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Treatment outcomes in high-risk prostate cancer: a single-centre experience

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ABSTRACT

Aim: The aim of that study was to evaluate the treatment results of patients with high-risk prostate cancer who received image-guided intensity-modulated radiotherapy with curative intent.

Material and Method: Patients who underwent curative radiotherapy (RT) for high-risk prostate cancer were evaluated retrospectively in our clinic from April 2010 to April 2021. Demographics, prostate specific antigen (PSA) levels, gleason score (GS), the TNM stage of the tumor, and the success of treatment and complications were noted.

Results: Eighty-two patients were evaluated. The mean follow-up time was 39.1 months. The mean age was 71.2±6.2 (range 50-84 years) years. The mean PSA levels of the patients was 41.1±33.8, and the median was 27 ng/ml (range 8-129 ng/ml). The mean GS of the patients was 8.3±0.6, and the median was 8 (range 7-10). The mean overall survival (OS) rate was 75.6%; survival rates for 24 months and 36 months were 91.1% and 80.4% respectively. The progression-free survival (PFS) was found to be 62.8%. Moreover, the PFS time was found to be 66,6 months. Twenty-four months and 36 months PFS rates were 83.6% and 65.4%, respectively.

Conclusion: Intensity-modulated radiotherapy (IMRT) combined with androgen deprivation therapy is a safe and effective treatment modality for elderly patients with high-risk prostate cancer.

Keywords: Prostate cancer, IMRT, high risk, treatment

INTRODUCTION

With a projected 1 414 259 new cancer cases and 375 304 deaths in 2020, prostate cancer is the second most commonly diagnosed cancer and the sixth leading cause of cancer mortality among men globally (1). Prostate cancer is categorized as very low risk, low risk, intermediate-risk, high risk, and very high risk according to PSA levels, GS, and TNM stage. Most patients with low-risk diseases can safely prefer active surveillance, while RT or radical prostatectomy (RP) is curative for patients with intermediate-risk prostate cancer (2). Radical prostatectomy or external beam radiotherapy with androgen deprivation treatment (ADT) should be considered for high-risk prostate cancer patients with PSA levels greater than 20 ng/ml, Gleason grade group 4 or 5, and/or clinical stage T3 or higher. Patients with high-risk prostate cancer are at an increased risk of oncological progression, so a multidisciplinary treatment approach is recommended for the ideal treatment of high-risk prostate cancer. Whether surgery or RT, treatment-related side effects, such as urinary, bowel, and sexual dysfunction, should be considered regardless of the treatment method chosen. In a systematic review that analysed the benefits and risks of surgery and RT in high-risk patients with localized and locally advanced prostate cancer, quality of life data mainly found that surgery was associated with genitourinary toxicity and sexual dysfunction, and radiotherapy was associated with bowel problems (3). Past studies have compared RP with RT applied to conventional RT techniques; modern RT techniques can deliver high doses to the tumor while minimizing toxicity to healthy tissues. So, RT-related side effects decreased with technological advances in radiotherapy. Intensity-modulated radiotherapy is associated with a substantial reduction in acute grade 2 gastrointestinal system (GIS) toxicity with decreasing trend in late grade 2 GIS toxicity (4,5). Pasalic et al. (6) showed that dose escalation from 70 Gray (Gy) to 78 Gy improved biochemical, clinical failure, and prostate cancer-specific mortality. In a study evaluating the efficacy of dose escalation in patients with localized and very high-risk localized prostate cancer: the external beam radiotherapy (EBRT) group treated with 70-72 Gy, the high

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dose EBRT(HDEBRT) group treated with 74-80 Gy, and the high-dose-rate brachytherapy (HDR)+EBRT(HDR boost) groups were compared using multi-institutional retrospective data. In the results of this study, the actuarial 5-year biochemical disease-free survival (bDFS) rate, prostate cancer-specific survival (PSS) rate, and overall survival rate were 75.8%, 96.8%, and 93.5%. Group HDEBRT showed superior 5-year bDFS rate (81.2%) as compared to the group EBRT (66.5%) (p<0.0001) with a hazard ratio of 0.397. Equivocal 5-year PSS (98.3% and 94.8% in group HDEBRT and group EBRT) and OS (93.7%) were found. When the three groups were compared in terms of late grade ≥2 toxicities in gastrointestinal and genitourinary system, the results were found to be similar. Therefore, both HDEBRT and HDR boost could be good options for improving the bDFS rate in cT3-T4 localized prostate cancer without affecting PSS and OS (7).

IMRT with Image Guided Radiotherapy (IGRT) dose-escalated irradiation of prostate cancer has been applied as a standard in our clinic. This study evaluated our institutional experience with high-risk prostate cancer patients treated by definitive high dose IMRT with IGRT.

MATERIAL AND METHOD

The study was initiated with the approval of the University of Health and Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Studies Ethics Committee (Date: 11/12/2021, Decision No:2021-11/3). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration.

We retrospectively reviewed the clinical data of 82 patients treated between April 2010 and April 2021 with IMRT for high-risk prostate cancer. All patients had RT combined with ADT or orchiectomy.In addition to a bone scan, all patients had pelvic computed tomography or magnetic resonance imaging. Prostate-specific membrane antigen positron emission tomography was used on certain patients. Prostate cancer had been histologically verified in men above the age of 18. The inclusion criteria were high-risk prostate cancer according to D'Amico's risk classification criteria (≥T2c or a GS 8-10 or PSA level >20 ng/dl). Patients with clinical pelvic lymph node involvement were not included in the study.All of the patients received IMRT with daily imaging guidance.All treatment plans were generated by using inverse planning and the IMRT technique. The planning CT scan was performed with 3-mm slices in the supine position. RT was delivered in 2 Gy daily fractions with 6 MV photon beams five days a week. In some patients, pelvic lymph nodes were also selectively irradiated. Partin nomograms are used to decide elective pelvic lymph node RT, Pelvic RT applied to patients with pelvic lymph node involvement risk over 20% (8). Prostate and entire seminal vesicles were included in the CTV. The planning treatment volume (PTV) was generated by adding an 8-mm isotropic expansion to the CTV, excepting 6 mm posteriorly. According to the International Commission of Radiation Units and Measurements recommendations, the dose was prescribed at the isocentre. For treatment planning, the dose-volume constraints for the bladder were V65 Gy<50%; for the small bowel V45≤195 cc; for the rectum: V50 Gy≤50%, V60 Gy≤35%, and V70 Gy≤ 20%. Dose constraints for the organs at risk (OAR) were selected based upon Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) data (9). All patients were treated using bowel- and bladder-filling protocols. KV images and a cone beam-CT (CBCT) scan were taken prior to each delivery. Shifts were performed by aligning finally to soft tissue on CBCT.

The information about post-treatment follow-up of the patients was obtained from the hospital files. The treatment outcomes were assessed in biochemical failure, progression free survival (PFS) rates, and OS rates. BF was defined by a nadir PSA level+2 ng/ml. The final status of the patients was checked from the national death notification system.

Statistical analysis

Analyses were evaluated in 22 package programs of SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL).The study shows descriptive data as n and % values in categorical data and mean±standard deviation (Mean±SD) values in continuous data. The Chi-square analysis (Pearson Chi-square) test was used to compare categorical variables between groups. Conformity of continuous variables to normal distribution was evaluated with the Kolmogorov Smirnov test. Kruskal-Wallis test was used in the measurement comparison of more than two groups. Log Rank (Mantel-Cox) analysis was performed to compare overall survivals between categories. The statistical significance level was accepted as p<0.05

RESULTS

The study included 82 patients with high-risk prostate cancer who received IMRT in our radiation oncology department between April 2010 and April 2021. The mean follow-up time was 39,1 months. The mean age was 71.2±6.2 (range 50-84 years) years. The mean PSA value of the patients was 41.1±33.8, and the median was 27 ng/ml (range 8 -129 ng/ml). While 71 (86.6%) of the patients had a PSA level<100 ng/ml, 11 (13.4%) had a PSA level≥ 100 ng/ml. The mean GS of the patients was 8.3±0.6, and the median was 8 (range 7-10). While 52 patients (63.4%) had a GS≤8, 30 (36.6%) had a GS>8.

The TNM stage of 31 (37.8%) patients were T2N0M0, and 51 (62.2%) were T3N0M0 and T4N0M0. The mean RT dose of the patients was 76.4±1.7 Gray (Gy), and the median was 78 Gy (range 74-78 Gy). Twenty-four patients

(29.3%) received 74 Gy RT, 17 patients (20.7%) received 76 Gy RT and 41 patients (50%) received 78 GyRT. Thirty-four (41.5%) patients received pelvic radiotherapy, while the others received only local (including seminal vesicles and prostate) RT. When the last status of the patients was analysed, 49 (59.8%) complete responses, 13 (15.9%) local recurrence, and 16 (19.5%) distant metastasis was observed. There was no follow-up in 4 (4.9%) patients. Twenty (24.4%) deaths were observed during the follow-up time. Fifteen of these deaths (78.9%) were caused by cancer. The OS rate was 75.6%; survival rates for 24 months and 36 months were 91.1% and 80.4% (**Figure 1**).

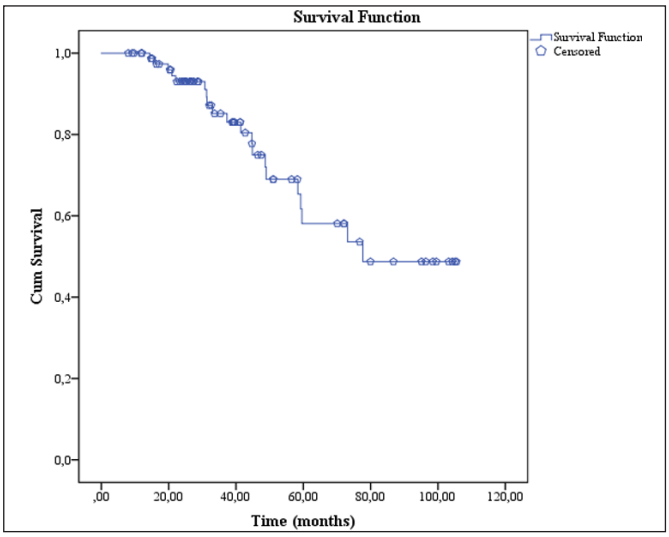

Figure 1. Overall Survival

GIS and genitourinary system (GUS) side effects due to RT were also evaluated according to RTOG toxicity criteria (10). While 52 of the patients (63.4%) had no GIS side effects, 18 (22%) of them had grade 1(increased frequency of bowel habits), and two of them (14.6%) had grade 2 GIS (diarrhea requiring drugs) side effects. While 38 (46.3%) of the patients had no GUS side effects, 33 (40.2%) of them had grade 1 (frequency of urination, urgency not requiring medication) and 11 (13.4%) had grade 2 (dysuria, urgency, bladder spasm) GUS side effects. Patients' characteristics and the results are summarized in **Table 1**.

Table 1. Patients' characteristics and results

		n	%
Age (years) , Mean±SD		71.2±6.2	
PSA (ng/ml)	<100	71	86.6
	≥100	11	13.4
Gleason score	≤8	52	63.4
	>8	30	36.6
TNM stage	II	31	37.8
	III-IVA	51	62.2
RT dose Gy, Mean±SD		76.4±1.7	
Pelvic RT	Yes	34	41.5
	No	48	58.5
GIS side effects	No	52	63.4
	Grade 1	18	22.0
	Grade 2	12	14.6
GUS side effects	No	38	46.3
	Grade 1	33	40.2
	Grade 2	11	13.4
Status at last control date	Complete response	49	59.8
	Local recurrence	13	15.9
	Distant metastasis	16	19.5
	No follow-up	4	4.9
Death	yes	20	24.4
	no	62	75.6
Cause of death	cancer	15	78.9
	Non-cancerous	4	21.1

Abbreviations; SD=standard deviation; RT=Radiotherapy; PSA=Prostate specific antigen GIS=gastrointestinal; GUS=genitourinary

The effects of PSA level, Gleason score, pelvic RT, treatment response, and TNM stage on OS were evaluated. The mean survival rate of those with a PSA value below 100 ng/ml was significantly higher than the mean survival time of those with a PSA value of 100 ng/ml and above (81.7% vs. 36.4%; p<0.001). The OS rate was significantly higher in the complete responder group than in the local recurrences and metastatic group (91.8% vs. 69.2% vs. 25%; p<0.001). There was no significant effect of GS, TNM stage, and pelvic RT on OS (p=0.931, p=0.810, p=0.137). Results of OS and comparison by various parameters are summarized in **Table 2**.

Table 2. Overall survival and comparison by various parameters

		OS rate	Mean	Standard Deviation	95% CI	p*
PSA (ng/ml)	<100	81.7	81.486	5.273	71.152-91.821	<0.001
	≥100	36.4	40.633	5.898	29.074-52.193	
Gleason score	≤8	76.9	79.256	5.882	67.727-90.785	0.283
	>8	73.3	66.191	7.934	50.639-81.742	
TNM stage	T2N0M0	77.4	74.834	7.915	59.321-90.347	0.810
	T3N0M0-T4N0M0	74.5	75.658	6.470	62.977-88.338	
Pelvic RT	Yes	61.8	66.278	6.015	54.488-78.068	0.137
	No	85.4	84.020	7.045	70.211-97.829	
Status at last control date	Complete response	91.8[a]	95.015	4.724	85.755-104.274	<0.001
	Local recurrence	69.2[b]	60.075	11.329	37.871-82.279	
	Distant metastasis	25.0[b]	40.789	4.482	32.006-49.573	

*Log Rank (Mantel-Cox) analysis was performed. Abbreviations: PSA=Prostate specific antigen, RT= Radiotherapy, OS=Overall survival

Local recurrence was observed in 13 patients, and distant metastasis was observed in 15 patients. The PFS rate was found to be 62.8%. The PFS time was found to be 66.6 months. 24-month and 36-month PFS rates were 83.6% and 65.4%, respectively. (**Figure 2**)

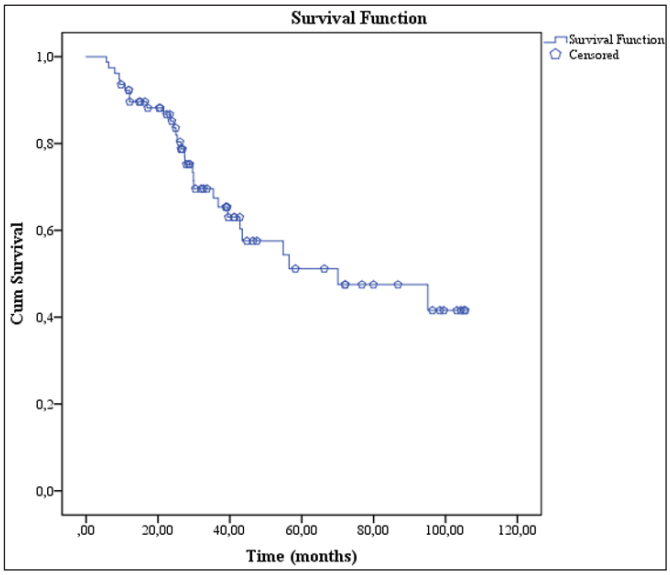

Figure 2. Progression-free Survival

The mean PFS of those with a PSA level<100 ng/ml was significantly higher than the mean survival of those with a PSA level≥100 ng/ml (70.6% vs. 10%; p<0.001). The mean PFS of those with a GS≤8 was significantly higher than the mean of survival of those with aGS> 8 (68.8% vs. 53.3%; p=0.042). There was no significant TNM stage and pelvic RT effect on PFS. Results of PFS and its comparison according to various parameters are summarized in **Table 3**.

For ADT only three patients had orchiectomy before RT, and all other patients received gonadotropin-releasing hormone agonist for 24 months.

Table 3. Progression-free survival and its comparison according to various parameters

	PFS rate	mean	Standard deviation	%95 Confidence Interval	p*
PSA ng/ml					<0.001
<100	70.6	74.110	5.616	63.103-85.117	
≥100	10.0	30.227	6.057	18.354-42.099	
Gleason score					0.042
≤8	68.8	72.223	6.487	59.509-84.936	
>8	53.3	55.848	7.983	40.201-71.495	
TNM stage					0.592
II	69.0	71.034	8.851	53.686-88.382	
III-IVA	59.2	64.311	6.500	51.572-77.051	
Pelvic RT					0.593
Yes	63.6	65.503	6.957	51.868-79.139	
No	62.2	67.984	6.949	54.365-81.603	

*Log Rank (Mantel-Cox) analysis was performed. Abbreviations: PSA= Prostate specific antigen, RT= Radiotherapy, PFS=Progression-free survival

DISCUSSION

IMRT with long-term ADT is a standard treatment option for localized high-risk prostate cancer patients. The effect of RT with ADT on cancer-specific survival and OS has been demonstrated by studies (11,12). In the EORTC 22863, the 10-year disease-free survival (48% vs. 23%) and OS (58% vs. 40%) were improved with a combination therapy compared with RT alone. Also, prostate cancer mortality was decreased from 30% to 10% with combination therapy (11). Clinical studies have been conducted to compare short-term and long-term ADT to investigate the toxicity associated with long-term ADT. RTOG 92-02 has investigated four months versus 28 months of ADT, and EORTC 22961 investigated six months versus 36 months of ADT. Both studies demonstrated improvements in OS with prolonged ADT. There was no statistically significant difference in ADT toxicity between long-term and short-term ADT (13,14). Nabid et al. (15) compared long-term (36 months) and short-term (18 months) ADT with RT; they showed no significant difference in survival between the two groups. ADT toxicity was high for hot flushes, sore or enlarged nipples or breasts, and sexual activity in the 36-month group. When evaluated with both the treatment results and toxicity, 18 months of ADT seems to be an attractive alternative for patients not tolerating the ADT. In this study, all patients had RT combined with ADT or orchiectomy. The Duration of ADT was 24 months in all patients who received ADT. No significant side effects were observed due to ADT. In this study, when evaluated together with our survival and disease-free survival results, it was found that 24-month ADT use is a safe treatment period in terms of both treatment results and side-effect profile.

Pelvic lymph node irradiation is controversial in patients with high-risk prostate cancer without lymph node involvement. Based on Partin tables or other tools, whole-pelvis radiation therapy (WPRT) can be considered in men with an estimated risk of nodal involvement exceeding 20%. WPRT for high-risk and very high-risk prostate cancer resulted in significantly improved biochemical failure-free survival (95.0% vs. 81.2% p<0.0001) and disease-free survival (89.5% vs. 77.2% p=0.002) as compared with only prostate RT, but did not impact OS (92.5% vs. 90.8% p=.83) (16). A randomized trial evaluated the role of WPRT and did not demonstrate a clear benefit of WPRT compared with prostate-only radiation therapy; 5-year PFS rates were 66% and 65.3% for the pelvis+prostate and prostate alone arms, respectively (p=.34) (17). In our study, thirty-four (41.5%) patients received pelvic radiotherapy. In contrast, the others received only local (including seminal vesicles and prostate) RT; there was no significant pelvic RT effect on OS and PFS.

In a study evaluating the results of hypo-fractionated IMRT for localized prostate cancer for patients with high-risk disease, the 10-year biochemical relapse-free survival(b-RFS) rate was 42% (p<0.0001), and the 10-year clinical relapse-free survival was 72% (p<0.0001) (18). Our biochemical outcomes are consistent with other trials reported in the literature, despite petite sample sizes. According to a risk assessment study, the probability of 5-year relapse-free after RP ranges from 49%-80% (19). In our study, the PFS rate was 62.8%. Twenty-four-month and 36-months PFS rates were 83.6% and 65.4%, respectively. These results are comparable with the RP results in Yossepowitch et al.'s (19) study.

A metaanalysis by Petrelli et al. (20) included trials that compared the outcomes of high-risk prostate cancer patients treated with RT or RP and showed that surgery was associated with better OS and prostate cancer-specific mortality than RT. However, RT was associated with a slightly better b-RFS than RP alone. Moreover, their study showed that most older RT patients had comorbidities and had adverse clinical features (e.g., higher rate of Gleason score ≥8, higher median PSA values) than RP patients. Also, in this study, RT techniques were old, and the RT doses were lower than the suggested current RT doses. There were 82 patients with high-risk prostate cancer who received definitive RT in this study, and their mean age was 71.2±6.2 (range 50-84 years) years. While 71 (86.6%) of the patients had a PSA<100 ng/ml, 11 (13.4%) had a PSA≥100 ng/ml. The mean PSA level of the patients was 41.1±33.8, and the median was 27 ng/ml (range 8 -129 ng/ml). While 52 patients (63.4%) had a GS ≤8, 30 (36.6%) had a GS > 8. The mean GS of the patients was 8.3±0.6, and the median was 8 (range 7-10). IMRT and IGRT are the standard of RT for prostate cancer. Dutch Trial compared conventional fractionation(39 fractions of 2 Gy) and hypofractionation (19 fractions of 3.4 Gy); there was no difference in 5-year relapse-free survival; gastrointestinal toxicity was more common in the hypofractionation group (21). In our study, the mean RT dose of the patients was 76.4±1.7 Gy, and the median was 78 Gy (range 74-78 Gy). Twenty-four patients (29.3%) received 74 Gy RT, 17 patients (20.7%) received 76 Gy RT and 41 patients (50%) received 78 GyRT. Thirty-four (41.5%) patients received pelvic RT, while the others received only local (including seminal vesicles and prostate) RT.

Gleason scores 8-10 are typically considered one grade category within the literature (22). GS 9-10 tumors have almost twice the risk of progression compared to GS 8, as demonstrated in the study by Pierorazio et al. (23), biochemical recurrence was not seen at 2 years in 70.9%, and 73.7% of men with GS 8 on biopsy and RP, respectively. For men with GS 9 and 10 on biopsy and RP, 66.7% and 58.5%, respectively, had no biochemical recurrence at 2 years. In our findings, the mean PFS of those with a GS≤8 was significantly higher than the mean survival of those with aGS 9-10 (68.8% vs. 53.3%; p=0.042).

In a study by Ang et al. (24) evaluating the effect of PSA level at the time of diagnosis on OS and prostate cancer-specific mortality; patients with a PSA >100 ng/ml at the time of diagnosis had significantly worse survival outcomes than those with PSA≤20 or 20-≤100 (p<0.001). Five-years survivals for each group (≤20; 20-≤100; >100) were: 87%, 62.5% and 29.1% respectively. The ten-year survivals for each group were 70.7%, 36.7%, and 18.2%, respectively. We obtained similar results in our study; the mean PFS of those with a PSA<100 ng/ml was found to be significantly higher than the mean of survival of those with a PSA≥100 ng/ml (70.6% vs. 10%; p<0.001).

The toxicity of RT is related to the dose of radiation delivered to surrounding healthy organs. Most related trials related to radiation toxicity included patients treated with older radiation techniques. Today IMRT is the mainly used technique for prostate cancer. When we evaluated the toxicities in our study, in the literature in which the patients treated using the dose and technique as in our clinic were evaluated, the toxicity rates were found as follows: 38.1% of patients experienced ≤ grade 2 GIS toxicity (grade1 12.4%, grade 2 25.6%). There was no grade 3 GIS toxicity. GUS late toxicity was reported at 4.1%: grade 1 0.8%, grade 2 3%, grade 3 only in 1. Only 21 patients (5.3%) developed chronic proctitis (25). In our findings, While 52 of the patients (63.4%) had no GIS side effects, 18 (22%) of them had grade 1, and 2 (14.6%) had grade 2 GIS side effects. While 38 (46.3%) of the patients had no GUS side effects, 33 (40.2%) of them had grade 1, and 11 (13.4%) had grade 2 GUS side effects.

CONCLUSION

As a result of our study, treatment decision in high-risk prostate cancer remains unclear; we think that RT combined with ADT may be the preferred treatment modality, especially in well-selected elderly patients with tolerable risk of side effects. In the elderly patient group with high-risk patient groups, starting treatment with a single modality may be recommended instead of burdening the patient with two significant treatment stresses. In some high-risk prostate cancer groups, it may be necessary to have adjuvant radiotherapy after surgery.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the University of Health and Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Studies Ethics Committee (Date: 11/12/2021, Decision No:2021-11/3).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: Both of authors declare that they have all participated in the design, data collection, analysis and interpretation of the data for the work and that they have approved the final version.

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