Table 2 Situation of SRT for lung tumor

	Responding institution (*n*)	Classification	*n*	Ratio (%)
Institutions equipped for SRT	473		205	43.3
Types of body immobilization system (multiple answers allowed)	195	Stereotactic body frame	13	6.7
		Vacuum cushion with a sheet covering a patient	32	16.4
		Thermoplastic shell	80	41.0
		Baseplate	53	27.2
		Vacuum cushion	144	73.5
		Others	12	6.2
Methods against respiratory motion in RT planning CT (multiple answers allowed)	204	Long-time scan CT	61	29.9
		4DCT	76	37.3
		Respiratory phase fusion	78	38.2
		Multicycle CT fusion	46	22.5
		Others	46	22.5
		None	5	2.5
Methods of control for respiratory motion during irradiation (multiple answers allowed)	165	Respiratory depression	93	56.4
		Breath hold	58	35.2
		Synchronism	48	29.1
		Real-time tracking	5	3.0
		Others	8	4.8
Methods of respiratory depression during irradiation	92	Chest and abdomen	26	28.3
		Abdomen	37	40.2
		Chest	4	4.3
		Others	25	27.2
Breath-hold timing during irradiation	55	Expiration	32	58.2
		Inspiration	16	29.1
		Others	7	12.7
Controllable beam linked to respiration monitoring	128		55	43.0

SRT, stereotactic radiotherapy; CT, computed tomography; 4DCT, four-dimensional computed tomography.

IGRT Situation

Table 4 shows the actual conditions of IGRT. Institutions equipped for IGRT were at a ratio of 46.8%. Institutions with all patients treated with IGRT were at a ratio of 25.7%. The most general or common site treated with IGRT was the prostate, and only 40% of the institutions treated all brain and head and neck sites with IGRT. Daily registration and repositioning of IGRT were implemented mainly by RTTs and MPs/RQMs under ROs cooperation. Metal marker was used in only 13% of the institutions.

QA/QC Situation of High-Precision RT

Table 5 shows the actual conditions of QA/QC in high-precision and conventional RT. In most of the institutions, points of QA/QC were clearly stated, while QA/QC records were under storage. In about a half of the institutions, the quality manager of both RT unit and RT planning system was RTT. Transferred beam data from RT planning systems were checked by two or more RTTs or MPs/RQMs in ~90% of the institutions. The median time required for QA of IMRT at any site of brain, head and neck and prostate was 4 h, and the time ranges were very broad among institutions. QA activity of IMRT was in operation after clinical hours in >60% of the institutions.

DISCUSSION

This study clearly indicated one major issue of the current high-precision RT in Japan. The issue is a manpower shortage, especially in the area relevant to QA/QC. We demonstrated that MPs and/or RQMs were not involved in more than

Table 3 Situation of IMRT

	Responding institution (*n*)	Classification	*n*	Ratio (%)
Institutions equipped for IMRT	478		156	32.6
Sites treated with IMRT (multiple answers allowed)	151	Brain	72	46.8
		Head and neck	92	59.7
		Prostate	149	96.8
		Others	63	40.9
Median interval between initial consultation and IMRT start (days)	73	Brain	10 days (2–28)	
	89	Head and neck	14 days (3–42)	
	122	Prostate without NHT	21 days (2–365)	
	120	Prostate with NHT	90 days (5–365)	
IMRT methods (multiple answers allowed)	150	Step and shoot	60	40.0
		Sliding window	80	53.3
		VMAT	31	20.7
		Helical tomotherapy	13	8.7
		Others	1	0.7
Calculation algorithm	150	Monte Carlo	5	3.3
		Superposition	58	38.7
		AAA	60	40.0
		Convolution	10	6.7
		Others	17	11.3
Inhomogeneity correction	148		145	98.0
Absorption correction of bed in monitor units (MU) calculation	148		80	54.1
Use of shell necessary for absorption correction in MU calculation	147		37	25.2
Absorption correction of shell in MU calculation	36		24	66.7

IMRT, intensity-modulated radiotherapy; MU, monitor units, NHT, neoadjuvant hormonal therapy.

one-third of the institutions. The process of RT essentially requires the understanding of the principles of medical physics, radiobiology, radiation safety, dosimetry, RT planning, the simulation and interaction of RT (5). Each process needs QA/QC to treat patients correctly. Ishikura (5) strongly intensified the importance of QA in the review article entitled 'Quality Assurance of Radiotherapy in Cancer Treatment: Toward Improvement of Patient Safety and Quality of Care'. A jarring fact was cited in this article that up to 2% of patients had died due to radiation overdose toxicity in middle- and high-income countries in the last three decades. In addition, most incidents had occurred in the planning stage during the introduction of new systems and/or equipment. Especially for the new high-precision RT techniques such as SRT and IMRT, activities or actions, testing and measurements are essential to maintain the quality. However, the approval of the Cancer Control Act in 2006 encouraging an increase of ROs and MPs to support QA/QC specialization for RT, might improve these situations in a future. On the other hand, we need to recognize that the establishment of adequate IMRT requires not only a sufficient number of operating staffs, but also the preparation of IMRT training programs, depending on

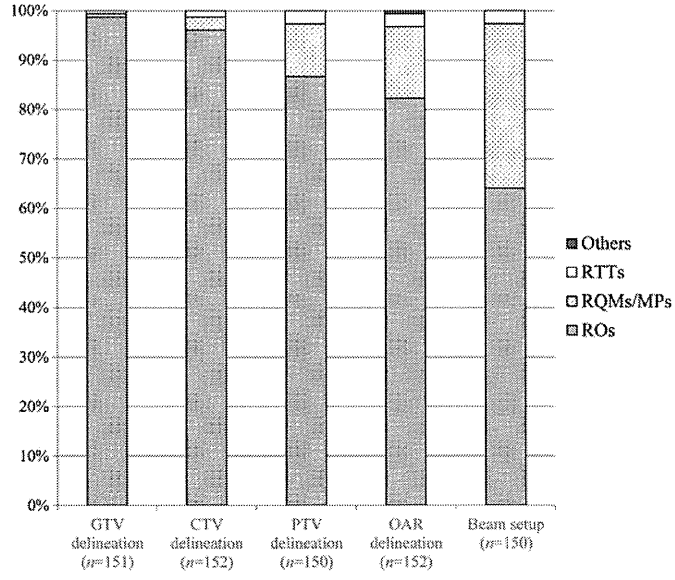

Figure 2. Assigned tasks among radiation oncologists (ROs), radiotherapy technologists (RTTs), medical physicists (MPs) and radiotherapy quality managers (RQMs) in intensity-modulated radiotherapy (IMRT) planning. GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; OAR, organs at risk.

Table 4 Situation of image-guided radiation therapy (IGRT)

	Responding institution (*n*)	Classification	*n*	Ratio (%)
Institutions equipped for IGRT	485		227	46.8
IGRT use	226	All cases	58	25.7
		Partial cases	155	68.6
Sites treated with IGRT	155	Brain	66	42.6
		Head and neck	68	43.9
		Lung	102	65.8
		Breast	8	5.2
		Uterus	32	20.6
		Prostate	149	96.1
Daily registration and repositioning in IGRT	225	ROs	70	31.1
		RTTs	210	93.3
		RQMs/MPs	68	30.2
Types in two-dimensional (2D) matching	222	None	24	10.8
		kV 2D	210	69.4
		EPID	68	32.9
		Others	9	4.1
Types in three-dimensional (3D) matching	226	None	23	10.2
		kV cone beam CT	150	66.4
		CT on rail	17	7.5
		MV cone beam CT	29	12.8
		Helical MVCT	13	5.8
		Others	8	3.5
Types in other IGRT methods	201	None	165	82.1
		RTRT	5	2.5
		Metal marker	21	10.5
		Ultrasonic device	7	3.5
		Others	8	4.0
Use of skin marker in IGRT	224		211	94.2

IGRT, image-guided radiation therapy; EPID, electronic portal imaging device; MVCT, megavoltage computed tomography; RTRT, real-time tumor-tracking radiotherapy.

the operating staff in a radiation department (6). The ranges of the time required for QA of IMRT were very broad among institutions, as shown in Table 5. The time required for QA of IMRT is considered to depend on mainly two factors. One of the factors is the use of a convenient tool for QA of IMRT. For example, in the institutions equipped with MapCHECK (7) the time required for QA of IMRT is considered to be shorter than in the institutions without such a useful tool. A second factor may be due to the level of proficiency of IMRT QA. IMRT QA is a time-consuming task in the institutions at the start of IMRT. Our study also indicated the oppressive working conditions of MPs and RQMs because they also worked in part as RTTs (the workload reaching around 20% of the workload as MPs/ROMs along the rule of Japanese public health insurance reimbursement). In addition, IMRT QA activity was operated after clinical hours in >60% of the institutions. These results revealed the fact that their role in the clinic was not recognized as a full-time position only for services as MPs and RQMs. On the other hand, transferred MU data from RT planning systems were not verified in ~10% of the institutions, as shown in Table 5. From an international viewpoint, the QA/QC systems are insufficient in terms of the staff number in hospitals in Japan (8). An adequate QA/QC system should be established in every hospital for the use of advanced RTTs (9).

The professional RT team is composed of ROs, RTTs, MPs, RQMs and certified nurses. Each process fulfilled by these specialists is requisite for the start and continuation of RT. This study clearly indicates a shortage of RT nursing certified staffs. They were assigned in only 18.4% of the

Table 5 Situation of QA and QC in high-precision and conventional RT

	Responding institution (*n*)	Classification	*n*	Ratio (%)
Cleary-stated points of QA/QC	475		358	75.4
Save of QA/QC record	479		467	97.5
Quality manager of RT unit	480	RTTs	282	58.8
		MPs	71	14.8
		RQMs	127	26.5
Quality manager of RT planning system	474	ROs	40	8.4
		RTTs	227	47.9
		MPs	92	19.4
		RQMs	115	24.3
Verification of transferred beam data from RT planning system	472	Two or more	411	87.1
		One	57	12.1
		None	4	0.8
Verification of transferred MU data from RT planning system	474	428	90.3	
Methods of verification of transferred MU data from RT planning system (multiple answers allowed)	424	Other software or manual calculation	347	81.8
		Actual measurement by phantom	195	46.8
		Others	14	3.3
Median time required for IMRT QA (h)	72	Brain	4 h (0.5–48)	
	95	Head and neck	4 h (0.5–72)	
	144	Prostate	4 h (0.3–48)	
Hours of QA for IMRT	151	Usual business hours	56	37.1
		After hours	95	62.9

QA, quality assurance; QC, quality control .

institutions, although nurses assigned to linear accelerator operation were at a ratio of 73.2% of the institutions. Such a certified nurse undertakes mainly three important roles; high-level nursing to patients and families using the skilled nursing art, education to other nurses in the nursing technique and counseling to other nurses. RT nursing certified staffs are expertise in the prevention, relief and self-care support of the side-effects conditions following RT and the offer of safe and comfortable medical treatment environment. Their work will be increasingly important to cope effectively with the increase of treatment intensity such as the combination with molecular target drugs in RT clinical practice (10).

Table 2 shows various methods in SRT for lung tumor. The most general or common type of body immobilization systems was a vacuum cushion. Methods against respiratory motions in RT planning CT were also diverse. As every system has some drawback and advantage, additional institutional QA tests are required to prevent errors and to give high confidence that patients will receive the prescribed treatment correctly. As shown in Table 4, various methods were also used for IGRT like SRT. Nakamura et al. (11) reported the prevalence of treatment techniques including IMRT and IGRT for prostate cancer in Japan. Their study reported a great variety of treatment methods among facilities such as radiation doses and the pretreatment condition of bladder and rectum. Our current study plays an important role as future reference data because the questionnaire represented on the graphical user interface of the web access can be reused in a future survey. JASTRO has published guidelines for quality management in SRT, IMRT and IGRT for domestic RT institutions (12). We can now provide a reference material for revision of the QA/QC guidelines.

Institutions equipped for IMRT and IGRT occupied 32.6 and 46.8%, respectively, of the responded institutions. The most general or common site treated with IMRT or IGRT was the prostate in this questionnaire. In 2020, prostate will be at the highest prevalence in men (13). Localized prostate cancer patients usually have some radical treatment choices such as radical prostatectomy, IMRT, brachytherapy, particle therapy and robotic surgery of which implementation has been started recently. However, high-risk prostate cancer is still at a large ratio in Japan (14). As all localized prostate cancer patients can have an indication for RT regardless of their T-stage, the spread of high-precision RT owing to IMRT combined with

IGRT for prostate cancer is considered to be a favorable situation. RT operation for patients with cancers initially diagnosed remains at a ratio as low as 27.6%, less than half that recorded in USA and European countries (1). In developed countries in Europe, as well as in the USA, RT for cancer treatment is carried out at a ratio as high as 50% or more because there are sufficient RT facilities and personnel, such as ROs, MPs and RTTs (14). Therefore, monitoring these structural data is significant.

There is one problem that limits the interpretation of this questionnaire-based survey. The response ratios of the similar structure survey studies were 90.9 and 94.2% (1,15). The response ratio of our current survey was lower than those of other studies. We think that this low response ratio was mainly due to the institutions which had not carried out the high-precision RT. As people in those institutions might understand that they were unrelated with our survey, they could not reply to this questionnaire.

In conclusion, our results of the questionnaire in 2012 about personnel, treatment planning and processes, QA/QC relating to SRT, IMRT and IGRT in institutions equipped with RT machines in Japan clearly suggested a manpower shortage in the current high-precision RT, especially in the area relevant to QA/QC. The manpower shortage should be corrected to prevent errors on high-precision RT. We also reveal that various methods are available in high-precision RT. Thus, this report apparently plays an important role as reference data in the future of radiation oncology in Japan.

Acknowledgements

The authors thank all members for response and replies to this questionnaire. Their cooperation in providing valuable information makes this study possible.

Funding

This study was supported by the grant-in-aid for Scientific Research: Third Term Comprehensive Control Research for Cancer (H23-007) from the Ministry of Health, Labor and Welfare in Japan.

Conflict of interest statement

None declared.

References

1. Teshima T, Numasaki H, Nishio M, et al. Japanese structure survey of radiation oncology in 2009 based on institutional stratification of the Patterns of Care Study. *J Radiat Res* 2012;53:710–21.
2. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? *Int J Radiat Oncol Biol Phys* 2011;81:1352–8.
3. Alicikus ZA, Yamada Y, Zhang Z, et al. Ten-year outcomes of high-dose, intensity-modulated radiotherapy for localized prostate cancer. *Cancer* 2011;117:1429–37.
4. Tomita N, Soga N, Ogura Y, et al. Preliminary results of intensity-modulated radiation therapy with helical tomotherapy for prostate cancer. *J Cancer Res Clin Oncol* 2012;138:1931–6.
5. Ishikura S. Quality assurance of radiotherapy in cancer treatment: toward improvement of patient safety and quality of care. *Jpn J Clin Oncol* 2008;38:723–9.
6. MacKay RI, Staffurth J, Poynter A, Routsis D. UK guidelines for the safe delivery of intensity-modulated radiotherapy. *Clin Oncol (R Coll Radiol)* 2010;22:629–35.
7. Jursinic PA, Sharma R, Reuter J. MapCHECK used for rotational IMRT measurements: step-and-shoot, TomoTherapy, RapidArc. *Med Phys* 2010;37:2837–46.
8. Teshima T. Patterns of care study in Japan. *Jpn J Clin Oncol* 2005;35:497–506.
9. Shikama N, Tsujino K, Nakamura K, Ishikura S. Survey of advanced radiation technologies used at designated cancer care hospitals in Japan. *Jpn J Clin Oncol* 2014;44:72–7.
10. Okano S, Yoshino T, Fujii M, et al. Phase II study of cetuximab plus concomitant boost radiotherapy in Japanese patients with locally advanced squamous cell carcinoma of the head and neck. *Jpn J Clin Oncol* 2013;43:476–82.
11. Nakamura K, Akimoto T, Mizowaki T, et al. Patterns of practice in intensity-modulated radiation therapy and image-guided radiation therapy for prostate cancer in Japan. *Jpn J Clin Oncol* 2012;42:53–7.
12. http://www.jastro.or.jp/guideline/ (November 2013, date last accessed).
13. Tabata N, Ohno Y, Matsui R, et al. Partial cancer prevalence in Japan up to 2020: estimates based on incidence and survival data from population-based cancer registries. *Jpn J Clin Oncol* 2008;38:146–57.
14. Ogawa K, Nakamura K, Sasaki T, et al. Radical external beam radiotherapy for clinically localized prostate cancer in Japan: changing trends in the patterns of care process survey. *Int J Radiat Oncol Biol Phys* 2011;81:1310–8.
15. Numasaki H, Shibuya H, Nishio M, et al. Japanese structure survey of radiation oncology in 2007 with special reference to designated cancer care hospitals. *Strahlenther Onkol* 2011;187:167–74.

APPENDIX

Hodaka Numasaki[1], Masahiko Koizumi[2], Yuki Otani[2], Naoto Shikama[3], Naoki Nakamura[4], Kiyotomo Matsugi[5], Hidetaka Arimura[6], Yoshiyuki Shioyama[7] and Tomonari Sasaki[8]

[1]Department of Medical Physics & Engineering, Osaka University Graduate School of Medicine, Osaka, Japan.

[2]Department of Radiation Oncology, Osaka University Graduate School of Medicine, Osaka, Japan.

[3]Department of Radiation Oncology, Saitama Medical University International Medical Center, Saitama, Japan.

[4]Department of Radiation Oncology, St Luke's International Hospital, Tokyo, Japan.

[5]Department of Radiotherapy, Shiga Medical Center for Adults, Shiga, Japan.

[6]Department of Health Sciences, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan.

[7]Department of Heavy Particle Therapy and Radiation Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

[8]Department of Clinical Radiology, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan.

Journal of Radiation Research, 2014, 55, 996–1001
doi: 10.1093/jrr/rru041 Advance Access Publication 8 June 2014

Delayed renal dysfunction after total body irradiation in pediatric malignancies

Miho WATANABE NEMOTO[1,2,*], Koichi ISOBE[3], Gentaro TOGASAKI[2], Aki KANAZAWA[2], Marie KUROKAWA[2], Makoto SAITO[2], Rintaro HARADA[2], Hiroyuki KOBAYASHI[2], Hisao ITO[1] and Takashi UNO[1,2]

[1]Diagnostic Radiology and Radiation Oncology, Graduate School of Medicine, Chiba University, 1–8–1 Inohana, Chuo-ku, Chiba, 260–8677, Japan
[2]Department of Radiology, Chiba University Hospital, Chiba, Japan
[3]Department of Radiology, Sakura Medical Center, Toho University, Chiba, Japan
*Corresponding author. Diagnostic Radiology and Radiation Oncology, Graduate School of Medicine, Chiba University, 1–8–1 Inohana, Chuo-ku, Chiba, 260–8677, Japan. Tel: +81-43-226-2100; Fax: +81-43-226-2101; Email: mwatanabe@hospital.chiba-u.jp

(Received 5 March 2014; revised 3 April 2014; accepted 24 April 2014)

The purpose of this study was to retrospectively evaluate the incidence of delayed renal dysfunction after total body irradiation (TBI) in long-term survivors of TBI/hematopoietic stem cell transplantation (HSCT). Between 1989 and 2006, 24 pediatric patients underwent TBI as part of the conditioning regimen for HSCT at Chiba University Hospital. Nine patients who survived for more than 5 years were enrolled in this study. No patient had any evidence of renal dysfunction prior to the transplant according to their baseline creatinine levels. The median age at the time of diagnosis was 6 years old (range: 1–17 years old). The follow-up period ranged from 79–170 months (median: 140 months). Renal dysfunction was assessed using the estimated glomerular filtration rate (eGFR). The TBI dose ranged from 8–12 Gy delivered in 3–6 fractions over 2–3 d. The patients were treated with linear accelerators in the supine position, and the radiation was delivered to isocentric right–left and left–right fields via the extended distance technique. The kidneys and the liver were not shielded except in one patient with a left adrenal neuroblastoma. No patient required hemodialysis. The eGFR of four patients (44.4%) progressively decreased. The remaining patients did not demonstrate any eGFR deterioration. Only one patient developed hypertension. By evaluating the changes in eGFR, renal dysfunction among long-term survivors of TBI/HSCT could be detected. Our results suggested that the TBI schedule of 12 Gy in 6 fractions over three consecutive days affects renal function.

Keywords: renal toxicity; long-term survivor; total body irradiation; pediatrics

INTRODUCTION

The use of hematopoietic stem cell transplantation (HSCT) after intensive chemotherapy and total body irradiation (TBI) is a widely accepted therapeutic approach for a number of hematological conditions as well as various malignant or benign diseases. Improvements in patient management, conditioning regimens, and TBI techniques have led to longer patient survival and better quality of life for patients. As the number of long-term survivors of HSCT grows, the assessment of late complications becomes increasingly important, particularly in children with a greater chance of long-term survival. In long-term survivors of TBI/HSCT, various complications such as cataracts, pulmonary fibrosis, veno-occlusive disease, graft-versus-host disease (GVHD), endocrine dysfunction, cognitive impairment, secondary malignancy, and renal dysfunction have been reported [1, 2]. Post-transplant renal dysfunction is one of the major complications that adversely affect the quality of life of patients that undergo HSCT. While multiple causes for these injuries have been identified, the administration of TBI at the time of conditioning is a major cause of injury [3–6]. Late renal dysfunction is

mainly attributable to radiation-induced nephropathy, which is characterized by increased serum creatinine levels, proteinuria, anemia and high blood pressure [7, 8].

Studies of HSCT patients have demonstrated an association between TBI and nephrotoxicity; however, most published reports have involved short follow-up periods [2–4, 9]. Therefore, the incidence of radiotherapy-associated renal injuries might have been underreported due to its long latency period [7]. The long latency period for clinical renal toxicity was highlighted in a study of 67 patients with peptic ulcers, but without pre-existing hypertension, who were treated with 20 Gy over 3 weeks using a field that encompassed the left kidney [10]. Of these 67 patients, 31 (46%) developed renal toxicities within 8–19 years of undergoing radiotherapy, including seven patients who developed fatal uremia or malignant hypertension. Hence, renal toxicity is of great clinical significance in long-term survivors of TBI/HSCT. The purpose of this study was to retrospectively elucidate the delayed renal dysfunction after TBI in long-term survivors of TBI/HSCT.

MATERIALS AND METHODS

Between 1989 and 2006, 24 pediatric patients underwent TBI as part of the conditioning regimen for HSCT at Chiba University Hospital. Follow-up data on patients were obtained from the medical records with Institutional review board (IRB) approval. Nine patients who survived for more than 5 years were used as the subjects of this study. The patients' characteristics and diagnoses are described in Table 1. The predominant underlying diseases were acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). The most common preparative regimen was TBI and cyclophosphamide. No patient exhibited any evidence of renal dysfunction prior to transplantation, as determined from their baseline creatinine levels, except for one patient who had a left adrenal neuroblastoma, which was treated with tumor extirpation and 12 Gy of intraoperative radiotherapy before the TBI. The median age at the time of diagnosis was 6 years old (range: 1–17 years old), and the follow-up period ranged from 79–170 months in length (median: 140 months).

Renal dysfunction was assessed using the estimated glomerular filtration rate (eGFR). We used the formula developed by Schwartz *et al.* to calculate the eGFR [11]. Based on a statistical analysis of the data of 186 children, they produced the following formula, which allows a subject's GFR to be accurately estimated from their plasma creatinine levels and height: $eGFR = kL/Pcr$, where eGFR is expressed in ml/min/1.73 m^2, L represents height in cm, Pcr is the plasma creatinine level in mg/dl, and k is a constant of proportionality that depends on age and sex. In pediatric patients (under 21 years of age), we defined renal dysfunction as displaying an eGFR that was lower than the lower limit of normal value [11]. For patients who were older than 21, we defined renal dysfunction as exhibiting an eGFR of < 90 ml/min/1.73 m^2 that continued to decrease in accordance with the chronic kidney disease guidelines of the Japanese Society of Nephrology [12].

Table 1. Patient characteristics

Age at diagnosis (year)	
Median	6
Range	1–17
Follow-up time (months)	
Median	140
Range	79–170
Gender	
Male	7 (77.8%)
Female	2 (22.2%)
Diagnosis	
ALL	4 (44.4%)
AML	3 (33.3%)
Other[a]	2 (22.2%)
TBI dose (Gy)	
12 Gy/6 fr	6 (66.7%)
10 Gy/3–4 fr	2 (22.2%)
8 Gy/3 fr	1 (11.1%)
Donor type	
Matched sibling	2 (22.2%)
Matched unrelated	3 (33.3%)
Mismatched related	
Autologous	1 (11.1%)
NA[b]	1 (11.1%)
Conditioning chemotherapy	
Cy[c]	5 (55.6%)
Cy + VP-16	2 (22.2%)
Other	2 (22.2%)

[a]Other diagnoses include: aplastic anemia ($n = 1$) and neuroblastoma ($n = 1$). [b]NA = not available, [c]Cy = cyclophosphamide.

RESULTS

Patient characteristics

The TBI doses ranged from 8–12 Gy and were delivered in 3–6 fractions over 2–3 d. Treatment was delivered at a nominal dose rate of 200 cGy/min at 1 m. The patients were treated using linear accelerators in the supine position, and the radiation was delivered to isocentric right–left and left–right fields via the extended distance (4 m) technique. The kidneys and liver were not shielded, except in one case involving a patient with a left adrenal neuroblastoma.

Cyclosporine or cyclosporine combined with methotrexate was given to each patient for GVHD prophylaxis. The majority of patients were exposed to potentially nephrotoxic drugs during the post-transplant period, namely cyclosporine, aminoglycosides, vancomycin, amphotericin, and/or antiviral drugs.

Renal dysfunction

The patients' characteristics and renal function are described in Table 2. No patient required hemodialysis. Individual eGFR at TBI, and at two years and five years after TBI are shown in Table 3. The eGFR of four patients decreased progressively but remained within normal limits (Fig. 1). The remaining patients did not demonstrate any eGFR deterioration (Fig. 2). One patient developed hypertension. She had a left adrenal neuroblastoma, which was treated with tumor extirpation and 12 Gy of intraoperative radiotherapy followed by cisplatin-containing chemotherapy. Although her eGFR was fluctuated between 80 and 100 ml/min/1.73 m^2, it did not decline (Fig. 3). Ultrasonography and renography revealed that the patient's left kidney was atrophic and had lost its function. Hypertension was detected 13 years after the TBI.

DISCUSSION

Assessing the risk of treatment-related late renal dysfunction is very important, particularly in children. However, there are some difficult problems in assessing renal function. The definition of late renal toxicities varies between the studies, with the diagnosis involving elevated blood urea nitrogen, serum creatinine level [1, 9, 13], biopsy [2], kidney size [14], uremia [10], GFR [6] and eGFR [3]. In this study we used eGFR by Schwartz's formula in order to detect pre-clinical changes in renal function after TBI and to take height into account. In pediatric survivors, TBI/HSCT may lead to growth impairment due to endocrine dysfunction and impaired growth of bone. Recently, in the USA, the abbreviated Modification of Diet in Renal Disease (MDRD) equation [15] and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [16] are commonly used. Although these methods are more accurate than Schwartz's formula, they have not been validated in pediatric patients. Exposure to other multiple potentially nephrotoxic agents such as cyclosporine and antibiotics are another concern. Cheng *et al.* [17] suggested that pharmacotherapy has a major impact on kidney function and can modify the dose response. We were unable to ascertain how much each factor affected the incidence or severity of renal toxicities, as per previous similar studies. We consider that this issue needs to be clarified in further study.

The tolerance dose associated with a 5% risk of renal dysfunction at 5 years after unilateral whole kidney irradiation was estimated to be ~23 Gy [18]. Nevertheless, a dose–response relationship between the renal radiation dose and

Table 2. Clinical data of nine patients

Patient No.	1	2	3	4	5	6	7	8	9
Age at diagnosis	1	6	3	15	17	16	15	2	6
Age at last exam.	12	17	13	26	23	23	22	16	18
Diagnosis	ALL	ALL	AA	AML	ALL	AML	AML	NB	ALL
TBI conditioning	8 Gy	12 Gy	10 Gy	12 Gy	12 Gy	12 Gy	12 Gy	10 Gy	12 Gy
Chemotherapy conditioning	Cy	Cy, VP-16	Cy	Cy	Cy	Cy, VP-16	Cy	Others	Others
Donor type	Matched unrelated	Matched sibling	Matched unrelated	Mismatched related	Mismatched related	Matched unrelated	NA	Auto	Matched sibling
Disease status	NED	NED	NED	NED	Relapse	NED	NED	NED	NED
Renal function		Decline		Decline		Decline	Decline	Hypertension	

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, AA = anaplastic anemia, NB = neuroblastoma, Cy = cyclophosphamide, VP-16 = etoposide, NED = no evidence of disease.

Table 3. eGFR of all patients at TBI and at two years and five years later

Patient	eGFR (ml/min/1.73 m^2)		
	TBI	24 months	60 months
1	124.1	108.8	135.5
2	143	127.2	127.7
3	100.1	126.7	119.9
4	171.5	165.6	143.3
5	106	NA	101
6	169	141	149
7	167	139.2	140.8
8	85.9	89	87
9	105	106.5	115.3

Normal values of eGFR in children = 133 ± 27 ml/min/l.73 m^2.

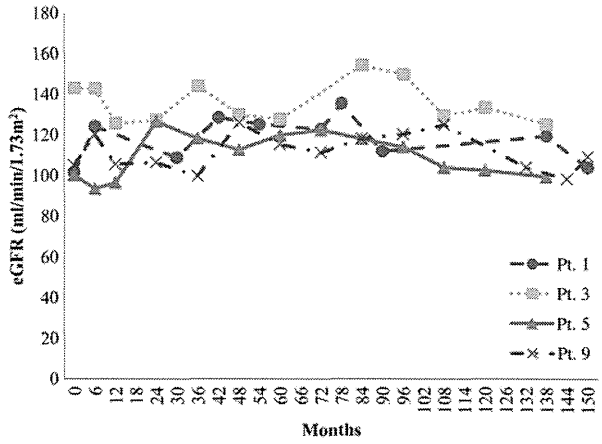

Fig. 2. This graph shows the variation in eGFR over time in Pts 1, 3, 5 and 9, who received 8 Gy, 10 Gy, 12 Gy and 12 Gy, respectively. Five of the nine patients did not suffer any eGFR deterioration.

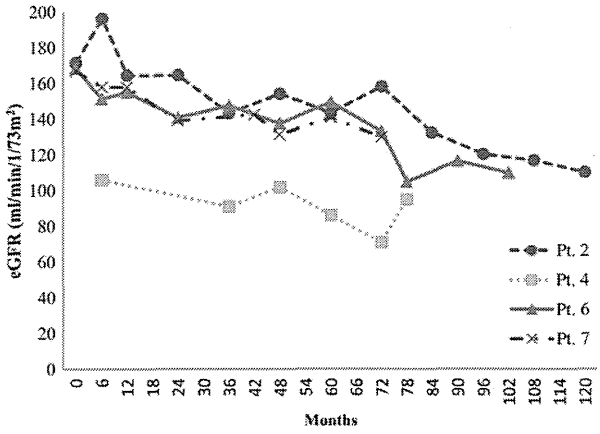

Fig. 1. This graph shows the deterioration of eGFR in Patients (Pts) 2, 4, 6 and 7, who each received 12 Gy. The patients' eGFR progressively decreased.

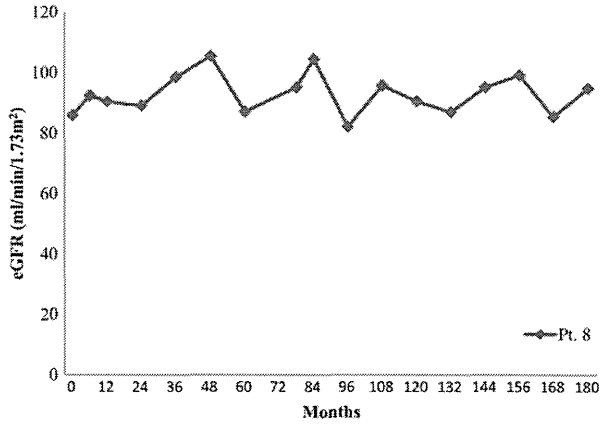

Fig. 3. This graph shows the variation in eGFR over time in Pt. 8, in whom hypertension subsequently developed. The patient's eGFR was 80–100 ml/min/1.73 m^2 and did not decline.

the incidence of chronic renal dysfunction has never been demonstrated. The renal tolerance dose and the optimal schedule for fractionated TBI have also never been established. A recent extensive review by Kal *et al.* [19] reported the incidence of late renal dysfunction after TBI as a function of the biologically effective dose (BED). The tolerance dose for the kidneys during TBI was suggested to be ~16 Gy ($\alpha/\beta = 2.5$ Gy), which can be realized with fractionated TBI involving six fractions of 1.7 Gy. The total dose of 12 Gy that was prescribed for most of the patients in our study is higher than Kal's tolerance dose, suggesting that long-term survivors would develop late renal injuries following this administration. Most patients in our hospital received a total dose of 12 Gy in 6 fractions over three consecutive days, including all four patients with progressively decreasing eGFR. These findings suggest that this TBI schedule might reduce renal function, although it is difficult to reach definitive conclusions from such a small number of cases.

Some investigators who used selective renal shielding blocks have suggested that they reduced the risk of radiation-induced renal toxicities without decreasing the overall survival rate [3, 4, 20]. For example, it was reported that the use of selective renal-shielding blocks that restricted the renal dose to 10 Gy reduced the rate of renal dysfunction. Although the authors of the latter study concluded that the use of selective renal shielding did not appear to reduce the survival rate, such blocks might unintentionally decrease the dose delivered to the adjacent organs. In addition, TBI with selective renal-shielding blocks can be better performed with specific radiotherapy methods (such as anteroposterior and posteroanterior fields) using a moving-table technique, which is still uncommon in Japan.

The latency period for clinical renal toxicity has not been fully elucidated. It has been suggested that renal function stabilizes at one or two years after HSCT [21, 22]. Berg and Bolme did not observe any further deterioration of the eGFR after the first year after HSCT [21]. Patzer *et al.* reported that only two of 36 patients (6%) developed an eGFR of < 90 ml/min/1.73m^2 in the 2 years after HSCT [22]. Half of their study patients were treated with autologous HSCT, which is less toxic than allogeneic HSCT. Frisk *et al.* measured renal function in children after autologous bone marrow transplantation [6]. A total of 26 patients had received TBI as part of their conditioning regimen. Seven patients in this group developed chronic renal impairment after bone marrow transplantation. Of all the patients, the lowest eGFR value was observed within 6 months of the bone marrow transplantation. After improving to some extent, the patient's eGFR stabilized. Although patients experienced some improvement in their eGFR, their latest values were below the normal limits. In our study, eGFR values of four patients progressively decreased, which suggests that the patients' renal function deteriorated over the long-term. This is comparable with the results of the above-mentioned peptic ulcer study. If the GFR continues to decrease, then patients might develop chronic kidney disease, which increases the risk of cardiovascular conditions such as stroke and myocardial infarction. Therefore, long-term follow-up is necessary for the assessment of late renal complications.

We should mention particularly the patient with a neuroblastoma, who developed hypertension 13 years after undergoing TBI. As well as the TBI, this case involved many additional nephrotoxic factors, e.g. the use of cisplatin and the administration of intraoperative irradiation to the left adrenal gland. In this case, the left kidney became atrophic and lost its function. It should be noted that this patient had a different background from the other patients, who had suffered only hematological conditions.

We should acknowledge the limitations of our study. We only evaluated a small number of patients. Given that only nine of 24 patients were assessed, there is a strong possibility of selection bias, with patients having severe or even fatal renal toxicities not being reported due to insufficient follow-up. In addition, our analysis was retrospective in nature. However, based on the extremely long follow-up time of this study (median, 140 months), our results suggested that the eGFR of four patients (who received 12 Gy) progressively decreased after TBI with an unexpectedly long latency. In addition, the majority of these patients underwent allogeneic transplant, which is by far the most concerning scenario for renal toxicity. Hence, a larger prospective follow-up study involving a pediatric hematologist is necessary in order to determine renal toxicity profiles and their clinical significance among long-term survivors of TBI/HSCT.

ACKNOWLEDGEMENTS

We thank Dr Junna Yamaguchi for providing helpful assistance with the nephrological aspects of this study. Data from this investigation was presented at the 24th Annual Meeting of the Japanese Society for Therapeutic Radiology and Oncology.

REFERENCES

1. Chou R-H, Wong G-B, Kramer J-H *et al.* Toxicities of total-body irradiation for pediatric bone marrow transplantation. *Int J Radiat Oncol Biol Phys* 1996;**34**:843–51.
2. Tarbell NJ, Guinan EC, Niemeyer C *et al.* Late onset of renal dysfunction in survivors of bone marrow transplantation. *Int J Radiat Oncol Biol Phys* 1988;**15**:99–104.
3. Lawton CA, Cohen EP, Murray KJ *et al.* Long-term results of selective renal shielding in patients undergoing total body irradiation in preparation for bone marrow transplantation. *Bone Marrow Transplant* 1997;**20**:1069–74.
4. Lawton CA, Barber-Derus SW, Murray KJ *et al.* Influence of renal shielding on the incidence of late renal dysfunction associated with T-lymphocyte deplete bone marrow transplantation in adult patients. *Int J Radiat Oncol Biol Phys* 1992;**23**:681–6.
5. Cohen EP. Radiation nephropathy after bone marrow transplantation. *Kidney Int* 2000;**58**:903–18.
6. Frisk P, Bratteby LE, Carlson K *et al.* Renal function after autologous bone marrow transplantation in children: a long-term prospective study: *Bone Marrow Transplant* 2002;**29**:129–36.
7. Dawson LA, Kavanagh BD, Paulino AC *et al.* Radiation-associated kidney injury. *Int J Radiat Oncol Biol Phys* 2010;**76**:S108–15.
8. Cassady J. Clinical radiation nephropathy. *Int J Radiat Oncol Biol Phys* 1995;**31**:1249–56.
9. Borg M, Hughes T, Horvath N *et al.* Renal toxicity after total body irradiation. *Int J Radiat Oncol Biol Phys* 2002;**54**:1165–73.
10. Thompson PL, Mackay IR, Robson GS *et al.* Late radiation nephritis after gastric x-irradiation for peptic ulcer. *Q J Med* 1971;**40**:145–57.
11. Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. *Pediatr Clin North Am* 1987;**34**:571–90.
12. Japanese Society of Nephrology. *Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2009.* Tokyo: Igakusha, 2009.
13. Esiashvili N, Chiang K-Y, Hasselle MD *et al.* Renal toxicity in children undergoing total body irradiation for bone marrow transplant. *Radiother Oncol* 2009;**90**:242–6.
14. Yang G-Y, May K-S, Iyer R-V *et al.* Renal atrophy secondary to chemoradiotherapy of abdominal malignancies. *Int J Radiat Oncol Biol Phys* 2010;**78**:539–46.
15. Rule AD, Larson TS, Bergstralh EJ *et al.* Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. *Ann Intern Med* 2004;**141**:929–37.
16. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12.

17. Cheng J-C, Schultheiss TE, Wong JYC. Impact of drug therapy, radiation dose, and dose rate on renal toxicity following bone marrow transplantation. *Int J Radiat Oncol Biol Phys* 2008;**71**:1436–43.
18. Emami B, Lyman J, Brown A *et al.* Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991;**21**:109–22.
19. Kal HB, van Kempen-Harteveld ML. Renal dysfunction after total body irradiation: dose–effect relationship. *Int J Radiat Oncol Biol Phys* 2006;**65**:1228–32.
20. Igaki H, Karasawa K, Sakamaki H *et al.* Renal dysfunction after total-body irradiation. Significance of selective renal shielding blocks. *Strahlenther Onkol* 2005;**181**:704–8.
21. Berg U, Bolme P. Renal function in children following bone marrow transplantation. *Transplant Proc* 1989;**21**: 3092–4.
22. Patzer L, Ringelmann F, Kentouche K *et al.* Renal function in long-term survivors of stem cell transplantation in childhood. A prospective trial. *Bone Marrow Transplant.* 2001;**27**: 319–27.

JJCO Japanese Journal of Clinical Oncology

Case Report

Jpn J Clin Oncol 2014;44(7)692–695
doi:10.1093/jjco/hyu066
Advance Access Publication 16 May 2014

Successful Use of Endoscopic Argon Plasma Coagulation for Hemorrhagic Radiation Cystitis: A Case Report

Sho Suzuki[1,*], Akiko Chino[1], Iwao Fukui[2], Tatsuro Hayashi[2], Takuyo Kozuka[3], Takanori Suganuma[1], Teruhito Kishihara[1], Yoshiro Tamegai[1], Junko Fujisaki[1], Masahiko Oguchi[3], Junji Yonese[2] and Masahiro Igarashi[1]

[1]Department of Gastroenterology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, [2]Department of Genitourinary Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo and [3]Department of Radiation Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

*For reprints and all correspondence: Sho Suzuki, Department of Gastroenterology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan.
E-mail: sho.suzuki@jfcr.or.jp

Received January 29, 2014; accepted April 22, 2014

Hemorrhagic radiation cystitis is an example of a typical radiotherapy-induced adverse event. However, the optimal treatment for hemorrhagic radiation cystitis is not known. There are limited data regarding the use of argon plasma coagulation for hemorrhagic radiation cystitis. Here, we present the use of argon plasma coagulation using a gastrointestinal endoscope to treat hemorrhagic radiation cystitis. The patient was a 75-year-old male patient with hemorrhagic radiation cystitis due to external beam irradiation for prostate adenocarcinoma. Six years after radiotherapy, the patient presented with macroscopic hematuria over the preceding 4 months, and laboratory investigations revealed a low hemoglobin level. The hematuria was not controlled with 2 days of bladder irrigation using normal saline. Thus, argon plasma coagulation using an upper gastrointestinal endoscope was considered for treatment of the hemorrhagic radiation cystitis. The cystoscopic examination revealed diffuse radiation cystitis with oozing telangiectasia and coagula. All of the bleeding sites and telangiectasia were coagulated using argon plasma coagulation. Following treatment, the patient's clinical symptoms improved and did not recur. The hemoglobin level also recovered. No complications associated with the treatment were observed during the 6-month follow-up period. Thus, argon plasma coagulation using a gastrointestinal endoscope is a safe and effective treatment for hemorrhagic radiation cystitis.

Key words: radiation cystitis – argon plasma coagulation – endoscopic treatment – radiation toxicity

INTRODUCTION

External and internal radiotherapy are highly effective and minimally invasive treatments for a variety of pelvic malignances such as prostate cancer and gynecologic tumors. Because radiation energy is distributed to various pelvic organs near the target lesion, radiotherapy-induced adverse events often occur.

Hemorrhagic radiation cystitis (HRC) is an example of a typical radiotherapy-induced adverse event, occurring in up to 10% of patients and appearing months to years after the pelvic radiotherapy (1–3). Pelvic radiotherapy-related changes to the bladder include vascular endothelial necrosis, chronic tissue hypoxia and fibrosis of vesicular tissue (4), resulting in the adverse events. Clinically, HRC usually involves mild bleeding, but sometimes causes severe and intractable bleeding. Chronic HRC may lead to anemia and require a blood transfusion. However, the most appropriate treatment for HRC is still not clear.

In hemorrhagic radiation proctitis (HRP), which is another typical radiotherapy-induced adverse event, endoscopic argon plasma coagulation (APC) is widely performed as first-line treatment. However, there are few reports regarding the use of endoscopic APC in HRC, and the efficacy and safety of APC

for HRC is unknown. Here, we present a case of HRC successfully treated with the novel application of endoscopic APC.

CASE REPORT

A 75-year-old male patient was treated with external beam irradiation (71 Gy) for 8 weeks for Gleason 10 (5 + 5) prostate adenocarcinoma (cT4, N0, M0, cStage4) in 2007. He had a history of HRP that had been successfully treated with endoscopic APC 11 months after the radiotherapy. His medication history included aspirin for a previous cerebral infarction.

Six years after radiotherapy, the patient presented to the emergency room at our hospital complaining of urinary frequency, dysuria and hematuria that had progressed rapidly over the previous 4 months. Laboratory investigations resulted in a low serum hemoglobin level (9.3 mg/dl). Pelvic enhanced computed tomography showed diffuse thickness of the bladder wall with no evidence of local recurrent prostate cancer.

The aspirin was discontinued, and we performed bladder irrigation using normal saline for 2 days following hospitalization; however, the hematuria was not controlled. Thus, endoscopic APC was considered as a treatment option for HRC, similar to its therapeutic use for HRP. The procedure was reviewed and approved by the hospital's institutional review board, and the patient provided informed consent prior to treatment.

We inserted a narrow-diameter (5.8 mm) upper gastrointestinal endoscope (GIF-XP290N; Olympus, Tokyo, Japan) in the urethra and advanced the endoscope into the bladder under sedation with midazolam. The fluid in the bladder was then emptied using routine endoscopy suction, after which the bladder was infused with the least amount of carbon dioxide necessary to enable the endoscopic view of the bladder wall. Care was taken not to overinflate the bladder to avoid an air embolism. No devices were used to measure intrabladder pressure. The cystoscopic examination revealed diffuse radiation cystitis; in particular, multiple oozing telangiectasia and coagula were observed on the posterior wall and trigone (Fig. 1A and B).

Then, a 2.3-mm diameter front firing flexible APC probe (APC probe 2200A; Erbe Elektromedizin, Tübingen, Germany) was passed through the accessory channel of the endoscope and extended ~1.0 cm from the top of the scope. This was connected to the argon gas source and an electrosurgical unit (APC2; Erbe Elektromedizin). The argon gas flow and electrical power were set at 0.6 l/min and 30 W, respectively. The APC probe was directed at the telangiectatic lesions and held near the mucosal surface avoiding direct contact. First, the area of active bleeding and oozing were coagulated (Fig. 2); the areas that were not bleeding or oozing but appeared as possible sources of bleeding were also coagulated. Following the APC treatment, the treated mucosa appeared as a pale, well-circumscribed ulcer with discrete margins (Fig. 3). The total procedure time was 30 min.

The patient was discharged from the hospital on the following day, without evidence of macroscopic hematuria. Aspirin was administered again on the following day after discharge.

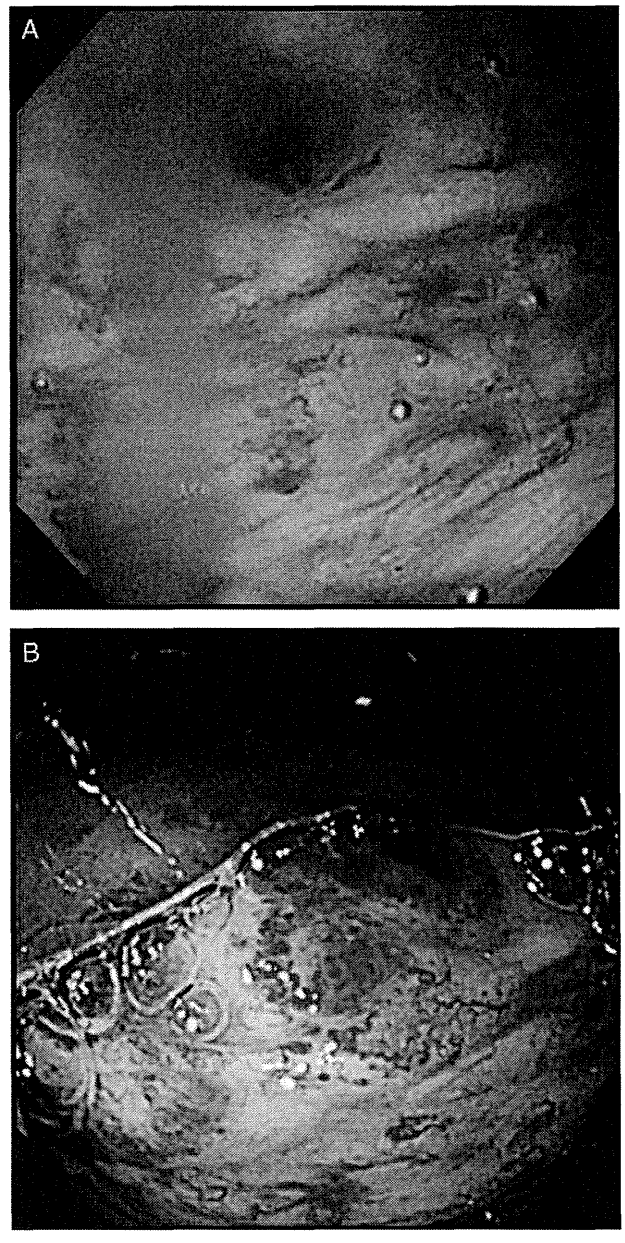

Figure 1. Cystoscopic examination using a gastrointestinal endoscope revealed (A) multiple oozing telangiectasia on the posterior wall of the bladder and (B) clearly observed lesions after filling the bladder with carbon dioxide.

The serum hemoglobin level also recovered (11.4 mg/dl) 3 months later. The patient's urinary symptoms of hematuria and dysuria improved and did not recur over the 6-month observation period. Only mild frequent urination remained, but the symptom did not worsen. No adverse events occurred during the observation period.

DISCUSSION

Various interventions have been used historically to treat HRC, including simple bladder irrigation, cystoscopic

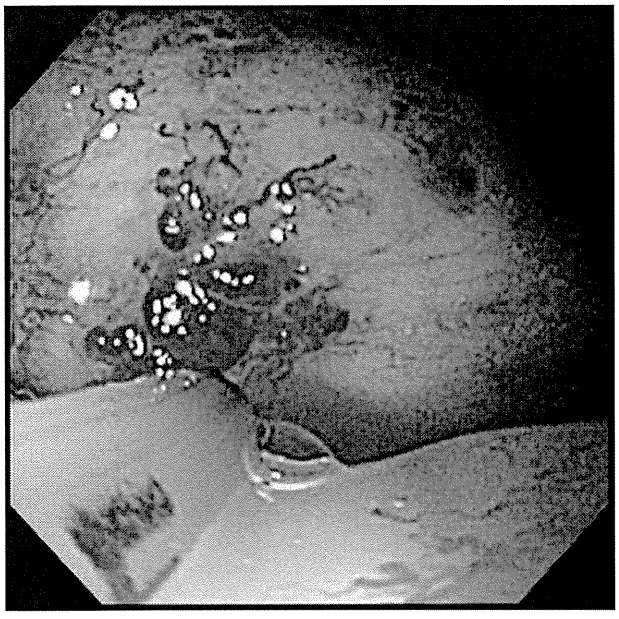

Figure 2. Argon plasma coagulation (APC) treatment for hemorrhagic radiation cystitis using a narrow endoscope (5.8 mm); the APC probe can be seen at the front of the endoscope.

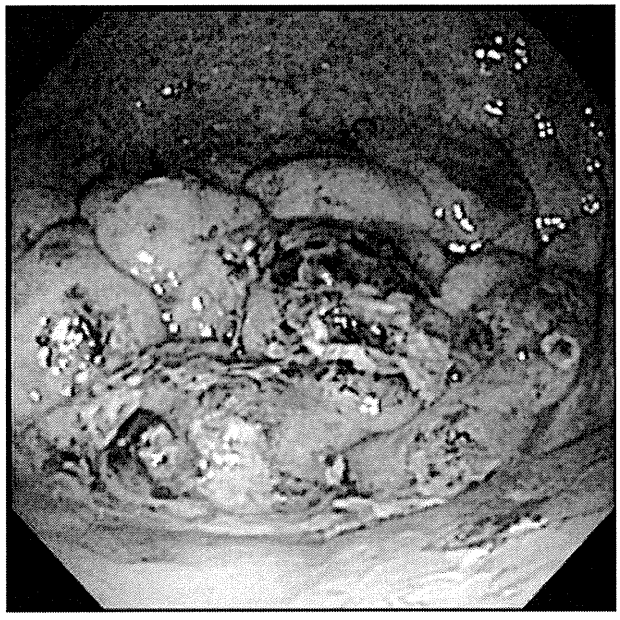

Figure 3. Areas of ulcers immediately following APC treatment for hemorrhagic radiation cystitis are shown.

fulguration, intravesical treatment with alum or formalin, hydrodistention, hyperbaric oxygenation, internal iliac embolization and cystectomy (5,6). However, there is a paucity of data regarding the effectiveness of these treatments for HRC. Thus, the optimal treatment for HRC has still not been determined (4).

APC involves the delivery of unipolar diathermy current in a non-contact fashion using the inert gas argon as the conducting medium; it is promising primarily owing to its superficial effect, with a coagulation depth of only 2–3 mm (7–9). APC has been shown to be a safe, highly effective and long-lasting therapy in patients with mild-to-moderate rectal HRP (10), and APC treatment of HRP results in success rates of 80–100% with long-term adverse events in up to only 5% of patients (11,12). As a result, APC is increasingly recommended as the first-line treatment for HRP (13).

In contrast, there is limited evidence for the use of APC via a gastrointestinal endoscope for the treatment of HRC. Owing to our experience with APC for HRP, we considered it as a therapy in the current patient with HRC; as a result, the APC was a successful and effective treatment for HRC in this patient. While bladder irrigation treatment did not resolve his long-standing hematuria, the APC treatment did. Furthermore, the patient did not experience any symptoms of bladder irritation or require further intervention during the follow-up period.

To the best of our knowledge, only one report exists of seven cases with HRC treated by APC with a power setting of 40–60 W and gas flow rate of 1.5 l/min (14). Six cases were completely treated after one session, while one case required re-treatment (mean follow-up, 15 months) with no significant adverse events for any of the patients. Therefore, APC has been reported as one of the endoscopic laser coagulation treatments such as neodymium:yttrium-aluminum-garnet (Nd:YAG), potassium titanyl phosphate, and 980 nm diode lasers with success rates of 93–100% (15). Specifically, Nd:YAG is a typical laser coagulation treatment that coagulates only a restricted area to considerable depths of 4–6 mm (16,17). Large tissue necrosis is commonly seen with the use of Nd:YAG treatment, which can result in long-lasting irritation caused by the sloughing off of necrotic tissue (18). Because APC can coagulate relatively superficial layers and wider areas than other laser coagulation methods, APC could be a more effective and safe treatment for HRC.

Another advantage of APC via a gastrointestinal endoscope is the availability and routine use of argon gas delivery electrosurgical units and gastrointestinal endoscopes in most hospitals with an established gastrointestinal endoscopy unit. Thus, the establishment costs for this treatment are low. However, other laser coagulation treatment systems are not available in most hospitals.

There is no consensus regarding the optimal APC settings (power and gas flow rate) for successful and safe coagulation in HRP, with reported power settings and argon flow rates ranging from 25 to 80 W and 0.6 to 2 l/min, respectively (13,19). However, it has been reported that low-power settings are better for safe and effective outcomes using APC (20); we have also successfully used low-power APC settings (30 W) with an argon flow rate of 0.6 l/min for HRP treatment. These same settings were also successfully used in the present HRC case, without any adverse events.

A gastrointestinal endoscope is able to approach from any direction owing to its freely flexible point, and is also able to perform suction and infusion. In this case, the use of the APC probe and a narrow-diameter endoscope (5.8 mm) allowed us

to access the bladder through the urethra; in addition, the accessory channel enabled us to perform suction and carbon dioxide infusion in the bladder.

Despite the benefits of APC treatment for HRP, and potentially HRC, it is not appropriate in severe HRP with mucosal ulcerations, because it may result in perforation and/or intractable enlarged ulcerations. Therefore, we also suggest that APC may not be appropriate in cases of severe HRC with mucosal ulcerations.

Conventional treatments for HRC are often not successful. Our experience suggests that APC can effectively and safely be used in the treatment of HRC. Further assessment and comparison of this modality to other currently available treatments is needed. In the meantime, we suggest that patients with HRC should be treated with endoscopic APC before using more radical approaches, such as cystectomy or urinary diversion.

Acknowledgements

We sincerely thank the staff of the endoscopy unit at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research for their valuable assistance in conducting this study.

Conflict of interest statement

None declared.

References

1. Levenback C, Eifel PJ, Burke TW, Morris M, Gershenson DM. Hemorrhagic cystitis following radiotherapy for stage Ib cancer of the cervix. *Gynecol Oncol* 1994;55:206–10.
2. Gardner BG, Zietman AL, Shipley WU, Skowronski UE, McManus P. Late normal tissue sequelae in the second decade after high dose radiation therapy with combined photons and conformal protons for locally advanced prostate cancer. *J Urol* 2002;167:123–6.
3. Kaplan JR, Wolf JS, Jr. Efficacy and survival associated with cystoscopy and clot evacuation for radiation or cyclophosphamide induced hemorrhagic cystitis. *J Urol* 2009;181:641–6.
4. Crew JP, Jephcott CR, Reynard JM. Radiation-induced haemorrhagic cystitis. *Eur Urol* 2001;40:111–23.
5. Denton AS, Clarke NW, Maher EJ. Non-surgical interventions for late radiation cystitis in patients who have received radical radiotherapy to the pelvis. *Cochrane Database Syst Rev* 2002;3:1–38.
6. Fergany AF, Moussa AS, Gill IS. Laparoscopic cystoprostatectomy for radiation-induced hemorrhagic cystitis. *J Endourol* 2009;23:275–8.
7. Reich O, Schneede P, Mseddi A, Zaak D, Siebels M, Hofstetter A. Argon plasma coagulation (APC) for endo-urological procedures: *ex-vivo* evaluations of hemostatic properties. *Eur Urol* 2003;44:272–6.
8. Rotondano G, Bianco MA, Marmo R, Piscopo R, Cipolletta L. Long-term outcome of argon plasma coagulation therapy for bleeding caused by chronic radiation proctopathy. *Dig Liver Dis* 2003;35:806–10.
9. Dees J, Meijssen MA, Kuipers EJ. Argon plasma coagulation for radiation proctitis. *Scand J Gastroenterol Suppl* 2006;243:175–8.
10. Zinicola R, Rutter MD, Falasco G, et al. Haemorrhagic radiation proctitis: endoscopic severity may be useful to guide therapy. *Int J Colorectal Dis* 2003;18:439–44.
11. Karamanolis G, Triantafyllou K, Tsiamoulos Z, et al. Argon plasma coagulation has a long-lasting therapeutic effect in patients with chronic radiation proctitis. *Endoscopy* 2009;41:529–31.
12. Swan MP, Moore GT, Sievert W, Devonshire DA. Efficacy and safety of single-session argon plasma coagulation in the management of chronic radiation proctitis. *Gastrointest Endosc* 2010;72:150–4.
13. Karamanolis G, Psatha P, Triantafyllou K. Endoscopic treatments for chronic radiation proctitis. *World J Gastrointest Endosc* 2013;5:308–12.
14. Wines MP, Lynch WD. A new minimally invasive technique for treating radiation cystitis: the argon-beam coagulator. *BJU Int* 2006;98:610–2.
15. Mendenhall WM, Henderson RH, Costa JA, et al. Hemorrhagic radiation cystitis. *Am J Clin Oncol* 2013; (Epub ahead of print).
16. Gerber GS, Chodak GW, Rukstalis DB. Combined laparoscopic and transurethral neodymium: yttrium-aluminum-garnet laser treatment of invasive bladder cancer. *Urology* 1995;45:230–3.
17. Ravi R. Endoscopic neodymium:YAG laser treatment of radiation-induced hemorrhagic cystitis. *Lasers Surg Med* 1994;14:83–7.
18. Bachmann A, Ruszat R. The KTP-(greenlight-) laser—principles and experiences. *Minim Invasive Ther Allied Technol* 2007;16:5–10.
19. Lam MC, Parliament M, Wong CK. Argon plasma coagulation for the treatment of hemorrhagic radiation colitis. *Case Rep Gastroenterol* 2012;6:446–51.
20. Kaassis M, Oberti E, Burtin P, Boyer J. Argon plasma coagulation for the treatment of hemorrhagic radiation proctitis. *Endoscopy* 2000;32:673–6.

Qual Life Res (2014) 23:1641–1650
DOI 10.1007/s11136-013-0603-6

Longitudinal change in health-related quality of life after intensity-modulated radiation monotherapy for clinically localized prostate cancer

Shinya Yamamoto · Yasuhisa Fujii · Hitoshi Masuda · Shinji Urakami · Kazutaka Saito · Takuyo Kozuka · Masahiko Oguchi · Iwao Fukui · Junji Yonese

Accepted: 6 December 2013 / Published online: 13 December 2013

Abstract
Purpose The purpose of the study is to assess longitudinal changes in general and disease-specific health-related quality-of-life (HRQOL) indices after intensity-modulated radiotherapy (IMRT) monotherapy for patients with localized prostate cancer (PCA).
Methods Between 2006 and 2010, 91 patients with localized PCA underwent IMRT monotherapy and were enrolled into this prospective study. At baseline, and at 3, 6, 12, and 24 months after IMRT, the general and prostate-specific HRQOL were estimated using physical (PCS) and mental component summaries (MCS) calculated using the Medical Outcomes Study 8-Item Short Form Health Survey and Expanded Prostate Cancer Index Composite (EPIC).
Results For 2 years, there were no significant changes in EPIC scores in all subscales of urinary domain, hormonal function, and bother. Bowel and sexual function scores decreased after IMRT and did not return to those at baseline ($p = 0.006$ and < 0.001, respectively). PCS began to decrease at 3 months after IMRT and then returned to the baseline score at 24 months. In contrast, the MCS score began to significantly increase after IMRT, and thereafter the score remained constant until 24 months ($p < 0.001$). On multivariate logistic regression analysis, urinary ($p = 0.003$) and sexual functions ($p = 0.0005$) at baseline were identified as significant predictors of EPIC urinary irritative/obstructive score and sexual function at 24 months after IMRT.
Conclusion Urinary function, including irritative/obstruction symptoms and hormonal function, was not affected by IMRT. However, bowel and sexual function decreased after IMRT. These findings will provide important information for PCA patients considering IMRT.

Keywords Prostate cancer · Quality of life · Radiotherapy · Intensity-modulated

Abbreviations

EBRT	External-beam radiation therapy
RP	Radical prostatectomy
PCA	Prostate cancer
HRQOL	Health-related quality of life
IMRT	Intensity-modulated radiotherapy
ADT	Androgen deprivation therapy
UCLA-PCI	University of California-Los Angeles Prostate Cancer Index
EPIC	Expanded Prostate Cancer Index Composite
SF-8	Medical Outcomes Study 8-Item Short Form Health Survey
CTV	Clinical target volume
PTV	Planning target volume
IPSS	International prostate symptom score
PCS	Physical component summary
MCS	Mental component summary
SD	Standard deviation
PDE-5-I	Phosphodiesterase-5-inhibitor

Introduction

External-beam radiation therapy (EBRT) and radical prostatectomy (RP) have been the gold standard treatments for

S. Yamamoto (✉) · Y. Fujii · H. Masuda · S. Urakami · K. Saito · I. Fukui · J. Yonese
Department of Urology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31, Ariake, Tokyo, Koto-ku 135-8550, Japan
e-mail: shinya.yamamoto@jfcr.or.jp

T. Kozuka · M. Oguchi
Department of Radiation Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

clinically localized prostate cancer (PCA), and they have resulted in an excellent disease-free survival outcome for patients [1, 2]. Therefore, since EBRT improves patients' chances of achieving normal longevity, EBRT is believed to yield a good health-related quality of life (HRQOL) with excellent oncological outcomes [1–3].

Intensity-modulated radiotherapy (IMRT), which recently replaced conventional radiation therapy [1, 2], has become a popular treatment for patients with clinically localized PCA. A higher dose of radiation can be delivered to the prostate and seminal vesicles during IMRT, while lower amounts of radiation reach the adjacent organs, such as the rectum, urinary bladder, and urethra [4, 5]. Alicikus et al. [3] reported that the 10-year likelihood of developing grade 2 and grade 3 late genitourinary toxicity in patients treated with IMRT was 11 and 5 %, respectively, and the 10-year actuarial incidence of developing post-IMRT erectile dysfunction was 44 %. Several investigators have also reported a longitudinal change in HRQOL after IMRT [6–11]. However, because the patients in most of these reports underwent IMRT combined with some androgen deprivation therapy (ADT) [6, 7, 9, 10], HRQOL after IMRT alone has not been well studied. Moreover, because a researcher has analyzed the change in HRQOL after IMRT using the University of California-Los Angeles Prostate Cancer Index (UCLA-PCI) [6], the effect on irritative symptoms and hormonal function after IMRT also remains unclear. The Expanded Prostate Cancer Index Composite (EPIC) was developed in 2000 to include questions concerning irritative/obstructive symptoms and hormonal functions in the UCLA-PCI [12]. Recently, there have been a few large studies using the EPIC for patients who underwent EBRT alone [13, 14]; however, some patients received three-dimensional conformal radiotherapy. These reports were not longitudinal studies. Before treatment, patients are naturally concerned with possible changes in various functions (for example, urinary and bowel functions) following treatment. For this reason, it is very important for patients who are considering IMRT monotherapy to have information about the longitudinal changes in QOL after treatment. Thus, we prospectively evaluated the longitudinal changes in general and disease-specific HRQOL after IMRT monotherapy for patients with localized PCA using the EPIC and the Medical Outcomes Study 8-Item Short Form Health Survey (SF-8).

Patients and methods

Between August 2006 and February 2010, 96 Japanese patients, who were diagnosed with clinically localized PCA, underwent IMRT at our hospital and enrolled in this prospective HRQOL study. All patients had a histologic diagnosis of PCA from needle biopsy specimens. Clinical staging was determined using digital rectal examination, abdominopelvic computed tomography, pelvic magnetic resonance imaging, and bone scans. After the patients were informed of their cancer diagnosis and staging, we proposed RP and IMRT for localized PCA patients. The final decision on treatment strategy was made by the patients themselves. Of the 96 patients, 91 patients with pretreatment HRQOL data and data from at least three later times were finally included in this study. No patients received any ADT during this study period. This study was approved by the Institutional Review Board of our hospital.

Planning CT scans were obtained from patients with a full bladder and an empty rectum. The clinical target volume (CTV) was defined as the base of the seminal vesicle and the prostate with a 5-mm margin excluding the rectum. The margins for defining the planning target volume (PTV) were 5 mm in all directions of the CTV. Daily positioning verification was performed before every treatment. Electronic portal images of two orthogonal pelvic views were taken with a full bladder and no rectum preparation, and they were compared with the digitally reconstructed radiographs from the planning CT scan, using bone landmarks.

After informed consent was obtained, the general and prostate-specific HRQOL were estimated using SF-8, EPIC (50-item), and the International Prostate Symptom Score (IPSS). These questionnaires had already been translated into Japanese, and their validity and reliability have been tested previously [15–17]. The SF-8 contains 8 items: general health, physical functioning, physical role, bodily pain, vitality, social functioning, mental health, and emotional role [15]. In the present study, physical (PCS) and mental component summaries (MCS), which were constructed from the 8 items, were used to evaluate the general HRQOL [15]. PCS and MCS were measured using the norm-based scoring method, which is based on a large-scale population study conducted in Japan. EPIC scores were divided into four domains (urinary, bowel, sexual, and hormonal), and for each domain, the summary score and two subscale scores (function and bother) were constructed [16]. The urinary domain also includes urinary incontinence and urinary irritative/obstructive subscales [16]. Each subscale score was calculated on a scale of 0–100 with higher scores representing better quality of life (QOL). The IPSS contains 7 items about the frequency of irritative and obstructive urinary symptoms [17]. Each question is answered on a scale of 1–5. Scores were added together, with a possible total ranging from 0 to 35, with higher scores representing worse QOL. The questionnaires were prospectively administered at five time points: before IMRT (baseline), and at 3, 6, 12, and 24 months after IMRT. The questionnaire was personally administered at each follow-up visit or mailed at regular intervals to the

patient with a prepaid envelope to assist with returning the questionnaire. The patients voluntarily returned the self-reported questionnaire by mail, at the next follow-up visit or in the waiting room. The submission rates for the questionnaire were 91 (100 %), 87 (96 %), 89 (98 %), 90 (99 %), and 85 (93 %) at baseline, 3, 6, 12, and 24 months after IMRT, respectively.

All patients were also divided into two groups by pre-IMRT IPSS score as follows: the good urinary function group (<8 points) and the poor urinary function group (8 or more points) [18, 19]. The longitudinal changes in the four urinary subscales in the EPIC were evaluated in each group.

Erectile function at baseline was analyzed using the response to EPIC question 18 ("How would you describe the usual quality of your erections during the last 4 weeks?"). Patients selecting 1 or 2 (1, none at all; 2, not firm enough for any sexual activity) were classified as impotent, with all other responses defined as potent. The longitudinal changes in sexual function and bother in the patients who were potent at baseline were also analyzed.

All scores are presented as mean ± standard deviation (SD). Changes in function and bother scores throughout the 2-year follow-up after IMRT were tested using a mixed-effects linear regression model. Differences in the four urinary subscale scores at baseline between the good and poor urinary function groups were tested using the Mann–Whitney *U* test. An EPIC score decrease greater than one-half of the SD of the baseline value for each domain was considered a clinically significant decrement [20]. Multivariate logistic regression analysis was used to assess predictors of urinary irritative/obstructive symptoms, incontinence, bowel function, sexual function, PCS, and MCS at 24 months after IMRT. Age, body mass index (BMI), comorbidity status, the use of phosphodiesterase-5-inhibitor (PDE-5-I), total IPSS score at baseline, incontinence score at baseline, and sexual function score at baseline were evaluated as possible predictors. All *p* values were two-sided. A *p* value less than 0.05 was considered statistically significant. Statistical analyses were performed using JMP version 9 (SAS Institute Inc., Cary, NC, USA).

Results

Patient population

Table 1 shows the baseline characteristics of the 91 patients. The median age of the entire cohort was 70 years, and the median pre-IMRT PSA level was 7.7 ng/mL. Most of the patients were classified in the low- and intermediate-risk groups according to National Comprehensive Cancer Network guidelines [21]. Prostate-specific antigen (PSA) failure was defined according to the Phoenix consensus

Table 1 Baseline characteristics according to pre-IMRT urinary and sexual functions

Variable	Pre-IMRT urinary function			Pre-IMRT sexual function		
	Good ($n = 50$)	Poor ($n = 40$)	p	Potent ($n = 27$)	Impotent ($n = 64$)	p
Median age (range)	69 (56–78)	70 (58–79)	0.32	66 (57–76)	70 (56–79)	0.008
Median PSA (range) (ng/mL)	7.6 (4.1–28.1)	7.7 (4.1–19.5)	0.78	7.7 (4.0–25.6)	7.6 (4.0–28.1)	0.65
Clinical *T* stage *n*, (%)			0.62			0.06
T1c-2	49 (98.0)	39 (97.5)		25 (92.6)	64 (100.0)	
T3a	1 (2.0)	1 (2.5)		2 (7.4)	0 (0.0)	
Biopsy GS *n*, (%)			0.76			0.25
4–6	8 (16.0)	6 (15.0)		5 (18.5)	9 (14.1)	
7	39 (78.0)	30 (75.0)		19 (70.4)	50 (78.1)	
8–10	3 (6.0)	4 (10.0)		3 (11.1)	5 (7.8)	
Median BMI (range) (kg/m^2)	23.7 (19.1–27.5)	22.8 (15.5–35.3)	0.73	22.3 (19.1–25.9)	23.5 (15.5–35.3)	0.30
Having smoking history *n*, (%)	24 (53.3)	19 (47.5)	0.59	16 (64.0)	27 (44.3)	0.09
Comorbidity *n*, (%)						
HT	20 (40.0)	13 (32.5)	0.46	7 (25.9)	27 (42.2)	0.14
DM	10 (20.0)	6 (15.0)	0.53	2 (7.4)	14 (21.9)	0.08
CVD	4 (8.0)	1 (2.5)	0.24	1 (3.7)	4 (6.3)	0.61
Median dose (Gy)	78 (70–78)	78 (70–78)	0.32	78 (70–78)	78 (70–78)	0.57
Use of PDE-5-I *n*, (%)	5 (10.0)	7 (17.5)	0.30	7 (25.9)	5 (8.5)	0.03

IMRT intensity-modulated radiotherapy, *PSA* prostate-specific antigen, *GS* Gleason score, *BMI* body mass index, *HT* hypertension, *DM* diabetes mellitus, *CVD* cerebral vascular disease, *PDE-5-I* phosphodiesterase-5-inhibitor

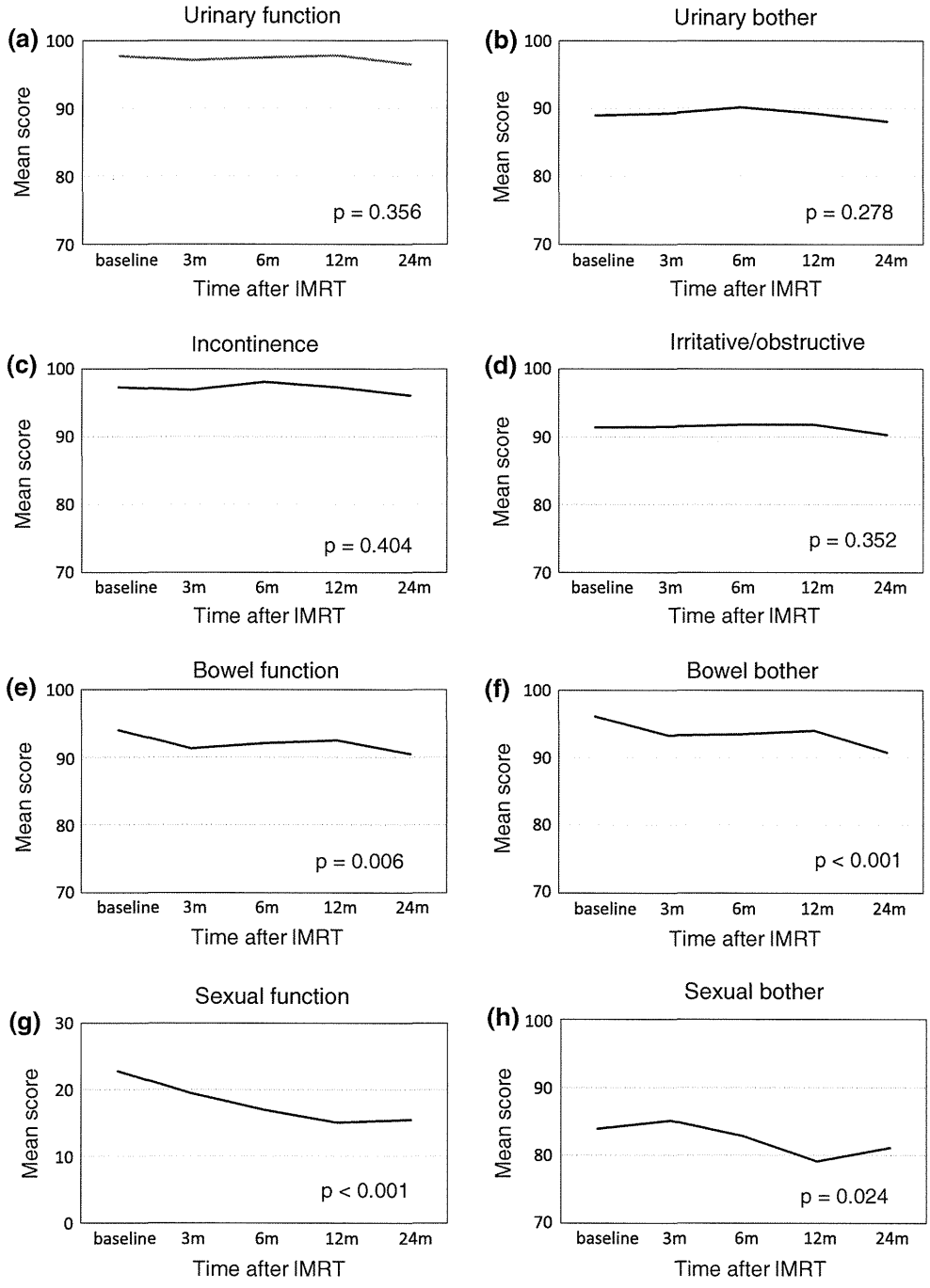

Fig. 1 Longitudinal changes in domain and subdomain scores of the EPIC and scores of SF-8 (PCS and MCS) in patients treated with IMRT. High scores indicate better outcomes. **a** Urinary function, **b** urinary bother, **c** incontinence, **d** irritative/obstructive, **e** bowel function, **f** bowel bother, **g** sexual function, **h** sexual bother, **i** hormonal function, **j** hormonal bother, **k** PCS, and MCS

definition of the PSA nadir plus 2 ng/mL. No patients had PSA failure during this study period. The IMRT dose administered to the PTV was 70 Gy in 18 patients (20 %), 72 Gy in 13 patients (14 %), 76 Gy in 1 patient (1 %), and 78 Gy in 59 patients (65 %). The IMRT dose 70 or 72 Gy was administered to all patients until June 2007; thereafter, 78 Gy was administered to the majority of patients.

Longitudinal changes in HRQOL after IMRT (Fig. 1; Table 2)

Figure 1 and Table 2 show the EPIC scores for the urinary, bowel, sexual, and hormonal domains at baseline, 3, 6, 12, and 24 months after IMRT in the 91 patients. There was no significant change of the EPIC scores throughout the 2-year

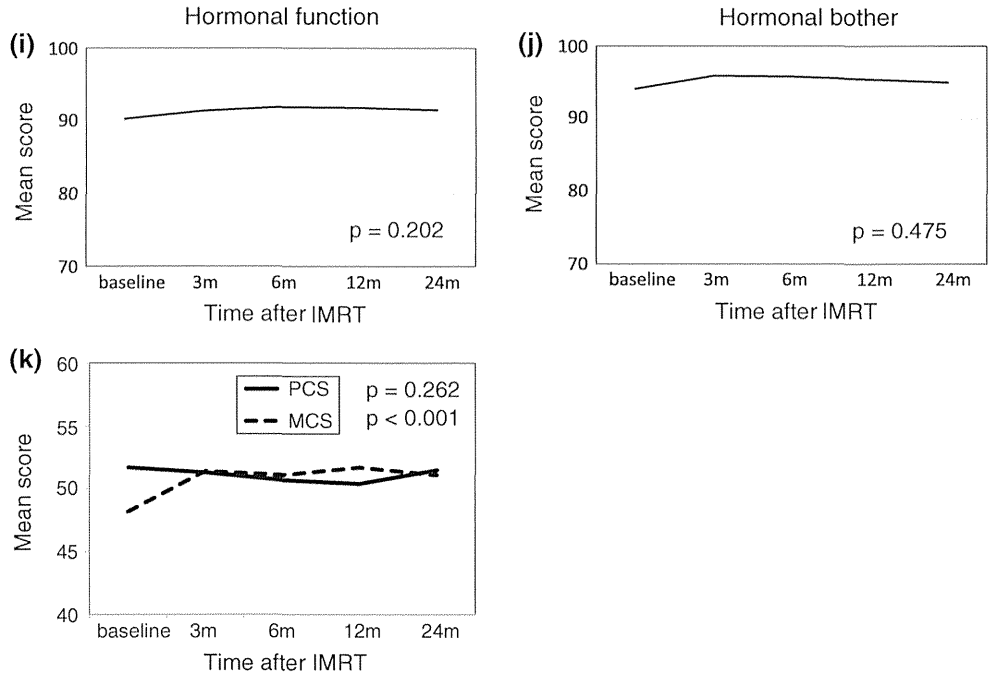

Fig. 1 continued

follow-up after IMRT in all four urinary subscales. Bowel function and bother EPIC scores began to decrease at 3 months after IMRT, and these scores did not return to baseline for 24 months (bowel function $p = 0.006$; bowel bother $p < 0.001$). The EPIC scores for sexual function gradually decreased after IMRT and then reached a plateau at 24 months; however, the scores at 24 months did not return to those at baseline ($p < 0.001$). Sexual bother scores began to decrease after 3 months, and the scores also did not return to those of baseline for 24 months ($p = 0.024$). The hormonal function EPIC scores did not change throughout the 2-year follow-up after IMRT, and although the hormonal bother scores tended to increase at 3 months after IMRT, there was no significant change throughout the 2 years after IMRT.

PCS scores began to decrease at 3 months after IMRT, followed by a decrease to the lowest scores at 12 months, and a return to the baseline scores at 24 months. However, the MCS scores began to significantly increase at 3 months after IMRT and they then reached a plateau until 24 months ($p < 0.001$).

Even when all patients were divided into two groups by IMRT dose (low-dose group [less than 76 Gy] and high-dose group [78 Gy]), there was no difference in the longitudinal changes in general and disease-specific HRQOL after IMRT between the two groups (data not shown).

Longitudinal changes in urinary subscale scores after IMRT for patients stratified by pre-IMRT IPSS scores (Fig. 2)

Before IMRT, 50 (55.6 %) patients had good urinary function and 40 (44.4 %) patients had poor urinary function. There were no significant differences in baseline variables between the two groups (Table 1). At baseline, patients with good urinary function had better urinary bother, incontinence, and irritative/obstructive scores than patients with poor urinary function (urinary bother $p < 0.001$, urinary incontinence $p = 0.03$, and urinary irritative/obstructive $p < 0.001$). In patients in the poor urinary function group, all 4 urinary subscale scores at 3 months after IMRT exceeded those at baseline. In this group, urinary bother, incontinence, and irritative/obstructive scores reached a maximum point 6 months after IMRT, and thereafter, these scores decreased slowly until 24 months (Fig. 2) This trend was particularly notable for the urinary bother score. There was no significant change of the EPIC scores throughout the 2-year follow-up after IMRT in all 4 urinary subscales in the poor urinary function group.

In the group with good urinary function, although there were no significant changes, all 4 urinary subscale scores at 3 months after IMRT were lower than those at baseline.