Original Article

Evaluating the Predictive Value of the Dose-volume Parameters and Vascular Endothelial Growth Factor Expression on Rectal Toxicity in Prostate Cancer Patients

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Abstract

Background: The response to radiation varies widely among people. Despite recent advances to conform the dose distribution to the tumor volume, it is still impossible to perform radiotherapy based on the biological characteristics of each individual. In this case, identifying a biomarker can be a step toward personalizing treatment. This research was carried out to evaluate the predictive value of dose-volume parameters and vascular endothelial growth factor (VEGF) expression on rectal proctitis toxicity in prostate cancer patients. **Materials and Methods:** Eighteen patients with prostate cancer who underwent helical tomotherapy were included in the study. VEGF serum level before and after treatment was obtained. Furthermore, dosimetric parameters, including rectal volume, maximum dose, V50, V60, V65, V70, and V75 were extracted. Spearman's correlation coefficient of VEGF-related and dosimetric parameters with the grade ≥1 rectal proctitis was calculated. **Results:** In the rectal toxicity group, the mean value of VEGF increased significantly after treatment compared to before ($P = 0.008$). Despite lower values of pre- and post-treatment VEGF in the toxicity group, this difference was not statistically significant ($P > 0.05$). Among the dosimetric parameters, only V65 had a significantly higher value in the toxicity group ($P = 0.033$). The highest correlation coefficients were obtained for pretreatment VEGF values and V65 (−0.446 and 0.450). **Conclusion:** The results of the study confirm the correlation of VEGF expression with the pathobiology process of rectal radiation proctitis. However, the pathobiology process of radiation proctitis is complicated. More research is needed to prove the involvement of VEGF expression in the early detection of proctitis.

Keywords: Biomarkers, proctitis, prostatic neoplasms, rectum, vascular endothelial growth factors

Received on: 27-03-2024 **Review completed on:** 12-08-2024 **Accepted on:** 17-08-2024 **Published on:** 18-12-2024

Introduction

Management of side effects is one of the challenges after radiotherapy (RT).[1] The incidence of rectal toxicity reduces the benefits of RT for prostate cancer patients.[2-4] The chronic radiation proctitis (ChRP) occurs after pelvic RT to the rectum. Acute proctitis occurs immediately up to 3 months after RT and late side effects may occur after 3 months.[5] ChRP can be divided into three phases: subacute chronic up to 1 year, a chronic phase between 1 and 5 years after RT, and a late chronic phase 5 years after RT.[5] Therefore, it is essential to consider the factors predicting the occurrence of ChRP. Currently, the primary basis for predicting the radiation-induced side effects is calculating the dose-volume histogram (DVH), and the influence of biological factors related to treatment planning is not considered. DVH-based parameters are a simple tool to evaluate the designed plans in the target volume and normal tissues, without providing the biological effect of the dose on the healthy organs.[6] Additionally, the information on dosimetric factors extracted from DVH may not be complete or may not recognize slight differences between each patient's treatment plan.[6,7] The association of DVH

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Quick Response Code:

Website: www.jmp.org.in

DOI: 10.4103/jmp.jmp_67_24

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How to cite this article: Mirzaeiyan M, Khanahmad H, Hemati S, Etehadtavakol M, Sharifonnasabi Z, Shokrani P. Evaluating the predictive value of the dose-volume parameters and vascular endothelial growth factor expression on rectal toxicity in prostate cancer patients. J Med Phys 2024;49:539-44.

criteria with gastrointestinal complications after RT for prostate cancer has been demonstrated.[8,9] In today's medical era, it is crucial to personalize the treatment according to the individual characteristics of the patient. It seems that the functional aspects and structural physiology of healthy organs around the tumor in each patient lead to different reactions of that organ to radiation.[10] Therefore, it is necessary to use biomarkers to predict radiation toxicity specifically for each patient. The various mechanisms involved in the pathophysiology of radiation proctitis have not been fully elucidated. According to studies, microvascular damage in blood vessels seems to be the main site of damage, and several molecular events including inflammation, neovascularization and fibrosis may play a role in this process.[5,11] Angiogenesis plays a crucial role in many chronic inflammatory diseases.[11] Among the factors involved in angiogenesis is vascular endothelial growth factor (VEGF).[11] Angiogenesis is the process of new blood vessel formation through new branches that sprout from existing blood vessels.[11] There is limited and contradictory experimental data on the role of angiogenesis in postradiation proctitis, particularly, in its chronic form.[5,12,13] Recent studies have shown that the expression of the VEGF in rectal mucosa biopsies, as well as in serum levels, had a significant relationship with the incidence of rectal proctitis toxicity.[5,12] In another *in vivo* study, VEGF expression increased after irradiation of the abdominal region in rats.[13]

Therefore, this study aimed to investigate the ability of dosimetric parameters and VEGF expression to predict chronic phase of proctitis after RT for prostate cancer patients.

Materials and Methods

In this prospective study, blood samples and the dose-volume data from 18 patients who underwent helical tomotherapy (HT) for prostate cancer between May 2021 and September 2022 were collected. The inclusion criteria for this study were patients with prostate cancer involving pelvic lymph nodes (LNs) (or patients requiring pelvic prophylactic treatment). In this study, the history of previous RT of the pelvic region and gastrointestinal diseases were considered as exclusion criteria. Rectal chronic proctitis scores were assessed using the Common Terminology Criteria for Adverse Event (CTCAE). The follow-up period ranged from 12 to 18 months for all patients. After toxicity grading, patients were divided into two groups with and without toxicity.

Computed tomography (CT) simulation and treatment were performed with the patient in a supine position, with a full bladder and empty rectum. Abdominal and pelvic thermoplastic were used for immobilization. CT images for HT treatment planning with a thickness of 3–5 mm were obtained using a Siemens CT scanner (SOMATOM Definition AS or SOMATOM Confidence, Germany). The treatment plans were designed via the Precision treatment planning system (Accuray Precision, USA, version 2.0.1.1). The planning target volume (PTV), including the prostate/prostatic bed, seminal vesicles, and pelvic LNs (PTV LN), was prescribed a dose of 50–54 Gray, with a simultaneous boost to the PTV up to 64–78 Gray. The dose per fraction ranged from 1.63 to 1.92 Gray for PTV LN and from 2 to 2.69 Gray for PTV. Daily position reproducibility was ensured using megavoltage CT.

Blood samples with a volume of two mililiters were taken from patients before the start of treatment (VEGF1) and after the end of RT (VEGF2). After centrifugation for 7 min at 6000 rpm, the blood serums were separated and placed in a freezer at −70 for conducting enzyme-linked immunosorbent assay (ELISA) tests until all the blood samples from the 18 patients were collected. The relative changes of VEGF (ΔVEGF) in each group were calculated as the difference between pre-treatment VEGF and post-treatment VEGF, divided by the value of pre-treatment VEGF. Serum levels of VEGF were analyzed using a commercially available Human VEGF ELISA kit (Catalog Number: KPG-VEGF, karmania Pars Gene, Iran) following the manufacturer's instructions.

Dosimetric data for all patients were collected including rectal volume, maximum dose, and dose-volume suggestions from the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC), which included V50, V60, V65, V70, and V75. Vx represents the percentage of the rectal volume exposed to a dose equal to or greater than x Gray. The tolerance doses suggested by QUANTEC for the dose-volume values mentioned above are, respectively, <50%, <35%, <25%, <20%, and <15%. A QUANTEC score was obtained for each patient based on the dose-volume tolerances provided by QUANTEC. The scoring ranged from 0 to 5 where a score of 0 means that none of the dose-volume limitations recommended by QUANTEC are met, and conversely, a score of 5 means that all limits are in line with QUANTEC's recommendations. VEGF1 and VEGF2 values within each group were compared using the Wilcoxon test. VEGF1, VEGF2, ΔVEGF, and all dosimetric parameters for the two defined groups (with and without rectal toxicity) were compared using independent *t*-test or Welch test for parametric data, and Mann–Whitney *U*-test for nonparametric data. Spearman's correlations between VEGF1, VEGF2, ΔVEGF expression, and dosimetric parameters with grade ≥1 chronic rectal proctitis were determined. IBM SPSS version 27 software (Armonk, NY: IBM Corp) was used for all statistical analysis, and a $P \leq 0.05$ was considered statistically significant.

Results

The age range of all patients was 54–78 years with a median age of 69 years. All patients were followed up for 12 and 18 months after RT to evaluate rectal ChRP toxicity. Clinical assessment using CTCAE protocol showed that 39% of patients had grade 1 ChRP and 11% had grade 2 or 3 ChRP. VEGF increased significantly after RT in the toxicity group (15.87 ± 38.36 vs. 31.94 ± 44.11 pg/mL, $P = 0.008$). The boxplot of VEGF changes for two groups with and without ChRP is shown in Figure 1. However, the reduction of VEGF expression in the group without toxicity was not statistically

significant (90.12 ± 110.38 vs. 64.29 ± 68.75 pg/mL, $P = 0.678$). Despite the lower values of VEGF1 and VEGF2 and the higher value of ΔVEGF in the toxicity group compared to the group without toxicity, the difference was not statistically significant ($P \geq 0.05$) [Figure 2]. The mean values and standard deviation of dosimetric parameters are shown in Table 1. The QUANTEC score in the groups with/without toxicity was 3, 4, and 5 in 1/0, 2/2, and 6/7 patients, respectively.

Although all dosimetric parameters had higher values in the group with toxicity compared to the group without toxicity, only V65 showed a significantly higher value in the toxicity group ($P = 0.033$). V65, VEGF1, and V75 had the highest Spearman correlation coefficient with grade ≥1 ChRP, respectively (0.450, −0.446, and 0.445). However, Spearman's correlation analysis for VEGF1, VEGF2, ΔVEGF, and the dosimetric parameters with grade ≥1 ChRP did not yield statistically significant results ($P > 0.05$) [Table 2].

Discussion

A high dose of prostate RT is necessary for complete tumor response to treatment. However, escalating the dose to more than 70 Gray will cause rectal side effects.[14-17] Modern RT techniques have led to a more conformal dose distribution and sparing of organs at risk.[2,14,16-18] While some benefits of modern RT techniques have been reported, their relative benefit in terms of radiation-related complications in prostate cancer treatment remains unclear.[14] Furthermore, radio-sensitivity varies greatly among patients with the same condition, even after receiving the same dose of RT. Currently, the attention of radiation oncology has been drawn toward the possibility of personalizing RT using biomarkers. Dosimetric parameters cannot fully predict the radiation-induced complications.[7,19-22] It has been shown in previous studies that VEGF expression is involved in the pathobiology process of ChRP.[5,12,13] Therefore, in this study, we tried to evaluate the prediction of dosimetric parameters and VEGF expression in predicting ChRP. In this study, ChRP was evaluated using the criteria of the CTCAE protocol, which has been utilized in several studies to assess rectal damage.[23,24] Grade 1 proctitis was observed in 39% of cases, while grades 2–3 were observed in 11%, which did not align with the results of some previous studies.[23,25] However,

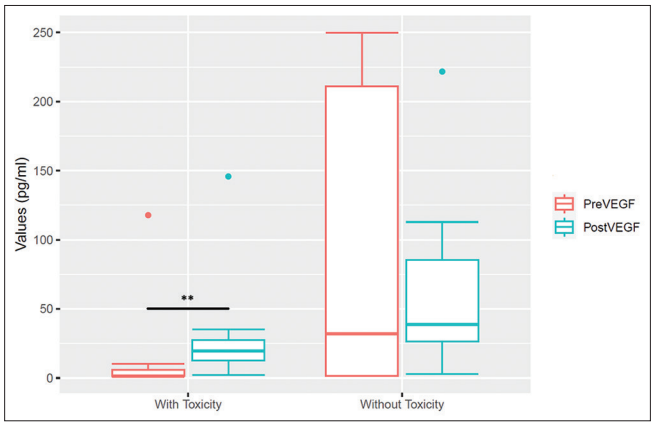

Figure 1: Box plot to compare the before and after treatment vascular endothelial growth factor (VEGF) values in each group of with and without rectal proctitis toxicity. Mean values of VEGF before and after treatment in the toxicity group: 15.87 ± 38.36 and 31.94 ± 44.11 ($P = 0.008$). Mean values of VEGF before and after treatment in the without-toxicity group: 90.12 ± 110.38 and 64.29 ± 68.74 ($P = 0.678$). VEGF: Vascular endothelial growth factor

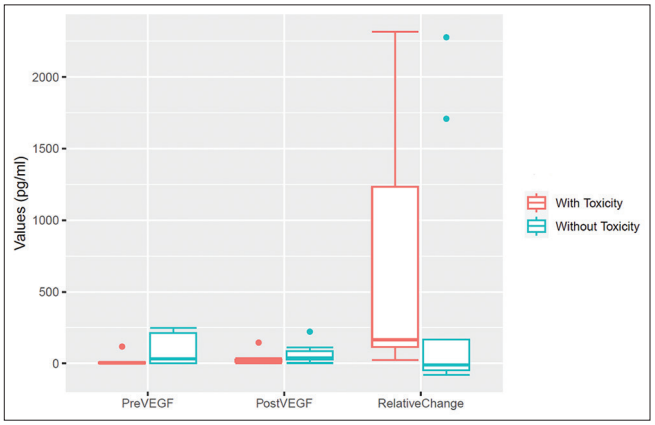

Figure 2: Box plot to compare the before, after, and relative changes of vascular endothelial growth factor (VEGF) values between the two groups of with and without rectal proctitis toxicity. Mean values of VEGF before treatment (PreVEGF) with and without toxicity group: 15.87 ± 38.36 and 90.12 ± 110.38 ($P = 0.094$). Mean values of VEGF after treatment (PostVEGF) with and without toxicity group: 31.94 ± 44.11 and 64.29 ± 68.74 ($P = 0.190$). Mean values of relative changes of VEGF after treatment compared to before treatment (relative change) with and without toxicity group: 728.83 ± 850.74 and 447.59 ± 891.03 ($P = 0.113$)

Table 1: The mean values and standard deviation of dosimetric parameters for two groups of with and without toxicity

Dosimetric parameters	With toxicity group, mean±SD	Without toxicity group, mean±SD	*U* Mann–Whitney (*P*)	Independent *t*-test (*P*)	Welch test (*P*)
Rectal-volume (mL)	66.50±17.20	66.17±14.06	0.730	-	-
Maximum-dose (gray)	72.38±6.34	69.43±2.94	-	-	0.231
V50%	43.67±17.52	41.50±16.16	-	0.789	-
V60%	20.50±10.21	17.28±8.22	-	0.472	-
V65%	12.44±7.06	5.84±4.67	-	0.033	-
V70%	3.68±4.46	0.04±0.07	0.222	-	-
V75%	0.90±1.91	0.00±0.00	0.258	-	-

V50–75: A volume of the rectum that receives a dose equal to or greater than the indicated value. SD: Standard deviation

Table 2: The Spearman's correlation coefficients of before, after, relative changes of vascular endothelial growth factor, and dosimetric parameters with grade ≥1 rectal proctitis

Dosimetric and VEGF-related parameters	Correlation coefficient	*P*
VEGF1	−0.446	0.063
VEGF2	−0.332	0.178
ΔVEGF	0.396	0.104
Rectal volume	−0.268	0.283
Maximum dose	0.225	0.370
V50	0.064	0.800
V60	0.182	0.469
V65	0.450	0.061
V70	0.342	0.165
V75	0.445	0.064

VEGF: Vascular endothelial growth factor, VEGF1: Before treatment VEGF value, VEGF2: After treatment VEGF value, ΔVEGF: Relative changes of VEGF (the difference before and after treatment VEGF divided by the value of before treatment VEGF), V50–75: A volume of the rectum that receives a dose equal to or greater than the indicated value

the follow-up time of the patients in these studies is different, and the toxicity scoring system may be different. By comparing the dosimetric factors between the two groups, no significant relationship was found between the dosimetric factors and rectal toxicity. These results indicate that the dosimetric factors in this study cannot to fully predict ChRP. In contrast to our study's findings, several studies have demonstrated a significant relationship between the incidence of late rectal damage and the volume of rectum receiving >50 Gray.[23,25-27] In this study, V65 and V75 had the highest correlation coefficient with ChRP, but this relationship was not statistically significant. Additionally, V65 in the toxicity group was significantly higher than in the group without toxicity. However, the follow-up time and toxicity grading system in the mentioned studies are not the same as our study. Consistent with our results, Liu *et al*. concluded in their research that the relationship between rectal complication and V50–70 is not significant.[28] Among all patients, seven were injured despite complying with all dose-volume limits set by QUANTEC. In agreement with our study's results, Ozkan *et al*. showed in their study that the compliance of patients' dosimetric factors with the tolerance dose values recommended by QUANTEC did not result any reduction in the incidence of rectal proctitis.[29] Although the tolerance dose suggested by QUANTEC is for RT with a fraction size of 2 Gray,[30] in the present study, the fraction size was ≥2 Gray. In addition, in their study, there was no correlation between the incidence of rectal damage and the maximum dose received by the rectum, which was consistent with our results.[29] However, in their study, the only significant factor associated with rectal proctitis was rectal volume, which contradicted our results.[29] However, in their study, acute rectal toxicity was investigated, and the prescribed dose was 70 Gy, unlike our study, where all patients were treated with a fraction size of 2 Gray. The pathobiology of rectal proctitis is not completely clear. In past studies, endoscopic examinations of the rectal mucosa have shown the presence of telangiectasia.[5] There is minimal and contradictory experimental data on the role of angiogenesis in postradiation proctitis, especially in the chronic form. The significant increase in VEGF expression in the group of patients with toxicity in this study was consistent with the results of recent studies.[5,12,13] However, in some studies, the relationship of VEGF with tumor response to treatment has been investigated, and the results of the relationship of VEGF with rectal damage should be investigated considering the lack of involvement of tumor biology and its relationship with VEGF expression. For example, Yu *et al*.[31] investigated the relationship between tumor pathological response and serum levels of VEGF in patients with esophageal cancer undergoing concurrent chemotherapy. Their results showed a significant decrease in serum VEGF levels during and after chemo-RT in patients with a severe tumor pathological response. At present, the personalization of treatment in radiation therapy based on the individual characteristics and biology of each patient is of interest. Based on the results of the current research and studies,[5,12,13,31] it is suggested that the following steps be taken to better understand the potential of using VEGF in the clinic practice: Conduct more extensive studies involving a larger number of patients. For this, it is better for the radiation oncologist to routinely prescribe a VEGF expression test for the patient. However, it is important to note that the cost of this test is high. The effect of tumor response to RT on possible changes in VEGF expression level as a confounding factor should be investigated. VEGF expression levels may vary at different time intervals during RT. Therefore, it is advisable to assess VEGF expression during treatment, as well as at 6-month intervals posttreatment, to monitor the patients for rectal toxicity. Furthermore, more accurate methods such as rectal magnetic resonance imaging and endoscopy should be employed to predict rectal damage more accurately.

This study had several limitations as follows: (1) Due to the small sample size, nonparametric statistical evaluation was used in several analyses, (2) Assessment of rectal proctitis was conducted over a short follow-up period, (3) Rectal toxicity was evaluated using a questionnaire in this study, which may have resulted in each patient expressing their personal opinion about rectal complications, (4) There was an absence of any objective evaluation such as proctoscopy or pathological examination, (5) In this study, patients had high variability of PTV boost dose from 64 to 78 Gray, and such a wide range would result in a large variation of late rectal toxicity. It is suggested to consider the effect of the dose on the amount of VEGF factor changes and its effect on the incidence of rectal toxicity. Furthermore, it is possible that the amount of received dose has an effect on the relationship between the dosimetric parameters investigated in this study and the rectal toxicity.

Conclusion

Our study showed that the tolerance dose proposed in the QUANTEC is not fully capable of predicting rectal ChRP.

The results of the study confirm the correlation of VEGF expression with the pathobiology process of rectal radiation proctitis. However, the pathobiology process of radiation proctitis is complicated. More research is needed to prove the involvement of VEGF expression in the early detection of proctitis. An intensive assessment of changes in specific rectal biomarkers during a longer follow-up after RT may be useful for the early detection of rectal ChRP. To personalize the treatment, it is necessary to use biological markers to more accurately predict the specific injuries of each patient. This can improve the management of prostate cancer patients and their quality of life.

Acknowledgments

This article is the result of the thesis entitled "Prediction of normal rectum radiation induced complications in pelvis RT using the rectum dosimetric parameters and change in VEGF expression" with the code 399668, which was approved and financially supported by the Isfahan University of Medical Sciences. The efforts of the research assistants of Isfahan University of Medical Sciences are hereby appreciated and thanked. In addition, the cooperation of medical physics department of Omid Hospital in Isfahan and central laboratory of the faculty of medicine, Isfahan University of Medical Sciences is appreciated and acknowledged.

Financial support and sponsorship

This research received specific grant from the Isfahan University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

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