radiomodulation properties. Different technological modalities are possible, resulting in different modalities of brachytherapy: low dose rate brachytherapy releases dose continuously (seeds, iridium wires). Remotely, afterloaded brachytherapy presents two alternatives: either fractionated high dose rate or pulsed dose rate is possible, depending on the activity of the source used in the afterloading machine. In both cases, dose is released in short fractions, or pulses, with a variable interval [1].

Radiation therapy can exploit the properties of the tissues it interacts with to improve the therapeutic ratio. It has special conditions depending on the technological solution used, as every modality creates a different dose-rate condition, and the mechanisms involved at the molecular level are probably different. Knowledge of tissue kinetics parameters can lead to optimized brachytherapy treatments with more antitumoral effect without excess of normal tissue toxicity. Promising trials are being envisaged.

Thanks to the work of Pierre and Marie Curie in the beginning of the twentieth century, it was found that the preparation of radium into needles and tubes can result in a continuous irradiation in which the total time required to give an optimal dose of 60 Gy is reduced to 5 or 6 days. Clinical results quickly followed, showing that tumors were better controlled with low dose rate radiation over several days than by fractionated high dose rate radiation over several weeks. The developments coming after, during the rest of the century, can be summed up as a quest to optimize the therapeutic ratio by exploiting the differential effect on tumors and normal tissues of ionizing radiations delivered as fast as possible.

In the last 40 years, a considerable effort was made, first by the French school and then by rest of the radiation oncology community, to understand the relationships between delivered dose, dose rate, and irradiated volume. By the late 1970s, it became clear that low dose rate brachytherapy was an optimal treatment in a variety of tumors, including head and neck, and breast [2]. This created the basis of the clinical radiobiology applied to optimize treatments with radiotherapy.

Brachytherapy has played a major role during the last 20 years 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 opened 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 near future to better surgical results.

Modern brachytherapy relies on the paradigm built around the triad dose–volume–fraction. Small doses per fraction (or small dose rate) to doses in the range of 65-70 Gy are used for tumor cures depending on disease extent but with local toxicity kept low. Volume was related to dose and later, with the advent of computed tomography

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(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 were in place and the lack of temporal information for organ motion, which is 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 knowledge of the basic rules for tissue response to ionizing radiation. However, in recent years, technological advances in radiology and nuclear medicine have given us a greater understanding of tumor topography and metabolism and a new dimension to optimize radiation therapy, including brachytherapy. Genomics, on the other hand, open the possibility to understand individual tumor characteristics and to personalize radiation therapy to the individual patient. All those developments are leading to a change in paradigm, forcing us to revisit our concepts and to adapt to the new circumstances.

High doses per fraction with high-precision delivery are used for external-beam radiotherapy in a variety of situations (prostate cancer, extracranial stereotactic radiotherapy, and others) with good results. High doses per fraction have been used for 20 years in intraoperative radiation, combined with external-beam radiotherapy, with good long-term results. In brachytherapy, high or very high doses per fraction are now possible, with a very precise delivery, and total doses ≥ 90 Gy to small subvolumes (dominant lesions) are feasible. It is anticipated that doses in this range will control all the clonogens present in the tumor (in most situations), but the risk of misadministration and late toxicity make it necessary to track dose to verify its precise deposition in the tissues. To accomplish this objective, precise in vivo dosimetry and imaging are required. Real-time in vivo dosimetry is needed to assess the delivered dose within the body. Implanted radiofrequency-enabled dosimeters could measure dose distribution just before dose delivery, comparing it with the planned dose and providing the opportunity to adjust intended dose to planned volume.

For precise dose deposition, novel imaging techniques are also needed. In the new paradigm (dose-guided brachytherapy), imaging is used to determine the exact 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 recent years: positron emission tomography (PET), magnetic resonance imaging/magnetic resonance spectroscopy (MRI-MRS) and power Doppler ultrasound (US) imaging are among them. All those image modalities give twofold information: morphological on one hand and metabolical on the other. Combining the two 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 offers the intrinsic advantages already mentioned. The rapid dose falloff would serve to precisely sculpt dose around these subvolumes. This process is know 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), each one being adapted to different clinical situations. US is very suitable in circumstances in which brachytherapy is performed. It can be intraoperative, it is fast, it gives no radiation exposure to the staff, it is cheap, and would allow direct visualization of the applicator and the intended dose overlaid 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 these modalities that could translate into better treatments, more conformal to the target volume, more dose intense, and less toxic to the surrounding tissues.

Taking the classical 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 individual patient response to the given treatment. As mentioned above, functional imaging gives a picture of the tumor biology, allowing dose delivery to be much better adapted to the actual tumor. Dose prescription will be individualized, with different dose levels to the whole target volume and the different subvolumes, including the dominant lesion or the more radioresistant hypoxic regions.

Predictive assays are very useful tools to model the behavior 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 [3]. However, predictive assays for local relapse after surgery or radiation therapy are lacking but are needed to personalize local treatments, giving different dose levels to good and poor responders, adding biomodulators 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 tumor coordinates and genetic profiling followed by 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. Hypofractionated, accelerated, and highly conformal protocols are already being put into place, and the whole paradigm could be a reality in 2-4 years. The digital operating room for brachytherapy could integrate the different sources of preoperative information and intraoperative image guidance, making it the effective center of the brachytherapy workflow. In the near future, targeted brachytherapy, biologically optimized, could open new clinical possibilities to cure cancer patients.

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