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SBRT in the treatment of prostate cancer nodal relapse: A single-center experience and a brief literature review

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Abstract

Nodal recurrence after primary treatment of prostate cancer is increasingly encountered in the clinic. Although there is no specific recommended technique and dose schedule for radiotherapy applications, stereotactic body radiotherapy (SBRT) applications have been reported in most studies. This study aimed to retrospectively report the cases that underwent SBRT for prostate cancer nodal recurrence. Patients diagnosed with prostate cancer due to isolated nodal recurrence and undergoing SBRT were evaluated retrospectively. The patients' radiotherapy doses and target volume details were obtained from the technical file and planning system patient files and patient interviews. The primary endpoint of the study was a disease-free survey (DFS). Data were recorded and analyzed using SPSS ver. 24. The time from relapsed nodal SBRT to recurrence in or out of the SBRT area was defined as DFS after nodal RT. Kaplan Meier test was used for survival analysis. In the current study, a total of 10 field irradiation of 8 patients with prostate cancer who underwent RT for nodal recurrence between 16.8.18-18.2.21 in Ankara City Hospital were evaluated retrospectively. In the follow-up after diagnosis, isolated nodal recurrence developed in all the patients. The median DFSprimer was 6.9 (range 1.1-31.3) months. Median follow-up time after RT for nodal recurrence mean follow-up is 7 months (range 1-31.3). The median DFSafternodalRT was 3.5 months (range 1-26 months). During the follow-up period, intra-field recurrence was observed in one patient and extra-field recurrence was observed in two patients, and a total of 3 recurrences were observed. According to the results of the analysis, N stage at the time of diagnosis with DFSafternodalRT (p0.24); T stage at diagnosis (p0.47); diagnosis GS (p0.28); risk group at the time of diagnosis (p0.53); initial therapy (p0.67); baseline RT area (p0.057), presence or absence of surgery (p0.35); type of surgery (p0.64); PSA at diagnosis (p0.56); the relationship between the first RT dose (p0.053) were not statistically significant. The median duration of local-DFSafternodalRT is 3.7 months (Range 1-30 months). During the follow-up period, only one patient in the irradiated area had a recurrence. This case was unresponsive after RT and progression were observed. Nodal recurrence after RT Local-DFSafternodalRT diagnosis N stage (p0.28); T stage at diagnosis (p.36); diagnosis GS (p0.24); PSA at diagnosis (p0.52); risk group at the time of diagnosis (p0.57); initial therapy (p0.71); presence or absence of surgery (p0.38); type of surgery (p0.68); The relationship between the first RT total dose (p0.056), first RT areas (p0.054) were not statically significant. The only patient who did not respond and had local recurrence was the case who progressed after treatment, the primary RT area was quite large, and LV and PLN irradiation of the prostate lodge was performed. SBRT is a treatment choice for nodal recurrent prostate cancer; however, optimal dose scheme and timing are not determined.

Keywords: Prostate cancer, recurrence, radiotherapy

Introduction

With the advances in imaging methods and the new Positron Emission Computerised Tomography (PET-CT) tracers specific to prostate cancer, patients with nodal recurrence are increasingly seen in the clinic. Previously, only hormonal therapy was applied to these patients. However, local treatments came to the fore in well-selected patients after the benefit of metastasis-targeted treatments was demonstrated [1,2]. One of the reasons for applying local treatment in oligorecurrent disease is the postponement of systemic treatment in the group that can be considered low risk. Another aim is to destroy the castration-resistant clone that may be found in the recurrence area with local treatments and thus to increase the success rate of hormone therapy. Although there is no standard treatment scheme in this patient group today, salvage surgery-LND and salvage RT are modalities that can be used to treat recurrent nodal disease [3-7]. However, data on optimal timing, dose, and technique for each treatment modality are limited, and the optimal treatment scheme has not yet been developed.

Stereotactic body radiotherapy (SBRT) is an ablative treatment method by applying radiotherapy to the target with high accuracy and high dose with a limited number of fractions, together with the developing technology. Although it was applied only to cranial targets before, it can be applied to different body parts thanks to the developing technology [8,9]. In the latest guideline of the

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European Association of Urology (EAU guide 2020 European Association of Urology), metastasis-targeting therapy was defined in patients with relapsed cN1 and well-selected M1 after local treatment. Radiotherapy or SBRT and surgery were specified as treatment modalities that could be used in this definition [10].

There are limited data on the use of SBRT in the treatment of prostate cancer nodal recurrence. This study, it was aimed to present the treatment details, treatment side effects, and treatment results of patients who underwent stereotactic body radiotherapy for nodal recurrence of prostate cancer in our clinic. Besides, the literature on the subject has been searched and summarized in tables. It is also aimed to present a general review of SBRT for prostate cancer nodal recurrence.

Materials and Methods

Among the patients diagnosed with prostate cancer with isolated nodal recurrence in our center, patients treated with SBRT were analyzed retrospectively. The data of the cases were obtained from the hospital follow-up file, the technical file of the radiotherapy, and the patient phone calls. One patient whose follow-up data could not be reached was excluded from the study. The patients' radiotherapy doses and target volume details were obtained from the technical file and planning system patient files and patient interviews. The primary endpoint of the study was a disease-free survey (DFS). The time from diagnosis to nodal recurrence was expressed as DFS primary. The start date for DFSprimer is the date of diagnosis; the end date is the date of nodal recurrence. The time to RT after nodal recurrence was expressed as DFSafternodalRT. The start date for DFSafternodalRT was determined as the last day of RT for nodal recurrence; the end date was the relapse date for relapsed patients (both infield and outfield) and the last control date for non-relapsed patients. In DFSafternodalRT, both in-field and out-field recurrence were included. In addition, local-DFSafternodalRT was also calculated, in which out-of-field recurrence was excluded and only intra-field recurrences were evaluated. The start date for local-DFSafternodalRT was determined as the last day of RT for nodal recurrence; the end date was the infield relapse date and the last control date for non-relapsed patients. Ethics committee approval of the study was obtained from Ankara City Hospital No. 1 ethics committee.

Statistical analysis

Data were recorded and analyzed using SPSS v.24. Kaplan Meier test was used for survival analysis. The conformity of the variables to the normal distribution was evaluated by visual and analysis methods, and non-parametric tests were used as it was seen that they did not fit the normal distribution. Categorical demographic characteristics of the patients were calculated with Chi-square and Fisher's exact tests. Kaplan-Meirer was used in univariate survey analyzes and compared with the log-rank test. Cox regression test was used in multivariate analysis. A statistically significant limit was accepted as below 0.05.

Results

In the current study, 10 different radiotherapy-target areas, which were treated between 03.12.20 and 17.10.18 and applied RT for nodal recurrence of 8 prostate cancers, were evaluated. The median age of the patients was 62 (range 50-71). The median PSA at the time of diagnosis was 19.6 (range 8.15-105). At the time of diagnosis, 5 of 8 patients (62.5%) were N0; 3 (37.5%) patients were N1; 4 (50%) patients were T2 and 4 (50%) were T3. At the time of diagnosis, the Gleason score was 5 patients (62.5%) 7; it was 9 in 3 (37.5%) patients and 6 (75%) of the patients are high risk, while 2 (25%) are medium risk. As the initial treatment, RT was applied to all patients, and the treatment details are as follows: only RT rot 1 (12.5%) patient; surgery and RT for 3 (37.5%) patients; RT and HT for 3 (37.5%) patients; surgery, RT and HT for 1 (12.5%) patient. Initially; 3 (37.5%) patients had only prostate lodge RT; 4 (50%) patients had Prostate + LV RT and 1 (12.5%) patient had Prostate, SV, and Pelvic LN RT. The first RT total dose is median 73 (range 66-80). Surgery was performed in 4 patients in total, RP was performed in 1 (12.5%) patient and RP+PLND was performed in 3 (37.5%) patients. No side effects were observed in 2 (25%) patients in the primary treatment; Grade 1 side effects in 4 patients (50%); 2 (25%) Grade 2 side effects were observed. The median follow-up period of the patients is 7 (range 1-26) months and there is no ex during the follow-up period (Table 1).

Table 1. SBRT dose schema and recurrence information

Lesion Number (Patient)	Location	SBRT dose/frc	Recurrence at the same nodal target	Recurrence at the different distant metastases
1 (Pt1)	Left common iliac	35 Gy/5 frc	Yes @22 mo	Yes @ 18 mo
2 (Pt 1)	Left external iliac	35 Gy/5 frc	No	Yes @4 mo
3 (Pt 1)	Paraaortic and left common iliac	35 Gy/5 frc	No (follow up after last treatment:8 mo)	No
4 (Pt 2)	Right internal iliac	32.5 Gy / 5 frc	No (followup:10 mo)	No
5 (Pt 3)	Left internal iliac	35 Gy/5 frc	No (follow up: 11 mo)	No
6 (Pt 4)	Left external iliac	30 Gy /3 frc	No (follow up 24 mo)	No
7 (Pt 5)	Left external iliac and paraaortic	30 Gy/5 frc	Yes @3 mo	Yes
8 (Pt 6)	Bilateral internal iliac	35 Gy/5frc	No (follow up: 19 mo	No
9 (Pt 7)	Right internal iliac	25 Gy/5 frc	No (follow up: 11 mo	No
10 (Pt 8)	Right obturator	45 Gy/10 frc	No (follow up: 14 mo)	No

In the follow-up after diagnosis, isolated nodal recurrence developed in all the patients. The date of nodal recurrence from diagnosis was defined as DFSprimer and the median DFSprimer was 6.9 (range 1.1-31.3) months. The median PSA value at the time of the first recurrence is 1.7 (range 0.98-3) There were 2 intra-irradiated and 3 extra-irradiated nodal recurrences. (Table 2 and 3). Median follow-up time after RT for nodal recurrence mean follow-up is 7 months (range 1-31.3). The median DFSafternodalRT was 3.5 months (range 1-26 months). Detailed COX regression analysis was performed for DFSafternodalRT. According to the results of the analysis, N stage at the time of diagnosis with DFSafternodalRT (p0.24); T stage at diagnosis (p0.47); diagnosis GS (p0.28); risk group at the time of diagnosis (p0.53); initial therapy (p0.67); baseline RT area (p0.057), presence or absence of surgery (p0.35); type of surgery (p0.64); PSA at diagnosis (p0.56); the relationship between the first RT dose (p0.053) were not statistically significant.

Table 2. Trials of nodal dissection at nodal recurrence for prostate cancer

Study	Patient number	Primary treatment	Imaging modality for nodal recurrence	Salvage Surgery	BCR free survival	CR free survival	Time to ADT	Med fu
Suardi et al. 2014 [8]	59	RP	11C-choline PET/CT	Pelvic± Retroperitoneal LND	22.1% @8 yr	38.2% @8 yr	ADT 1 yr after salvage LND 44.1% ADT 3 yr after salvage LND 62.7% ADT 5 yr after salvage LND 66.1%	81 mo
Bravi et al. 2020 [9]	189	RP	11C-choline PET/CT or PSMA PET/CT	Pelvic± Retroperitoneal LND	11% @10yr	31% @ 10 yr	Med time 41 mo	87 mo
Claeys et al. 2014 [10]	17	RP RT High-intensity, focused ultrasound	11C-choline PET/CT or PSMA PET/CT	Extended SLND	Med 4.1 mo	NS	NS	22 mo
Tilki et al. 2015 [11]	58	RP	18F-fluoroethylcholine PET/CT	Pelvic± Retroperitoneal LND	0% @5 yr	35.9% @5 yr	NS	39 mo

Abbreviations; PET/CT: Positron Emission Tomography, SLND: Salvage Lymph Node Dissection, BCR: Biochemical Recurrence, CR: Clinical Recurrence, ADT: Androgen Deprivation Therapy, fu: follow up, mo: month, PSMA: Prostate-Specific Membrane Antigene, RP: Radical Prostatectomy, NS: Non-specified.

Table 3. Trials of SBRT at nodal recurrence for prostate cancer

Study	Patient number	Primary therapy	Imaging modality for recurrence	Fractionation Scheme	Recurrent Lymph node number-localization	Time to biochemical recurrence	Time to ADT	Follow up
Oehler, 2019[18]	25	RP ± salvage RT	18F-Choline PET/CT	10 Gy x3 frc 11 Gy x 3 frc 12 Gy x 3 frc 13 Gy x 3 frc 15 Gy x 3 frc	1-3 N1 and M1a	Med 11.9 mo	32% @18mo	Med 18 mo
Ponti, 2015[19]	16	-Definitive RT, -RP+Salvage RT, -BRT	11C-choline PET/CT	12 Gy x1 frc 7.5 Gy x4 frc 8 Gy x 4 frc 7 Gy x 5 frc	1-2 Upper abdomen, Lower abdomen SCV	45% @ 2 yr	Mean 23.7% mo	Med 29.38 mo
Loi 2018[20]	23	--NSRP Definitive RT	18F-choline PET/CT	24 Gy x 1 frc	1-2 Pelvic	26% @2 yr	Med 18 mo	Med 22 mo
Ingrosso 2017 [21]	40	-EBRT, -prostatektomi± LND, -RP+PORT, -BRT	11C-choline PET/CT PET/CT	12 Gy x 1 frc 5Gy x 5 frc 7.5 Gy x 4 frc 6 Gy x 5 frc 8 Gy x 4 frc 7 Gy x 5frc 8 Gy x 5 frc 10 Gy x 5 frc	Pelvic, SCV	44% @ 2 yr	40% ADT free @2 yr	Med 30.18 mo
Detti, 2015[22]	30	-RP ± adjuvant RT + HT, -Definitive RT ± HT	11C-choline PET/CT	24 Gy x 1 frc 9 Gy x 3frc 10 Gy x 3rc 6 Gy x 5 frc 12 Gy x 3 frc	Pelvic	NS	NS	Med 12 mo

BRT: Brachytherapy, SCV: supraclavicular fossa, RP: Radical prostatectomy, RT: radiotherapy, EBRT: external beam radiotherapy, PORT: Postoperative radiotherapy, BRT: Brachytherapy, frc: fraction, NS: non-specified

The median duration of local-DFSafternodalRT is 3.7 months (Range 1-30 months). During the follow-up period, only one patient in the irradiated area had a recurrence. This case was unresponsive after RT and progression were observed. Nodal recurrence after RT Local-DFSafternodalRT diagnosis N stage (p0.28); T stage at diagnosis (p.36); diagnosis GS (p0.24); PSA at diagnosis (p0.52); risk group at the time of diagnosis (p0.57); initial therapy (p0.71); presence or absence of surgery (p0.38); type of surgery (p0.68); the relationship between the first RT total dose (p0.056), first RT areas (p0.054) were not statically significant. The only patient who did not respond and had local recurrence was the case who progressed after treatment, the primary RT area was quite large, and LV and PLN irradiation of the prostate lodge was performed.

Discussion

In the current study, 10 irradiation field data of 8 patients were analyzed retrospectively. In the median follow-up period of 7 months, DFSafternodalRT is 3.5 months and local-DFSafternodalRT is 3.7 months. No serious toxicity of SBRT was observed for isolated nodal recurrence of prostate cancer. No statistically significant relationship was found between DFSafternodalRT, local-DFSafternodalRT, and the parameters examined in the study. However, the relationship between the first RT total dose and the first RT field width DFSafternodalRT, local-DFSafternodalRT are close to the limit of statistical significance. This relationship may become statistically significant with the increase in the number of patients.

Thanks to improved imaging methods, patients with prostate cancer with nodal recurrence are increasingly seen in the clinic. Previously, only hormonal therapy was applied to these patients. However, local treatments came to the fore in well-selected patients after the benefit of metastasis-targeting treatments was demonstrated. One of the reasons for applying local treatment in oligorecurrent disease is the postponement of systemic treatment in the group that can be considered low risk. Another aim is to destroy the castration-resistant clone that may be found in the recurrence area with local treatments and thus increase the success rate of hormone therapy. Although there is no standard treatment scheme in this patient group today, salvage surgery-LND and salvage RT are modalities that can be used to treat recurrent nodal disease [11-13].

Since we are a new center, the number of patients is limited. Although the follow-up period is short, local control rates are satisfactory with SBRT. On the other hand, it is not possible to generalize because of the differences in the dose schedules and safety margins applied by the clinician and differences between the systemic treatment schedules of the patients.

Even in the early stages of biochemical recurrences with PET-CT, the onset of nodal oligo-recurrent diseases has made local treatments important in this patient group. One of the important studies that showed improvement in clinical outcomes with local treatment is the study of Steuber et al., in which metastasis targeting therapy (n=263) and standard approach (n=1812) patients were compared in a large case series. Metastasis targeting therapy consisted of salvage LN resection (n = 166) and stereotactic ablation RT (SABR) (n = 97). After a mean follow-up of 70 months, the MDT group showed significantly better CSS (5-year survival 98.6% vs. 95.7%, $p < 0.01$) [1].

There are no randomized studies comparing radiotherapy and surgical treatments for local nodal recurrence. Success has been demonstrated with both treatments. However, surgery can be applied primarily on experienced centers in medically fit patients who can undergo LND. At the same time, radiotherapy is mainly preferred in patients who cannot be operated on due to medical reasons and who cannot undergo surgical dissection due to their anatomical location. Again, it is thought that there is a tendency to radiotherapy due to reasons such as postponing surgeries under pandemic conditions.

SLND at nodal recurrence

Studies evaluating the success of LND dissection in patients with pelvic nodal recurrence after radical prostatectomy are presented. Although the type of lymph node resection applied in the studies is similar, the tracers used to detect recurrence differ.

In a new study evaluating the types of surgical dissection to be performed in nodal recurrence after radical prostatectomy, the pathological positivity rate of the contralateral LN station was evaluated in patients with unilateral LN positivity detected by PET. In this context, it was determined that the group with the lowest risk of contralateral LN involvement was the patients scanned with PSMA PET and were positive for a single LN. It was stated that bilateral LN dissection could not be performed in this patient group [15].

Suardi et al. In their study where they evaluated the long-term results of salvage LN dissection in patients with prostate cancer nodal recurrence, they reported the results of 59 patients. In this study, LN recurrences were detected with 11C-choline PET/CT, and Pelvic and/or retroperitoneal salvage LND was applied in the treatment. Although biochemical recurrence is observed in most patients, clinical recurrence-free survival was observed in 40% [14].

Radiotherapy at nodal recurrence

Radiotherapy is another treatment method used in nodal recurrences after primary treatment of prostate cancer. Although conventional or hypofractionated schemes are applied in the studies, it is seen that the primary treatment modality and the prevalence of the recurrent disease generally affect the selection [18-20].

In a study conducted in Switzerland, the choice of centers was questioned through a questionnaire when deciding on radiotherapy and hormonotherapy in patients with pelvic nodal recurrence. At the end of the study, it was reported that the general performance status of the patients was influential in the choice of treatment and that ADT was mainly applied in medically unfit patients. In medical fit patients, it has been emphasized that the prognostic features of the disease and then the number of involved lymph nodes are effective in the decision to use radiotherapy scheme and simultaneous hormonal therapy in the treatment decision. Accordingly, SBRT alone is primarily recommended in patients with medical fit who have favorable features and one LN metastasis. In contrast, combined hormonal therapy with pelvic radiotherapy in the pelvic region is recommended if multiple LN involvement

is observed in patients with medical fit unfavorable features [18].

A recent review evaluated the efficacy of ADT administered intermittently with involved-field SBRT in nodal recurrence of hormone-sensitive prostate cancer. The researchers suggested that the hypothesis of eliminating castration-resistant disease with radiotherapy and thus prolonging survival with ADT may be effective in cases with a limited number of nodal metastases in this treatment scheme. However, different radiotherapy recipients and fraction schemes make it difficult to generalize [21].

There are also studies evaluating elective nodal irradiation (ENI) in nodal recurrence of prostate cancer. Tran et al. Long-term results of 58 disease series in which ENI and ADT were used together were reported in 2018. In this study, after a median follow-up after ENRT of 44 months (range, 2 to 133), the 5-year biochemical disease-free and distant progression-free survival (DPFS) rates were 43% and 58%. Again, in the same study, it was reported that DPFS was worse in cases with a PSA doubling time of <3 months [22]. It is thought that the results of STORM, which is a phase II study like this, will provide more information about the radiotherapy recipient and dose selection, and the results are eagerly awaited [23].

Prostate Cancer In isolated nodal recurrences, SBRT was mainly chosen as the radiotherapy scheme, and its results were reported. These studies are summarized in Table 3.

One of the current studies comparing ENI and SBRT in Metastasis Targeting Therapy is the study of Bleser et al., based on a retrospective analysis of 506 patients. This multicenter study reported that SBRT was applied to 309 patients, and ENI was applied to 197 patients. The primary endpoint was metastasis-free survival. ENRT was associated with fewer nodal recurrences compared with SBRT ($p<0.001$). In a multivariable analysis, patients with one LN at recurrence had longer MFS after ENRT (hazard ratio: 0.50, 95% confidence interval 0.30–0.85, $p = 0.009$). Late toxicity was higher after ENRTcompared with that after SBRT (16% vs. 5%, $p<0.01$). Limitations include higher use of hormone therapy in the ENRT cohort and non-standardized follow-up [2].

Study limitations

The number of cases in this study is minimal. On the other hand, the treatment schemes applied at the first diagnosis and the systemic treatment methods and durations followed also differ. The doses administered and the biologically effective dose equivalents also differ. Due to all these factors, it is not possible to generalize the results of the study.

Conclusion

Prostate cancer nodal recurrence is increasingly encountered in the clinic with advances in systemic therapy and breakthroughs in imaging methods. Although no randomized study shows the overlap between treatment modalities, it is debatable whether this generalization can be reached for patient groups with different treatment and disease characteristics. Again, data on which technique (SBRT vs. ENI) and which dose schedules should be applied in radiotherapy are very limited. Although the scheme widely used in this study is 35Gy/5 frc, there is a need for studies in which more cases are evaluated in terms of biologically effective doses.

Conflict of interests
The authors declare that they have no competing interests.

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Ethical approval
Ethics committee approval of the study was obtained from Ankara City Hospital No. 1 ethics committee.

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