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Anatomic Patterns of Recurrence Following Biochemical Relapse in the Dose-Escalation Era for Prostate Patients Undergoing External Beam Radiotherapy

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Abstract

Purpose—To provide a comprehensive analysis of anatomic patterns of recurrence following external beam radiotherapy (EBRT) for localized prostate cancer (PC) patients.

Materials and Methods—This retrospective analysis included 2694 patients with localized PC receiving definitive dose-escalated EBRT from 1991 to 2008. First-recurrence sites (FRS) were defined as initial sites of clinically detected recurrence (CDR) and any subsequent CDR within 3 months. Anatomic recurrence patterns were classified as local (prostate/seminal vesicles only), lymphotropic (lymph nodes [LN] only), and osteotropic (bones only) for patients with disease confined solely to these respective sites for at least 2 years from initial CDR.

Results—Prostate was the most common FRS for all risk groups (8-year cumulative incidence, 3.5%, 9.8%, and 14.6% for low-, intermediate-, and high-risk patients, respectively). Eight-year risk of isolated pelvic LN relapse as FRS was 0%, 1.0%, and 3.3%, respectively. For the 474 patients experiencing CDR, the most common FRSs were local (55.3%), bones (33.5%), pelvic LN (21.3%), and abdominal LN (9.1%). Patients displayed unique relapse distributions, including local (41.6%), lymphotropic (9.7%), osteotropic (20.3%), and multiorgan/visceral (28.5%) patterns. Anatomic recurrence pattern was the strongest predictor for PCSM in a multivariate analysis of CDR patients.

Conclusions—The most common FRS after dose-escalated EBRT for PC is within the prostate and SV for all risk groups. By contrast, patients treated without elective pelvic LN irradiation have a relatively low risk of isolated pelvic LN relapse. Recurrence patterns displayed a tropism for specific anatomic distributions, with divergent prognoses, suggesting underlying biological differences amongst tumors.

Keywords

Prostate cancer; radiotherapy; patterns of failure

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The fundamental nature of localized prostate cancer, including its long natural history and its predilection for afflicting elderly men with significant competing comorbidities, requires clinical trials to have long follow-up and large patient numbers to produce meaningful results. Partly as a result of this, uncertainties and controversies surround nearly every aspect of this disease, including the optimal definitive modality,¹⁻³ the role of androgen-deprivation therapy (ADT),⁴ the use of elective pelvic lymph node (PLN) radiation,^{5, 6} and whether many patients should be receiving treatment at all.^{7, 8} However, a less appreciated issue underlying the many uncertainties in prostate cancer management is a relatively poor understanding of the anatomic patterns of recurrence in relapsed patients.

Understanding the anatomic patterns of recurrence for prostate cancer, particularly following radiotherapy, has been challenging. In contrast to malignancies such as breast cancer, local and regional recurrences are often not readily apparent clinically. Digital rectal exam lacks sensitivity and specificity for detecting local recurrence (LR), and the draining regional lymphatics of the prostate are not palpable. Additionally, standard imaging modalities like endorectal ultrasound, computed tomography (CT), and fluorodeoxyglucose positron-emission tomography have low sensitivity for detecting locally recurrent disease or prostate cancer micrometastases, although recurrence detection may be better with endorectal magnetic resonance imaging, magnetic resonance spectroscopy, or novel positron-emission tomography tracers.^{9, 10} In part because of these challenges, a detailed patterns-of-recurrence analysis for prostate cancer following definitive radiotherapy has not been reported to date. As a better understanding of anatomical patterns of recurrence could have important ramifications for dose escalation, PLN management, and the utility of salvage therapies, we analyzed recurrence patterns in a large cohort of patients receiving external beam radiotherapy (EBRT) for localized prostate cancer.

MATERIALS AND METHODS

Patient Selection and Pretreatment Evaluation

This study included 2694 consecutive patients with localized prostate cancer treated with EBRT and doses of at least 75.6 Gy at Memorial Sloan Kettering Cancer Center from 1991 to 2008. The National Comprehensive Cancer Network (NCCN) risk-stratification system was used to define low-, intermediate-, and high-risk groups.¹¹ All patients received pretreatment evaluation with CT or MRI of the pelvis to rule out pelvic lymph adenopathy. Our institutional review board granted approval prior to data collection.

Treatment

Our radiation techniques have been described previously.¹² Additionally, until 2009 our departmental policy was to avoid elective PLN irradiation in all clinically node-negative prostate cancer patients. Thus, no patient in this study received PLN irradiation. The timing of and necessity for salvage treatment was also determined by the treating oncologist (Supplementary Table 1). Of note, 6 patients developed clinically detected recurrence (CDR) while receiving adjuvant ADT, and 110 patients received 1 dose of ADT prior to CDR.

Data Analysis and Endpoints

The data was analyzed in two phases. First, cumulative incidences of initial patterns of recurrence were calculated among the entire 2694 patient cohort. In this analysis, first recurrence site (FRS) was defined as the earliest CDR site following treatment. Additionally, given that diagnostic tests might be ordered sequentially rather than simultaneously, any additional recurrence sites detected within the first 3 months of the initial CDR were also classified as FRSs. An isolated FRS was defined as a CDR confined to a specific anatomic compartment (e.g., the pelvic lymph nodes) without evidence of prostate cancer in other sites for 3 months after initial detection.

The second phase of the analysis focused on the 474 patients with CDR following EBRT. For this analysis, anatomic patterns of recurrence were defined *a priori* before initiation of data analysis. A local pattern of recurrence was defined as recurrence confined entirely to the prostate and seminal vesicles for at least 2 years from the initial recurrence. Similarly, lymphotropic and osteotropic patterns of recurrence were defined as recurrent prostate cancer confined entirely to the lymph nodes or the bones, respectively, for at least 2 years from the date of the first CDR. Patients with recurrent prostate cancer in more than one anatomic compartment during the first 2 years following initial CDR or with visceral organ involvement were considered to have a multiorgan/visceral pattern of recurrence. As only 9 patients had visceral organ involvement as a FRS with or without disease involvement of other organs site, this group was not analyzed separately.

LR was defined as either a post-treatment transrectal biopsy demonstrating viable prostate cancer or radiographic imaging consistent with relapse in the prostate or seminal vesicles. In total, 71% of LRs were confirmed by post-treatment biopsy. All CDR sites outside of the prostate were either confirmed pathologically, clearly responded to the initiation of ADT, or progressed in combination with an increasing prostate-specific antigen (PSA) in the setting of castration-resistant disease. Prostate cancer-specific mortality (PCSM) was defined as either death from causes directly related to prostate cancer or a death from unknown causes in a patient with castration-resistant disease. Biochemical recurrence (BR) was defined as a PSA 2 ng/mL above the post-treatment nadir. Time to events were calculated either from the end of radiotherapy or from the initial date of CDR, depending on the analysis.

Statistical Methods

The primary purpose of this analysis was to describe the incidence of recurrence in various anatomic sites for patients undergoing dose-escalated EBRT. The cumulative incidence of FRS, isolated FRS, and any recurrence was estimated using a competing-risks analysis with FRS at other anatomic locations and death as competing risks. For these analyses, time zero was the last day of radiotherapy. In analyses using anatomic recurrence pattern as a variable, we used a landmark of 2 years from the initial CDR as time zero, given that a patient's anatomic pattern of recurrence could change to a multiorgan pattern during this time interval. The Fine and Gray method was employed for multivariate analyses of PCSM. PSA doubling time was calculated as previously described.¹³ All statistical analysis was performed using R version 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline clinical characteristics are listed in Table 1. The median follow-up for the entire cohort was 71 months, and the median follow-up for patients with CDR was 111 months. Six hundred nine patients experienced BR. The 8-year cumulative incidences of FRSs involving local sites (prostate/seminal vesicles), PLNs, abdominal lymph nodes, thoracic lymph nodes, bones, and visceral organs for the entire 2694 patient cohort following EBRT are detailed in Tables 2 and 3. For the overall cohort and each NCCN risk group, the most common FRS was local. The risk of LR increased with increasing NCCN risk group, with 8-year cumulative incidences of experiencing a LR as a FRS of 3.5% (95% CI, 1.8-5.2%), 9.8% (7.9-11.8%), and 14.6% (12.0-17.2%) for low-, intermediate-, and high-risk patients following EBRT. In total, of the 474 patients with CDR, 262 (55.3%) had a FRS that was local, including 229 patients with an isolated local FRS. Further, although the estimated 8-year incidence of a high-risk patient having a FRS involving the pelvic LN was 8.3% (6.3-10.5%), only 3.3% (1.9-4.6%) of high-risk patients developed an isolated pelvic LN recurrence as a FRS following EBRT. Bone was a relatively uncommon site of initial recurrence for low- and intermediate-risk patients. By contrast, 14.2% (11.7-16.8%) of high-risk patients had an initial CDR in the bones within 8 years of completing EBRT, including 9.8% (7.6-11.9%) with bone as an isolated FRS.

In total, 474 of 609 patients with BR had CDR during follow-up. Of these patients, 197 had local (41.6%), 46 had lymphotropic (9.7%), 96 had osteotropic (20.3%), and 135 had multiorgan/visceral patterns of recurrence (28.5%) in the 2 years following initial CDR (Fig 1). In univariate analysis, lymphotropic (hazard ratio [HR], 4.15; 95% confidence interval [CI], 2.03-8.45; $P<.0001$), osteotropic (HR, 8.11; 95% CI, 4.64-14.20; $P<.0001$), and multiorgan/visceral patterns of recurrence (HR, 9.56; 95% CI, 5.47-16.73; $P<.0001$) were associated with a significantly higher risk of PCSM than a local only pattern from 2 years after initial CDR. Further, anatomic pattern of recurrence remained highly predictive of PCSM following CDR in multivariate analysis; the only other independent predictor in our multivariate model was a Gleason score of 8-10 (HR, 2.20; 95% CI, 1.10-4.41; $P=.023$) (Table 4).

DISCUSSION

This study is to our knowledge the first detailed analysis of the anatomic patterns of recurrence occurring after EBRT for definitive prostate cancer treatment. Based on our results, we believe that several fundamental issues impacting therapeutic recommendations and future clinical trial design for these patients should be noted.

First, and surprisingly, the most common initial site of CDR for patients treated with dose-escalated EBRT was in the prostate itself for all NCCN risk groups, both as an isolated recurrence site and as a component of any initial CDR pattern. The 8-year cumulative incidence of LR as a first site of CDR was 3.5%, 9.8%, and 14.6% for patients with NCCN low-, intermediate-, and high-risk prostate cancer, respectively. Moreover, 101 of 267 (37.8%) of high risk patients with CDR had isolated local disease as the only detectable site of recurrence. This is consistent with previous studies also demonstrating the highest rates of

residual or recurrent prostate cancer following EBRT occur in high-risk patients.^{14, 15} Although the higher LR rates for high risk patients could be indicative of more radioresistant biology, these results may also reflect the high volume of local disease present in these patients. It should be noted that the cumulative incidence rates we report almost certainly underestimate the incidence of persistent local disease following EBRT, given that post-treatment biopsies were only performed in 238 of 609 patients (39%) experiencing BR in our study. Thus, although high-risk patients are at a higher risk for distant metastasis following BR than low- and intermediate-risk patients, they are also at higher absolute risk for isolated LR and may benefit from imaging of the prostate, post-treatment biopsy, or both if they are candidates for salvage local therapy.

This high propensity for locally recurrent, or locally persistent, disease also has important implications for future prostate cancer studies and therapeutic recommendations. Randomized controlled trials have unequivocally demonstrated that locoregional radiotherapy leads to improved survival in locally advanced prostate cancer.^{16, 17} For patients with high-risk disease, further improvement in local control via dose escalation with combined brachytherapy and EBRT, an approach capable of achieving biologically equivalent doses far exceeding EBRT alone,¹⁸ multimodality therapy combining surgery, radiation, and ADT, or novel radiosensitizers may lead to improved survival outcomes in this population.

Another unique aspect of our study is that we were able to report the incidence of clinically detectable PLN recurrence in the absence of elective PLN irradiation, given that our institution did not employ elective PLN irradiation until relatively recently, even for patients with high-risk prostate cancer. We found that, for all risk groups, the PLNs represented a relatively uncommon site of isolated anatomic recurrence. For example, the 8-year cumulative incidence of PLN metastasis as an isolated first site of relapse following EBRT without elective PLN irradiation was 3.3% in patients with NCCN high-risk prostate cancer. This could partially explain the lack of survival benefit from elective PLN irradiation reported in two randomized trials.^{19, 20} However, it should be noted that most,^{14, 21-23} but not all,^{24, 25} of the randomized trials showing a benefit from the addition of ADT to EBRT have required elective PLN irradiation.¹⁹ Because of this, since 2009 our institution has decided to treat all high-risk prostate cancer patients with ADT and elective PLN. Nevertheless, our current data, although hypothesis generating, suggest that local and distant recurrences are more likely to be the predominant factors influencing survival for patients receiving EBRT, and the benefit of elective PLN irradiation in prostate cancer remains unclear at this time.

Finally, we noted that many cancers seemed to demonstrate a tropism for a particular anatomic compartment, without evidence of spread to other anatomic compartments for many years. In a multivariate analysis, anatomic pattern of recurrence was the most important predictor of PCSM following CDR. The only other independent predictor was a Gleason score of 8-10, whereas numerous other variables that strongly predicted for outcome in univariate analysis were no longer significant when accounting for anatomic pattern of recurrence. This raises the possibility that most commonly used prognostic variables are primarily surrogates for the underlying oncologic biology driving the tumor to

display a specific recurrence pattern. Although rapid advancements in genomic technology have allowed an unprecedented understanding of the genetic lesions underlying the development of prostate cancer,²⁶ the impact of the molecular aberrations driving prostate cancer behavior, including tropism for spread to specific anatomic compartments, remains poorly understood and warrants further investigation.

This study has several weaknesses. First of all, it is a retrospective study, subject to the limitations, biases, and caveats of all retrospective analyses. Second, we made no attempt to adjust for use of salvage therapies given the difficulties of such analyses,²⁶ but we cannot exclude the possibility that salvage therapies impacted our results (Supplementary Table 1). Third, given that according to our definitions a patient's anatomic pattern of recurrence grouping could not be determined for at least 2 years from initial CDR, we chose to employ a landmark analysis, with time zero set at 2 years from the initial CDR date, for multivariate analyses. A more rigorous analysis would be a time-dependent multivariate analysis, but we decided against this given the complexities of using the competing-risks method in time-dependent analyses. Fourth, diagnostic studies, including imaging and post-treatment biopsies, were performed at the discretion of the treating physician during follow-up after EBRT, which could introduce bias into our results in several ways. For example, ascertainment bias, such as ordering a post-treatment biopsy for a patient originally treated for low-risk prostate cancer at time of BR but ordering a bone scan and pelvic CT scan for a patient with high-risk disease, could certainly have impacted the incidences of recurrence at specific anatomic locations. Additionally, satisfaction of search bias, for example occurring when a patient with a positive bone scan does not receive further work-up to identify local or regionally persistent disease, may also have impacted the outcomes. Lastly, the follow-up period of 71 months is relatively short for a disease with a long natural history such as prostate cancer, although the 111-month median follow-up for patients with CDR is more robust.

Despite these caveats, most applicable to nearly any analysis similar to ours, we feel that our results emphasize several important and novel insights into the natural history and patterns of recurrence of prostate cancer treated with EBRT. First, the prostate is the most common initial site of recurrence for patients from all risk groups, with increasing absolute incidence correlating with increasing NCCN risk group. Second, isolated PLN relapse is rare in all patients, including high-risk patients treated without elective PLN irradiation, at least when utilizing CT scans for detection. Lastly, many patients' tumors display a tropism for specific anatomic compartments, and these anatomic patterns of recurrence independently predict for PCSM following CDR. In summary, these results provide multiple insights that generate hypotheses for future prospective studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

ADT	androgen-deprivation therapy
BR	biochemical recurrence
CDR	clinically detected recurrence
CI	confidence interval
CT	computed tomography
EBRT	external beam radiotherapy
FRS	first recurrence site
HR	hazard ratio
LR	local recurrence
LN	nodes
NCCN	National Comprehensive Cancer Network
PC	prostate cancer
PCSM	prostate cancer-specific mortality
PLN	pelvic lymph node
PSA	prostate-specific antigen
PSA-DT	prostate-specific antigen doubling time

Figure 1.

Cumulative incidence of prostate cancer–specific mortality (PCSM) following clinically detected recurrence for patients with local, lymphotropic, osteotropic, and multiorgan/visceral patterns of recurrence.

Table 1

Baseline clinical characteristics of the study cohort

	All Patients		Patients with CDR	
	N	%	N	%
Number of patients	2694		474	
Median follow-up	83 months		111 months	
Biochemical recurrence	609	22.6%		
Age				
Median	69 years		68 years	
70	1531	56.8%	321	67.7%
>70	1163	43.2%	153	32.3%
Clinical Stage				
T1c	1307	48.5%	130	27.4%
T2a	548	20.3%	86	18.1%
T2b-c	532	19.7%	127	26.8%
T3a	121	4.5%	36	7.6%
T3b-T4	186	6.9%	95	20.0%
Gleason Score				
6 or less	1083	40.2%	115	24.3%
3+4=7	760	28.2%	119	25.1%
4+3=7	416	15.4%	96	20.3%
8	268	9.9%	83	17.5%
9-10	167	6.2%	61	12.9%
PSA				
Median	8.07		12.09	
10	1685	62.5%	214	45.1%
>10	1009	37.5%	260	54.9%
% positive cores				
< 50%	1375	51.0%	144	30.4%
50%	761	28.2%	207	43.7%
Unknown	558	20.7%	123	25.9%
NCCN Risk				
Low	590	21.9%	34	7.2%
Intermediate	1289	47.8%	173	36.5%
High	815	30.3%	267	56.3%
Radiation Dose				
Median	81 Gy		81 Gy	
75.6 Gy	467	17.3%	136	28.7%
79.2-82.8 Gy	1162	43.1%	170	35.9%
86.4 Gy	1065	39.5%	168	35.4%
ADT				
No	1245	46.2%	211	45.5%

	All Patients		Patients with CDR	
	N	%	N	%
Yes	1449	53.8%	263	55.5%
Median duration	6 months		6 months	

Table 2

Estimated 8-year cumulative incidences of a patient experiencing a first-recurrence site (FRS) in a given anatomic location for National Comprehensive Cancer Network low-, intermediate-, and high-risk prostate cancer patients undergoing dose-escalated external beam radiotherapy

8-Year Rates (95% confidence interval)	Low Risk	Intermediate Risk	High Risk	All Patients
Any FRS				
Local	3.5% (1.8-5.2%)	9.8% (7.9-11.8%)	14.6% (12.0-17.2%)	9.9% (8.6-11.2%)
Pelvic lymph nodes	0%	2.7% (1.7-3.8%)	8.3% (6.3-10.5%)	3.9% (3.1-4.8%)
Abdominal lymph nodes	0.5% (0-1.2%)	1.2% (0.1-1.9%)	2.9% (1.6-4.2%)	1.6% (1.1-2.2%)
Thoracic lymph nodes	0%	0.7% (0.2-1.1%)	0.3% (0-0.8%)	0.4% (0.1-0.7%)
Bone	0.9% (0.1-1.7%)	3.9% (2.6-5.2%)	14.2% (11.7-16.8%)	6.5% (5.4-7.9%)
Visceral	0%	0.1% (0-0.4%)	1.0% (0.3-1.7%)	0.4% (0.1-0.6%)
Isolated FRS				
Local	3.5% (1.8-5.2%)	8.5% (6.7-10.3%)	12.2% (9.8-14.7%)	8.5% (7.3-9.8%)
Pelvic lymph nodes	0%	1.0% (0.3-1.7%)	3.3% (1.9-4.6%)	1.5% (1.0-2.1%)
Abdominal lymph nodes	0.2% (0-0.5%)	0.1% (0-0.3%)	0.6% (0-1.2%)	0.4% (0-0.6%)
Thoracic lymph nodes	0%	0.1% (0-0.3%)	0%	0.05% (0-0.14%)
Bone	0.9% (0.1-1.7%)	2.3% (1.3-3.3%)	9.8% (7.6-11.9%)	4.3% (3.5-5.2%)
Visceral	0%	0%	0.7% (0.08-1.3%)	0.2% (0.02%-0.4%)

Note: Any FRS counts all sites of recurrence within the first 3 months of the first detected site of clinical recurrence. For a patient to have an isolated FRS at a given site, the initial site of recurrence must be the only site of disease for at least 3 months from initial detection.

Table 3

Number (and percentage) of patients in each risk group having a given anatomic location as a first recurrence site among the 474 patients with clinically detected recurrence

	Low Risk	Intermediate Risk	High Risk	All Patients
Local	25 (73.5%)	117 (67.6%)	120 (44.9%)	262 (55.3%)
Pelvic lymph nodes	0 (0%)	33 (19.1%)	68 (25.4%)	101 (21.3%)
Abdominal lymph nodes	2 (5.9%)	16 (9.2%)	25 (9.4%)	43 (9.1%)
Thoracic lymph nodes	0 (0%)	7 (4.0%)	3 (1.1%)	10 (2.1%)
Bone	8 (23.5%)	43 (24.9%)	108 (40.4%)	159 (33.5%)
Visceral	0 (0%)	1 (0.6%)	8 (3.0%)	9 (1.9%)
Total clinically detected recurrences	34	173	267	474

Note: Patients could have multiple first recurrence sites, so percentages may not sum to 100%.

Table 4

Univariate and multivariate analyses of candidate prognostic variables for PCSM

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Recurrence				
Pattern				
Local	1.00	Reference	1.00	Reference
Lymphotropic	4.15 (2.03-8.45)	<.0001	3.83 (1.57-9.33)	.0026
Osteotropic	8.11(4.64-14.20)	<.0001	8.97 (4.22-19.06)	<.0001
Multiorgan	9.56 (5.47-16.73)	<.0001	9.19 (4.49-18.82)	<.0001
Gleason Score				
6 or less	1.00	Reference	1.00	Reference
3+4	1.01 (0.59-1.73)	.97	1.49 (0.74-3.00)	.26
4+3	1.86 (1.13-3.05)	.013	1.75 (0.80-3.83)	.15
8-10	2.48 (1.57-3.90)	<.0001	2.20 (1.10-4.41)	.023
Log PSA	1.03 (0.90-1.17)	.70	1.00 (0.83-1.20)	.98
T stage				
T1c or less	1.00	Reference	1.00	Reference
T2a	1.60 (0.90-2.83)	.1	1.70 (0.84-3.45)	.13
T2b-c	1.50 (0.90-2.49)	.11	1.27 (0.69-2.34)	.44
T3a	1.24 (0.57-2.68)	.58	0.71 (0.20-2.52)	.59
T3b-T4	2.25 (1.39-3.64)	.0008	1.42 (0.75-2.69)	.28
Neoadjuvant ADT	1.50 (1.09-2.07)	.012	0.84 (0.49-1.44)	.51
Time to BR	0.79 (0.72-0.88)	<.0001	1.02 (0.90-1.15)	.77
Age	1.01 (0.99-1.04)	.25	1.00 (0.97-1.03)	0.88
PSA-DT	0.98 (0.97-1.00)	.0079	0.99 (0.97-1.01)	.17

Note: A landmark analysis was performed, with time zero equal to 2 years from the initial clinical recurrence.