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Rectal/urinary toxicity after hypofractionated *vs.* conventional radiotherapy in high risk prostate cancer: systematic review and meta analysis

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Abstract. – OBJECTIVE: The aim of our report was to review the literature concerning the toxicity of radiation therapy in patients treated for high-risk prostate cancer, and to evaluate the differences in toxicity between conventional fractionation and hypofractionated treatments, in view of different techniques used in high-risk prostate cancer patients.

MATERIALS AND METHODS: PubMed database has been explored for studies concerning acute and late urinary/gastrointestinal toxicity in high-risk prostate cancer patients treated with radiotherapy. Prospective studies, concerning potential relationship between acute/late genitourinary (GU)/gastrointestinal (GI) toxicity and prostate radiotherapy in patients with high-risk prostate cancer, were included in the final analysis. Data collected from single arm, phase II non-randomized and randomized studies have been evaluated to perform odds ratio for toxicity risk. Furthermore, meta-analysis randomized prospective trials were considered suitable because they had recruited high-risk prostate cancer patients who didn't undergo surgery, with available data on ≥ G2 toxicity frequency.

RESULTS: The initial search provided 606 results, but only 35 manuscripts met all eligibility requirements and were included in this report. In order to perform odds ratio we observed a decrease in late gastrointestinal toxicity for patients treated with hypofractionated schemes compared to CV treated ones. Among patients who underwent conventional treatment, SIB seemed to decrease acute genitourinary side effects; SIB-Hypo treated patients suffered less toxicity than patients treated with hypofractionated- sequential boost schemes. Hypo-SIB schemes would seem less toxic in terms of acute gastrointestinal and late genitourinary side effects than CV-SIB. Therefore, our focus shifted to 6 clinical trials evaluating genitourinary and gastrointestinal toxicity in patients who had been randomized to receive conventional fractionation or hypofractionated treatment, in both cases with IMRT technology. Our meta-analysis of these randomized trials involving patients with high-risk prostate cancer showed a statistically significant increase in late genitourinary toxicity for hypo-treated patients; no difference was observed in acute genitourinary/gastrointestinal toxicity, and in late gastrointestinal toxicity.

CONCLUSIONS: Our analysis doesn't want to establish a definitive truth; very few trials assessed only high risk-class patients. Our purpose is to stimulate further randomized prospective trials focusing both on the effectiveness and toxicity profile (toxicity/effectiveness ratio), taking into account the use of different technologies and doses.

Key Words
High risk, Prostate cancer, Radiotherapy, Toxicity, Meta-analysis, Review.

Introduction

High-risk prostate cancer is defined as a disease with distinctive clinical features and risk of relapse after local therapy; therefore, patients suffering from it require a multimodal treatment, involving radiation therapy (RT) associated with

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androgen deprivation therapy (ADT)[1-6]. Randomized trials have shown excellent long-term biochemical-recurrence free survival (BRFS) with higher radiation doses[7]. The hypofractionated radiotherapy (HFRT) is based on the lower α/β ratio of prostate cancer compared to adjacent organs at risk (OAR). Higher dose per fraction can improve local disease control by increasing the biological effective dose (BED) to neoplastic tissue, without increasing the risk for late effects. Furthermore, a lower total dose can be unsafe in high-risk patients with a Gleason score higher than 7, because α/β ratio should not be that low in these patients[8]. 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), have led to a greater sparing of adjacent normal tissue and as a consequence have 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 before each treatment delivery[9]. IMRT is now considered an efficient technique for dose escalation in localized prostate cancer, and allows a better conformation of dose to pelvic lymph nodes in higher-risk prostate cancer. Although pelvic lymph node irradiation is still controversial, randomized data supported its use[10] and several randomized trials have shown that pelvic irradiation with concomitant long-term ADT yields a survival benefit[1,2]. Dose-escalated radiotherapy improves local and biochemical disease control in localized prostate cancer[11-14]. The MRC RT01 study[13] has shown an equivalent overall survival of 10 years between 64Gy in 32 fractions and 74Gy in 37 fractions despite a continued significant improvement in biochemical free progression in escalated treatment group. Five large randomized trials demonstrated that increasing the dose up to 74-80 Gray (Gy), fractionated in standard 1.8-2 Gy, resulted in a longer BRFS and disease free survival (DFS)[14-18]. Therefore, patient selection is pivotal 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[20]. In high-risk localized prostate cancer radiotherapy is indicated with dose escalation in association with long-term ADT for 2-3 years (in relation to comorbidities, performance status, and a number of unfavorable prognostic factors: ≥ T2c, Gleason score ≥8, PSA > 20 ng / mL). The elective irradiation of pelvic lymph nodes, although not unequivocally indicated, is often performed. According to 2015 EAU (European Association of Urology) within the high-risk zone guidelines recommend a total dose of 76-78 Gy with 2-3 years of ADT (evidence level 1b, grade of recommendation A)[21]. Androgen deprivation therapy should be started either after radiotherapy or 2-3 months before it (neoadjuvant). In a randomized phase III trials, including patients suffering from high-risk and locally advanced disease (EORTC 22863), the combination of radiotherapy and hormonal therapy with LHRH analogues reduced the recurrence rate more than radiotherapy alone, followed, at the time of relapse, by hormonal therapy[22,23]. The advantage of the combination therapy (LHRH analogue plus radiation therapy) was confirmed in a meta-analysis and several revisions[24]. A recommended total dose to prostate patients with high-risk disease is 76-81 Gy in conventional fractionation[25,26]. The hypofractionated treatment in high-risk patients, which is often associated with the treatment of pelvic lymph nodes, was evaluated in several prospective trials and retrospective studies that included the hypofractionated treatment of prostate and simultaneous conventional treatment of the lymph nodes. This type of treatment seems to have an acceptable toxicity profile, although prolonged follow-up is needed for definitive conclusions[27,28]. The extreme hypofractionated treatment with IMRT/SBRT in centers with documented experience enables a better conformation of dose, delivering a very high dose for each fraction (> 5 Gy) in few sessions (up to 6)[20]. The aim of our work was to make a review of the literature concerning the toxicity of radiation therapy in patients with high-risk prostate cancer, and to evaluate the differences in toxicity between conventional fractionation and hypofractionated treatments, also in view of different techniques used in these patients.

Materials and Methods

Study Selection

In December 2016 by using PubMed on-line database (http://www.ncbi.nlm.nhi.gov/pubmed), "rectal toxicity", "urinary toxicity", "radiotherapy" and "high risk localized prostate cancer" were the searched terms, with no limitation on publication date. Duplicates, retrospective studies, brachytherapy, methodology only, dosimetry, old techniques, advanced disease, after-surgical treatment or low-intermediate risk patients' studies were excluded. Prospective studies, concerning potential relationship between acute/late genitourinary (GU)/gastrointestinal (GI) toxicity and prostate radiotherapy in patients with high-risk prostate cancer, were included in the final analysis. Data collected from single arm, phase II non randomized and randomized studies have been evaluated in order to perform odds ratio for toxicity risk, by using SPSS 19 (IBM Software, Armonk, NY, USA). Furthermore, we considered suitable for the meta-analysis, randomized prospective trials that had recruited high-risk prostate cancer patients who didn't undergo surgery, with available data on ≥ G2 toxicity frequency. Because our purpose was to evaluate a sample with a treatment volume as homogeneous as possible, we included in our analysis trials with at least 48-50% 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, the author's name, the year of publication, the 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 3 groups (exclusive Hypo; exclusive CV; randomized exclusive Hypo/CV). The detected acute and late toxicity frequency differences between Hypo and CV treatments were analyzed by calculating odds ratio: in a dichotomous point-of-view, we chose 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 matching previously mentioned criteria by using comprehensive meta-analysis software (Biostat 14 North Dean Street, Englewood, CO, USA). The 95% confidence interval was estimated, considering p-values ≤ 0.05 statistically significant.

Results

Study Selection

The research results are summarized in Figure 1. The initial search yielded 606 results. 355 publications were excluded (brachytherapy, only low-intermediate risk, only methodology), which dropped the initial number down to 251. These articles were reviewed and 102 studies, which evaluate advanced disease, were removed. 149 full-text articles were finally evaluated, but further 114 studies were discarded because assessing after-surgery treatments, old techniques, retrospective studies or they had few data. Only 35 manuscripts met all the eligibility requirements and were included in this report. Among the selected articles, three groups were obtained. Group I gathers 11 articles regarding prospective studies on conventional fractionation (Table I). Group II includes 18 prospective studies of treatments with hypofractionated radiotherapy (Table II). Group III includes 6 randomized studies hypofractionated/conventional radiotherapy (Table III). We considered the percentage of patients with toxicity ≥ G2 in each treatment group: odds ratios are shown in Table IV. In this Table we summarized odds ratio (OR) resulted from comparing patients grouped according to different fractionation schemes (hypofractionated/conventional), and boost delivering (sequential or concomitant). In view of these results, it has been possible to postulate that the comparison between Hypo *vs.* CV fractionated treatments showed a statistically significant greater risk in terms of G2 or worse late gastrointestinal toxicity (OR 0.72; p=0.0009) for CV-group. SIB-technology in conventional fractionation treated patients showed a significant reduced risk of acute genitourinary toxicity (OR 0.42 p=0.0001) than standard CV, as well as Hypo-SIB treated-patients who suffered less from each

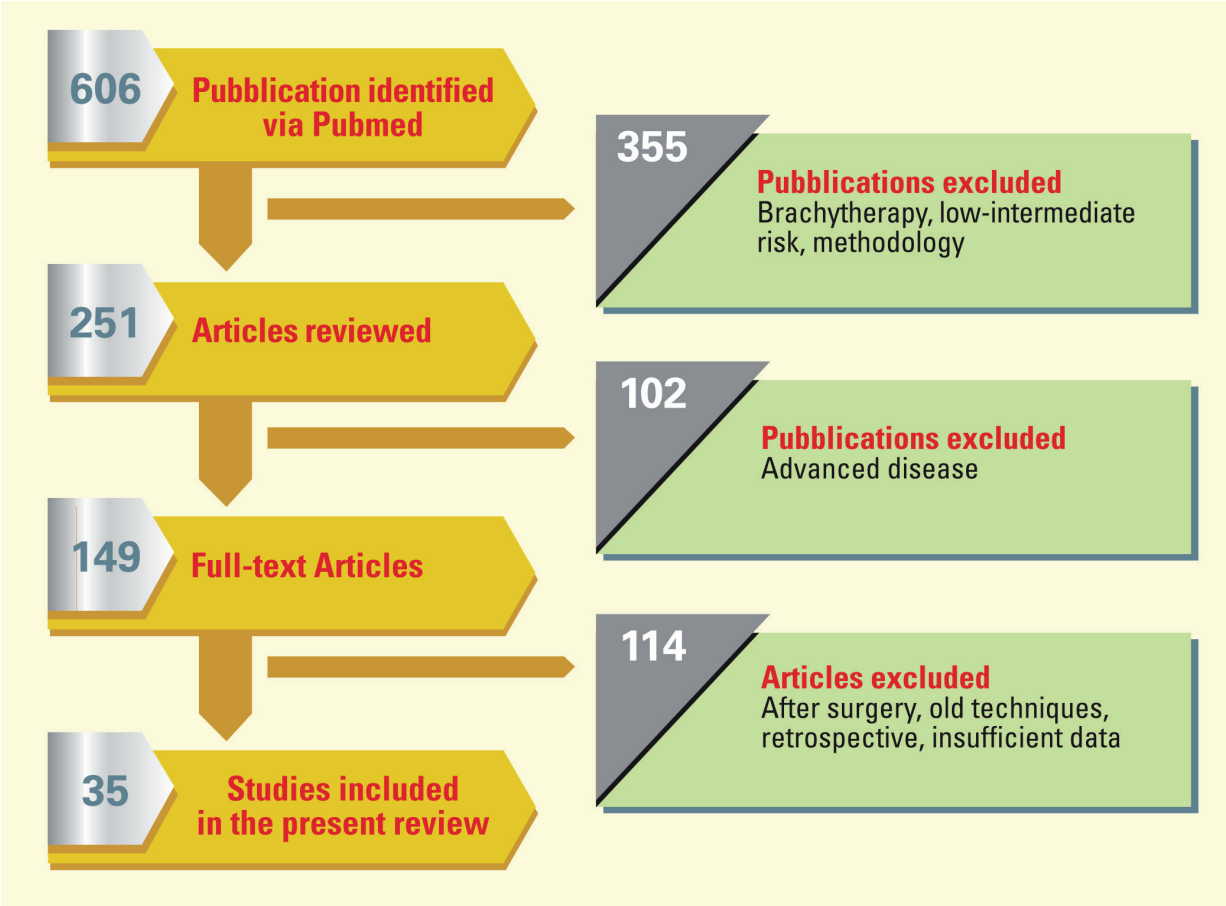

Figure 1. Analysis flow-chart of published literature evaluating the acute and late genitourinary and gastrointestinal toxicity following prostate radiation therapy. The initial search yielded 606 results, but only 35 papers met all eligibility requirements and were included in this report.

toxicity than the Hypo counterparts. Finally, by comparing Hypo-SIB with CV-SIB, a reduction for acute gastrointestinal and late genitourinary toxicity for the Hypo-treated patients was observed. In Figure 2 we showed the meta-analysis of six randomized trials, comparing toxicities of patients treated with HYPO scheme with those treated with conventional fractionation. Patients who underwent hypofractionated radiotherapy schemes suffered from late genitourinary toxicity to the extent of nearly 28% more than CV-treated counterparts (p-value = 0.038; confidence interval: 1.014-1.625). No difference was found in terms of acute gastrointestinal, acute genitourinary and late gastrointestinal toxicity between the two-fractionation schemes. We believe that pelvic irradiation and the increased total dose to the target volume could underlie higher toxicity in organs at risk in the hypofractionated treatment, with an increased dose/fraction ratio, particularly to the bladder.

Discussion

In our review we evaluated a first group of prospective studies on the radiation treatment with conventional fractionation of patients with high-risk prostate cancer, assessing the percentage of genitourinary and gastrointestinal acute and late toxicity equal to or greater than G2. In this group, we included 9 studies using techniques 3DCRT, IMRT with conventional fractionation (1.8-2 Gy/fz) for a total dose of 50 to 55 Gy to the pelvis and 78-80 Gy to the prostate with a number of fractions 34-42. In the first study, Zurlo et al[29] assessed only acute toxicities, which registered a rate of acute genitourinary toxicity ≥ G2 of 20 and 33% in patients treated with doses less than 68 Gy and between 68-70 Gy. Acute gastrointestinal toxicity was 38% and 26%, respectively. In the second study, Zapatero et al[30] evaluated 355 patients, 189 high-risk treated with 76-82Gy in 38-41 fractions of 2 Gy, and recorded a late genitourinary toxicity ≥ G2 of 18% and late gastrointestinal of 20%.

Table I. Summary of trials on prospective treatments with conventional treatment of radiotherapy. 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); EQ (Equivalent Dose); VMAT (Volumetric Modulated Adactive Radiotherapy); IMRT (Image Modulated Radiotherapy); GU (Genitourinary); GI (Gastrointestinal); ADT (Androgen Deprivation Therapy).

PROSPECTIVE TRIALS ON RADIOTHERAPY WITH CONVENTIONAL FRACTIONATED													
Author	**No. pt**	**FU median**	**Risk groups (L/I/H) %**	**Technique**	**LN/P+VS/P**	**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)**
Zurlo (30)	45 360		H:100	3DCRT	LN/P+VS/P	<68 Gy/(2) 68-70 Gy/34-35 fz (2)	[<68 Gy] [68-70 Gy]	50	G≥2:20 G≥2:33	G≥2:38 G≥2:26	-	-	WHO
Zapatero (31)	355	63 M	L:47; H:53	3DCRT	LN/P+VS/P	76-82 Gy/38-41 fz (2)	[76-82 Gy]	100	-	-	G≥2:18	G≥2:20	EORTC/ RTOG
Matzinger (32)	652 139	-	H:100	3DCRT IMRT	P+VS/P	70-74-78 Gy/35-37-39 fz (2) 74-78 Gy/37-39 fz (2)	[70-74-78 Gy] [74-78 Gy]	-	G≥2:41/40/46 G≥2:36/50	G≥2:23/19/10 G≥2:7/23	-	-	CTCAE
Bayley (33)	103	23 M	H:100	IMRT	LN/P+VS/P	55.1 Gy/29 fz (1.9) 79.8 Gy/42 fz (1.9)	[55.1 Gy] [79.8 Gy]	-	G≥2:47	G≥2:33	-	-	RTOG
Ghadjar (34)	39	29 M	L-I:39; H:61	IMRT	P+VS	80 Gy/40fz (2)	[80 Gy]	76	G≥2:64	G≥2:3	G≥2:29	G≥2:8	CTCAE
Fan (35)	92	32 M	L-I:39; H:61	IMRT	LN/P+VS/P	<60 Gy/(2) 60-70 Gy/30-35 fz (2) >70 Gy/(2)	[<60 Gy] [60-70 Gy] [<70 Gy]	83	G≥2:7	G≥2:7	G≥2:26	G≥2:6	RTOG
Manabe (36)	44	47 M	H:100	IMRT	LN/P+VS/P	74-78 Gy/37-39 fz (2)	[74-78 Gy]	86	G≥2: 10	G≥2:1	G≥2:6	G≥2:13	CTCAE
Saracino (37)	37	57 M	H:100	IMRT-SIB	LN/P+VS/P	76-80 Gy/38-40 fz (2)	[76-80 Gy]	100	G≥2:32	G≥2:62	G≥2:20	G≥2:10	RTOG
Ishii (38)	100	3M	H:100	VMAT-SIB	LN/P+VS/P	46.8 Gy/26 fz (1.8-2) 26 Gy/13 fz (2)	[46.8 Gy] [78 Gy]	96	G≥2:13	G≥2:16	-	-	CTCAE
Tomita (39)	128 76	37 M	L-I:33; H:67 L-I:30; H:70	DCAT-HO	LN/P+VS/P	70 Gy/35fz (2) 74 Gy/37fz (2)	[70 Gy] [74 Gy]	128 76	G≥2:2	G≥2:1	G≥2:4 G≥2:1.3	G≥2:2 G≥2:5	RTOG
Bryant (40)	PR03 229	66 M	H:100	Protoni	P+VS/P	74-78 Gy/37-39 fz(2)	[74-78 Gy]	18	-	-	G≥2:3	G≥2:1	CTCAE

Table II. Summary of trials on prospective treatments with hypofractionated treatment of radiotherapy. 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); EQ (Equivalent Dose); VMAT (Volumetrice Modulated Adactive Radiotherapy); IMRT (Image Modulated Radiotherapy); HT (Helical Thomotherapy); GU (Genitourinary); GI (Gastrointestinal); ADT (Androgen Deprivation Therapy).

PROSPECTIVE TRIALS ON HYPOFRACTIONATED RADIOTHERAPY													
Author	**No. pt**	**FU median**	**Risk groups (L/I/H) %**	**Technique**	**LN/P+VS/P**	**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)**
Thomson (41)	60	84 M	I:2; H:98	IMRT	P+VS P	57Gy/19 fz (3) 60Gy/20 fz (3)	[73.3 Gy] [77.1 Gy]	100	G≥2:70	G≥2:30	G≥2:67	G≥2:34	RTOG
Adkinson (42)	53	25.4 M	H:100	IMRT	WP+P	56Gy/28 fz (2) 70/28 fz (2.5)	[56 Gy] [80 Gy]	94	G≥2:38	G≥2:32	G≥2:27	G≥2:8	RTOG/CTCAE
Wu (43)	27	11.4 M	I: 17; H:83	IMRT	WP/P+VS/P	50.4Gy/28fz (1.8) 70Gy/28fz (2.5)	[50.4 Gy] [80 Gy]	100	G≥2:74	G≥2:22	-	-	RTOG
Valeriani (44)	82	31 M	H:100	IMRT/IGRT	WP/P+VS/P	45Gy/25fz (1.8) 55Gy/25fz (2.2) 68.75Gy/25fz (2.75)	[45 Gy] [58.1 Gy] [83.5 Gy]	100	G≥2:3	G≥2:13	G≥2:0	G≥2:1.2	RTOG
Pervez (45)	60	3 M	H:100	HT/IMRT	WP/P+VS/P	45/25 fz (1.8) 68Gy/25 fz (2.72)	[45 Gy] [82 Gy]	100	G≥2:33	G≥2:35	-	-	CTCAE/ RTOG
Lips (46)	331	36 M	L-I:20; H:80	IMRT	WP/P+VS/P	76Gy/35 fz (2.17)	[79.7 Gy]	29	G≥2:50	G≥2:30	G≥2:25	G≥2:10	RTOG/CTCAE
Joo (47)	70	19 M	H:100	IMRT	WP/P+VS/P	72.6Gy/33 fz (2.2) 76Gy/38 fz (2) 46-70-80 Gy/1.8-2.0	[76.7 Gy] [76 Gy] [46-70-80 Gy]	89	G≥2:2	G≥2:23	G≥2:6	G≥2:5	CTCAE/ RTOG
Zilli (48)	78	57 M	H:100	IMRT	WP/P+VS/P	48-50.4 Gy/28 fz (1.8) Boost 72-74.4 Gy/18 fz (4)	[48-50.4 Gy] [113.1/116.9 Gy]	100	G≥2:10	G≥2:6	G≥2:8	G≥2:4	CTCAE
Sundahl (49)	185 225	72 M	L-I:52; H:48	IMRT-SIB	WP WP	78 Gy/38 fz (2.05) 82 Gy/38 fz (2.15)	[79.1 Gy] [85.5 Gy]	94	G≥2:3 G≥2:0	G≥2:3 G≥2:2	G≥2:3 G≥2:4	G≥2:3 G≥2:1	RTOG
Hegazy (50)	29	34 M	L-I:31; H:69	VMAT-SIB	WP	70 Gy/28 fz (2.5)	[80 Gy]	83	G≥2:17	G≥2:28	G≥2:10	G≥2:0	RTOG
Lim (51)	66	20.7 M	H:100	IMRT-SIB	WP/P+VS/P	45 Gy/25 fz (1.8)+ 56.2 Gy/25 fz (2.25)	[45 Gy] [60.3 Gy]	100	G≥2:44	G≥2:39	-	-	CTCAE
Quon (52)	97	39 M	H:100	IMRT+SIB	WP/P+VS/P	67.5 Gy/25 fz (2.7)	[81 Gy]	-	G>2:43	G>2:37	G>2:9	G>2:7	EPIC
Engels (53)	28	10 M	H:100	HT- SIB	WP/P+VS/P	54 Gy/28 fz (1.8) 70.5 Gy/28 fz (2.51)	[54 Gy] [80.9 Gy]	100	G≥2:18	G≥2:7	G≥2:4	G≥2:7	RTOG
Habl (54)	40	24 M	H:100	HT-IMRT SIB	WP/P+VS/P	51.0 Gy/34 fz (1.5) 76.5/34 fz (2.25)	[51 Gy] [82 Gy]	100	G≥2:55	G≥2:22	G≥2:3	G≥2:0	CTCAE
Lin (55)	41	42 M	H: 100	CV+ SBRTboost	WP+ SBRTboost	45 Gy/25 fz (1.8)+ 21 Gy/3 fz (7)	[45 Gy] [51 Gy]	90	G≥2:27	G≥2:12	G≥2:10	G≥2:0	CTCAE
Kim (56)	39	54M	I:51; H:49	CV+ SBRTboost	WP+ SBRTboost	45 Gy/25 fz (1.8)+ 21 Gy/3 fz (7)	[45 Gy] [51 Gy]	0	G≥2:23	G≥2:21	G≥2:10	G≥2:13	RTOG
Bauman (57)	16	-	H:100	SBRT	WP/P	25 Gy/5 fz (5) 40 Gy/5fz(8)	[46.4 Gy] [108.6 Gy]	100	G≥2:25	G≥2:0	G≥2:38	G≥2:50	-
Ishikawa (58)	17	36 M	L:19; H:81	C-ion-RT	P+VS	66 GyE/3.3	[90.5 Gy]	81	G≥2:0	G≥2:0	G≥2:5	G≥2:2	RTOG

Table III. Summary of randomized trials on treatment with Radiotherapy. 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); EQ (Equivalent Dose); VMAT (Volumetric Modulated Adactive Radiotherapy); IMRT (Image Modulated Radiotherapy); GU (Genitourinary); GI (Gastrointestinal); ADT (Androgen Deprivation Therapy).

RANDOMIZED TRIALS ON TREATMENT WITH HYPO/CV RADIOTHERAPY

Author	No. pt	FU median	Risk groups (L/I/H) %	Technique	LN/P+VS/P	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)
Pollack (59)	153	68.4 M	L-I:50; H:50	CV-IMRT	P+VS/P	76 Gy/38 fz (2)	[76 Gy]	139	G≥5:2	G≥2:23	G≥2:15	G≥2:23	RTOG
	154			Hypo-IMRT		70.2 Gy/26 fz (2.7)	[84.2 Gy]		G≥2:11	G≥2:18	G≥2:15	G≥2:18	
Arcangeli (60)	85	32 M	H:100	CV - 3DCRT	P+VS/P	80 Gy/40 fz (2)	[80 Gy]	100	G≥2:40	G≥2:21	G≥2:14	G≥2:11	LENT-SOMA
	83			Hypo-3DCRT		62 Gy/20 fz (3.1)	[81.5 Gy]		G≥2:47	G≥2:35	G≥2:17	G≥2:16	
Norkus (61)	57	60 M	H:100	CV	LN/P+VS/P	76 Gy/38 fz (2)	[76 Gy]	100	G≥2:28	G≥2:40	G≥2:4	G≥2:13	RTOG/CTCAE
	67			HYPO		63 Gy/20 fz (3.15)	[83.7 Gy]		G≥2:23	G≥2:39	G≥2:2	G≥2:4	
McDonald (62)	82	78 M	H:100	CV-IMRT	LN/P+VS/P	75-77 Gy/(1.8-2)	[75-77 Gy]	93	G≥2:49	G≥2:35	G≥2:3	G≥2:25	RTOG
	75			Hypo-IMRT		70 Gy/28 fz (2.5)	[80 Gy]	91	G≥2:44	G≥2:36	G≥2:6	G≥2:13	
Aluwini (63,64)	410	60 M	I:27; H:73	CV-IMRT	P	78 Gy/39 fz(2)	[78 Gy]	261	G≥2:23	G≥2:13	G≥2:52	G≥2:20	RTOG
	410		I:26; H:74	Hypo-IMRT	P+VS	64.4 Gy/19 fz(3.4)	[90.2 Gy]		G≥2:24	G≥2:13	G≥2:60	G≥2:25	
De Felice (65)	23	25 M	H: 100	CV- IMRT	LN/P+VS/P	50.4-70.4 Gy/1.8-2.0	[50.4-70.4 Gy]	100	G≥2:39	G≥2:22	G≥2:26	G≥2:35	CTCAE
	20			HYPO-IMRT/SIB	LN/P+VS/P	45-56.25-68.75/ 1.8-2.25-2.75	[45-60.3-83.5 Gy]		G≥2:25	G≥2:10	G≥2:15	G≥2:30	

Table IV. Values of odds ratio (OR) of toxicity > G2 for each treatment group.

Comparison of the groups	Toxicity	OR (95%CI)	*p*
Hypo *vs.* CV	**AGU**	1.01 (0.88-1.16)	0.9141
	AGI	0.94 (0.80-1.09)	0.4030
	LGU	1.06 (0.90-1.26)	0.4555
	LGI	0.72 (0.59-0.87)	0.0009
CV-SIB *vs.* CV	**AGU**	0.42 (0.27-0.66)	0.0001
	AGI	1.13 (0.77-1.67)	0.5274
	LGU	0.98 (0.42-2.29)	0.9612
	LGI	0.63 (0.22-1.81)	0.3875
Hypo-SIB *vs.* Hypo	**AGU**	0.23 (0.17-0.31)	< 0.0001
	AGI	0.42 (0.31-0.56)	< 0.0001
	LGU	0.35 (0.25-0.50)	< 0.0001
	LGI	0.44 (0.27-0.72)	0.0011
Hypo-SIB *vs.* CV-SIB	**AGU**	0.62 (0.38-1.02)	0.0599
	AGI	0.35 (0.22-0.54)	< 0.0001
	LGU	0.36 (0.15-0.87)	0.0234
	LGI	0.34 (0.11-1.05)	0.0604

In the third study, Matzinger et al[31] evaluated a group of patients treated with 3DCRT to a dose of 70-74-78Gy, (dose-escalation), and a second group of patients treated with IMRT at 74-78Gy, in conventional fractionation. The acute genitourinary toxicity ≥ G2 was 41-40-46% in the first group, 36-50% in the second. The percentage of acute gastrointestinal toxicity ≥ G2 instead of 23-19-10% was found in the first group, and 7-23% in the second. Then, we evaluated four studies of treatment with IMRT technique to a total dose of 74-80Gy, and showed that acute genitourinary toxicity was 7-15% in the treatments up to 78 Gy, but that reached 64% in the delivery of 80Gy. We found no big differences in terms of the proportion of acute and late gastrointestinal/genitourinary toxicity ≥ G2 between the different dose levels[32-35]. Saracino et al[36] instead report the IMRT treatment data with simultaneous boost to a total dose of 76-80 Gy and an acute genitourinary toxicity ≥ G2 of 32% and gastrointestinal 62%, while a late genitourinary toxicity ≥ G2 of 20% and gastrointestinal of 10%. Ishii et al[37] instead evaluated a VMAT-treatment with 1.8Gy/fz on pelvis and SIB of 2 Gy/fz on prostate and vesicles for a total dose of 46.8 Gy on the pelvis and 78 Gy on prostate and vesicles with acute genitourinary/gastrointestinal toxicity ≥ G2 of 13% and 16%. Tomita et al[38] evaluated 204 patients (70% high risk) treated with dynamic conformal arc radiotherapy with 70-74 Gy in 35-37 fz. The percentage of acute toxicity ≥ G2 was 2% for genitourinary and 1% for gastrointestinal; late toxicity genitourinary/gastrointestinal were 4% and 5%, respectively.

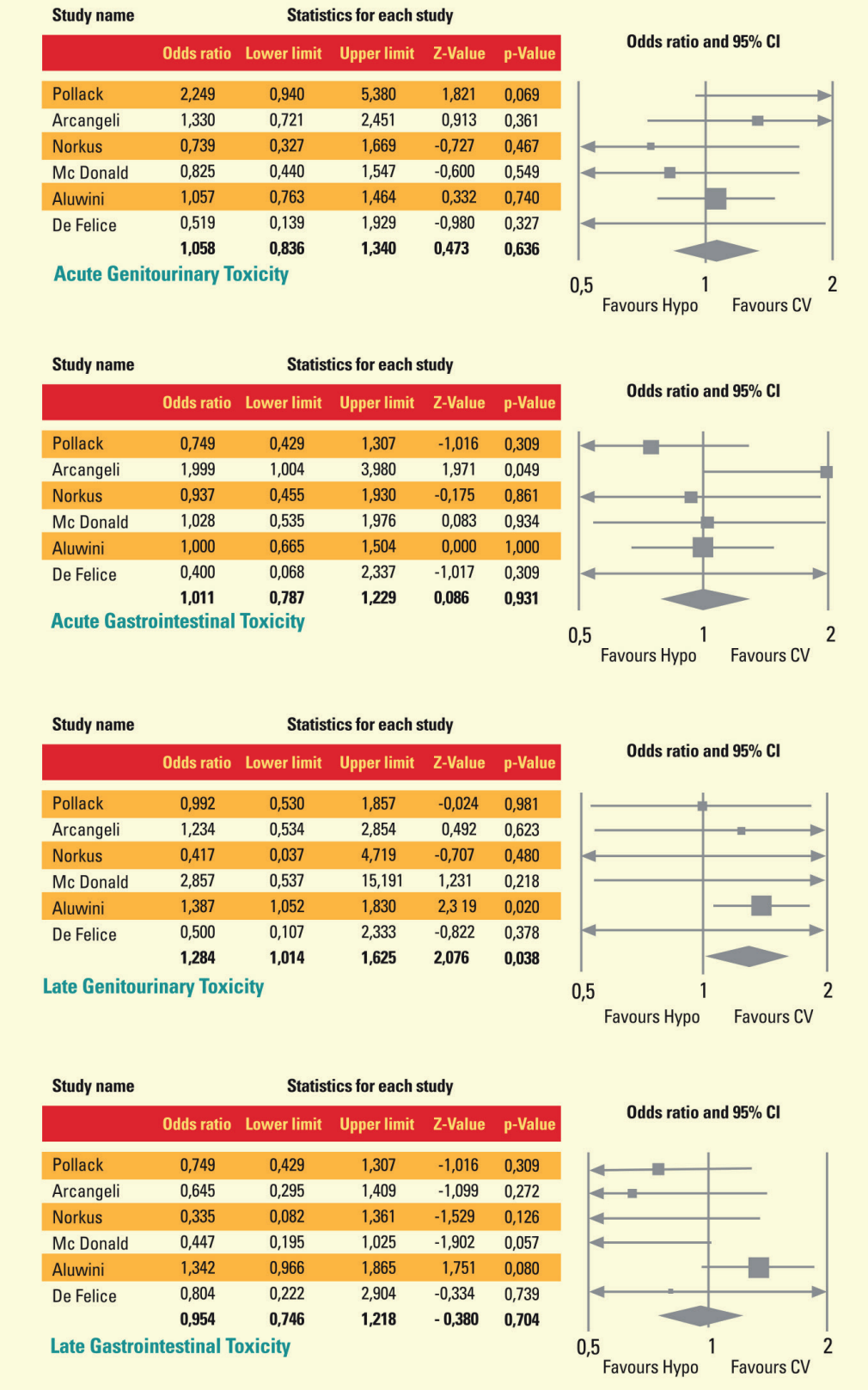

Figure 2 . Meta-analysis of six randomized trials, which compare toxicities of patients treated with HYPO scheme with those treated with conventional fractionation. Patients who underwent hypofractionated radiotherapy schemes suffered from late genito-urinary toxicity to the extent of near 28% more than CV-treated counterparts (p-value < 0.038; Confidence Interval: 1.014- 1.625).

The latest study was that by Bryant et al[439] that evaluated 229 patients treated with protons at a dose of 74-78 Gy in 37-39 fz and recorded a late genitourinary and gastrointestinal toxicity ≥ G2 of 3% and 1%, respectively. The second group includes studies of hypofractionated treatments, the first 8 are studies evaluating treatment of pelvis, prostate and seminal vesicles at decreasing volumes, with a dose between 45-56 Gy to the pelvis up to 80 Gy to the prostate, with dose fraction between 1.8-2.0 for the pelvis and up to 4 Gy to the prostate[40-47]. In some studies there has been increased toxicity, due to the increase of total dose, or increasing the dose/fraction. Six other investigations evaluated treatments with simultaneous boost on the prostate; this type of treatment allows to simultaneously treating 2 volumes with different dose, with a reduction of the number of fractions and a total dose of 70 to 82 Gy in 28-38 fractions, with a greater equivalent dose, 80-82 Gy to the prostate. Also in this group it was interesting to evaluate the percentage of toxicity, because the simultaneous boost increased the dose/fraction on target, with a better control of the disease, but with an increased toxicity[48-53]. Among these six studies, two have used thomotherapy3,54 that showed no major differences in terms of toxicity. Then, we evaluated three papers that used a stereotactic treatment, two conventional treatment of the pelvis with 45 Gy boost to the prostate with stereotactic dose of 21Gy in 3 fz of the prostate with an equivalent dose of 51Gy, a total of 96 Gy. These two researches have found a lower rate of toxicity, especially late toxicity. Finally, Bauman et al[54-56] evaluated a treatment of the pelvis with 25 Gy in 5 fz and prostate with 4.0 Gy in 5 fz, with an equivalent dose of 108.6Gy, and recorded a very low toxicity only in acute gastrointestinal. The latest work is with ion-C with the delivery of 66 GyE in doses of 3.3 and 90.5Gy equivalent dose which recorded a very low percentage of acute and late toxicity, despite the high total dose delivered[57]. We gathered single-arm study patients not only in view of fractionation (conventional *vs.* hypofractionated) but also of boost delivering (simultaneous boost – SIB *vs.* sequential) in order to perform odds ratio. We observed a decrease in late gastrointestinal toxicity for patients treated with hypofractionated schemes compared to CV treated ones. Among patients who underwent conventional treatment, SIB seemed to decrease acute genitourinary side effects; interestingly, SIB-Hypo treated patients suffered from each toxicity less than patients treated with hypofractionated-sequential boost schemes. It's even more noteworthy that the comparison between schemes with concurrent boost but differently fractionation; indeed, Hypo-SIB schemes would seem less toxic in terms of acute gastrointestinal and late genitourinary side effects than CV-SIB. These data do not derive entirely from randomized trials, although prospective trials, and the need to assess data as homogenous as possible led us to perform a meta-analysis. Therefore, our focus shifted to 6 clinical trials evaluating genitourinary and gastrointestinal toxicity in patients who had been randomized to receive conventional fractionation or hypofractionated treatment, in both cases with IMRT technology. Our meta-analysis of these randomized trials involving patients with high-risk prostate cancer showed a statistically significant increase in late genitourinary toxicity for hypo-treated patients[58-64]; no difference was observed in acute genitourinary/gastrointestinal toxicity, and in late gastrointestinal toxicity. In a previous work concerning low-intermediate risk prostate cancer patients, with a target volume involving only the gland, or prostate/seminal vesicles, conventional fractionation seemed to be less toxic in terms of acute gastrointestinal toxicity than hypofractionation[65]. In this meta-analysis, acute gastrointestinal toxicity doesn't differ between CV and Hypo-treated patients, probably because treatment volumes in conventional fractionation are such as to determine the same dose distribution to rectum. Conversely, we noticed an increased late genitourinary toxicity after Hypo-treatments, probably due to a greater sensitivity of the bladder trigonal region and urethra to a higher dose/fraction ratio. Ghadjar et al[67] suggested bladder hot spots as responsible for late occurrence of genitourinary toxicity, despite the use of IMRT. Little is known about the role of the bladder trigone in micturition. It was suggested that the trigone contracts during bladder filling, helping to keep the ureteral orifices open and the bladder neck shut. Micturition may be initiated by trigone relaxation and consecutive funneling of urine into the urethra. Bladder irradiation might lead to increased early or late GU toxicity by damaging different tissues including the urothelium, smooth muscle, and vasculature, and GU toxicity after RT might also involve nerve activation changes. Ghadjar et al[66] claimed that the application of high doses to small volumes of the bladder trigone was significantly associated with relevant changes in the IPSS sum during follow-up, and suggested that late GU toxicity might

be decreased by limiting the dose to the bladder trigone. Furthermore, we can't disregard important factors in genitourinary toxicity assessment, as well as treatment reproducibility, identified by a bladder always filling equally in each session. Other factors affecting GU toxicity are anatomic variants, both of bladder and prostate/seminal vesicles, whose volumetric variations may result in a substantial variation of the treatment volume. Last but not least the factor related to an increased late GU side effects is dose escalation, which in hypofractionated schemes could mostly affect toxicity compared to conventional ones.

Conclusions

Our analysis doesn't want to establish a definitive truth: seeing as very few trials assessed only high risk-class patients. Therefore, our purpose is to stimulate further randomized prospective trials focusing both on the effectiveness and toxicity profile (toxicity/effectiveness ratio), taking into accounts the use of different technologies and doses.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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