

## Efficacy and Toxicity of Whole Pelvic Radiotherapy Versus Prostate-Only Radiotherapy in Localized Prostate Cancer: A Systematic Review and Meta-Analysis

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Wang S, Tang W, Luo H, Jin F and Wang Y (2022) Efficacy and Toxicity of Whole Pelvic Radiotherapy Versus Prostate-Only Radiotherapy in Localized Prostate Cancer: A Systematic Review and Meta-Analysis. Front. Oncol. 11:796907. doi: 10.3389/fonc.2021.796907 **Background:** There is little level 1 evidence regarding the relative efficacy and toxicity of whole pelvic radiotherapy (WPRT) compared with prostate-only radiotherapy (PORT) for localized prostate cancer.

**Methods:** We used Cochrane, PubMed, Embase, Medline databases, and ClinicalTrials.gov to systematically search for all relevant clinical studies. The data on efficacy and toxicity were extracted for quality assessment and meta-analysis to quantify the effect of WPRT on biochemical failure-free survival (BFFS), progression-free survival (PFS), distant metastasis-free survival (DMFS), overall survival (OS), gastrointestinal (GI) toxicity, and genitourinary (GU) toxicity compared with PORT. The review is registered on PROSPERO, number: CRD42021254752.

**Results:** The results revealed that compared with PORT, WPRT significantly improved 5year BFFS and PFS, and it was irrelevant to whether the patients had undergone radical prostatectomy (RP). In addition, for the patients who did not receive RP, the 5-year DMFS of WPRT was better than that of PORT. However, WPRT significantly increased not only the grade 2 or worse (G2+) acute GI toxicity of non-RP studies and RP studies, but also the G2+ late GI toxicity of non-RP studies. Subgroup analysis of non-RP studies found that, when the pelvic radiation dose was >49 Gy (equivalent-doses-in-2-Gy-fractions, EQD-2), WPRT was more beneficial to PFS than PORT, but significantly increased the risk of G2+ acute and late GU toxicity.

**Conclusions:** Meta-analysis demonstrates that WPRT can significantly improve BFFS and PFS for localized prostate cancer than PORT, but the increased risk of G2+ acute and late GI toxicity must be considered.

Systematic Review Registration: PROSPERO CRD42021254752.

Keywords: localized prostate cancer, meta-analysis, whole pelvic radiotherapy, survival, genitourinary toxicity (GU)

## BACKGROUND

Prostate cancer is the most frequent cancer in men, accounting for more than 1 in 5 new diagnoses (1, 2). In western societies, prostate cancer has a high cure rate, but it is also the second leading cause of cancer deaths for men (3, 4). The main treatments for prostate cancer are radical prostatectomy (RP), radiotherapy (RT), and hormone therapy (HT). RT is a crucial treatment strategy for men who received a diagnosis of localized prostate cancer (5, 6). However, there has been considerable controversy over whether to choose whole pelvic radiotherapy (WPRT) or prostate-only radiotherapy (PORT) for localized prostate cancer.

At present, there is little level 1 evidence regarding the relative efficacy and toxicity of WPRT compared with PORT for localized prostate cancer, and relevant clinical randomized controlled trials have drawn confusing conclusions (7-12). A Phase III clinical trial, the Radiation Therapy Oncology Group (RTOG) 9413, showed that for localized prostate cancer, WPRT improved progression-free survival (PFS) compared with PORT (12-14). However, the French Genitourinary Study Group (GETUG)-01 found that compared with PORT, WPRT had no statistically significant improvement in PFS, event-free survival (EFS), and overall survival (OS) (11, 15). A recent Phase III randomized clinical trial of prostate-only or whole-pelvic radiation therapy in high-risk prostate cancer (POP-RT) pointed out that WPRT for localized prostate cancer improved the biochemical failure-free survival (BFFS) and distant metastasis-free survival (DMFS) compared with PORT, but resulted in a significant increase in late grade 2 or worse (G2+) genitourinary (GU) toxicity (9, 16).

This study systematically reviewed clinical studies comparing WPRT to PORT for localized prostate cancer. The data on efficacy and toxicity were extracted for quality assessment and meta-analysis to quantify the effect of WPRT on BFFS, PFS and DMFS, OS, gastrointestinal (GI) toxicity, and GU toxicity compared with PORT.

## METHODS

#### **Literature Search**

We used Cochrane, PubMed, Embase, Medline databases, and ClinicalTrials.gov to systematically search for eligible trials from inception until October 10, 2021, by two study investigators independently. The following search terms were used: "Prostatic Neoplasms" [Mesh] AND "Radiotherapy" [Mesh] AND "Pelvis" [Mesh]. Detailed search terms were shown in **Supplementary Table 1**. The review is registered on PROSPERO, number: CRD42021254752.

# Inclusion Criteria, Study Eligibility, and Data Extraction

The Preferred Reporting Items for Systematic Reviews and Metaanalysis (PRISMA) criteria were used for article selection (**Figure 1**). Two investigators independently searched and selected literature, included in randomized controlled trials (RCTs) and cohort studies (CRS), and excluded articles with metastatic prostate cancer. The article must include one of the biochemical failure-free survival (BFFS), progression free survival (PFS), distant metastasis-free survival (DMFS), survival overall (OS), gastrointestinal (GI) toxicity, and genitourinary (GU) toxicity for data extraction. For studies with multiple publications, or where there was overlap in the patients studied, the most recent publication was chosen. Any queries were checked by a second reviewer and resolved by consensus.

#### **Statistical Analysis**

The results of time-to-event outcomes, BFFS, PFS, DMFS, and OS, were reported as hazard ratios (HRs) with 95% confidence interval (CIs), and the most fully adjusted HRs were extracted to prevent interference from other variables. The results of GI toxicity and GU toxicity were recorded as risk ratios (RRs) with 95% CIs. The following effect modifiers on the end points were tested using subgroup analysis: radical prostatectomy (RP), androgen deprivation therapy (ADT), radiation dose, and radiotherapy technology.

Heterogeneity was assessed using the  $\chi^2$  test and the  $I^2$  statistic. Significant heterogeneity was indicated by p < 0.05 in Cochrane Q tests and a ratio greater than 50% in  $I^2$  statistics, which led to the use of random-effects models according to the DerSimonian and Laird method (17, 18). Otherwise, these tests were negative for heterogeneity, and fixed-effects models were chosen. Statistical analyses were performed using the Cochrane Review Manager, version 5.3. A confidence level of 95% (p < 0.05) was considered statistically significant.

#### **Risk of Bias**

RCTs were evaluated using the Cochrane Risk of Bias Tool (19), and the CRS were analyzed using the Newcastle-Ottawa Scale (20). Furthermore, funnel plots of standard errors vs. effect estimates were inspected for publication bias (21, 22).

## RESULTS

#### **Included Studies**

A total of 4,680 publications and 52 registered clinical studies were identified from the literature search, and 16 studies that met the eligibility criteria were finally selected, including 6 randomized controlled trials (RCTs) (7-12) and 10 cohort studies (CRS) (23-32). Four studies that met the inclusion criteria were excluded because of no hazard ratio available for survival (33-36). The PRISMA study selection diagram is shown in Figure 1. Of the 16 studies, 9 studies did not perform radical prostatectomy (non-RP), and the patients of the other 7 studies received radical prostatectomy (RP). A total of 10,212 participants were enrolled, of which 3,393 participants received whole pelvic radiotherapy (WPRT), and 6,819 participants received prostate-only radiotherapy (PORT). The overall median follow-up time for efficacy was 64.8 months, and toxicity was 50.5 months. A summary of the studies characteristics is presented in Table 1.



#### **Biochemical Failure-Free Survival**

Six studies (9, 10, 26, 29–31) with a total of 3,795 patients examined BFFS at 5 years. The forest plot (**Figure 2A**) indicated that for the patients did not undergo prostatectomy, WPRT was associated with superior BFFS relative to PORT (HR 0.23, CI 0.10–0.52, p < 0.001). Similarly, WPRT also improved the 5-year BFFS when the patients had undergone prostatectomy (HR 0.58, CI 0.50–0.68, p < 0.001). Overall, WPRT significantly improved 5-year BFFS (HR 0.56, CI 0.48–0.66, p < 0.001) compared with PORT ( $I^2 = 40\%$ , p = 0.14). All patients who did not undergo prostatectomy received ADT, whereas the studies of patients treated with prostatectomy were divided into three subgroups based on the use of ADT. The subgroup analysis of the RP

studies showed that WPRT had excellent BFFS than PORT, free from the effect of ADT (**Supplementary Figure 1A**).

#### **Progression-Free Survival**

Progression-free survival (PFS) data were available from four studies (7, 10–12), 3,278 patients. The forest plot (**Figure 2B**) indicated that, in comparison with PORT, WPRT significantly improved PFS for non-RP studies (HR 0.85, CI 0.73–0.98, p = 0.03) and RP studies (HR 0.71, CI 0.51–0.98, p = 0.04). In the subgroup of non-RP studies, when all patients received ADT, WPRT remained improved PFS (HR 0.83, CI 0.71–0.98, p = 0.02). Conversely, when patients received ADT selectively, the

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Author (year or trial name)	Patient charao	cteristics		Follow-up	San	nple	Radiation [	ose*	Other	Outcome		
	Inclusion criteria	Radiotherapy	Country	(median)	WP	Ро	Prostate	Pelvis	therapies	Survival	ū	Ъ
Blanchard et al. (GETUG 12) (7)	High-risk localized, lymphadenectomy	3D-CRT	France	8.8 years	208	150	74–78	48	ADT	PFS	×	>
Braunstein et al. (2015) (23)	T1c-T3, N0, M0	NR	NSA	3.3 years	486	2237	NR	44.25	ADT	SO	$\times$	$\times$
Dearnaley et al. (PIVOTAL) (8)	Localized, T3b/T4	IMRT	Ч	37.6 months	60	62	74	58.1	ADT	×	>	$\times$
Deville et al. (2011) (24)	GS>7, T2a-c	IMRT	NSA	25 months	36	ю 1	20	44.25	<b>RP/ADT</b>	×	>	>
Ishii et al. (2017) (25)	Localized	Arc	Japan	24 months	126	108	78	46.02	ADT	×	>	>
Link et al. (2019) (26)	GS >6, Localized	IMRT/Arc	Germany	62.2 months	43	77	79/71	44	<b>RP/ADT</b>	BFFS	$\times$	$\times$
Mantini et al. (2011) (27)	Localized	3D-CRT	Italy	52 months	168	190	70/74	44.25	ADT	×	>	>
McDonald et al. (2014) (28)	Localized	Tomo/Arc/IMRT	NSA	4 years	103	109	72.92	49.56	ADT	×	>	>
Moghanaki et al. (2012) (29)	GS≥8,Lymph node-negative	3D-CRT	NSA	48.5 months	112	135	59–74	49.56	<b>RP/ADT</b>	BFFS	$\times$	$\times$
Murthy et al. (POP-RT) (9)	Lymph nodal risk≥20%, localized	IMRT	India	68 months	110	114	72.08	50	ADT	BFFS, DMFS, OS	>	>
Pollack et al. (RTOG 0534) (10)	GS ≤ 9,T2-T3N0/Nx	3D-CRT/IMRT	NSA	5.4 years	574	578	63.92-68.83	44.25	<b>RP/ADT</b>	BFFS, PFS, DMFS, OS	$\times$	$\times$
Pommier et al. (GETUG-01) (11)	T1b-T3, cN0pNx, localized	FFRT/3D-CRT	France	11.4 years	225	221	66-70	46	ADT	PFS	>	>
Ramey et al. (2017) (30)	pT1-4, Nx/0, cM0,GS≥8	2D-RT/3D-CRT/IMRT	NSA	51 months	245	1616	66	ЯN	<b>RP/ADT</b>	BFFS, DMFS	$\times$	$\times$
Roach et al. (RTOG 9413) (12)	Lymph nodal risk≥15%, GS>6, localized	3D-CRT	NSA	8.8 years	661	661	69.03	49.56	ADT	PFS	>	>
Song et al. (2019) (31)	Lymph node-negative	3D-CRT/IMRT	Korea	66 months	108	83	66	46	<b>RP/ADT</b>	BFFS	$\times$	$\times$
Waldstein et al. (2017) (32)	GS≥8, node-negative	3D-CRT	Austria	49 months	128	447	67	47.5	RP/ADT	×	>	>
3D-CRT, three-dimensional confo	srmal radiotherapy; 2D-RT, two-dimensional radi	otherapy; FFRT, four-field bo	x radiothera	py; IMRT, intensity-mo	odulated	radiatio	n therapy; Arc, v	olumetric	modulated a	arc therapy; Tomo, tomothe	rapy; V	ď,
whole-pelvic radiotherapy; PO, pr	ostate-only radiotherapy; GS, Gleason score; RP,	, radical prostatectomy; ADT,	androgen di	eprivation therapy; BT,	brachyth	ierapy; (	OS, overall survi	/al; BFFS,	biochemical	failure-free survival; PFS, pro	ogressi	-uc
free survival; DMFS, Distant meta	istasis-free survival, Gl, gastrointestinal; GU, gen	nitourinary; NR, not reported.										
*Equivalent-doses-in-2-Gy-fractio.	ns, EQD-2.											

results showed no difference in PFS between WPRT and PORT (HR 0.96, CI 0.64–1.43, p = 0.84; Supplementary Figure 1B).

#### **Distant Metastasis-Free Survival**

Three studies (9, 10, 30) with a total of 3,237 patients reported on DMFS at 5 years. The forest plot (Figure 2C) of non-RP studies showed that WPRT was more beneficial for DMFS than PORT (HR 0.35, CI 0.15–0.82, p = 0.02). However, for the patients who had undergone RP, no significant difference had been found in DMFS between WPRT and PORT (HR 0.81, CI 0.56-1.17, p = 0.26).

#### **Overall Survival**

Three studies (9, 10, 23) (4,099 patients) analyzed OS at 5 years (Figure 2D). The forest plot (Figure 2D) demonstrated that there was no significant difference in OS between WPRT and PORT, regardless of whether the patient underwent prostatectomy. However, the further subgroup analysis of non-RP studies indicated that when all patients received ADT, WPRT was not superior than PORT in OS (HR 0.93, CI 0.75–1.15, p =0.50). Conversely, when no patients received ADT, WPRT significantly improved OS (HR 0.58, CI 0.38–0.89, p = 0.01; Supplementary Figure 1C) than PORT.

#### Subgroup Analysis of Potential **Heterogeneity Factors for Survival Outcomes in Non-RP Studies**

Further subgroup analysis of non-RP studies indicated that the PFS and OS of younger patients (age  $\leq$  66 years) did not benefit from WPRT (p = 0.67 and 0.34, respectively; **Table 2**). Meanwhile, long-term ADT did not have significant advantages in improving PFS and OS (p = 0.85 and 0.98, respectively) over short-term ADT. Moreover, there was still no significant difference in PFS between the higher-risk (intermediate- and high-risk) and low-risk patients (p = 0.34; Supplementary Figure 2). Although when pelvic radiation dose was >49 Gy (equivalent-doses-in-2-Gy-fractions, EQD-2), compared with PORT, WPRT significantly improved PFS (HR 0.83, CI 0.70–0.98, p = 0.03), and the higher pelvic radiation dose (>49Gy, EQD-2) did not seem to have a significant advantage in improving PFS over dose  $\leq$ 49 Gy (*p* = 0.53).

## Gastrointestinal Toxicity

Eight studies (8, 9, 12, 24, 25, 27, 28, 32) evaluated acute GI toxicity and six studies (8, 9, 12, 24, 28, 32) examined late GI toxicity. According to the forest plots (Figure 3), WPRT significantly increased the grade 2 or worse (G2+) acute GI toxicity of non-RP studies (RR 1.75, CI 1.41-2.18, p < 0.001) and RP studies (RR 1.76, CI 1.40–2.22, *p* < 0.001). The forest plots (Figure 3B) illustrated that WPRT also significantly increased G2+ late GI toxicity of non-RP studies (RR 2.19, CI 1.47-3.27, p < 0.001).

#### **Genitourinary Toxicity**

Acute GU toxicity was assessed in eight studies (9, 11, 12, 24, 25, 27, 28, 32) and late GU toxicity was evaluated in seven studies (7-9, 11, 12, 24, 32). The forest plots (Figure 3C) showed that

	BFFS			в	DMFS		
		Hazard Ratio	Hazard Ratio			Hazard Ratio	Hazard Ratio
Study or Subgroup log[H	lazard Ratio] SE V	leight IV. Fixed, 95% C	IV. Fixed, 95% CI	Study or Subgroup log[H	lazard Ratio] SE We	eight IV, Random, 95% CI	IV, Random, 95% Cl
1.1.1 Patients did not under	go radical prostatector	у		1.3.1 Patients did not under	go radical prostatectomy		
Murthy POP-RT	-1.4697 0.4149	3.6% 0.23 [0.10, 0.52]		Murthy POP-RT	-1.0498 0.4323 21	1.0% 0.35 [0.15, 0.82]	
Subtotal (95% CI)		3.6% 0.23 [0.10, 0.52]		Subtotal (95% CI)	21	1.0% 0.35 [0.15, 0.82]	
Heterogeneity: Not applicable				Heterogeneity: Not applicable			
Test for overall effect: Z = 3.5	4 (P = 0.0004)			Test for overall effect: Z = 2.4	3 (P = 0.02)		
1.1.2 Patients underwent rad	dical prostatectomy			1.3.2 Patients underwent ra	dical prostatectomy		
Link 2019	-0.7072 0.3072	6.6% 0.49 [0.27, 0.90]		Pollack PTOG 0534	-0.4432 0.2543 35	5.7% 0.64 [0.39, 1.06]	
Moghanaki 2012	-0.2345 0.3098	6.5% 0.79 [0.43, 1.45]		Ramey 2017	-0.0583 0.1839 43	3.4% 0.94 [0.66, 1.35]	
Pollack PTOG 0534	-0.4005 0.1432	30.4% 0.67 [0.51, 0.89]		Subtotal (95% CI)	79	9.0% 0.81 [0.56, 1.17]	-
Ramey 2017	-0.5978 0.119	4.1% 0.55 [0.44, 0.69]	<b>•</b>	Heterogeneity: Tau <sup>2</sup> = 0.02; C	;hi <sup>2</sup> = 1.50, df = 1 (P = 0.22)	); l <sup>2</sup> = 34%	
Song 2019	-0.8074 0.2675	8.7% 0.45 [0.26, 0.75]		Test for overall effect: Z = 1.1	2 (P = 0.26)		
Subtotal (95% CI)		96.4% 0.58 [0.50, 0.68]	◆				
Heterogeneity: Chi2 = 3.45, df	= 4 (P = 0.49); I <sup>2</sup> = 0%			Total (95% CI)	100	0.0% 0.67 [0.41, 1.09]	
Test for overall effect: Z = 6.6	8 (P < 0.00001)			Heterogeneity: Tau <sup>2</sup> = 0.11; C	hi <sup>2</sup> = 5.04, df = 2 (P = 0.08)	); l <sup>2</sup> = 60%	0.1 0.2 0.5 1 2 5
				Test for overall effect: Z = 1.6	2 (P = 0.11)		Favours WPRT Favours PORT
Total (95% CI)	1	0.0% 0.56 [0.48, 0.66]	•	Test for subgroup differences	: Chi <sup>2</sup> = 3.17, df = 1 (P = 0.0	08), I <sup>2</sup> = 68.4%	
. /							
Heterogeneity: Chi <sup>2</sup> = 8.32, df	= 5 (P = 0.14); I <sup>2</sup> = 40%			100			
Heterogeneity: Chi <sup>2</sup> = 8.32, df Test for overall effect: Z = 7.2	<sup>1</sup> = 5 (P = 0.14); l <sup>2</sup> = 40% 3 (P < 0.00001)		0.01 0.1 1 10 Favours WPRT Favours PORT	100			
Heterogeneity: Chi <sup>2</sup> = 8.32, df Test for overall effect: Z = 7.2 Test for subgroup differences:	<sup>1</sup> = 5 (P = 0.14); I <sup>2</sup> = 40% 3 (P < 0.00001) : Chi <sup>2</sup> = 4.87, df = 1 (P = 0	1.03), I² = 79.4%	0.01 0.1 1 10 Favours WPRT Favours PORT	100			
Heterogeneity: Chi <sup>2</sup> = 8.32, df Test for overall effect: Z = 7.2 Test for subgroup differences:	r = 5 (P = 0.14); i <sup>2</sup> = 40% 3 (P < 0.00001) : Chi <sup>2</sup> = 4.87, df = 1 (P = 0	1.03),  ² = 79.4%	0.01 0.1 1 10 Favours WPRT Favours PORT	<b>D</b>	05		
Heterogeneity: Chi <sup>2</sup> = 8.32, df Test for overall effect: Z = 7.2 Test for subgroup differences:	r = 5 (P = 0.14);   <sup>2</sup> = 40% 3 (P < 0.00001) : Chi <sup>2</sup> = 4.87, df = 1 (P = 0 <b>PFS</b>	1.03), I² = 79.4% Hazard Ratio	0.01 0.1 1 10 Favours WPRT Favours PORT	<b>D</b>	os	Hazard Ratio	Hazard Ratio
Heterogeneity: Chi <sup>2</sup> = 8.32, df Test for overall effect: Z = 7.23 Test for subgroup differences: Study or Subgroup	r = 5 (P = 0.14); l <sup>2</sup> = 40% 3 (P < 0.0001) ; Chi <sup>2</sup> = 4.87, df = 1 (P = 0 <b>PFS</b> [Hazard Ratio] SE	1.03), I² = 79.4% Hazard Ratio Veight IV. Fixed, 95% (	0.01 0.1 1 10 Favours WPRT Favours PORT Hazard Ratio	D Study or Subaroup Ioal	OS Hazard Ratio] SE W	Hazard Ratio /eight IV. Fixed, 95% Cl	Hazard Ratio IV. Fixed, 95% CI
Heterogeneity: Chi <sup>2</sup> = 8.32, df Test for overall effect: Z = 7.2: Test for subgroup differences: Study or Subgroup log[ 1.2.1 Patients did not under	<sup>1</sup> = 5 (P = 0.14); I <sup>2</sup> = 40% 3 (P < 0.00001) : Chi <sup>2</sup> = 4.87, df = 1 (P = 0 <b>PFS</b> [Hazard Ratio] <u>SE</u> 1 go radical prostatectom	1.03), I <sup>2</sup> = 79.4% Hazard Ratio Veight IV. Fixed, 95% (	0.01 0.1 1 10 Favours WPRT Favours PORT Hazard Ratio	D 1.4.1 Patients did not unde	OS <u>Hazard Ratio] SE W</u> reo radical prostatectom	Hazard Ratio Veight IV, Fixed, 95% Cl	Hazard Ratio IV. Fixed. 95% Cl
Heterogeneity: Chi <sup>2</sup> = 8.32, df Test for overall effect. Z = 7.2: Test for subgroup differences: <u>Study or Subgroup log(</u> 1.2.1 Patients did not underg Blanchard GETUG 12	<sup>1</sup> = 5 (P = 0.14); I <sup>2</sup> = 40% 3 (P < 0.00001) : Chi <sup>2</sup> = 4.87, df = 1 (P = 4 <b>PFS</b> [Hazard Ratio] <u>SE</u> <sup>1</sup> go radical prostatectom -0.1278 0.204	1.03), I² = 79.4% Hazard Ratio Veight IV. Fixed, 95% ( / 1.1.1% 0.88 (0.59, 1.31	0.01 0.1 1 10 Favours WPRT Favours PORT Hazard Ratio I.V. Fixed, 95% CI	D Study of Subgroup log[ 1.4.1 Patients did not unde Braussien 2015	OS Hazard Ratio] SE W 20 radical prostatectom -0.0726 0.1111 7	Hazard Ratio /eight IV. Fixed, 95% CI y 78.3% 0.93 (0.75, 1.16)	Hazard Ratio IV. Fixed, 95% Cl
Heterogeneity: Chi <sup>2</sup> = 8.32, df Test for overall effect: Z = 7.2: Test for subgroup differences: Study or Subgroup log( 1.2.1 Patients did not underg Blanchard GETUG 12 Pommier GETUG-10	<sup>i =</sup> 5 (P = 0.14); I <sup>2</sup> = 40% 3 (P < 0.00001) : Chi <sup>2</sup> = 4.87, df = 1 (P = ( PFS [Hazard Ratio] <u>SE</u> <sup>1</sup> go radical prostatectom -0.1278 0.204 -0.048 0.2045	.0.3), I² = 79.4% Hazard Ratio Veight IV. Fixed, 95% ( / 11.1% 0.88 [0.59, 1.31 11.1% 0.86 [0.64, 1.43	0.01 0.1 1 10 Favours WPRT Favours PORT	D Study or Subgroup log 1.4.1 Patients did not unde Braunstein 2015 Murthy POP-RT	OS Hazard Ratio] SE W rgo radical prostatectom -0.0726 0.1111 7 -0.0840 0.4086	Hazard Ratio /eight IV. Fixed. 95% CI y 78.3% 0.93 [0.75, 1.16] 5.8% 0.92 [0.41.2.05]	Hazard Ratio IV. Fixed, 95% Cl
Heterogeneity: Chi <sup>2</sup> = 8.32, df Test for overall effect: Z = 7.2: Test for subgroup differences: Study or Subgroup logf 1.2.1 Patients did not underg Blanchard GETUG 12 Pommier GETUG-01 Roach RTOG 9413	I = 5 (P = 0.14); I <sup>2</sup> = 40% 3 (P < 0.00001) : Chi <sup>2</sup> = 4.87, df = 1 (P = 0 PFS [Hazard Ratio] SE ] go radical prostatectom -0.1278 0.204 -0.0408 0.2045 -0.1912 0.0872	Hazard Ratio Hazard Ratio Veight IV. Fixed, 95% (J 11.1% 0.88 [0.59, 1.31 11.1% 0.96 [0.64, 1.43 60.9% 0.83 [0.70, 0.88	0.01 0.1 1 10 Favours WPRT Favours PORT Hazard Ratio I.V.Fixed, 95% CI	D Study or Subgroup log 1.4.1 Patients did not unde Braunstein 2015 Murthy POP-RT Subtotal (85% cl)	OS Hazard Ratio] SE W rgo radical prostatectom -0.0726 0.1111 7 -0.0834 0.4086	Hazard Ratio /eight V. Fixed, 95% Cl V 78.3% 0.93 [0.75, 1.16] 5.8% 0.92 [0.41, 2.05] 8.41% 0.93 (0.75, 1.15]	Hazard Ratio
Heterogeneity. Chil = 8.32, df Test for overall effect: Z = 7.2: Test for subgroup differences: Study or Subgroup log[ 1.2.1 Patients did not under Blanchard GETUG 12 Pommier GETUG-10 Roach RTOG 9413 Subtotal (95% C0)	i= 5 (P = 0.14); I <sup>2</sup> = 40% 3 (P < 0.0001) : ChI <sup>2</sup> = 4.87, df = 1 (P = ( <b>PFS</b> [Hazard Ratio] <u>SE</u> go radical prostatectom -0.1278 0.204 -0.0408 0.2045 -0.1912 0.0872	Hazard Ratio Veight IV. Fixed. 95% ( / 11.1% 0.88 [0.59, 1.31 11.1% 0.96 [0.64, 1.43 60.9% 0.63 [0.70, 0.98 3.1% 0.85 [0.73, 0.98]	0.01 0.1 1 10 Favours WPRT Favours PORT	D Study or Subgroup log[ 1.4.1 Patients did not unde Braunstein 2015 Murthy POP-RT Subtotal (95% CI) Heterconentiv: Ch <sup>2</sup> = 0.00.d	OS Hazard Ratio] SE W rgo radical prostatectom -0.0726 0.1111 7 -0.0834 0.4086 f = 1 (P = 0.98): P = 0%	Hazard Ratio feight IV, Fixed, 95% CI V 78.3% 0.93 [0.75, 1.16] 5.8% 0.92 [0.41, 2.05] 84.1% 0.93 [0.75, 1.15]	Hazard Ratio IV. Fixed, 95% Cl
Heterogeneity: Chi <sup>2</sup> = 8.32, df Test for overall effect. Z = 7.22 Test for subgroup differences: Study or Subgroup log1 1.2.1 Patients did not underg Blanchard GETUG 12 Pommier GETUG-01 Roach RTOG 9413 Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0.49, df	i= 5 (P = 0.14); P = 40% 3 (P < 0.00001) : ChP = 4.87, df = 1 (P = ( PFS (Hazard Ratio) SE - 1 go radical prostatectom -0.1278 0.204 -0.0408 0.2045 -0.1912 0.0872 = 2 (P = 0.78); P = 0%	Hazard Ratio Hazard Ratio Veight IV. Fixed, 95% / 11.1% 0.88 [0.59, 1.31 11.1% 0.96 [0.64, 1.43 0.9% 0.83 [0.70, 0.98 83.1% 0.85 [0.73, 0.98]	O.1 O.1 I I IO     Favours WPRT Favours PORT     Hazard Ratio     V. Fixed, 95% CI	D Study or Subgroup log 1.4.1 Patients did not unde Braunstein 2015 Murthy POP-RT Subtol (85% CI) Heterogeneity: Chi <sup>2</sup> = 0.00, d Test for overall effect; Z = 0.1	OS Hazard Ratio] SE W -0.0726 0.1111 7 -0.0834 0.4086 f = 1 (P = 0.98); P = 0% 18 (P = 0.49)	Hazard Ratio V. Fixed, 95% CI V 78.3% 0.93 [0.75, 1.16] 5.8% 0.92 [0.41, 2.05] 84.1% 0.93 [0.75, 1.15]	Hazard Ratio
Heterogeneity: Chill e 8.32, df Test for overall effect: Z = 7.2: Test for subgroup differences: Study or Subgroup log( 1.2.1 Patients did not under Blanchard GETUG 12 Pommier GETUG-01 Roach RTOG 9413 Subtotal (95% CI) Heterogeneity: Chill = 0.49, df Test for overall effect Z = 2.1	i= 5 (P = 0.14); P = 40% 3 (P < 0.0001) : ChiP = 4.87, df = 1 (P = ( <b>PFS</b> Hazard Ratio) SE 1 go radical prostatectom -0.1278 0.2045 -0.1912 0.0872 = 2 (P = 0.78); I <sup>2</sup> = 0% 8 (P = 0.03)	Hazard Ratio Hazard Ratio Weight IV. Fixed. 95%. ( 11.1% 0.88 [0.59, 1.31 11.1% 0.96 [0.64, 1.43 00.9% 0.83 [0.70, 0.98 83.1% 0.85 [0.73, 0.98]	0.01 0.1 1 10 Favours WPRT Favours PORT Hazard Ratio I. IV. Fixed. 95% Cl	D Study or Subgroup log( 1.4.1 Patients did not unde Braunstein 2015 Murthy POP-RT Subtotal (6%% C1) Heterogeneity: Ch <sup>2</sup> = 0.00, Test for overall effect: Z = 0.0	OS <u>Hazard Ratio] SE W</u> rgo radical prostatectom -0.0726 0.1111 7 -0.0834 0.4086 4 f= 1 (P = 0.98); I <sup>2</sup> = 0% 18 (P = 0.49)	Hazard Ratio y 78.3% 0.93 (0.75, 1.16) 5.5% 0.92 (0.41, 2.05) 84.1% 0.93 (0.75, 1.15)	Hazard Ratio IV. Fixed, 95% Cl
Heterogeneity: Chi <sup>2</sup> = 8.32, df Test for overall effect. Z = 7.2 Test for subgroup differences: Study or Subgroup log 1.2.1 Patients did not unders Blanchard GETUG 12 Pommier GETUG-01 Roach RTOG 9413 Subtotal (85% CI) Heterogeneity: Chi <sup>2</sup> = 0.49, df Test for overall effect. Z = 2.18	i= 5 (P = 0.14); P = 40% 3 (P < 0.00001) ChP = 4.87, df = 1 (P = ( <b>PFS</b> [Hazard Ratio] SE _ 1 go radical prostatectom -0.1278 0.204 -0.0408 0.2045 -0.1912 0.0872 = 2 (P = 0.78); P = 0% 8 (P = 0.03)	0.03), I <sup>2</sup> = 79.4% Hazard Ratio Veght IV, Fixed, 35% ( 11.1% 0.88 [0.59, 1.31 11.1% 0.96 [0.64, 1.43 60.9% 0.83 [0.70, 0.98 83.1% 0.85 [0.73, 0.98]	Hazard Ratio	D Study or Subgroup log 1.4.1 Patients did not unde Braunstein 2015 Murthy POP-RT Subtota (165% cl) Heterogeneity: Chi <sup>2</sup> = 0.00, Test for overall effect: Z = 0.4 1.4.2 Patients underwent ra	OS           Hazard Ratio]         SE W           rgo radical prostatectom         -0.0726 0.1111 7           -0.0834 0.4086         4           f = 1 (P = 0.98); P = 0%         8           8 (P = 0.49)         dical prostatectomy	Hazard Ratio (eight IV, Fixed, 85%, CI V 8.03% 0.93 (0.75, 1.16) 5.8% 0.92 (0.41, 2.05) 84.1% 0.93 (0.75, 1.15)	Hazard Ratio IV. Fixed, 95% Cl
Heterogeneity: Chi <sup>2</sup> e 8.32, df Test for overall effect: Z = 7.2: Test for subgroup differences: Study or Subgroup long 1.2.1 Patients did not underg Blanchard GETUG 12 Pommier GETUG 12 Pommier GETUG-01 Roach RTOG 9413 Subtotal (95% G1) Heterogeneity: Chi <sup>2</sup> e 0.49, df Test for overall effect: Z = 2.1 1.2.2 Patients underwent rac	i= 5 (P = 0.14); P = 40% 3 (P < 0.0001) : Chi <sup>2</sup> = 4.87, df = 1 (P = ( <b>PFS</b> <u>Hazard Ratio</u> <u>SE</u> 1 gor adical prostatectom -0.1278 0.204 -0.0408 0.2045 -0.1912 0.0872 i= 2 (P = 0.03); I <sup>2</sup> = 0% df (P = 0.03) df cal prostatectomy	Hazard Ratio Hazard Ratio Weight IV. Fixed. 95% ( 11.1% 0.88 [0.59, 1.31 11.1% 0.96 [0.54, 1.43 60.9% 0.83 [0.70, 0.98 83.1% 0.85 [0.73, 0.38]	0.01 0.1 1 10 Favours WPRT Favours PORT	D Study or Subgroup log( 1.4.1 Patients did not unde Braunstein 2015 Murthy POP-RT Subtota (69% Ct) Heterogeneity: Ch <sup>2</sup> = 0.0, d Test for overall effect: Z = 0.1 1.4.2 Patients underwent Tr Pollock PTOG 0534	DS           Hazard Ratio]         SE W           rgo radical prostatectom         -0.0726 0.1111           -0.0834 0.4086         1111           if = 1 (P = 0.98); P = 0.98         8 (P = 0.49)           idcal prostatectomy         -0.0101 0.2462	Hazard Ratio leight IV, Fixed, 95% CI y X83% 0.93 [0.75, 1.16] 5.8% 0.92 [0.41, 2.05] 4.1% 0.93 [0.75, 1.15] 15.9% 0.99 [0.61, 1.60]	Hazard Ratio IV. Fixed. 95% Cl
Heterogeneity: Chi <sup>2</sup> = 8.32, df Test for voral effect. Z = 7.2. Test for subgroup differences: Study or Subgroup log 1.2.1 Patients did not unders Blanchard GETUG 12 Pommier GETUG-01 Roach RTOG 9413 Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0.49, df Test for overall effect. Z = 2.11 1.2.2 Patients underwent rac Poliack RTOG 0534	= 5 (P = 0.14); P = 40% 3 (P < 0.0001) : ChP = 4.87, df = 1 (P = ( <b>PFS</b> (Hazard Ratio) SE 1 go radical prostatectom -0.1278 0.204 -0.0408 0.2045 -0.1912 0.0872 = 2 (P = 0.78); P = 0% 8 (P = 0.03) dical prostatectomy -0.3425 0.1568	1.03), I <sup>2</sup> = 79.4%           Hazard Ratio           Weight         N. Fixed, 35% of           11.1%         0.88 [0.59, 1.31]           11.1%         0.86 [0.59, 1.31]           0.96 [0.64, 1.43]         0.96 [0.64, 1.43]           0.98 [0.70, 0.98]         0.83 [0.70, 0.98]           16.9%         0.71 [0.51, 0.98]	Hazard Ratio	D Study or Subgroup log( 1.4.1 Patients did not unde Braunstein 2015 Murthy POP-RT Subtota (16%; Cl) Heterogeneity: Chi <sup>2</sup> = 0.00, d Test for overall effect: Z = 0.1 1.4.2 Patients underwent re Poliack PTOG 0034 Subtota (16%; Cl)	DS           Hazard Ratio]         SE W           rgo radical prostatectom         -0.0726 0.1111 7           -0.0834 0.4086         4           f = 1 (P = 0.98); I <sup>2</sup> = 0%         30           30 (P = 0.49)         4           dical prostatectomy         -0.0101 0.2462 1	Hazard Ratio (eight IV, Fixed, 85% CI V 78.3% 0.93 [0.75, 1.16] 5.8% 0.92 [0.41, 2.05] 84.1% 0.93 [0.75, 1.15] 15.9% 0.99 [0.61, 1.60]	Hazard Ratio IV. Fixed. 95%. Cl
Heterogeneity: Chi <sup>+</sup> = 8.32, df Test for overall effect: Z = 7.2: Test for subgroup differences: Study or Subgroup log( 1.2.1 Patients did not underg Blanchard GETUG 12 Pommier GETUG-12 Pommier GETUG-04 Roach RTOG 9413 Subtotal (95% CI) Heterogeneity: Chi <sup>+</sup> = 0.49, df Test for overall effect: Z = 2.11 <b>1.2.2 Patients underwent rac</b> Pollack RTOG 0534 Subtotal (95% CI)	= 5 (P = 0.14); P = 40% 3 (P < 0.0001) : Chi <sup>2</sup> = 4.87, df = 1 (P = 6 <b>PFS</b> <u>Hazard Ratio</u> <u>SE</u> 1 go radical prostatectom -0.1278 0.204 -0.0408 0.2045 0.0408 0.2045 = 2 (P = 0.78); P = 0% 8 (P = 0.03) dical prostatectomy -0.3425 0.1658	1.03), I <sup>2</sup> = 79.4% Hazard Ratio Weight IV. Fixed. 85% ( / 11.1% 0.88 [0.59, 1.31 11.1% 0.88 [0.59, 1.31 11.1% 0.88 [0.59, 1.31 11.9% 0.85 [0.73, 0.98] 16.9% 0.71 [0.51, 0.98] 16.9% 0.71 [0.51, 0.98]	0.01 0.1 1 10 Favours WPRT Favours PORT	D Study or Subgroup log( 1.4.1 Patients did not unde Braunstein 2015 Murthy POP-RT Subtotal (95% C1) Heterogeneity: Chi <sup>at</sup> = 0.00, d Test for overall effect. Z = 0.1 1.4.2 Patients underweht re Pollack PTOG 053/4 Subtotal (95% C1) Heterogeneity: Not applicabile	DS           Hazard Ratio         SE W           rgo radical prostatectom         -0.0726 0.1111           -0.0834 0.4086         4           f = 1 (P = 0.98); P = 0.9         4           idcal prostatectomy         -0.0101 0.2462 1           ,         ,	Hazard Ratio (eight W. Fixed. 35% Cl y 7.83% 0.93 [0.75, 1.16] 5.8% 0.92 [0.41, 2.05] 84.1% 0.93 [0.75, 1.15] 15.9% 0.99 [0.61, 1.60]	Hazard Ratio IV. Fixed. 95% Cl
Heterogeneity: Chi <sup>2</sup> = 8.22, df Test for overall effect: 2 = 7.22 Test for subgroup differences: Study or Subgroup log[ 1.2.1 Patients did not underg Bianchard GETUG-12 Pommier GETUG-01 Roach RTOG 9413 Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0.49, df Test for overall effect: 2 = 2.11 1.2.2 Patients underwent rac Pollack RTOG 0534 Subtotal (95% CI) Heterogeneity: Not applicable	[= 5 (P = 0.14); P = 40% 3 (P < 0.0001) : ChP = 4.87, df = 1 (P = ( <b>PFS</b> [Hazard Ratio] SE 1 go radical prostatectom -0.1278 0.204 -0.0408 0.2045 -0.1912 0.0872 = 2 (P = 0.78); P = 0% 8 (P = 0.03) dical prostatectomy -0.3425 0.1658	10.3), I² = 79.4%           Hazard Ratio           Veight         IV. Fixed, 35% of           11.1%         0.88 [0.59, 1.31]           11.1%         0.86 [0.59, 1.31]           11.1%         0.86 [0.59, 1.31]           10.9%         0.81 [0.70, 0.98]           83.1%         0.85 [0.73, 0.98]           16.9%         0.71 [0.51, 0.98]           16.9%         0.71 [0.51, 0.98]	0.01 0.1 1 10 Favours WPRT Favours PORT	D Study or Subgroup log 1.4.1 Patients did not unde Braunstein 2015 Murthy POP-RT Subtoal (65% c1) Heterogeneity: Chi <sup>2</sup> = 0.00, d Test for overall effect; Z = 0.1 1.4.2 Patients underwent ra Poliack PTCG 0534 Subtoal (65% c1) Heterogeneity: Not applicable Test for overall effect; Z = 0.0	DS           Hazard Ratio]         SE W           rgo radical prostatectom         -0.0726 0.1111           -0.0834 0.4086         4           f = 1 (P = 0.98); P = 0%         8           8 (P = 0.49)         udical prostatectomy           -0.0101 0.2462         1           ',         (P = 0.97)	Hazard Ratio (eight IV, Fixed, 85% CI V X 8.3% 0.93 [0.75, 1.16] 5.8% 0.92 [0.41, 2.05] 84.1% 0.93 [0.75, 1.15] 15.9% 0.99 [0.61, 1.60]	Hazard Ratio IV. Fixed. 95%. Cl
Heterogeneity: Chill = 8.32, df Test for overall effect: Z = 7.2: Test for subgroup differences: Study or Subgroup logd 1.2.1 Patients did not underg Blanchard GETUG 12 Pormier GETUG-12 Pormier GETUG-04 Heterogeneity: Chill = 0.49, df Test for overall effect: Z = 2.18 1.2.2 Patients underwent rac Pollack RTOG 0534 Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 2.18	= 5 (P = 0.14); P = 40% 3 (P < 0.0001) : Chi <sup>2</sup> = 4.87, df = 1 (P = t PFS Hazard Ratio) SE 1 go radical prostatectom -0.1278 0.204 -0.0408 0.2045 -0.9192 0.0872 = 2 (P = 0.78); I <sup>2</sup> = 0% 6 (P = 0.03); I <sup>2</sup> = 0% 6 (P = 0.03); I <sup>2</sup> = 0% 6 (P = 0.04)	Hazard Ratio Hazard Ratio Weight IV. Fixed. 95% ( 11.1% 0.88 [0.59, 1.31 11.1% 0.98 [0.64, 1.43 0.9% 0.81,070, 0.98 83.1% 0.85 [0.73, 0.98] 16.9% 0.71 [0.51, 0.98]	0.01 0.1 1 10 Favours WPRT Favours PORT	D Study or Subgroup log( 1.4.1 Patients did not unde Braunstein 2015 Murthy POP-RT Subtotal (69% CI) Heterogeneity: Chi <sup>#</sup> = 0.00, d Test for overall effect: Z = 0.0 1.4.2 Patients underwent rz Polisick PTOG 0534 Subtotal (69% CI) Heterogeneity: Not applicable Test for overall effect: Z = 0.0	DS           Hazard Ratio]         SE W           rgo radical prostatectom         -0.0726 0.1111           -0.0834 0.4086         4           f = 1 (P = 0.98); P = 0%         38 (P = 0.49)           udical prostatectomy         -0.0101 0.2462 1           -0.101 0.2462 1         -0.111           -0.010 1 0.2462 1         -0.111	Hazard Ratio /elght /V, Fixed, 85% CI y 78.3% 0.93 [0.75, 1.16] 5.8% 0.92 [0.41, 2.05] 84.1% 0.93 [0.75, 1.15] 15.9% 0.99 [0.61, 1.60] 15.9% 0.99 [0.61, 1.60]	Hazard Ratio
Heterogeneity: Chi <sup>2</sup> = 8.32, df Test for overall effect: Z = 7.23 Test for subgroup differences: Study or Subgroup log( 1.2.1 Patients did not unders Blanchard GETUG 12 Pommier GETUG-10 Roach RTOG 9413 Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0.49, df Test for overall effect: Z = 2.16 1.2.2 Patients undersent rac Pollack RTOG 0534 Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 2.07	$\begin{array}{l} = 5 \ (P = 0.14); \ P = 40\% \\ s \ (P < 0.0001) \\ : \ ChP = 4.87, \ df = 1 \ (P = 0) \\ \hline \end{array} \\ \hline \begin{array}{l} \textbf{PFS} \\ \hline \end{array} \\ \hline \begin{array}{l} \textbf{Idazard Ratio} \\ -0.1278 \ 0.204 \\ -0.0408 \ 0.2045 \\ -0.1912 \ 0.204 \\ -0.0408 \ 0.2045 \\ \hline \end{array} \\ \hline \begin{array}{l} s \ (P = 0.03) \\ \hline \end{array} \\ \hline \begin{array}{l} s \ (P = 0.03) \\ \hline \end{array} \\ \hline \begin{array}{l} s \ (P = 0.03) \\ \hline \end{array} \\ \hline \end{array} \\ \hline \begin{array}{l} s \ (P = 0.03) \\ \hline \end{array} \\ \hline \end{array} \\ \hline \begin{array}{l} s \ (P = 0.04) \\ \hline \end{array} \\ \hline \begin{array}{l} r \ (P = 0.04) \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \hline \begin{array}{l} r \ (P = 0.04) \\ \hline \end{array} \\ \hline \begin{array}{l} r \ (P = 0.04) \\ \hline \end{array} \\ \hline \begin{array}{l} r \ (P = 0.04) \\ \hline \end{array} $ \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \\ \hline \end{array} \\ \hline \end{array} \\ \\ \hline \end{array} \\ \hline \end{array}  \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array} \\ \\ \hline \end{array}  \\ \hline \end{array}  \\ \hline  \\ \hline \end{array} \\ \hline \end{array} \\ \hline \end{array}  \\ \hline \end{array}  \\ \hline \end{array}  \\ \hline \end{array}  \\ \hline \end{array}  \\ \hline \end{array}  \\ \hline \end{array}  \\ \hline \end{array}  \\ \hline \end{array}  \\ \hline \end{array}  \\ \hline \end{array}  \\ \hline \end{array}  \\ \hline \end{array} \\ \\ \hline \end{array}  \\ \hline \end{array}  \\ \hline \end{array}  \\ \hline \\ \\ \end{array}  \\ \hline \end{array}  \\ \hline \end{array}  \\ \hline \\ \end{array}  \\ \hline \\ \\ \hline \end{array}  \\ \\ \hline \end{array}  \\ \hline \\ \\ \end{array}  \\ \\ \\ \\ \end{array}   \\ \\ \\ \hline \end{array}  \\ \\ \\ \end{array}  \\ \\ \\ \\ \end{array}   \\ \\ \\ \\ \end{array}  \\ \\ \\ \\	1.03), I <sup>2</sup> = 79.4% Hazard Ratio Veight IV, Fixed, 35% of (1.0, 0.86 [0.59, 1.31 11.1% 0.86 [0.59, 1.31 11.1% 0.96 [0.54, 1.43 0.9% 0.85 [0.70, 0.98 83.1% 0.85 [0.73, 0.98] 16.9% 0.71 [0.51, 0.98 16.9% 0.71 [0.51, 0.98]	0.01 0.1 1 1 Favours WPRT Favours PORT Hazard Ratio 1 V. Fixed, 95% Cl	D Study or Subgroup log( 1.4.1 Patients did not unde Braunstein 2015 Murthy POP-RT Subtoal (65% CI) Heterogeneity: Chi <sup>2</sup> = 0.00, 1.4.2 Patients underwent ra Polack PTGG 0534 Subtoal (65% CI) Heterogeneity: Not applicable Test for overail effect: Z = 0.0 Total (95% CI)	DS           Hazard Ratio)         SE W           rgo radical prostatectom         -0.0726 0.1111           -0.0834 0.4086         4           f=1 (P=0.98); P=0%         8           8(P=0.49)         10           udical prostatectomy         -0.0101 0.2462           i4 (P=0.97)         11	Hazard Ratio (eight IV, Fixed, 85% CI Y X8% 0.93 [0.75, 1.16] 5.8% 0.92 [0.41, 2.05] 84.1% 0.93 [0.75, 1.15] 15.9% 0.99 [0.61, 1.60] 15.9% 0.99 [0.61, 1.60] 0.99 (0.61, 1.60] 0.99 (0.61, 1.60]	Hazard Ratio IV. Fixed. 95% Cl
Heterogeneity: Chi <sup>2</sup> = 8.32, df Test for overall effect: Z = 7.2; Test for subgroup differences: Study or Subgroup long 1.2,1 Patients did not unders Blanchard GETUG 12 Pommier GETUG-01 Roach RTOG 9413 Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0.49, df Test for overall effect: Z = 2.18 1.2,2 Patients underwent rac Poliaek RTOG 0634 Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 2.00 Total (95% CI)	i= 5 (P = 0.14); P = 40% 3 (P < 0.0001) : Chi <sup>2</sup> = 4.87, df = 1 (P = i PFS (Hazard Ratio) SE 1 go radical prostatectom -0.1278 0.204 -0.0408 0.2045 -0.1912 0.0872 = 2 (P = 0.78); I <sup>2</sup> = 0% 8 (P = 0.03) dical prostatectomy -0.3425 0.1558 7 (P = 0.04)	103), I² = 79.4%           Hazard Ratio           Veight         W. Fixed, 85% (           /         1.1%           11.1%         0.88 [0.59, 1.31]           11.1%         0.88 [0.59, 1.31]           0.60 (0.41, 1.43)         0.85 [0.70, 0.88]           83.1%         0.85 [0.70, 0.88]           16.9%         0.71 [0.51, 0.98]           00.0%         0.82 [0.72, 0.94]	0.01 0.1 1 10 Favours WPRT Favours PORT	D Study or Subgroup log( 1.4.1 Patients did not unde Braunstein 2015 Murthy POP-RT Subtral (95% C1) Heterogeneity: Chi = 0.00, d Test for overall effect. Z = 0.0 1.4.2 Patients underwent zr Poliack PTOG 0534 Subtral (95% C1) Heterogeneity: Chi = 0.06, d Total (95% C1) Heterogeneity: C1	DS           Hazard Ratio]         SE W           rgo radical prostatectom         -0.0726 0.1111           -0.0834 0.4086         1           f = 1 (P = 0.98); P = 0%         1           i8 (P = 0.99)         1           udical prostatectomy         -0.0101 0.2462           i4 (P = 0.97)         1           f = 2 (P = 0.97); P = 0%         1	Hazard Ratio /elght /V, Fixed, 85% CI y X83% 0.93 [0.75, 1.16] 5.8% 0.92 [0.41, 2.05] 84.1% 0.93 [0.75, 1.15] 15.9% 0.99 [0.61, 1.60] 15.9% 0.99 [0.61, 1.60] 00.0% 0.94 [0.77, 1.14]	Hazard Ratio IV. Fixed. 95% CI
Heterogeneity: Cohile 3.22, df Test for overall effect: Z = 7.23 Test for subgroup differences: Study or Subgroup log( 1.2.1 Patients did not unders Blanchard GETUG 12 Pommier GETUG-01 Roach RTOG 9413 Subtotal (95% CI) Heterogeneity: Chile 0.49, df Test for overall effect: Z = 2.11 1.2.2 Patients underwent rac Pollack RTOG 0534 Subtotal (95% CI) Heterogeneity: Chile 1.47, df Heterogeneity: Chile 1.47, df	= 5 (P = 0.14); P = 40% 3 (P < 0.0001) : ChP = 4.87, df = 1 (P = ( <b>PFS</b> [Hazard Ratio] SE = 1 go radical prostatectom -0.1278 0.204 -0.0408 0.2045 2 (P = 0.03) 8 (P = 0.03) Hick prostatectomy -0.3425 0.1658 7 (P = 0.04) = 3 (P = 0.69); P = 0%	1.03), I² = 79.4%           Hazard Ratio           Yeight         IV, Fixed, 35% of           11.1%         0.86 [0.59, 1.31]           11.1%         0.86 [0.59, 1.31]           11.1%         0.86 [0.70, 0.86]           0.9%         0.83 [0.70, 0.86]           83.1%         0.86 [0.73, 0.98]           16.9%         0.71 [0.51, 0.98]           16.9%         0.71 [0.51, 0.98]           00.0%         0.82 [0.72, 0.94]	Hazard Ratio	D Study or Subgroup log 1.4.1 Patients did not unde Braunstein 2015 Murthy POP-RT Subtoal (65% C1) Heterogeneity: Chi <sup>2</sup> = 0.00, d Test for overall effect: Z = 0.4 1.4.2 Patients underwent ra Polack PTOG 0534 Subtoal (65% C1) Heterogeneity: Not applicable Test for overall effect: Z = 0.0 Total (95% C1) Heterogeneity: Chi <sup>2</sup> = 0.0, d, d Test for overall effect: Z = 0.0	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Hazard Ratio feight IV, Fixed, 85% CI V 78% 0.93 [0.75, 1.16] 5.8% 0.92 [0.41, 2.05] 84.1% 0.93 [0.75, 1.15] 15.9% 0.99 [0.61, 1.60] 15.9% 0.99 [0.61, 1.60] 0.0% 0.94 [0.77, 1.14]	Hazard Ratio IV. Fixed. 95% Cl

FIGURE 2 | Forest plots of BFFS (A), PFS (B), DMFS (C) and OS (D). CI, confidence interval; WPRT, whole-pelvic radiotherapy; PORT, prostate-only radiotherapy; BFFS, biochemical failure-free survival; PFS, progression-free survival; DMFS, distant metastasis-free survival; OS, overall survival.

TABLE 2 | Subgroup analysis of other potential heterogeneity factors for survival outcomes in non-prostatectomy studies.

Heterogeneity factors	Hazard ratio (95% CI) WPRT vs. PORT	<i>p</i> -Value	<i>p</i> -Value for Interaction	l² (%)
Age > 66 for PFS				
Yes	0.77 [0.60, 1.00]	p = 0.05	p = 0.67	0
No	0.83 [0.70, 0.98]	p = 0.03		
Duration of ADT for PFS				
Long-term ADT	0.88 [0.59, 1.31]	p = 0.53	p = 0.85	0
Short-term ADT	0.85 [0.72, 0.99]	p = 0.04		
Dose >49 Gy* for PFS				
Yes	0.83 [0.70, 0.98]	p = 0.03	p = 0.53	0
No	0.92 [0.66, 1.02]	p = 0.56		
Risk goup for PFS				
Low risk	0.71 [0.41, 1.21]	p = 0.21	p = 0.34	0
Intermediate and high risk	0.95 [0.75, 1.20]	p = 0.66		
Age > 66 for OS				
Yes	0.95 [0.77, 1.18]	p = 0.64	p = 0.34	0
No	0.55 [0.18, 1.64]	p = 0.28		
Duration of ADT for OS				
Long-term ADT	0.92 [0.41, 2.05]	p = 0.84	p = 0.98	0
Short-term ADT	0.93 [0.75, 1.16]	p = 0.52		

WPRT, whole-pelvic radiotherapy; PORT, prostate-only radiotherapy; ADT, androgen deprivation therapy; BT, brachytherapy; BFFS, biochemical failure-free survival; PFS, progression-free survival; DMFS, Distant metastasis-free survival; OS, overall survival.

\*Equivalent-doses-in-2-Gy-fractions, EQD-2.

there was no statistically significant difference in the G2+ acute GU toxicity of non-RP studies (RR 1.06, CI 0.91–1.25, p = 0.43) and RP studies (RR 1.15, CI 0.80–1.66, p = 0.45). According to the forest plots (**Figure 3D**), there was still no significant difference in the G2+ late GU toxicity of non-RP studies (RR 1.33, CI 0.83–2.13, p = 0.23) and RP studies (RR 1.36, CI 0.97–1.91, p = 0.07). The risk difference of toxicity has been presented in **Supplementary Figure 3**.

#### Subgroup Analysis of Potential Heterogeneity Factors for GI Toxicity and GU Toxicity in Non-RP Studies

Further subgroup analysis of non-RP studies indicated that when pelvic radiation dose was >49 Gy (EQD-2), WPRT significantly increased the G2+ acute GU toxicity (RR 1.26, CI 1.04–1.54, p = 0.02; **Figure 4A**) and late GU toxicity (RR 2.04, CI 1.33–3.15, p = 0.001; **Figure 4B**). On the contrary, when pelvic radiation dose

		cute G	Risk Ratio	Risk Patio		-	WPRT	PORT	cute Gt	Risk Ratio	Risk Ratio
Study or Subgroup	Events Total Events Total	Weight	M-H. Fixed, 95% CI	M-H. Fixed, 95%	6 CI	Study or Subgroup	Events Total E	Events Total	Weight	M-H. Fixed, 95% Cl	M-H. Fixed, 95% CI
1.1.1 Patients did not	undergo radical prostatectom	у				1.3.1 Patients did not u	ndergo radical p	rostatectomy	1		
Dearnaley PIVOTAL	3 62 2 61	1.2%	1.48 [0.26, 8.53]			Mantini 2011	19 168	29 190	10.5%	0.74 [0.43, 1.27]	
Mantini 2011	17 168 19 190	10.4%	1.01 [0.54, 1.88]			McDonald 2014	54 103	52 109	19.5%	1.10 [0.84, 1.44]	
McDonald 2014	38 103 19 109	10.8%	2.12 [1.31, 3.42]			Murthy POP-RT	35 107	26 107	10.0%	1.35 [0.87, 2.07]	
Murthy POP-RT	35 107 27 107	15.7%	1.30 [0.85, 1.98]			Pommier GETUG-01	59 225	68 221	26.5%	0.85 [0.63, 1.14]	
Roach RTOG 9413	144 309 27 131	22.1%	2.26 [1.58, 3.23]			Roach RTOG 9413	97 309	29 131	15.7%	1.42 [0.99, 2.03]	
Subtotal (95% CI)	749 598	60.2%	1.75 [1.41, 2.18]	•		Subtotal (95% CI)	912	758	82.4%	1.06 [0.91, 1.25]	T
Total events	237 94					Total events	264	204			
Heterogeneity: Chi <sup>2</sup> = 7.	.54, df = 4 (P = 0.11); l <sup>2</sup> = 47%					Heterogeneity: Chi <sup>2</sup> = 7.5	53, df = 4 (P = 0.1	1); l² = 47%			
Test for overall effect: Z	2 = 5.02 (P < 0.00001)					l est for overall effect: Z	= 0.79 (P = 0.43)				
1 1 2 Patiente underw	ent radical prostatectomy					1.3.2 Patients underwe	nt radical prosta	tectomy			
Douillo 2011	22 26 0 21	E 69/	2 10 11 14 2 971		-	Deville 2011	8 36	3 31	1.2%	2.30 [0.67, 7.91]	
Jehii 2016	17 119 7 105	4 39/	2.10 [1.14, 3.07]		_	Ishii 2016	15 119	11 105	4.5%	1.20 [0.58, 2.50]	
Waldstein 2017	54 128 115 447	29.8%	1 64 [1 27 2 12]	-		Waldstein 2017	20 128	69 447	11.9%	1.01 [0.64, 1.60]	
Subtotal (95% CI)	283 583	39.8%	1.76 [1.40, 2.22]	•		Subtotal (95% CI)	283	583	17.6%	1.15 [0.80, 1.66]	+
Total events	93 131					Total events	43	83			
Heterogeneity: Chi <sup>2</sup> = 0	.83, df = 2 (P = 0.66); I <sup>2</sup> = 0%					Heterogeneity: Chi <sup>2</sup> = 1.5	52, df = 2 (P = 0.4	7); I <sup>2</sup> = 0%			
Test for overall effect: Z	z = 4.79 (P < 0.00001)					Test for overall effect: Z	= 0.75 (P = 0.45)				
Total (95% CI)	1032 1181	100.0%	1.76 [1.49, 2.06]	•		Total (95% CI)	1195	1341	100.0%	1.08 [0.93, 1.25]	T
Total events	330 225					Total events	307	287			
Heterogeneity: Chi <sup>2</sup> = 8	.37, df = 7 (P = 0.30); l <sup>2</sup> = 16%			0.01 0.1 1	10 100	Heterogeneity: Chi+ = 9.1	14, df = 7 ( $P = 0.2$	4); 1* = 23%			0.1 0.2 0.5 1 2 4
Test for overall effect: Z	2 = 6.86 (P < 0.00001)			Favours WPRT Favou	ITS PORT	Test for overall effect: 2	= 1.05 (P = 0.30)				Favours WPRT Favours POR
						Toot for aubaroup diffore	000011100 = 11116	AT = 1 AA = 0	7(1) 12 = 0.97		
Test for subgroup differ	rences: Chi <sup>2</sup> = 0.00, df = 1 (P = 0	).98), I <sup>2</sup> = 0%	6			Test for subgroup differe	nces: Cni* = 0.15,	, df = 1 (P = 0.	70), I <sup>2</sup> = 0%	3	
Test for subgroup differ	ences: Chi <sup>2</sup> = 0.00, df = 1 (P = 0	0.98), I² = 0%	6			Test for subgroup differe	nces: Cni* = 0.15,	, at = 1 (P = 0.	70), I <sup>2</sup> = 0%	5	
Test for subgroup differ	ences: Chi <sup>2</sup> = 0.00, df = 1 (P = 0 L WPRT PORT	.98), I <sup>2</sup> = 09 ate GU	6 Risk Ratio	Risk Ratio		Test for subgroup differe	WPRT	, df = 1 (P = 0.	70), 1² = 0% .ate GU	Risk Ratio	Risk Ratio
Test for subgroup differ	ences: Chi <sup>2</sup> = 0.00, df = 1 (P = 0 L WPRT PORT Events Total Events Total	0.98), I <sup>2</sup> = 09 ate GU Weight	Risk Ratio M-H. Fixed, 95% CI	Risk Ratio M-H. Fixed, 95%		Test for subgroup differe D	WPRT Events Total E	PORT	70), l <sup>2</sup> = 0% .ate GU .Weight M	Risk Ratio I-H. Random. 95% CI	Risk Ratio M-H. Random, 95% Cl
Test for subgroup differ  Study or Subgroup  1.2.1 Patients did not u	ences: Chi <sup>2</sup> = 0.00, df = 1 (P = 0 WPRT PORT <u>Events Total Events Total</u> undergo radical prostatectomy	0.98), I <sup>z</sup> = 09 <b>ate GU</b> <u>Weight</u>	Kisk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H. Fixed. 95%	. <u>Cl</u>	Test for subgroup differe D Study or Subgroup 1.4.1 Patients did not ur	WPRT Events Total Endergo radical pro	PORT vents Total	70), l <sup>2</sup> = 0% .ate GU .Weight M	Risk Ratio 1-H. Random. 95% CI	Risk Ratio M-H. Random. 95% Cl
Study or Subgroup     1.2.1 Patients did not u     Dearnaley PIVOTAL	ences: Chi <sup>2</sup> = 0.00, df = 1 (P = 0 WPRT PORT <u>Events Total Events Total</u> undergo radical prostatectomy 15 62 10 62	0.98), 1 <sup>2</sup> = 09 <b>.ate GU</b> <u>Weight</u> y 16.1%	6 Risk Ratio <u>M-H. Fixed, 95% CI</u> 1.50 [0.73, 3.08]	Risk Ratio <u>M-H. Fixed. 95%</u>	. <u>Cl</u>	Test for subgroup differe     Study or Subgroup     1.4.1 Patients did not ur     Blanchard GETUG 12	WPRT Events Total E 1dergo radical pro 17 171	PORT vents Total ostatectomy 13 125	70), I <sup>2</sup> = 0% .ate GU <u>Weight N</u> 12.4%	Risk Ratio 1-H. Random. 95% CI 0.96 [0.48, 1.89]	Risk Ratio M-H. Random. 95% Cl
Test for subgroup differ <u>Study or Subgroup</u> 1.2.1 Patients did not u Dearnaley PIVOTAL McDonald 2014	ences: Chi <sup>p</sup> = 0.00, df = 1 (P = 0 WPRT PORT <u>Events Total Events Total</u> undergo radical prostatectomy 15 62 10 62 16 103 6 109	0.98), I <sup>2</sup> = 0% .ate GU 	<ul> <li>Risk Ratio</li> <li>M-H, Fixed, 95% CI</li> <li>1.50 [0.73, 3.08]</li> <li>2.82 [1.15, 6.93]</li> </ul>	Risk Ratio M-H. Fixed, 95%	. <u>cı</u>	Test for subgroup differe <b>D</b> <u>Study or Subgroup</u> 1.4.1 Patients did not ur Blanchard GETUG 12 Dearnaley PIVOTAL	WPRT Events Total E ndergo radical pro 17 171 3 62	PORT vents Total ostatectomy 13 125 3 62	70), I <sup>2</sup> = 0% .ate GU <u>Weight N</u> 12.4% 3.5%	Risk Ratio 1-H. Random. 95% CI 0.96 [0.48, 1.89] 1.00 [0.21, 4.76]	Risk Ratio M-H. Random. 95% Cl
Test for subgroup differ <u>Study or Subgroup</u> 1.2.1 Patients did not u Deamaley PIVOTAL McDonald 2014 Murthy POP-RT	ences: Chi <sup>p</sup> = 0.00, df = 1 (P = 0 WPRT PORT Events Total Events Total undergo radical prostatectomy 15 62 10 62 16 103 6 109 9 110 5 112	0.98), I <sup>2</sup> = 09 ate GU <u>Weight</u> y 16.1% 9.4% 8.0%	Kisk Ratio M-H. Fixed, 95% CI 1.50 [0.73, 3.08] 2.82 [1.15, 6.93] 1.83 [0.63, 5.30]	Risk Ratio M-H, Fixed, 95%	. <u>ci</u>	Test for subgroup differe D <u>Study or Subgroup</u> 1.4.1 Patients did not ur Blanchard GETUG 12 Dearnaley PIVOTAL Murthy POP-RT	WPRT Events Total E ndergo radical pro 17 171 3 62 22 110	December 2014 Percent	70), I <sup>2</sup> = 0% ate GU <u>Weight N</u> 12.4% 3.5% 12.1%	Risk Ratio <u>1-H. Random. 95% CI</u> 0.96 [0.48, 1.89] 1.00 [0.21, 4.76] 2.24 [1.11, 4.51]	Risk Ratio M-H, Random, 95% Cl
Test for subgroup differ 	ences: Chi <sup>p</sup> = 0.00, df = 1 (P = 0 WPRT PORT Events Total Events Total undergo radical prostatectomy 15 62 10 62 16 103 6 109 9 110 5 112 55 309 9 131	0.98), I <sup>2</sup> = 09 ate GU Weight 9 16.1% 9.4% 8.0% 20.4%	<ul> <li>Risk Ratio</li> <li>M-H. Fixed, 95% CI</li> <li>1.50 [0.73, 3.08]</li> <li>2.82 [1.15, 6.93]</li> <li>1.83 [0.63, 5.30]</li> <li>2.59 [1.32, 5.09]</li> </ul>	Risk Ratio M-H. Fixed, 95%	. <u>cı</u>	Test for subgroup differe D Study or Subgroup 1.4.1 Patients did not ur Blanchard GETUG 12 Dearnaley PIVOTAL Murthy POP.RT Pommier GETUG-01	WPRT           Events         Total         E           ndergo         radical         product           17         171         3         62           22         110         84         225	, or = 1 (P = 0. PORT vents Total postatectomy 13 125 3 62 10 112 90 221	70), I <sup>2</sup> = 0% ate GU Weight N 12.4% 3.5% 12.1% 26.6%	Risk Ratio <u>1-H. Random. 95% CI</u> 0.96 [0.48, 1.89] 1.00 [0.21, 4.76] 2.24 [1.11, 4.51] 0.92 [0.73, 1.16]	Risk Ratio M-H. Random. 95% Cl
Test for subgroup differ Study or Subgroup 1.2.1 Patients did not u Deamaley PIVOTAL McDonald 2014 Murthy POP-RT Roach RTOG 9413 Subtotal (95% CI)	ences: Chi <sup>2</sup> = 0.00, df = 1 (P = 0 WPRT PORT Events Total Events Total undergo radical prostatectomy 15 62 10 62 16 103 6 109 9 110 5 112 55 309 9 131 584 414	0.98), I <sup>2</sup> = 09 ate GU Weight 9 16.1% 9.4% 8.0% 20.4% 53.9%	<ul> <li>Risk Ratio</li> <li>M-H. Fixed, 95% CI</li> <li>1.50 [0.73, 3.08]</li> <li>2.82 [1.15, 6.93]</li> <li>1.83 [0.63, 5.30]</li> <li>2.59 [1.32, 5.09]</li> <li>2.19 [1.47, 3.27]</li> </ul>	Risk Ratio M-H. Fixed. 95%	. CI	Test for subgroup differe D <u>Study or Subgroup</u> 1.4.1 Patients did not ur Blanchard GETUG 12 Dearnaley PIVOTAL Murthy POP-RT Pormier GETUG-01 Roach RTOG 9413	WPRT Events Total E ndergo radical pro- 17 171 3 62 22 110 84 225 60 309	A of a 1 (P = 0. PORT vents Total postatectomy 13 125 3 62 10 112 90 221 12 131	70), I <sup>2</sup> = 0% ate GU Weight N 12.4% 3.5% 12.1% 26.6% 14.8% 26.6%	Risk Ratio 1.H. Random, 95% CI 0.96 [0.48, 1.89] 1.00 [0.21, 4.76] 2.24 [1.11, 4.51] 0.92 [0.73, 1.16] 2.12 [1.18, 3.81] 4.90 F.00 e.01	Risk Ratio M-H. Random. 95% Cl
Test for subgroup differ Study or Subgroup 1.2.1 Patients did not t Dearnaley PIVOTAL McDonald 2014 Murthy POP-RT Roach RTOG 9413 Subtotal (95% CI) Total events	ences: Chi <sup>2</sup> = 0.00, df = 1 (P = 0 WPRT PORT Events Total Events Total undergo radical prostatectomy 15 62 10 62 16 103 6 109 9 110 5 112 55 309 9 131 584 414 95 30	0.98), I <sup>2</sup> = 09 ate GU Weight 16.1% 9.4% 8.0% 20.4% 53.9%	<ul> <li>Risk Ratio</li> <li>M-H. Fixed. 95% CI</li> <li>1.50 [0.73, 3.08]</li> <li>2.82 [1.15, 6.93]</li> <li>1.83 [0.63, 5.30]</li> <li>2.59 [1.32, 5.09]</li> <li>2.19 [1.47, 3.27]</li> </ul>	Risk Ratio M-H. Fixed. 95%	- CI	Test for subgroup differe D <u>Study or Subgroup</u> 1.4.1 Patients did not ur Bianchard GETUG 12 Dearnaley PIVOTAL Murthy POP.RT Pommier GETUG-01 Racch RTOG 9413 Subtotal (95% CI)	WPRT Events Total E tdergo radical pro 17 171 3 62 22 110 84 225 60 309 877	A T = 1 (P = 0. PORT vents Total postatectomy 13 125 3 62 10 112 90 221 12 131 651	70), I <sup>2</sup> = 0% ate GU Weight N 12.4% 3.5% 12.1% 26.6% 14.8% 69.4%	Risk Ratio 1.H. Random. 95% CI 0.96 [0.48, 1.89] 1.00 [0.21, 4.76] 2.24 [1.11, 4.51] 0.92 [0.73, 1.16] 2.12 [1.18, 3.81] 1.33 [0.83, 2.13]	Risk Ratio M-H. Random. 95% Cl
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Test for subgroup differ <u>study or Subgroup</u> . 1.2.1 Patients did not to Dearnaley PIVOTAL McDonald 2014 Murthy POP-RT Roach RTOG 9413 Subtotal (85% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1. Test for overall effect. Z 1.2.2 Patients underwo Deville 2011 Waldstein 2017 Subtotal (85% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.	ences: Chi <sup>2</sup> = 0.00, df = 1 (P = 0 WPRT PORT Events: Total Events Total undergo radical prostatectom 15 62 10 62 16 103 6 109 9 110 5 112 55 309 9 131 554 414 72, df = 3 (P = 0.63); I <sup>2</sup> = 0% = 3.84 (P = 0.0001) ent radical prostatectomy 1 36 0 437 18 128 63 447 19 6 0 58): I <sup>2</sup> = 0 63 447 19 6 0 58): I <sup>2</sup> = 0 19 7 10 6 0 43 10 6 0 43 10 6 0 43 10 6 0 44 10 6 0 45 10 6	0.98),   <sup>2</sup> = 0? <b>ate GU</b> <u>Weight</u> 16.1% 9.4% 8.0% 20.4% 53.9% 0.9% 45.2% 46.1%	Risk Ratio           M.H. Fixed. 95% CI           1.50 (0.73, 3.08)           1.83 (0.63, 5.30)           2.82 [1.15, 6.93]           2.85 [1.32, 5.09]           2.19 [1.47, 3.27]           2.59 [0.11, 61.49]           1.00 [0.61, 1.62]           1.03 [0.64, 1.66]	Risk Ratio	<u>.</u> .	Test for subgroup differe D Study or Subgroup 1.4.1 Patients did not ur Bianchard GETUG 12 Dearnaley PIVOTAL Murthy 20P-401 Roach RT00 8413 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.1 Test for overall effect: Z = 1.4.2 Patients underven Devilie 2011 Wadstein 2017 Subtotal (95% CI) Total events	WPRT Events Total E thdergo radical pro 17 171 3 62 22 110 84 225 60 309 877 186 77 Ch <sup>2</sup> = 11.87, df 1.20 (P = 0.23) 1 tradical prostate 10 36 31 128 164	at = 1         (P = 0.           PORT         PORT           vents         Total           postatectomy         13           12         12           90         221           12         131           651         128           i= 4 (P = 0.02)         6           80         447           86         94           86         94	70),  2 = 0% ate GU Weight N 12.4% 3.5% 12.1% 26.6% 69.4% (3.2 = 66% 8.8% 21.8% 30.6%	Risk Ratio 1-H. Random. 95% CI 0.96 (0.46, 1.69) 1.00 (021, 4.76) 2.24 (1.11, 4.51) 0.22 (0.73, 1.61) 1.32 (0.73, 2.13) 1.33 (0.83, 2.13) 1.44 (0.59, 3.50) 1.36 (0.94, 1.95) 1.36 (0.97, 1.91)	Risk Ratio M-H. Random. 95% Cl
Test for subgroup differ Study or Subgroup 1.2.1 Patients did not t Dearnaley PIVOTAL McDonald 2014 Murthy POP-RT Roach RTOG 9413 Subtotal (95% CI) Total events Heterogeneity: Chill = 1. 1.2.2 Patients underwic Deville 2011 Waldstein 2017 Subtotal (95% CI) Total events Heterogeneity: Chill = 0. Subtotal (95% CI) Total events Heterogeneity: Chill = 0. Heterogeneity: Chill = 0.	ences: Ch <sup>2</sup> = 0.00, df = 1 (P = 0 WPRT PORT Events Total Events Total undergo radical prostatectomy 15 62 110 62 16 103 6 100 9 110 5 112 55 309 9 131 584 414 95 300 72, df = 3 (P = 0.63); P = 0% := 3.84 (P = 0.001) ent radical prostatectomy 1 36 0 31 18 126 63 447 19 63 34, df = 1 (P = 0.5); P = 0% := 0.11 (P = 0.91)	0.98),   <sup>2</sup> = 0? <b>ate GU</b> Weight y 16.1% 9.4% 8.0% 20.4% 53.9% 0.9% 45.2% 46.1%	<ul> <li>Risk Ratio</li> <li>M.H. Fixed. 35% CI</li> <li>1.50 (0.73, 3.08)</li> <li>2.82 (1.16, 6.93)</li> <li>1.83 (0.63, 5.30)</li> <li>2.59 [10, 22, 5.09]</li> <li>2.19 [1.47, 3.27]</li> <li>2.59 [0, 11, 61, 49]</li> <li>1.00 [0, 61, 1.62]</li> <li>1.03 [0, 64, 1.66]</li> </ul>	Risk Ratio	. <u>ci</u>	Test for subgroup differe <b>D</b> Study or Subgroup 1.4.1 Patients did not un Bianchard GETUG 12 Dearnaley PWOTAL Murthy POP-RT Pommier GETUG-01 Roach RTGG 9413 Subtotal (95% G) Total events Heterogeneity: Tau <sup>2</sup> = 0.1 Test for overall effect: 2 = 1.4.2 Patients underest Deville 2011 Waldstein 2017 Subtotal (95% G) Total events Heterogeneity: Tau <sup>2</sup> = 0.0 Heterogeneity: Heterogeneity: Het	WPRT Events Total E forgo radical pr 17 171 3 62 22 110 84 225 60 309 877 186 7; Ch <sup>2</sup> e 11.87, df 10 36 11 28 164 10 36 31 128 164 41 90; Ch <sup>2</sup> e 0.03, 0 187 188 198 198 198 198 198 198 198	c) of = 1 (P = 0.           PORT           Yents           Total           pstatectormy           13           12           10           112           90           11           128           i= 4 (P = 0.02)           estimation           estimation           6           31           90           21           121           128           i= 4 (P = 0.02)           estomy           6           30           447           86           = 1 (P = 0.90);	70),  2 = 0% <b>ate GU</b> <u>Weight N</u> 12.4% 3.5% 26.6% 14.8% 69.4% 69.4% (1 <sup>2</sup> = 66% 8.8% 21.8% 30.6%   <sup>2</sup> = 0%	Risk Ratio 1-H. Random. 95% CI 1-00 [0 21, 4.76] 2.24 [1.11, 4.51] 0.92 [0.73, 1.16] 2.12 [1.18, 3.81] 1.33 [0.83, 2.13] 1.44 [0.59, 3.50] 1.35 [0.94, 1.95] 1.35 [0.97, 1.91]	Risk Ratio M-H. Random. 95% Cl
Test for subgroup differ Study or Subgroup 1.2.1 Patients did not to Deamaley PIVOTAL McDonald 2014 Murthy PO-P413 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1. Test for overall effect: 2 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0. Total events Heterogeneity: Chi <sup>2</sup> = 0. Total events Heterogeneity: Chi <sup>2</sup> = 0. Test for overall effect: Z	ences: Chi <sup>2</sup> = 0.00, df = 1 (P = 0 WPRT PORT Events. Total. Events. Total undergo radical prostatectomy 15 62 10 62 15 103 6 0 51 112 55 309 9 131 55 30 4 (P = 0.0001) ent radical prostatectomy 1 36 0 31 18 128 6 347 19 63 34, df = 1 (P = 0.56); I <sup>2</sup> = 0% = 0.51 (P = 0.56); I <sup>2</sup> = 0% = 0.51 (P = 0.56); I <sup>2</sup> = 0%	0.98), I <sup>2</sup> = 09 ate GU Weight 9 16.1% 9.4% 8.0% 20.4% 53.9% 0.9% 45.2% 46.1%	<ul> <li>Risk Ratio</li> <li>M:H. Fixed, <u>95% CI</u></li> <li>1.50 (0.73, 3.08)</li> <li>2.82 (115, 6.93)</li> <li>1.83 (0.63, 5.30)</li> <li>2.59 (1.22, 5.09)</li> <li>2.19 (1.47, 3.27)</li> <li>2.59 (0.11, 61, 49)</li> <li>1.00 (0.61, 1.62)</li> <li>1.03 (0.64, 1.66)</li> </ul>	Risk Ratio	.ci	Test for subgroup differe D Study of Subgroup 1.4.1 Patients di not un Blanchard GETUG 12 Marthy POP-RT Pormire GETUG-11 Roach RTGC 9413 Subtral 10% C01 Total events Heterogeneity: Tau' = 0.1 1.4.2 Patients undervent Devilie 2011 Waldstein 2017 Subtral 10% C01 Total events Heterogeneity: Tau' = 0.0 Total events Heterogeneity: Tau' = 0.0 Total events Heterogeneity: Tau' = 0.0 Total events Heterogeneity: Tau' = 0.0 Total events Heterogeneity: Tau' = 0.0 Test for overall effect: 2 =	WPRT           Events         Total         E           Idergo radical pro         7         17           17         71         71           22         110         62         22           60         309         877         186           7: Chi? = 11.87, di         7: Chi? = 11.87, di         128           17: Chi? = 11.87, di         128         164           10         36         31         128           10: GC Chi? = 0.01, df         164         41           0: Chi? = 0.01, df         = 0.01, df         154	c) of = 1 (P = 0.           PORT           Yents           Total           postatectomy           13           12           3           10           12           90           121           121           651           128           121           128           121           128           121           128           129           et (P = 0.02)           https://doc/doc/doc/doc/doc/doc/doc/doc/doc/do	70),  2 = 0% <b>ate GU</b> Weight N 12.4% 3.5% 12.1% 26.6% 69.4% 69.4% 512 = 66% 8.8% 21.8% 30.6% 12 = 0%	Risk Ratio 0.96 (0.48, 189) 1.00 (02.1, 4.76) 0.92 (0.73, 1.16) 0.92 (0.73, 1.16) 2.12 (1.14, 54) 1.33 (0.83, 2.13) 1.44 (0.59, 3.50) 1.36 (0.97, 1.91]	Risk Ratio MHJ. Random 95% Cl
Test for subgroup differ Study or Subgroup 12.1 Patients did not t Dearnaley PIVOTAL McDonal 2014 Murthy POP-RT Roach RTOG 9413 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = 1. Test for overall effect: Z 1.2.2 Patients underwo Devile 2011 Waldstein 2017 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = 0. Test for overall effect: Z Total (95% CI)	$\label{eq:cost: Chi^2 = 0.00, df = 1 (P = 0 \\ \begin{tabular}{lllllllllllllllllllllllllllllllllll$	0.98, I <sup>2</sup> = 0% ate GU Weight y 16.1% 9.4% 8.0% 20.4% 53.9% 0.9% 45.2% 46.1% 100.0%	<ul> <li>Risk Ratio</li> <li>MH.F. Excel. 95% CI</li> <li>1.50 (0.73, 3.06)</li> <li>2.82 (1.16, 6.93)</li> <li>1.83 (0.63, 5.30)</li> <li>2.19 (1.47, 3.27)</li> <li>2.59 (0.11, 61, 49)</li> <li>1.00 (0.61, 1.62)</li> <li>1.03 (0.64, 1.66)</li> <li>1.66 [1.22, 2.24]</li> </ul>	Risk Ratio	. <u>ci</u>	Test for subgroup differe <b>D</b> Study or Subgroup 1.4.1 Patients did not un Blanchard GETUG 12 Dearnaley PWOTAL Murthy POP-RT Pommier GETUG-01 Roach RTGG 9413 Subtotal (95% C) Total events Heterogeneily: Tau <sup>2</sup> = 0.1 Test for overall effect: Z 1.4.2 Patients under Zent Dwelle 2011 Heterogeneily: Tau <sup>2</sup> = 0.0 Total (95% C) Total (95% C)	WPRT           textonis         Construction           indergo radical pro         17           17         17           3         62           22         110           84         225           60         309           186         7. Ch? = 11.87. dl           7. Ch? = 11.87. dl         12.0 (P = 0.23)           11 204 (P = 0.23)         1164           10         36           31         128           140. ch.27 = 0.01, df         1.80 (P = 0.07)           1.80 (P = 0.07)         1041	$\begin{array}{c} \sigma = 1 \ (P = 0, \\ PORT \\ \hline PORT \\ 13 \ 125 \\ 3 \ 62 \\ 10 \ 112 \\ 90 \ 221 \\ 12 \ 131 \\ 128 \\ 128 \\ 128 \\ 14 \ (P = 0, 02) \\ 80 \ 447 \\ 80 \ 447 \\ 86 \\ 86 \\ 1 \ (P = 0, 90); \\ 1129 \end{array}$	70),  2 = 0% <b>ate GU</b> Weight N 12.4% 3.5% 14.8% 69.4% ;  2 = 66% 8.8% 21.8% 30.6%  2 = 0% 100.0%	Risk Ratio H. Random. 95% CI 1.00 [02.1, 4.76] 2.24 [1.11, 4.51] 0.92 [0.73, 1.16] 2.12 [1.13, 3.81] 1.33 [0.83, 2.13] 1.44 [0.59, 3.50] 1.35 [0.94, 1.95] 1.35 [0.97, 1.91] 1.32 [0.97, 1.80]	Risk Ratio M-H. Random. 95% CI
Test for subgroup differ Study or Subgroup 1.2.1 Patients did not t Deamaley PIVOTAL McDonald 2014 McDonald 2014 McDonald 2014 McDonald 2014 McDonald 2014 Subtotal (95% CI) 1.2.2 Patients underw Deville 2011 Waldstein 2017 Total events Total (95% CI) Total events	$\label{eq:cost: Chi^2 = 0.00, df = 1 (P = 0 \\ \begin{tabular}{lllllllllllllllllllllllllllllllllll$	0.98),   <sup>2</sup> = 09 <b>ate GU</b> Weight 9 16.1% 9.4% 8.0% 20.4% 53.9% 0.9% 45.2% 46.1% 100.0%	<ul> <li>Risk Ratio</li> <li>M:H. Fixed, <u>95%</u> CI</li> <li>1.50 (0.73, 3.08)</li> <li>2.82 (11.6, 693)</li> <li>1.83 (0.63, 5.30)</li> <li>2.59 (1.32, 5.09)</li> <li>2.19 [1.47, 3.27]</li> <li>2.59 [0.11, 61.49]</li> <li>1.00 (0.61, 1.62)</li> <li>1.03 [0.64, 1.66]</li> <li>1.66 [1.22, 2.24]</li> </ul>	Risk Ratio	.ci	Test for subgroup differe D Study of Subgroup 1.4.1 Patients did not un Blanchard GETUG 12 Dearnaley PWOTAL Murthy POP-RT Pormiser GETUG 12 Reach RTOG 9413 Subtotal (95% CI) Total events 1.4.2 Patients underven Deville 2011 Waldstein 2017 Subtotal (95% CI) Total events Total (95% CI) Total events	WPRT         Events         Total           17         13         62         22         110         84         225         110         84         225         110         87         75         186         31         120         17         136         137         162         121         110	$\begin{array}{c} \mathbf{r} = 1 \ (P = 0, \\ \mathbf{r} = 1 \ (P = 0, \ (P = 0, \\ \mathbf{r} = 1 \ (P = 0, \ (P = $	70),  2 = 0% <b>ate GU</b> Weight N 12.4% 3.5% 12.1% 26.6% 14.8% 69.4% 59.4% 59.4% 21.8% 30.6% 12 = 0% 100.0%	Risk Ratio 1-H. Random. 95% CI 109 (2014, 76) 109 (2014, 76) 109 (2014, 76) 109 (2017, 116) 109 (2017, 116) 1133 (0.59, 3.50) 1.36 (0.94, 195) 1.36 (0.97, 1.91] 1.32 (0.97, 1.80)	Risk Ratio M-H. Random. 95% Cl
Test for subgroup differ Study or Subgroup 12.1 Patients did not t Dearnaley PIVOTAL McDonald 2014 Murthy POP-RT Roach RTOG 9413 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = 1. Test for overall effect: Z 1.2.2 Patients underwo Devile 2011 Waldstein 2017 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = 0. Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = 7.	ences: Chi <sup>2</sup> = 0.00, df = 1 (P = 0 WPRT PORT Events Total Events Total undergo radical prostatectormy 15 62 10 62 16 103 6 10 62 16 103 6 10 62 16 103 6 10 62 15 309 9 113 55 309 9 113 55 309 9 113 55 30 72, df = 3 (P = 0.63); F = 0% = 3.84 (P = 0.0001) ent radical prostatectormy 1 36 0 31 18 126 0 31 18 126 0 31 18 26 0 34 19 63 34, df = 1 (P = 0.56); F = 0% = 0.11 (P = 0.19); F = 33 14, df = 5 (P = 0.19); F = 33	0.98),  ² = 0% ate GU weight y 16.1% 9.4% 8.0% 20.4% 53.9% 0.9% 45.2% 46.1% 100.0%	<ul> <li>Risk Ratio</li> <li>MH-J. Fixed. 95% CI</li> <li>1.50 (0.73, 3.06)</li> <li>2.82 (1.15, 6.93)</li> <li>1.83 (0.63, 5.30)</li> <li>2.19 (1.47, 3.27)</li> <li>2.59 (0.11, 61.49)</li> <li>1.00 (0.61, 1.62)</li> <li>1.03 (0.64, 1.66)</li> <li>1.66 [1.22, 2.24]</li> </ul>	Risk Ratio M-H. Fixed. 95%	. <u>ci</u>	Test for subgroup differe <b>D</b> Study or Subgroup 1.4.1 Patients did not un Blanchard GETUG 12 Dearnaley PWOTAL Murthy POP-RT Pommier GETUG-11 Roach RTGG 9413 Subtotal (95% C) Total events Heterogeneily: Tau <sup>2</sup> = 0.1 Test for overall effect: Z 1.4.2 Patients underzen Dwide 2011 Total events Heterogeneily: Tau <sup>2</sup> = 0.0 Total events	WPRT           Events Total           17         17           3         62           22         10           44         22           188         77           77. Chill         1.20 (P = 0.23)           3         162           41         164           41         164           41         207           1.80 (P = 0.01, df         1.50 (P = 0.01, df           41         227           1.80 (P = 0.01, df         1.20 (P = 0.01, df           1.80 (P = 0.01, df         1.20 (P = 0.01, df	$\begin{array}{c} \text{c} \text{d} = 1 \ (P = 0, \\ \text{PORT} \\ \hline \text{PORT} \\ \text{Vents Total} \\ \text{Statectormy} \\ \text{13} \ 125 \\ \text{3} \ 62 \\ 12 \\ 12 \\ 12 \\ 12 \\ 12 \\ 12 \\ 12 \\$	70),  2 = 0% ate GU Weight N 12.4% 3.5% 12.1% 26.6% 14.8% 69.4% (21.8% 21.8% 21.8% 100.0% (2 = 0%) 100.0% (2 = 54%)	Risk Ratio 14. Random. 95% CI 100 [02.1, 4.76] 2.24 [1.11, 4.51] 0.92 [0.73, 1.16] 2.12 [1.13, 3.81] 1.33 [0.83, 2.13] 1.44 [0.59, 3.50] 1.36 [0.97, 1.91] 1.36 [0.97, 1.91]	Risk Ratio M-H. Random. 95% CI
Test for subgroup differ Study or Subgroup. 12.1 Patients did not t Deamaley PIVOTAL McDonal 2014L McDonal	ences: Chi <sup>2</sup> = 0.00, df = 1 (P = 0 WPRT PORT Events Total Events Total undergo radical prostatectomy 15 62 10 62 16 103 6 100 9 110 5 112 55 309 9 131 5584 414 95 300 ent radical prostatectomy 1 36 0 31 18 128 6 3 447 16 4 3 447 1748 892 114 93 44, df = 5 (P = 0.19); P = 33% = 3.26 (P = 0.001)	0.98),   <sup>2</sup> = 0% ate GU Weight 9 16.1% 9.4% 8.0% 20.4% 53.9% 0.9% 45.2% 46.1% 100.0%	<ul> <li>Risk Ratio</li> <li>M:H. Fixed, 35% CI</li> <li>1.50 (0.73, 3.08)</li> <li>2.82 (11.6, 693)</li> <li>1.83 (0.63, 530)</li> <li>2.59 (13.2, 5.00)</li> <li>2.59 (13.2, 5.00)</li> <li>2.19 (1.47, 3.27)</li> <li>2.59 (0.11, 61.49)</li> <li>1.00 (0.61, 1.62)</li> <li>1.03 (0.64, 1.66)</li> <li>1.66 [1.22, 2.24]</li> </ul>	Risk Ratio M-H. Fixed, 95%	.ci	Test for subgroup differe D Study or Subgroup 1.4.1 Patients did not un Bianchard GETUG 12 Dearnaley PWOTAL Murthy POP-RT Pommier GETUG 11 Roach RTOG 9413 Subtotal (95% CI) Total events Heterogeneity: Tau' = 0.1 Test for overall effect: 2 = 1.4.2 Patients undervent Devilie 2011 Waldstein 2017 Subtotal (95% CI) Total events Heterogeneity: Tau' = 0.0 Test for overall effect: 2 = Total (95% CI) Total events Heterogeneity: Tau' = 0.0 Test for overall effect: 2	WPRT           Evenis         Total           17         17           3         62           22         10           84         225           188         7.07           186         7.07           17.07         183           1.10 (P=0.23)         11.20           1.12 (P=0.23)         11.21           1.130 (P=0.07)         1041           227         287           1.157 (P=1.30.7), d1.30, (P=0.07)         1041	$\begin{array}{c} \text{c} \text{c} \text{c} = 1 \ (P = 0, \\ \text{c} \text{c} \text{c} \text{c} \text{c} \text{c} \text{c} \text{c}$	70),  2 = 0% <b>ate GU</b> Weight N 12.4% 3.5% 12.1% 26.6% 69.4% 5,  2 = 66% 8.8% 21.8% 30.6%  2 = 0% 100.0% 5,  2 = 54%	Risk Ratio 1-H. Random. 95% CI 0.96 (0.48, 1.89) 1.09 (02.1, 4.76) 0.92 (0.73, 1.16) 0.92 (0.73, 1.16) 2.12 (1.14, 5.11) 1.33 (0.59, 3.50) 1.36 (0.94, 1.95) 1.36 (0.97, 1.91) 1.32 (0.97, 1.80)	Risk Ratio M-H. Random. 95% Cl
Test for subgroup differ Study or Subgroup 1.2.1 Patients did not t Dearnaley PIVOTAL McDonald 2014 Murthy POP-RT Roach RTOG 9413 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = 1. Test for overail effect Z 1.2.2 Patients underwo Devile 2011 Waldstein 2017 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = 0. Test for overail effect: Z Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = 7. Test for overail effect: Z Test for overail effect: Z	ences: Chi <sup>2</sup> = 0.00, df = 1 (P = 0 WPRT PORT Events Total Events Total undergo radical prostatectormy 15 62 10 62 16 103 6 109 9 110 5 112 55 309 9 131 584 414 95 300 72, df = 3 (P = 0.63); F = 0% = 3.84 (P = 0.0001) ent radical prostatectomy 1 36 0 31 18 128 63 447 19 63 34, df = 1 (P = 0.56); F = 0% = 0.11 (P = 0.56); F = 0% = 0.11 (P = 0.19); F = 33% 41, df = 5 (P = 0.01); F = 33% = 3.86 (P = 0.001) enso: Chi <sup>2</sup> = 555, df = 1 (P = 0	0.98), I <sup>2</sup> = 09 <b>ate GU</b> Weight 9.4% 9.4% 8.0% 20.4% 53.9% 0.9% 45.2% 46.1% 100.0% 0.02), I <sup>2</sup> = 82	<ul> <li>Risk Ratio</li> <li>MH.J. Fixed, 95% CI</li> <li>1.50 (0.73, 3.08)</li> <li>2.82 (1.15, 6.93)</li> <li>1.83 (0.63, 5.30)</li> <li>2.59 (13, 2.16)</li> <li>2.59 (12, 147, 3.27)</li> <li>2.59 (0, 11, 61, 49)</li> <li>1.00 (0, 61, 1, 62)</li> <li>1.03 (0, 64, 1, 166)</li> <li>1.66 [1.22, 2.24]</li> <li>3%</li> </ul>	Risk Ratio M-H. Fixed. 95%	.cl	Test for subgroup differe <b>D</b> <b>Study or Subgroup</b> <b>1.4.1 Patients did not un</b> Bianchard GETUG 12 Dearnaley PWOTAL Murthy POP-RT Pormire GETUG-01 Roach RTOG 9413 Subtotal (9% C)1 Total events Heterogeneity: Tau <sup>2</sup> = 0.1 Test for overall effect: 2 = <b>1.4.2 Patients undervent</b> Watstan 2017 Subtotal (9% C)1 Total events Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: 2 = Total (9% C)1 Total events Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: 2 = Test for subgroup different	WPRT           Events Total           17         17           3         62           22         10           44         22           188         77           77         64           189         71           11         120 (P = 0.23)           11         120 (P = 0.23)           11         120 (P = 0.01, of 1           100         76 (P = 0.01, of 1           11.00 (P = 0.01, of 1         1.00 (P = 0.01, of 1           11.00 (P = 0.01, of 1         1.00 (P = 0.03)           11.00 (P = 0.03, or 0.01, of 1         1.00 (P = 0.03)           11.00 (P = 0.03, or 0.01, of 1         1.00 (P = 0.03)           11.00 (P = 0.03, or 0.01, of 1         1.00 (P = 0.03)           11.00 (P = 0.03, or 0.01, of 1         1.00 (P = 0.03)           11.00 (P = 0.03, or 0.01, of 1         1.00 (P = 0.03)           11.00 (P = 0.03, or 0.01, of 1         1.00 (P = 0.03)           11.00 (P = 0.03, or 0.01, of 1         1.00 (P = 0.03)           11.00 (P = 0.03, or 0.02)         1.00 (P = 0.03)           11.00 (P = 0.03, or 0.02)         1.00 (P = 0.03)           10.00 (P = 0.03, or 0.02)         1.00 (P = 0.03)           10.00 (P = 0.03)	$\begin{array}{c} \begin{array}{c} \text{c} \text{c} \text{c} \text{c} \text{c} \text{c} \text{c} \text$	70),  2 = 0% <b>ate GU</b> <u>Weight N</u> 12.4% 3.5% 12.1% 26.6% 14.8% 69.4% (2 = 66% 8.8% 21.8% 30.6% 12 = 66% 14.8% (2 = 66% (2 = 66%)) (2 = 66% (2 = 66%)) (2 = 66%) (2 = 66%) (2 = 66%) (2	Risk Ratio 14. Random, 95% CI 1.00 [02.1, 4.76] 2.24 [1.11, 4.51] 0.92 [0.73, 1.16] 2.12 [1.18, 3.81] 1.43 [0.83, 2.13] 1.44 [0.59, 3.50] 1.38 [0.97, 1.91] 1.38 [0.97, 1.80]	Risk Ratio M-H. Random. 95% CI

only radiotherapy; GI, gastrointestinal; GU, genitourinary.

was  $\leq$ 49 Gy (EQD-2), there was no significant difference in the G2+ acute GU toxicity (RR 0.82, CI 0.63–1.06, p = 0.14; **Figure 4A**) and late GU toxicity (RR 0.92, CI 0.74-1.15, p = 0.46; **Figure 4B**). Moreover, the higher pelvic radiation dose (>49 Gy, EQD-2) had a significant increase in G2+ acute and late GU toxicity of WPRT (p = 0.009 and 0.001, respectively; **Figure 4**). On the other hand, meta-regression analysis showed no significant correlation between prostate radiation dose and GU toxicity (**Supplementary Table 2**).

In addition, subgroup analysis of radiotherapy technology indicated that compared with intensity-modulated radiation therapy (IMRT), three-dimensional conformal radiotherapy (3D-CRT) increased G2+ late GI toxicity of WPRT without significant difference (**Figure 5**). The risk difference of radiation dose and radiotherapy technology on GU toxicity has been presented in **Supplementary Figures 4**, **5**.

#### **Quality Assessment and Risk of Bias**

We used the Cochrane Risk of Bias Tool to evaluate the risk of bias in RCTs, and the results showed that most of the evidence was moderate-to-good quality (**Supplementary Figure 6**). The included CRS demonstrated Newcastle-Ottawa scores consistent with a low to moderate risk of bias (**Supplementary Table 3**). We assessed the publication bias using funnel plots comparing effect size and measure of precision across our primary analysis (**Supplementary Figure 7**). Although some comparisons involved a small number of studies, we did not identify evidence of a publication bias.

## DISCUSSION

There has been considerable controversy over whether to choose whole pelvic radiotherapy (WPRT) or prostate-only radiotherapy (PORT) for localized prostate cancer (37). This meta-analysis included six randomized controlled studies (RCTs) (7-12) and ten cohort studies (CRS) (23-32). Of the 16 studies, 9 studies did not perform radical prostatectomy (non-RP), and the patients of the other 7 studies received radical prostatectomy (RP). The effects of WPRT and PORT on biochemical failure-free survival (BFFS), progression-free survival (PFS), distant metastasis-free survival (DMFS), and overall survival (OS) were analyzed. The BFFS is strictly based on serum prostate-specific antigen (PSA) level and is a crucial outcome indicator for evaluating prostate cancer (38). Some adverse survival events of localized prostate cancer were caused by local progression, regional or nodal failure, and distant metastasis. Therefore, many studies also supplemented PFS as an outcome indicator (7, 10-12, 39). Recent studies found that DMFS was a strong surrogate of overall survival in localized prostate cancer that was associated with a significant risk of death from prostate cancer (40, 41). This meta-analysis revealed



pelvic radiotherapy; PORT, prostate-only radiotherapy; GU, genitourinary.

that compared with PORT, WPRT significantly improved 5-year BFFS and PFS, and it was irrelevant to whether the patients had undergone radical prostatectomy (RP). In addition, for the patients who did not receive RP, the 5-year DMFS of WPRT was better than that of PORT.

ADT and radical prostatectomy (RP) were factors that improved the survival rates of prostate cancer when comparing WPRT and PORT. Radiotherapy (RT) combined with ADT is the recommended radical treatment for high-risk localized prostate cancer (42–44). The Southwest Oncology Group (SWOG) 8794 (45) indicated that RT combined with RP was more beneficial to BFFS and DMFS. In addition, radiation dose, radiotherapy technology, and the extent of radiotherapy pelvic lymph node coverage also have an impact on survival and toxicity (37, 46). This meta-analysis attempted to evaluate the effect of WPRT on the survival and toxicity of localized prostate cancer compared with PORT under the influence of these factors.

The National Comprehensive Cancer Network (NCCN) recommends that if the prostate tumor is aggressive, ADT should be routinely used. However, RTOG 9601 cleared that

with the use of ADT, side effects also occurred (such as gynecomastia) (47). Ramey et al. (30) revealed a potentially additive effect to WPRT and ADT. WPRT+ADT was significantly beneficial for BFFS (HR = 0.56) compared with PORT+ADT, and the addition of ADT to WPRT could further improve BFFS than WPRT alone. In the postoperative setting, although there is no level 1 evidence for choosing WPRT or PORT, more than 70% of radiation oncologists suggest that WPRT should be used after prostatectomy (30, 48). The subgroup analysis of this study indicated that whether combined with ADT or not, WPRT significantly improved BFFS of patients undergoing RP compared to PORT (**Supplementary Figure 1A**).

Although a host's immune system may be able to remove a single tumor cell, it may be reasonable to advocate inclusion of the WPRT to eradicate or diminish residual cells with metastatic potential (49). However, it remains unclear how much of the survival outcomes that may be improved with the addition of WPRT is caused by the effect on micrometastasis or secondarily results from the improved local tumor control (50). On the other

	WPPT P	Acute (	GI Bick Patio	Pick Potio	Acute GU
Study or Subgroup Eve	rents Total Ever	nts Total Weight	M-H. Random, 95% Cl	M-H. Random, 95% Cl	Study or Subgroup Events Total Events Total Weight M-H. Random 95% Cl M-H. Random 95% Cl
1.1.1 3D-CRT					1.3.1 3D-CRT
Mantini 2011	17 168	19 190 17.5%	1.01 [0.54, 1.88]	-+-	Mantini 2011 19 168 29 190 12 1% 0.74 (0.43 1.27)
Roach RTOG 9413	144 309	27 131 29.9%	2.26 [1.58, 3.23]		Pommier GETUG-01 59 225 68 221 24 6% 0.85 (0.63 1.14)
Subtotal (95% CI)	477	321 47.4%	1.58 [0.72, 3.45]		Roach RTOG 9413 97 309 29 131 20.2% 1.42 (0.99.2.03)
Total events	161	46			Subtotal (95% Cl) 702 542 57.0% 0.98 [0.67, 1.44]
Heterogeneity: Tau <sup>2</sup> = 0.26;	; Chi <sup>2</sup> = 4.85, df =	1 (P = 0.03); I <sup>2</sup> = 79%	6		Total events 175 126
Test for overall effect: Z = 1	1.14 (P = 0.25)				Heterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 5.91, df = 2 (P = 0.05); l <sup>2</sup> = 66%
					Test for overall effect: Z = 0.08 (P = 0.93)
1.1.2 IMRT					
Dearnaley PIVOTAL	3 62	2 61 3.3%	1.48 [0.26, 8.53]		1.3.2 IMRT
McDonald 2014	38 103	19 109 23.3%	2.12 [1.31, 3.42]		McDonald 2014 54 103 52 109 26.6% 1.10 [0.84, 1.44]
Murthy POP-RT	35 107	27 107 26.1%	1.30 [0.85, 1.98]		Murthy POP-RT 35 107 26 107 16.5% 1.35 [0.87, 2.07]
Subtotal (95% CI)	2/2	211 52.6%	1.61 [1.14, 2.28]	•	Subtotal (95% CI) 210 216 43.0% 1.16 [0.93, 1.46]
lotal events	76	48	,		Total events 89 78
Heterogeneity: Tau* = 0.01; Test for everell offects 7 = 2	; Chi* = 2.26, df =	2 (P = 0.32); I* = 12%	6		Heterogeneity: $1au^{+} = 0.00$ ; Chr = 0.53, at = 1 (P = 0.43); P = 0%
rest for overall effect. Z = 2	2.09 (P = 0.007)				Test for overall effect: $Z = 1.50 (P = 0.19)$
Total (95% CI)	749	598 100.0%	1.65 [1.19, 2.29]	◆	Total (95% Cl) 912 758 100.0% 1.07 (0.86, 1.34)
Total events	237	94			Total events 264 204
Heterogeneity: Tau <sup>2</sup> = 0.06:	: Chi <sup>2</sup> = 7.54. df =	4 (P = 0.11);  2 = 479	6		Heterogeneity: Tau <sup>2</sup> = 0.03: Chi <sup>2</sup> = 7.53. df = 4 (P = 0.11): l <sup>2</sup> = 47%
est for overall effect: Z = 2	2.98 (P = 0.003)			0.01 0.1 1 10 100	Test for overall effect: Z = 0.61 (P = 0.54) 0.01 0.1 1 10
Fest for subgroup difference	es: Chi <sup>2</sup> = 0.00, df	= 1 (P = 0.96), I <sup>2</sup> = 0	1%	Pavours WPRT Pavours PORT	Test for subgroup differences: Chi <sup>2</sup> = 0.54, df = 1 (P = 0.46), l <sup>2</sup> = 0%
		Late C	SI		D Late GU
01	WPRI	PORT	Risk Ratio	Risk Ratio	WPRT PORT Risk Ratio Risk Ratio
Study or Subgroup EV	vents lotal Eve	ents i otai vveign	[ W-H, FIXed, 95% CI	M-H, Fixed, 95% CI	
Dearth DTOO 0440	55 000		0.50 /4.00 5.001		
KOACH KTUG 9413		0 101 0700	2 59 11 32 5 191		Dialicialu GETUG 12 17 171 13 123 19.0% 0.80 [0.40, 1.09]
Subtotal (95% CI)	209	9 131 37.8%	2 50 [1 22 5 00]	-	Permier GETUG-01 84 225 90 221 314% 0.9210 73 1.161
Subtotal (95% CI)	309 55 309 55	9 131 37.8% 131 37.8%	2.59 [1.32, 5.09]	•	Pommier GETUG-01 84 225 90 221 31.4% 0.92 [0.73, 1.16]
Subtotal (95% CI) Total events	55 309 309 55	9 131 37.8% 131 37.8% 9	2.59 [1.32, 5.09]	•	Pommier GETUG-01 84 225 90 221 31.4% 0.92 [0.73, 1.16] Roach RTOG 9413 60 309 12 131 22.3% 2.12 [1.18, 3.81] Subtodal (95% CI) 705 477 7.55% 1.19 [10 70, 2.04]
Subtotal (95% Cl) Total events Heterogeneity: Not applical	55 309 309 55 able	9 131 37.8% 131 37.8% 9	2.59 [1.32, 5.09]	•	Pommier GETUG-01 84 225 90 221 31.4% 0.92 [0.73, 1.16] Roach RT05 9413 06 309 121 31 22.3% 2.12 [1.18, 8.11] Subtobal (95%, 0) 705 477 73.5% 1.19 [0.70, 2.04] Total events 161 115
Subtotal (95% CI) Total events Heterogeneity: Not applica Fest for overall effect: Z = 2	55 309 309 55 2.77 (P = 0.006)	9 131 37.8% 131 37.8% 9	2.59 [1.32, 5.09]	•	Pommier GETUG-01 84 225 90 221 31.4% 0.02 [0.73, 1.16] Roach RT0G 9413 60 309 12 131 22.3% 2.12 [1.18, 3.81] Subtch [9% C]) 705 477 73.5% 1.19 [0.70, 2.04] Total events 161 115 Heterogeneity: Fau <sup>2</sup> − 0.1 C/m <sup>2</sup> = 2.0 = 0.03); P = 72%
Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z = 2 1.2.2 IMRT	309 55 2.77 (P = 0.006)	9 131 37.8% 131 37.8% 9	2.59 [1.32, 5.09]	•	Pommier GETUG-01 84 225 90 221 31.4% 0.02 [0.73, 1.16] Roach R/DG 9413 60 309 12 131 223 22 22 22 22 22 22 22 22 22 22 22 22
Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z = 2 1.2.2 IMRT Dearnaley PIVOTAL	309 55 309 55 3ble 2.77 (P = 0.006)	9 131 37.8% 131 37.8% 9	2.59 [1.32, 5.09]	•	Pommier GETUG-01 84 225 90 221 31.4% 0.02 [0.73, 1.16] Roach FUTO 9413 00 309 12 131 223% 2.12 [113.83] Subtotal (95% Cl) 705 477 73.5% 1.19 [0.70, 2.04] Total events 115 Heterogeneity: Tau' = 0.16; Chi' = 7.20, df = 2 (P = 0.03); P = 72% Test for overall effect: Z = 0.65 (P = 0.52)
Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z = 2 1.2.2 IMRT Dearnaley PIVOTAL McDonald 2014	309 55 309 55 3ble 2.77 (P = 0.006) 15 62 16 103	9 131 37.8% 131 37.8% 9 10 62 29.9% 6 109 17.4%	5 1.50 [1.32, 5.09] 5 1.50 [0.73, 3.08] 5 2.82 [1.15, 6.93]	<b>◆</b>	Pommier GETUG-01 84 225 90 221 31.4% 0.02 [0.73, 1.16] Roach R/T05 9413 06 309 12 131 22.3% 2.12 [1.18, 381] Subtotal (8% C1) 705 477 73.5% 1.19 [0.76, 2.04] Total events 161 151 Heterogeneity: Tau* = 0.16; Ch* = 7.20, df = 2 (P = 0.03); P = 72% Test for covarial effect: Z = 0.65 (P = 0.52) 1.4.2 IMRT
Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z = 3 1.2.2 IMRT Dearnaley PIVOTAL McDonald 2014 Wurthy POP-RT	309 309 55 able 2.77 (P = 0.006) 15 62 16 103 9 110	9 131 37.8% 131 37.8% 9 10 62 29.9% 6 109 17.4% 5 112 14.8%	5 1.50 [0.73, 3.08] 5 2.82 [1.15, 6.93] 5 1.80 [0.75, 3.08]	◆ + 	Pommier GETUG-01 84 225 90 221 31.4% 0.92 [0.73, 1.16] Roach FUTO S413 00 309 121 31 223 % 212 [113.831] Subtobal (95% C) 705 477 73.5% 1.19 [0.76, 2.04] Total events 161 15 Heterogeneity: Tau <sup>2</sup> = 0.16; Ch <sup>2</sup> = 7.20, df = 2 (P = 0.03); P = 72% Test for overall effect: Z = 0.05 (P = 0.52) 1.4.2 IMRT Desmalay PIVOTAL 3 62 3 62 7.1% 1.00 [0.21, 4.76]
Subtotal (95% CI) Total events Heterogeneity: Not applical rest for overall effect: Z = 2 I.2.2 IMRT Jearnaley PIVOTAL McDonald 2014 Murthy POP-RT Subtotal (95% CI)	55 309 55 able 2.77 (P = 0.006) 15 62 16 103 9 110 275	9 131 37.8% 131 37.8% 9 10 62 29.9% 6 109 17.4% 5 112 14.8% 283 62.2%	5 1.50 [0.73, 3.08] 5 2.69 [1.32, 5.09] 5 2.62 [1.15, 6.93] 5 1.83 [0.63, 5.30] 6 1.95 [1.19, 3.20]	• •	Pommier GETUG-01 84 225 90 221 31.4% 0.02 [0.73, 1.16] Roach RT05 9413 60 309 12 131 22.3% 2.12 [1.18, 3.81] Subtotal (05% C1) 705 477 73.5% 1.19 [0.76, 2.04] Total events 161 115 Heterogeneity: Tay = 0.16; Ch <sup>2</sup> = 7.20, df = 2 (P = 0.03); P = 72% Test for covarial effect: Z = 0.65 (P = 0.52) 1.4.2 IMRT Dearnalay PIVOTAL 3 62 3 62 7.1% 1.00 [0.21, 4.76] Murthy POPRT 22 110 10 112 19.4% 2.24 [1.11, 4.51]
Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z = 2 1.2.2 IMRT Dearnaley PIVOTAL McDonald 2014 Murthy POP-RT Subtotal (95% CI) Total events	309 309 55 able 2.77 (P = 0.006) 15 62 16 103 9 110 275 40	9 131 37.8% 131 37.8% 9 10 62 29.9% 6 109 17.4% 5 112 14.8% 283 62.2% 21	<ul> <li>2.59 [1.32, 5.09]</li> <li>2.59 [1.32, 5.09]</li> <li>1.50 [0.73, 3.08]</li> <li>2.82 [1.15, 6.93]</li> <li>1.83 [0.63, 5.30]</li> <li>1.95 [1.19, 3.20]</li> </ul>	• •	Pommier GETUG-01 84 225 90 221 31.4% 0.02 [0.73, 1.16] Roach RTOG 9413 00 309 121 31 22.3% 2.12 [1.18, 381] Subtolal (95% C) 705 477 73.5% 1.19 [0.70, 2.04] Haterogenehy: Tai $= 0.16$ ; Ch <sup>2</sup> = 7.20, df = 2 (P = 0.03); P = 72% Test for overall effect: Z = 0.65 (P = 0.52) 1.4.2 IMRT Dearnaley PIVOTAL 3 62 3 62 7.1% 1.00 [0.21, 4.76] Murthy POP-RT 22 [10 10 112 19.4% 2.24 [1.11, 4.51] Murthy POP-RT 22 110 10 112 19.4% 2.34 [1.14, 4.51] Subtolal (95% C) 717 174 22.5%
Subtotal (95% CI) Total events Heterogeneity: Not applical Test for overall effect: Z = 2 1.2.2 IMRT Dearnaley PIVOTAL McDonald 2014 Murthy POP-RT Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.18.	309 309 55 able 2.77 (P = 0.006) 15 62 16 103 9 110 275 40 3, df = 2 (P = 0.56)	9 131 37.8% 131 37.8% 9 10 62 29.9% 6 109 17.4% 5 112 14.8% 283 62.2% 21 1 <sup>2</sup> = 0%	<ul> <li>1.50 [0.73, 3.08]</li> <li>2.82 [1.15, 6.93]</li> <li>1.83 [0.63, 5.30]</li> <li>1.95 [1.19, 3.20]</li> </ul>	• •	Pommier GETUG-01 84 225 90 221 31.4% 0.02 [0.73, 1.16] Roach RT05 9413 60 309 12 131 22.3% 2.12 [1.18, 3.81] Subtotal (8% C) 705 477 73.5% 1.19 [0.76, 2.04] Total events 161 115 Heterogeneity: Tay = 0.16; Ch <sup>2+</sup> = 7.20, df = 2 (P = 0.03); P = 72% Test for covarial effect: Z = 0.65 (P = 0.52) 1.4.2 IMRT Dearnalsy FIVOTAL 3 62 3 62 7.1% 1.00 [0.21, 4.76] Murthy POR-RT 22 110 10 112 19.4% 2.24 [1.11, 4.51] Subtotal (9% C) 17 21 174 28.5% 1.98 [1.03, 3.71] Total events 25 m 13 74 28.5%
Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z = 2 1.2.2 IMRT Dearnaley PIVOTAL Worthy POP-RT Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.18, Test for overall effect: Z = 2	55 309 55 309 55 2.77 (P = 0.006) 15 62 16 103 9 110 275 40 8, df = 2 (P = 0.56) 2.65 (P = 0.008)	9 131 37.8% 131 37.8% 9 10 62 29.9% 6 109 17.4% 5 112 14.8% 283 62.2% 21 ; l <sup>2</sup> = 0%	<ul> <li>2.59 [1.32, 5.09]</li> <li>1.50 [0.73, 3.08]</li> <li>2.82 [1.15, 6.93]</li> <li>1.83 [0.63, 5.30]</li> <li>1.95 [1.19, 3.20]</li> </ul>	◆  •	Pommier GETUG-01 84 225 90 221 31.4% 022 [07.3, 1.6] Roach RT05 9413 60 309 121 31 22.3% 2.12 [11.8, 81] Subtotal (95% C) 705 477 73.5% 1.19 [0.70, 2.04] Total avents 161 115 Heterogeneity: Tau* = 0.16; Ch* = 7.20, df = 2 (P = 0.03); P = 72% Test for overall effect: Z = 0.65 (P = 0.52) 1.4.2 IMRT Dearnalay PIV/OTAL 3 62 3 62 7.1% 1.00 [0.21, 4.76] Muthy PO-RT 2 100 112 104% 2.24 [1.11, 4.51] Subtotal (95% C) 172 174 26.5% 1.96 [1.03, 3.71] Total events 25 13 Heterogeneity: Tau* = 0.00; Ch* = 0.85; df = 1 (P = 0.36); P = 0%
Subtotal (95% CI) Total events Teat for overall effect: Z = 2 1.2.2 IMRT Dearnaley PIVOTAL McDonald 2014 Wurthy POP-RT Subtotal (95% CI) Total events Teat overall effect: Z = 2	309 309 55 able 2.77 (P = 0.006) 15 62 16 103 9 110 2.75 40 8, df = 2 (P = 0.56) 2.65 (P = 0.008)	9 131 37.8% 131 37.8% 9 10 62 29.9% 6 109 17.4% 5 112 14.8% 283 62.2% 21 ; <sup>P</sup> = 0%	<ul> <li>2.59 [1.32, 5.09]</li> <li>1.50 [0.73, 3.08]</li> <li>2.82 [1.15, 6.93]</li> <li>1.83 [0.63, 5.30]</li> <li>1.95 [1.19, 3.20]</li> </ul>	• •	Pommier GETUG-01 84 225 90 221 31.4% 0.22 [07.3, 1.6] Roden, RTOG 9413 60 309 121 12.23 $\times$ 1.12 [1.8, 8.1] Subtotal (8% C) 705 477 73.5% 1.19 [0.76, 2.04] Heterogeneity: Tai* 0.16; Ch* 2.50, df = 2 (P = 0.03); P = 72% Test for overall effect: Z = 0.65 (P = 0.52) 1.4.2 IMRT Dearnaley PIVOTAL 3 62 3 62 7, 1% 1.00 [0.21, 4.76] Muthy POPRT 22 110 10 112 19.4% 2.24 [1.11, 4.51] Dearnaley FIVOTAL 3 57 13 774 28.5% 1.98 [1.03, 3.71] Total events Heterogeneity: Tai* 0.0C h* 0.55 (f = 1 (P = 0.36); P = 0% Test for overall effect: Z = 2.05 (P = 0.04)
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hand, Conventional imaging modalities perform poorly in detecting lymph node metastases from prostate cancer, and 25%-40% of patients who undergo radical prostatectomy with an extended pelvic lymphadenectomy have these identified by histology (51). Since patients with lymph node metastases have been shown to benefit from pelvic radiotherapy, these falsenegative diagnosis errors may also be one of the reasons that WPRT has an advantage over PORT in the clinical benefit. We further analyzed the possible dependence between the clinical benefit of WPRT and patient characteristics (including age, Gleason score, and Nodal Risk). The results showed that younger patients (age ≤66 years) seemed to derive a greater benefit for BFFS and DMFS with WPRT (p = 0.03 and 0.01, respectively). However, the Gleason score and nodal risk of localized prostate cancer did not have a significant effect on the clinical benefit of WPRT (Table 3).

The extent and adequacy of radiotherapy pelvic lymph node coverage may also be a critical factor affecting the benefit of WPRT in prostate cancer (37). Proponents of WPRT argue that the lack of benefit demonstrated by the GETUG-01 and RTOG 9413 trials may be due in part to inadequate coverage of the pelvic lymph nodes, given that the respective superior field borders of S1/2 and L5/S1 would not provide full dose coverage to the entire superior pelvic lymph node basins (52). Spratt et al. (53) looked at lymph node recurrence patterns after external beam radiotherapy of the prostate in men who did not have their lymph nodes treated. It was found that there was a high incidence of pelvic lymph node recurrences above the internal and external iliac lymph node

regions. The recent Phase III trial, POP-RT, evaluated the benefit of WPRT with extended superior coverage to L4/5, and pointed out that WPRT improved the BFFS, disease-free survival (DFS), and DMFS compared with PORT, but resulted in a significant increase in late grade 2 or worse (G2+) genitourinary (GU) toxicity (**Table 4**).

The RTOG 9413 (12) reported that WPRT plus neoadjuvant hormonal therapy (NHT) significantly improved PFS and BFFS and there was no difference between groups in grade 3 or worse (G3+) late GU toxicity, but caused a significant increase in the risk of G3+ gastrointestinal (GI) toxicity. Our meta-analysis further demonstrated that the toxicity of WPRT on G2+ acute and late GU was related to whether the pelvic radiation dose was >49 Gy (EQD-2). On the other hand, the toxicities of GI and GU are also related to radiotherapy technology (54). Wortel et al. concluded that intensity-modulated radiation therapy (IMRT) resulted in significant reductions in G2+ acute and late GI toxicity and acute GU toxicity compared to three-dimensional conformal radiation therapy (3D-CRT) (55, 56). Our subgroup analysis of radiotherapy technology indicated that compared with IMRT, 3D-CRT increased G2+ late GI toxicity of WPRT without significant difference (Figure 5).

This study has several limitations. First, subgroup analyses were restricted by the study-level nature of the data. Second, a follow-up only longer than 5 years is inadequate to thoroughly evaluate the impact of one therapeutic approach over another, especially with respect to "harder clinical end-points" such as DMFS, overall, and cancer-specific survival. At present, two

Heterogeneity factors	RCT	No. of events/Tota	al no.WPRT PORT	Hazard ratio (95% CI) WPRT vs. PORT	p-Value
Age years for BFFS	POP-RT				
≤66		2/59	22/58	0.08 [0.02, 0.35]	0.03
>66		5/51	7/54	0.66 [0.21, 2.10]	
Gleason for BFFS	POP-RT				
<8		2/57	9/56	0.22 [0.05, 1.01]	0.88
≥8		5/53	20/56	0.24 [0.09, 0.64]	
Nodal Risk for BFFS	POP-RT				
≤40%		4/59	11/60	0.36 [0.12, 1.14]	0.28
<40%		3/51	18/52	0.15 [0.04, 0.50]	
Gleason for PFS	GETUG 12				
<8		52/111	27/89	1.26 [0.76, 2.09]	0.20
≥8		53/97	30/61	0.95 [0.59, 1.53]	
Age years for DMFS	POP-RT				
≤66		2/59	17/58	0.11[0.03, 0.49]	0.01
>66		5/51	3/54	1.63[0.39, 6.85]	
Gleason for DMFS	POP-RT				
<8		2/57	6/56	0.32[0.06, 1.60]	0.88
≥8		5/53	14/56	0.37[0.13, 1.04]	

WPRT, whole-pelvic radiotherapy; PORT, prostate-only radiotherapy; RCT, randomized controlled trial; BFFS, biochemical failure-free survival; PFS, progression-free survival; DMFS, distant metastasis-free survival.

First Author	Institution	Area of Pelvic CTV Lymph Node	Key Findings
Blanchard	GETUG	The upper limit of the pelvis could be either S1-S2 (small pelvis) or L5-S1 (large pelvis)	There was no association between biochemical PFS and the use of WPRT
Braunstein	Harvard	Beginning at the bifurcation of the aorta to the common iliac arteries (approximating vertebral levels L4 and L5) and included internal and external iliac chains	A decreased risk of ACM was noted with the use of WPRT versus PORT. However, a combination of WPRT and ADT did not further improve ACM compared with PORT with ADT
Dearnaley	CRUK	Lower border L5 on sagittal CT	WPRT had a modest side effect profile.
Ishii	Tane General Hospital, Japan	Obturator vessels, the common, external and internal iliac vessels	WPRT resulted in no significant increase in acute GU toxicity when compared with PORT
Mantini	Catholic University, Italy	Presacral, obturator, internal iliac, and external iliac chains	No significant differences were seen in acute and late GI and GU toxicity among the patients treated with WPRT or PORT
McDonald	University of Alabama, USA	Starting at L5-S1 junction	WPRT increases the rates of acute and late GI toxicity
Murthy	Tata Memorial Centre, India	Starting at L4-5 junction to include bilateral common iliac, external iliac, internal iliac, presacral	WPRT improved BFFS and DFS as compared with PORT, but OS did not appear to differ. WPRT resulted in increased G2+ late GU toxicity as compared to PORT
Pommier Roach	GETUG RTOG	Routine radiation field coverage to the S1/2 interspace The pelvic CTV lymph node volumes at the L5/S1 interspace (the level of the distal common iliac and proximal presacral lymph nodes)	WPRT was well tolerated but did not improve PFS. NHT plus WPRT improved PFS compared with NHT plus PORT albeit increased risk of grade 3 or worse intestinal toxicity

GETUG, French Genitourinary Study Group; CRUK, Cancer Research UK; RTOG, Radiation Therapy Oncology Group; WPRT, whole-pelvic radiotherapy; PORT, prostate-only radiotherapy; PFS, progression-free survival; ACM, all-cause mortality; ADT, androgen deprivation therapy; NR, not reported; GU, genitourinary; GI, gastrointestinal; BFFS, biochemical failure-free survival; DFS, disease-free survival; OS, overall survival; G2+, grade 2 or worse; NHT, neoadjuvant hormonal therapy.

randomized controlled trials of longer than 10 years of follow-up have been published. The GETUG-01 showed that pelvic nodes irradiation did not statistically improve 10-year event-free survival (EFS) or OS in the whole population but may be beneficial in selected low- and intermediate-risk prostate cancer patients treated with exclusive radiation therapy (11). The RTOG 9413 demonstrated that WPRT plus NHT improved 10-year PFS compared with PORT plus NHT (12). More research publications with longer than 10 years of follow-up are needed for the next longer follow-up meta-analysis. In conclusion, this meta-analysis demonstrates that WPRT significantly improved 5-year BFFS and PFS compared with PORT in localized prostate cancer. Moreover, for the patients who did not receive RP, the 5-year DMFS of WPRT was better than that of PORT. However, WPRT significantly increased not only the grade 2 or worse (G2+) acute GI toxicity of non-RP studies and RP studies, but also the G2+ late GI toxicity of non-RP studies. Subgroup analysis of non-RP studies found that when the pelvic radiation dose was >49 Gy (equivalent-doses-in-2-Gy-fractions, EQD-2), WPRT was more beneficial to PFS than

PORT, but significantly increased the risk of G2+ acute and late GU toxicity.

#### DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

## **AUTHOR CONTRIBUTIONS**

Study concept and design: FJ and SW. Data collection and collation: SW and WT. Statistical analysis: SW, WT, and HL. Writing—original draft: SW. Writing—review and editing: all authors. Study supervision: YW, FJ, and HL. All authors

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#### SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.796907/full#supplementary-material

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