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SBRT and extreme hypofractionation: A new era in prostate cancer treatments?

Filippo Alongi[a,*], *Alba Fiorentino*[a], *Berardino De Bari*[b]

[a] *Radiation Oncology Department, Sacro Cuore Hospital, Negrar-Verona, Italy*
[b] *Radiation Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanna, Switzerland*

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ABSTRACT

Aim: Radiation therapy (RT) is a standard therapeutic option for prostate cancer (PC). In the last decades, several innovative technology applications have been introduced. 3-Dimensional conformal RT, volumetric/rotational intensity modulated RT associated or not with image-guided RT, are becoming largely diffused in the treatment of PC.
Background: Considering that PC could have a low α/β ratio, similar to late-reacting normal tissues, it could also be highly responsive to fraction size. Thus, the reduction of the number of fractions and the increase of the dose/fraction seem to be reasonable choices in the treatment of this cancer. This review reported the technology evolution, the radiobiological and the clinical data about the role of extreme hypofractionated RT in the treatment approach of PC patients.
Materials and methods: Medline search and analysis of published studies containing key words: prostate cancer, radiotherapy, stereotactic radiotherapy.
Results: Recent technological developments, combined with an improved knowledge of the radiobiological models in favor of a high sensitivity of PC to larger fraction sizes are opening a new scenario in its treatment, reporting favorable efficacy and acceptable toxicity, despite short follow-up.
Conclusion: Thus, thanks to technological improvement and the recent radiobiological data, "extreme hypofractionated RT" has been strongly introduced in the last years as a potential solid treatment option for PC.

* *Corresponding author at*: Radiation Oncology Department, Sacro Cuore Hospital, Via Don Sempreboni 5, 37139 Negrar-Verona, Italy. Tel.: +39 0456014800.
E-mail address: filippo.alongi@sacrocuore.it (F. Alongi).

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1. Background

According to all international guidelines, radiation therapy (RT) is a standard therapeutic option for prostate cancer (PC).[1–3]

In the last two decades, several innovative technology applications have been routinely introduced in external beam RT (EBRT). At the turn of the century, 3-dimensional conformal RT (3DCRT) became available in almost all radiation oncology departments, but thereafter, intensity modulated RT (IMRT) gained large diffusion and it is now suggested as a gold standard in the treatment of PC.[1,4] Robotic or volumetric/rotational IMRT delivery techniques, associated or not with image-guided RT (IGRT), are becoming largely diffused in the treatment of PC.[4–9] Thus, the evidence of the clinical impact of these technology advancements push clinicians to implement these precise techniques in daily clinical practice, and the benefits of the current technology revolution are promising.[10,11]

Concomitantly, feedback from radiobiology estimations seems to be even more robust and a lot of these data are in favor of a reduced duration of radical RT treatment without a detrimental impact on clinical outcomes, both in terms of efficacy and safety.[12–14]

Finally, available technological improvements and the quite well established radiobiology data support extreme hypofractionation for PC, which has been rapidly introduced in the last few years and which is now considered as a potential treatment option for PC patients candidate to EBRT.[1]

2. Modern stereotactic body Rt: the technology revolution

In the last 30 years, several crucial steps have built the bases of the improvements in RT delivery. After the introduction of computer tomography (CT) in radiation departments, there has been a dramatic growth in the implementation of 3DCRT in clinical practice. IMRT was born as an evolution of the conformal techniques and is able to obtain deep gradient and rapid fall-off of doses, for example between the prostate and rectal wall, or close to the intestinal bowel when the pelvic nodes are included in the treatment plan, with a potential impact in decreasing both acute and late toxicities in PC treatments.[10] Thus, IMRT is currently recommended over 3DCRT for the treatment of localized PC with a radical intent, in particular when a dose escalation is considered suitable.[15,16]

Zaorsky et al. recently described as a 'technologically advanced RT', each RT modality allowing a more favorable benefit/risk ratio than standard RT approaches. The technology gain derives from the use of upgraded IGRT, IMRT or integration of both.[4,17]

The principal end point of stereotactic body RT (SBRT) is to minimize the dose to the surrounding critical normal structures while delivering high dose/fraction to the target volume. Up until a few years ago, SBRT was usually adopted by using spatial coordinates to define the position of the target to be irradiated with ablative doses.

Nowadays, the term of SBRT is rapidly changing toward a concept describing a "philosophy" for treating cancer not necessarily with spatial coordinates, but essentially prescribing high precise doses in one or few fractions. Modern SBRT adopts static, dynamic or volumetric IMRT techniques to provide sharper dose fall-offs and better dose conformity.

In this context of high precision, extreme accuracy is essential. In particular, a special attention should be given to the problem of organ motion, typical of the irradiation of extra-cranial organs. Several techniques have been adopted: intraprostatic coils visible with portal imaging (stereoscopic kVCT, megavoltage portal images), CT scans images obtained immediately before the treatment delivery (kV cone-beam CT, megavoltage cone-beam CT), CT images with helical acquisition (helical tomotherapy), ultrasound (B mode adapting targeting), and electromagnetic online verification with microprobes placed in the patient. Pre-treatment 3D-CT scans are probably better systems, but also 2D-system adopting invasive fiducial markers is a good alternative.

Finally, all these systems allow the verification of the position of the tumor (or of the target volume) before each treatment session delivery, and substantially they reduce patient setup error and allow a reduction of the margin around the target. The delivery of SBRT badly needs these verification tools, because they allow a reduction of the uncertainty of target position.[18] All these technological needs seem difficult to be accepted from a cost-effectiveness point of view. Nevertheless, many studies have concluded that SBRT is cost effective, as it allows a better organ sparing and dose escalation on the target volume, and they are also cost saving.[19–21]

Although SBRT in PC could not be considered yet a standard option, due to the small number of patients treated worldwide and the relatively short follow-up of most of the published experiences, its preliminary results are promising and SBRT adoption is rapidly increasing in the radiation oncology departments.[1,18,22]

Moreover, technological innovations should not replace the clinical aspects of PC, and indications for SBRT should be reserved to those patients who would really benefit from this treatment. Patients presenting T3 tumors and/or with a high risk of nodal diffusion are not the best candidates for highly focalized treatments and NCCN guidelines do not consider SBRT amongst the treatment options for these patients.[1] SBRT in these high risk patients could be considered as boost in some particular cases after the first course of standard external beam irradiation (as it is frequently done with high dose rate brachytherapy in high risk PC patients) and always in the context of controlled, prospective clinical trials (as in the trial NCT01839994, available online at www.clinicaltrials.gov)..

3. A radiobiology based approach

The α/β ratio is the radiobiologic parameter to explain the behavior of tissues and cancer with respect to radiation schedules. In radiobiology, the α/β ratio is defined as the dose at which killing of cells by linear (α) and quadratic (β) components is equal. Recent investigations on biochemical control in PC suggested an α/β value between 1 and 3 Gy for PC, which

is somewhat lower than the value typically ascribed to surrounding organs, such as bladder and rectum.[23–27]

Considering that PC would have a low α/β ratio, similar to late-reacting normal tissues, it could be highly responsive to fraction size. Thus, the reduction of the number of fractions and the increase of the dose/fraction seem to be reasonable choices in the treatment of this cancer.

Hypofractionation would offer a unique opportunity to optimize the therapeutic ratio taking advantage of the potential heightened sensitivity of PC to higher dose/fraction (compared to surrounding organs at risk). Moreover, it means that the total length of the radiotherapy course is shortened, becoming less distressing and more rapid for the patients, with an obvious impact in improving the quality of life and health costs.

To date, several controlled randomized trials comparing standard RT schedules with moderate hypofractionation for PC cancer have been published.[28–33] Despite some differences in the treatment schedules adopted in the experimental arms, in all these reports hypofractionated regimes appear to be associated with optimal tolerability profiles, comparable to those observed for standard courses. These results seem to confirm the radiobiological assumption regarding the low α/β value of PC and the clinical and radiobiological background, supporting the further reduction of the number of fractions and overall treatment time, the so-called "extreme hypofractionation". This approach could potentially drive up the biological effective dose for tumor control; decrease the equivalent dose for late tissue response and it is performed in 4–5 fractions, with very large dose per fraction (usually 7–9 Gy) in the context of various stereotactic body techniques. Moreover, SBRT add a novel radiobiological mechanism of radiation-induced damage. Emerging data suggest that higher doses per fraction (ablative doses) could add to direct cytotoxicity a microvascular damage which could substantially increase tumor cell killing.[34] Finally, targeting the tumor vasculature for obliteration with ultra-high-dose radiation has been assumed to be beneficial for tumor control.[35,36]

Finally, the possibility to deliver higher doses/fraction precisely delivered on the target can offer a safe opportunity to increase the therapeutic ratio of PC radiotherapy.

4. Published data

A safe delivery of extreme hypofractionated RT regimes, other than the favorable therapeutic ratio offered by the low prostate cancer α/β ratio, requires the use of highly focused irradiation techniques, delivering full doses to the prostate only volume with a rapid falloff to minimize the dose to the surrounding critical normal structures as well as the use of radiation techniques that allow an optimal treatment accuracy by daily patient repositioning and correction for inter-and intra-fraction organ movements.[37,38]

Most of the experiences reporting data about prostate SBRT have been performed with Cyberknife.[39–51]

One of the earliest reports on CyberKnife® SBRT was conducted on 44 PC patients treated with a total dose of 32–36 Gy in 4 fractions.[39] After a median follow-up of 13 months, overall toxicity was mild and the 3-year actuarial biochemical freedom from failure (BFF) rate was only 78%, but this low rate was explained by the large proportion of intermediate- and high-risk patients enrolled in the study.

Friedland et al.[40] reported the results on 112 patients with early stage PC treated with 35–36 Gy in 5 consecutive fractions. After a median follow-up of 24 months, the mean PSA value was 0.78 ng/ml. Two patients developed biopsy-proven local recurrence and one patient developed distant metastases. Authors report only one case of grade 3 rectal toxicity. Moreover, 82% of patients able to achieve erections prior to therapy maintained their potency.[34]

Bolzicco et al. reported preliminary data on 45 low- and intermediate-risk PC patients and, more recently, updated their data on 100 patients treated with 35 Gy (7 Gy/fraction) delivered with Cyberknife®.[41,42] No acute Grade 3 or higher acute toxicities were reported. Late Grade 3 genitourinary (GU) toxicities occurred in 1% of the patients and no late G3-4 gastrointestinal (GI) toxicities were observed. No evidence of biochemical or clinical recurrence was shown in 96/100 patients.[42]

A larger study, conducted by Katz et al.,[43] involved 304 patients: the first 50 patients were treated with 35 Gy (5 fractions) and the remaining 254 patients were treated with 36.25 Gy (5 fractions). Results at 6 years showed excellent biochemical control rates and a low toxicity profile.[44] Late Grade 3 GU toxicities occurred in 2% of patients who were treated with 36.25 Gy. Bowel and urinary quality of life (QOL) scores came back to baseline values after a few months from SBRT and 75% of the patients who were potent before the treatment remained sexually potent. Actuarial 5-year BFF was 97% for low-risk, 90.7% for intermediate-risk, and 74.1% for high-risk patients, respectively.[44]

King et al.[45] enrolled, in a phase II trial, 69 patients with low risk PC to receive 36.25 Gy in five fractions with SBRT alone. The authors reported excellent PSA responses, a low toxicity profile and QOL outcomes comparable to other radiotherapy approaches. Another analysis on 211 patients reported the same results of SBRT Cyberknife (35–36.25 Gy in 5 fractions) showing outcomes comparable to conventionally fractionated RT or brachytherapy.[46]

Freeman et al.[47] reported the results on 41 patients receiving SBRT with CyberKnife® (35–36.25 Gy in 5 fractions) for clinically localized, low-risk PC. After a median follow-up of 5 years, the BFF was 93%, no late grade ≥3 rectal toxicity occurred, and only one patient experienced late grade 3 GU toxicity.

Recently, a SBRT dose escalation study on 70 patients (37.5 Gy vs. 35–36.25 Gy in 5 fractions) was conducted by Oliai et al.[48] with favorable efficacy and acceptable toxicity: grade 3 GU toxicities included 4% acute and 3% late (for high dose group).

A pooled analysis on SBRT using the CyberKnife (median dose of 36.25 Gy in 4–5 fractions) has been published by King et al.: the authors report the outcomes of a total of 1100 patients with clinically localized PC enrolled in different multicentric prospective phase II clinical trials (8 institutions, treatment period: 2003–2011). With a median follow-up of 36 months, 49 patients experienced a PSA failure (4.5%), 9 of which have been lately classified as benign PSA bounces. The 5-year BFF rate was 93% for all patients, but for 135 patients

Table 1 – Stereotactic radiotherapy in prostate cancer.

Study	Treatment	# of patients	Risk group(s)	Median follow-up (months)	Late Grade 3 GU toxicity	Late Grade 3 GI toxicity	FFBF
Gantry-based systems							
Madsen et al.[52]	33.5 Gy in 5 fx	40	Low	41	None	None	90% 4-years actuarial
Boike et al.[53]	45–50 Gy in 5 fx	45	Low and int	30, 18, 12	4%	2% plus 1 Grade 4	100%
Alongi et al.[54]	35 Gy in 5 fx	40	Low and int	11	None	None	–
Loblaw et al.[56]	35 Gy in 5 fx Once a week	84	Low	55	1%	None	98% 5-year
Cyberknife							
King et al.[45]	36.25 Gy in 5 fx	69	Low	32	3.5%	None	97%
Friedland et al.[40]	35 Gy in 5 fx	112	Low, int, and high	24	< 1%	None	98%
Katz et al.[43]	35–36.25 Gy in 5 fx	304	Low, int and high	48	2%	None	97, 93, 75% 4-year actuarial
Freeman et al.[47]	7–7.25 Gy in 5 fx	41	Low	60	< 1%	None	93% 5-year actuarial
Bolzicco et al.[42]	35 Gy in 5 fx	100	Low, int and high	36	None	None	96%
McBride et al.[51]	36.25–37.5 Gy in 5 fx	45	Low	44	< 1%	None	100%
Ju et al.[50]	35–36.25 Gy in 5 fx	41	Int	21	None	None	97.56%
Chen et al.[49]	35–36.25 Gy in 5 fx	100	Low, int and high	26	None	None	99%
Kang et al.[37]	32–36 Gy in 4 fx	44	Low, int and high	40	None	None	100%, 100%, 90.9%
Oliai et al.[48]	37.5 Gy vs. 35–36.25 Gy in 5 fractions	70	Low, int and high	27–37	4%	None	100%, 95%, 77.1% 3-years
King et al.[22]	36.25 Gy in 4–5 fractions	1100	Low, int and high	36	–	–	93% 5-years

FFBF: free from biochemical failure; int.: intermediate; GU: genitourinary; GI: gastrointestinal.

with a minimum of 5 years of follow-up, the 5-year BFF rate for low- and intermediate-risk patients was 99% and 93%, respectively.[22]

Despite the large use of the Cyberknife in the delivery of SBRT treatments for PC patients, several reports on the use of linear accelerators (LINAC) have been published.[52–57]

Madsen et al.[52] reported the clinical experience on 40 prostate cancer patients treated with 33.5 Gy in 5 fractions. With a median follow-up of 41 months, the 4-year BFF was 90%. Acute grade 3 GU toxicity was registered in 5% of cases, while no grade 3 late toxicity was reported.

Boike et al.[53] enrolled 45 patients in a multi-institutional prospective dose-escalation study to evaluate the maximum-tolerated dose (MTD) of five fractions of SBRT: groups of 15 patients received 45 Gy, 47.5 Gy, and 50 Gy in five fractions. The overall incidence of G3+ GI and GU toxicities were 2 and 4%, respectively. The authors concluded that dose escalation to 50 Gy was feasible and the MTD was not reached.

Alongi et al.[54] reported a prospective phase I–II study evaluating the feasibility and early side effects of a short course hypo-fractionated SBRT delivered with volumetric modulated arc therapy (VMAT) and flattening filter free (FFF) beams. After a median follow-up of 11 months, 40 patients were enrolled: no acute G3 (or higher) toxicity was recorded. Moreover, a good patient-reported QOL perception was reported for the first year after treatment.[55]

Loblaw et al.[56] conducted a phase I-II study to report the efficacy and the safety outcomes of patients with a low risk PC treated once weekly with SBRT (35 Gy in 5 fractions), delivered with a standard LINAC. Authors reported acute grade ≥3 GI and GU toxicity of 0% and 1%, respectively, and late grade ≥3 GI and GU toxicity of 1% for both. Post-treatment biopsies were negative in 96% of the patients and the 5-year BFF was 98%.

Table 1 reported the available data on SBRT for PC.

Up to now, no significant clinical or dosimetric differences have been showed in the published studies, and no comparative studies have been performed. Finally, none of these techniques of irradiation could be considered superior over the other and the choice could be made in the single radiotherapy department, taking into account local availability of the machines, their intrinsic planning and delivery time (shorter for techniques other than Cyberknife) and local medical and physics expertise.[57]

5. Conclusion

Recent technological developments, combined with an improved knowledge of radiobiological models in favor of a

high sensitivity of PC to larger fraction sizes are opening a new scenario in its treatment. Indeed, selected patients will probably benefit from the feasibility of high focused RT in one or few fractions with robust dose conformality and modulation, with a rapid dose fall off and delivered with higher accuracy. The old "*paradigm*" of the standard dose fractionation (35–40 sessions), assumed as the optimal compromise between efficacy and safety, is rapidly changing with the introduction of modern radiation techniques.[58] The combination of IGRT and IMRT/VMAT in the context of SBRT treatments allows the delivery of higher total biological equivalent doses and/or higher dose per fraction.

Although more mature results are needed, the available experiences with patients with more than 5 years of follow up seem to support this wide diffusion of SBRT in the treatment of well selected PC patients. The ongoing randomized clinical trials will add important clinical comparative data and allow a more precise definition of a better fractionation, efficacy and safety of SBRT in the treatment of PC patients (as, for example, in the trials NCT01737151, NCT01584258, NCT01764646, NCT01434290 available online at www.clinicaltrials.gov).

Conflict of interest

None declared.

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