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# Practice of Fiducial Marker in Prostate Cancer: A Single-Center Experience with up to 6 Years' Follow-up Results

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**Abstract**

We aimed to evaluate the long-term follow-up results of patients with prostate cancer implanted with ultrasound-guided fiducial marker(FM). Forty patients, between 2012-2017 were evaluated. Firstly, the gastrointestinal-genitourinary system side effects were questioned twice immediately after FM implant and in the median 6.5th year and the grading was performed via the NCI CTCAE-V5.0 test and compared. Secondly, in the late period, questions assessing genitourinary-gastrointestinal symptoms were asked using the EORTC QLQ-PR25 Module,and the complication status and patient comfort were assessed The mean symptom value for all patients in the EORTC QLQ-PR25 module was 17,33%. In the first assessment made according to the results obtained by questioning the genitourinarygastrointestinal symptoms related to the FM procedure both after the procedure and in the median 6.5th year,rectal bleeding was present in 2(4%),dysuria 3(6%),hematuria 5(11%) and frequency of urination in 5(11%) patients and in the second assessment,no new symptoms were added and the overall symptom rate decreased. In the first assessment,it was determined via NCI CTCAE-V 5.0 scale that the adverse effects of 9 patients (20%),who were identified with adverse effects,were grade 1 corresponding to mild side effects,and none of the patients experienced grade 2 or higher adverse events. In the second assessment,side effects were defined in 3 patients (7,5%) and grade 1 was mild. The ultrasound-guided FM implant procedure,which is used in prostate cancer radiotherapy is an easy,tolerable and safe technique that does not lead to adverse effects and loss of comfort in patients with long-term follow-up

***Keywords:*** Fiducial markers; prostate cancer; radiotherapy.

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## 1. Introduction

It is well known that there is a significant correlation between dose increase and disease control in prostate cancer radiotherapy [1-4]. However, the radiotherapy technique to be chosen gains importance since an increase in adverse effects may occur due to an increase in dose. It has been demonstrated that in treatments performed with conformal radiotherapy techniques, normal tissues are protected better and late adverse effects associated with radiotherapy are reduced [5]. Apart from the importance of the treatment technique, another effective method in reducing the adverse effect profile is fiducial marker (FM) applications [6-9]. The most remarkable advantages of this technique are the ability to reach high doses safely, higher disease control, and lesser adverse effect profile. Fiducial marker applications in prostate cancer are an effective and exclusive method for accurately identifying the anatomy of the prostate, which is subject to changes due to bladder and rectal contents and constitutes a target, reducing the side effect profile and allowing high rates of disease control. Several published patient series have reported low side effect profiles [10]. Transperineal approach is safe and recommended [11]. There are various types of it, which are made up of gold, Polyether ether ketone (PEEK), and carbon-containing materials. Although the most used type is gold FM, PEEK FM usage experiences have also been revealed [12]. FM applications require a multidisciplinary approach with Urology or Radiology Clinics. As the experience increases, the application duration of the technique decreases, and its quality increases. It is vital that FMs are placed in the prostate on xyz coordinates in a way that allows 3-dimensional assessment spatially (Figure 1-2). Patient tolerability and adverse effects of FM application technique have been reported commonly [13,14]. Knowing particularly late-term adverse effects together with acute adverse effects and assessing their effects on the patient's quality of life would enable us to make better decisions about the future of these applications. Assessment of adverse effects can be performed by subjective criteria based on the statements of the patient or by using objective criteria. Pre-prepared, validated, measurable, easy-to-apply, and repeatable tools should be used in the assessment with objective criteria. The first of the modules selected in this study is the European Organization for Research and Treatment of Cancer, Quality of Life Group-Prostate 25 (EORTC QLQ-PR25). It consists of 25 items that assess urinary and intestinal symptoms, sexual activity, the functioning and adverse effects of the treatment, and it has been translated into 14 different languages [15]. As the second evaluation module, National Cancer Institute, Common Terminology Criteria for Adverse Events-Version 5.0 (NCI CTCAE-V 5.0) was used [16]. With the use of these modules, it is aimed to assess the late period adverse effects of patients who underwent radiotherapy with FM application for prostate cancer in our clinic, based on the objective criteria.

## 2. Material-Method

In the study, 40 patients who were diagnosed with prostate cancer, treated with FM, and received radiotherapy between 2012 and 2017 were assessed retrospectively (Table 1). All patients treated with Varian Trilogy model linear accelerator were evaluated using the Volumetric Modulated Arc Therapy (VMAT) planning technique and Image-Guided Radiotherapy (IGRT) in the Eclipse (ver.13.6) treatment planning system. Informed consent from the patient/patient's family and institutional approval was obtained for this study. Patients who accepted the fiducial marker application, completed the treatment and were followed up regularly were included in this study. Patients who received radiotherapy without fiducial marker application, who were treated with fiducial marker,

but who did not want to participate in the study and were not followed up were not included in this study. Six patients who were treated with FM-guided radiotherapy but died due to non-illness causes during follow-up, and 14 patients who were treated after 2017 - since late-term complications would be assessed - were not included in the study. Before radiotherapy, 35 patients received gold FM and 5 patients received PEEK FM. The first of the NCI CTCAE-V 5.0 module was applied immediately after the FM procedure, and the second was repeated at the median 6.5th year (4 years-9 years). The module was performed immediately after the FM procedure. Hence, the effects of radiation were excluded, and only the adverse effects of the FM implant procedure were recorded. EORTC QLQ-PR25 Turkish Symptom Module was performed once following radiotherapy and it was applied with NCI CTCAE-V 5.0 module in median 6.5th years. Forty patients were included in the study, the number of patients was the same in both the first measurement and the second measurement. SPPS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) statistical package program was used to evaluate the data. Variables are expressed using mean ± standard deviation, percentage and frequency values (Table 2). Variables were evaluated after checking the preconditions for normality and homogeneity of variances (Shapiro Wilk and Levene Test). While analyzing the data, Independent 2 group t test (Student's t test) was used for the comparison of two groups, and Mann Whitney-U test was used if the prerequisites were not met (Table 3). A value of $p < 0.05$ was accepted for the significance level of the tests. The meaning of the p values in Table 3; it can be said that the differences in the sample size were not statistically different and the randomization was successful.

**3. Results**

The mean symptom value for all patients was 17,33%. The lowest symptom value was 0% and the highest symptom value was 62,5%. The mean symptom value for patients implanted with Gold FM was 16% and for patients implanted PEEK FM was 17,33%. No significant correlation was found between Gold FM and PEEK FM in terms of symptom value. Symptoms such as fever, rectal bleeding, dysuria, hematuria, hematospermia, and frequency of urination were questioned for the assessment of genitourinary and gastrointestinal system adverse effects associated with FM procedure. In the presence of symptoms in patients, the degree of symptom was labeled as "yes," "a little," or "no". The same assessment was repeated and compared after a median of 6.5 years following the FM procedure (Table 4). NCI CTCAE-V 5.0 was used to rate the severity of responses. Severity grades for each adverse event were categorized as follows; grade 1: mild adverse event, grade 2: moderate adverse event, grade 3: severe adverse event, grade 4: life-threatening adverse event, and grade 5: death related to the adverse event. In the first assessment, 6 (15%) patients described adverse effects, 34 (85%) patients had no adverse effects. In the second assessment, this rate was 3 (7.5%) and 37 (92.5%) patients, respectively. In the first assessment, rectal bleeding was present in 2 (4%), dysuria 3 (6%), hematuria 5 (11%), and frequency of urination in 5 (11%) patients. In the second assessment, there was no rectal bleeding and hematuria, and dysuria was determined to be 2 (5%) and frequency of urination was 4 (10%). In the comparison, it was found that no new symptoms were added and there was a decrease in the overall symptom rate. In the first assessment, it was determined that the adverse effects of 9 patients (20%) who answered "yes" and "a little" to the questions about genitourinary and gastrointestinal system adverse effects were grade 1, corresponding to mild side effects, and none of the patients experienced grade 2 or higher adverse events. On the other hand, in the second assessment, this rate was at grade 1 in only 6 patients (15%). Fever and hematospermia were not

detected in any patient, both in the first measurement and in the second measurement.

## 4. Discussion

The advancement of radiotherapy techniques has contributed to the reduction of gastrointestinal and specifically genitourinary system adverse effects [17-20]. Thanks to this situation, it is possible to observe the adverse effect profile of FM applications without being masked by the adverse effects of radiotherapy. For FM applications, it is very crucial to know particularly the late complications [21-24]. Because FM implant is not a necessity for radiotherapy application, and late complications might cause negligence of the application. It has been revealed that the questionnaire questions of the EORTC QLQ-PR25 Symptom Module were answered by patients with high compliance [25]. We also observed this patient compliance in our study. The use of modern radiotherapy techniques can be shown as the reason for fewer observed gastrointestinal adverse effects compared to previous studies. Developing radiotherapy techniques allows a lesser intestinal toxicity. Some side effects such as frequent urination might be taken for granted by elderly patients due to their age and they might not consider these complaints as severe. However, it is not possible to make a differential diagnosis of this condition.

## 5. Conclusion

The important limitation of this single-center study is the small number of patients. However, the length of the follow-up period can be considered an advantage. In the study, objective evaluation criteria were preferred as much as possible. Subjective evaluations were supported by objective evaluation criteria. As a result of this study, it can be suggested that ultrasound-guided fiducial marker applications used in prostate radiotherapy are a well-tolerated and safe technique that does not lead to adverse effects and loss of comfort in patients with long-term follow-up.

**Table 1:** Patient characteristics

| | |
|---|---|
| **Age; median,range** | 71 (55-81) |
| **TNM T category ; n(%)** | T1-2; 39 (%97,5)<br>T3; 1 (%2,5) |
| **TNM N Category; n(%)** | N0; 38 (%95)<br>N1; 2 (%5) |
| **PSA, before treatment; median, range** | 8,7 (1.23-75) |
| **Gleason score; median, range** | 7 (6-10) |
| **Radiotherapy dose** | 7800 cGy |
| **Radiotherapy technique** | IGRT |
| **Fiducial markers; n (%)** | Gold marker; 35 (87,5)<br>PEEK marker; 5 (12.5) |

**Table 2:** The EORTC QOL-PR 25 QOL descriptive statistics

| | | Functional scales | Symptom scales | Urinary symptoms | Incontinence aid | Bowel symptoms |
|---|---|---|---|---|---|---|
| **Gold marker** | N | 35 | 35 | 35 | 35 | 35 |
| | Mean | 82,78 | 17,22 | 15,12 | 1,90 | 4,05 |
| | Std. Deviation | 5,33 | 5,33 | 13,14 | 7,85 | 6,51 |
| | Median | 84,00 | 16,00 | 12,50 | 0,00 | 0,00 |
| | Minimum | 62,67 | 10,67 | 0,00 | 0,00 | 0,00 |
| | Maximum | 89,33 | 37,33 | 62,50 | 33,33 | 25,00 |
| **Peek marker** | N | 5 | 5 | 5 | 5 | 5 |
| | Mean | 81,87 | 18,13 | 17,50 | 0,00 | 3,33 |
| | Std. Deviation | 3,07 | 3,07 | 9,04 | 0,00 | 4,56 |
| | Median | 82,67 | 17,33 | 12,50 | 0,00 | 0,00 |
| | Minimum | 78,67 | 14,67 | 8,33 | 0,00 | 0,00 |
| | Maximum | 85,33 | 21,33 | 29,17 | 0,00 | 8,33 |
| **Total** | N | 40 | 40 | 40 | 40 | 40 |
| | Mean | 82,67 | 17,33 | 15,42 | 1,67 | 3,96 |
| | Std. Deviation | 5,08 | 5,08 | 12,63 | 7,36 | 6,26 |
| | Median | 84,00 | 16,00 | 12,50 | 0,00 | 0,00 |
| | Minimum | 62,67 | 10,67 | 0,00 | 0,00 | 0,00 |
| | Maximum | 89,33 | 37,33 | 62,50 | 33,33 | 25,00 |

**Table 3:** The EORTC QOL-PR 25 QOL results at the groups

| | **Gold marker** n=35 | **Peek marker** n=5 | p |
|---|---|---|---|
| **Functional scales** | 82,78±5,33 | 81,87±3,07 | 0,710[¥] |
| **Symptom scales** | 17,22±5,33 | 18,13±3,07 | 0,710[¥] |
| **Urinary symptoms** | 15,12±13,14 | 17,5±9,04 | 0,700[Ψ] |
| **Incontinence aid** | 1,9±7,85 | 0±0 | 0,590[¥] |
| **Bowel symptoms** | 4,05±6,51 | 3,33±4,56 | 0,810[Ψ] |
| **Hormonal treatment-related symptoms** | 3,33±4,09 | 3,33±4,97 | 0,999[Ψ] |

[Ψ] Mann Whitne-U test; [¥] Student's t test;

**Table 4:** Evaluation and comparison of genitourinary and gastrointestinal system side effects.

| | measurement | yes, n (%) | a little, n (%) | no, n (%) |
|---|---|---|---|---|
| **fever** | first | 0/40 (0) | 0/40 (0) | 0/40 (0) |
| | second | 0/40 (0) | 0/40 (0) | 0/40 (0) |
| **rectal bleeding** | first | 0/40 (0) | 2/40 (4) | 0/40 (0) |
| | second | 0/40 (0) | 0/40 (0) | 0/40 (0) |
| **dysuri** | first | 0/40 (0) | 3/40 (6) | 0/40 0) |
| | second | 0/40 (0) | 2/40 (5) | 0/40 (0) |
| **hematuria** | first | 0/40 (0) | 5/40 (11) | 0/40 (0) |
| | second | 0/40 (0) | 0/40 (0) | 0/40 (0) |
| **hematospermia** | first | 0/40(0) | 0/40 (0) | 0/40 (0) |
| | second | 0/40 (0) | 0/40 (0) | 0/40 (0) |
| **frequency of urination** | first | 1/40 (2) | 4/40 (9) | 0/40 (0) |
| | second | 0/40 (0) | 4/40 (10) | 0/40 (0) |


**Figure 1:** Treatment planning system. Axial, coronal and sagittal views of the markers

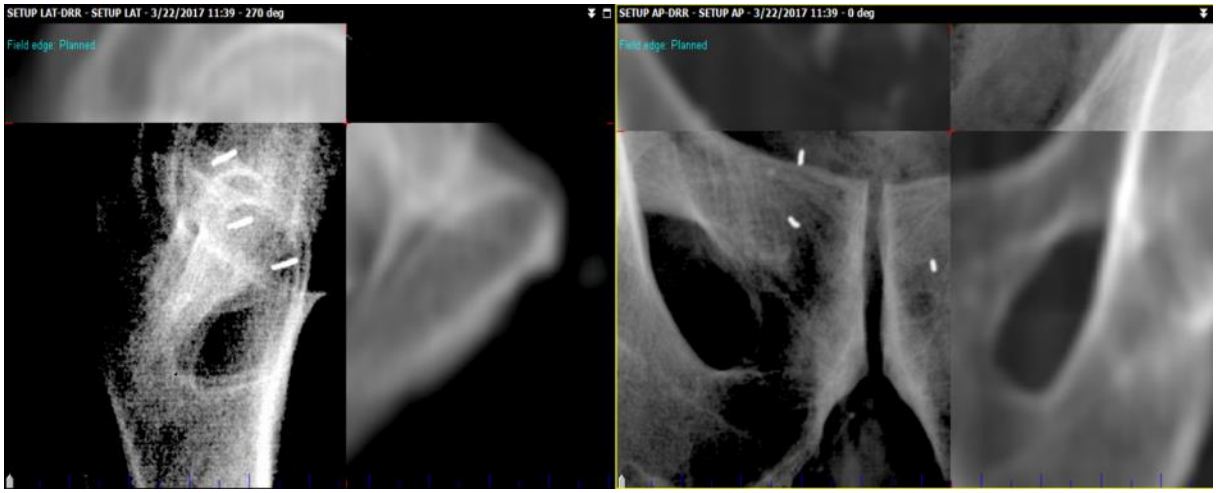


**Figure 2:** Portal imaging system. Lateral and anteroposterior views of the markers

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