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LETTER TO THE EDITOR

Dose per fraction and dose rate effect

To the Editor: We read with interest the clinical case reported by De Cicco *et al.* dealing with high dose rate (HDR) brachytherapy as a salvage treatment approach after external beam radiotherapy for locally recurrent prostate cancer[1]. The patient was given 4 fractions of 7 Gy each, administered *bis in die* in 2 consecutive days, up to a total nominal dose of 28 Gy, employing a remote after-loading unit. The definition of the optimal salvage strategy in this subset of patients represents an interesting medical challenge. The decision process is mainly based upon clinical, technological and expectational considerations, as pointed out by the authors.

Conversely, within a radiotherapeutic context, we would like to focus our attention on radiobiological issues supposedly influencing the preference between HDR brachytherapy and low dose rate (LDR) brachytherapy with permanent implants. The general assumption for prostate cancer is that it might show a low sensitivity to changes in fractionation. This characteristic would be depicted by a low α/β ratio (in the range of 1 to 4 Gy)[2]. Hence, we might suppose at least a comparable (some would say even smaller) sensitivity to fractionation between prostate cancer and the neighboring surrounding organs and tissues[3].

Nullified in this context the rationale for conventionally fractionating the total dose, hypofractionated schedules thus would be able to achieve similar or even higher tumor control probability rates and comparable late-responding normal tissue control probability compared to classical schedules. HDR brachytherapy, with few delivered high-dose fractions, would thereby be a means to improve the 'therapeutic index' by escalating the biological equivalent dose.

On the contrary, the so-called 'dose-rate effect' is a biological process by which the radiosensitivity of cells decreases as the dose rate is lowered (compared to the common external beam radiotherapy range of 1-5 Gy min^{-1}). This is due by the occurrence of repair, reassortment, repopulation and reoxygenation during a longer irradiation period. The range of influence upon cellular response depends on the speed of these events[4]. Repair is the fastest between these processes, thus affecting radiosensitivity over the dose-rate range of 1 to 0.1 cGy min^{-1}. Conversely, repopulation takes much more time to occur, influencing cellular response below a lower range of dose rates (2 cGy min^{-1}). Reoxygenation, as reassortment, might act over an intermediate dose-rate range[5].

The dose-rate effect on cell survival might be extrapolated from cell survival curves for human cell lines, deriving radiation dose values at the same surviving fraction for different dose rates and calculating the so-called dose-recovery factor, using the ratio of the obtained radiation doses[3]. Using the incomplete repair model, it is possible to demonstrate the equivalence between dose per fraction within fractionated radiation therapy and dose rate within continuous radiation exposure[6]. Hence, as in fractionated radiation therapy diminishing the dose per fraction might be an option to spare late-responding normal tissues characterized by a low α/β ratio (such as rectal bleeding), so lowering the dose rate (thus the increasing dose-recovery factor) in a brachytherapy setting might be an equivalent possibility. This might be noteworthy dealing with re-treatment in order to minimize late effects, leading to the possibility of sparing normal tissues with the LDR brachytherapy treatment device.

In conclusion, the choice between the two brachytherapy options (HDR or LDR) might also be driven by radiobiological considerations, influenced by the need of favoring tumor control probability over normal tissue control probability, or vice versa, according to the appropriate clinical context.

Pierfrancesco Franco, Debora Beldì, and Marco Krengli
Radiotherapy Department,
University Hospital Maggiore della Carità, Novara, Italy

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In reply: We read with interest the letter of Franco et al. We fully agree that the choice of salvage therapy in prostate cancer is a highly patient-tailored decision. Indeed, more and more salvage modalities are being investigated for isolated primary recurrent prostate cancer, including prostatectomy, high-intensity focused ultrasound, cryotherapy, radiofrequency interstitial tumor ablation and re-irradiation[1].

Isolated locally recurrent prostate cancer constitutes a particular clinical situation. Most recurrent prostate cancer patients have been treated with high-dose radiotherapy (>70 Gy), and clinically evident or subclinical normal tissue damage may be present. Due to the long natural

history of the disease, the diagnosis of recurrent tumor is usually done more than 5 years after the primary radiotherapy course, so aging and comorbidity make the clinical decision on the salvage approach even more challenging than the primary treatment choice. In fact, the recent reports on the high risk of rectal fistulae following salvage high-intensity focused ultrasound after combined brachytherapy and external beam radiotherapy emphasize the fragility of this patient population[2]. Definitely, the emerging ablative therapies regarded as less invasive than traditional therapies must be used with caution.

Re-irradiation is probably the most investigated local approach for recurrent prostate cancer. Re-irradiation may be performed in numerous ways including low dose rate and high dose rate (HDR) brachytherapy, linac-based stereotactic irradiation or robotic image-guided stereotatic irradiation using a CyberKnife unit.

We fully agree with Franco *et al.* that the choice of the re-irradiation modality should be based on the clinical and radiobiological context. In the case of our patient, the choice of HDR brachytherapy was based on the absence of radiotherapy late toxicity and the emerging data on the low α/β of the prostate cancer[3-4]. According to the linear quadratic model, the equivalent biological dose EQD given at 2 Gy per fraction (EQD2 = $D[\alpha/\beta+d]/[\alpha/\beta+2]$, where D is the total dose given at the dose per fraction d) of our HDR schedule, is 64.3 Gy, 61.2 Gy or 53.5 Gy, assuming the α/β value of 1.5 Gy, 1.85 Gy or 3.1 Gy, respectively. Obviously, the entire knowledge on the α/β of prostate cancer comes from the primary tumor, whereas the radiobiology of recurrent prostate cancer (different α/β ratio?) still has to be investigated.

Low dose rate brachytherapy might be a better choice in a patient who has experienced late injury or severe acute toxicity during the first radiotherapy course that might evolve in the clinically evident late events due to consequential effects.

Reports on the low α/β of prostate cancer have stimulated the introduction of hypofractionated radiotherapy for the malignancy[5]. Actually, HDR brachytherapy is a form of extreme hypofractionation when the whole therapy is given in a very short overall time. HDR schedules have been transferred to high precision external beam radiotherapy using the CyberKnife. Indeed, the recent planning study from San Diego, CA (USA), showed that it is possible to construct CyberKnife plans that closely recapitulate HDR dosimetry and deliver the plans noninvasively[6]. In 2007, we started using CyberKnife re-irradiation for prostate cancer patients with isolated local recurrence after external beam radiotherapy. Our preliminary report on 6 cases showed excellent local tumor control and toxicity profile[7]. However, half of the patients experienced distant disease progression, even though androgen deprivation was employed in 4 of the 6 patients. Such patterns of failure call for better definition of selection criteria and optimization of systemic treatment in patients undergoing salvage re-irradiation for prostate cancer.

Barbara Alicja Jereczek-Fossa[1,2], Andrea Vavassori[1], and Roberto Orecchia[1,2]

[1]Dept of Radiotherapy, European Institute of Oncology, Milan; [2]University of Milan, Milan, Italy

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ERRATA CORRIGE: In the article by

Maurizio Mascarin, Annalisa Drigo, Andrea Dassie, Marco Gigante, Giovanni Franchin, Giovanna Sartor, and Mauro G Trovò: Optimizing craniospinal radiotherapy delivery in a pediatric patient affected by supratentorial PNET: a case report. Tumori, 96: 316-321, 2010.

on page 316 the following affiliations should appear:

Maurizio Mascarin[1], Annalisa Drigo[3], Andrea Dassie[3], Marco Gigante[2], Giovanni Franchin[2], Giovanna Sartor[3], and Mauro G Trovò[2]

[1]Pediatric Radiotherapy Unit and Divisions of [2]Radiation Oncology and [3]Medical Physics, Centro di Riferimento Oncologico, National Cancer Institute, Aviano (PN), Italy.

An error occurred in Figure 1, pag 318. The correct figure is shown below.