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Title

Patterns of Recurrence after Prostate Bed Radiotherapy

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Abstract

Background and Purpose

Prostate bed radiotherapy is a standard treatment after radical prostatectomy. Recent evidence suggests that, for patients with a PSA> 0.34 ng/ml, the radiotherapy treatment volume should include not only the prostate bed but also the pelvic lymph nodes. We describe the patterns of failure after prostate bed radiotherapy, focussing on the proportion of patients with radiologically confirmed pelvic nodal failure only, in the absence of distant disease.

Materials and Methods

Patients included were men receiving prostate bed radiotherapy at the Royal Marsden Hospital between 1997 and 2013. The key outcome of interest was the pattern of radiologic failure after prostate bed radiotherapy. Baseline characteristics of patients experiencing pelvic nodal failure without distant disease were compared versus all other relapse patterns. Comparisons were by Chi-square test, with multiple testing adjusted $p<0.005$ significant.

Results

140 of 322 patients developed biochemical failure after salvage RT. Radiologic failure occurred in 89 patients. 35 of the 89 patients (39%) with radiologic failure had pelvic nodal failure without distant disease, with no significant differences in baseline characteristics when compared to all other patients. The rate of pelvic nodal failure was the same for patients with PSA above or below 0.34 ng/ml (16/149, 95% CI = 6 - 17% vs 19/171, 95% CI = 7 – 17%).

Conclusions

Pelvic lymph node disease, without more distant disease, is a common site of failure in men receiving radiotherapy to the prostate bed, including those with PSA < 0.34ng/ml. This observation informs the case for including the pelvic lymph nodes in the radiotherapy treatment volume.

Main Body

Introduction

Prostate bed radiotherapy is a standard treatment after radical prostatectomy. It is recommended as a salvage treatment for men with a rising PSA level, and has also been studied as an adjuvant to surgery (1–3). Recently, two strands of evidence have raised the possibility that the radiotherapy treatment volume should include not only the prostate bed but also the pelvic lymph nodes.

First, PSMA PET-CT studies in men with PSA failure after radical prostatectomy have reported that the pelvic lymph nodes are a frequent site of post-surgical recurrent disease (4). Second, the NRG Oncology/RTOG 0534 SPPORT trial in men receiving salvage post-operative radiotherapy found an improvement in biochemical control for whole pelvic versus prostate bed radiotherapy (5). Exploratory subgroup analysis of the trial raised the possibility that the benefit for nodal irradiation may be limited to men with a PSA > 0.34 ng/L at the time of salvage treatment.

The aim of this study was to describe the pattern of failure after prostate bed radiotherapy in order to inform the decision regarding whole pelvic versus prostate bed radiotherapy. The main objective was to describe the proportion of patients with pelvic nodal failure only, in the absence of distant disease. The higher the proportion of such patients, the stronger the argument for including pelvic lymph nodes in the treatment volume. A secondary objective was to explore the relationship between PSA at the time of salvage treatment and the subsequent pattern of failure. Given the results of the SPPORT trial, we planned to describe the rate of pelvic nodal failure without distant disease in men with a PSA above or below 0.34 ng/L at the time of post-operative radiotherapy.

Patients and Methods

Patient Identification

All men receiving prostate bed radiotherapy, either as an adjuvant or salvage treatment, at our institution between 01/07/1997 – 01/10/2013 were identified through the local radiotherapy database. All patients had histologically confirmed prostate cancer and had undergone radical prostatectomy (RP), with or without lymphadenectomy. RP procedures were performed at numerous referring centres to our institution. This date range was chosen to allow at least a 5-year window for recurrence following radiotherapy in all patients. Patients were then excluded from the main analysis if they met any of the following: (i) recurrence outside of the prostate bed known at the time of radiotherapy; (ii) treated in the RADICALS trial; (iii) fewer than two years follow-up data available, generally due to subsequent follow-up at another institution; (iv) received whole pelvic radiotherapy.

Of secondary interest, biochemical and radiological failure information was collected for those with < 2 years follow-up or receiving whole pelvic radiotherapy, for reporting in the CONSORT style flow diagram.

From 2007, the prostate bed treatment volume was defined according to the RADICALS protocol, and the dose used was 66 Gy in 33 fractions. Prior to 2007, the standard dose was 64Gy in 32 fractions and there was no single protocol for localising the prostate bed. Androgen deprivation for 6-24 months was commonly used in combination with prostate bed radiotherapy, according to clinical judgement.

Post Radiotherapy Management

The institutional policy was to manage men with PSA failure after radiotherapy by observation until the radiologic pattern of recurrence was known (in preference to empirical ADT) (6). Imaging was typically performed after each doubling of PSA level. Imaging modalities used to detect patterns of recurrence have evolved over time, with CT and bone scan being standard in 1997, but being superseded by choline PET and subsequently by PSMA-PET. Therefore, data regarding the scan(s) used to detect first recurrence were collected.

Data Collection

A case report form was prospectively designed for data collection and a blank template example is shown in the **supplementary appendix**. The patient data were retrieved from the institutional electronic patient record by a single investigator (JP), and checked by two physicians specialising in urological malignancies (DB, CP).

Data Categorisation

Relapse patterns were defined as: never failed (no biochemical or radiological evidence of failure); PSA-only failure; prostate bed only failure; pelvic lymph node failure with or without prostate bed failure, para-aortic nodal failure without more distant disease; distant disease. The para-aortic disease category has been reported separately given recent interest in extended lymph node dissection or radiotherapy techniques (7). The key item of interest was pelvic nodal failure without distant disease. A pragmatic decision was taken to include patients who had pelvic nodal and prostate bed failure, since not all patients in the study time period would have received the now contemporary dose-escalated (66Gy / 33 fractions) prostate bed dose.

Since prostate staging has evolved over the time period examined, for T-staging, we adopted a simplified allocation of: T2 (organ confined), T3a (capsule breach), T3b (seminal vesicle invasion) and T4. Due to the small numbers of T4, these were grouped with the T3b patients. Groupings were chosen for some quantitative variables. Pre-operative PSA was divided into: <10 ng/mL, 10-20 ng/mL and >20 ng/L; as per National Comprehensive Cancer

Network (NCCN) risk stratification guidelines (8). Number of nodes dissected was pragmatically divided into 0, 1-3, 4-7 and 8+ nodes dissected. Max PSA pre-salvage was divided as: <0.2ng/L, 0.2 - <0.5 ng/L, 0.5-2.0 ng/L and ≥2.0 ng/L (9, 10). PSA doubling time (PSAdt) pre PBRT was divided as <6 months (11), 6 - <12 months (12) and ≥12 months. Time from surgery to RT was pragmatically divided as <6 months, 6 months - <1 year, 1 - <2 years, 2 - <3 years, ≥3 years. For the comparative analysis of failure patterns above and below a PSA cut-point, 0.34 ng/L was pre-specified, as per the SPPORT trial results.

Statistical Analyses

Differences in baseline characteristics between those experiencing pelvic nodal failure without distant disease versus all other patients were compared by Chi-square test, except for age, which was compared by Mann Whitney Rank Sum. Chi-square testing was used to compare the proportion of patients with pre-RT PSA > 0.34 ng/L in two groups: i) those with pelvic nodal failure without distant disease, ii) all other patients. Patients with missing data in a specific comparison were excluded, but remained eligible for other comparisons. By Bonferroni adjustment, a p-value of 0.005 was considered statistically significant. A post-hoc chi-square comparison was made between conventional (bone scan, CT, MRI) and PET-CT imaging, regarding the proportion of radiological failures seen in each modality group that were pelvic lymph node failure without distant disease, with the p-value presented for information only.

Median follow-up was calculated by the reverse Kaplan-Meier method (13). Regarding disease time-to-event data, biochemical failure events were defined as PSA > 0.2 ng/mL; radiological failure events were any confirmed site of prostate disease on imaging. Kaplan-Meier plots were constructed, with patients being censored at the time of death or final follow-up.

The data were collated onto spreadsheet software (Excel version 2010 onwards, Microsoft, CA, USA), before being analysed using a combination of R (Version 3.5.3, R Foundation for Statistical Computing) and Stata (Version 15.1, StataCorp, TX, USA). The STROBE Statement was observed for the purposes of reporting (14).

Study Approval

This study was prospectively approved by our institutional clinical research review board (Study ID SE734).

Results

Data collection occurred between 14/08/2018 and 14/09/2018. A total of 544 consecutive patients were identified, who had received post-operative radiotherapy on or before 01/10/2013. Of these, a total of 322 patients were suitable for inclusion in the main study

(See Figure 1 for exclusion criteria). **Table 1 (Left data column)** shows baseline characteristics for all patients. 319 patients (99%) received salvage radiotherapy for PSA failure, while 3 patients (1%) received adjuvant post-operative radiotherapy. Median follow-up was 7.3 years after radiotherapy.

The radiotherapy regimens used were: 64 Gy in 32 fractions (n=187, 58%); 66 Gy in 33 fractions (n=93, 29%); 70 Gy in 35 fractions (n=30, 9%); Other (n=10, 3%). For androgen deprivation therapy given at the time of salvage radiotherapy, the duration of therapy was: No ADT (n=48, 15%); <=6 months (n=226, 70%); 6 – 24 months (n=22, 7%); >24 months (n=26, 8%). Of the 273 patients receiving ADT, 237 (87%) received an LHRH agonist, and 36 (13%) received bicalutamide monotherapy.

Of the 322 patients, 140 (43.5%) developed biochemical failure after salvage RT. Radiologic failure occurred in 89 patients (27.6%). Kaplan-Meier analysis of the time to occurrence of biochemical failure and time to radiologic failure is shown in **Figure 2**. The imaging modalities used to confirm failure are shown over time are shown in **Supplementary Appendix Figure 1**.

The radiologically confirmed failure pattern seen is detailed in **Table 2,** with pseudo-anatomical representation in **Figure 3**. Notably, 35 of the 89 patients (39%) with radiologic failure had pelvic nodal failure without distant disease. The crude rate of pelvic nodal failure without distant disease was 11% (35/322, 95% Confidence Interval (CI) = 8 - 15%). In men with a pre-RT PSA of >= 0.34 ng/L, the crude rate of pelvic nodal failure without distant disease was 11% (16/149, 95% CI = 6 - 17%), compared with 11% (19/171, 95% CI = 7 – 17%) in those with a pre-RT PSA of <0.34 ng/L, (p=0.915). A Venn diagram to illustrate overlap of the failure sites is shown in **Figure 4**. By comparison, of the 32 patients who were excluded from the analysis because they received whole pelvic radiotherapy, none had pelvic nodal failure without distal disease.

Of the 89 patients with radiologic failure, 40 were detected on 'conventional' imaging using CT, MRI or bone scan, and 49 were detected on PET. The proportion of patients with pelvic nodal failure without distal disease was 10/40 (25%) and 25/49 (51%), respectively (p=0.012).

The baseline characteristics of those patients with pelvic nodal failure without distal disease are compared to all other patients in **Table 1 (Right 3 data columns)**. Adjusted for multiple testing, no significant differences were seen in the baseline characteristics, between the two groups.

Discussion

Current prostate cancer guidelines recommend the use of prostate bed radiotherapy for men with PSA failure after radical prostatectomy (10). We found that pelvic lymph node disease is a common site of failure in men receiving post-operative radiotherapy to the prostate bed. In this series, around 11% of men receiving post-operative radiotherapy (39% of those with radiologic recurrence) experienced pelvic nodal-only failure. This figure of 11% is a best-case scenario, and will increase with longer-term follow up. These considerations strengthen the case for treating not only the prostate bed, but also the pelvic lymph nodes, in patients receiving post-operative radiotherapy after radical prostatectomy.

The pattern of failure after prostate bed radiotherapy has not previously been well studied. It is challenging to identify the pattern of failure because it requires long-term follow-up of large numbers of patients and because many centres use early androgen deprivation therapy for PSA failure, which further delays identification of the site of failure. Our results are consistent with those of Byrne and colleagues, who examined 310 patients treated 2006-2016 with prostate bed only radiotherapy, using PSMA-PET to define failure sites (15). Of 50 patients with failure detected on PSMA-PET, the sites of failure were prostate bed only (n=2, 4%), pelvic nodal only (n=18, 36%), distant disease (n=23, 46%), multi-site (n=7, 14%). It should be noted that this distant figure includes patients with pelvic nodal plus PAN/distant nodes. Our equivalent figures would be prostate bed only (n=10, 11%), pelvic nodal only (n=34, 38%), distant only (n=39, 44%), multi-site (n=6, 6%), which appear broadly concordant. Our results are also consistent with the reported pattern of failure after radical prostatectomy alone. Several imaging studies have found that the pelvic lymph nodes are a common site of failure after surgery (16–21). It is therefore unsurprising that this would also be a common site of failure after post-operative prostate bed radiotherapy alone.

Rather different result were reported by Jackson and colleagues, based on 574 men treated 1987 – 2013, who received prostate bed only or prostate bed plus pelvic (n=23) salvage radiotherapy after prostatectomy (22). Among 104 patients with known initial recurrence pattern, these were: local failure (n= 5, 4.8%), Pelvic Nodal only (n=12, 11.5%), distant disease (n=87, 84%). Notably 63.5% of recurrences were first in bone. This much higher proportion of distant metastatic failure might reflect a lack of sensitive cross-sectional imaging in the earlier part of the study period. Our data suggest that the detection of pelvic nodal failure without distal disease increases when contemporary PET imaging methods are used.

The SPPORT trial compared whole pelvic versus prostate bed radiotherapy in 1792 men with PSA failure after radical prostatectomy. The early results have shown an improvement in biochemical control for the use of whole pelvic treatment. This is impressive, especially given the 45 Gy in 25 fraction pelvic dose utilised, as dose escalation beyond this appears tolerable and might further increase the beneficial effect seen (23).Data are not yet available from SPPORT regarding the patterns of failure. The trial generated the hypothesis

that the pre-radiotherapy PSA level, specifically with a threshold of 0.34 ng/ml, could be used to identify men most likely to benefit from pelvic nodal radiotherapy. Our results do not support this hypothesis. We found that the rate of pelvic nodal failure without distant disease was no different in men with a pre-radiotherapy PSA level below or above 0.34ng/ml. Indeed, our findings did not identify any pre-treatment predictive factors for pelvic nodal recurrence. Based on our data, all men having salvage radiotherapy for PSA failure after radical prostatectomy should be considered for pelvic node, as well as prostate bed, treatment.

Pelvic nodal treatment may increase the risk of toxicity in comparison with treatment to the prostate bed alone. The SPPORT results suggested only a small increase in bone marrow related grade ≥2 toxicity (5); the older RTOG 94-13 trial of pelvic radiotherapy in primary disease showed 5% (prostate + pelvis) vs 1% (prostate only) grade ≥3 GI toxicity, although applicability of this data is questionable given the non-conformal delivery techniques (24). The PIVOTAL phase II trial, using intensity modulated radiotherapy in the primary setting, showed cumulative grade ≥2 GI toxicity was 16.9% (95% CI 8.9%-30.9%) for prostate only and 24.0% (95% CI 8.4%-57.9%) with pelvis included; bladder toxicity was similar (25).

Strengths of our study include the long-term follow-up of a large cohort of patients, with treatment after radiotherapy delayed until the site of recurrence is known. The majority of patients received hormone therapy as an adjuvant to their salvage radiotherapy. Supported by the results of the RTOG 96-01 and GETUG-AFU-16 trials (26, 27) this is now standard practice. The broad inclusion criteria in this study strengthen external generalisability of the findings. Although we have long-term follow-up, our data are not fully mature. For example, 51 patients with biochemical failure have not yet had any site of radiologic failure identified. Thus, it is likely that the number of patients with pelvic nodal failure without distant disease will increase with further follow-up. If one assumes that 39% of all men with recurrent disease have pelvic nodal failure without distant disease, then we would expect an additional 20 (39% of the 51 men with PSA failure only) with this pattern of disease. This would represent a total of 55 of all 322 men (17%) treated with prostate bed radiotherapy who have developed, or are predicted to develop, pelvic nodal failure without distant disease.

Limitations of our study include the retrospective design and changes in clinical practice over the last 20 years, particularly with respect to imaging. It is striking that the proportion of patients with pelvic nodal failure without distal disease was twice as high for those found on PET than for those detected on more traditional imaging modalities. Our results are applicable to men who have salvage radiotherapy for a rising PSA alone. In centres with access to PSMA PET, a new alternative is ‘late’ salvage treatment, delayed until the site of post-surgical recurrence is detected. One potential advantage of late salvage treatment is that the site of recurrence informs the choice of radiotherapy treatment volume (19).

Surgical practice has also evolved. Most of the patients in this series had either no node dissection, or a limited node dissection. The results may not therefore be applicable to those receiving an extensive lymph node dissection.

Conclusions

Current guidelines recommend the use of salvage radiotherapy to the prostate bed in men with PSA failure after radical prostatectomy. Our data inform the case for including the pelvic lymph nodes in the radiotherapy treatment volume. This is supported by the frequency of pelvic nodal failure after treating the prostate bed alone, the early outcomes of SPPORT, and the relative lack of toxicity from pelvic nodal radiotherapy (25). Future studies examining the role of PSMA PET directed salvage treatment (e.g. NCT03582774) may help to refine individual treatment volume decisions.

Figures

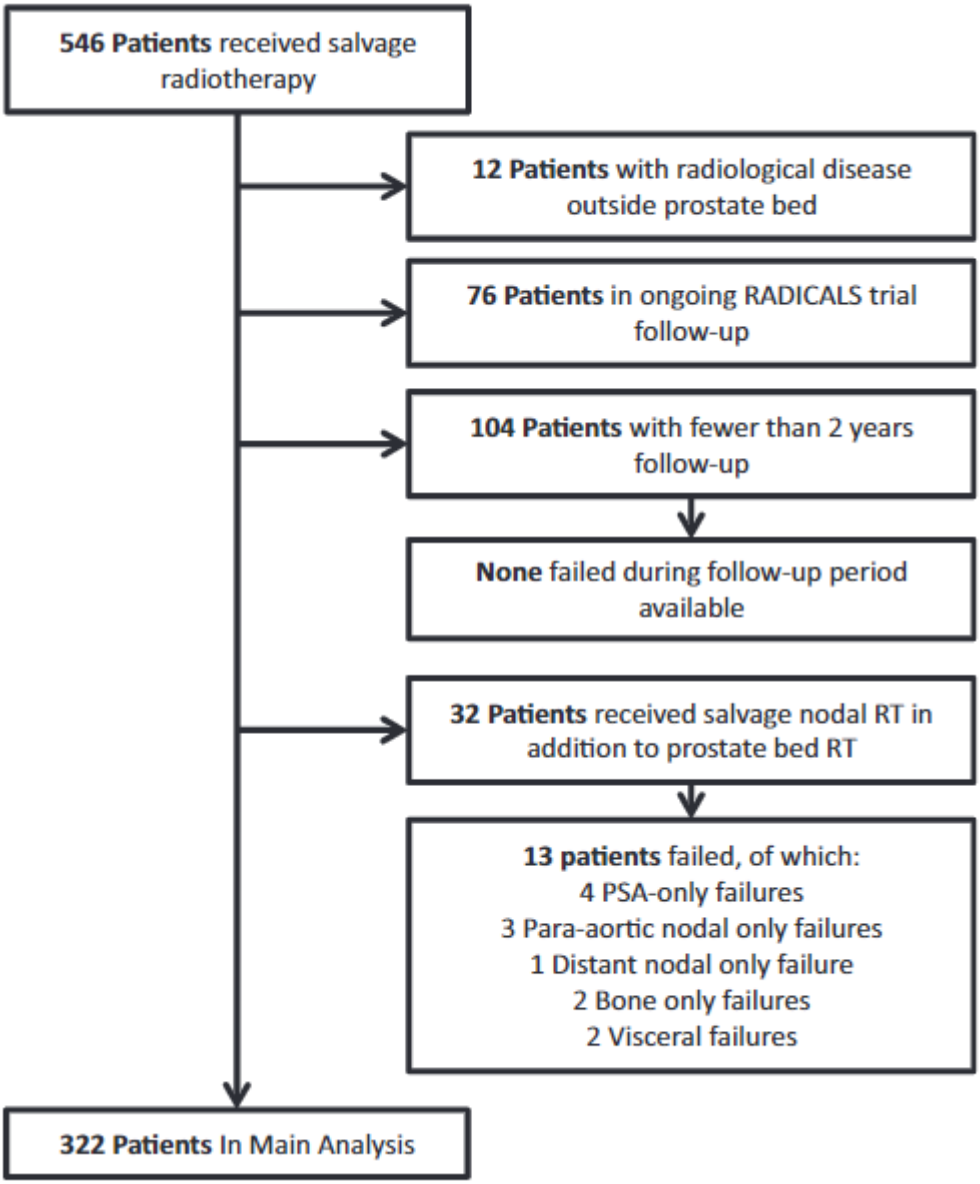

Fig.1. Flowchart demonstrating the selection process for patients in this study. Failure information is provided for patients with fewer than two years follow-up and those receiving nodal irradiation at the time of initial salvage RT. Abbreviations: RT = radiotherapy; PSA = prostate specific antigen.

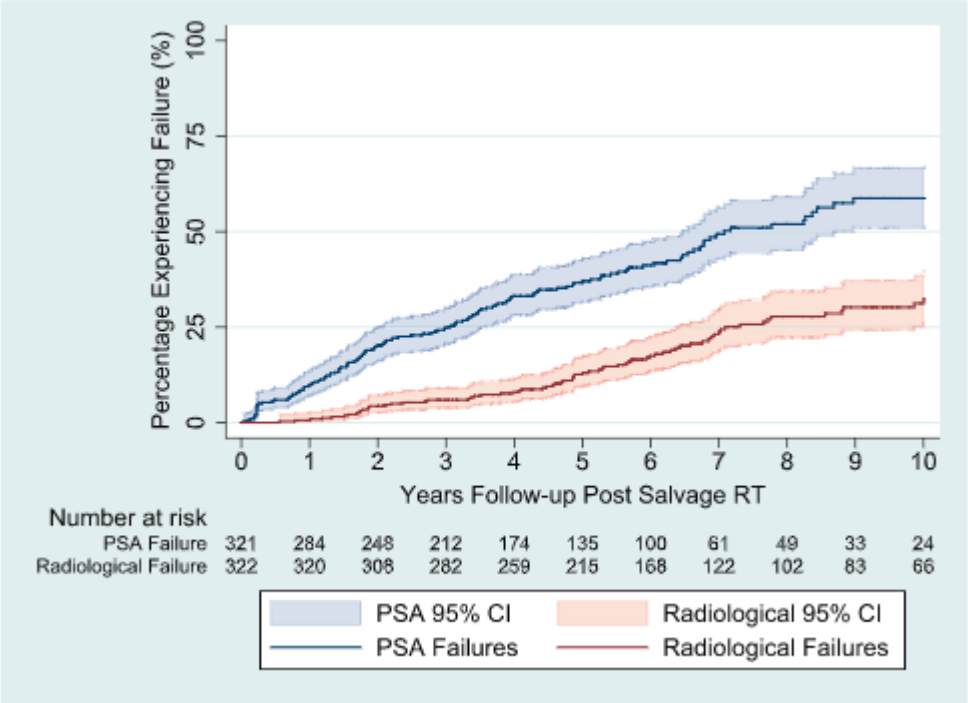

Fig.2. PSA and radiological failure after post-operative RT. Abbreviations: PSA = prostate specific antigen; RT = radiotherapy; 95% CI = 95% confidence interval

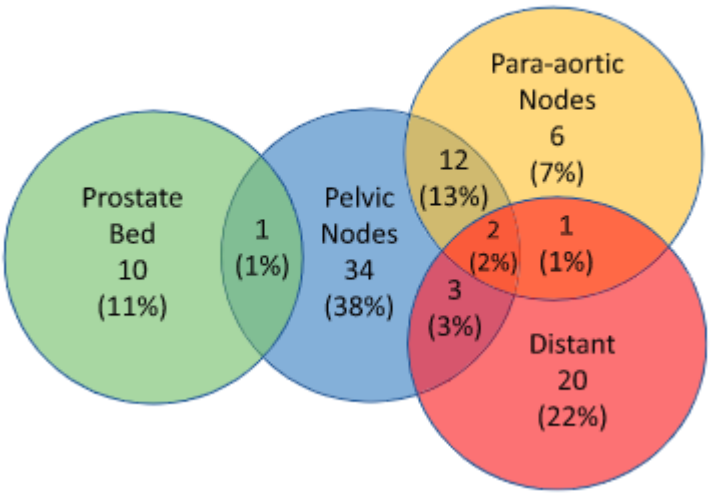

Fig.3. Venn diagram of radiologically confirmed failure patterns distribution of sites of failure in 89 of the 322 treated patients who developed a radiological recurrence.

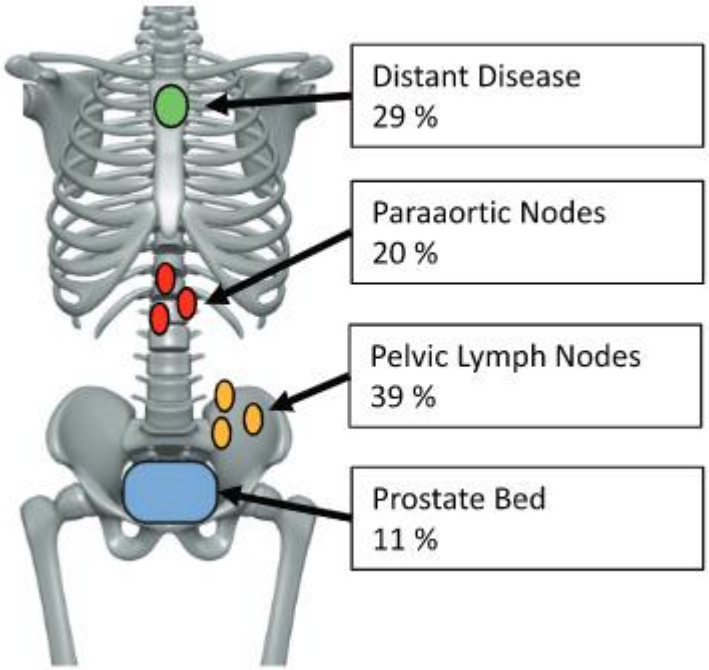

Fig.4. Most distal failure pattern. Diagram depicting the most distal failure positions for those with radiologically confirmed failure after post-prostatectomy radiotherapy (n= 89). Abbreviations: PA = para-aortic; PSA = prostate specific antigen.

Tables:

Baseline Characteristics	Total All Patients		Subgroup Comparison Pelvic Nodal Failure Without Distant Disease		All Other Patients		Chi-Square
	No.	%	No.	%	No.	%	p-value
Age							
Mean	64.4 years		63.3 years		64.5 years		0.1963
Median	65 years		65 years		65 years		Rank-sum
Range	43–78 years		50–76 years		43–78 years		
Pre-op PSA							
<10 ng/mL	172	53.4%	14	40.0%	158	55.1%	
10–20 ng/mL	94	29.2%	12	34.3%	82	28.6%	0.204
>20 ng/mL	21	6.5%	4	11.4%	17	5.9%	
Missing	35	10.9%	5	14.3%	30	10.5%	
Pathological T-Stage							
pT2	154	47.8%	13	37.1%	141	49.1%	
pT3a	94	29.2%	10	28.6%	84	29.3%	0.220
T3b/T4	53	16.5%	9	25.7%	44	15.3%	
Missing	21	6.5%	3	8.6%	18	6.3%	
Pathological Nodal Status							
N0	183	56.8%	17	48.6%	166	57.8%	
NX	116	36.0%	16	45.7%	100	34.8%	0.226
Missing	23	7.1%	2	5.7%	21	7.3%	
Nodes Dissected							
No nodes	116	36.0%	16	45.7%	100	34.8%	
1–3 nodes	36	11.2%	5	14.3%	31	10.8%	
4–7 nodes	27	8.4%	2	5.7%	25	8.7%	0.249
8 + nodes	22	6.8%	0	0.0%	22	7.7%	
Missing	121	37.6%	12	34.3%	109	38.0%	
Post-Surgical Gleason Score							
Gleason 6 or less	104	32.3%	9	25.7%	95	33.1%	
Gleason 3 + 4	127	39.4%	15	42.9%	112	39.0%	
Gleason 4 + 3	53	16.5%	7	20.0%	46	16.0%	0.816
Gleason 8–10	36	11.2%	4	11.4%	32	11.1%	
Missing	2	0.6%	0	0.0%	2	0.7%	
Surgical Resection Margin							
R0	105	32.6%	13	37.1%	92	32.1%	
R1	196	60.9%	20	57.1%	176	61.3%	0.565
Missing	21	6.5%	2	5.7%	19	6.6%	
Max PSA Pre-Salvage							
<0.2 ng/mL	93	28.9%	8	22.9%	85	29.6%	
0.2–<0.5 ng/mL	114	35.4%	16	45.7%	98	34.1%	
0.5–<2.0 ng/mL	91	28.3%	7	20.0%	84	29.3%	0.258
2.0 + ng/mL	21	6.5%	4	11.4%	17	5.9%	
Missing	3	0.9%	0	0.0%	3	1.0%	
PSA Doubling Time Pre-RT							
0–6 months	133	41.3%	16	45.7%	117	40.8%	
6–12 months	73	22.7%	13	37.1%	60	20.9%	0.031
12 + Months	86	26.7%	4	11.4%	82	28.6%	
Missing	30	9.3%	2	5.7%	28	9.8%	
Time From Surgery to RT							
<6 months	15	4.7%	2	5.7%	13	4.5%	
6–<12 months	54	16.8%	2	5.7%	52	18.1%	
1–<2 years	98	30.4%	13	37.1%	85	29.6%	0.43
2–<3 years	50	15.5%	5	14.3%	45	15.7%	
3 + years	105	32.6%	13	37.1%	92	32.1%	
Total	322	100%	35	100%	287	100%	

Table 1. Baseline characteristics

Initial Pattern of Radiological Failure	All Patients	Pre-Salvage PSA (ng/L)	
	Total No. (%)	<0.34 No. (%)	≥0.34 No. (%)
Prostate bed only	10 (11%)	1 (3%)	9 (18%)
Pelvic Nodal Failure Without Distant Disease	35 (39%)	19 (47%)	16 (33%)
Para-aortic nodal disease (and no other distant metastases)	18 (20%)	8 (20%)	10 (20%)
Distant metastases	26 (29%)	12 (30%)	14 (29%)
Total	89	40	49

Table 2. Initial pattern of radiologic failure

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