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Rectal toxicity of 3-dimensional conformal radiation therapy following hydrogel spacer (Space OAR) injection for men with prostate cancer

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Abstract

Purpose: To evaluate whether hydrogel spacer injection, which increases the distance between the prostate and rectum, prior to local radiation therapy for prostate cancer reduces rectal and bladder toxicity.

Patients and methods: With institutional review board approval (05-004), we retrospectively reviewed rectal and bladder toxicity after local radiation therapy in patients with prostate cancer who were followed up for more than 1 year.

Results: We included 156 patients who had received local radiation therapy. Their ages ranged from 63 to 86 years, with an average of 75 years. Most patients were treated only on the prostate and seminal vesicles. All prostate sites were irradiated as follows: whole pelvis with prostate in 10 patients, whole pelvis with prostate and metastatic sites in six, and prostate and metastatic sites in eight. Radiation therapy (70–74 Gy) was performed for the prostate. Irradiation of 45–46.8 Gy was applied to whole pelvic and para-aortic lymph nodes, with 54–60 Gy applied to bone metastatic sites. In one case, stereotactic body radiation therapy (36 Gy) was performed for a sacral bone metastatic site. The hydrogel spacer was injected in 39 patients. Rectal toxicity was reported in 21 patients without (17.9%) and 3 patients with (7.7%) the hydrogel spacer. Bladder toxicity was reported in five patients without and only one patient with the hydrogel spacer.

Conclusion: Hydrogel spacer injection prior to local radiation therapy for prostate cancer reduces rectal radiation exposure, lowers the risk of rectal complications, and may be a promising method for boosting the irradiation dose in the future.

Keywords

Prostate cancer, radiation therapy, hydrogel spacer, rectal toxicity

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Introduction

With advances in diagnostic and therapeutic techniques for prostate cancer, such as multiparametric magnetic resonance imaging (MRI), MR/transrectal ultrasound fusion biopsy, and image-guided radiotherapy, radiation therapy has become an indispensable treatment for prostate cancer patients.[1] Radiotherapy is often selected as a treatment, but radiation proctitis is a relatively common complication.[1] Recently, intensity-modulated radiation therapy (IMRT) has been used for prostate cancer radiotherapy.[2,3] With the advent of IMRT, it has become possible to both increase the dose to the target (prostate ± seminal vesicle) and reduce the dose to the rectum and bladder, and it has fewer side effects than conventional three-dimensional conformal radiation therapy (3D-CRT). If 3D-CRT is selected, the recommended radiation dose is usually lower than with IMRT to reduce the risk of adverse

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events such as proctitis.[4] In Japan, many facilities have to perform curative radiotherapy using conventional 3D-CRT due to facility standards.[5] Our hospital also utilizes conventional 3D-CRT for radical prostate radiotherapy in accordance with institutional standards. It is located in an area with a low population density, broad medical district, and rapidly aging population. Under these circumstances, our situation presents challenges when referring patients to IMRT facilities. Since our hospital opened, we have been utilizing a dose of 74 Gy, which is slightly higher than the standard for 3D-CRT.[4] However, the radiation dose to the rectum is high, and reducing it has been a concern.

Recently, we started to insert a hydrogel spacer, such as the SpaceOAR system, between the rectum and prostate gland to reduce the radiation dose to the rectum, aiming to enhance the safety of radical radiation therapy for prostate cancer.[4–11]

This study was aimed to investigate the effect of hydrogel spacer injection, which increases the distance between the prostate and rectum, on rectal toxicity when administered prior to 3D-CRT for prostate cancer based on the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring scheme.

Materials and methods

This is an observational study. This study included cases of patients undergoing 3D-CRT for prostate cancer at our hospital between June 2015 and August 2022.

Patients and settings

Our hospital opened in June 2015. We have been performing 3D-CRT for prostate cancer since that time in accordance with facility standards. Since November 2020, our hospital has been performing 3D-CRT with the use of SpaceOAR to reduce the risk of radiation-induced proctitis. We conducted a retrospective analysis of rectal and bladder toxicity following local radiation therapy in patients with prostate cancer who were monitored for more than 1 year.

The participants included in this study were patients with a pathological diagnosis of prostate cancer who were deemed eligible for local prostate radiotherapy and who provided informed consent. The exclusion criteria consisted of patients who chose not to undergo local prostate radiotherapy.

This study was approved by the Ethical Committee of the Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital (approval no. 05-004). Written informed consent from the subjects and from the legally authorized representatives of the deceased subjects for the publication of this study was waived by the Ethical Committee of Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital. This study was conducted in accordance with the Declaration of Helsinki.

Spacer injection

A hydrogel spacer (SpaceOAR system; Boston Scientific, Marlborough, MA, USA) was injected approximately 7–10 days prior to the initiation of 3D-CRT. Hydrogel (10 mL) was injected into the perirectal space between the prostate and rectum using a transperineal approach with transrectal ultrasound guidance. General or spinal anesthesia was used for the procedure. A few days after hydrogel spacer placement, patients underwent MRI to confirm the positioning of the spacer.

3D-CRT planning

TrueBeam® ver. 2.7 (Varian Medical Systems, CA, USA) was used as the radiotherapy device, and Eclipse ver. 13.6 was applied as the radiation treatment planning system (Varian Medical Systems, CA, USA). The policy was to administer a curative dose to the primary lesion of the prostate and lymph node metastases. Regarding the primary lesions, the clinical target volume (CTV) was defined as the prostate and base of the seminal vesicles or the entire seminal vesicles. An 8-mm margin was added to CTV to specify the planning target volume in all directions except posteriorly at the interface with the rectum, where the margin was reduced to 4 or 5 mm. A 3D-conformal arc technique was used for radiotherapy planning. The prostate received 70 Gy in 35 fractions to 74 Gy in 37 fractions at the isocenter. If lymph node metastases were distant from the small intestine, they were administered 60 Gy in 30 fractions. Image-guided approaches with daily target localization was used in all patients except for whole-pelvis irradiations.

Evaluation

Radiotherapy-related GI and genitourinary toxicities were retrospectively graded according to RTOG acute and late toxicity criteria.[12] The scheme is detailed in Table 1. In both cases, 0 indicates the absence of radiation effects and 5 means the effects led to death. The severity of reactions was graded from 1 through 4.

Statistical analysis

Patients undergoing irradiation with/without a hydrogel spacer, those receiving/not receiving antithrombotic drug therapy, and those undergoing irradiation of the whole pelvis or prostate, were examined using the Mann–Whitney *U* test. Differences between groups were assessed using two-tailed tests and considered to be significant at a p-value < 0.05. IBM SPSS Statistics Ver.27. (https://www.ibm.com/us-en) was used as the statistical software.

Table 1. RTOG/EORTC late radiation morbidity scoring scheme.

Grade	Criteria
Lower G.I. including pelvis	
0	No change
1	Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics
2	Diarrhea requiring parasympatholytic drugs (e.g., Lomotil)/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics
3	Diarrhea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops)
4	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
Genitourinary	
0	No change
1	Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication
2	Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium)
3	Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/without clot passage
4	Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration, or necrosis

Source: Cox et al.[12]

Results

We included 156 patients who had received local radiation therapy (Table 2). Their ages ranged from 63 to 86 years, with an average of 75 years. Of the 156 patients, 128 were negative for pelvic lymph node metastasis, and 28 were positive for metastasis. A total of 135 patients received combination therapy with androgen deprivation therapy (ADT) and 21 patients did not receive the therapy. Among these 156 patients, 122 were not treated with antithrombotic drugs, while 34 patients received antithrombotic treatment. Also, among the 156 patients, 117 received radiotherapy without hydrogel spacer injection, and 39 underwent radiotherapy after hydrogel spacer injection.

Out of these 117 patients, 99 were negative for pelvic lymph node metastasis, and 18 were positive for metastasis. Ninety-seven patients received combination therapy with ADT, and 20 patients did not receive ADT. Among the 117 patients without hydrogel spacer injection, 94 were not treated with antithrombotic drugs, while 23 patients received antithrombotic treatment.

Out of 39 patients, 29 were negative for pelvic lymph node metastasis, and 10 were positive for metastasis. A total of 38 patients received combination therapy with ADT, and only one patient did not receive ADT. Among these 39 patients, 28 were not treated with antithrombotic drugs, while 11 patients received antithrombotic treatment.

Among the initial total of 156 patients, irradiation sites included: the local region of the prostate or both the prostate and seminal vesicles in 132 cases; the local region and entire pelvis in ten cases; the local region, entire pelvis, and para-aortic lymph nodes in six cases; the local region and irradiation of metastatic sites in eight cases.

Of the 117 patients without hydrogel spacer injection, irradiation sites included the local region of the prostate or both the prostate and seminal vesicles in 100 cases; the local region and entire pelvis in eight cases; the local region, entire pelvis, and para-aortic lymph nodes in four cases; the local region and metastatic sites in five cases.

Of the 39 patients with hydrogel spacer injection, the irradiation sites included the local region of the prostate or both the prostate and seminal vesicles in 32 cases; the local region and entire pelvis in two cases; the local region, entire pelvis, and para-aortic lymph nodes in two cases; the local region and metastatic sites in three cases. No cases of metastases in the current study affected the rectum regarding the extent of irradiation except for whole-pelvis irradiation.

Radiation therapy (70–74 Gy in 35–37 fractions) was administered to the prostate. Irradiation of 45–46.8 Gy in 25–26 fractions was applied to the whole pelvic and para-aortic lymph nodes, and 54–60 Gy in 27–30 fractions was administered to bone metastatic sites. In one case, stereotactic body radiation therapy (36 Gy in four fractions) was administered to a sacral bone metastatic site.

Among the 156 patients, adverse events involving the rectum were reported in 24 patients, with 14 classified as grade 1 and 10 cases classified as grade 2. Of the 117 patients without hydrogel spacer injection, adverse events involving the rectum were reported in 21 cases, with 11 cases classified as grade 1 and 10 cases classified as grade 2. Of the 39 cases with hydrogel spacer injection, adverse events involving the rectum were reported in 3 cases, classified as grade 1.

Among the 156 patients, adverse events involving the bladder were reported in four, with one case classified as grade 2 and one case classified as grade 3, and two cases classified as grade 4. Of the 117 patients without hydrogel spacer injection, adverse events involving the bladder were reported in three, with one case classified as grade 3 and two cases classified as grade 4. Of the 39 cases with hydrogel spacer injection, adverse events involving the bladder were reported in only one case, classified as grade 2.

Of the 117 patients without hydrogel spacer injection, 94 were not treated with antithrombotic drugs, while 23 patients received antithrombotic treatment (Tables 3 and 4). Of the 23 patients without hydrogel spacer injection, adverse events involving the rectum occurred in seven patients, with five cases

Table 2. Patients characteristics and rectal and bladder toxicity.

	Total	Hydrogel spacer (−)	Hydrogel spacer (+)
Patients	**156**	**117**	**39**
Age (average)	63–86 (75)	64–86 (76)	63–82 (72)
N0	128	99	29
N1	28	18	10
ADT (+)	135	97	38
ADT (−)	21	20	1
Antithrombotic drugs (−)	122	94	28
Antithrombotic drugs (+)	34	23	11
Radiation area			
Prostate	132	100	32
Whole pelvis	10	8	2
Whole pelvis + PAN	6	4	2
Prostate + mets sites	8	5	3
Rectal toxicity	**24/156 (15%)**	**21/117 (18%)**	**3/39 (8%)**
RTOG/EORTC 1	14	11	3
RTOG/EORTC 2	10	10	0
RTOG/EORTC 3	0	0	0
Bladder toxicity	**4/156 (3%)**	**3/117 (3%)**	**1/39 (2%)**
RTOG/EORTC 2	1	0	1
RTOG/EORTC 3	1	1	0
RTOG/EORTC 4	2	2	0

Table 3. Rectal and bladder toxicity in patients receiving antithrombotic drug therapy and the whole pelvis irradiation.

	Total	Hydrogel spacer (−)	Hydrogel spacer (+)
Patients receiving antithrombotic drug therapy			
Rectal toxicity		**7/23 (30%)**	**1/11 (10%)**
RTOG/EORTC 1		5	1
RTOG/EORTC 2		2	0
RTOG/EORTC 3		0	0
Bladder toxicity		1/23	0/11
RTOG/EORTC 2		0	0
RTOG/EORTC 3		0	0
RTOG/EORTC 4		1	0
Patients receiving the whole pelvis irradiation			
Rectal toxicity		**4/12 (33%)**	**0/4 (0%)**
RTOG/EORTC 1		4	0
RTOG/EORTC 2		0	0
RTOG/EORTC 3		0	0
Bladder toxicity		0/12 (0%)	1/4 (25%)
RTOG/EORTC 2		0	1
RTOG/EORTC 3		0	0
RTOG/EORTC 4		0	0

Table 4. Rectal and bladder toxicity in patients without hydrogel spacer receiving antithrombotic drug therapy and the whole pelvis irradiation.

	Anticoagulant (+)	Anticoagulant (−)
Patients receiving antithrombotic drug		
Rectal toxicity	7/23 (30%)*	14/94 (15%)*
RTOG/EORTC 1	5	6
RTOG/EORTC 2	2	8
RTOG/EORTC 3	0	0
Bladder toxicity	1/23	2/94
RTOG/EORTC 2	0	0
RTOG/EORTC 3	0	1
RTOG/EORTC 4	1	1
	Irradiation on the whole pelvis	Irradiation on the prostate
Irradiation on the whole pelvis or the		
Rectal toxicity	4/12 (33%)#	17/105 (16%)#
RTOG/EORTC 1	4	7
RTOG/EORTC 2	0	10
RTOG/EORTC 3	0	0
Bladder toxicity	0/12 (0%)	3/105 (3%)
RTOG/EORTC 2	0	0
RTOG/EORTC 3	0	1
RTOG/EORTC 4	0	2

*$p = 0.042$, #$p = 0.083$.

classified as grade 1 and two cases classified as grade 2. Among the 94 patients who did not receive antithrombotic treatment, adverse events involving the rectum occurred in 14 patients, with six cases classified as grade 1 and eight cases classified as grade 2. There was a significant difference between patients with and without antithrombotic treatment in those without hydrogel spacer injection ($p = 0.042$) (Table 4). Of the 23 patients who did not undergo hydrogel spacer injection but were receiving antithrombotic treatment, one patient experienced grade 4 adverse events involving the bladder.

Of the 11 patients who underwent hydrogel spacer injection and received antithrombotic treatment, only one experienced adverse events involving the rectum, classified as grade 1. No patient developed bladder toxicity.

Of the 105 patients undergoing irradiation of local regions, adverse events involving the rectum occurred in 17 patients, with seven cases classified as grade 1 and ten cases classified as grade 2. Of the 12 patients undergoing irradiation of local regions and the entire pelvis, adverse events involving the rectum occurred in four patients, classified as grade 1. There was no significant difference between the patients undergoing irradiation of local regions and those receiving irradiation for both local regions and the entire pelvis ($p=0.083$) (Table 4). Four patients who underwent hydrogel spacer injection and received radiation therapy for local regions and the entire pelvis did not experience any adverse events involving the rectum.

Discussion

Radiation therapy is an essential treatment for prostate cancer, ranging from curative to palliative care.[1] Radiation therapy with curative intent for prostate cancer aims to deliver high doses of radiation to the prostate while minimizing the potential for side effects.[1–3] Technological advances in external beam radiation therapy have led to the development of IMRT, which can precisely target tumor tissue while limiting the dose to surrounding normal tissue. IMRT also allows for an increased radiation dose to the tumor without raising toxicity levels, and it is widely utilized in definitive radiotherapy for prostate cancer. In the United States, the rate of IMRT use in external beam radiation therapy treatment for prostate cancer rapidly increased from 28% in 2002 to 82% in 2005.[1] In addition to 3D-CRT and IMRT, new treatment techniques such as moderate hypofractionated radiotherapy, high-dose-rate brachytherapy, proton beam therapy, carbon-ion therapy, and image-guided radiotherapy are being utilized.[13–15] These advancements are anticipated to lead to further improvements in treatment outcomes. The effectiveness of rectal spacers, such as SpaceOAR, has also been reported in emerging treatment techniques, including proton beam therapy.[11,16]

However, compared with 3D-CRT, IMRT requires more equipment, physical technicians, and time. In Japan, due to issues such as facility standards, many facilities, like ours, currently do not have access to IMRT, and so 3D-CRT is still used for the treatment of prostate cancer patients.[5] As a result, our hospital decided to apply 3D-CRT for prostate cancer. If 3D-CRT is selected, the recommended radiation dose is usually lower than with IMRT to reduce the risk of adverse events, such as proctitis.[4] According to the guidelines, the recommended radiation dose for local radiotherapy for prostate cancer is 70–72 Gy for 3D-CRT and 74–78 Gy for IMRT.[4] In order to perform definitive radiation therapy similar to IMRT, it will be necessary to devise ways to reduce the risk of adverse events, such as proctitis.

Rectal toxicity can be reduced by injecting a spacer, such as SpaceOAR, between the rectum and prostate. SpaceOAR is a hydrogel spacer placed between the prostate and rectum.[4–11] It is used during radiation therapy to treat prostate cancer. The use of a spacer, such as SpaceOAR, is considered to reduce the radiation dose to the rectum and, therefore, decrease the incidence of radiation proctitis.

Spacers help protect adjacent organs, especially the rectum, from excessive radiation exposure. There have been numerous reports of their use in IMRT for the treatment of prostate cancer.[6] In our study, when a hydrogel spacer was not injected, there was a trend toward increased rectal toxicity after whole-pelvic irradiation or in patients receiving treatment with platelet aggregation inhibitors. We previously investigated the differences in prostate and rectal doses with and without SpaceOAR, as well as the changes in rectal dose when increasing the prescribed dose while using SpaceOAR. Our findings indicate that the use of SpaceOAR can effectively reduce the dose to the rectum during 3D-CRT for prostate cancer, while also allowing for an increase in the dose to 78 Gy over 39 fractions (Unpublished data). The results of our previous study, along with the current study, indicate that 3D-CRT can offer curative treatment for patients with prostate cancer without elevating the risk of rectal adverse events. It is significant that the effectiveness of the hydrogel spacer has been confirmed even in facilities that can only perform 3D-CRT according to facility standards, making it possible to provide curative radiation therapy to prostate cancer patients.

Technological advances such as multiparametric MRI, image-guided radiation therapy, and high dose rate radiation therapy have transformed the diagnosis and treatment of prostate cancer, improving cancer control and quality-of-life outcomes.[1] Ongoing studies using novel androgen receptor-targeted agents show promise for significantly improving clinical outcomes, such as metastasis-free prostate cancer-specific and overall survival rates, as well as health-related quality of life.[17]

This study had various limitations. This study was conducted at a single institution and included a limited number of cases; therefore, the calculation and justification of the sample size were not performed. Adverse events were retrospectively searched for in doctors' medical records. Therefore, it is possible that such events experienced by patients were not accurately identified. The spacer injection group included a limited number of patients surveyed and short observation period. However, there was a trend toward a lower incidence of adverse events involving the rectum in this group.

Conclusion

The injection of a hydrogel spacer prior to 3D-CRT for prostate cancer can lower rectal radiation exposure and reduce the likelihood of rectal complications, and may enable the use of higher radiation doses in the future.

Authors' contribution

TN is the corresponding author, managed the study with the design and implementation of the research with the analysis of the results, and oversaw the medical procedures. GK collected the data, managed the study with the design and implementation of the research with the analysis of the results, and oversaw the medical procedures. KI, HN, YI, and NH contributed to the design, implementation of the research and the analysis of the results. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Declaration of conflicting interests

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Ethical approval

The present study was approved by the Ethical Committee of the Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital (approval no. 05-004).

Informed consent

Written informed consent from the subjects and from the legally authorized representatives of the deceased subjects for the publication of this study was waived by the Ethical Committee of Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital. This study was conducted in accordance with the Declaration of Helsinki. We adopted patient-centered medical and health information management. Informed consent consisted of offering an option to opt-out.

Trial registration

Not applicable.

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