Original Article

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Association of Pelvic Lymph Nodes Inclusion with Late Side Effects in Prostate Cancer Patients Undergoing Curative Radiotherapy

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Abstract

Objective: Curative radiotherapy is one of the two leading definitive treatment options for prostate cancer, along with surgery. The inclusion of pelvic lymph nodes in curative radiotherapy for prostate cancer is controversial. In our study, we aimed to investigate the association of pelvic lymph node irradiation with late gastrointestinal system (GIS) and genitourinary system (GUS) side effects in intermediate and high-risk prostate cancer patients who underwent curative radiotherapy.

Materials and Methods: Patients who underwent curative radiotherapy for intermediate and high-risk prostate cancer between 2015 and 2022 were evaluated retrospectively. GIS and GUS side effects were graded according to the Radiation Therapy Oncology Group scale. Patients were divided into 2 groups: those who received treatment of the pelvic lymph node (group 1) and those who received treatment of the prostate and seminal vesicle (group 2). We analyzed whether there was a difference in late GIS and GUS side effects between the groups. The independent samples t-test was used to compare late side effects between the groups. A p-value of $p<0.05$ was considered statistically significant.

Results: Seventy-one patients treated for intermediate and high-risk prostate cancer were analyzed. Thirty seven patients received a radiotherapy regimen in group 1, and 34 patients received a radiotherapy regimen in group 2. Intermediate risk patients received radiotherapy in group 2, and high-risk patients received radiotherapy in the group 1 regimen. The mean age of the patients was 70 years and the mean follow-up period was 39 months. All patients received hormone therapy. Late GUS and GIS side effect rates were found to be extremely low. There was no statistically significant difference between the groups in terms of side effect rates.

Conclusion: In localized prostate cancer, including pelvic lymph nodes in the treatment area does not increase long-term GIS and GUS side effects.

Keywords: Prostate cancer, radiotherapy, side effect, pelvic lymph node irradiation

Introduction

Curative radiotherapy is one of the two leading definitive treatment options in prostate cancer along with surgery. The different side effect profiles of the applied modalities play a role in the choice of treatment (1,2). Gastrointestinal system (GIS) and genitourinary system side effects that may develop after curative treatments for localized prostate cancer are possible complications and may cause morbidity in the patient's life (3-5). The inclusion of pelvic lymph nodes in curative radiotherapy for localised prostate cancer is a controversial issue. Although some studies have found that pelvic radiotherapy is not beneficial, other studies have found that it may increase progression-free survival (PFS), disease-free survival (DFS) and biochemical recurrence-free survival (BRFS). Studies suggest that the practice of including pelvic lymph nodes based on the risk of lymph node involvement has gained prominence (6-9). To assess the risk of lymph node involvement, the Roach formula has been used (10). If the risk is above 15%, the inclusion of pelvic lymph nodes is recommended. When including pelvic lymph nodes, the question that the treatment-related side effect profile may increase comes to mind. In our study, we aimed to investigate the relationship between pelvic lymph node irradiation and late GIS and GUS side effects in intermediate and high-risk prostate cancer patients who underwent curative radiotherapy.

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Materials and Methods

The study protocol was approved by the Clinical Research Ethics Committee of Gaziantep City Hospital (approval number: 32/2024, date: 26.6.2024). Patients who underwent curative radiotherapy for intermediate and high-risk prostate cancer between 2015 and 2022 were retrospectively evaluated. Patients who received postoperative-adjuvant radiotherapy, as well as those with low-risk prostate cancer, lymph node involvement, or distant metastasis, were excluded from the study. GIS and GUS side effects were graded according to the Radiation Therapy Oncology Group (RTOG) scale (Table 1). Toxicities were graded and recorded by the physicians during outpatient follow-up. Side effects 6 months after the end of radiotherapy were defined as late side effects. Patients were divided into 2 groups: those who received treatment to the pelvic lymph node (group 1) and those who received treatment to the prostate and seminal vesicle (group 2). Intermediate risk patients received radiotherapy in group 2 and high-risk patients received radiotherapy in group 1 regimen. As per our department policy, all high-risk patients underwent pelvic irradiation, and intermediate-risk patients underwent prostate and seminal vesicle irradiation. In group 1, obturator, external iliac, internal iliac, and distal common iliac lymph nodes were included in the treatment area. All patients received radiotherapy with the intensity-modulated radiation therapy (IMRT). Quantitative Analysis of Normal Tissue Effects in the Clinic dosimetric limitations were followed in radiotherapy planning. We analyzed whether there was a difference in late GIS and GUS side effects between the groups.

Statistical Analysis

A normal distribution test was performed with the Kolmogorov-Smirnov test. Independent samples t-test was used to compare the late side effects between the groups. P<0.05 was accepted for statistical significance. SPSS version 23.0 was used for the statistical analysis of this study.

Results

Seventy-one patients treated for intermediate and high-risk prostate cancer were analyzed. Thirty seven patients received radiotherapy regimen in group 1 and 34 patients in group 2. The mean age of the patients was 70 years (52-85) and the mean follow-up period was 39 months (9-79). Mean pretreatment prostate-specific antigen (PSA) (ng/mL) was 27.3 (range: 5-188), and mean testosterone was 3.2 (ng/dL). The mean prostate size before radiotherapy was 47 cubic centimeters (11-128), and there was no significant difference between the groups. The mean positive quadrant ratio in prostate biopsy was 46% (7-100) and was significantly higher in the high-risk group (p<0.01). Half of the patients had no comorbidities before treatment, while the most common comorbidities were hypertension, coronary artery disease, and diabetes mellitus. None of the patients had bowel disease before radiotherapy. Patient characteristics are shown in Table 2. Patients in group 1 received 46 Gy to the pelvis, 54 Gy to the prostate + seminal vesicle, and 78 Gy to the prostate. Patients in group 2 received 54 Gy to the prostate and seminal vesicle and 76-78 Gy to the prostate. The mean PSA value within 1 month after radiotherapy was 0.55 (range: 0-12), and there was no significant difference between the groups. All patients received hormone therapy, and the mean duration of hormone therapy was 24 months (6-72). Neoadjuvant hormone therapy was administered to 32% of the patients. There was no significant difference in side effect rates between patients who received neoadjuvant hormone therapy and those who did not. The rates of late GUS and GIS side effects are shown in Figures 1 and 2, and were found to be extremely low. Observed grade 2 GUS side effects were nocturia and dysuria, while GIS side effects were rectal bleeding and tenesmus. It is noteworthy that a grade 3 GUS side effect was seen in only 1 patient, and the patient underwent surgery because of urethral stenosis. A Grade 3 GIS side effect was not observed. There was no statistically significant difference between the groups in terms of side effect rates.

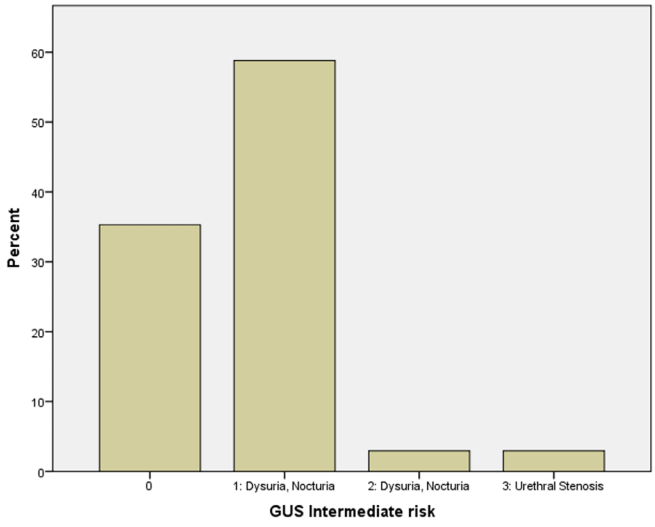
Table 1. RTOG late toxicity grading

0: No symptoms
1: Mild symptoms that do not require treatment
2: Symptoms that improve with local - non-invasive treatment and do not significantly affect daily life
3: Serious symptoms that do not require immediate intervention; hospitalization may be required
4: Life-threatening symptoms
5: Death due to side effects
RTOG: Radiation Therapy Oncology Group

Table 2. Patient characteristics

Patients number	Group 1	37
	Group 2	34
Age	Group 1	70.8 (49-88)
	Group 2	70.2 (57-81)
Follow-up	Group 1	42.6 (13-62)
	Group 2	34.8 (9-79)
Comorbidity (%)	Group 1	51.3
	Group 2	47
Pretx PSA (ng/dL)	Group 1	43.6 (5-188)
	Group 2	10 (3.4-18.4)
Pretx testosterone (ng/dL)	Group 1	3.5 (1-12)
	Group 2	3 (1.3-5.5)
Pretx prostate size (cc)	Group 1	43.8 (11-88)
	Group 2	51.7 (18-128)
Positive quadrant ratio in Bx (%)	Group 1	68.3 (7-100)
	Group 2	35.9 (7-80)
ADT duration (m)	Group 1	41(15-66)
	Group 2	6 (6-9)
Neoadjuvant ADT	Group 1	37.8%
	Group 2	26.5%
Radiotherapy dose (Gy)	Group 1	78
	Group 2	76 (76-78)

PSA: Prostate-specific antigen, ADT: Androgen deprivation therapy, Bx: Biopsy



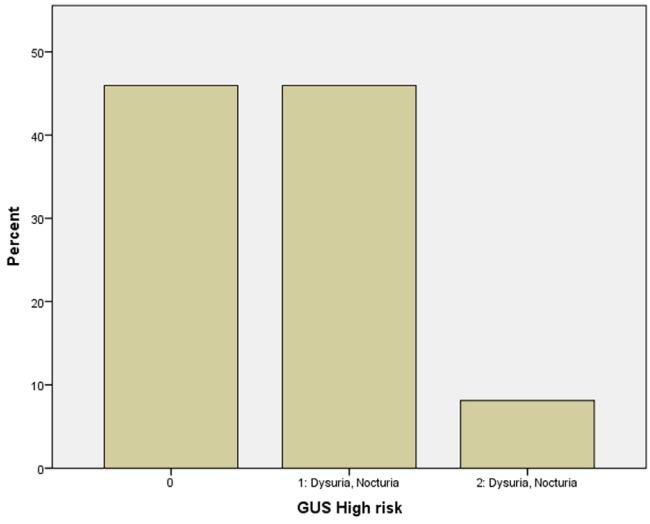
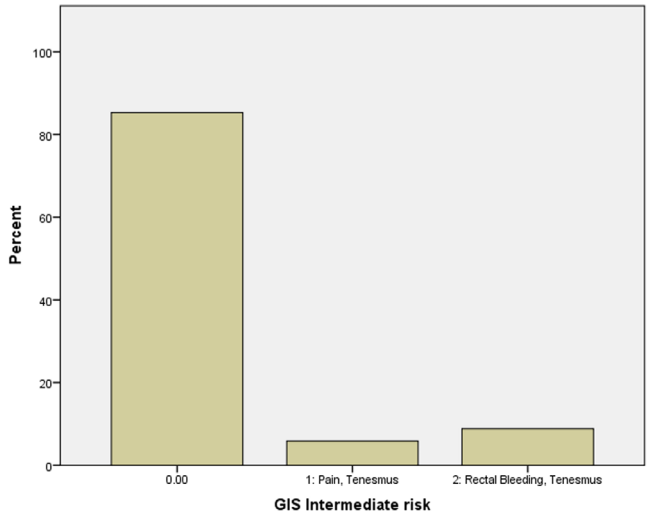


Figure 1. Late GUS side effect rates

GUS: Genitourinary system



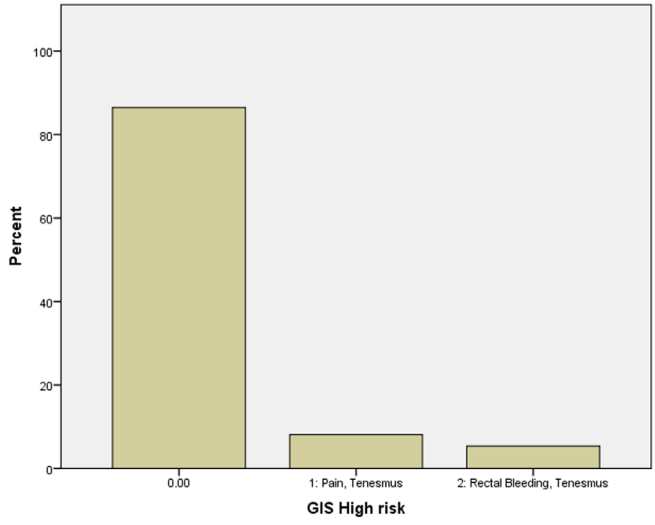


Figure 2. Late GIS side effect rates

GIS: Genitourinary system

Discussion

Elective pelvic field irradiation in localized prostate cancer radiotherapy is controversial. In the RTOG 9,413 study, patients with a risk of lymph node involvement >15% were included (6). There is a 2x2 study design defined by hormone therapy initiation time (neoadjuvant-adjuvant) and radiotherapy area (pelvic lymph node included and prostate-only irradiation group). As a result of the study, PFS was higher in the group that received neoadjuvant hormonotherapy + pelvic lymph node treatment; than in the group that received neoadjuvant hormonotherapy + prostate-directed radiotherapy; and adjuvant hormonotherapy + pelvic lymph node radiotherapy. In the Gastrointestinal Tumor Study Group-01 study, no benefit of pelvic lymph node irradiation was found (7). In the POP-RT study, it was found that BRFS and DFS rates increased with pelvic lymph node irradiation in the patient group with an estimated lymph node involvement risk ≥20 percent (8). In the systematic review by De Meerleer et al., (9) it was reported that pelvic lymph node irradiation was beneficial in patients with a lymph node involvement risk of ≥35% according to the Roach formula. In the literature, according to Roach's formula, pelvic lymph node irradiation may be beneficial considering the risk of lymph node involvement. In our study, pelvic radiotherapy was applied to high-risk patients according to our clinical protocol, but not to intermediate-risk patients.

Survival in localized prostate cancer is long and GIS and GUS side effects related to definitive radiotherapy may affect the quality of life of patients (3-5). Whether long-term GIS and GUS toxicities are increased in patients who receive pelvic lymph node irradiation compared to patients who receive prostate-only radiotherapy, is a question that needs to be answered. In our study, no increase in long-term toxicity was found with pelvic radiotherapy. In a retrospective study conducted by Deville et al. (11) on patients who received definitive radiotherapy using IMRT, no difference was observed in late GIS and GUS toxicities, although an increase was observed in rectal and bladder dosimetric parameters in the pelvic lymph node

irradiated group compared to the other group. In the study conducted by Ogino et al., (12) the rate of serious toxicities was found to be very low in both groups and no significant difference was found between the toxicity rates the groups. In this study, volumetric-modulated arc therapy (VMAT) was used as the planning technique. It was emphasized that it would not be correct to omit pelvic radiotherapy in high-risk prostate cancer considering the toxicities. In a retrospective dosimetric analysis by Guckenberger et al. (13) using the IMRT technique, it was concluded that pelvic lymph node irradiation did not increase bladder and rectal toxicity, although it could increase normal organ doses. In Takemura et al.'s (14) retrospective study including 112 high-risk prostate cancer patients who received pelvic field radiotherapy, late GIS and GUS side effects were found to be extremely low. In this study, VMAT was used for radiotherapy planning. In studies comparing different radiotherapy techniques in prostate cancer, it is noteworthy that in terms of normal organ sparing is better with IMRT and VMAT than with 3-dimensional-conformal radiotherapy (15,16). In curative radiotherapy for localized prostate cancer using IMRT and VMAT, including the pelvic area in the treatment does not increase long-term toxicities. The result obtained in our study is consistent with the literature data. Based on the results of our study, we conclude that if we use advanced radiotherapy techniques, there is no need to avoid pelvic radiotherapy for localized prostate cancer.

Study Limitations

The retrospective nature and the relatively small number of patients are among its limitations.

Conclusion

In curative radiotherapy for localized prostate cancer using IMRT and VMAT, including the pelvic lymph nodes in the treatment area does not increase long-term toxicities. It is not a logical approach to omit pelvic lymph node treatment because of increased side effects.

Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of Gaziantep City Hospital (approval number: 32/2024, date: 26.6.2024).

Informed Consent: Retrospective study.

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Contribution: There is not any contributors who may not be listed as authors.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.U.A., Concept: S.U.A., M.S., Design: S.U.A., M.S., Data Collection or Processing: S.U.A., M.S., Analysis or Interpretation: S.U.A., M.S., Literature Search: S.U.A., M.S., Writing: S.U.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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