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Androgen-independent Prostate Cancer

The Clinical Problem of a Growing Pelvic Tumour

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This retrospective study describes three clinically different groups of patients with symptomatic androgen-independent prostate cancer (AIPC) referred to palliative radiotherapy (RT): those with a symptomatic pelvic tumour and pelvis-confined disease (M0 P-RT: 35 patients), those with a symptomatic pelvic tumour and distant metastases (M+ P-RT: 97 patients) and those with painful bone metastases (BM-RT: 193 patients). The study emphasises the need of a combined surgical and radiotherapeutic palliation in AIPC patients with symptomatic pelvic tumours. Median overall survival from time of palliative RT was 19, 9 and 8 months for M0 P-RT, M+ P-RT and BM-RT patients, respectively ($p < 0.001$). The significantly prolonged natural course of P-RT patients without distant metastases has to be accounted for in clinical trials of AIPC patients in whom survival represents an endpoint. Furthermore, the optimal palliation regimens for P-RT patients are still to be defined.

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Androgen-independent prostate cancer (AIPC) is defined by biochemical and/or clinical disease progression during androgen deprivative treatment with castration levels of serum testosterone. The majority of patients with symptomatic AIPC require palliation due to painful bone metastases and/or decreased general condition. However, at least 10% of AIPC patients develop soft tissue pelvic tumours causing micturition problems, haematuria, ureteric obstruction, lymphoedema, rectal stenosis and/or pelvic pain (1–3). These tumours are frequently a conglomerate of a large primary tumour and regional lymph node metastases; the two components are not easily discriminated from each other in the individual patient. In the present report such 'symptomatic soft tissue masses' are consequently referred to as 'symptomatic pelvic tumours'.

During the past decades symptomatic Norwegian AIPC patients are traditionally referred to palliative radiotherapy (RT) relatively late during their clinical course. This relates in particular to patients with symptomatic pelvic tumours, in whom transurethral resection of the prostate (TUR-P), urinary and/or bowel diversions provides temporary relief from local problems. The increasing oncological treatment options available for AIPC patients may, however, gradually change this situation. Palliative chemotherapy has become more common for these patients in both clinical routine and clinical trials (4–6). In the context of clinical trials AIPC has often been viewed as a homogeneous entity, consisting mainly of patients with bone metastases. This view may, however, be debated on the background of the above-mentioned clinically different presentations.

The oncological and urological literature on treatment and outcome of AIPC patients with symptomatic pelvic tumours is surprisingly limited. There are indications, however, that the clinical course for these patients differs from AIPC patients with symptomatic bone metastases as to palliative needs and survival. Lankford et al. (7) reported a 60% 2-years survival after palliative pelvic RT of pelvis-confined AIPC. Our group has recently shown a median survival time from the first TUR-P after diagnosis of symptomatic AIPC of 14 months (8) as compared to 8–10 months in AIPC patients with irradiated painful bone metastases (1).

Each year about 90 AIPC patients receive palliative RT at the Norwegian Radium Hospital (NRH). The majority of patients have palliative RT to bone metastases, but about 10–15 of these patients receive RT to symptomatic pelvic tumours. Our preliminary clinical observations resulted in the hypothesis of these patients representing a subgroup of AIPC patients with different symptomatology, different palliative needs and different survival compared to AIPC patients with irradiated bone metastases. The aim of the present study was to investigate this hypothesis by reviewing

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the medical records of AIPC patients receiving palliative RT to a symptomatic pelvic tumour and compare the results with those from AIPC patients requiring palliative RT to bone metastases.

MATERIAL AND METHODS

The NRH's computerised patient registries enabled the identification of the approximately 900 AIPC patients who received palliative RT between 1 January 1990 and 31 December 1999 (Fig. 1). Based upon the target volumes of palliative RT and the presence or absence of distant metastases at this time, three groups were defined: 1) AIPC patients with symptomatic pelvic tumours and pelvis-confined disease (M0 P-RT), 2) AIPC patients with symptomatic pelvic tumours and distant metastases (M+ P-RT) and 3) AIPC patients with symptomatic bone metastases (BM-RT). To enable adequate comparison to all patients with symptomatic pelvic tumours (P-RT patients) the third group, initially comprising about 750 patients, was subsequently adjusted for age and year of diagnosis resulting in about 600 patients (Fig. 1). A random selection among these 600 patients identifying 300 patients would, from a statistical point of view, enable comparison of P-RT and BM-RT patients at a ratio of 1:2.

Eligibility criteria for all three groups were histologically proven adenocarcinoma of the prostate and diagnosis of symptomatic AIPC, generally after at least 3 months of androgen deprivation resulting in castration levels of serum testosterone (<2 nmol/L). Patients were also eligible if undoubted symptomatic progression occurred before 3 months had elapsed after start of hormone treatment (primary AIPC). Patients with a previous history of RT and those receiving hemibody irradiation were excluded from the present study a priori to avoid BM-RT patients with very advanced disease. This latter ineligibility criterion principally explains the last reduction from 300 to finally 193 BM-RT patients (Fig. 1).

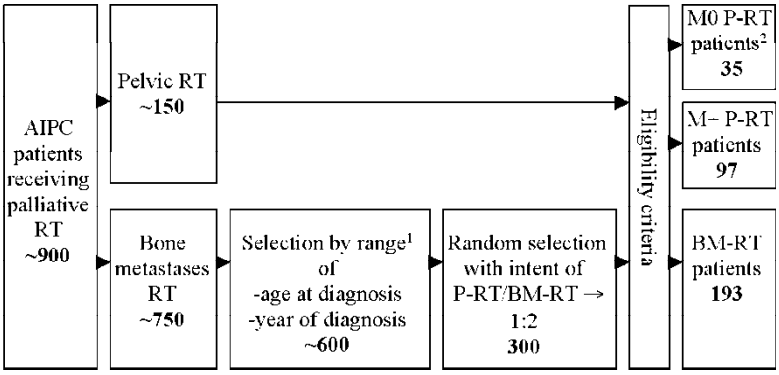
At referral for AIPC the following routine examinations were performed in all patients: skeletal x-ray, haematological and biochemical laboratory tests. Computed tomography (CT) of the abdominal/pelvic region was routinely performed in P-RT patients only. In general, bone scans were to be undertaken, but could be omitted in patients with undoubtedly radiological evidence of bone metastases. As proposed by Soloway et al. (9), the size of one lesion was recorded as half the size of a vertebral body. The number of bone lesions were categorised as none, 1–10 and >10 lesions.

In general, the radiation target volume in P-RT patients comprised the pelvic tumour manifestations as visualised by CT scans with a safety margin of 2 cm. The planned target dose was 2 Gy $\times$ 25 (5 weeks) or 3 Gy $\times$ 10 (2 weeks), mostly dependent upon the availability of RT resources and the patients' general condition. Radiotherapy was given with an anterior and posterior pelvic field. The BM-RT patients received 3 Gy $\times$ 10 to the most painful bone metastases, up to three target volumes treated simultaneously.

For the purpose of the study the following parameters were extracted from the medical records:

Initial diagnosis and treatment: date, symptoms, extent of the disease categorised as localised, regional or distant metastases according to the Norwegian Cancer Registry (10) and histological grade (WHO criteria) as revised by the Department of Pathology at the NRH, date of start and type of androgen deprivation, and date and type of subsequent symptomatic progression. Data regarding surgical palliation procedures were collected. Assessment of serum levels of prostate-specific antigen (PSA) was not routine practice at initial diagnosis for most patients of the present study, and pretreatment PSA values are therefore not recorded.

Palliative RT with clinical status at referral: main palliation-requiring symptom, main radiation target volume and dose (Gy), patients' performance status (WHO criteria) and pretreatment haematological and biochemical parameters.



[1]Range similar to that of all the final P-RT patients [2]M-stage at time of palliative RT

Fig. 1. Selection of AIPC patients included in the present study all receiving palliative RT at the NRH 1990–1999.

Post RT period: referral to additional palliative RT owing to symptomatic bone metastases and last observation (death or 1 January 2001) with survival status.

Statistics

The data were analysed using the computer-based program SPSS version 10.1. Categorical variables were analysed by the χ^2-test. Ordinal and continuous variables were compared between groups by the Kruskal–Wallis test. Overall survival was estimated by the Kaplan–Meier method from first palliative RT up to last observation/death. The logrank test was applied to assess statistical significance. p-values of < 0.05 were regarded as statistically significant.

RESULTS

Initial diagnosis

A total of 35 M0 P-RT patients, 97 M+ P-RT patients and 193 BM-RT patients fulfilled both the selection and eligibility criteria (Fig. 1). Eighty-seven of the 97 M+ P-RT patients had bone metastases at time of palliative pelvic RT, whereas 10 M+ P-RT patients displayed soft tissue metastases only. Thirty-three percent of all the patients were diagnosed before 1990, that is in the pre-PSA era (median year of initial diagnosis 1991; range 1973–1998). At time of initial diagnosis 69% of M+ P-RT patients displayed M0 disease as compared to 44% of BM-RT patients ($p < 0.01$) (Table 1A). Primary androgen deprivation was initiated within a median of 0.5, 2 and 1 month after initial diagnosis for M0 P-RT, M+ P-RT and BM-RT patients, respectively. Detailed data on additional non-curative therapy at the time of initial diagnosis were not available.

Diagnosis of symptomatic AIPC and clinical course

Clinical progression despite castration levels of serum testosterone had occurred for all patients within a median of 20–27 months after initial diagnosis (Table 1B). Three M0 P-RT patients (9%), seven M+ P-RT patients (7%) and nine BM-RT patients (5%) displayed primary androgen independence. At diagnosis of AIPC 96% of M+ P-RT patients had symptomatic pelvic tumours as compared to 16% of BM-RT patients ($p < 0.001$).

Surgical palliation prior to palliative RT

About 2/3 of the M0 P-RT and M+ P-RT patients as compared to 1/4 of the BM-RT patients had undergone palliative surgery of the genito-urinary and/or gastrointestinal tract at least once prior to palliative RT ($p < 0.001$) (Table 2). The most common surgical procedure was TUR-P performed 131 times in 80 P-RT patients and 57 times in 46 BM-RT patients.

Radiotherapeutic palliation

The time elapsed from diagnosis of AIPC to start of first palliative RT was significantly shorter for BM-RT patients (median 2.9 months) compared to M0 P-RT patients (median 4.0 months) and M+ P-RT patients (median 4.7 months) ($p < 0.001$). At the time of referral to palliative RT,

Table 1A

Demographics at initial diagnosis

	P-RT patients		BM-RT patients	
	M0 (35)	M+ (97)	(193)	p-value[1]
Age (years)	67 (49–83)[2]	66 (44–79)	69 (45–82)	0.07
Stage[3]				
Local	26 (74%)[4]	49 (51%)	72 (37%)	< 0.01[5]
Regional	9 (26%)	17 (18%)	14 (7%)	
Distant metastases	–	31 (32%)	106 (55%)	
Unknown	–	–	1 (1%)	
Grade (WHO criteria)				
Grade 1	4 (11%)	6 (6%)	11 (6%)	0.17
Grade 2	11 (31%)	42 (43%)	96 (50%)	
Grade 3	20 (57%)	46 (48%)	67 (35%)	
Unknown	–	3 (3%)	19 (10%)	
Symptoms from the primary tumour at initial diagnosis				
Yes	28 (80%)	76 (78%)	106 (55%)	< 0.001
No	–	7 (7%)	35 (18%)	
Unknown	7 (20%)	14 (14%)	52 (27%)	

[1]Evaluable patients only.
[2]Median (range).
[3]Categorised according to Cancer Registry of Norway (10).
[4]Number of patients (%).
[5]M+ P-RT vs. BM-RT patients.

Table 1B

Diagnosis of symptomatic AIPC

	P-RT patients		BM-RT patients	
	M0 (35)	M+ (97)	(193)	p-value
Age (years)	70 (54–84)[1]	70 (45–83)	72 (46–84)	0.12
Interval (months)				
Initial diagnosis to diagnosis of AIPC	20 (3–157)	27 (1–248)	25 (3–187)	0.91
Symptomatic pelvic tumour at diagnosis of AIPC				
Yes	35 (100%)[2]	93 (96%)	31 (16%)	< 0.001
No	–	4 (4%)	162 (84%)	
Micturition problems	21 (60%)	54 (58%)	29 (15%)	
Haematuria	3 (9%)	10 (11%)	–	
Rectal stenosis	2 (6%)	11 (12%)	2 (1%)	
Lymphoedema	2 (6%)	7 (8%)	–	
Pelvic soft tissue tumour pain	7 (20%)	11 (12%)	–	

[1]Median (range).
[2]Number of patients (%).

patients with symptomatic pelvic tumours presented with a better performance status than BM-RT patients (Table 3). The principal palliation-requiring symptoms in P-RT patients were micturition problems and pelvic pain. Eleven percent of both M0 P-RT and M+ P-RT patients reported defecation problems due to different degrees of rectal stenosis. The efficacy of palliative pelvic RT could only exceptionally be evaluated by the hospital charts due to general lack of follow-up information. An example of tumour reduction after palliative pelvic RT (60 Gy) is, however, presented in Fig. 2a,b.

Survival

In patients alive at the last date of observation the median (range) observation time from start of first palliative RT was 35 months (range 15–123). Median overall survival was 19 months for M0 P-RT patients (95% CI 7–30), 9 months for M+ P-RT patients (95% CI 7–11) and 8 months for BM-RT patients (95% CI 7–9) ($p < 0.001$) (Fig. 3). Six percent

Table 2

Surgical palliation in AIPC patients prior to palliative RT

	P-RT patients		BM-RT patients	
	M0 (35)	M+ (97)	(193)	p-value
Surgical palliation (any procedure)				
Yes	23 (66%)[1]	74 (76%)	48 (25%)	< 0.001
No	12 (34%)	23 (24%)	145 (75%)	
TUR-P				
None	13 (37%)	39 (40%)	146 (76%)	< 0.001
Once	15 (43%)	26 (27%)	38 (20%)	
Twice	5 (14%)	24 (25%)	6 (3%)	
More than twice	2 (6%)	8 (8%)	2 (1%)	
Upper urinary tract diversion				
None	31 (89%)	72 (74%)	191 (99%)	< 0.001
Unilateral	4 (11%)	6 (6%)	2 (1%)	
Bilateral	–	19 (20%)	–	
Lower urinary tract diversion				
Yes	2 (6%)	6 (6%)	2 (1%)	0.04
No	33 (94%)	91 (94%)	191 (99%)	
Bowel diversion				
Yes	4 (11%)	9 (9%)	–	< 0.001
No	31 (89%)	88 (91%)	193 (100%)	

[1]Number of patients (%).

Table 3

Presentation at palliative RT

	P-RT patients		BM-RT patients	
	M0 (35)	M+ (97)	(193)	p-value[1]
Age (years)	70 (55–85)[2]	71 (45–83)	72 (46–89)	0.16
Main palliation-requiring symptom				
Micturition problems	12 (34%)[3]	28 (29%)	–	[4]
Haematuria	4 (11%)	12 (12%)	–	
Rectal stenosis	4 (11%)	11 (11%)	–	
Lymphoedema	2 (6%)	10 (10%)	–	
Pelvic soft tissue tumour pain	13 (37%)	34 (35%)	–	
Pelvic soft tissue tumour neuropathy	–	2 (2%)	–	
Symptomatic bone metastases	–	–	193 (100%)	
Performance status (WHO criteria)				
0–1	26 (74%)	66 (68%)	62 (32%)	< 0.001
2	7 (20%)	24 (25%)	52 (27%)	
3–4	1 (3%)	7 (7%)	64 (38%)	
Unknown	1 (3%)	–	5 (3%)	
Number of bone lesions (by bone scan)				
None	32 (91%)	10 (10%)	–	< 0.001[5]
1–10 lesions	–	47 (49%)	39 (20%)	
> 10 lesions	–	33 (34%)	121 (63%)	
Unknown	3 (9%)	7 (7%)	33 (17%)	
Haematological and biochemical parameters				
PSA (< 4 ng/mL)[6]	12.9 (0.2–810)[2]	72.0 (0.2–2200)	140.0 (0.2–25660)	< 0.001
Hb (12.5–16.5 g/dL)	11.9 (8.7–14.1)	11.3 (8.3–15.7)	12.3 (7.3–18.8)	0.05
LDH (≤ 60 years < 450 U/L, > 60 years < 540 U/L)	443 (321–2128)	467 (283–7500)	480 (189–3376)	0.18
Creatinine (< 120 μmol/L)	96 (63–242)	108 (56–929)	85 (34–206)	< 0.001
ALP (≤ 70 years < 275 U/L, > 70 years < 400 U/L)	168 (16–290)	234 (117–2441)	429 (47–5925)	< 0.001
Planned target dose × treatment days[7]				
8–10 Gy × 1	3 (9%)	6 (6%)	7 (4%)	[4]
3 Gy × 10	1 (3%)	8 (8%)	163 (84%)	
2 Gy × 20–30	31 (89%)	79 (81%)	10 (5%)	
Others	–	4 (4%)	17 (9%)	
Subsequent palliative RT (bone metastases)				
Yes	4 (11%)	21 (22%)	4 (2%)	< 0.001
No	31 (89%)	76 (78%)	189 (98%)	

Abbreviations: LDH = lactate dehydrogenase; ALP = alkaline phosphatase.
[1]Evaluable patients only.
[2]Median (range).
[3]Number of patients (%).
[4]Not applicable due to study design.
[5]M+ P-RT vs. BM-RT patients.
[6]Normal range.
[7]Main target volume.

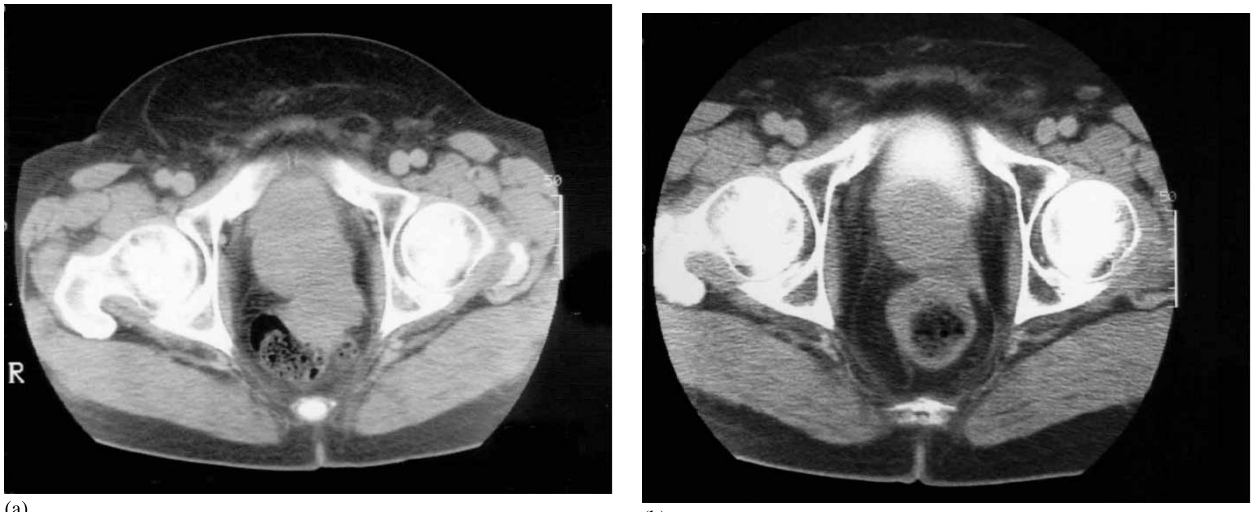
of M0 P-RT patients and 4% of M+ P-RT patients were still alive more than 4 years after start of palliative RT, whereas all patients from the BM-RT group were dead.

DISCUSSION

The present study confirms that AIPC patients requiring palliative RT represent an inhomogeneous population consisting of clinically different subgroups. The largest group is characterised by symptomatic bone metastases. In the two much smaller groups symptomatic pelvic tumours dominate and many of these patients need a combined surgical and radiotherapeutic approach. The survival from time of palliative RT of M0 AIPC patients with symptomatic pelvic tumours significantly exceeds that of AIPC patients with distant metastases.

AIPC with symptomatic pelvic tumours—a clinical problem

Along with the serum PSA era there has been a stage migration towards less extended local disease in M0 prostate cancer patients at initial diagnosis, although there are still prostate cancer patients initially diagnosed with extracapsular and/or regional lymph node metastases (11,



(a) (b)

Fig. 2. An example of objective response to palliative pelvic RT in one M0 P-RT patient with imminent rectal stenosis. (a) Pre-RT CT scans of the prostatic tumour infiltrating the anterior rectal wall. (b) Post-RT CT scans illustrating tumour reduction after 60 Gy.

12). Patients with initially locally advanced tumours and/or regional disease but without or only few distant metastases are most probably the ones at risk of developing AIPC with symptomatic pelvic tumours during their lifetime. Although many of these patients are initially palliated by androgen deprivation, not all achieve a durable control of the primary tumour. Fosså et al. previously indicated that about 18% of all AIPC patients referred to palliative RT presented urinary symptoms and pelvic soft tissue pain as the dominating symptoms at diagnosis of AIPC (1). The clinical scenario in these patients and their clinical course after development of AIPC has only limitedly been dealt with in the medical literature (3, 7, 13, 14). The P-RT patients of the present study probably represent a 'worst case scenario' of patients with very large tumours resistant to repeated surgical procedures. In addition, our number of P-RT patients may not represent the 'true' fraction of AIPC patients who need palliation due to symptomatic pelvic tumours. In a retrospective study Otnes et al. previously estimated the number of these AIPC patients in a urology practice to be 10% (2). In comparison, Catalona stated that 'about 30% of the patients with nodal metastases treated conservatively with hormonal therapy will require transurethral resection for local disease' (15).

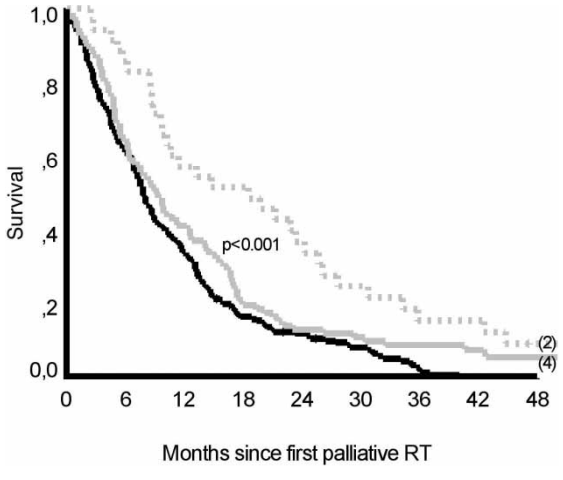


Fig. 3. Overall survival for 35 P-RT patients without distant metastases at time of palliative RT (broken line) compared to 97 P-RT patients with distant metastases at time of palliative RT (grey line) and 193 BM-RT patients (black line) ($p < 0.001$). Figures in parentheses are number of patients under observation after 48 months.

Clinical course and palliation

AIPC patients with symptomatic pelvic tumours represent a therapeutic dilemma yet to be resolved. Surgical procedures such as repeated TUR-P may provide temporary relief, although the scientific literature lacks extended documentation about the palliation effect and its duration.

Palliative chemotherapy. There is mounting evidence that chemotherapy in AIPC patients may result in palliation, in particular mitoxantrone combined with prednisone (4–6). However, most results of chemotherapy trials are derived from AIPC patients with bone metastases, and do not specifically address the palliation needs in the subgroup with symptomatic pelvic tumours. Furthermore, the potential palliative effect versus known side effects is an important issue in symptomatic AIPC patients presenting with reduced bone marrow resources, high prevalence of comorbidity and poor general health.

Palliative pelvic RT. Pelvic RT is another palliative treatment option, although the medical literature in AIPC patients is not sufficient to indicate response rates. It was not possible in the present study to document the rates of palliation or of objective response of RT. However, pallia-

tive pelvic RT should probably have been considered earlier as 20–33% of the P-RT patients underwent TUR-P twice or more before referral to RT. Optimal time for referral, appropriate radiation schedules and efficacy of palliative pelvic RT should be explored in prospective clinical trials.

Survival

Our results demonstrate a significantly superior survival from time of palliative RT in AIPC patients with symptomatic pelvic tumours and pelvis-confined disease as compared to those with distant metastases. Of particular interest is the fact that a small percentage of the M+ P-RT patients lived for ≥ 4 years after palliative pelvic RT, whereas all patients with palliation requiring bone metastases had died.

Because of the selection of patients for the present study, its retrospective design and the unsystematic referral practice in Norway, our comparative observations as to survival should be interpreted with caution. Another limitation of the present work is the lack of regular serum PSA measurements. Furthermore, we could not report on the efficacy of palliative RT by means of systematic quality of life evaluations. Nevertheless, the present analysis emphasises two aspects of clinical value for the oncologist seeing AIPC patients: first, the optimal palliative treatment of AIPC patients with symptomatic pelvic tumours has still to be defined, and in particular the role of pelvic RT requires evaluation in prospective trials. Second, oncologists conducting clinical trials in AIPC patients should be aware of the significantly prolonged natural course of AIPC patients presenting with symptomatic pelvic tumours and pelvis-confined disease.

CONCLUSIONS

In this retrospective series we have demonstrated the need of palliation by both surgical and oncological means in AIPC patients with symptomatic pelvic tumours. In symptomatic AIPC patients with pelvis-confined disease the survival after palliative RT significantly exceeds that of AIPC patients with distant metastases. This difference in prognosis has to be considered when designing clinical trials in AIPC patients. The optimal palliative treatment of AIPC patients with symptomatic pelvic tumours remains to be identified.

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