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Outcomes and Toxicities of Proton and Photon Radiation Therapy for Testicular Seminoma

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Abstract

Purpose: To determine the clinical outcomes and toxicities of proton beam therapy (PBT) versus 3D-conformal photon radiation therapy (XRT) in patients with testicular seminoma.

Materials and Methods: This observational study evaluated consecutive patients with testicular seminoma who were treated with inguinal orchiectomy and radiation therapy at a single, tertiary, high-volume center in 2008-19. Acute toxicity was scored with the Common Terminology Criteria for Adverse Events V 4.0. Organs at risk were contoured retrospectively by 2 investigators. Recurrences and secondary malignancies were based on routine follow-up imaging, either computed tomography or magnetic resonance imaging.

Results: Fifty-five patients were treated with radiation therapy, 11 in the PBT-arm and 44 in the XRT-arm, with a median follow-up interval of 61 months (interquartile range [IQR]: 32-79 months). Acute treatment-related diarrhea, grade 1 to 2, was more common among XRT-treated patients (0% vs 29.5%, $P = .039$), and dermatitis, grade 1, was more likely among PBT-treated patients (27.3% vs 2.3%, $P = .004$). Dosimetrically, PBT-treated patients, relative to XRT-treated patients, had lower dose to organs at risk including the kidney, bladder, femoral head, spinal cord, bowel, pancreas, and stomach. The 5-year overall survival rate was 100% and disease-free survival rate was 96.4% for all patients. Two patients, all in the XRT-arm, had disease recurrence: 1 in the pelvis and 1 in the lung. Three patients, all in the XRT-arm, were diagnosed with a secondary malignancy: 1 in-field pancreaticoblastoma, 1 in-field colon adenocarcinoma, and a stage IV T-cell lymphoma.

Conclusion: Proton beam therapy for testicular seminoma resulted in excellent clinical outcomes and was associated with lower rates of acute diarrhea but higher rates of acute dermatitis. Proton beam therapy resulted in no in-field secondary malignancies and a more favorable dosimetric profile for organs at risk relative to XRT. Reduced dose to organs at risk, such as the kidneys, may result in long-term improvement in function.

Keywords: testicular cancer; particle therapy; PBT; XRT

Introduction

Testicular seminoma is the most common solid malignancy affecting adolescent and young adult men and its incidence is rising worldwide [1]. After standard-of-care orchiectomy, adjuvant treatment options include chemotherapy and/or radiation therapy, both of which can have long-term effects on organ function and secondary malignancies.

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The young age of onset and the excellent long-term survival rates have increased emphasis on reducing radiation therapy–related morbidity by minimizing normal tissue exposure [2, 3]. Standard photon radiation therapy (XRT) for seminoma includes an anterior and posterior field that inadvertently passes through normal tissues such as the heart, kidneys, and gastrointestinal organs. Alternatively, proton beam therapy (PBT) uses posterior beam(s) without anterior exit dose, thereby sparing normal structures [4]. To date, apart from small case series and dosimetric analyses, no studies have directly compared these 2 radiation modalities in terms of long-term outcomes and toxicities [4, 5].

Materials and Methods

Patients

The institutional review board approved the data collection for this retrospective study evaluating consecutive patients treated with radiation therapy at a single tertiary cancer center in 2008-19. The start date of 2008 represented the first year a patient with testicular seminoma was treated with PBT. Disease was staged by using the American Joint Committee on Cancer (AJCC) 8th edition. All patients underwent abdominal/pelvic computed tomography (CT) scans; lung disease was ruled out with chest CT or x-ray. All patients underwent a radical inguinal orchiectomy and testicular seminoma and was confirmed pathologically, in most cases at our institution (90.9% [50 of 55]). Patients were referred for either adjuvant radiation therapy, defined as radiation therapy starting within 3 months of orchiectomy, or salvage radiation therapy, defined as failure after observation or systemic therapy. Patients were followed up every 6 to 12 months after radiation therapy with laboratory tests and imaging such as magnetic resonance imaging or CT of the chest, abdomen, or pelvis. Patient medical history was abstracted from the electronic health record. Liver disease was defined as any history of nonalcoholic steatohepatitis or cirrhosis, and cardiac disease was defined as any history of coronary artery disease, chronic heart failure, or cardiomyopathy.

Radiation Planning

Patients underwent treatment simulation while supine. The CT images acquired during simulation were imported to an XRT (Pinnacle, Philips Radiation Oncology Systems, Fitchburg, Wisconsin) or PBT (Eclipse, Varian Medical Systems, Palo Alto, California) treatment planning system to define target structures and organs at risk. To ensure consistency, 2 authors (D.P., S.P.) retrospectively contoured organs at risk (ie, stomach, liver, pancreas, large bowel, gastrointestinal bag, bladder, kidneys, kidney cortex, spinal cord, ipsilateral femoral head); original treatment fields were not altered. The ipsilateral femoral head was defined in relation to the side of the pelvic radiation field. The gastrointestinal bag was defined as all hollow organs (ie, stomach, small bowel, and colon) in the treatment field. Organs at risk were contoured in the same axial plane as the treatment field, plus 1 cm cranially and 1 cm caudally from the edge of the treatment field for serial structures (eg, bowel and spinal cord). Dose prescriptions for the PBT group used cGyRBE (henceforth referred to as cGy to be consistent with XRT prescription) and assumed a relative biological effectiveness of 1.1.

Patients with stage I disease were treated with a "para-aortic strip" field intended to target the para-aortic lymph node region [6, 7]. For XRT-treated patients, this typically entailed using a treatment field planning target volume (PTV) with cranial border at the top of the T12 vertebral body and caudal border at the bottom of the L5 vertebral body. For PBT-treated patients, a clinical target volume (CTV) was contoured that included the para-aortic lymph node region; a beam-specific PTV was generated based on the CTV because of range uncertainty to ensure adequate coverage from the top of the T12 vertebral body to the bottom of the L5 vertebral body. Patients with stage I disease were prescribed 2000 cGy in 200 cGy per fraction.

Patients with stage II disease were treated with a "modified dogleg," which included a para-aortic strip plus pelvic radiation field targeting the common, internal, and external iliac lymph node regions [7, 8]. For XRT-treated patients, this typically entailed a PTV with cranial border at the top of the T12 vertebral body and caudal border at the top of the acetabulum. For PBT-treated patients, a CTV of the para-aortic, common iliac, external iliac, and internal iliac lymph node regions was contoured; based on the CTV, a beam-specific PTV was generated because of range uncertainty to ensure adequate coverage from the top of the T12 vertebral body to the top of the acetabulum. For both PBT-treated and XRT-treated patients, the gross tumor volume was contoured and expanded to generate a PTV_boost volume. Patients with stage II disease were typically prescribed 2000 cGy in 200 cGy per fraction to the PTV followed by a boost of 1000 to 1600 cGy in 200-cGy fractions to the PTV_boost.

Photon radiation therapy was delivered by using an anterior and posterior 3D-conformal field. Proton beam therapy was delivered by using a single posterior field or 2 oblique posterior fields with final field arrangement determined from patient

anatomy and dose-distribution homogeneity. Proton beam therapy technique included passive scatter (36.4% [4 of 11]) or scanning beam (63.6% [7 of 11]). All plans were reviewed by at least 2 radiation oncologists for quality assurance.

Toxicity

Acute toxicity during radiation therapy was scored with the Common Terminology Criteria for Adverse Events version 4.0. Renal function was determined by using the estimated glomerular filtration rate (eGFR) based on the Chronic Kidney Disease Epidemiology Collaboration equation, which is adjusted for age, sex, race, and body surface area. Chronic kidney disease (CKD) was defined as stage 1 (normal) to 5 (kidney failure) according to the Improving Global Outcomes Clinical Practice Guideline [9].

Statistical Analysis

Patient, treatment, and toxicity characteristics in the PBT and XRT arms were compared by using a Pearson χ^2 test for categorical variables and Mann-Whitney *U* test for continuous variables. Continuous-variable dosimetric analyses comparing the PBT and XRT arms were analyzed by using a Mann-Whitney *U* test. Pairwise changes in eGFR and CKD were analyzed by using Wilcoxon signed rank tests. Statistical tests were based on a 2-sided significance level. *P* values of less than .05 were considered to indicate statistically significant differences. All analyses were completed by using SPSS Version 24.0 (IBM, Armonk, New York).

Results

Fifty-five patients were treated, 11 (20%) with PBT and 44 (80%) with XRT. The median follow-up time of 61 months for all patients (interquartile range [IQR]: 32-79 months) did not differ between the PBT group (median, 60 months) and XRT group (median, 62 months) ($P = .93$). No significant differences were found in patient or treatment characteristics (**Table 1**). Acute treatment-related diarrhea (grades 1-2) was more common among XRT-treated patients (0% vs 29.5%, $P = .039$), and dermatitis (all grade 1) was more likely among PBT-treated patients (27.3% vs 2.3%, $P = .004$; **Table 2**). No differences in acute nausea/emesis, fatigue, or dysuria were found between the XRT and PBT groups.

Dosimetric comparisons for PBT-treated patients versus XRT-treated patients are summarized in **Table 3**. Among 9 PBT-treated patients versus 25 XRT-treated patients with a para-aortic and pelvic radiation field, PBT-treated patients had lower average bladder doses (197 cGy [IQR: 107-329] vs 581 cGy [IQR: 234-731]; $P = .012$), and lower average femoral head doses (105 cGy [IQR: 84-196] vs 1051 cGy [IQR: 122-1666]; $P = .045$) (**Table 3**). Among the entire patient cohort, PBT-treated patients, versus XRT-treated patients, had a lower average spinal cord dose (1653 cGy [IQR: 1580-1734] vs 1937 cGy [IQR: 1873-2108]; $P < .0001$), lower maximum spinal cord dose (2233 cGy [IQR: 1941-2305] vs 2684 cGy [IQR: 2189-3084]; $P = .005$), lower average gastrointestinal bag dose (346 cGy [IQR: 210-516] vs 860 cGy [IQR: 771-958]; $P < .0001$), lower average colon dose (114 cGy [IQR: 44-266] vs 588 cGy [IQR: 455-717]; $P < .0001$), lower maximum colon dose (2154 cGy [IQR: 1994-2341] vs 2709 cGy [IQR: 2105-3161]; $P = .008$), lower average pancreas dose (692 cGy [IQR: 480-1274] vs 1789 cGy [IQR: 1392-1990]; $P = .001$), lower average stomach dose (24 cGy [IQR: 4-65] vs 469 cGy [IQR: 174-691]; $P < .0001$), lower maximum stomach dose (1782 cGy [IQR: 198-1963] vs 2121 cGy [IQR: 1903-2209]; $P = .010$), lower median unilateral kidney dose (47 cGy [IQR: 21-164] vs 142 cGy [IQR: 114-192]; $P = .010$; **Appendix Figure**), and lower median bilateral kidney dose (72 cGy [IQR: 40-208] vs 221 cGy [IQR: 172-280]; $P = .009$) (**Table 3**).

Given the dosimetric differences to the kidneys, we explored the effect of PBT versus XRT on eGFR and CKD in patients who had a baseline eGFR and at least 1 follow-up eGFR with no history of chemotherapy exposure (**Appendix Table 1** and **Appendix Table 2**). The median baseline eGFR was 106 mL/min/1.73 m^2 (IQR: 96-118) for PBT-treated patients and 95 mL/min/1.73 m^2 (IQR: 80-104) for XRT-treated patients ($P = .054$). The median time between baseline and most recent follow-up eGFR was 43 months (IQR: 28-58 months) for PBT-treated patients and 76 months (IQR: 43-103 months) for XRT-treated patients ($P = .033$). At the follow-up period of 36 to 47 months for PBT-treated patients, the median eGFR was 95 mL/min/1.73 m^2 (IQR: 91-103) and was a median decline of 9 points from baseline ($P = .144$; **Appendix Table 1**). At the follow-up period of 72 to 84 months for the XRT-treated patients, the median eGFR was 87 mL/min/1.73 m^2 (IQR: 81-95) with a median decline of 10 points from baseline ($P = .043$; **Appendix Table 1**). Among PBT-treated patients, eGFR did not differ from baseline versus most recent follow-up (median eGFR, 106 mL/min/1.73 m^2 [IQR: 96-118] vs 108 mL/min/1.73 m^2 [IQR: 91-118], $P = .161$). In contrast, XRT-arm patients experienced a decrease in eGFR from baseline to last follow-up (median eGFR, 95 mL/min/1.73 m^2 [IQR: 80-104] vs 76 mL/min/1.73 m^2 [IQR: 68-101], $P = .033$). Comparing CKD stage from baseline to the most recent

Table 1. Patient and treatment characteristics.

	PBT-Arm (n = 11), % (n)	XRT-Arm (n = 44), % (n)	*P* value[a]
Age, median (range), y	36 (17-65)	39 (21-65)	.080
Adjuvant radiation therapy treatment[b]	54.5 (6)	77.3 (34)	.130
Ethnicity			.192
Caucasian	63.6 (7)	81.8 (36)	
Hispanic	36.3 (4)	18.2 (8)	
History of diabetes mellitus	0	11.4 (5)	.241
History of hypertension	9.1 (1)	31.8 (14)	.130
History of liver disease	0	6.8 (3)	.373
History of cardiac disease	0	9.1 (4)	.299
History of smoking	36.4 (4)	27.3 (12)	.553
History of hyperlipidemia	0	25 (11)	.064
Any comorbidity risk factor[c]	45.5 (5)	56.8 (25)	.498
History of platinum chemotherapy	9.1 (1)	15.9 (7)	.566
One cycle	0	2.3 (1)	
Two cycles	9.1 (1)	0	
Three cycles	0	2.3 (1)	
Four cycles	0	9.1 (4)	
Seven cycles	0	2.3 (1)	
History of etoposide chemotherapy	9.1 (1)	15.9 (7)	.566
One cycle	0	2.3 (1)	
Two cycles	9.1 (1)	0	
Three cycles	0	4.5 (2)	
Four cycles	0	6.8 (3)	
Seven cycles	0	2.3 (1)	
Pathologic tumor stage			.366
T1	81.8 (9)	61.4 (27)	
T2	9.1 (1)	29.5 (13)	
T3	9.1 (1)	9.1 (4)	
Clinical nodal stage			.754
N0	54.5 (6)	47.7 (21)	
N1	18.2 (2)	25.0 (11)	
N2	27.3 (3)	20.5 (9)	
N3	0	6.8 (3)	
Summative stage			.854
IA	45.5 (5)	36.4 (16)	
IB	9.1 (1)	11.4 (5)	
IIA	18.2 (2)	25.0 (11)	
IIB	27.3 (3)	20.5 (9)	
IIC	0	6.8 (3)	
Pathologic tumor size, median (range), cm	3.5 (2-12)	4.5 (0.7-13)	.082
Pathologic lymphovascular invasion			.250
Yes	18.2 (2)	36.4 (16)	
No	81.8 (9)	63.6 (28)	
Pathologic spermatic cord invasion			.194
Yes	0	13.6 (6)	
No	100 (11)	86.4 (38)	
Pathologic rete testis invasion			.243
Yes	18.2 (6)	29.5 (13)	
No	0	6.8 (3)	
Not mentioned	45.4 (5)	63.6 (28)	

Table 1. Continued.

	PBT-Arm (n = 11), % (n)	XRT-Arm (n = 44), % (n)	*P* value[a]
Radiation dose, median (range), cGy	3000 (2000-3000)	2600 (2000-3600)	.070
Radiation field type			.127
Para-aortic only	18.2 (2)	43.2 (19)	
Para-aortic + pelvic	81.8 (9)	56.8 (25)	

[a]Assessed by using Pearson χ^2 tests for categorical variables and Mann-Whitney *U* tests for continuous variables.

[b]Defined as radiation therapy that was administered within 3 months after orchiectomy.

[c]Defined as patient having any risk factor such as hypertension, liver disease, cardiac disease, smoking, or hyperlipidemia.

Abbreviations: PBT, proton beam therapy; XRT, photon radiation therapy.

follow-up, PBT-arm patients had relatively constant CKD stage (median, 1 [IQR: 1-1] vs 1 [IQR: 1-1], $P = .317$); similarly, XRT-arm patients also had relatively constant CKD stage (median, 1 [IQR: 1-2] vs 2 [IQR: 1-2], $P = .102$).

Among all patients, the 5-year overall survival and disease-free survival rates were 100% and 96.4%. Two patients, both in the XRT arm, experienced disease relapse within 5 years: 1 pelvic (7 months after XRT) and 1 lung (26 months after XRT). Three patients, all in the XRT arm, had a secondary malignancy: pancreaticoblastoma (in-field, occurring 99 months after XRT), transverse colon adenocarcinoma (in-field, occurring 59 months after XRT), and T-cell lymphoma (stage IV, occurring 38 months after XRT). The low secondary malignancy event rate precluded adequate statistical analysis.

Discussion

To our knowledge, this is the first study demonstrating a clinical benefit from PBT, compared with XRT, among consecutively treated patients with testicular seminoma. Although PBT led to higher rates of mild nondesquamating acute skin toxicity, PBT was also associated with lower rates of acute gastrointestinal toxicity and did not compromise long-term clinical outcomes. The lower doses from PBT to organs at risk such as bladder, femoral head, spinal cord, bowel, stomach, pancreas, and kidney may decrease morbidity, but this would require vigilant follow-up and investigation.

Seminal publications over the past 2 decades have led to a paradigm shift in the treatment of early-stage testicular seminoma, with a trend toward judicious surveillance and deintensification of therapy [3, 10, 11]. Given the high probability for cure, the oncologic community has become more mindful of the morbidity associated with treatment, as both adjuvant chemotherapy and radiation therapy have inherent long-term risks [12]. The late morbidities associated with systemic therapy include secondary solid tumor malignancies and leukemias, pulmonary toxicity secondary to bleomycin, nephrotoxicity secondary to platinum agents, cardiovascular disease as a result of nephrotoxicity, and infertility [13–20]. Meanwhile, XRT late effects relate to treatment fields and include nephrotoxicity, secondary solid tumor malignancies, and cardiovascular disease [2, 19]. De-escalation of XRT has already been implemented in a variety of ways over the years, from shrinking field sizes to reductions in dose [3, 6, 21]. Proton beam therapy has the potential to further improve the therapeutic ratio given the inherent physical properties that minimize exit dose to organs at risk [4].

Table 2. Toxicities during radiation therapy treatment.

	PBT-Arm (n = 11), % (n)	XRT-Arm (n = 44), % (n)	*P* value[a]
Nausea and/or emesis	54.5 (6)	75.0 (33)	.182
Grade 1	45.5 (5)	75.0 (33)	
Grade 2	9.1 (1)	0	
Diarrhea	0	29.5 (13)	.039
Grade 1	0	25.0 (11)	
Grade 2	0	4.5 (2)	
Dermatitis (grade 1)	27.3 (3)	2.3 (1)	.004
Dysuria (grade 1)	0	0	1.000
Fatigue (grade 1)	45.5 (5)	22.7 (10)	.130

[a]Assessed by using Pearson χ^2 tests.

Abbreviations: PBT, proton beam therapy; XRT, photon radiation therapy.

Table 3. Organs-at-risk dosimetric analysis for patients receiving photon radiation therapy versus proton beam therapy.

	PBT (n = 11), Median Value (IQR)	XRT (n = 44), Median Value (IQR)	*P* value[a]
Bladder average dose, cGy[b]	197 (107-329)	581 (234-731)	.012
Bladder max dose, cGy[b]	1910 (1634-2074)	2096 (1942-2134)	.163
Ipsilateral femoral head average dose, cGy[b]	105 (84-196)	1051 (122-1666)	.045
Ipsilateral femoral head, max dose, cGy[b]	1531 (1105-1706)	2050 (1208-2082)	.072
Spinal cord average dose, cGy	1653 (1580-1734)	1937 (1873-2108)	<.0001
Spinal cord max dose, cGy	2233 (1941-2305)	2684 (2189-3084)	.005
Gastrointestinal bag, average dose, cGy[c]	346 (210-516)	860 (771-958)	<.0001
Gastrointestinal bag, max dose, cGy[c]	3153 (2777-3177)	2779 (2218-3239)	.556
Colon average dose, cGy	114 (44-266)	588 (455-717)	<.0001
Colon max dose, cGy	2154 (1994-2341)	2709 (2105-3161)	.008
Liver average dose, cGy	62 (27-156)	158 (51-242)	.058
Liver max dose, cGy	2114 (2042-2156)	2096 (1636-2166)	.514
Pancreas average dose, cGy	692 (480-1274)	1789 (1392-1990)	.001
Pancreas max dose, cGy	2086 (1886-2179)	2104 (2056-2146)	.705
Stomach average dose, cGy	24 (4-65)	469 (174-691)	<.0001
Stomach max dose, cGy	1782 (198-1963)	2121 (1903-2209)	.010
Unilateral kidney average dose, cGy[d]	306 (288-492)	429 (338-546)	.377
Unilateral kidney V5, %	20 (18-33)	24 (18-31)	.899
Unilateral kidney V20, %	3 (1-6)	1 (0-5)	.509
Unilateral kidney D50%, cGy	47 (21-164)	142 (114-192)	.010
Bilateral kidney average dose, cGy)[e]	479 (467-871)	633 (496-808)	.752
Bilateral kidney V5, %	31 (30-53)	36 (26-45)	.449
Bilateral kidney V20, %	4 (1-9)	2 (0-6)	.337
Bilateral kidney D50%, cGy	72 (40-208)	221 (172-280)	.009

[a]Assessed XRT and PBT group by using Mann-Whitney *U* tests.

[b]Assessed only patients with para-aortic plus pelvic radiation field (n = 9 PBT; n = 25 XRT).

[c]Defined as all hollow organs (ie, stomach, small bowel, and colon) in the treatment field.

[d]Unilateral is defined as the kidney, left or right, receiving the highest dose.

[e]Bilateral is defined as left and right kidney combined.

Abbreviations: PBT, proton beam therapy; IQR, interquartile range; XRT, photon radiation therapy; V5, volume of kidney receiving at least 500 cGy; V20, volume of kidney receiving at least 2000 cGy; D50%, median dose to the kidney.

In the current study, PBT produced clinical outcomes similar to those for XRT at a median follow-up interval of 5 years. From an acute toxicity standpoint, PBT was associated with higher rates of dermatitis and lower rates of diarrhea. These results are consistent with observational studies of disease at other sites, as PBT tends to have high entrance and skin doses, particularly when passive scatter techniques are used; however, unlike other disease sites, PBT had no desquamation or long-term sequelae given the relatively low doses [22]. Moreover, we would expect the rates of dermatitis to improve if all patients were treated with modern scanning beam proton radiation therapy, as opposed to passive scatter technique [23]. Lower mean doses to gastrointestinal organs such as the small bowel, colon, and stomach were probably the reason for decreased acute diarrhea, but PBT did not impact nausea or emesis. Analogously, lower rates of acute gastrointestinal toxicity have been observed with PBT, relative to intensity-modulated radiation therapy, among patients with gastrointestinal malignancies as a result of the dosimetric differences between the 2 modalities [24, 25].

Beyond the improved dose distribution to hollow gastrointestinal organs, additional dosimetric advantages with PBT included lower dose to the bladder, femoral head, spinal cord, pancreas, and kidney. The long-term clinical implications of statistically lower dose to organs at risk are unclear and cannot be answered by the present study, with its median 5-year follow-up period. However, the main concern is the risk of secondary solid tumors, which was noted in the present study for 2 patients who experienced an in-field solid secondary tumor, all in the XRT arm. A thoughtful approach is necessary, as these patients are at much higher risk of developing secondary tumors than is the general population [13]. Although chemotherapy alone and radiation therapy alone are comparable in the risk of secondary malignancy (relative risks of 2.0 and 1.8), combination therapy poses the greatest risk (relative risk 2.9) [13]. As treatment patterns have already shifted to upfront curative systemic monotherapy, radiation oncologists will surely encounter more salvage therapy scenarios. Combining de-

escalation strategies through shrinking fields, lower doses, and minimizing organ-at-risk exposure with PBT may be the natural path forward to ensure optimal local control while reducing treatment sequelae.

Beyond secondary malignancy rates, minimizing dose to organs at risk may also preserve organ function. In our exploratory analysis of nephrotoxicity based on the observed dosimetric differences to the kidney, the effects of PBT, relative to XRT, were not entirely clear. Because chemotherapy agents can lead to an eGFR decline in upwards of 30% or patients, when we excluded patients who had received chemotherapy we observed stable renal function in those treated with PBT, but those in the XRT-arm were noted to have a decline in renal function [19, 26]. This phenomenon could be related to dosimetric effects, as the renal parenchyma is exquisitely sensitive to low doses of radiation therapy, even the remarkably low median unilateralkidney dose in both the PBT-arm (47 cGy) and XRT-arm (142 cGy) (Table 3) [19, 27, 28]. Alternatively, the small patient population, inconsistent renal function testing across set time points, and general treatment-arm imbalances could be confounding the results. In particular, XRT-arm patients had longer eGFR follow-up, which may give the appearance of worse renal function when PBT-treated patients had not had enough time to develop renal changes. Further follow-up and external confirmation will be necessary, given that patients such as ours may continue to develop renal changes up to 12 to 15 years after radiation therapy [19].

Despite the clinical and dosimetric advantages of PBT, numerous access barriers are present for patients with testicular seminoma. Although national policy recommendations for PBT include intra-abdominal malignancies (eg, hepatobiliary and adrenal) and malignancies affecting pediatric patients, PBT for testicular seminoma has not been embraced despite its intra-abdominal/retroperitoneal location and high incidence among young adults [29]. Currently, the American Society for Radiation Oncology Model Policies and the National Comprehensive Cancer Network guidelines do not address PBT as an option for testicular seminoma; consequently, only 1 insurance company policy covers its use routinely [30]. Given the growing body of evidence, we advocate that national policy recommendations and insurance coverages be revised to include PBT as a possible treatment option.

Several limitations should be noted when interpreting our results. Most importantly, the retrospective nature of this study has inherent imbalances between the 2 treatment groups, which can be accounted for only in a randomized controlled trial (RCT) setting. However, these results may represent the highest level evidence as an RCT is unlikely in this setting because of the tendency for observation after orchiectomy, low disease incidence, and lack of widespread PBT availability. Another point of consideration is the small number of patients treated with PBT in comparison difficult to XRT-treated patients, which makes drawing firm conclusions difficult. However, a factor contributing to the limited numbers of patients undergoing PBT is insurance coverage, since several XRT-treated patients were initially planned for PBT but ultimately denied by insurers. In turn, insurance denial makes it difficult to accumulate meaningful numbers of patients to compare and contrast treatments.

In conclusion, for patients with testicular seminoma, PBT was associated with superior acute gastrointestinal toxicity, worse mild nondesquamating acute skin toxicity, and no differences in clinical outcomes compared with XRT. Proton beam therapy dose reductions to organs at risk such as bladder, femoral head, spinal cord, bowel, stomach, pancreas, and, particularly, kidney may decrease morbidity but requires vigilant follow-up and investigation. Among patients being considered for radiation therapy, our findings support updating guidelines to include PBT as a treatment option and to encourage providers to refer patients to a high-volume center to discuss PBT as a treatment option.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: Steven J. Frank, MD, is an Associate Editor of the *International Journal of Particle Therapy*. The authors report no other conflicts of interest relevant to this work. Steven J. Frank, MD, reports personal fees from Varian, C4 imaging, Hitachi, Boston Scientific, and the National Comprehensive Cancer Center; grants from C4 Imaging, Eli Lilly, Elekta, and Hitachi; and advisory board positions for Breakthrough Chronic Care, Hitachi, and Varian.
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Appendix Table 1. Estimated glomerular filtration rate differences from baseline to various follow-up time points among patients who received proton and photon radiation therapy without history of chemotherapy exposure.

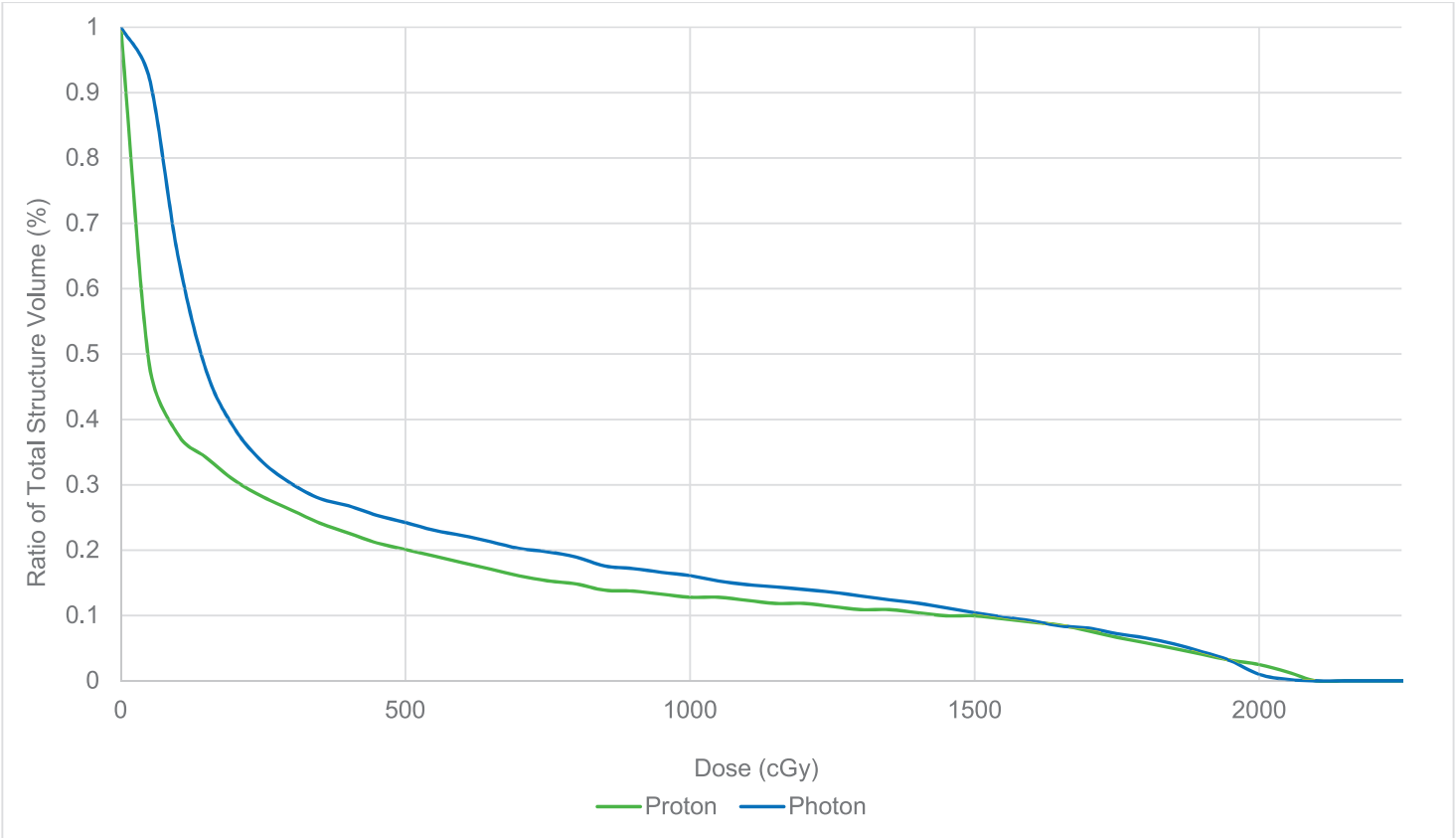
	Months after Baseline										
	6-11	12-23	24-35	36-47	48-59	60-71	72-83	84-95	96-107	108-119	120-132
Proton therapy											
Median eGFR difference from baseline	1	2	−3	−9	−8	1	1	−9			
IQR	0 to 5	1 to 7	−4 to −2	−10 to −6	−13 to −1	1 to 1	1 to 1	−9 to −9			
P value[a]	.345	.249	.345	.144	.273	.317	.317	.317			
Photon therapy											
Median eGFR difference from baseline	1	3	0	−4	−5	0	−10	−4	−17	−15	
IQR	−7 to 12	−1 to 11	−5 to 7	−11 to 1	−7 to 2	−6 to 11	−21 to −5	−6 to 8	−20 to −5	−17 to −13	
P value[b]	.398	.374	.799	.176	.398	.345	.043	.686	.043	.180	

[a]Wilcoxon signed rank test comparing baseline median eGFR values to median eGFR values at each time point among patients who received proton radiation therapy.
[b]Wilcoxon signed rank test comparing baseline median eGFR values to median eGFR values at each time point among patients who received photon radiation therapy.
Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range.

Appendix Table 2. Estimated glomerular filtration rate differences from baseline to various follow-up time points among all patients who received proton and photon radiation therapy.

	Months after Baseline										
	6-11	12-23	24-35	36-47	48-59	60-71	72-83	84-95	96-107	108-119	120-132
Proton therapy											
Median eGFR difference from baseline	0	2	−3	−9	−8	1	1	−9			
IQR	−1 to 4	1 to 6	−5 to −2	−10 to −6	−13 to −1	1 to 1	1 to 1	−9 to −9			
P value[a]	.612	.176	.237	.144	.273	.317	.317	.317			
Photon therapy											
Median eGFR difference from baseline	−5	−1	−5	−11	−6	−5	−10	−4	−17	−19	−35
IQR	−14 to 4	−11 to 9	−13 to 4	−19 to −2	−12 to −2	−9 to 9	−21 to −5	−6 to 8	−20 to −5	−26 to −15	−35 to −35
P value[b]	.363	.691	.215	.015	.075	.866	.028	.686	.063	.109	.317

[a]Wilcoxon signed rank test comparing baseline median eGFR values to median eGFR values at each time point among patients who received proton radiation therapy.
[b]Wilcoxon signed rank test comparing baseline median eGFR values to median eGFR values at each time point among patients who received photon radiation therapy.
Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range.



Appendix Figure. Dose-volume histogram for kidney receiving highest radiation dose for all patients in the photon versus proton radiation therapy group.