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Prostate Cancer

Combination of Adjuvant Hormonal and Radiation Therapy Significantly Prolongs Survival of Patients With pT2–4 pN+ Prostate Cancer: Results of a Matched Analysis

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Abstract

Background: Previous prospective randomised trials have shown a positive impact of adjuvant radiation therapy (RT) in patients with locally advanced prostate cancer. However, none of these trials included patients with lymph node invasion (LNI).
Objective: The aim of this study was to assess the impact of combination adjuvant hormonal therapy (HT) and RT on the survival of patients with prostate cancer and histologically documented lymph node metastases (pN+).
Design, setting, and participants: Data on 703 consecutive patients with LNI treated with radical prostatectomy, pelvic lymph node dissection, and adjuvant treatments between September 1986 and November 2002 at two large academic institutions were reviewed.
Measurements: For study purposes, patients treated with adjuvant HT plus RT and patients treated with adjuvant HT alone were matched for age at surgery, pathologic T stage and Gleason score, number of nodes removed, surgical margin status, and length of follow-up. Differences in cancer-specific survival (CSS) and overall survival (OS) were compared using the Kaplan-Meier method and life table analyses.
Results and limitations: Following the matching process, 117 pT2–4 pN1 patients of 171 (68.4%) treated with adjuvant HT plus RT (group 1) were compared with 247 pT2–4 pN1 patients of 532 (46.4%) receiving adjuvant HT alone (group 2). After matching, the two groups of patients were comparable in terms of pre- and postoperative characteristics (all $p \geq 0.07$). Mean follow-up was 100.8 mo (median: 95.1 mo; range: 3.5–229.3 mo). Overall, prostate CSS and OS rates at 5, 8, and 10 yr were 90%, 82%, and 75%, and 85%, 70%, and 60%, respectively. Patients treated with adjuvant RT plus HT had significantly higher CSS and OS rates compared with patients treated with HT alone at 5, 8, and 10 yr after surgery (95%, 91%, and 86% vs 88%, 78%, and 70%, and 90%, 84%, and 74% vs 82%, 65%, and 55%, respectively; $p = 0.004$ and $p < 0.001$, respectively). Similarly, higher survival rates associated with the combination of HT plus RT were found when patients were stratified according to the extent of nodal invasion (namely, two or fewer vs more than two positive nodes; all $p \leq 0.006$). Lack of standardised HT and RT protocols represents the main limitations of our retrospective study.
Conclusions: Adjuvant RT plus HT significantly improved CSS and OS of pT2–4 pN1 patients, regardless of the extent of nodal invasion. These results reinforce the need for a multimodal approach in the treatment of node-positive prostate cancer.

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1. Introduction

Radical prostatectomy (RP) is an effective treatment for patients with organ-confined prostate cancer (PCa) [1]. Large clinical series have demonstrated that RP also represents a valid treatment modality for patients with locally advanced disease [2–7]. According to the European Association of Urology guidelines, RP is indicated in selected patients with low-volume, high-risk localised PCa (cT3a or Gleason score 8–10 or prostate-specific antigen [PSA] >20) [1].

Although in the PSA era the diagnosis of PCa has shifted to early clinical stages, nodal metastases are indeed still diagnosed in a wide range of patients [8–12]. Several studies reported excellent cancer-specific outcomes of patients with histologically proven nodal metastases submitted to RP [13–18], especially in the presence of a low volume of nodal burden [18,19]. Oncologic outcomes of surgically treated node-positive patients has improved by early administration of adjuvant hormonal therapy (HT) [20]. Nevertheless, the effect of adjuvant radiation therapy (RT) in node-positive PCa has never been prospectively assessed. Indeed, none of the most recent large prospective randomised studies supporting the role of adjuvant RT in preventing disease recurrence and death in locally advanced PCa included patients with concomitant nodal metastases [21–23]. The idea of testing adjuvant RT in the presence of lymph node invasion (LNI) came from the evidence that node-positive PCa is not always a systemic and noncurable disease [13–19]. Administration of adjuvant RT would aim at optimising local control, thus preventing distant metastases and death [21–24]. A recent retrospective study reported a significant positive impact of RT in combination with HT in patients with PCa and nodal metastases treated with RP and extended pelvic lymph node dissection (PLND) [25]. However, this study was limited by a potential patient selection bias mainly due to its retrospective and unmatched design. In fact, patients treated with adjuvant RT were those affected by more aggressive disease. For this reason, no effect of adjuvant RT on cancer-specific survival (CSS) was demonstrated on univariate survival analyses. Whether adjuvant RT was effective in preventing progression and recurrence according to the extent of nodal invasion was not tested in that study. This is key, since the number of positive nodes represents a strong predictor of survival of patients with LNI [13–19]. To solve these issues, we assessed the effect of adjuvant RT in node-positive PCa including two homogeneous matched patient cohorts exposed to either adjuvant RT plus HT or adjuvant HT alone after surgery.

Table 1 – Descriptive characteristics of the study cohort, stratified according to the type of adjuvant treatment administered

Variables	Unmatched population				Matched population			
	All patients (*n* = 703) No. (%)	Adjuvant RT + HT (*n* = 171) No. (%)	Adjuvant HT (*n* = 532) No. (%)	*p* value	All patients (*n* = 364) No. (%)	Adjuvant RT + HT (*n* = 117) No. (%)	AdjuvantHT (*n* = 247) No. (%)	*p* value
Age, yr				0.05				0.1
Mean (median)	65 (66)	64.1 (64.5)	65.3 (66)		65.7 (66)	64.9 (65)	66.1 (66.7)	
Range	47–80	47–80	47–80		47–80	48–72	47–80	
Preoperative PSA				0.55				0.5
Mean (median)	28.9 (17.2)	30.6 (19)	28.4 (16.2)		32.0 (18.5)	29.8 (19.5)	33.1 (18.5)	
Range	0.9–616	0.9–321	1.6–616		1.6–616	2.8–321	1.6–616	
Pathologic stage (2002 TNM)				<0.001				0.4
pT2a/b/c	82 (11.7)	6 (3.5)	76 (14.3)		7 (1.9)	3 (2.6)	4 (1.6)	
pT3a	118 (16.8)	20 (11.7)	98 (18.4)		31 (8.5)	10 (8.5)	21 (8.5)	
pT3b	452 (64.3)	115 (67.3)	337 (63.3)		302 (83.0)	83 (79.5)	209 (84.6)	
pT4	51 (7.3)	30 (17.5)	21 (3.9)		24 (6.6)	11 (9.4)	13 (5.3)	
Pathologic Gleason score				0.02				0.7
≤6	148 (21.1)	29 (17.0)	119 (22.4)		34 (9.3)	11 (9.4)	23 (9.3)	
7	347 (49.4)	77 (45.0)	270 (50.8)		207 (56.9)	63 (53.8)	144 (58.3)	
8–10	208 (29.5)	65 (38.0)	143 (26.8)		123 (33.8)	43 (36.8)	80 (32.4)	
Surgical margin status				<0.001				0.7
Positive	444 (63.2)	131 (76.6)	313 (58.8)		259 (71.2)	85 (72.6)	174 (70.4)	
Negative	259 (36.8)	40 (23.4)	219 (41.2)		105 (28.8)	32 (27.4)	73 (29.6)	
No. lymph nodes removed and examined				<0.001				0.08
Mean (median)	13.9 (13)	16.4 (15)	13.1 (12)		13.6 (13)	14.3 (14)	13.2 (13)	
Range	2–52	2–52	2–44		2–33	2–32	2–33	
No. positive lymph nodes				0.36				0.07
Mean (median)	2.3 (1)	2.4 (2)	2.2(1)		2.4 (2)	2.1 (2)	2.6 (2)	
Range	1–31	1–16	1–31		1–19	1–10	1–19	
Two or fewer positive lymph nodes	532 (75.7)	121 (70.8)	411 (77.3)	0.10	265 (72.8)	85 (72.6)	180 (72.9)	0.53
More than two positive lymph nodes	171 (24.3)	50 (29.2)	121 (22.7)		99 (27.2)	32 (27.4)	67 (27.1)	
Length of follow-up, mo				<0.001				0.26
Mean (median)	113.7 (112.5)	101.3 (91.5)	117.7 (124.7)		100.8 (95.1)	96.4 (84)	102.8 (104.2)	
Range	3.5–243	12.2–243	3.5–227.5		3.5–229.3	12.2–229.3	3.5–227.5	

PSA = prostate-specific antigen.

2. Materials and methods

We analysed data on 703 consecutive pT2–4 pN+ M0 patients treated with RP, PLND, and adjuvant treatments at two large academic institutions between September 1988 and January 2003. All patients were preoperatively staged with abdominal computed tomography (CT) and bone scan to exclude the presence of visceral and bone metastases, respectively.

Of these patients, 171 (24.3%) received a combination of adjuvant HT and RT, and 532 (75.7%) received adjuvant HT alone. The decision to administer one or both adjuvant treatments followed surgeon and patient discussions about possible treatment options. Therefore, no standardised indication or guideline was used in the selection of the adjuvant protocol. Clinical and pathologic characteristics of this cohort have been already described and are summarised in Table 1 [18]. All patients had complete clinical and pathologic data including age at surgery, preoperative PSA, pathologic stage defined according to the 2002 American Joint Committee on Cancer staging system [26], pathologic Gleason score, surgical margin status, and number of nodes removed as well as number of positive nodes.

The effect of adjuvant RT on CSS as well as on overall survival (OS) was assessed using a matched analysis that allowed us to examine survival rates according to the type of adjuvant treatment administered (namely adjuvant HT plus RT vs adjuvant HT alone) after adjustment for patient and tumour characteristics. Each patient treated with adjuvant RT was matched with up to four patients unexposed to RT. Assignment of up to four controls maximises the power of matched comparisons [27]. Exact matches were made for variables being statistically significantly different between the two unmatched groups of patients (ie, patients treated with adjuvant RT plus HT vs patients treated with adjuvant HT alone). These included age at surgery (every 10 yr), pathologic Gleason score (6 vs 7 vs 8–10), pathologic T stage (T2a–c vs T3a vs T3b vs T4), surgical margins (positive vs negative), number of nodes removed (every five nodes), and length of follow-up ($<$144 vs $\geq$144 mo). After matching for the variables just listed, the difference in the CSS and OS rates between patients receiving adjuvant RT and those unexposed to adjuvant RT after RP was tested with the log-rank statistic, and its magnitude was quantified with the hazard ratio (HR). Kaplan-Meier analyses were used to depict survival rates graphically at 5, 8, and 10 yr after surgery according to the adjuvant treatment administered (HT plus RT vs HT alone) as well as the extent of nodal invasion [18]. Actuarial survival rates at various time points after RP were calculated using life table analyses. Independent-sample t test and chi-square tests were used for comparisons of means and proportions, respectively. All statistical tests were performed with S-PLUS Professional v.1 (MathSoft Inc, Seattle, WA, USA). All tests were two sided with a significance level at 0.05.

2.1. Radiotherapy technique

Patients were routinely treated with a three- to four-field technique with 18-mV x-rays from a Varian Clinac 1800. The details of the RT techniques were previously published [28]. In this context, we only emphasise that for a number of patients (55%), a conventional nonconformal treatment was delivered, and rectangular or minimally blocked beams were used. This was mainly due to the gradual introduction of the beam's eye view optimised conformal techniques in clinical practice in the last 90 yr. For the remaining cases (45%), a three-dimensional (3D) conformal approach (3DCRT) was used: The clinical target volume (CTV) was drawn on CT images by the physicians and always included the prostatic fossa (CTV1). In the case of seminal vesicle invasion (pT3b), a CTV2 (prostatic plus vesicular bed) was also identified. The planned target volume (PTV) was defined as the CTV(s) plus a 1-cm margin (to account for organ motion and setup error). During the study period, the pelvic lymph-nodal area was not contoured. In most cases (85%), adjuvant radiotherapy consisted of a four-field (anteroposterior [AP]-posteroanterior plus latero-lateral) whole-pelvis irradiation to a median dose of 50.4 Gy (range: 45–50.4 Gy), followed by a three-field (AP plus latero-lateral) boost to the prostatic bed (PTV1) to a median dose of 68.4 Gy (range: 55.8–72 Gy). The median dose to PTV2, if present, was 60 Gy. All patients were treated with the conventionally fractionated regimen (1.8 Gy per fraction, five fractions per week) and received adjuvant RT within 3 mo after surgery, regardless of postoperative PSA value.

Of all patients, 44% underwent orchiectomy, and the remaining 56% were treated with adjuvant androgen-deprivation therapy (ADT) therapy for a median of 37.5 mo (range: 4–158 mo), mainly as a combined androgen blockade (82%). For a more limited fraction of patients, ADT consisted of antiandrogen (15%) or luteinising hormone-releasing hormone agonist (3%) only. ADT was usually started immediately after radical retropubic prostatectomy regardless of PSA value after surgery.

3. Results

The study cohort characteristics are stratified according to the type of adjuvant treatment administered (namely adjuvant RT plus HT vs HT alone) as well as to analysis type (unmatched vs matched; Table 1). In the unmatched population, patients treated with adjuvant HT plus RT were younger and had higher Gleason score distribution, higher rate of pT4 disease, higher mean number of nodes removed, and higher rates of positive surgical margins (all $p \leq 0.05$). Patients receiving adjuvant RT plus HT had a significantly shorter mean follow-up as compared with patients receiving adjuvant HT alone (104 vs 127 mo, respectively; $p < 0.001$).

After matching for age at surgery, pathologic T stage, and Gleason score, surgical margins status, number of nodes removed, and length of follow-up, 364 of 703 pT2–4 pN1 patients (51.8%) were left in the analyses. Of these, 117 patients (32.1%) received adjuvant RT plus HT (group 1); 247 patients (67.9%; group 2) received adjuvant HT alone. At the end of the matching process, no significant differences in terms of pre- and postoperative characteristics were found between the two groups of patients (all $p \geq 0.07$; Table 1). Similarly, no differences were found between group 1 and group 2 when patients were stratified according to the extent of nodal invasion (two or fewer vs more than two positive lymph nodes; all $p \geq 0.07$; Table 2).

Mean follow-up was 100.8 mo (median: 95.1 mo; range: 3.5–229.3 mo). Of 364 matched patients, 358 (98%), 347 (95%), 337 (93%), and 284 (78%) had $>$1-, 2-, 3-, and 5-yr follow-up, respectively. Overall, CSS rate at 5, 8, and 10 yr was 90%, 82%, and 75%, respectively. Overall survival rate at 5, 8, and 10 yr was 85%, 70%, and 60%, respectively.

The life table analyses that addressed the matched adjuvant RT plus HT and adjuvant HT alone cases demonstrated 5, 8, and 10-yr CSS rates of 95%, 91%, and 86% for patients receiving adjuvant RT plus HT versus 88%, 78%, and 70% for patients receiving adjuvant HT alone, respectively (Fig. 1; $p = 0.004$). Patients treated with adjuvant RT plus HT had a 2.5-fold higher chance of being free from cancer mortality as compared with patients treated with adjuvant HT alone. Significantly, higher CSS

Table 2 – Descriptive characteristics of the matched cohort ($n = 364$) stratified according to the extent of nodal invasion

Variables	Patients with two or fewer positive lymph nodes				Patients with more than two positive lymph nodes			
	All patients ($n = 265$) No. (%)	Adjuvant RT plus HT ($n = 85$) No. (%)	Adjuvant HT ($n = 180$) No. (%)	p value	All patients ($n = 99$) No. (%)	Adjuvant RT plus HT ($n = 32$) No. (%)	Adjuvant HT ($n = 67$) No. (%)	p value
Age, yr				0.07				0.93
Mean (median)	66.3 (66.2)	65.2 (65)	65.9 (67)		64.2 (65)	64.3 (65.6)	64.2 (65)	
Range	48–80	48–78.3	50–80		47–79.3	51–75	47–79.3	
Preoperative PSA				0.66				0.59
Mean (median)	30.9 (16)	28.9 (16)	31.9 (15.9)		35.0 (22.4)	32.2 (22)	36.4 (24.8)	
Range	1.6–616	2.8–321	1.6–616		4.1–248.0	4.2–148	4.1–248	
Pathologic stage (2002 TNM)				0.30				0.51
pT2a/b/c	6 (2.3)	2 (2.4)	4 (2.2)		1 (1)	1 (3.1)	0 (0)	
pT3a	23 (8.7)	7 (8.2)	16 (8.9)		8 (8.1)	3 (9.4)	5 (7.5)	
pT3b	219 (82.6)	67 (78.8)	152 (84.4)		83 (83.8)	26 (81.2)	57 (85.0)	
pT4	17 (6.4)	9 (10.6)	8 (4.4)		7 (7.1)	2 (6.3)	5 (7.5)	
Pathologic Gleason score				0.75				0.4
≤6	31 (11.7)	11 (12.9)	20 (11.1)		3 (3)	0 (0)	3 (4.5)	
7	152 (57.4)	46 (54.1)	106 (58.9)		55 (55.6)	17 (53.1)	38 (56.7)	
8–10	82 (30.9)	28 (32.9)	54 (30)		41 (41.4)	15 (46.9)	26 (38.8)	
Surgical margin status				0.78				0.98
Positive	180 (67.9)	59 (69.4)	121 (67.2)		79 (79.8)	26 (81.3)	53 (79.1)	
Negative	85 (32.1)	26 (30.6)	59 (32.8)		20 (20.2)	6 (18.8)	14 (20.8)	
No. lymph nodes removed and examined				0.09				0.47
Mean (median)	13.4 (13)	14.0 (14)	12.9 (12)		15.1 (15)	14.6 (14.5)	15.4 (15)	
Range	2–33	2–32	2–33		5–29	5–25	6–29	
No. positive lymph nodes				0.57				0.08
Mean (median)	1.4 (1)	1.3 (1)	1.4(1)		5.4 (4)	4.9 (3.2)	5.8 (4.6)	
Range	1–2	1–2	1–2		3–19	3–10	3–19	
Length of follow-up, mo				0.12				0.82
Mean (median)	101.3 (97)	94.7 (85.8)	104.5 (105.4)		99.2 (85.3)	101.1 (84)	98.3 (94.8)	
Range	3.5–227.5	15.9–218.5	3.5–227.5		5.3–229.3	12.2–229.3	5.3–220.4	

PSA = prostate-specific antigen.

rates were found in patients treated with adjuvant RT plus HT versus adjuvant HT alone regardless of the extent of nodal invasion. CSS rates at 5-, 8-, and 10-yr follow-up for men treated with adjuvant RT plus HT versus HT alone were 98%, 92%, and 86% versus 91%, 81%, and 74% in patients with two or fewer positive nodes and 87%, 87%, and 87% versus 78%, 70%, and 62% in patients with more than two positive nodes, respectively (all $p = 0.04$; HRs: 2.3 and 2.9, respectively; Fig. 2 and 3, respectively). Similar results were found considering OS as the end point (Fig. 4–6; all $p \leq 0.006$).

4. Discussion

Although the incidence of PCa nodal metastases has dramatically decreased in the PSA era [1,29], LNI is still diagnosed in up to 40% of patients submitted to extended

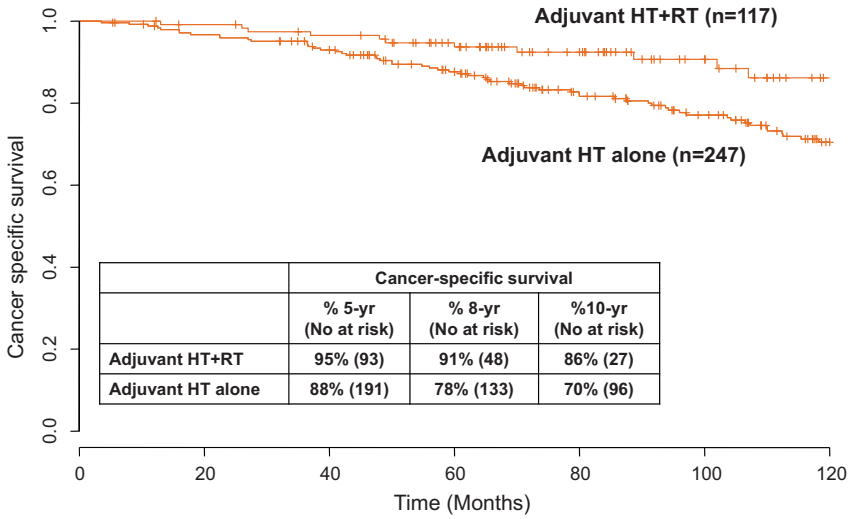
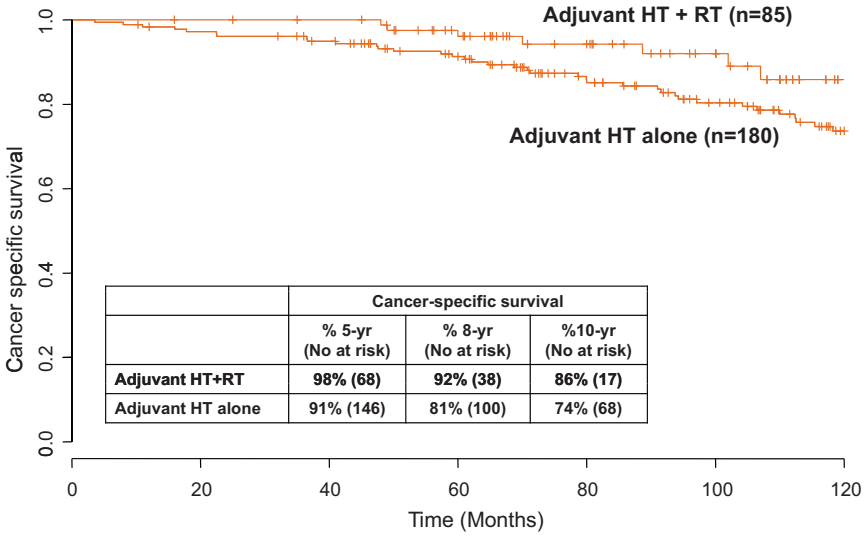


Fig. 1 – Kaplan-Meier estimates of cancer-specific survival after surgery according to the type of adjuvant treatment administered (adjuvant radiation therapy [RT] plus hormonal therapy [HT] vs adjuvant HT alone) in the overall matched population ($n = 364$; log-rank test: $p = 0.004$; hazard ratio: 2.5).

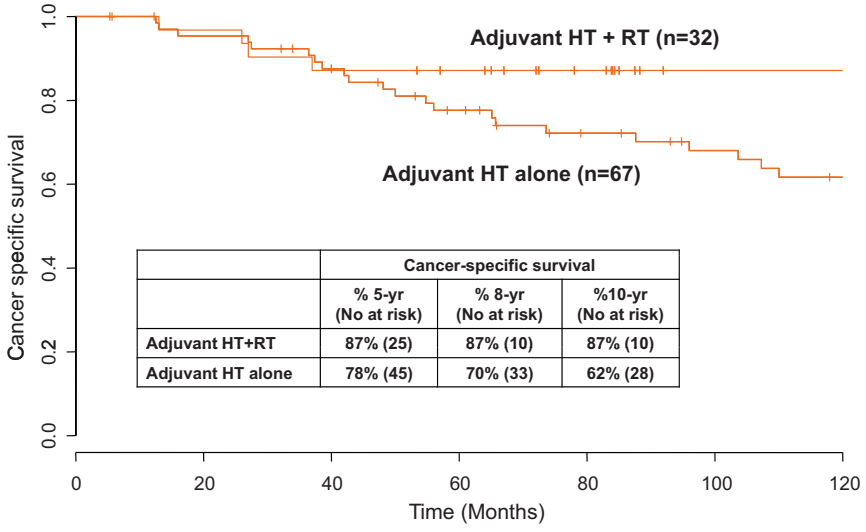


	Cancer-specific survival		
	% 5-yr (No at risk)	% 8-yr (No at risk)	%10-yr (No at risk)
Adjuvant HT+RT	98% (68)	92% (38)	86% (17)
Adjuvant HT alone	91% (146)	81% (100)	74% (68)

Fig. 2 – Kaplan-Meier estimates of cancer-specific survival after surgery according to the type of adjuvant treatment administered (adjuvant radiation therapy [RT] plus hormonal therapy [HT] vs adjuvant HT alone) in patients with two or fewer positive lymph nodes (n = 265; log-rank test: p = 0.04; hazard ratio: 2.3).

PLND [8,10]. Historically, patients with LNI were considered affected by a systemic and noncurable disease. They were therefore not considered suitable for a surgical approach. However, several surgical series have shown that the long-term outcome of surgically treated patients with LNI is not invariably poor. Overall, 10-yr CSS rates ranged between 60% and 86% in the most recent surgical series [13–19]. Patients with a low volume of nodal disease have significantly higher survival rates compared with patients with a higher volume of LNI, regardless of adjuvant treatment administration [13–19]. Therefore, not all node-positive patients are at the same risk of PCa progression and death. The optimal treatment of patients with node-positive disease after surgery is still controversial. A single prospective randomised trial showed significantly higher CSS rates for patients treated with adjuvant HT as compared with those receiving HT at clinical progression [20]. However, this trial was limited by the low number of noncontemporary patients mainly affected by macro-metastatic lymph nodes enrolled in the early PSA era. For these reasons, several authors have questioned the current applicability of these findings [8,19]. Moreover, the only level 1 evidence trial addressing the role of RT in patients with node-positive disease included only a few patients previously treated with RP. The outcomes of these patients were not separately studied in the survival analyses [29].

In this study, we hypothesised that the combination of adjuvant RT plus HT might improve the CSS and OS of patients with LNI. Previous studies have shown that local control of PCa (ie, pathologic T stage and Gleason score,



	Cancer-specific survival		
	% 5-yr (No at risk)	% 8-yr (No at risk)	%10-yr (No at risk)
Adjuvant HT+RT	87% (25)	87% (10)	87% (10)
Adjuvant HT alone	78% (45)	70% (33)	62% (28)

Fig. 3 – Kaplan-Meier estimates of cancer-specific survival after surgery according to the type of adjuvant treatment administered (adjuvant radiation therapy [RT] plus hormonal therapy [HT] vs adjuvant HT alone) in patients with more than two positive lymph nodes (n = 99; log-rank test: p = 0.04; hazard ratio: 2.9).

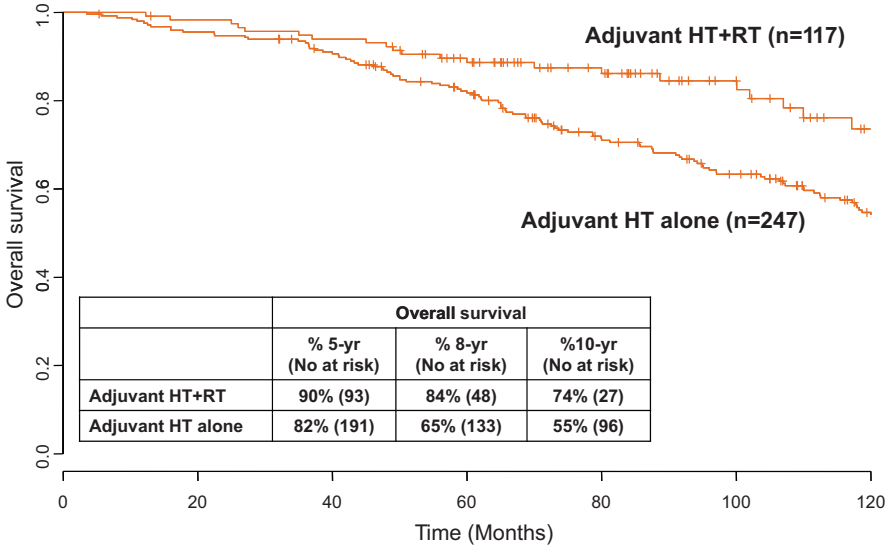


Fig. 4 – Kaplan-Meier estimates of overall survival after surgery according to the type of adjuvant treatment administered (adjuvant radiation therapy [RT] plus hormonal therapy [HT] vs adjuvant HT alone) in the overall matched population (n = 364; log-rank test: p < 0.001; hazard ratio: 2.3).

status of surgical margins) is key even in the presence of nodal involvement [17,18]. Therefore, optimising local disease control with adjuvant RT would prevent development of local failure, distant metastases, and death from PCa [21–24].

We explored the long-term outcome of a large series of patients with LNI treated with RP, PLND, and adjuvant treatments at two large academic institutions. We demonstrated a significant beneficial effect of adjuvant RT plus HT on the survival of node-positive patients by using a matched analysis that allowed us to examine CSS according to the type of adjuvant treatment administered after adjustment for all available tumour characteristics. Differences in tumour characteristics according to treatment type may confound unmatched analyses, especially when important differences at baseline exist between groups that are being compared. Interestingly, patients treated with adjuvant RT plus HT had a significantly higher CSS as compared with matched patients receiving HT alone. The 5-, 8-, and 10-yr CSS survival rates for patients receiving adjuvant RT plus HT versus those treated with adjuvant HT alone were 95%, 91%, and 86% versus 88%, 78%, and 70%, respectively (Fig. 1; p = 0.004). Patients treated with adjuvant RT plus HT had a 2.5-fold higher chance of being free from cancer mortality as compared with patients treated with adjuvant HT alone. The beneficial effect of adjuvant RT on CSS was confirmed regardless of the extent of nodal invasion (all p = 0.04; Fig. 2 and 3). Similar results were obtained when OS was considered as the end point (Fig. 4–6).

Our study represents one of the few series assessing the role of adjuvant RT in node-positive PCa. Cozzarini et al reported on an initial subgroup of 153 node-positive

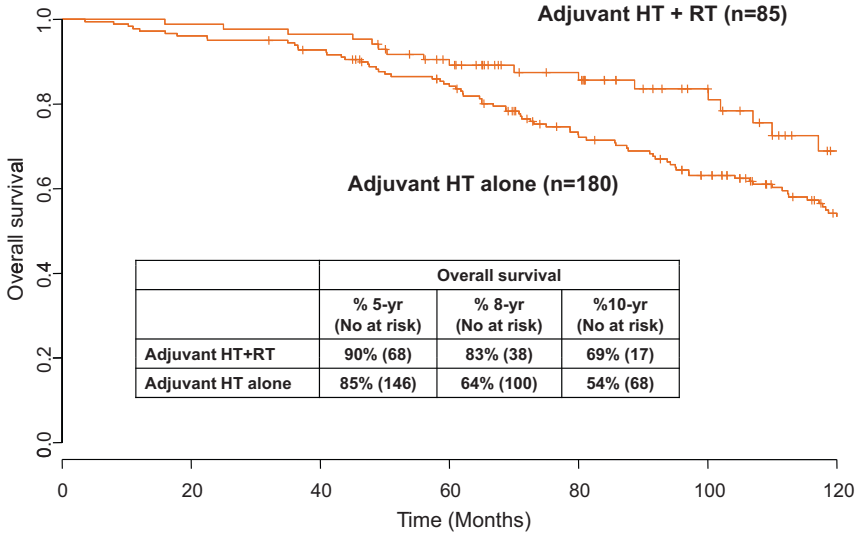


Fig. 5 – Kaplan-Meier estimates of overall survival after surgery according to the type of adjuvant treatment administered (adjuvant radiation therapy [RT] plus hormonal therapy [HT] vs adjuvant HT alone) in patients with two or fewer positive lymph nodes (n = 265; log-rank test: p = 0.006; hazard ratio: 2.01).

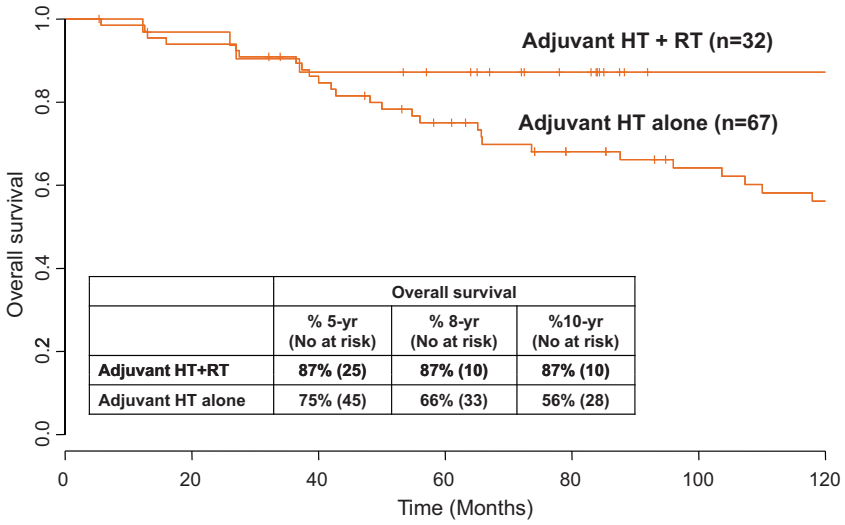


Fig. 6 – Kaplan-Meier estimates of overall survival after surgery according to the type of adjuvant treatment administered (adjuvant radiation therapy [RT] plus hormonal therapy [HT] vs adjuvant HT alone) in patients with more than two positive lymph nodes ($n = 99$; log-rank test: $p = 0.003$; hazard ratio: 3.9).

patients treated with either adjuvant RT plus HT ($n = 55$) or salvage/no RT ($n = 98$) after RP and PLND [28]. These authors found a significant advantage of adjuvant RT on systemic progression and CSS as compared with salvage/no RT ($p < 0.001$ and $p = 0.04$, respectively). However, the two groups of patients significantly differed in terms of preoperative cancer characteristics, which might have biased the results of the subanalysis performed. Patients receiving salvage RT were also included in the control group together with patients not receiving RT. Da Pozzo et al recently tested the role of adjuvant RT on CSS in a cohort of 250 node-positive patients [25]. They found that adjuvant RT was a significant predictor of CSS at multivariable analyses. However, these authors were not able to find any association between adjuvant RT and CSS at univariate analysis, which may be explained by the fact that patients receiving adjuvant RT were affected by more aggressive disease as compared with patients receiving adjuvant HT alone. The effect of adjuvant RT was thus unlikely to be shown at univariable analysis. We circumvented this limitation by using a matched-controlled analysis that allowed us to compare two homogeneous patient populations. Da Pozzo et al did not study the effect of adjuvant RT on patient survival according to the extent of nodal invasion, which represents a key predictor of the outcome of patients with LNI [11–19].

The effect of the combined approach using RT plus HT in patients with LNI was also addressed in a prospective randomised trial comparing early androgen suppression plus RT versus RT and delayed HT [29]. Early HT plus RT had a significant impact on absolute survival, disease-specific failure, metastatic failure, and biochemical recurrence–free survival. Interestingly, a subgroup of 42 patients enrolled had previously undergone RP, but they were not considered separately in the statistical analysis.

Finally, our results are strengthened by the large number of node-positive patients included and by the extremely long follow-up (mean: 100.8 mo; median: 95.1 mo; range: 3.5–229.3 mo). All our patients were treated in the PSA era, which avoids any bias related to the current applicability of our findings [30].

Despite several advantages, our study is not devoid of limitations. First, no standardised template and doses of adjuvant RT were used for all patients. Although all patients treated with adjuvant RT received treatment within 3 mo from surgery, data on PSA value at the time of RT initiation were not available. Second, the type of adjuvant HT was not standardised, and its duration was extremely heterogeneous. Therefore, the study is strongly limited by the lack of standardised adjuvant protocols. Third, it must be stressed that our series did not include patients without adjuvant treatments after surgery. The combination of adjuvant RT plus HT has indeed been compared with adjuvant HT alone. Therefore, caution is needed in comparing our data with data from other studies that did not use adjuvant treatments after surgery. Although the role of adjuvant HT in patients with LNI was supported in a previous prospective randomised trial [20], previous studies also questioned the need for adjuvant HT, especially in patients with a low volume of nodal burden [19,31]. In addition, it is currently unknown whether the efficacy of early salvage protocols might be comparable with the results obtained from the administration of adjuvant therapies in patients treated with curative intent. A previous trial of immediate versus deferred ADT in patients with newly diagnosed PCa not suitable for local treatment showed no significant difference in PCa mortality or symptom-free survival [32]. Based on all these considerations, it might be argued that some patients included might have been exposed to a certain risk of overtreatment. We hope this will be addressed in future prospective randomised trials. Finally, no standardised nodal and pathologic sampling was performed between the two institutions. The lack of pre- and postoperative testosterone levels represents another limitation of our study.

Despite these limitations we were able to demonstrate a survival benefit of adjuvant RT plus HT in node-positive PCa.

These data support the use of a combined multimodal approach in the treatment of advanced node-positive PCa. However, additional larger randomised studies are needed to address the role of adjuvant treatments on cancer outcomes of contemporary node-positive patients.

5. Conclusions

We demonstrated that the adjuvant combination treatment with long-term HT and RT after RP is associated with significantly better long-term survival as compared with adjuvant HT alone in node-positive PCa. This survival benefit was demonstrated regardless of the extent of nodal invasion. These results reinforce the need for a multimodal approach in the treatment of node-positive PCa patients. Further long-term randomised trials are needed to confirm the role of adjuvant RT in patients with PCa and nodal metastases. Future studies will also be needed to address the optimal type and duration of adjuvant HT in patients with node-positive disease.

Author contributions: Alberto Briganti had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Briganti, Capitanio, Gallina, Suardi, Karnes.
Drafting of the manuscript: Briganti, Montorsi, Karnes, Cozzarini, Di Muzio, Rigatti, Blute.
Critical revision of the manuscript for important intellectual content: Briganti, Montorsi, Karnes, Cozzarini, Di Muzio, Rigatti, Blute, Salonia.
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