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ORIGINAL ARTICLE

Does pelvic lymph nodes irradiation using intensity modulated radiation therapy increase rectal and bladder toxicities in patients with prostate carcinoma?

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Summary

Purpose: *This study compared the radiation-related rectal (R) and bladder (B) toxicities in prostate carcinoma patients receiving additional pelvic lymph nodes (PLN) irradiation with those receiving prostate (P) and seminal vesicle (SV) irradiation only.*

Methods: *Thirty-three patients treated with intensity modulated radiation therapy (IMRT) were included. RT doses ranged between 60- 66.6 Gy to SV, 74-77.7 Gy to P and 50.4-60 Gy to PLN. Max acute R toxicity was graded by a physician according to the RTOG side effect criteria during the period from the initiation of therapy until the end of the third month. Max late R and B toxicities were graded 3 months after the completion of RT by a physician using the RTOG GI and urogenital toxicity score and by patients using EORTC QLQ - PR25 self questionnaire separately. The effects of R and B doses and additional PLN irradiation on acute and late R and B toxicities and compatibility of patient- and physician-graded toxicity scores were investigated. RTOG GI and urogenital toxicity scores and EORTC QLQ - PR25 self questionnaire results were correlated.*

Results: *Significant factors for acute R toxicity were: max R; R volume receiving ≥68 Gy; and PLN irradiation. PLN irradiation was marginally significant for late R toxicity; the mean B dose was a significant factor for late B toxicity.*

Conclusion: *The results of this study suggest that although PLN irradiation increased acute R toxicity, it has no effect on late R and B toxicity. Patient- and physician-evaluated late R and B toxicity scores were concordant.*

Key words: bladder, EORTC QLQ-PR25, prostate cancer, radiotherapy, rectum, side effects

Introduction

Radiation-related normal tissue side effects increase with higher radiation doses and expozed volume [1-3]. However, tumor control rates improve with RT dose escalation in prostate carcinoma which results in better disease-specific survival, metastasis-free survival and biochemical relapse-free survival rates [4-7]. The positive contribution of PLN irradiation to local control and disease-free survival rates was reported for a selected group of patients with high risk prostate carcinoma [8,9]. Therapeutic gain is not only influenced by increased tumor control rate, but also decreased treatment-related side effects, therefore PLN irradiation is not widely used in practice. PLN irradiation is recommended for radiologically or pathologically proven PLN metastasis or salvage RT.

IMRT technology provides higher radiation doses in the target volume while limiting radiation doses within tolerance levels in organs at risk (OAR) [6]. Consequently, it was postulated that a radiation-exposed normal tissue volume could be reduced and potential side effects might decrease. Decreasing side effect rates with IMRT in comparison with three dimensional (3D) conformal RT has been reported previously [10]. Some studies pointed out a marked difference between patient and physician/health care professional in evaluating side effect scores [11,12]. Muanza et al. claimed that patients graded side effect scores more reliably [12].

This study investigated whether the IMRT technique could eliminate additional normal tissue toxicity in patients with prostate carcinoma receiving PLN irradiation compared to prostate (P) and seminal vesicle

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(SV) irradiation only. Furthermore, differences between toxicity scores graded by patients and physicians were evaluated.

Methods

Patient population

Thirty-three consecutive prostate carcinoma patients that received IMRT with at least 6 months of follow-up, and that agreed to fill in a form containing self- assessed toxicity scoring questions were included. Twenty-four patients received irradiation to P and SV only. The remaining 9 patients with high risk criteria (≥T3, N+, high Gleason score and PSA level for primary cases or with lymph node metastasis for postoperative cases) received RT to PLN in addition to P and SV.

Treatment protocol

All patients underwent a diagnostic prostate MRI scan; patients with intact prostate underwent gold marker placement via transrectal ultrasonography (US).

All patients were positioned in the supine position; knee support and a leg holder were used for immobilization. Patients were instructed to maintain a full bladder and empty rectum during simulation and treatments. Simulation CT images were acquired at a slice thickness of 3 mm, then registered with MRI images; treatment volumes and OAR were defined. Lymph nodes were included in the treatment volume only if they were found to be radiologically or pathologically positive.

Target volumes were defined as PTVp and PTVsv which were derived by expanding CTVp and CTVsv 3-5 mm posteriorly and 7-10 mm in other directions. PTVp was subtracted from PTVsv, therefore proximal sv volumes were included in PTVp. PTVLN was defined by expanding CTV lymph nodes by 10 mm in all directions, excluding the PTVp and PTVsv. Critical structures were defined on planning CT, and included rectum (R), bladder (B), penile bulb, and any small bowel extending 3 cm distal to the targets and bilateral femoral heads. The entire bladder and rectum from its origin at the rectosigmoid flexure were contoured.

IMRT plans were designed for each patient with 5 coplanar 6 MV beams and sliding windows technique using the Eclipse Treatment Planning System. A simultaneous integrated boost approach was chosen: RT doses ranged from 74-77.7 Gy with 2-2.12 Gy fraction doses for PTVp and 60- 66.6 Gy with 1.8 Gy fraction doses for PTVsv. Two phase planning was applied for patients receiving lymph node irradiation; PTVLN doses ranged from 50 to 60 Gy with 1.8- 2.1 Gy fraction doses, 60 Gy was given only to macroscopic disease sites.

Maximum (max) and 15% doses of R and B were limited to 74 Gy and 60 Gy respectively. In order to avoid hot spots in R and B volumes intersecting with PTV, these volumes were defined as PTVR, PTVB and constraints were limited to 74-77 Gy (Figure 1).

Daily on-line set-up accuracy was obtained using MV imaging via fiducial markers.

All patients received neoadjuvant and/or adjuvant hormonal therapy.

Side effect scoring: Study endpoints

All patients were seen weekly by their radiation oncologist while undergoing therapy. Max acute R toxicity occurring during treatment and until the end of the third month after the completion of RT was graded prospectively according to RTOG side effect criteria [7]. Most of the patients already had genitourinary symptoms prior to treatment. The urinary toxicities were graded during treatment; however, the data was not enough to compare with the symptoms prior to radiation. Therefore, acute genitourinary toxicity evaluation was not included in the analysis. Late R and B toxicities were graded by the treating physician three months after the completion of RT based on RTOG side effect criteria.

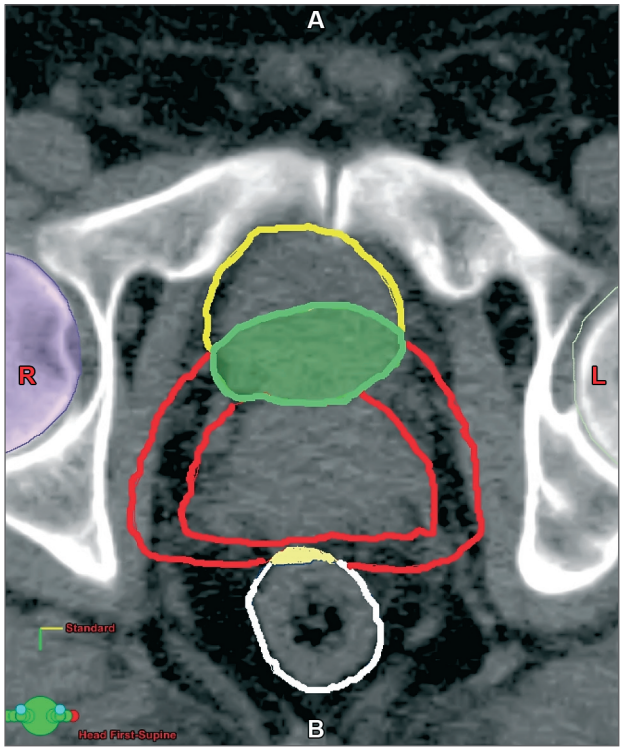

Figure 1. Counted volumes for PTVp (PTV prostate), bladder and rectum are shown. Rectum and bladder volumes intersecting with PTV were defined as PTVR (green), PTVB (yellow).

Separately, patients were offered to participate in the quality of life component of the study with an EPIC (The Expanded Prostate Cancer Index Composite) which is a self-assessed questionnaire, designated to measure a broad spectrum of symptoms. QLQ-PR25 self questionnaire translated to the mother tongue by EORTC was used. EPIC measures a broad spectrum of symptoms; however, it was used for domains most pertinent to this study: rectal and urinary. The questionnaire is scored on a scale of 0-100, with a higher score correlated to higher function and health-related quality of life (HRQOL). Then, "raw scores" for R and B were calculated using the answers for R and B and symptom scores were calculated according to the formula [7,13,14].

Statistics

The effects of mean, maximum, maximum 2 cc R and B doses, R and B volume exposed ≥ 68 Gy and additional PLN irradiation on R and B toxicities were investigated. The correlation between acute and late toxicities was tested. Furthermore, the compatibility of patient-and physician-graded toxicity scores were studied. Mann-Whitney U test was used to evaluate differences between the subjects. The relation between any factors was examined by the Spearman's rho test.

Results

After a mean follow-up of 14 months (range 6-40), biochemical relapse occurred in 2 patients and disease progression was seen in 1 patient who received salvage RT 10 years after radical prostatectomy. This particular patient had bulky tumor larger than 5 cm and multiple macroscopic lymph node metastases before starting RT. This patient was excluded from study since the disease-related local symptoms could affect radiation-related side effects.

Median (range) age, Gleason score and PSA values for the whole group were 69 years (range 46-84), 7 (range 6-9) and 13 ng/mL (3.6-58), respectively. The median age was 69 years for P+SV alone group and 65 years for PLN added group. The median Gleason score was 7 for both groups. The median initial PSA values were 12.5 ng/mL for the P+SV alone group whereas it was 21 ng/mL for the LN added group; there was a significant difference between the groups (p=0.012).

Dosimetric data for R and B, such as mean, maximum and max 2 cc volume doses and >68 Gy exposed volume as cc, according to PLN added and P+SV groups are summarized in Table 1. As seen in Table 1, there were significant differences between the two groups in the mean R and B doses.

Physician-evaluated early R, late R and late B side effect rates are given in Table 2. No late R side effects

Table 1. Rectal (R) and bladder (B) doses

	Whole group n= 32	*P+SV n= 24*	*PLN added n= 8*	*p-value*
Mean R dose (cGy)	3904	3736	4406	0.059
Max R dose (cGy)	7404	7379	7478	0.95
Mean B dose (cGy)	3803	3353	5151	0.001
Max B dose (cGy)	7656	7620	7767	0.68
Receiving >6800 cGy R volume (cc)	3.2	2.7	4.5	0.8
Receiving >6800 cGy R volume (%)	3.2	2.7	3.2	0.5
Receiving >6800 cGy B volume (cc)	8.1	5.4	16.3	0.16
Receiving >6800 cGy B volume (%)	17.5	14	27.8	0.13

P: prostate, SV: seminal vesicles, PLN: pelvic lymph nodes

Table 2. Physician-evaluated acute rectal and late rectal-bladder side effects

	Whole group (n= 32) n (%)	*P+SV (n= 24) n (%)*	*PLN added (n= 8) n (%)*
Acute rectal side effect	14* (43.8)	8* (33.3)	6* (75)
Late rectal side effect (GI symptom scores)	0 (0)	0 (0)	0 (0)
Late bladder side effect (Urological symptom scores)	15 (46.8)	9 (37.5)	6 (75)
Grade III late bladder side effects	1 (3.1)	0 (0)	1 (12.5)

*all of them were grade I-II. For abbreviations see footnote of Table 1

were observed despite the high acute R side effect rates. Late B side effect rates were much higher than late R side effect rates (Table 2). Patient-assessed late toxicities were mainly related to B. However, most of the side effects were grade I-II. The necessity to use alpha blockers was accepted as a side effect.

Physician-evaluated late RTOG gastrointestinal and urogenital toxicity scores and EPIC EORTC QLQ - PR25 self questionnaire (gastrointestinal symptom score and urologic symptom score) results were correlated to bladder ($r=0.668$ and $p<0.01$) and rectum ($r=0.427$ and $p=0.021$) side effects.

Significant factors concerning acute R toxicity were: max R dose, R% volume receiving ≥68 Gy, additional PLN irradiation. PLN irradiation was significant ($p=0.046$) on physician-evaluated and marginally significant ($p=0.08$) on patient-evaluated late R side effect. Mean B dose was marginally significant factor on physician-evaluated late B toxicity ($p= 0.07$; Table 3).

Discussion

IMRT is more efficient than 3D conformal RT technique to achieve higher doses in target while keeping R and B doses within tolerance level in prostate carcinoma [3-10]. Since irradiated B and R volume is larger for the PLN added group than the P + SV alone group, it is difficult to reduce R and B doses and the related side effects using 3D conformal RT techniques. Therefore, theoretically, IMRT is particularly helpful for the PLN added group. As seen in Table 1, the intended dose constrains for targets, B and R were achieved using IMRT for both groups. Since the contoured rectum segment is longer for the PLN added group, the mean rectal dose was less than in the P+SV group. But the mean B dose was higher in the PLN added group because there was no change in bladder contouring in both groups. It was shown that these dosimetric advantages resulted in reduced R and B doses which provided fewer side effect rates in comparison to 3D conformal RT [10].

Table 3. Factors affecting physician and patient-assessed side effects

	Factor	*p-value*
Acute rectal side effects*	Mean rectal dose	0.6
	Maximum rectal dose	0.03
	PLN irradiation	0.04
	>68 Gy volume cc	0.18
	>68 Gy volume %	0.012
Late rectal side effects*	Mean rectal dose	0.19
	Maximum rectal dose	0.86
	PLN irradiation	0.046
	>68 Gy volume cc	0.82
	>68 Gy volume %	0.94
GI symptom score**	Mean rectal dose	0.8
	Maximum rectal dose	0.7
	PLN irradiation	0.08
	>68 Gy R volume cc	0.8
	>68 Gy R volume %	0.6
Late bladder side effects*	Mean B dose	0.07
	Maximum B dose	0.7
	PLN irradiation	0.19
	>68 Gy B volume cc	0.78
	>68 Gy B volume %	0.39
Urological symptom score**	Mean B dose	0.35
	Maximum B dose	0.7
	PLN irradiation	0.8
	>68 Gy B volume cc	0.32
	>68 Gy B volume %	0.5

*physician-assessed score, **patient-assessed score, PLN: pelvic lymph nodes, GI: gastrointestinal, R: rectal, B: bladder

In this study, acute R side effects were not related to the mean rectal dose; rather they were related to receiving >6800 cGy and maximum 2 cc R volume dose. This result is compatible with previous reports [15,16]. Since the rectum is a hollow organ, the mean R dose does not represent the rectum dose. We assume that using the IMRT technique in a limited higher radiation dose in a small part of the rectum, the affected R volume was decreased, resulting in reduced injury. These acute side effects were easily healed in a short time interval. Consequently, no late rectal side effect was seen.

In the present study, radiation exposed R and B volumes were higher in the PLN added group but all patients completed the planned treatment without modification. However, the acute R toxicity rate was 43.8%, and all side effects were grade I-II. Grade III-IV acute R toxicity was not seen. In other studies using IMRT, the chosen target was P+SV alone, acute R toxicity rates were between 4.5-29%, and all were grade I-II [17-19]. In the present study, the acute R toxicity rate was 33% in the P and SV group, compatible with other reported series [17-19]. While the acute R side effect rate was 75% in the PLN added group, it was markedly higher than the P+SV group in earlier studies [17-19]. Despite the fact that there was no difference between PLN added and P+SV alone on max R dose and % R volume receiving > 68 Gy, the acute R side effect rate was markedly higher in the PLN added group since the irradiated R segment volume was higher in this particular group like in other reports [20,21].

Other studies have pointed out the relationship between mean R dose and late side effects and the importance of mean R dose >50 Gy [22]. This matches well with our results; there was no R side effect with a mean R dose < 50 Gy. The mean R dose was 4406 cGy in the PLN added group in comparison to 3736 cGy in the P +SV group.

Some authors claim that late R toxicity is correlated to acute R toxicity and there is a potential association between acute and late R toxicity [23,24]. Nevertheless, in this study, despite a higher acute R toxicity rate, no late R toxicity was seen. We assume that another reason for high acute R toxicity is the overscoring of physicians. Dose escalation could have led to a more strict evaluation of side effects and an overestimation of physicians.

Evaluating acute B toxicity includes some drawbacks that might lead to imprecise grading. Given the nature of the disease, most of the patients had urination problems prior to RT and changes in intensity of urination problems were graded as toxicity. Because we did not have a detailed initial evaluation, acute B toxicity was not included in this study. Late B toxicity was seen in 46.8% of the patients, which is quite high. Except one patient with grade III side effects, all of them were grade I such as needed to use "alpha 1 adrenoreceptors blocker" for urination problems. Grade III B toxicities were seen in one particular patient who was in the PLN added group; he underwent bladder operation for differential diagnosis of bladder carcinoma. He started having urinary incontinence after surgery (14 months after completion of RT). As seen in this example, combined treatment, especially surgical intervention, could increase and lead to excessive toxicity. Other studies reported similar increased treatment-related toxicity [8,17,25]. Uncontrolled disease is the other main reason for excessive toxicity. Most of the time, disease symptoms and side effects symptoms are not easily distinguished because patients could have edema and inflammation in the prostate or urethra leading to urination problems. Irradiated volume size is important in radiation-related side effect according to the Normal Tissue Complication Probability (NTCP) model [26]. Guckenberger et al. estimated RT-related side effect rates using dosimetric data interpreted according to the NTCP in prostate carcinoma patients treated to P + SV and PLN [20,21]. They claimed that, despite radiation exposed R and B volume increase, the side effects were mainly seen with doses > 4500 cGy [21]. IMRT technology provided better dose distribution; therefore, volume exposed to > 4500 cGy could be limited and comparable in two groups as PLN added and P + SV groups. R and B side effects could be diminished in the PLN added group if IMRT was used and if the expected treatment-related side effects could be similar for the P + SV group [21]. In the present study, radiation exposed R and B volumes were higher in the PLN added group in comparison to the P+SV group. Although mean and maximum R and B doses, and volume exposed to >45 Gy were comparable in both groups, R and B side effects were relatively higher in the PLN added group. Presumably, high toxicity rate in PLN added group was related to their pretreatment clinical condition. The number of patients with urinary complaints was higher in the PLN added group because they had undergone surgery or had relapsed macroscopic disease or advanced disease stage. Cheng et al. showed that similar side effect rates could be diminished in prostate carcinoma patients that underwent prostatectomy and received IMRT; however, the side effects were still higher compared to patients receiving primary RT. Therefore, different dose constrains should be defined for postoperative cases [17].

Inconsistencies between patient and physician-evaluated toxicity scoring have been noted previously [11,12]. Some authors claimed that patient-evaluated side effect scoring was more reliable since it did include physician's bias [12]. However, in our study there was a good correlation between patient-and physician-assessed R and B side effects scoring like in another study [27]. We believe the reason is RTOG R and B side effects scoring Is mainly based on patients' complaints. Toxicity evaluation is a very important issue in prostate carcinoma since RT improves only disease-specific survival and metastases-free survival [28,29]. There is no consensus regarding a positive influence on survival time [8,9]. We believe relapse-free survival is very important for the quality of life. On the other hand, treatment-related morbidity should be accounted for and reduced. Before advocating a treatment, one needs to make sure that it will not decrease the quality of life. For these reasons, we are keen on treatment-related side effects and patient-evaluated toxicity scoring. Because RTOG and EPIC scores depend on patient reporting, patient and physician-evaluated R and B toxicities were in good agreement in this study, as other authors noted previously [30].

Despite reported better disease-free survival, metastases-free survival and biochemical relapse-free survival in PLN irradiation, its use is very limited. We assume that the reason for this is the concern of increasing radiation side effects. According to the results of this small patient experience using IMRT technology, decreased rectum volume exposed to higher radiation dose and PLN irradiation have become safer.

Conclusion

According to the results of the present study, IMRT provides comparable dose distribution for R and B between P+ SV and PLN added groups; PLN irradiation increased acute R toxicity, however had no effect on late R and B toxicity. Combined treatment modalities and pretreatment clinical conditions will influence side effects. Patient and physician-evaluated R and B toxicities were in concordance.

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