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Papers

Adjuvant Radiotherapy Following Radical Prostatectomy—Results of 56 Patients

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Patients with adenocarcinoma of the prostate with positive surgical margins and/or seminal vesicle invasion after radical prostatectomy (RP) have a high risk of local recurrence or distant spread of disease. Several investigators reported increased local control rates following adjuvant radiotherapy (RT). However, it is unclear whether this procedure, with or without hormonal therapy (HT), improves the outcome. From 1975 to 1987, 56 patients with adenocarcinoma of the prostate underwent adjuvant RT following RP (pathological stage C1, $n = 19$; stage C2, $n = 17$; stage D1, $n = 20$). In 27 of 56 patients an additional immediate orchiectomy was performed. 48 patients received 4000–5000 cGy to the pelvic lymphatics, including the prostatic fossa, followed by a boost to the prostatic fossa to complete 6400–7000 cGy, whereas 8 patients were treated to the prostatic fossa only. With a median follow-up of 89 months, the overall survival rate of patients with stages C1, C2 and D1 did not differ significantly (10-year overall survival rate 84, 74 and 71, respectively). The local control rate for 5- and 10-years was 96 and 90%, respectively. A significant advantage in overall survival (5- and 10-year rate: 92 versus 93% and 92 versus 63%; $P < 0.05$, respectively) and clinical disease-free survival (5- and 10-year rate: 92 versus 72% and 92 versus 49%; $P < 0.05$, respectively) was seen in 27 patients with orchiectomy compared with 29 patients without HT. A total of 15 patients (26%) developed at least one form of late toxicity, in most cases a mild proctitis, cystitis, or penile or leg oedema. However, 6 patients (11%) had severe grade 3 or 4 side-effects that necessitated a cystectomy in 2 cases as well as a colostomy in 2 cases. In all patients with grade 3 or 4 side-effects, 70 Gy as a tumour-encompassing isodose were applied. Adjuvant RT, following RP in stage C and D1 prostate cancer with positive surgical margins and/or seminal vesicle invasion increases local control. Whether immediate HT influences the outcome, as seen in this study, should be proven in prospective clinical trials.

Key words: carcinoma of the prostate, irradiation, prostatectomy
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INTRODUCTION

RADICAL PROSTATECTOMY (RP) is commonly employed for the treatment of prostatic carcinoma limited to the gland (stage A and B) [1–4]. Obviously, almost all the available staging methods underestimate the pathological tumour stage, but in up to 20%, it will be overestimated [5]. Up to 40% of the patients, who were pre-operatively staged as A2 and B, had tumours that histologically showed a capsule crossing growth (stage C) or lymph node metastases (Stage D1) [6]. Several risk factors for local disease recurrence and distant spread have been identified [7]. There is controversy over the value of adjuvant radiotherapy (RT) with or without hormonal therapy (HT) following RP in the literature. Some investigators have demonstrated an increased local control rate, but there is no proven advantage for prolongation of overall survival. Therefore, we analysed the outcome of 56 patients who underwent adjuvant RT with or without immediate orchiectomy following RP from 1975 to 1987 at the Department of Radiotherapy of the University Hospital Hamburg-Eppendorf. All patients included in the study presented stage C1, C2 or D1 adenocarcinomas of the prostate. The aim of this adjuvant treatment was a higher local control rate, thus prolonging the disease-free survival time.

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MATERIALS AND METHODS

Patients

From 1975 to 1987, 56 patients with stage C1 (invasion of periprostatic tissue, $n = 19$), C2 (involvement of the seminal vesicles, $n = 17$) or D1 (evidence of lymph node metastases, $n = 20$) adenocarcinoma of the prostate, with a mean age of 63 years (range 49–84), underwent adjuvant RT following RP with curative intent. The tumours were staged according to the system developed by the American Joint Committee on Cancer

Table 1. Patients' characteristics

	Stage C1	Stage C2	Stage D1
Number of patients	19	17	20
Mean age (years)	60	65	64
Median follow-up (months)	133	129	77
Clinical stage			
B1	1	—	—
B2	6	8	4
C	12	9	16
Positive margins	17	15	15
Capsule penetration	19	17	16
Seminal vesicles (+)	0	17	16
Grade of malignancy			
I	2	1	—
II	4	4	2
III	13	12	18
Increased value of acid phosphatase			
Yes	3	2	6
No	16	15	14
PSA available as a measure of disease in follow-up			
Total 46 patients	15	15	16
<0.5 ng/ml	12	10	13
>0.5 ng/ml	3	5	3
Number of lymph nodes involved			
1 (microscopic)			3
1 (macroscopic)			8
2			7
>2			2

in 1988 [8]. The grading was carried out based on the recommendations of the German grade of malignancy [9]. Only 13 patients had well or moderately differentiated tumours, whereas 43 patients had poorly differentiated tumours. Table 1 gives detailed information about the patient characteristics. With regard to the nodal status of patients staged D1, 3 had one microscopically positive node, 8 patients had one grossly positive node, 7 had two and 2 patients had three or more positive lymph nodes.

Urological treatment

The treatment policy, in general, was to prostatectomise patients with localised disease (stages A–C) [4]. Until 1987, RP was not performed when metastases were seen intra-operatively at pelvic lymph node dissection (PLND). In those cones, the operation was completed with bilateral orchiectomy with or without additional RT. Patients with fixed stage C tumours underwent a PLND and an orchiectomy and were then referred to RT. This policy was changed in 1987 because results from the Mayo Clinic indicated a better outcome for patients with stage C and D1 following RP and immediate HT [10, 11]. From this time onwards, RP was performed for all patients. There were some patients with RP and positive nodes between 1975 and 1987, when postoperatively lymph node metastases were found by the pathologist. The patients were referred to RT with stage C and D1 tumours in case of positive margins (n = 46) and/or widespread within the surrounding periprostatic tissue or the seminal vesicles (n = 7), when bladder function was quite normal. 3 patients with postivie lymph nodes had stage B2 without positive margins or capsule penetration. In these patients, the nodal state was the indication for RT (Table 1). All 56 patients underwent RP as previously prescribed [4, 5] including a staging PLND, which comprised bilateral samples from four lymph vessel areas (arterialiaca communis, a. iliaca interna, a. iliaca externa and fossa obturatoria). Samples from the presacral and presciatic nodes were not taken. 27 of 56 patients underwent an immediate orchiectomy, and of these, most patients staged D1 (14/20) had this additional HT, while the other 13 patients had widespread tumour into the periprostatic tissue or invasion of the seminal vesicles. 29 patients had no immediate HT (Table 2). In case of orchiectomy, urological treatment was carried out with additional medication with androcur.

Radiotherapy

Patients were treated until 1978 with Co^{60} (n = 5) and from then on either with 42 MV photons from a betatron or 16 MV photons from a linear accelerator.

Adjuvant RT following RP was initiated, usually 2 or 3 months after the operation, in order to allow sphincter function to consolidate. 48 of 56 patients underwent RT of the pelvic lymphatics. The pelvic fields included the prostate, periprostatic tissue and pelvic lymph nodes up to the promontorium. All fields were subjected to daily treatment. Until 1987, the pelvic lymphatics were treated delivering 4000 cGy to the isocentre (n = 36), but after this time, 5000 cGy were applied as tumour-encompassing isodose (range of the maximum 108–125%) (n = 12). The pelvic portals were usually treated, until 1986, with five or six fixed fields and, after 1986, with a four field box (AP/PA and lateral). This was followed by a boost of 1000–2500 cGy with photons through reduced fields to complete 6000–6500 cGy (median 6500 cGy) as the tumour-encompassing isodose to the prostatic fossa. After 1987, a total dose of 7000 cGy to the boost was applied as the tumour-encompassing isodose (range of the maximum 108–125%, n = 12). Boost treatment was usually carried out by a four field box technique (AP/PA and lateral) or with 120° bilateral arcs. Daily dose consisted of 200 cGy for the pelvic portals, and for the prostatic fossa reduced fields, five fractions per week. 8 patients were treated to the prostate only for individual reasons to complete 6500 cGy to the isocentre (7 patients with stage C tumours and 1 patient with a stage D1 tumour).

Follow-up

Continued observation of all patients varied from 44 to 228 months after RP (median follow-up for patients with stage C: 132 months, range 44–228; for patients staged D1: 77 months, range 47–186). The follow-up examinations routinely included complete history, physical examination including rectal palpation, chest X-ray, an annual bone scintigraphy, serological

Table 2. Grade of malignancy and tumour staging in 27 patients with and 29 patients without orchiectomy

	With orchiectomy (n = 27)	Without orchiectomy (n = 29)
Grade		
I	1	2
II	6	3
III	20	24
Stage		
C	13	23
D1	14	6

determination of prostatic acid phosphatase and prostate-specific antigen levels (PSA). PSA determination has been part of the follow-up since November 1987. 46 of 56 patients had PSA determinations. 10 patients died without one determination of PSA and were classified clinically. 2 of these patients died from their tumour and 8 with no evidence of disease (NED). Patients were staged as NED with a PSA in the undetectable region (<0.5 ng/ml). Tumour progress was implicated by the continuous increase in PSA levels over a period of 6 months, although no signs of local relapse or metastases occurred. A verifying histological investigation was performed if, after rectal palpation, a local recurrence was suspected.

Side-effects

Complications were scored according to the Radiation Therapy Oncology Group/European Organization for Research in the Treatment of Cancer (RTOG/EORTC) radiation morbidity grading system.

Statistical analysis

For all patients, survivals from the beginning of RT to death, regardless of course or detection of any progression (local and systemic), were estimated by the Kaplan–Meier method [12]. Comparison of subgroups was done by the log rank test [13]. Differences were considered significant when P-values of less than 0.05 were obtained.

RESULTS

Overall survival (OS)

The median follow-up of all patients was 89 months (range 44–228) derived from 52 patients for 5 years, 26 patients for 10 years and 4 patients for 15 years under observation. 20 of 56 patients died—14 patients with stage C tumours and 6 patients with stage D1 tumours. The 5- and 10-year OS rates were 95% and 84% for stage C1 patients, 94 and 74% for stage C2 patients and 90 and 71% for stage D1 patients, respectively. 6 patients died from their tumour and 14 died of intercurrent disease. No significant differences were found between the three groups (P values between 0.40 and 0.97) (Figure 1).

Disease-free survival (DFS)

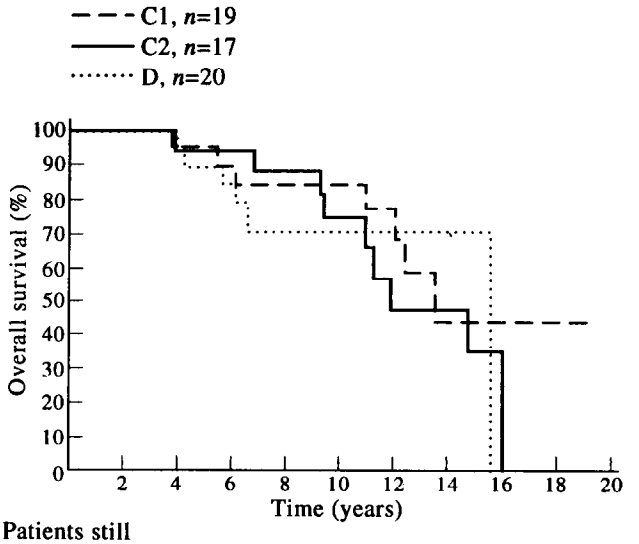
11 patients showed clinical progression of disease (median time to progression 38 months). The DFS rates for 5- and 10-years were 95 and 71% for stage C1, 71 and 64% for stage C2 and 80 and 70% for stage D1, respectively. There were no significant differences between the three groups (P values between 0.36 and 1.1) (Figure 2).

Local control (LC)

4 of 56 patients developed local progression between 5 and 103 months following RT (3 patients staged C, 1 patient staged D1). The LC rates for 5- and 10-years were 96 and 90%, respectively (Figure 3).

Hormonal deprivation

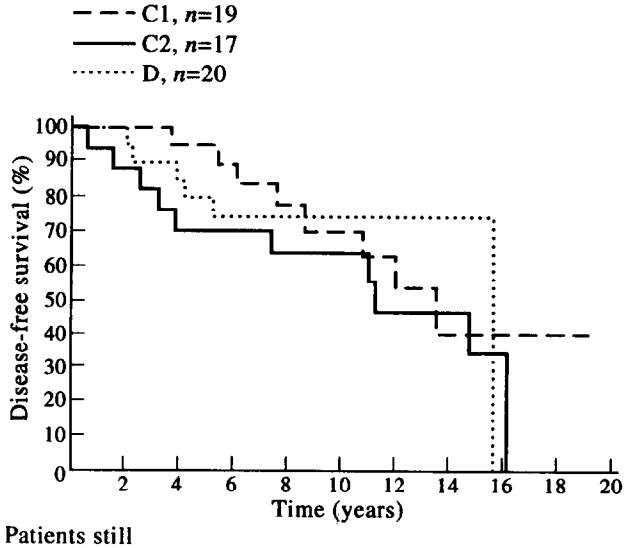
27 patients underwent orchiectomy at the time of RP. 13 of these had stage C and 14 had stage D1 tumours (with a shorter follow-up). 6 patients with orchiectomy developed tumour progression and/or died, thus the 5- and 10-year DFS rate was 92%. In the group of 29 patients without an orchiectomy, 23 had stage C and 6 had stage D1 tumours. 18 patients developed tumour progression and/or died; the 5- and 10-year DFS rates were 72 and 49%, respectively (P = 0.0017) (Figure 4). The OS rates for 5 and 10 years for patients with orchiectomy compared to patients without were 92 versus 93% and 92 versus 63%, respectively (P = 0.017) (Figure 5, Table 2).



Patients still under observation:

Stage C1	19	18	12	1
Stage C2	17	16	11	2
Stage D	20	18	3	1

Figure 1. Overall survival rate of 56 patients.



Patients still under observation:

Stage C1	19	18	10	1
Stage C2	15	12	10	2
Stage D	20	16	3	1

Figure 2. Disease-free survival rate of all 56 patients.

Grade of malignancy

The 5- and 10-year DFS rate of the 13 patients with a grade I or II tumour was 100%. In contrast, 43 patients with grade III tumours had DFS rates for 5- and 10-years of 77 and 59%, respectively (P = 0.046).

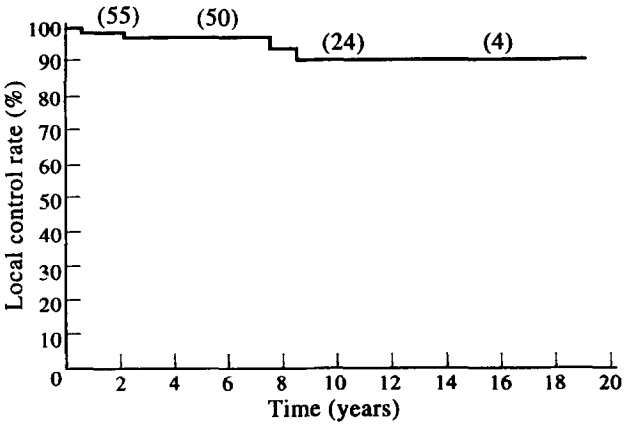


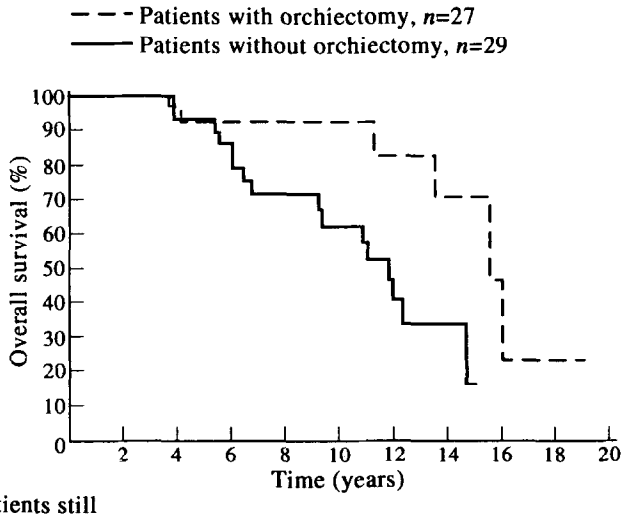
Figure 3. Local control rate of all 56 patients (numbers in parentheses pertain to patients still under observation).

Radiation techniques

In 48 patients (designated as group I), the pelvic lymphatics and the periprostatic region were irradiated. 8 patients (designated as group II) underwent only RT of the periprostatic region for individual reasons. There were no significant differences for OS (5- and 10-year OS rates for group I 92 and 78% versus group II 100 and 71%, $P = 0.1$) or for cause-specific survival (CSS) (CSS rates for 5 and 10 years for group I 100 and 89% versus group II 100% and 85%, $P = 0.1$). However, the results for DFS (DFS rates for 5- and 10-years for group I 85 and 72% versus group II 63 and 50%, $P = 0.32$) and metastases-free survival (MFS) (MFS rates for 5 and 10 years for group I 85 and 75 versus group II 62 and 50%, $P = 0.31$) were slightly better for patients with RT of the pelvic lymphatics, but they did not reach significance (Figure 6).

PSA-free survival

PSA assessment was available in 46 patients. 10 patients died without measurement of PSA and were staged clinically. 2 of these patients died from tumour progression. There were 4 patients with a PSA between 0.7 and 1.1 ng/ml but without an increase over a period of at least 8 months (range 8–36). These were staged as disease progression. The PSA-free survival rate for 10 years for stage C1 was 83%, for stage C2 58% and for stage D1 81%, respectively (P values between 0.2 and 0.9) (Figure 7).



Patients still under observation:

with orchiectomy	27	25	12	4
without orchiectomy	29	27	14	

Figure 5. Overall survival rate in 27 patients with orchiectomy compared to 29 without hormonal manipulation.

Acute toxicity

A total of 14 patients (25%) showed moist or dry desquamation of the skin. 24 of 56 patients (43%) complained about

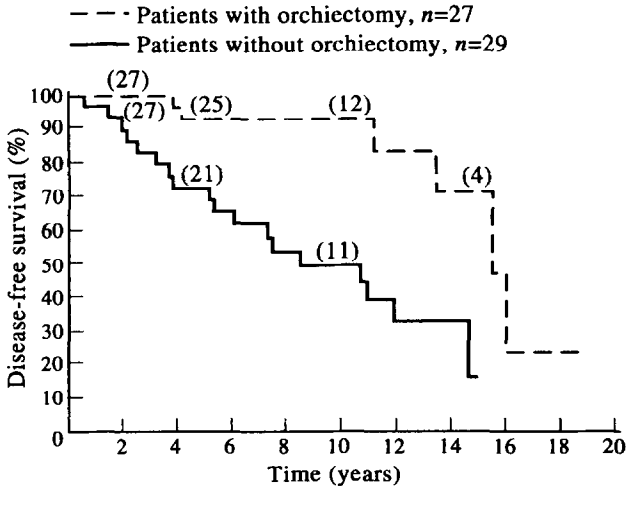


Figure 4. Disease-free survival rate in 27 patients with orchiectomy compared to 29 without hormonal manipulation (numbers in parentheses pertain to patients still under observation).

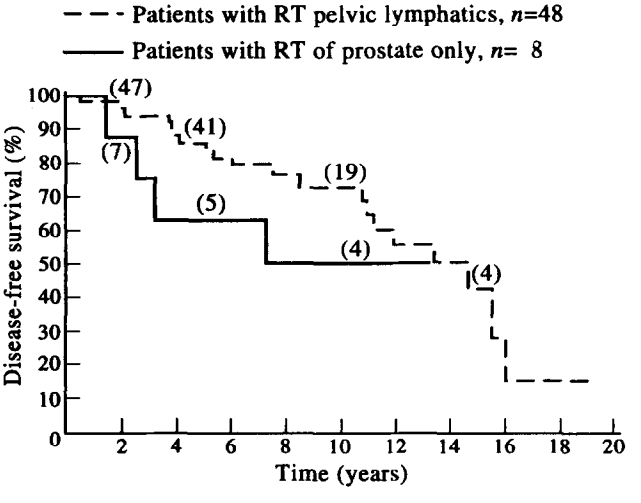
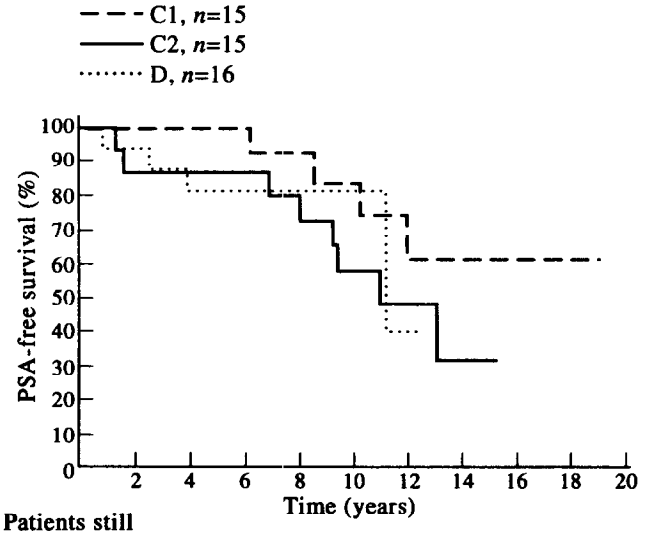


Figure 6. Disease-free survival in 48 patients with radiotherapy (RT) of the prostatic fossa and the pelvic lymphatics compared with 8 patients with RT of the prostatic fossa only (numbers in parentheses pertain to patients still under observation).



Patients still under observation:

Stage C1	15	15	9	1
Stage C2	13	13	8	1
Stage D	15	13	2	

Figure 7. Prostate-specific antigen (PSA)-free survival in 46 out of 56 patients with at least one PSA measure.

pollacissuria or dysuria during RT (grade 1/2). 25 of 56 patients (45%) developed diarrhoea RTOG 1/2. 4 patients suffered from an acute but moderate proctitis.

Late toxicity

6 patients developed incontinentia, which is a common toxicity following RP and might be a combined toxicity. 4 of 56 patients had a mild leg and/or penile oedema, as a combined toxicity after PLND and RT. 3 of 56 patients showed urinary bladder symptoms grade 1/2. However, in 4 patients, a severe cystitis appeared that made a cystectomy necessary in two cases. 8 patients presented with moderate radiation-induced proctitis grade 1/2; in 2 patients, a colostomy became necessary (grade 4). Overall, 15 of 56 patients (26%) showed at least one form of late toxicity (Table 3).

DISCUSSION

Radical prostatectomy has been considered the classic approach to the management of operable patients in prostatic carcinoma clinically confined to the gland (stage A and B) [2, 4]. However, in up to 70%, a higher tumour stage is detected postoperatively, often with tumour invasion into the peripros-

Table 3. Late side-effects (EORTC/RTOG score)

Score	Skin	Bladder	Rectum	Oedema
0	56 (100%)	49 (86%)	46 (82%)	52 (93%)
1	0	2 (4%)	5 (9%)	3 (5%)
2	0	1 (2%)	3 (5%)	1 (2%)
3	0	2 (4%)	0 (0%)	0 (0%)
4	0	2 (4%)	2 (4%)	0 (0%)

In total, 15 of 56 (27%) patients showed at least one form of side-effect.

tatic tissue and/or the seminal vesicles (stage C1/C2 [14, 15]. Those patients show an increased risk of local recurrence. Twenty to thirty per cent of these tumours recurred within 10 years, and the rate of distant metastases was up to 50% [7, 16, 17]. The results of salvage treatment of palpable local recurrence remains unsatisfactory. These patients have a 10-year survival rate of only 20–40%, following RT with or without adjuvant HT [16, 18]. Therefore, several risk factors for local disease recurrence and distant spread have been identified. These include extracapsular extension, positive margins and elevated PSA levels postRP [7, 17, 19]. Particularly in the case of seminal vesicle invasion, distant failures predominate [7]. Adjuvant RT aims at an increased local tumour control, thus prolonging the DFS time (for an overview, see Table 4; [15, 20, 21]).

Numerous investigators have reported increased LC rates in patients with adjuvant RT in stage C and D1 prostate cancer. The local recurrence rates for 10 years vary between 0 and 10% [20, 22–26] with which our results concur, with 5- and 10-year LC rates of 96 and 90%, respectively. When no adjuvant RT was given, reported local recurrences were between 12 and 28% [23 24, 27]. The problem is that these high LC rates do not correlate with a decreased incidence of distant metastases or prolonged OS [23, 25]. This indicated that most of these patients have micrometastases at the time of diagnosis, in which case, local RT would have only a marginal effect on survival. For this reason some institutions used RT of the pelvic lymphatics, aiming to eliminate undetected microscopic nodal disease.

However, the value of additional RT of the pelvic lymphatics remains unclear. Some authors suggested a trend for better outcome in patients with RT of the pelvic lymphatics, but this did not reach significance [15], as was seen in our patients. In contrast, other groups had comparable results without pelvic RT [20, 22], and there are no data concerning prospective clinical trials comparing pelvic RT with RT to the prostatic fossa.

Surprisingly, there is little information in the literature concerning adjuvant RT in combination with immediate orchiectomy. A possible explanation is that HT is often used when tumour progression is detected. There are interesting results in the present series about immediate HT with a significant advantage in OS and DFS for 27 patients with orchiectomy with a 10-year OS rate of 92% and a DFS rate of 92% compared with an OS rate of 63% and a DFS rate 49% in 29 patients without HT, respectively. The influence of immediate HT on patients treated with RT remains unclear. Zincke [28] reported a significant improved OS for 171 patients with stage D1 cancer following RP and immediate orchiectomy compared with patients with RP alone. These patients' survival was comparable with that expected [28]. There is no larger series in the literature concerning patients treated with RP, adjuvant RT and immediate orchiectomy. Reported data on small groups of patients showed no significant advantage for patients treated with immediate HT [23]. The best explanation for our results is that the combined treatment including RP, orchiectomy and RT (including the RT of the pelvic lymphatics) seems able to eliminate microscopic local tumour and that adjuvant HT could be able to eliminate microscopic distant metastases.

A major problem of most studies is that PSA as a measure of no evidence of disease (NED) was available only for a few of the patients. In most cases, this information was incorporated into the clinical follow-up data. There is no doubt that PSA is effective in detecting disease progression [29]. In 46 of our 56

Table 4. Outcome of various treatments for patients with adjuvant RT in pathological stage C or D1 prostate cancer following RP

First author [ref.]	*n*	Stage	CP	SV	M	RT	FU (months)	LCR	DFS (years)	DFS (PSA) (years)	OS (years)
Ami Sidi [22]	30	C	3	20	7	60 Gy local	56	96%	5 (76%)		
	26	D1	2	20	4	45 Gy pelvis 10–15 Gy boost	46 (med)	100%	5 (72%)		
Carter [26]	31	C	9	6	16	45–55 Gy local	60	97%	10 (92%)		
	16	D1	1		13	45–60 Gy local	60 (med)	100%	10 (86%)		
	(only 11 RT)										
Eisbruch [23]	29			8	21	50–60 Gy local	59	100%	10 (46%)		
	5	D1		+	+	40–50 Gy pelvis 10–20 Gy boost	(med)	100%	5 (40%)		5 (40%)
Hanks [36]	11		3	2	6	RT pelvis in 6 60–73 Gy prostate	7–8y (med)	100%	5 (86%)		
Kwon [20]	59	C	31	12	16	Au198 seeds 96.6 mCi average	64 (med)	98%		10 (79%)	
Paulson [21]	46				31	45–50 Gy pelvis 10–15 Gy boost					10 (65%)
Petrovich [25]	78	C/D1	18	37	20	45 Gy R1 local 55 Gy R2 local	5 years (med)	97%			
	50	C	35		15				10 (51%)		
	28	D1	3		22				10 (28%)		
	D1 24 with CT, 4 with HT										
Stein [27]	24	C	12	11	8	45–50 Gy pelvis 10–15 Gy boost	20%> 84	100%	7 (92%)	7 (54%)	
Wiegel (current study)	19	C1	19	0	17	48 patients	133	90%	10 (71%)		10 (84%)
	17	C2	17	17	15	40–50 Gy pelvis	129	95%	10 (64%)		10 (75%)
	20	D1	16	16	15	65–70 prostate	77 (med)	95%	10 (75%)		10 (71%)

CP, capsule penetration; SV, seminal vesicle invasion; M, positive margins; RT, radiotherapy; FU, follow-up; LCR, local control rate; DFS, disease-free survival; PSA, prostate-specific antigen level; OS, overall survival; R1, microscopic tumour; R2, macroscopic tumour; HT, hormonal therapy; CT, chemotherapy; med, median.

patients, at least one PSA measure was available, and the 10-year PSA DFS for these patients was 83% for stage C1, 58% for stage C2 and 81% for stage D1. Similar results have been reported by others, even for stage D1 [11, 26, 28]. A possible explanation for our stage D1 patients lies in the fact that the majority had early nodal disease including 3 patients with one microscopically positive node and 8 patients with one grossly positive node. This is important, as the tumour mass in the lymph nodes influences the outcome [30, 31].

These results suggest that RT for patients with postprostatectomy elevated PSA levels would be the best way for early adjuvant treatment. These patients show in 10–70% of cases, a decrease of PSA to undetectable levels (less than 0.4 ng/ml) [32–34]. However, in up to 30% of patients, PSA later increased, with development of clinical progression of disease [33, 35], but the follow-up of these patients was too short for definitive conclusions (median follow-up in most studies less than 30 months). Link reported that more patients exhibited a decrease of PSA to less than 0.3 ng/ml, following RT of the pelvic lymphatics (6/6), than in those treated to the prostatic fossa only (5/11) [33], thus indicating a beneficial effect of pelvic RT. However, further studies are needed to determine the long-term results in these patients.

There are some data indicating an increased rate of acute and late side-effects caused by RT following RP. However, most authors reported late side-effects in less than 5% of the patients [23, 26, 36]. Obviously, the level of side-effects depends on the side and site of the irradiated volume. However, RTOG study 75-06 with 526 analysable cases showed no significant differences between patients with RT to the pelvic lymphatics and patients treated to the prostate alone [37]. Ray and associates reported a proctitis and cystitis with partly severe clinical courses in approximately 16% of his cases [16]. The patients of Masons Hospital showed these side-effects in 14% following adjuvant RT compared to 6% after surgery alone. However, most of these were irradiated with cobalt [38]. Eighteen per cent of our patients developed proctitis and 14% cystitis, in 6 patients with RTOG grades 3/4. Of these, 1 patient had to be cystectomised, 1 patient received a colostomy and 1 patient underwent both. These severe side-effects were only seen in patients who received large treatment volumes, i.e. RT of the pelvic lymphatics and a 70-Gy boost to the prostatic fossa, both with hotspots of 1.25 fold. With respect to these late side-effects, we limited the total dose to 62 Gy for the prostatic fossa and 50 Gy for the pelvic lymphatics. This may especially reduce the incidence of late side-effects.

In summary, it is concluded that the local control rate of stage C and D1 prostate cancer following RP might increase up to 95% with adjuvant RT. The significant influence of immediate orchiectomy on the OS and the DFS, as seen in our patients, should be proven in prospective clinical trials. The impact of pelvic RT on the outcome remains unclear but it could have a beneficial effect in selected cases, although increased rates of late side-effects may result. 70 Gy as total dose with hotspots of 1.25-

fold are considered to produce unacceptable late side-effects and, therefore, the total dose was reduced to 62 Gy.

1. Jewett H, Eggleston J, Yawn D. Radical prostatectomy in the management of the prostate: probable causes of some therapeutic failures. *J Urol* 1972, **107**, 1034–1041.
2. Gibbons R, Correa R, Brannen G, Mason T. Total prostatectomy for localized prostatic cancer. *J Urol* 1984, **131**, 73–76.
3. Bressel M. Radikale retropubische Prostatektomie (RRP). In *Prostatakarzinom, Spektrum der Kurativen Therapie*. Altwein JE, Sommerkamp H, Basel-München, S. Karger GmbH, 1989, 146–173.
4. Bressel M. Radical prostatectomy-indication, surgical technique, results. *Akt Urol* 1990, (suppl I), 115–119.
5. Morgan WR, Bergstrahl EJ, Zincke H. Long-term evaluation of radical prostatectomy as treatment for clinical stage C(T3) prostate cancer. *Urology* 1993, **41**, 116–120.
6. Hanks GE. The challenge of treating node positive prostate cancer. *Cancer* 1993, **71** (suppl), 1014–1018.
7. Anscher M, Prosnitz L. Multivariate analysis of factors predicting local relapse after radical prostatectomy-possible indications for postoperative radiotherapy. *Int J Radiat Oncol Biol Phys* 1991, **21**, 941–947.
8. American Joint Committee on Cancer. Manual for Staging of Cancer, 3rd edition. Philadelphia, Lippincott Company, 1988, 177–182.
9. Helpap B, Böcking A, Dohm G, *et al.* Klassifikation, histologisches und zytologisches Grading sowie Regressionsgrading des Prostatakarzinoms. *Pathologe* 1985, **6**, 3–7.
10. Zincke H, Utz DC. Observations on surgical management of carcinoma of prostate with limited nodal metastases. *Urology* 1984, **24**, 137–145.
11. Zincke H, Utz DC, Thule PM, Taylor WF. Treatment options for patients with stage D1 (T0-3, N1-2, MO) adenocarcinoma of prostate. *Urology* 1987, **30**, 307–315.
12. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Ass* 1958, **53**, 457–462.
13. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J R Stat Soc A* 1972, **135**, 185–192.
14. Kastendieck H, Bressel M. Vergleichende Analyse der klinischen und morphologischen Klassifikationen (Staging) von 165 Prostatacarcinomen nach radikaler Prostatektomie. *Urologe A* 1980, **19**, 331–339.
15. Perez CA, Eisbruch A. Role of postradical prostatectomy irradiation in carcinoma of the prostate. *Semin Radiooncol* 1993, **3**, 198–209.
16. Ray G, Bagshaw M, Freiha F. External beam radiation salvage for residual or recurrent local tumor following radical prostatectomy. *J Urol* 1984, **132**, 926–930.
17. Schroeder F, Belt E. Carcinoma of the prostate: a study of 213 patients with stage C tumors treated by total perineal prostatectomy. *J Urol* 1975, **114**, 257–260.
18. Wiegel T, Bressel M, Arps H, Hübener KH. Radiotherapy of local recurrence following radical prostatectomy. *Strahlenther und Oncol* 1992, **168**, 333–336.
19. Boxer RJ, Kaufmann JJ, Goodwin WE. Radical prostatectomy for carcinoma of the prostate 1951–1976, a review of 329 patients. *J Urol* 1972, **107**, 91–97.
20. Kwon E, Loening S, Hawtrey C. Radical prostatectomy and adjuvant radioactive gold seed placement: results of treatment at 5 and 10 years for clinical stages A2, B1 and B2 cancer of the prostate. *J Urol* 1991, **145**, 524–531.
21. Paulson DF, Moul JW, Robertson JE, Walther PJ. Postoperative radiotherapy of the prostate for patients undergoing radical prostatectomy with positive margins, seminal vesicle involvement and/or penetration through the capsule. *J Urol* 1990, **143**, 1178–1182.
22. Ami Sidi A, Lange HP. Adjuvant radiation therapy in patients upstaged to stage C or D1 disease after radical prostatectomy. *Eur Urol* 1987, **13**, 238–241.
23. Eisbruch A, Perez CA, Roessler EH, Lockett MA. Adjuvant irradiation after prostatectomy for carcinoma of the prostate with positive surgical margins. *Cancer* 1994, **73**, 384–387.
24. Shevlin BE, Mittal BB, Brand WN, Shetty RM. The role of adjuvant irradiation following primary prostatectomy, based on histopathologic extent of tumor. *Int J Radiat Oncol Biol Phys* 1989, **16**, 1425–1430.
25. Petrovich Z, Lieskovsky G, Langholz B, Luxton G, Jozsef G, Skinner D. Radiotherapy following radical prostatectomy in patients with adenocarcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 1991, **21**, 949–954.
26. Carter GE, Lieskovsky G, Skinner DG, Petrovich Z. Results of local and/or systemic adjuvant therapy in the management of pathological stage C or D1 prostate cancer following radical prostatectomy. *J Urol* 1989, **142**, 1266–1270.
27. Stein A, de Kernion JB, Drey F. Adjuvant radiotherapy in patients post radical prostatectomy with tumor extending through capsule or positive seminal vesicles. *Urology* 1992, **39**, 59–62.
28. Zincke H. Combined surgery and immediate adjuvant hormonal treatment for stage D1 adenocarcinoma of the prostate: Mayo Clinic experience. *Semin Urol* 1990, **8**, 175–183.
29. Lightner DJ, Lange PH, Reddy PK, Moore L. Prostate specific antigen and local recurrence after radical prostatectomy. *J Urol* 1990, **144**, 921–926.
30. Wiegel T, Bressel M. Influence of the extent of nodal involvement on the outcome in stage D1 prostate cancer. *Radiat Oncol Invest*, in press.
31. Anscher MS, Prosnitz LR. Prognostic significance of extent of nodal involvement in stage D1 prostate cancer treated with radiotherapy. *Urology* 1992, **39**, 39–43.
32. Kaplan ID, Bragshaw MA. Serum prostate-specific antigen after post-prostatectomy radiotherapy. *Urology* 1992, **39**, 401–406.
33. Link P, Freiha F, Stamey T. Adjuvant radiation therapy in patients with detectable prostate specific antigen following radical prostatectomy. *J Urol* 1991, **145**, 532–534.
34. Schild SE, Buskirk SJ, Robinow JS, Tomera KM, Ferrigni RG, Frick LM. The results of radiotherapy for isolated elevation of serum PSA levels following radical prostectomy. *Int J Radiat Oncol Biol Phys* 1992, **23**, 141–145.
35. Hudson MA, Catalona WJ. Effect of adjuvant radiation therapy on prostate specific antigen following radical prostatectomy. *J Urol* 1990, **143**, 1174–1177.
36. Hanks GE, Dawson AK. The role of external beam radiation therapy after prostatectomy for prostate cancer. *Cancer* 1986, **58**, 2406–2409.
37. Pilepich MV, Krall JM, Sause WT, *et al.* Correlation of radiotherapeutic parameters and treatment related morbidity in carcinoma of the prostate-analysis of RTOG study 75–05. *Int J Radiat Oncol Biol Phys* 1987, **13**, 351–357.
38. Gibbons R, Cole BS, Richardson RG, *et al.* Adjuvante Strahlentherapie des lokal metastasierten Prostatakarzinoms. *Akt Urol* 1986, **17**, 74–76.

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