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Tumour Review

Extreme hypofractionation for early prostate cancer: Biology meets technology

Berardino De Bari [a], Stefano Arcangeli [b], Delia Ciardo [c,*], Rosario Mazzola [d], Filippo Alongi [d], Elvio G. Russi [e], Riccardo Santoni [f], Stefano M. Magrini [g], Barbara A. Jereczek-Fossa [c,h], on the behalf of the Italian Association of Radiation Oncology (AIRO)

[a] Division of Radiation Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
[b] Division of Radiation Oncology, Azienda Ospedaliera S. Camillo-Forlanini, Rome, Italy
[c] Division of Radiation Oncology, European Institute of Oncology, Milan, Italy
[d] Division of Radiation Oncology, Sacro Cuore Don Calabria Cancer Care Center, Negrar-Verona, Italy
[e] S.C. di Radioterapia Oncologica, Azienda ospedaliera S. Croce e Carle, Cuneo, Italy
[f] Università di Roma, Tor Vergata, U.O.C. di Radioterapia, Policlinico Tor Vergata, Roma, Italy
[g] Istituto del Radio "O. Alberti", Spedali Civili, Università di Brescia, Brescia, Italy
[h] Department of Oncology and Hemato-oncology, University of Milan, Milan, Italy

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ABSTRACT

The aim of this review is to present the available radiobiological, technical and clinical data about extreme hypofractionation in primary prostate cancer radiotherapy. The interest in this technique is based on the favourable radiobiological characteristics of prostate cancer and supported by advantageous logistic aspects deriving from short overall treatment time. The clinical validity of short-term treatment schedule is proven by a body of non-randomised studies, using both isocentric (LINAC-based) or non-isocentric (CyberKnife®-based) stereotactic body irradiation techniques. Twenty clinical studies, each enrolling more than 40 patients for a total of 1874 treated patients, were revised in terms of technological setting, toxicity, outcome and quality of life assessment. The implemented strategies for the tracking of the prostate and the sparing of the rectal wall have been investigated with particular attention. The urinary toxicity after prostate stereotactic body irradiation seems slightly more pronounced as compared to rectal adverse events, and this is more evident for late occurring events, but no worse as respect to conventional fractionation schemes. As far as the rate of severe acute toxicity is concerned, in all the available studies the treatment was globally well tolerated. While awaiting long-term data on efficacy and toxicity, the analysed studies suggest that the outcome profile of this approach, alongside the patient convenience and reduced costs, is promising. Forty-eight ongoing clinical trials are also presented as a preview of the expectation from the near future.

Introduction

Prostate cancer (PC) is the most common male malignancy in the Western countries and the second most frequently diagnosed cancer among males worldwide [1,2]. Approximately 80% of men with newly diagnosed PC will have organ-confined disease. Evidence-based and scientifically approved conventional treatment options for prostate-confined cancer include radical prostatectomy, external beam radiotherapy (EBRT), brachytherapy (BT) and active surveillance [1,3]. Since head-to-head comparison of different options is not available, the choice is based on the tumour stage and characteristics, patient general conditions and preferences and the centre expertise [1,4,5]. Radiation therapy (RT) is

Abbreviations: AIRO, Italian Association of Radiation Oncology; BT, brachytherapy; bRFS, biochemical relapse free survival; CT, computed tomography; CTV, clinical target volume; ERB, endorectal balloon; EBRT, external beam radiotherapy; EPIC, expanded prostate cancer index composite; GU, genitourinary; HDR, high dose-rate; IGRT, image-guided radiotherapy; IMRT, intensity modulated radiotherapy; IPSS, International Prostatic Symptoms Score; kV, kilo-voltage; LINAC, linear accelerator; MRI, magnetic resonance imaging; MU, monitor unit; MV, mega-voltage; PC, prostate cancer; PTV, planning target volume; QoL, quality of life; RT, radiation therapy; SBRT, stereotactic body radiation therapy; USC, universal survival curve.

* Corresponding author at: Delia Ciardo, Division of Radiation Oncology, Istituto Europeo di Oncologia, via Ripamonti 435, 20141 Milano, Italy.
E-mail address: delia.ciardo@ieo.it (D. Ciardo).

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Table 3
Stereotactic body radiation therapy trials: definition of the Regions of Interest (ROIs).

Region of Interest (ROI)	Definition	Reference
CTV	Prostate	[Aluwini 2013] [Mcbride 2012] [King 2012][Loblaw 2013][Madsen 2007][a][Kim 2014] [Boike 2011][a]
	Prostate (LR PC); Prostate + SV (IR and HR PC)	[Kang 2011][Alongi 2013][a]
	Prostate + SV (1 cm) + 3 mm (1 mm posteriorly)	[Freeman 2011]
	Prostate + SV (1/3)	[Bolzicco 2013][Chen 2013]
	Prostate (LR PC); Prostate + SV (2 cm, IR and HR PC)	[Oliai 2013]
	Prostate + SV	[Arscott 2014]
	Prostate + 2 mm (0 mm posteriorly, LR PC) or + 5 mm (0 mm posteriorly, IR PC).	[Fuller 2014]
	Prostate + proximal SV	[Janowsky 2014][Ju 2013]
	Prostate + involved SV	[Lee 2014]
	Prostate (LR PC); Prostate + SV (1 cm, IR and HR PC)	[Tree 2014]
PTV	CTV + 3 mm	[Aluwini 2013] [Arscott 2014] [Boike 2011][a]
	CTV + 5 mm (3 mm posteriorly)	[Mcbride 2012][King 2012][Bolzicco 2013] [Chen 2013] [Janowsky 2014][Tree 2014][Katz 2014] [Ju 2013]
	CTV + 4 mm (2 mm posteriorly)	[Kang 2011]
	CTV + 2 mm	[Freeman 2011]
	CTV + 2.5 mm	[Lee 2014]
	CTV + 4 mm	[Loblaw 2013]
	CTV + 2–3 mm	[Kim 2014][a]
	CTV + 3–5 mm	[Alongi 2013][a]
Rectum	Anterior rectal wall + rectal mucosa	[Aluwini 2013]
	Solid organ from the anus to the sigmoid	[Madsen 2007][a]
	The rectal wall has been divided and separately contoured into anterior, lateral, and posterior walls in the region of the PTV	[Kim 2014][a] [Boike 2011][a]
	From recto-sigmoid flexure to anal verge	[Tree 2014]
Bladder	Constant bladder filling of 1000 cc (obtained using a Foley catether)	[Aluwini 2013]
	Outer 5 mm of the entire bladder contour	[Kim 2014][a] [Boike 2011][a]
	Solid organ from base to dome	[Tree 2014]
Urethra	Defined using Foley catheter	[Aluwini 2013] [Fuller 2014][Kim 2014]
	Indwelling catheter and/or urethrogram.	[McBride 2011] [Bolzicco 2013]
	MRI based delineation, without catheter	[Katz 2014]
Bowel	Space within the peritoneal cavity that could contain bowel	[Tree 2014]

The description of the definition of femoral heads, penile bulb, sigmoid/bowel is never detailed in the analysed articles, even in those generally declaring that these ROIs had been contoured.
In the study by Boike et al. [68] an endorectal balloon was used.
Abbreviations: HR = high risk; IR = intermediate risk; LR = low risk; PC = prostate cancer; SV = seminal vesicles.
[a] LINAC based treatment, with or without non-coplanar fields.

Table 4
Constraints adopted in the available studies on prostate stereotactic body radiation therapy.

Region of Interest (ROI)	Constraints	Reference Author Year [Reference]
PTV	$V_{100\%} \geqslant 95\%$; $D_{max} < 150\%$	Aluwini 2013 [77]
	$V_{100\%} \geqslant 95\%$ (prescribed at the isodose of 70–90%)	McBride 2012 [73]
	$V_{100\%} \geqslant 95\%$ (prescribed at the isodose of 77–80%)	Kang 2011 [75], Bolzicco 2013 [78]
	$V_{100\%} \geqslant 95\%$ (prescribed at the isodose of 88–92%)	Freeman 2011 [74], King 2012 [76]
	$V_{100\%} \geqslant 95\%$ (prescribed at the isodose of $\geqslant 75\%$)	Chen 2013 [79], Arscott 2014 [82], Janowsky 2014[84]
	$V_{100\%} \geqslant 95\%$ (prescribed at the isodose of 75–85%)	Oliai 2013 [81]
	$D_{100\%} \geqslant 90\%$	Madsen 2007[a] [87]
	$V_{100\%} \geqslant 95\%$; $D_{max} \leqslant 150\%$	Fuller 2014 [72]
	$V_{100\%} > 95\%$	Lee 2014 [85]
	$V_{95\%} > 99\%$; $D_{max} < 105\%$	Loblaw 2013 [47]
	$V_{100\%} > 95\%$	Kim 2014 [89], Boike 2011[a] [69]
	$V_{95\%} > 95\%$	Alongi 2013[a] [88]
	$V_{100\%} \geqslant 95\%$ (prescribed at the isodose of 83–87%)	Katz 2014 [83]
	$V_{95\%} > 95\%$ (prescribed at the isodose of 91–94%)	Ju 2013 [80]
Rectum	$D_{max} \leqslant 38$ Gy (anterior rectal wall); $D_{1cm3} \leqslant 32.5$ Gy (85% of the PD)	Aluwini 2013 [77]
	$V_{36Gy} < 1$ cm^3	McBride 2012 [73], Oliai 2013 [81]
	ALARA; $D_{max} \leqslant 100\%$; $D_{50\%} \leqslant 50\%$	Kang 2011 [75]
	$V_{50\%} \leqslant 50\%$; $V_{80\%} \leqslant 20\%$; $V_{90\%} \leqslant 10\%$; $V_{100\%} \leqslant 5\%$; $V_{36Gy} \leqslant 1$ cm^3.	Freeman 2011 [74]
	$V_{50\%} \leqslant 50\%$; $V_{80\%} \leqslant 20\%$; $V_{90\%} \leqslant 10\%$; $V_{100\%} \leqslant 5\%$.	King 2012 [76]
	$D_{5\%} \leqslant 38$ Gy (mean 50 cm^3)	Bolzicco 2013 [78]
	$V_{50\%} < 50\%$; $V_{75\%} < 25\%$; $V_{80\%} < 20\%$; $V_{90\%} < 10\%$; $V_{100\%} < 5\%$; $V_{36Gy} < 1$ cm^3	Chen 2013 [79], Janowsky 2014 [84]
	$V_{50\%} < 50\%$; $V_{80\%} < 20\%$; $V_{90\%} < 10\%$; $V_{100\%} < 5\%$	Katz 2014 [83]
	$V_{36Gy} < 1$ cm^3; Posterior wall: $D_{max} \leqslant 50\%$	Oliai 2013 [81]
	ALARA	Madsen 2007[a] [87]
	$D_{max} \leqslant 100\%$; Rectal mucosa[b]: $D_{max} \leqslant 75\%$	Fuller 2014 [72]
	$D_{50\%} < 50\%$; $D_{100\%} < 5\%$	Lee 2014 [85]
	$V_{28Gy} \leqslant 40\%$; $V_{32Gy} \leqslant 33\%$	Loblaw 2013 [47]
	Anterior wall: $D_{max} \leqslant 105\%$; Lateral walls: $D_{3cm3} \leqslant 90\%$; Posterior wall: $D_{max} \leqslant 45\%$.	Kim 2014[a] [86], Boike 2011[a] [69]
	$D_{50\%} < 18.1$ Gy; $D_{20\%} < 29$ Gy; $D_{10\%} < 32.6$ Gy; $D_{5\%} < 36.25$ Gy; $V_{36Gy} < 1$ cm^3	Tree 2014 [86]
	$V_{18Gy} < 35\%$; $V_{28Gy} < 10\%$; $V_{32Gy} < 5\%$; $D_{1\%} < 35$ Gy	Alongi 2013[a] [88]
Bladder	$D_{max} \leqslant 41.8$ Gy; $D_{1\ cm3} \leqslant 38$ Gy	Aluwini 2013 [77]
	$V_{37.5\ Gy} < 5$ cm^3	McBride 2012 [73],
	$V_{37\ Gy} < 5$ cm^3; $V_{100\%} < 10\%$; $V_{50\%} < 40\%$	Chen 2013 [79], Janowsky 2014 [84]
	$D_{10\ cm3} \leqslant 37$ Gy	Oliai 2013 [81]
	ALARA	Kang 2011 [75]
	$V_{37\ Gy} \leqslant 10$ cm^3	Freeman 2011 [74]
	$V_{50\%} < 40\%$; $V_{100\%} < 10\%$	King 2012 [76], Chen 2013 [79], Katz 2014 [83]
	$D_{5\%} \leqslant 40$ Gy	Bolzicco 2013 [78]
	$D_{max} \leqslant 120\%$	Fuller 2014 [72]
	$V_{32\ Gy} \leqslant 40\%$	Loblaw 2013 [47]
	Outer 5-mm wall: $D_{max} < 105\%$; $D_{10\ cm3} \leqslant 18.3$ Gy	Kim 2014[a] [89], Boike 2011[a] [69]
	$D_{40\%} < 18.1$ Gy; $D_{10\%} < 36.25$ Gy; $V_{37\ Gy} < 10$ cm^3	Tree 2014 [86]
	$D_{1\%} < 35$ Gy.	Alongi 2013[a] [88]
Urethra	$D_{5\%} \leqslant 45.5$ Gy; $D_{10\%} \leqslant 42$ Gy; $D_{50\%} \leqslant 40$ Gy; $D_{max} \leqslant 45.6$ Gy.	Aluwini 2013 [77]
	$V_{49\ Gy} < 10\%$	McBride 2012 [73]
	$D_{5\%\ or\ 2\ cm3} \leqslant 40$ Gy	Bolzicco 2013 [78]
	$V_{37\ Gy} < 50\%$	Arscott 2014[c] [82], Chen 2013 [79]
	$D_{max} \leqslant 133\%$	Janowsky 2014 [84]
	$D_{max} \leqslant 120\%$	Fuller 2014 [72]
	$D_{max} \leqslant 105\%$	Kim 2014[a] [89], Boike 2011[a] [69]
	ALARA	Alongi 2013[a] [88]
	No urethral constraint	Katz 2014 [83]
Femoral Heads	$D_{max} \leqslant 24$ Gy	Aluwini 2013 [77]
	$V_{40\%} < 5\%$	King 2012 [76], Katz 2014 [83]
	$D_{25\%} \leqslant 25$ Gy	Bolzicco 2013 [78]
	$V_{14.5\ Gy} < 5\%$	Tree 2014 [86]
	ALARA	Alongi 2013[a] [88]
Bowel/Sigmoid	$D_{max} \leqslant 28.5$ Gy	Aluwini 2013 [77]
	$V_{30\ Gy} < 1$ cm^3	Chen 2013 [79], Janowsky 2014 [84]
	$V_{18.1\ Gy} < 5$ cm^3	Tree 2014 [86]
	ALARA	Alongi 2013[a] [88]

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Table 4 (*continued*)

Region of Interest (ROI)	Constraints	Reference Author Year [Reference]
Penile Bulb	$V_{29.5\ Gy} < 50\%$	McBride 2012 [73], Chen 2013 [79], Janowsky 2014 [84]
	$D_{25\%} \leqslant 29$ Gy;	Bolzicco 2013 [78]
	$V_{20\ Gy} \leqslant 90\%$	Loblaw 2013 [47]
	$V_{29.5\ Gy} < 50\%$	Tree 2014 [86]
	ALARA	Alongi 2013[a] [88]
Testes	$D_{20\%} < 2$ Gy	Chen 2013 [79], Janowsky 2014 [84]

In the study by Boike et al. [69] an endorectal balloon was used.
In the study by Alongi et al. [88] a spacer was injected before SBRT in some selected cases.
Abbreviations: ALARA = as low as reasonably achievable; P*D* = prescribed dose.
$D_{X\%} \leqslant Y\%$: The dose received by the *X*% of volume is $\leqslant$ of the *Y*% of the prescription dose.
$D_{X\%} \leqslant Y$ Gy: The dose received by the *X*% of volume is $\leqslant$ of *Y* Gy.
$DX\ cm^3 \leqslant Y\%$: The dose received by the *X* cm^3 of volume is $\leqslant$ of the *Y*% of the prescription dose.
$DX\ cm^3 \leqslant Y$ Gy: The dose received by *X* cm^3 of volume is $\leqslant$ of *Y* Gy.
D_{max}: maximum dose.
$V_{X\%} \leqslant Y\%$: The *X*% of the prescription dose is received by $\leqslant$ of the *Y*% of the volume.
$V_{X\%} \leqslant Y\ cm^3$: The *X*% of the prescription dose is received by $\leqslant$ of *Y* cm^3 of volume.
$V_{X\ Gy} \leqslant Y\%$: The dose of *X* Gy is delivered to $\leqslant$ of the *Y*% of the volume.
$V_{X\ Gy} \leqslant Y\ cm^3$: The dose of *X* Gy is delivered to $\leqslant$ of *Y* cm^3 of volume.

[a] LINAC based treatment, non-coplanar fields.
[b] The rectal mucosa was defined as a solid structure formed by a 3-mm contraction of the rectal wall.
[c] This constraint was applied to the membranous urethra, while no constraints were applied on the prostatic urethra.