Rectal/urinary toxicity after hypofractionated vs conventional radiotherapy in low/intermediate risk localized prostate cancer: systematic review and meta analysis

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ABSTRACT

Purpose: The aim of this review was to compare radiation toxicity in Localized Prostate Cancer (LPC) patients who underwent conventional fractionation (CV), hypofractionated (HYPO) or extreme hypofractionated (eHYPO) radiotherapy. We analyzed the impact of technological innovation on the management of prostate cancer, attempting to make a meta-analysis of randomized trials.

Methods: PubMed database has been explored for studies concerning acute and late urinary/gastrointestinal toxicity in low/intermediate risk LPC patients after receiving radiotherapy. Studies were then gathered into 5 groups: detected acute and chronic toxicity data from phase II non randomized trials were analyzed and Odds Ratio (OR) was calculated by comparing the number of patients with G0-1 toxicity and those with toxicity > G2 in the studied groups. A meta-analysis of prospective randomized trials was also carried out.

Results: The initial search yielded 575 results, but only 32 manuscripts met all eligibility requirements: in terms of radiation-induced side effects, such as gastrointestinal and genitourinary acute and late toxicity, hypofractionated 3DCRT seemed to be more advantageous than 3DCRT with conventional fractionation as well as IMRT with conventional fractionation compared to 3DCRT with conventional fractionation; furthermore, IMRT hypofractionated technique appeared more advantageous than IMRT with conventional fractionation in late toxicities. Randomized trials meta-analysis disclosed an advantage in terms of acute gastrointestinal and late genitourinary toxicity for Hypofractionated schemes.

Conclusions: Although our analysis pointed out a more favorable toxicity profile in terms of gastrointestinal acute side effects of conventional radiotherapy schemes compared to hypofractionated ones, prospective randomized trials are needed to better understand the real incidence of rectal and urinary toxicity in patients receiving radiotherapy for localized prostate cancer.

INTRODUCTION

Prostate cancer is one of the most frequent tumors affecting men in the world: external beam radiotherapy (EBRT) is a standard treatment modality for localized and locally advanced prostate cancer [1, 2].

Modern technologies, predictive biomarkers of response to a given therapy, potential new targets for biological therapy and advanced knowledge of radiobiology have changed the approach to prostate cancer radiotherapy [3-5].

Many publications suggest that prostate cancer has a low α/β ratio (ratio between "intrinsic radiosensitivity" and "reparative capacity"), compare to healthy tissues [1,2,6] with notable therapeutic implications [6-8]. In the treatment of prostate cancer, we can't disregard that organs at risk (OARs), as rectum or bladder, have an estimated α/β ratio of 3-5 Gy for late toxic effects and 10 Gy for acute toxicity, whereby prostate cancer cells are more responsive to a larger fraction size, with a clear therapeutic gain [9].

Five large randomized trials demonstrated that increasing the dose to 74-80 Gray (Gy), fractionated in standard 1.8-2 Gy, results in an improved biochemical recurrence-free and disease free survival [10-14]. Treatments planned with dose escalation and hypofractionation have been made possible thanks to the evolution of radiation therapy techniques. Further advances in radiation delivery techniques, such as intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT), led to a greater sparing of adjacent normal tissue and consequent reduced toxicity. Significant reduction of margins around the prostate, and thus irradiated normal tissue volume, has been achieved by the use of daily cone-beam computed tomography imaging prior to each treatment delivery [15].

Radiation techniques for localized prostate cancer involve both external beam radiation and brachytherapy. External beam techniques include IMRT, VMAT and helical tomotherapy. Extremely hypofractionated (eHYPO) radiation regimens, consisting of 5 treatment sessions or less, have also been investigated. Current approach in prostate HYPO and eHYPO radiotherapy trials utilizes a simultaneous integrated boost (SIB) technique to deliver higher dose to dominant intraprostatic lesions, while still delivering an adequate lower dose to the whole prostate. Cyber-knife system (CK) makes use of fiducial markers, allowing to follow the target organ and reduce the irradiation volume.

A second dose escalation strategy involves proton therapy: protons are charged particles that deposit a higher proportion of energy toward the end of their travel path in a tissue and little to no energy beyond. A very steep dose gradient can be created to minimize dose spill into adjacent tissues, compared to photon therapy. At the moment, the little experience of large proton centers do not show superiority in disease control or toxicity for proton therapy compared to photon therapy [16-18].

Patient selection is fundamental for the choice of treatment, which must consider various aspects in order to define the risk class. Based on pre-treatment prognostic parameters, several systems have been proposed to stratify prostate cancer into differing risk groups. In 2010, the seventh edition of the AJCC (American Joint Committee on Cancer) Staging Manual [19] added Gleason score and PSA to the TNM staging system, making this stage grouping roughly comparable to D'Amico's and NCCN ones, with notable differences between intermediate- and high-risk groups. NCCN (National Comprehensive Cancer Network) also added "very low-risk" and "very high-risk" categories. Nearly 50% of patients diagnosed with prostate cancer fall in prognostic AJCC Stage I, which includes patients with a clinical stage of T1-T2a, PSA≤10 and Gleason ≤ 6 [20].

Aim of this review is to compare radiation toxicity data detected in conventional fractionation (CV), hypofractionated (HYPO) and extreme hypofractionated (eHYPO) studies, based on different techniques used.

RESULTS

Study selection

Search results are summarized in Figure 1. The initial search yielded 575 results. 363 publications were excluded (brachytherapy, only high risk, only methodology, advanced disease), which dropped down the initial number to 212. These articles were reviewed and 54 studies, which did not evaluate both acute and chronic toxicity genitourinary GU and gastrointestinal GI, were removed. 158 full-text articles were finally evaluated but further 126 studies were discarded because assessing after-surgery treatments, old techniques, retrospective studies or had few data. In total 32 manuscripts met all eligibility requirements and were included in this report.

Among the selected articles, three groups were obtained. Group I gathers 11 articles regarding 3DCRT treatments, including 5 with conventional fractionation (3 with EBRT, 2 with Protons), 4 articles with hypofractionated radiotherapy (1 randomized) and 2 articles concerning mixed techniques application (3DCRT and SBRT with Cyberknife system) (Table 1). The second group includes 11 studies of treatments with IMRT techniques (4 with conventional fractionation and 4 with hypofractionated, 3 randomized studies hypofractionated/conventional) (Table 2). The third group includes 10 studies of extreme hypofractionated treatment (4 used Linac, 6 Cyberknife system) (Table 3). Table 4 shows mean of the percentage for toxicity G2 and > G3 detected in the different study groups.

Table 1: Summary of trials on 3DCRT treatments with conventional and hypofractionated treatment

Author	Year (No. pt)	Type of Study	FU (median)	Risk groups (L/I/H) %	Technique	RT (Total dose/n.fz) (daily fz)	[EQ D2] (daily fz) a/b 1,5	ADT	Acute GU Toxicity %	Acute GI Toxicity %	Late GU Toxicity %	Late GI Toxicity %	Toxicity (Criteria)
Schmid et al	2012 (123)	Prospective phase II	74 M	L:35;I:34;H:30	3DCRT CV	70Gy/35 (2)	[70 Gy]	135(+) 43(-)	≥G2:22	≥G2:15	≥ G2:23	≥G2:19	EORTC RTOG
	(55)					74Gy/37(2)	[74 Gy]						
Michalsky et al	2005 (119)	Prospective Phase I-II	6M	L:54% I: 46%.	3DCRT CV	78 Gy/39 (2) prostate	[78Gy]	43(+) 176(-)	G0-G1:60;: G2:36; G3:4%	G0-G1:60;: G2:36; G3:4%	G1:25; G2:14; G3: 3	G1:20; G2:19; G3: 2	RTOG
	(100)					78 Gy/39 (2) Prostate+vs			G0-G1:53;: G2:45; G3:2%	G0-G1:53;: G2:45; G3:2%	G1:19; G2:20; G3: 4	G1:25; G2:17; G3: 3; G4:2	
Zietman et al	2010 (197)	Prospective randomized	105 M	70,2 Gy L:57;I:38;H:5	3DCRT +boost protoni CV	70.2-79,2 Gy 50.4Gy/ (1.8) Boost 19.8GyE/11(1.8)	[70.2 Gy]+[19.8Gy]	393(-)	G1:37;G2:51;G3:3	G1:39;G2:44;G3:1	G1:42;G2:22;G3:2	G1:35;G2:13	RTOG
	(197)			79,2Gy L:59;I:35;H:4		70.2-79,2 Gy 50.4Gy/ (1.8) Boost 28.8GyE/16 (1.8)	[79.2 Gy]+[28.8Gy]		G1:29;G2:60;G3:2;G4:1	G1:26;G2:63;G3:1	G1:45;G2:27;G3:2	G1:41;G2:24;G3:1	
Coen et al	2011 (85)	Prospective Phase II	31,6 M	L-I:100	Protoni CV	78-79 Gy/39-40(2)	[82 Gy]	85(-)	G1:51;G2:13;G3:1	G1:19;G2:1	G1:33;G2:26; G3:11;G4:2	G1:33;G2:26;G3:11;G4:2	EORTC RTOG
Nihei et al	2011 (151)	Prospective phase II	43,4 M	L:77; I:74	Protoni CV	L: 74Gy/37 (2) pros I: boost 24Gy pros after 50Gy prostate+vs	[74 Gy] [24 Gy] [50 Gy]	42(+) 109(-)	G1:58;G2:12	G1:10;G2:1	G1:6;G2:5;G3:1	G1:18;G2:3	CTC
White et al	2015 (90)	Prospective Phase II	36 M	L:11;I:38;H:50	3DCRT Hypo	57Gy/17 (3)	[73,3 Gy]	71(+) 19(-)	G1:58,6;G2:10;G3:1,1	G1:75,6	G1:47,3;G2:2,4	G1:40;G2:9,3;G3:4,7	CTCAE
Tramacere et al	2015 (97)	Prospective Phase II	39M	L:19;I:41;H:40	3DCRT Hypo	62Gy/20 (3,1)	[81,5Gy]	94(+)	G1:43;G2:21;G3:3	G1:18;G2:15	G1:11;G2:5;G3:3	G1:2;G2:10;G3:1	RTOG EORTC
Jereczek-Fossa et al	2013 (337)	Prospective	19 M	L:40.9;I:43.32;H :14.2	3DCRT Hypo/IGRT	70Gy/28 (2,5)	[74 Gy] [24 Gy] [50 Gy]	243(+) 94(-)	≥G2:35≥G3:6.2	≥G2:11.3;≥G3:1.2	≥G2:10.4;≥G3:1.6	≥G2:7.5;≥G3:1.3	RTOG
Lukka et al	2005 (470)	Prospecitve randomized	67 M	/	3DCRT CV	66Gy/33(2)	[66Gy]	/	G3-G4:4.9	G3-G4:2.6	G3-G4:1.9	G3-G4:1.3	NCIC
	(466)				3DCRT Hypo	52.5Gy/20(2.62)	[61.9Gy]		G3-G4:8.6	G3-G4:4.1	G3-G4:1.9	G3-G4:1.3	
						Mixed Techniques							
Pontoriero et al	2016 (26)	Retrospective	21,5 M	L:35;I:46;H:19	EBRT + CK(boost)	38Gy/4(9.5)vs 9,5Gy/2(4.75) + 46Gy/23(2)	[119.4 Gy] [17 Gy] [46 Gy]	16(+) 20(-)	G1:46;G2:4	G1:23;G2:8	G1:12;G2:4	G1:4	CTCAE
Katz et al	2010 (75)	Prospective	33 M	I:57;H:43	EBRT + CK(boost)	21Gy/7(3) boost 18-19,5/2(9-9.75)	[27 Gy] [54 Gy] [62.7 Gy]	36(+) 39(-)	G1:83,6;G2:6,8	G1:78,1;G2:6,7	G1:5,5;G2:4,1;G3:1,4	G1:5,5;G2:8,2	RTOG

Risk classes, technique used, total dose, type of fractionation, equivalent dose, acute and late gastrointestinal and genitourinary toxicity. Abbreviations: FU (Follow up); Risk groups: L (Low), I (Intermediate), H (High); CV (conventional); Hypo (Hypofractionated); EQ (Equivalent Dose); CK (Cyberknife); EBRT (External Beam Radiation Therapy); IGRT (Image Guided Radiotherapy); GU (Genitourinary); GI (Gastrointestinal); ADT (androgen deprivation therapy).

Table 2: Summary of trials on treatment with IMRT technique

Author	Year (No. pt)	Type of Study	FU (median)	Risk groups (L/I/H) %	Tecnique	RT (Total dose/n.fz) (daily fz)	[EQ D2] a/b 1,5	ADT	Acute GU Toxicity %	Acute GI Toxicity %	Late GU Toxicity %	Late GI Toxicity %	Toxicity (Criteria)
Fang et al	2015 (213)	Prospective	24 M	L:53;I:37;H:7,4	IMRT CV	79,2Gy/44(1.8)	[74,7Gy]	IMRT 66 (-);27(+)	[IMRT] G0-G1:71,3; G2-G3:28,7	[IMRT] G0/G1:86,2;G2/G3:13,8	[IMRT] ≥ G2:18,3	[IMRT] ≥ G2:10,8	CTCAE
	(181)				PBT CV			PBT 79 (-);15(+)	[PBT] G0-G1:78,7;G2-G3:21,3	[PBT] G0-G1:95,7;G2-G3:4,3	[PBT] ≥G2:12,8	[PBT] ≥G2:12,8	
Goineau et al	2013 (38)	Prospective	54 M	L:18;I:60;H:32	IMRT CV	76Gy/38(2)	[76Gy]	23(+) 15(-)	G1:36,8;G2:5,3;G3:2,6	G1:23,7;G2:5,3 G30	G1:34,2;G2:5,3;G3:5,3	G1:23,7;G2:15,8	CTCAE
Marchand et al	2010 (55)	Prospective	18 M	L:18; I:60,2; H:21,8	IMRT CV	76Gy/38(2)	[76Gy]	25(+) 30(-)	G2:38;G3:2	G2:13	G2:15	G2:11	CTCAE
Petrongari et al	2013 (39)	Prospective phase II	71 M	I:100	IMRT CV	86Gy/43(2)	[86Gy]	39(-)	G2:51	G2:44	G2:5;G3:8	G2:18;G3-G4:2,5%	CTCAE
Wu et al	2012 (73)	Prospective phase II	54 M	L:25;I:75	Hypo-IMRT IGRT (fiducials)	55 Gy/16(3.43)	[77.6Gy]	11(+) 62(-)	G2:41;G3:3	G2:34;G3:4	G2:8	G2:8	RTOG
Zilli et al	2011 (82)	Prospective randomized phase III	48 M	L:28; I:44;H:28	Hypo-IMRT	54Gy/14 (3.85)	[82.7Gy]	11(+) 71 (-)	G1:22;G2:4	G1:8;G2:4	G1:9;G2:5	G1:13;G2:3	RTOG
Lock et al	2011 (66)	Prospective phase II	36 M	L:27;I:36; H:1	Hypo-IMRT VMAT	63,2Gy/20(3.16)	[84.1Gy]	6(+) 60(-)	G1:51,5;G2:33,8;G3:8,8	G1:42,4;G2:25;G3:10,3; G4:1,5	G1:54,7;G2:14,1; G3:4,7	G1:39,1;G2:25;G3:3,1; G4:1,6 .	CTCAE
Martin et al	2007 (92)	Prospective phase II	38 M	L:29;I:56; H:7	Hypo-IMRT	60Gy/20(3)	[77.1Gy]	8(+) 84(-)	G1:43;G2:25;G3:0	G1:22;G2:11;G3:1	G1:7;G2:3;G3:0	G1:2;G2:4;G3:0	RTOG
						Randomized Studies for Meta-Analysis							
Dearnaley et al	2016 (1065)	Prospective randomized phase III	62.4 M	L:15;I:73; H:12	IMRT CV	74Gy/37(2)	[74Gy]	239(+)	G≥2:46	G≥2:25	G2:9.1; G≥3:<1	G2:13.7; G≥3:0	RTOG/ LENT
	(1077)				Hypo-IMRT	57Gy/19(3)	[73.3Gy]		G≥2:46	G≥2:38	G2:6.6; G≥3:1	G2:11.3; G≥3:<1	
	(1074)				Hypo-IMRT	60Gy/20(3)	[77.1Gy]		G≥2:49	G≥2:38	G2:11.7; G≥3:<1	G2:13.7; G≥3:<1	
Pollack et al	2006 (50)	Prospective randomized	3 M	I:65; H:35	IMRT CV	76Gy/38(2)	[76Gy]	44(+) 56(-)	G1:28;G2:54;G3:0	G1:40;G2:8;G3:0	G1:31;G2:8;G3:0	G1:12;G2:2;G3:0	RTOG/ LENT
	(50)				Hypo-IMRT	70.2Gy/26(2.7)	[84.2Gy]		G1:44;G2:40;G3:8	G1:40;G2:18;G3:0	G1:30;G2:6;G3:0	G1:16;G2:0;G3:0	
Pollack et al	2013 (153)	Prospective randomized	68.4 M	L-I:50;H:50	IMRT CV	76Gy/38(2)	[76Gy]	139(+)	G≥2:5.2	G≥2:22.5	G≥2:14.6	G1:58,9;G2:20.5;G3:2	RTOG
	(154)				Hypo-IMRT	70.2Gy/26(2.7)	[84.2Gy]		G≥2:10.6	G≥2:18	G≥2:15.3	G1:53.7;G2:16.1;G3:2	

Risk classes, technique used, total dose, type of fractionation, equivalent dose, acute and late gastrointestinal and genitourinary toxicity. Abbreviations: FU (Follow up); Risk groups: L (Low), I (Intermediate), H (High); CV (conventional); Hypo (Hypofractionated); IMRT (Intensity Modulated Radiation Therapy); PBT (Proton Beam Therapy); EQ (Equivalent Dose); CK (Cyberknife); EBRT (External Beam Radiation Therapy); IGRT (Image Guided Radiotherapy); GU (Genitourinary); GI (Gastrointestinal); ADT (androgen deprivation therapy).

At a first analysis, the mean percentage of acute urinary and gastrointestinal G2 toxicity decreased in Hypo-3DCRT versus CV 3DCRT (22 and 13% vs 43% and 41% respectively), and in Hypo-IMRT versus CV 3DCRT (31 and 23% vs 43% and 41% respectively). There was an even greater reduction in eHYPO, especially with the Cyberknife system (10 and 11%). A reduction was also observed in the mean percentage of late urinary and gastrointestinal G2 and > G3 toxicity, in HYPO versus CV 3DCRT (6 and 9% vs 21 and 18% respectively), and with IMRT technique vs CV-3DCRT (9 and 12% vs 21 and 18% respectively). Even in SBRT treatment, there was a reduction of late urinary toxicity (6%) and late gastrointestinal toxicity (5%). Studies evaluating 3DCRT + CK showed a lower urinary and rectal toxicity. G3 toxicity presented values between 2-7% and wasn't reported in all

Table 3: Summary of trials on extreme hypofractionated Stereotactic Body Radiation Therapy (SBRT) treatment

Author	Year (No.pt)	Type of Study	FU (median)	Risk groups (L/I/H)%	SBRT	RT(total dose/n.f) (daily Fx)	[EQ D2] a/b 1,5	ADT	Acute GU Toxicity %	Acute GI Toxicity %	Late GU Toxicity %	Late GI Toxicity %	Toxicity (Criteria)
Rucinska et al.	2016 (68)	Prospective	24 M	L:10;I:90	Linac	33,5/5 (6,7)	[78,5Gy]	16(-) 52(+)	G1:32,3;G2:35,3;G3:1,5	G1:26,5;G2:10,3	G1:41,2;G2:11,8	G1:17,6;G2:4,4	RTOG/EORTC
Loblaw et al.	2013 (84)	Prospective phase I/II	55 M	L:100	Linac	35Gy/5(7) weekly	[85.0Gy]	1(+)	G1:71;G2:19;G3:1	G1:67; G2:10; G3:1	G1:2;G2:5	G1:35; G2:7; G4:1	CTCAE/RTOG
Madsen et al.	2007 (40)	Prospective phase I/II	41 M	L:40	Linac	33,5Gy/5(6,7)	[78,5Gy]	/	G1:28;G2:20,5;G3:3	G1:26;G2:13	G1:25;G2:20	G1:30;G2:7,5	CTC
Boike et al	2011 (48)	Prospective	30 M	L:20 I:80	Linac	45Gy/5(9)	[135Gy]	(+)27% (-)73%	G1:20; G2:27	G1:40;G2:0	G1:20; G2:13; G3:	G1:7; G2:7; G4:0	CTCAE
				L:53 I:47		47,5Gy/5(9.5)	[149.3Gy]	(+)13% (-)87%	G1:33;G2:7	G1:13; G2:27	G1:20; G2:13; G3:7	G1:27; G2:7; G4:0	
				L:47 I: 53		50Gy/5(10)	[164.3Gy]	(+)27% (-)73%	G1:33;G233	G1:47; G2:47	G1: 0; G2: 0; G3: 7	G1:33; G2:0;G4:7	
Fuller et al.	2014 (79)	Prospective phase II	72 M	L:51;I:49	CK	38Gy/4 (9.5)	[119,4Gy]	(-)	G2:10	G1:0;G2:0	G2:9;G3:6	G2:1	CTCAE
Bolzicco et al.	2013 (100)	Prospective	36 M	L:41;I:42; H:17	CK	35Gy/5(7)	[85.0Gy]	29(+)	G1:34; G2:12	G1:27; G2:18	G1:4;G2:3	G1:2;G2:1	RTOG
Katz et al.	2013 (50)	Prospective	60 M	L:69; I:27; H:4	CK	35Gy/5(7)	[85.0Gy]	57(+)	G1:72;G2:4	G1:76;G2:4	G2:4	G2:2	RTOG
	(254)					36,25Gy/5(7,25)	[90,6Gy]		G1:74,8;G2:4,7	G1:74,4;G2:3,5	G2:9;G3:2	G2:5	
King et al.	2012 (67)	Prospective phase II	31 M	L:100	CK	36,25Gy/5(7.25)	[90,6Gy]	67(-)	G1:23;G2:5;G3:3	G1:12,5;G2:3-0,2	G1:23; G2:5;G3:3,5	G1:14;G2:2	RTOG
Bolzicco et al.	2010 (45)	Prospective	20 M	L:49;I:51	CK	35Gy/5(7)	[85.0Gy]	17(+)	G1:35,5;G2:11,1	G1:24,4;G24,4	G1:8,8;G3:2,2	G2:2,2	RTOG
King et al.	2009 (41)	Prospective phaseII	33 M	L:100	CK	36,25Gy/5(7.25)	[90,6Gy]	(-)	G1:41;G2:24;G3:5	G1:33;G2:15	G1:14;G2:7;G3:3	G1:28;G2:19; G3:7	RTOG

Risk classes, technique used, total dose, type of fractionation, equivalent dose, acute and late gastrointestinal and genitourinary toxicity. Abbreviations: FU (Follow up); Risk groups: L (Low), I (Intermediate), H (High); EQ (Equivalent Dose); CK (Cyberknife); SBRT (Stereotactic Body Radiation Therapy); GU (Genitourinary); GI (Gastrointestinal); ADT (androgen deprivation therapy).

Table 4: Mean of percentage of toxicity G2 and > G3 in different type of studies

	Acute Toxicity G2		Late Toxicity G2		Acute Toxicity G3		Late Toxicity G3	
	GU	GI	GU	GI	GU	GI	GU	GI
IMRT-Hypo (8 studies)	31%	23%	9%	12%	7%	4%	3%	2%
IMRT-CV (7 studies)	31%	17%	11%	13%	2%	/	7%	2%
3DCRT-Hypo (4 studies)	22%	13%	6%	9%	5%	3%	2%	2%
3DCRT-CV (3 studies)	43%	41%	21%	18%	3%	2%	3%	2%
PBT-CV (2 studies)	13%	1%	16%	15%	/	/	6%	/
SBRT-Linac (4 studies)	24%	16%	13%	7%	2%	/	7%	/
SBRT-CK (6 studies)	10%	11%	6%	5%	4%	/	3%	/
3DCRT + CK (2 studies)	6%	7%	4%	/	/	/	/	/

Abbreviations: CV (conventional); Hypo (Hypofractionated); IMRT (Intensity Modulated Radiation Therapy); SBRT (Stereotactic Body Radiation Therapy); PBT (Proton Beam Therapy); CK (Cyberknife); GU (Genitourinary); GI (Gastrointestinal).

Table 5: Number of patients with acute or late genitourinary and gastrointestinal toxicity G0-G1 and > G2.

	Groups of Studies	N. total of pz	Acute GU Toxicity		Acute GI Toxicity		Late GU Toxicity		Late GI Toxicity	
			G0-1	>G2	G0-1	>G2	G0-1	>G2	G0-1	>G2
1	IMRT Hypo	*2668*	1519	1148	1747	921	2402	266	2340	328
2	IMRT CV	*1794*	1123	671	1426	369	1591	202	1542	252
3	3DCRT Hypo	*990*	693	213	916	74	932	60	904	59
4	3DCRT CV	*1261*	805	388	1043	351	1062	199	1100	161
5	SBRT	*873*	682	124	798	73	791	82	827	45

Abbreviations: Hypo (Hypofractionated); IMRT (Intensity Modulated Radiation Therapy); SBRT (Stereotactic Body Radiation Therapy); GU (Genitourinary); GI (Gastrointestinal).

studies, preventing us to perform an appropriate analysis. Table 5 shows patients with acute/late genitourinary and gastrointestinal toxicity G0-G1 and > G2 for each study group.

In Table 6 we summarized Odds Ratio (OR) results derived by comparing patients grouped according to different technology and fractionation schemes:

From the analysis of OR values, it has been possible to postulated that:

The comparison between IMRT Hypo *vs* IMRT CV showed a not statistically significant lower risk in terms of G2 or worse late GU (*OR 0,87; p = 0,1661*) and GI toxicity (*OR 0.86; p = 0,0878*) for Hypo Group; on the other hand, HYPO Group seemed to be more exposed to G2 or worse acute GU (*OR 1.26 ; p = 0,0002*) and GI toxicity (*OR 2.04 ; p < 0,001*) than the conventional fractionation counterpart.

3DCRT Hypo showed a better safety profile for each anatomical district, both in early and late toxicity, than the traditional fractionation scheme.

3DCRT CV treated patients compared to IMRT CV counterparts seemed to be affected by a worse toxicity profile in terms of acute GI (*OR 0.77; p = 0.0020*) and late GU side effects(*OR 0.67; p = 0.0001*), while having

Table 6: Values of Odds Ratio (OR) of toxicity > G2 and G0-1 in the compared different groups of study

Comparison of the groups		OR (95%CI)	p
1 vs 2 (IMRT Hypo vs IMRT CV)	Acute GU	**1.26** (1.12-1.43)	0.0002
	Acute GI	**2.04** (1.77-2.34)	0.0000
	Late GU	**0.87** (0.72-1.06)	0.1661
	Late GI	**0.86**(0.72-1.02)	0.0878
3 vs 4 (3DCRT Hypo vs 3DCRT CV)	Acute GU	**0.64**(0.52-0.78)	0.0000
	Acute GI	**0.24**(0.18-0.31)	0.0000
	Late GU	**0.34**(0.25-0.46)	0.0000
	Late GI	**0.45**(0.33-0.61)	0.0000
2 vs 4 (IMRT CV vs 3DCRT CV)	Acute GU	**1.24** (1.06-1.45)	0.0063
	Acute GI	**0.77** (0.65-0.91)	0.0020
	Late GU	**0.67** (0.54-0.82)	0.0001
	Late GI	**1.12** (0.90-1.38)	0.3087
1 vs 3 (IMRT Hypo vs 3DCRT Hypo)	Acute GU	**2.46**(2.07-2.92)	0.0000
	Acute GI	**6.53**(5.08-8.38)	0.0000
	Late GU	**1.72**(1.29-2.30)	0.0002
	Late GI	**2.15**(1.61-2.86)	0.0000
5 vs 1 (SBRT vs IMRT Hypo)	Acute GU	**0.24** (0.20-0.30)	0.0000
	Acute GI	**0.17** (0.13-0.22)	0.0000
	Late GU	**0.94** (0.72-1.21)	0.6190
	Late GI	**0.39** (0.28-0.54)	0.0000

Abbreviations: CV (conventional); Hypo (Hypofractionated); IMRT (Intensity Modulated Radiation Therapy); SBRT (Stereotactic Body Radiation Therapy); GU (Genitourinary); GI (Gastrointestinal); *p* (*p*-value).

a lower frequency of acute GU toxicity *(OR 1,24; p = 0,0063)*; no statistically significant difference was found for late GI toxicity.

IMRT Hypo showed an overall worse toxicity profile than the hypofractionated 3DCRT, with a 6,5 times higher frequency of acute GI side effects *(p < 0,001)*.
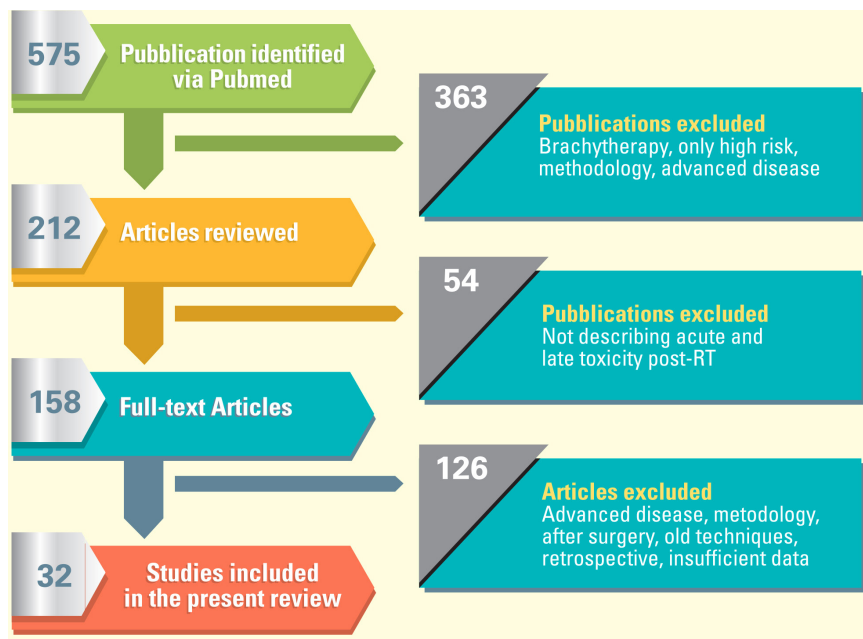
Figure 1: Analysis flow-chart of published literature evaluating the acute and late genitourinary and gastrointestinal toxicity following prostate radiation therapy. The initial search yielded 575 results, but only 32 manuscripts met all eligibility requirements and were included in this report.
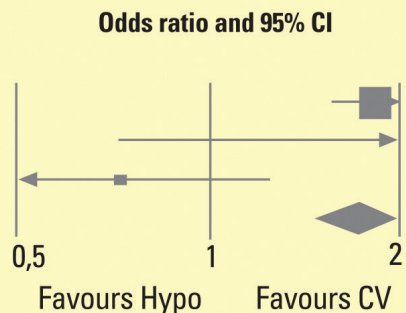
Study name	Statistics for each study				Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	p-Value	
Dearnaley et al 2016	1,060	0,915	1,228	0,436	
Pollack et al 2006	0,725	0,330	1,594	0,424	
Pollack et al 2013	2,249	0,940	5,380	0,069	
	1,068	0,926	1,232	0,364	

Acute Genitourinary Toxicity
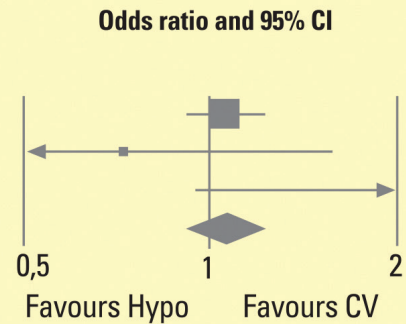
Study name	Statistics for each study				Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	p-Value	
Dearnaley et al 2016	1,840	1,562	2,167	0,000	
Pollack et al 2006	2,524	0,723	8,818	0,147	
Pollack et al 2013	0,722	0,415	1,257	0,250	
	1,717	1,469	2,007	0,000	

Acute Gastrointestinal Toxicity

Study name	Statistics for each study				Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	p-Value	
Dearnaley et al 2016	1,035	0,802	1,336	0,793	
Pollack et al 2006	0,734	0,156	3,462	0,696	
Pollack et al 2013	0,992	0,530	1,857	0,981	
	1,021	0,808	1,289	0,863	

Late Genitourinary Toxicity
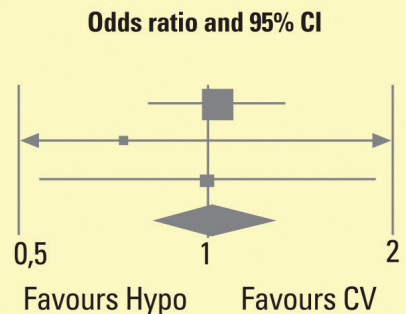
Study name	Statistics for each study				Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	p-Value	
Dearnaley et al 2016	0,890	0,718	1,103	0,287	
Pollack et al 2006	0,327	0,013	8,215	0,497	
Pollack et al 2013	0,749	0,429	1,307	0,309	
	0,867	0,710	1,059	0,162	

Late Gastrointestinal Toxicity

Each panel shows a forest plot with axis labels 0,5 — 1 — 2, "Favours Hypo" and "Favours CV".
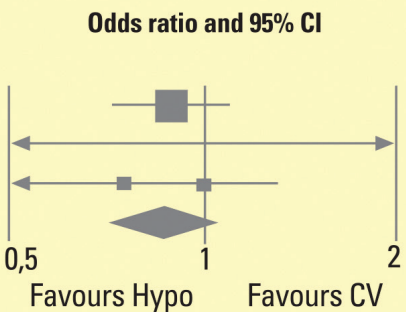
Figure 2: Meta-analysis of three randomized trials, which compare toxicities of patients treated with HYPO scheme with those treated with conventional fractionation. Patients who underwent hypofractionated radiotherapy schemes suffered from GI acute toxicity to the extent of near 71% more than CV-treated counterparts (p-value < 0,001; Confidence Interval: 1,469- 2,007): conversely, Hypo-IMRT treated patients experienced less late gastrointestinal toxicity to the extent of 13 % than CV treated patients, without reaching statistical significance (OR 0,867 ; p = 0,162).

Patients who underwent Stereotactic Radiotherapy (SBRT) have been affected to a lesser extent by acute GI and late gastrointestinal toxicity compared to patients treated with IMRT Hypo; no difference between these two study group was observed in terms of late genitourinary side effects, but in SBRT-group an higher risk of acute GU side effects was found.

Finally, in view of a not huge scientific soundness generated by comparing only single-arm, phase two studies data, we attempted to perform a meta-analysis involving IMRT groups, because, to date, randomized prospective trials have been carried out only with this technology.

In Figure 2 we showed the meta-analysis of three randomized trials, which compare toxicities of patients treated with HYPO scheme with those treated with conventional fractionation. Patients who underwent Hypofractionated radiotherapy schemes suffered from GI acute toxicity to the extent of near 71% more than CV-treated counterparts (*p-value* < 0,001; *Confidence Interval: 1,469- 2,007*): conversely, Hypo-IMRT treated patients experienced less late gastrointestinal toxicity to the extent of 13 % than CV treated patients, without reaching statistical significance *(OR 0,867 ; p = 0,162)*

Certainly, this is a preliminary analysis, and the lack of homogeneous data and phase III studies strengths the need of prospective randomized trials, supporting us to really know the incidence of radiotherapy-induced rectal and urinary toxicity, which are serious issues affecting the quality of life and compliance to treatment of prostate cancer patients.

DISCUSSION

The advent of image-based or image-guided RT, new therapeutical algorithms and technology advancement permitted the use of high-dose for fraction in prostate cancer treatment. Some tumors, such as prostate cancer, have a very low α/β ratio and higher single dose that can be applied with a better tumor control, without increasing side effects [21,22]. Randomized trials have shown a superior biochemical control when higher total doses of conventionally fractionated irradiation are delivered to prostate [23,24]. However, dose escalation with standard fractionation improves biochemical-free survival at the expense of an overall treatment duration, that is longer [10, 25-26].

Target localization prior to daily treatments is required and can be performed using X-ray imaging of implanted fiducial markers: this technique allows a smaller Planning Tumor Volume (PTV) expansion with a lower dose to the surrounding organs. The accuracy of different real-time localization systems can vary considerably: for example, with the Novalis or Varian True Beam systems, localization and target positioning

before each treatment fraction is needed. With the Calypso system, the operator sets a threshold (typically 3-5mm) beyond which the treatment is interrupted and the patient correctly repositioned. With the CyberKnife, continuous image acquisition and target correction occur routinely: correction for target motion must account for translational (anterior/posterior, right/left, and superior/inferior) motion. Stereotactic body radiotherapy (SBRT) delivers a very high-dose radiotherapy to body targets, with the treatment accomplishment in one to five fractions. The Quantitative Analysis of Normal Tissue Radiation Effects in the Clinic (QUANTEC) emphasizes the importance of an adequate organ volume delineation to get radiation dose-volume parameters and OARs radiation tolerance constraints [27].

The rectal morbidity (such as proctitis, ulceration) is lower when less than the 25% of rectal volume receives doses of < 70Gy. Rectal bleeding occurred in 1% of patients when V_{65} was < 23% and increased to 10% with $V_{65} \geq 28\%$, because the α/β *ratio* of rectum is usually assumed to be 3 Gy, but it might be higher [28-30]. In a study of 101 patients with prostate cancer patients treated with 3D-CRT or IMRT (mean dose 70-74Gy) and evaluated with proctoscopy within 1 year after treatment, V_{60} and V_{70} were related to incidence of rectal telangiectasias and bleeding. No data on late rectal tolerance to hypofractionated stereotactic irradiation (36-40 cGy in five fractions) are available. The α/β *ratio* of a normal bladder is assumed to be in the region of 3-5 Gy for late toxic effects and near to 10 Gy for acute toxicity. The trigonal area appears to be very radio-sensitive, sometimes resulting in fibrosis-related urethral obstruction. Regard to the tolerance of the urinary bladder, equivalent dose at 80Gy for partial organ and at 50Gy for the whole have been established. Marks et al. estimated a clinical complication rate of 5-10% with 50 Gy given to the whole bladder in 2Gy fractions. Similar toxicity has been observed with 60-65Gy to partial bladder volumes. The RTOG 0415 study of prostate cancer patients included a bladder dose-volume constraint of no more than 15% of the volume to receive >80 Gy, no more than 25% of the volume to receive > 75 Gy, no more than 35% of the volume to receive >70 Gy, and no more than 50% of the volume to receive >65 Gy. Urethral tolerance has been estimated at 65-70Gy with 2Gy external irradiation [31-35]. In this work, the acute and late urinary and gastrointestinal toxicity detected in patients with low-intermediate risk localized prostate cancer were analyzed, also in relation to used technique and fractionation scheme. Schmid et al. [36] conducted a prospective phase II study of 178 primary prostate-cancer patients, including 123 patients with low/intermediate risk treated with a dose of 70 Gy and 55 patients treated with 74 Gy in conventional fractionation: G2 acute GI and GU toxicity were 15% and 22% respectively, while G2 late GI and GU toxicity were 19% and 23% respectively. Authors concluded that most of radio-induced late GI and GU side

effects were transient.

Michalsky et al [37] evaluated 219 patients treated with 78 Gy in 39 fractions, 119 on prostate (first arm) and 100 patients treated both on prostate and seminal vescicles (second arm). The percentage of G2 acute urinary and rectal toxicity were 36% in the first arm, 45% in the second. Late GU toxicity G2 were 14% in the first arm and 20% in the second arm; the late GI toxicity were 19% in the first arm and 17% in the second arm.

Zietman et al [38] evaluated a total of 394 men, randomized to receive 50.4 Gy and a boost of 19.8 Gy protons in 11 fractions (first arm), or a boost of 28.8 Gy in 16 fractions: two percent of patients in both arms experienced late grade 3 genitourinary toxicity, 1% of patients in the high-dose arm experienced late grade 3 GI toxicity. Acute and late toxicity of grade 2 were 51 and 22% genitourinary and 44 and 13% gastrointestinal for low-dose arm; 60 and 27% genitourinary and 63 and 24% gastrointestinal for high-dose arm.

Two proton therapy with conventional fractionation trials were then evaluated: first trial, conducted by Coen et al. [39], with a dose of 78-79 Gy in 85 men, reported genitourinary/gastrointestinal acute toxicity of 51/19% Grade 1; of 13/1% Grade 2; of 1/0% Grade 3 respectively. Late genitourinary/gastrointestinal toxicity were of 33% Grade 1; 26% Grade 2; 11% Grade 3; 2% Grade 4. The second trial conducted by Nihei et al [40] with 50 Gy dose of Protons and boost of 24 Gy, reported genitourinary/gastrointestinal acute toxicity of 58/10% Grade 1; of 12/1% Grade2 respectively. Late genitourinary/gastrointestinal toxicity, were of 6/18% Grade 1; of 1/3% Grade 2 respectively.

In the first group of study with 3DCRT technique, five prospective studies with hypofractionated scheme were assessed. White et al [41] evaluated 90 patients treated with 57 Gy in 17 fz of 3Gy and have reported acute genitourinary toxicity G 1, 2 and 3 to 58.6%, 10% and 1.1% respectively; acute gastrointestinal toxicity to 75.6%, 9% and 0% respectively. Grade 1, 2 and 3 GU and GI late toxicity were 47.3%, 2.4%, 0%, and 40%, 9.3% and 4.7% respectively. Tramacere et al [42] evaluated 97 patients treated with a schedule of 62 Gy in 20 fractions over 5 weeks, 4 fractions of 3.1 Gy each for week, and reported genitourinary (GU) and gastrointestinal (GI) ≥ G2 acute toxicities of 21% and 15%, a late toxicity of 8% and 11% respectively. Jereczek-Fossa et al [43] evaluated 337 patients treated with 70 Gy in 28 fz of 2.5 Gy and reported a G2 urinary and rectal acute toxicity of 35% and 11.3%, a late toxicity of 10.4% and 7.5%. Martin et al [44] evaluated 92 patients treated with 60 Gy in 20 fz of 3Gy, reported a G2 acute urinary and rectal toxicity of 25% and 3%, a late urinary and rectal toxicity of 11% and 4%.

Lukka et al [45] randomized 936 patients into two treatment arms: 470 patients received 66 Gy in 33 fractions and 466 patients 52.5 Gy in 20 fractions. Acute toxicity was found to be slightly higher (11.4%) in the short arm compared to the long arm (7%). The late toxicity was similarly low in both arms (3.2%).

Two interesting studies have used 3DCRT technique, one with conventional fractionation and one with hypofractionated, followed by a SBRT-boost with Cyberknife system to 9.5-4.75/fz the first, 9-9.75/fz the second. The mean percentage of acute genitourinary and gastrointestinal toxicity was 5% and 7%; the mean percentage of late toxicity was 4% and 08% respectively [46,47].

Other research groups considered the use of IMRT technique: 4 prospective studies with conventional fractionation, 4 with hypofractionated schemes and 3 prospective randomized studies. In a prospective study with conventional fractionation, Fang et al [48] evaluated 394 patients treated with 79.2 Gy in 44 fractions of 1.8Gy (213 treated with IMRT photon, 181 with protons). The urinary and gastrointestinal acute G2 toxicity were 28.7% and 18.3% respectively in IMRT and 21.3% and 12.8% in PBT; G2 late toxicities were 13.8% and 10.8% in IMRT and 4.3% and 12.8% in PBT. The prospective study of Goineau et al [49] evaluated 38 patients treated with 76 Gy with conventional fractionation and reported acute urinary and gastrointestinal G2 toxicity of 5.3%, and late G2 toxicity of 5.3% and 15.8%. Marchand et al [50] assessed the same doses in 55 patients and reported acute urinary and gastrointestinal G2 toxicity of 38% and 15%, late G2 toxicities of 13% and 11%. The prospective study of Petrongari et al [51] evaluated 39 patients treated with 86 Gy dose escalation, in 43 fractions of 2 Gy. They recorded acute urinary and gastrointestinal G2 toxicity of 51% and 5%, and late G2 toxicities of 44% and 18%.

Wu et al [52] evaluated a dose/fraction of 3.43Gy for a total dose of 55Gy, Zilli et al [53] a dose/fraction of 3.85 Gy for a total dose of 54 Gy, Lock et al [54] a dose/fraction of 3.16Gy for a total dose of 63.2 Gy. They recorded acute urinary and gastrointestinal G2 toxicity of 41-8%; 22-2.5%; 33.8-14.1 % respectively, and late G2 toxicity of 34-8%; 4-3%; 25-25% respectively. Martin et al [55] evaluated 92 patients treated with hypofractionated RT with 60 Gy in 20 fractions. They recorded acute urinary and gastrointestinal G2 toxicity of 25% and 11%, late urinary and gastrointestinal G2 toxicity of 3% and 4%.

Dearnaley et al [56] in a prospective randomized trial and Pollack et al [57,58] in two studies compared the acute and late toxicity between the conventional fractionation arm and the hypofractionated one, all performed with IMRT. Dearnaley et al reported a greater genitourinary and rectal acute toxicity in the fractionation of 60Gy in 20 fz vs 74 Gy in 37 fz (49% and 38% vs 46% and 25%), while late toxicity frequencies were equivalent, but no significant difference in 5 years side-effects incidence after treatment was observed.

Pollack et al, in the first study reported a greater toxicity in the hypofractionated treatment group (70.2Gy in 26 fz vs 76Gy in 38fz) only for acute gastrointestinal

(18% vs 8%), instead G2 recorded in the lower genitourinary acute toxicity (48% vs 56%), in the late genitourinary (6% vs 8%), and in late gastrointestinal (0% vs 2%). In the second study, Pollack et al, showed increased toxicity genitourinary acute and late in hypofractionated scheme (70.2 Gy in 26 fz vs 76 Gy in 38 fz), lower the gastrointestinal. The meta-analysis showed an advantage in terms of acute gastrointestinal and late genitourinary toxicity for Hypofractionated schemes.

Finally, 10 studies of extreme hypofractionated scheme with SBRT technique, 4 SBRT with Linac, 6 SBRT with Cyberknife system were evaluated. The first 4 have evaluated treatments with dose/fraction of 6.7- 10 Gy for a total dose 33.5-50 Gy and number of fractions between 4 and 5. The mean of percentage of acute urinary and rectal G2 toxicity was between 24% and 16%, the late G2 toxicity was between 13% and 7% [59-62]. Regarding the studies that evaluated treatment using SBRT technique with Cyberknife system, were carried out using a 7-9.5 Gy dose/fraction for a total dose of 35-38 Gy and number of fractions between 4-5. The mean percentage of acute urinary and rectal G2 toxicity was 10% and 11%; the late G2 toxicity was 6% and 5% [63-68].

CONCLUSION

Our review suggests that hypofractionated schemes, which have a recognized radiobiological value, are usually characterized by a good tolerance to treatment. The new treatment systems combined with advanced technology, as well as SBRT with Cyberknife system, represent a promising approach in the radiation treatment of prostate cancer. Actually, our paper doesn't want to establish a definitive truth: very few trials assessed only low-intermediate risk-class patients, and our purpose is to "turn on" the debate about Fractionation Schedules, in order to stimulate further randomized prospective trials focusing both on the effectiveness and on the toxicity profile (toxicity/effectiveness ratio), in view of rising costs resulting from the use of new technologies.

MATERIALS AND METHODS

Study selection

In July 2016 by using PubMed on-line database (http://www.ncbi.nlm.nhi.gov/pubmed), "rectal toxicity", "urinary toxicity", "radiotherapy" and "localized prostate cancer" were the searched terms, with no limitation on publication date. Duplicates, retrospective studies, brachytherapy, only methodology, dosimetry, old techniques, advanced disease, after-surgical treatment or high-risk patients studies were excluded. Prospective studies, concerning potential relationship between acute/ late genitourinary (GU)/gastrointestinal (GI) toxicity and prostate radiotherapy in patients with low/intermediate risk localized prostate cancer, were included in the final analysis.

Data collected from single arm, phase II non randomized studies have been evaluated in order to perform OR for toxicity risk, by using SPSS 19 (IBM Software, Armonk, NY, USA, 2010).

Furthermore, we considered suitable for the metanalysis randomized prospective trials, that had recruited low/intermediate Prostate Cancer risk patients, with available data on ≥ G2 toxicity frequency: our choice fell on low/intermediate risk Prostate Cancer patients who didn't undergo surgery, because our purpose was to evaluate a sample with a treatment volume as homogeneous as possible. Unfortunately, we found no trial with this risk-class patients only: therefore, we decided to include in our analysis studies with no more than 50% of high risk patients.

Notwithstanding Hazard Ratio for toxicity-free survival was the endpoint in selected studies, we collected only event data and sample size in each group to perform Odds Ratio: in fact, our purpose was to determine whether there was a frequency difference in G2 or worse toxicity between the Hypofractionated and Conventional Treatment group, despite the time-to-event variable.

Data extraction and analysis of results

For each study first author name, year of publication, type of trial, median follow-up, risk class, RT protocol, total dose and equivalent dose, androgen deprivation therapy (ADT), Toxicity Criteria, percentage of acute and late genitourinary and gastrointestinal toxicity were considered. The studies have been combined according to the type of technique (3DCRT, IMRT, SBRT) and type of fractionation (CV, HYPO, eHYPO). The mean of the percentage for toxicity ≥ G2 in each group was then calculated. The studies were gathered into 5 groups (IMRT-Hypo; IMRT-CV; 3DCRT-Hypo; 3DCRT-CV and SBRT) and the detected acute and chronic toxicity frequency differences between groups were analyzed by calculating OR: in a dichotomous point-of-view, we chose a toxicity ≥ G2 as the outcome event variable, compared to G0-G1 toxicity as no event. Similarly, we performed a meta-analysis of randomized prospective studies meeting previously mentioned criteria by using Comprehensive Meta-Analysis software (Biostat 14 North Dean Street, Englewood, USA).

The 95% confidence interval was estimated, considering *p-values* ≤ 0.05 statistically significant.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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