Omar Fahmy^a
 Mohd Ghani Khairul-Asri^a
 Syed H.S.M. Hadi^a
 Georgios Gakis^b
 Arnulf Stenzl^b

^aDepartment of Urology, Universiti
 Putra Malaysia (UPM), Serdang, Malaysia;

^bDepartment of Urology, Eberhard-Karls
 University, Tuebingen, Germany

The Role of Radical Prostatectomy and Radiotherapy in Treatment of Locally Advanced Prostate Cancer: A Systematic Review and Meta-Analysis

Keywords

Advanced prostate cancer · Anti-hormonal therapy · Lymph-node positive · Prostate cancer · Radical prostatectomy · Radiotherapy

Abstract

Background: The role of radical prostatectomy (RP) is still controversial for locally advanced prostate cancer (PC). Radiotherapy (RT) and hormonal therapy (HT) are usually used as a primary treatment. **Material and Methods:** A systematic online search was conducted according to Preferred Reporting Items for Systematic Review and Meta-Analysis statement. Eligible publications reporting the overall survival (OS) and/or disease-specific survival (DSS) were included. A total of 14 studies, including 17,869 patients, were considered for analysis. The impact of therapeutic modalities on survival was assessed, with a risk of bias assessment according to the Newcastle Ottawa Scale. **Results:** For RP, RT, and HT, the mean 10-year OS was 70.7% (95% CI 61.3–80.2), 65.8% (95% CI 48.1–83.3), and 22.6% (95% CI 4.9–40.3; $p = 0.001$), respectively. The corresponding 10-year DSS was 84.1% (95% CI 75.1–93.2), 89.4% (95% CI 70.1–108.6), and 50.4% (95% CI 31.2–69.6; $p = 0.0127$), respectively. Among all treatment combinations, RP displayed significant improvement in OS when included in the treatment ($Z = 4.01$; $p < 0.001$). Adjuvant RT significantly improved DSS ($Z = 2.7$; $p = 0.007$). Combination of RT and HT favored better OS in com-

parison to monotherapy with RT or HT ($Z = 3.61$; $p < 0.001$).

Conclusion: Improved outcomes in advanced PC were detected for RP plus adjuvant RT vs. RP alone and RT plus adjuvant HT vs. RT alone with comparable survival results between both regimens. RP with adjuvant RT may present the modality of choice when HT is contraindicated.

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Introduction

Unlike localized prostate cancer (PC) for which recent studies have suggested that radical prostatectomy (RP) may provide superior long-term outcomes compared to radiotherapy (RT) [1], RT is still considered the treatment of choice in locally advanced PC stages [2].

Recent evidence suggested that RP can improve outcomes for patients with locally advanced PC within the framework of a multimodal setting [3]. Basically, different therapeutic options can be provided for patients diagnosed with advanced PC including RP, RT, and hormonal therapy (HT) [4]. However, due to the lack of solid evidence, current guidelines lack clear recommendations with regard to patient selection criteria for each modality. Furthermore, these modalities might be used as monotherapy or in combination as an adjuvant or salvage therapy [4]. In the past, RP was considered unfavorable for locally advanced PC due to the high positive surgical mar-

gin rates [2]. However, recently, it has gained more popularity. Still there is not enough evidence to advocate its benefits for the majority of patients [5].

For this reason, we aimed to compare the impact of different treatment modalities on survival after the diagnosis of locally advanced PC.

Methods

Search Strategy

Following the Preferred Reporting Items for Systematic Review and Meta-Analysis statement [6], a systematic online search in PubMed data base and Wiley online library was conducted using the following keywords; advanced prostate cancer, radical prostatectomy, radiotherapy, hormonal therapy. Only English publications between 1990 and 2016 were targeted. All retrieved publications were subjected to initial assessment of the title or abstract. Publications including patients with localized PC were excluded. Relevant publications were subjected to full-text assessment including a manual search in their reference lists. For this meta-analysis, we included only publications reporting hazard ratio (HR) of the used treatment and its 95% CI for overall survival (OS) and disease-specific survival (DSS).

Data Extraction

Data were initially extracted independently by 2 authors (O.F. and M.G.K.-A.), then they were cross-checked. The following variables were extracted: number of patients, age, stage, the used treatment modality, the 5-/10-year OS and DSS rates with the corresponding HR and 95% CI.

Outcome Measures

Locally advanced PC was defined as either clinical or pathological stage $\geq T3$, or any T-stage with locoregional lymph node positive disease (LN+). OS and DSS were the 2 endpoints of this study. The primary outcome of this analysis was the impact of RP and adjuvant therapy on OS and DSS, and the impact of the combination of RT and HT on OS and DSS vs. either RT or HT as a monotherapy.

Statistical Analysis

Review Manager (RevMan) software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen) was used for this meta-analysis. The estimated effect of the treatment modality on survival was calculated using log HR and SE. Fixed and random effect models were used according to the I^2 value of heterogeneity; for $I^2 \leq 50\%$, fixed effect model was applied and for $I^2 > 50\%$, a random model was applied. One-way ANOVA test was used to compare the mean of survival rates recorded for different therapeutic modalities. A p value < 0.05 was considered as significant.

Quality Assessment

All the included studies were subjected to the risk of bias assessment. For this assessment, the star-based Newcastle Ottawa Scale for cohort studies was used. For the 8 items of the assessment, a maximum of one star can be given for each item, except for com-

Fig. 1. CONSORT diagram for the selection process of the included studies. * Studies including patients with localized prostate cancer (T1–2, N0) were considered not eligible. ** Two publications for the same author were included as they reported on different cohorts [6, 10].

parability for which one or 2 stars can be given [7]. The risk of bias was considered as low, intermediate, or high for the scores ≥ 7 –9, 4–6, and < 4 , respectively.

Results

Search Results

The initial online search resulted in 3,745 results from which 3,701 were excluded after initial assessment. Of the 44 publications subjected to full-text assessment, 30 were excluded; 28 due to the absence of HR and/or its 95% CI, and 2 were repeated publications. Finally, 14 publications involving 17,869 patients were included [3, 8–20]. The selection process of the included studies is outlined in the CONSORT diagram (Fig. 1).

Of the 17,869 included patients, 13,708 (76.7%) underwent RP [3, 8–18]. A total of 5,835 of the 13,708 patients (42.6%) received adjuvant therapy after RP; 1,639 (12.0%) received adjuvant RT [9–13, 15, 17], 3,646 (26.6%) adjuvant HT [10, 12–17], and 550 (4%) both RT and HT.

The remaining included patients received the following: RT alone in 594 (3.3%) [3, 10, 15, 18], HT alone in 1,270 (7.1%) [9, 10, 15, 16, 19], and combined RT and HT in 885 (5.0%) [9, 10, 15, 19, 20]. In 1,412 patients (7.9%), no treatment was provided [8, 10, 18]. Tables 1 and 2 provide a summary of the included studies and outcomes.

Table 1. Summary of the included studies

First author, year	Design	Number of patients	Inclusion criteria	Follow up, months, mean (median)	Treatment, n (%)			Adjuvant therapy (post RP), n (%)			Age, years, mean (median)			
					RP	RT	HT	RT + HT	NT	RT	HT	both	total	RP
Gandaglia, 2014	Retrospective	948	≥cT3	N/A	474 (50)			474 (50)			69.6 (69)	69.8 (69)		69.4 (69)
Saito, 2006	Retrospective	209	≥cT3	N/A	30 (14)		101 (48)	78 (37)		30 (100)		64	69.3	78.1
Johnstone, 2006	Retrospective	1,093	cT4	N/A	72 (7)	82 (8)	400 (37)	258 (24)	281 (26)	4 (6)	13 (18)	5 (7)		
Messing, 2006	RCT	98	pTxN+	(55)	98 (100)					47 (48)		(65.5)		
Gandaglia, 2015	Retrospective	7,616	≥pT3	71.9 (66)	7,616 (100)					404 (5)	1,955 (26)	484 (6)	69	
Moschini, 2016	Retrospective	1,586	≥pT3	80 (72)	1,586 (100)					865 (55)	547 (34)		65.8 (66.1)	
Schumacher, 2008	Retrospective	122	pTxN+	(67)	122 (100)					18 (15)	61 (50)	(64)		
Engel, 2010	Retrospective	1,413	pTxN+	77 (67)	957 (68)	88 (6)	349 (25)	19 (1)		184 (19)	690 (72)		65.3 (65.4)	64.5 (65)
Ghavamian, 1999	Retrospective	158	pTxN+	N/A	79 (50)		79 (50)			79 (100)		65	66	
Mitchell, 2012	Retrospective	843	cT3	(172)	843 (100)					109 (13)	344 (40)	(65)		
Iversen, 2010	Retrospective	2,681	≥cT3 or pTxN+	N/A	1,719 (64)	305 (11)		657 (25)						
Fosså, 2016	RCT	682	cT3	(163)		341 (50)	341 (50)					N/A		
Souhami, 2009	RCT	189	T3orTxN+	(115)			189 (100)					(70)		
Yamamoto, 2014	Retrospective	231	cT3	(93)	112 (48)	119 (52)						(67)	(72)	

Table 2. Summary of the outcomes of the included studies

First author, year	OS, %	DSS, %									
		5-year					10-year				
		RP	RT	HT	NT		RP	RT	HT	NT	
Gandaglia, 2014	-	-	-	-	-		96.3	96.6	88.6	89.7	
Saito, 2006	87.3	94.9	66.1	-	-		93.8	-	-	-	
Johnstone, 2006	72.6	61.8	41.5	39.8	-		-	-	-	-	
Messing, 2006	90.0	-	-	-	-		95.0	-	-	-	
Gandaglia, 2015	-	-	-	-	-		97.9	-	-	-	
Moschini, 2016	-	-	-	-	-		98.0	-	-	-	
Schumacher, 2008	83.3	-	-	-	-		84.5	-	-	-	
Engel, 2010	84.0	-	-	-	60.0		-	-	-	-	
Ghavamian, 1999	85.6	-	64.2	28.0	-		88.0	-	68.4	-	
Mitchell, 2012	91.0	-	-	-	-		96.0	-	-	-	
Iversen, 2010	-	-	-	-	-		-	-	-	-	
Fosså, 2016	-	79.5	-	-	-		-	-	-	-	
Souhami, 2009	-	-	-	-	-		-	94.6	-	-	
Yamamoto, 2014	97.0	88.0	-	-	-		98.0	96.0	-	-	

Table 3. Newcastle Ottawa Scale for risk of bias assessment of the included studies (scores ≥ 7 –9, 4–6, < 4 are considered as low, intermediate, and high risk, respectively)

Study	Selection				Comparability	Outcome			Overall
	representativeness of exposed cohort	selection of non-exposed	ascertainment of exposure	outcome not present at start		assessment of outcome	adequate follow up length	adequacy of follow up	
Gandaglia, 2014	*	*	*	*	**	*	*	*	9/9
Saito, 2006	*	*	*	*	*	*	*	*	8/9
Johnstone, 2006	*	*	*	*	*	*	*	*	8/9
Messing, 2006	*	*	*	*	**	*	*	*	9/9
Gandaglia, 2015	*	*	*	*	*	*	*	*	8/9
Moschini, 2016	*	*	*	*	**	*	*	*	9/9
Schumacher, 2008	*	*	*	*	**	*	*	*	9/9
Engel, 2010	*	*	*	*	*	*	*	*	8/9
Ghavamian, 1999	*	*	*	*	**	*	*	*	9/9
Mitchell, 2012	*	*	*	*	**	*	*	*	9/9
Iversen, 2010	*	*	*	*	**	*	*	*	9/9
Fosså, 2016	*	*	*	*	*	*	*	*	8/9
Souhami, 2009	*	*	*	*	*	*	*	*	8/9
Yamamoto, 2014	*	*	*	*	*	*	*	*	8/9

Types of Included Studies

Of the 14 studies included, 11 were retrospective [3, 8–10, 12–18] and 3 were randomized controlled trials [11, 19, 20]. All the included studies had a low risk of bias according to Newcastle Ottawa Scale assessment (Table 3).

OS and DSS

Comparable survival rates were reported for RP and RT with significantly lower rates reported for HT. According to the used primary treatment, the mean of the reported 5-year OS rates was 86.4% (95% CI 78.2–94.5), 81.0% (95% CI 69.5–92.6), and 57.3% (95% CI 44.0–70.6) for RP, RT, HT, respectively ($p = 0.005$). The mean 10-year OS rate was 70.7% (95% CI 61.3–80.2), 65.8% (95% CI 48.1–83.3), and 22.6% (95% CI 4.9–40.3; $p = 0.001$), respectively. For 5-year DSS, the mean rate for RP, RT and HT was 94.2% (95% CI 89.8–98.6), 95.7% (95% CI 88.2–103.3), and 78.5% (95% CI 69.2–87.8; $p = 0.0149$), respectively. Likewise, the corresponding 10-year DSS was 84.1% (95% CI 75.1–93.2), 89.4% (95% CI 70.1–108.6), and 50.4% (95% CI 31.2–69.6; $p = 0.012$), respectively.

Impact of RP on OS and DSS

In 5 studies including 3,843 patients [3, 8, 10, 15, 16], RP displayed a significant impact on OS when included in the treatment vs. any other kind of therapy not including RP ($Z = 4.01$; $p < 0.001$; Fig. 2). In 4 studies including

1,546 patients [3, 8, 9, 16], DSS was significantly in favor of the inclusion of RP in the treatment ($Z = 4.71$; $p < 0.001$; Fig. 2).

Impact of Adjuvant Therapy after RP on OS and DSS

Adjuvant HT. In 4 studies including 2,732 patients undergoing RP [10, 11, 17, 18], adjuvant HT displayed no impact on OS after RP ($Z = 0.38$; $p = 0.71$; Fig. 3a). In 5 studies including 10,265 patients who were treated with RP [11–14, 17], adjuvant HT displayed no impact on DSS after RP ($Z = 0.62$; $p = 0.53$; Fig. 3a).

Adjuvant RT. In 9,202 patients who underwent RP [12, 13], adjuvant RT significantly improved DSS ($Z = 2.7$; $p = 0.007$; Fig. 3b).

Combination of RT and HT vs. RT alone. Combination of RT and HT favored better OS in comparison to monotherapy with RT or HT ($Z = 3.61$; $p < 0.001$; Fig. 4). Improved DSS was noted for the combination therapy, but the impact was not significant ($Z = 1.39$; $p = 0.16$; Fig. 4).

Discussion

Unlike localized PC, for which RP and RT are both established treatment options, the treatment of locally advanced PC is still a grey zone in PC management. Indeed, the current definition of locally advanced PC includes any patient with positive LNs, regardless of the actual ex-

Fig. 2. Forest and funnel plots of the impact of RP with or without adjuvant therapy on OS and DSS in comparison to other options not including RP.

tent of the tumor in the prostatic gland. Recently, high PSA was detected as an independent predictor for LNs invasion in high-risk patients [21]. This clinical variability between patients adds more challenge to the identification of a clear evidence-based approach for the management of these patients. Furthermore, each available treatment modality has its drawbacks on functional outcomes in terms of continence, potency, and quality of life (QOL) or treatment-related side effects. This complicates the appropriate selection of the primary treatment even more.

In this systematic review and meta-analysis, we compared the outcomes of RP and RT with each other and with HT regarding OS and DSS. By definition, locally advanced PC is different compared to localized PC with high risk of metastasis. During our literature research, we complied to the definition of locally advanced PC as stage T3–4, or any T with N+. Even though a higher number of studies included in our analysis were retrieved, inclusion of patients with localized disease (T1–2, N0) was an adequate reason to be excluded. Previously, the role of RP in locally advanced PC was limited as the capability to achieve complete surgical radicality was questionable due to the expected higher rate of positive surgical margin or LN metastasis

[22–24]. RP was usually aborted after intraoperative diagnosis of pelvic LN metastasis [25]. However, in retrospective analyses, it was demonstrated that patients who completed their RP despite positive LNs displayed better survival than patients with aborted RP [5, 11, 14]. Furthermore, an extended LN dissection carried better outcomes than a limited one [13]. The concerns about impaired functional outcomes after RP in locally advanced stages may also refrain surgeons from performing this operation. Nonetheless, the available data suggest acceptable continence rates and even preserved potency in some patients [26].

There is increasing evidence of a prognostic benefit of an extended pelvic LN dissection in patients with high risk and lymph node positive PC [5]. Therefore, there may be a rationale to advocate a pelvic LN dissection even if RP is not considered. This approach may also be a reasonable option when planning a RT-based approach [4]. The alternative of LN dissection, prior to RT, is a whole pelvic radiation with ADT with expected significantly higher toxicity than only prostatic radiation [4, 27]. Although the risk of incontinence is lower after RT than RP, other side effects include erectile dysfunction, acute and late genitourinary or gastrointestinal toxicity [4, 28]. However, there are no studies which compared in-depth

Fig. 3. Forest and funnel plots for the impact of adjuvant therapy on survival after RP. **a** Impact of adjuvant HT on OS and DSS. **b** Impact of adjuvant RT on DSS.

RP and RT regarding functional outcomes and health-related QOL. Only one of the included studies in this meta-analysis compared complication rates of RP vs. RT; 10% of patients after RP required pads vs. 0% after RT. On the contrary, grade ≥ 3 rectal bleeding or hematuria was reported in 10% of RT patients vs. 0% after RP [9]. Therefore, well-designed prospective trials comparing functional outcomes and side effects between both therapeutic modalities are needed.

Our results displayed clear superiority of both RP and RT over HT as the primary treatment for locally advanced PC. RP could significantly improve survival outcomes when compared to any other modality not including RP. Adjuvant RT could significantly improve the outcome of

RP, yet adjuvant HT after RP had no significant impact on survival outcomes. A significant beneficial prognostic impact of adjuvant HT after RT was found in high-grade localized PC [29]. Our analysis also displayed the same effect for patients with locally advanced PC with prolonged duration of HT for at least 3 years [20]. Based on these results, both RP plus adjuvant RT or primary RT plus adjuvant HT are suggested to provide the best survival outcome for patients presented with locally advanced non-metastatic PC. Further studies are needed to evaluate whether in patients with clinically positive LNs, priority can be given to RP including extended lymphadenectomy plus adjuvant RT instead of lymphadenectomy alone or total pelvic RT plus adjuvant HT. This may also

Fig. 4. Forest and funnel plots of the impact of combination of RT and HT on OS and DSS vs. RT or HT as a monotherapy.

carry less morbidity by decreasing the radiation dose and avoidance of HT.

This study is limited by the retrospective nature of the majority of included studies and the low number of included studies at the end-points of analysis. Wide disparity between the included studies in the used treatment and patients' criteria might carry additional confounders for the results. Inability to compare the impact of RP vs. RT in a head-to-head manner, regarding also their impact on QOL, which is critical during treatment discussion with patients, may limit their applicability for daily clinical practice. Altogether, based on our data, if there are contraindications for HT, RP with local RT represents a valid treatment alternative as addition of HT does not increase the effectiveness of RP.

Conclusion

In this meta-analysis on locally advanced PC, the best oncological outcomes were achieved by RP with adjuvant RT or RT with adjuvant HT. Therefore, these 2 approaches should be given equal importance when discussed in a multidisciplinary setting. Prospective trials with proper inclusion and exclusion criteria to compare these 2 combinations are mandatory.

Disclosure Statement

All authors have no conflict of interest.

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