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Research Article

The Effect of High Dose Nodal Radiation for Prostate Cancer on Long Term Toxicity

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Abstract

Background and Purpose: With modern radiation techniques, it is now possible to treat pelvic lymphatics to higher, potentially more effective doses of radiation. The long term benefit remains to be proven, so it is important to know the toxicity risks of that dose escalation.

Materials and Methods: To try to improve the efficacy of our prostate cancer treatment, we have been treating the prostate lymphatics to 54 Gy. As a standard practice, we have been collecting quality of life data utilizing the expanded prostate cancer index (EPIC) questionnaire. EPIC is a validated tool for evaluation of quality of life changes after prostate cancer treatment. The results are normalized to 100, that being considered normal function. We have also routinely collected urinary functional outcome data for the international prostate symptom score (IPSS). Data were collected at baseline and then 1.5 to 2.5 years after treatment. We had three groups of patients receiving radiation therapy; prostate only, prostate and lymphatics and prostate fossa and lymphatics (post prostatectomy patients).

Results: The baseline characteristics of the three groups were similar, except the post surgery group had more urinary issues. Overall, for the total population, with long term follow up, there was a median change of less than 2 for bowel function and less than 3 in the urinary domain. There was no statistical difference (or any appreciable trends) in outcome with the addition of 54 Gy to the pelvic lymphatics.

Conclusions: Modern radiation techniques allow for radiation dose escalation in treating prostate cancer. Our preliminary results show that the pelvic lymphatics can receive 54 Gy with no overt increase in toxicity compared to prostate only radiation.

Keywords: Prostate Cancer; Lymphatic Dose; Quality of Life

Introduction

As an oncological principle, nodal radiation improves local control and often survival in most cancers. In prostate cancer, retrospective data suggest a benefit, but without randomized studies, the absolute amount of benefit remains uncertain. Current guidelines [1] acknowledge the appropriate use of lymphatic radiation in both the primary and postoperative setting. As a radiation principle, higher doses are better able to eradicate cancer. This is certainly evident for the prostate itself [2,3]. Historically, doses used for nodal radiation in the abdomen and pelvis have not been so much determined by the most effective dose, but by the dose achievable due to toxicity. In the past, those doses have been on the order of 40-50 Gy. This is thought to be a minimally effective dose in microscopic disease. For example, in head and neck cancer, effective doses for treating microscopic disease are usually on the order of 54 Gy. It is as likely that higher doses in the abdomen and pelvis would improve the effectiveness of treatment. A recent survey of British oncologists indicate that more than 80% favor doses of 50 Gy or greater and a third favor greater than 54 Gy [4]. With modern radiation techniques, higher doses to the lymphatics are possible. The benefit of dose escalation is still to be determined, so it remains imperative that we have an understanding as to the cost in the way of toxicity. We have been treating patients with 54 Gy to the lymphatics and carefully tracking the effect on quality of life. We report those results in comparison with patients that are not receiving nodal radiation to try to determine the toxicological consequences of this dose escalation to the pelvic lymphatics.

Methods and Materials

Since 2009, we have routinely monitored the quality of life outcomes in our prostate cancer patients. For patients with intact prostate, depending on their prognostic risk, some received nodal radiation. The target volume included the external and internal iliac (with its branches) vessels up to the common iliac bifurcation. In addition, all patients receiving post-operative radiation also received nodal radiation. They were monitored at baseline and periodically with the expanded prostate cancer index composite (EPIC) questionnaire. EPIC is one of the few validated quality of life instruments for monitoring the effects of treatment in patients with prostate cancer [5]. We also recorded the International Prostate Symptom Score (IPSS) at each follow up. The IPSS was developed to assess the symptomatic effects of benign prostatic hypertrophy [6] and thereby gives an evaluation of urinary function. The quality of life questionnaires were obtained at each visit. Long term, most patients continued their follow up with the referring urologist. We are mostly concerned with the long-term effects and sought follow up starting 1 ½ to 2 ½ years post treatment. If not obtained at a clinic visit, long-term follow up was obtained via correspondence (the forms were mailed with a return envelope). Our goal was to obtain at least one follow up between 1 ½ and 3 years from the date of completing radiotherapy.

The EPIC quality of life tool is designed to assess level of function and the patients' satisfaction with that function. It is normalized from 0 to 100 with 100 being "normal" function. We focused on the urinary and bowel domains. The international prostate symptom score is designed to measure urinary function- primarily in the realm of lower urinary tract symptoms related to obstruction. It overlaps somewhat with the EPIC urinary domain (obstructive component). In EPIC the urinary and bowel domains can be subdivided into "function" and "bother". In addition, the urinary domain can also be subdivided into "incontinence" and irritative/obstructive". The bowel functional domain evaluates urgency/leakage, discomfort, frequency of stooling, bleeding and stool quality. The urinary domain includes general function (leakage/pads, dysuria, hematuria), incontinence (leakage, control, number of pads), and irritative/obstructive (frequency, nocturia and weak stream) questions.

For each functional item, the questionnaire covers a broad range, from minimal/normal to markedly dysfunctional. We were interested in how treatments changed the incidence of worse function. For consistency, we decided to follow the pattern in a previous paper [7] for urinary and bowel function. Under the urinary irritation classification, we evaluated "moderate" to "big problem" for dysuria (pain or burning), hematuria , weak stream (or incomplete emptying) and frequency (urinating frequently). In the incontinence classification, we evaluated leakage (more than once per day), urinary control (no control or frequent dribbling), any pad use (one or more per day), leaking problem (moderate to big) and overall urinary function in last 4 weeks (moderate to big problem). For bowel function we evaluated moderate to big problem for urgency to have bowel movement, increased frequency of bowel movement, bloody stools and rectal pain as well as overall how big a problem the bowel habits have been (moderate to big).

We had three groups of patients: intact prostate only radiation, intact prostate and lymphatics and post operative radiation (with treatment to prostate fossa and lymphatics). Prostate only patients were treated primarily 78 Gy to the prostate in 42 fractions. For those treated to the lymphatics, the dose to the lymphatics was 54 Gy. For patients post prostatectomy, 54 Gy was delivered to the lymphatics and a total of 70 Gy to the prostate fossa. Dose constraints were as follows: for the rectum, no more than 5% receiving 75 Gy, 20%-70Gy, 30%-60Gy, 40%-50 Gy and 50%-40 Gy [8]. For the bladder, the constraints were no more than 25%-70 Gy and 50%-40 Gy. Patient characteristics are shown in Table 1. Patients with prostate only radiation were more likely to have cancers of Gleason 7 or less. Patients radiated postoperatively were younger.

Table 1. Patient Characteristics. IQR is the interquartile range from the 25th to the 75th percentile.

	# patients	lymphatic dose (Gy)	Prostate area dose (Gy)	Median age (IQR)	Gleason Score		
					<7	7	>7
Prostate only	34	0	78	66.1 (61.6-75.9)	35%	51%	14%
Prostate and lymphatics	25	54	78	70.4 (64.7-77.4)	3%	42%	55%
Prostate fossa and lymphatics	38	54	70	64.6 (61.9-70.9)	8%	50%	42%

Statistical analysis

Within group differences of baseline values of EPIC domains and change scores were compared using the Kruskal-Wallis test. All computations were performed with R (v3.1+, Vienna, Austria).

Results

As with any urologic population, individual baseline function varied widely (Table 2). Across the 3 groups, there was no baseline difference in median bowel function (p. =0.41), but urinary function was worse for the post-operative patients (p=0.03), primarily in the urinary incontinence domain (p <0.001). There was no difference in the IPSS (p=0.68). With long term follow up after radiation, as we would expect, there were overall negative effects on function (Table 3). These effects were modest across the entire cohort; there was a median change of <2 for bowel function and < 3 in the urinary domain (with zero change in the obstructive subdomain and -6.3 in the incontinence sub domain). The IPSS essentially showed no change.

There was no statistical difference in the degree of change between the groups indicating no significant increase in toxicity to treating the lymphatics to 54 Gy. With the p values across the groups ranging from 0.17 to 0.54, there is not a suggestion of a trend. (Table 3). Conceptually, the area of greatest risk to the expanded volume for nodal radiation is the bowel, but there was no difference in the degree of change (Figure 1) of function.

Table 2. Baseline function for each of the three groups of patients.

Baseline	Median Bowel domain (range)	Median Urinary domain (range)	Median urinary irr/obs (range)	Median Urinary incontinence domain (range)	Median IPSS (range)
All patients	94.6 (33.9-100)	85.0 (36.1-100)	87.5 (31.3-100)	87.5 (8.25-100)	7(0-32)
Prostate only	92.9 (33.9-100)	91.7 (48.7-100)	87.5 (43.8-100)	100 (46-100)	7 (4-12)
Prostate and lymphatics	94.6 (71.4-100)	87.5 (36.1-100)	87.5 (31.3-100)	93.8 (39.5-100)	6 (4-14.5)
Prostate fossa and lymphatics	94.6 (58.9-100)	76.4 (40.3-100)	87.5 (50-100)	65.8 (8.25-100)	7 (2-11.25)
P value	0.41	0.03	0.96	<0.001	0.68

Table 3. Effect of radiation on function >1.5 years after therapy (median change).

Change	Median Bowel domain	Median Urinary domain	Median urinary irr/obs	Median Urinary incontinence domain	Median IPSS
All patients	-1.8	-2.8	0	-6.3	1
Prostate only	-3.6	-6.3	0	-8.3	1
Prostate and lymphatics	-3.6	0	0	0	-1
Prostate fossa and lymphatics	0	-1.4	0	-1.1	2
P value	0.31	0.17	0.31	0.41	0.54

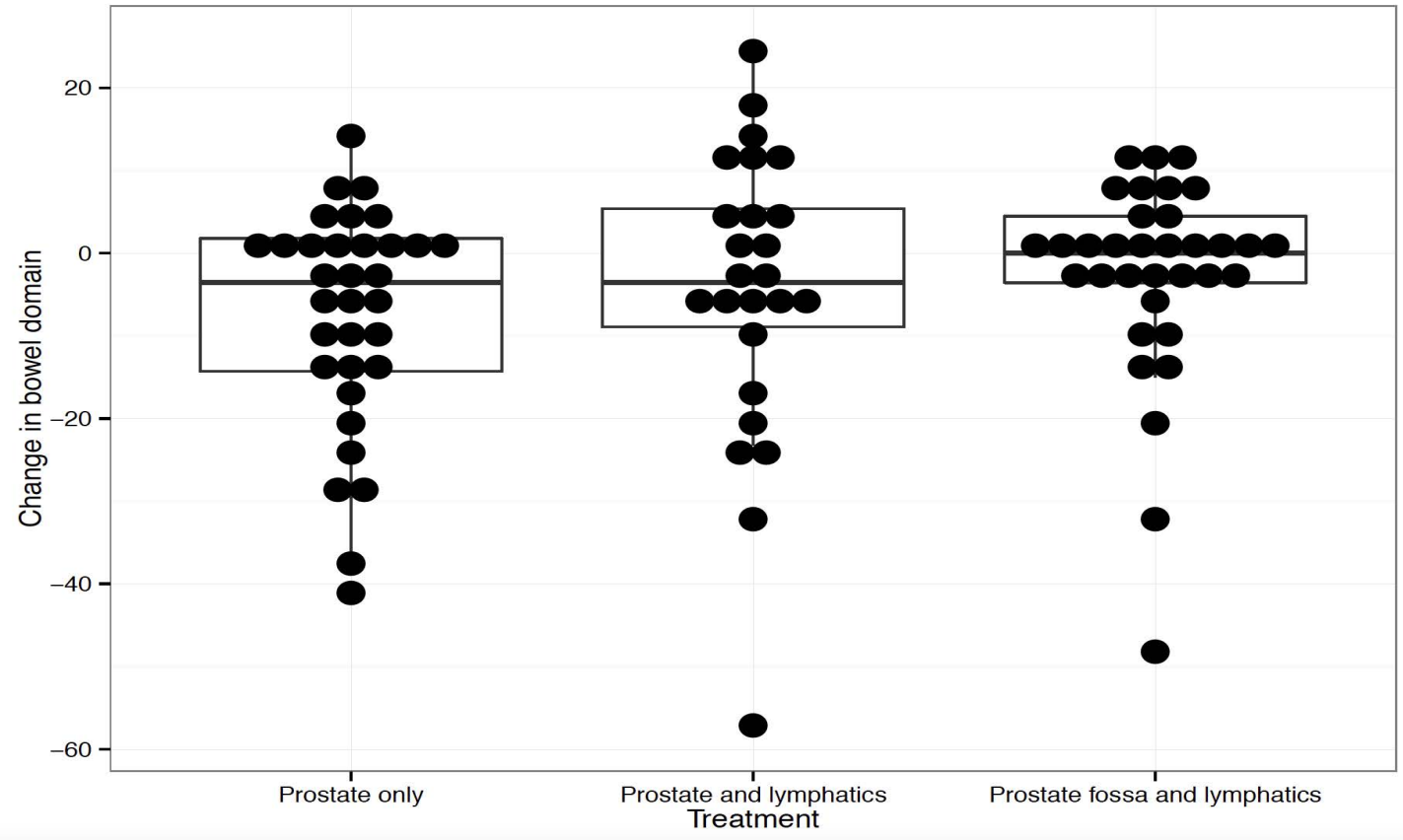

Figure 1. Boxplot of changes in bowel domain from baseline. Each dot represents one patient's change. The white box represents the span of the lower 25th and upper 75th percentiles, with the median (50th percentile) drawn in between. Although some individuals had dramatic improvement or decline, the overall baseline function declined slightly across all groups.

When we focused on "moderate to big problems" (Table 4), as expected, we again saw some modest changes, but nothing that appeared too dramatic. There was no statistical difference in functional changes between the three groups.

domain of ~87. These were very similar to our patients. At 24 months, they noted a ~7 point decline in the bowel domain, ~3 points in the urinary incontinence domain and virtually no change or a slight improvement in the irritative/obstructive

Table 4. Effect of treatment on incidence of functional "moderate to big problems".

		All patients		Prostate only		Prostate and lymphatics		fossa and lymphatics		P value
Domain		BL	Last	BL	Last	BL	Last	BL	Last	
Urinary irritation	Pain or burning	2	4	0	6	4	0	3	6	0.32
	Hematuria	0	4	0	3	0	4	0	6	0.86
	Weak stream	11	13	12	18	13	13	9	9	0.8
	Frequency	18	26	12	27	13	22	26	26	0.42
Incontinence	Leaking >1 per day	20	24	9	12	4	8	40	46	0.95
	No control or frequent dribbling	9	23	0	19	4	8	20	37	0.37
	>1 pad/day	25	29	9	18	12	12	50	50	0.5
	leaking	11	23	3	18	4	12	24	35	0.86
	Overall	19	25	9	24	17	13	29	34	0.31
Bowel function	urgency	5	11	6	21	4	8	6	3	0.1
	Frequency	0	8	0	12	0	4	0	6	0.48
	Fecal incontinence	1	7	3	13	0	8	0	0	0.19
	Bloody stool	1	7	3	9	0	8	0	3	0.67
	Rectal pain	2	9	3	12	0	4	3	9	0.81
	overall	0	2	0	6	0	0	0	0	0.16

Discussion

Patients have a wide range of baseline function. Even in patients without surgery, the baseline function in EPIC ranges from the 30's up to 100. As expected, the median function declined somewhat after radiation. It is encouraging that the decline was modest. In the largest published study using EPIC, for external beam radiation patients, Sanda, et al [7] (from Figure 1B) showed a baseline bowel domain of ~96, urinary incontinence domain of ~88 and the urinary irritative/obstructive domain. Our results were similar in the urinary domains, although our change in the bowel domain was only about half of what they saw. An earlier study using the UCLA index [9] showed changes of only a few points in the bowel domain similar to our findings. Neither study reported details on volumes or doses.

The strongest indicator of the lack of detriment to escalated dose nodal radiation is between the two 78 Gy groups (with one including 54 Gy to the lymphatics and the other no radi-

ation). This is then confirmed by the lack of detriment to the postoperative group which also received 54 Gy to the lymphatics. When we evaluated the more severe functional outcomes (Table 4), we again saw no difference between the groups. In the irritation domain, the biggest change from baseline was in frequency with an overall change of 8%. The postoperative patients, with a higher baseline problem, saw no change. In the incontinence domain, bothersome frequency for the entire cohort increased 14%. In the bowel function domain, the biggest change (8%) was in bothersome rectal discomfort. Our numbers were not large and perhaps with more patients, differences would be more apparent. Still, it is very encouraging to us that treating the lymphatics to 54 Gy did not result in a dramatic difference in functional outcome. This supports the concept that the lymphatics can be treated to more effective doses. (10-12)Ours is the first report of which we are aware that demonstrates using intensity modulated radiation therapy (IMRT) that lymphatic dose escalation can be accomplished with no appreciable change in functional outcome. As others and we confirm these findings, then higher lymphatic doses of radiation should become the standard for the potential of improved efficacy.

References

1. Mohler JL, Kantoff PW, Armstrong AJ, Bahnson RR, Cohen M et al. National Comprehensive Cancer Network. Prostate cancer, version 2.2014. J Natl Compr Canc Netw. 2014, 12(5):686-718.

2. Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys. 2008, 70 (1): 67-74.

3. Zelefsky MJ, Fuks Z, Hunt M, Lee HJ, Lombardi D et al. High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. J Urol. 2001, 166(3): 876-881.

4. Payne HA, Dearnaley D, Clarke N. Hot topics for debate in prostate cancer: part 2. Trends in Urology & Men's Health. 2012, 3(5): 37–39.

5. Wei J, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and Validation of the Expanded Prostate Cancer Index Composite (EPIC) for Comprehensive Assessment of Health-Related Quality of Life in Men with Prostate Cancer. Urology. 2000, 56(6): 899-905.

6. Barry MJ, Fowler FJ Jr, O'Leary MP, Bruskewitz RC, Holtgrewe HL et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol. 1992, 148: 1549-1557.

7. Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med. 2008, 358(12): 1250-1261.

8. Swanson GP, Stathakis S. Rectal dose constraints for intensity modulated radiation therapy of the prostate. Am J Clin Oncol. 2011, 34(2):188-195.

9. Litwin MS, Gore JL, Kwan L, Brandeis JM, Lee SP et al. Quality of life after surgery, external beam irradiation, or brachytherapy for early-stage prostate cancer. Cancer. 2007, 109(11): 2239-2247.

10. Engels B, Soete G, Tournel K, Bral S, De Coninck P et al. Helical tomotherapy with simultaneous integrated boost for high-risk and lymph node-positive prostate cancer: early report on acute and late toxicity. Technol Cancer Res Treat. 2009, 8(5): 353-359.

11. Bayouth JE, Pena J, Culp L, Brack C, Sanguineti G. Feasibility of IMRT to cover pelvic nodes while escalating the dose to the prostate gland: dosimetric data on 35 consecutive patients. Med Dosim. 2008, 33(3): 180-190.

12. Guerrero Urbano T, Khoo V, Staffurth J, Norman A, Buffa F et al. Intensity-modulated radiotherapy allows escalation of the radiation dose to the pelvic lymph nodes in patients with locally advanced prostate cancer: preliminary results of a phase I dose escalation study. Clin Oncol (R Coll Radiol). 2010, 22(3): 236-244.