Journal of Radiation Research, Vol. 58, No. 1, 2017, pp. 71–78
doi: 10.1093/jrr/rrw059
Advance Access Publication: 8 September 2016

A surveillance study of the current status of reirradiation and patterns of practice

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Received January 5, 2016; Revised March 24, 2016; Accepted May 1, 2016

ABSTRACT

The aim of this study was to survey the current status of reirradiation (Re-RT) and patterns of practice in Japan. An email questionnaire was sent to Kansai Cancer Therapist Group partner institutions, using questions similar to those in the Canadian radiation oncologist (RO) survey (2008). A total of 34 ROs from 28 institutions returned the survey. All 28 institutions experienced Re-RT cases in 2014. However, 26 of the 28 institutions (93%) reported difficulty in obtaining Re-RT case information from their respective databases. Responses from 19 institutions included the number of Re-RT cases; this rose from 183 in the period 2005–2009 (institution median = 4; 2–12.9) to 562 in the period 2010–2014 (institution median = 26; 2–225). Important considerations for indication of Re-RT were age (65%), performance status (83%), life expectancy (70%), absence of distant metastases (67%), and interval since previous treatment (73%). Previous total radiation dose (48%), volume of tissue irradiated (72%), and the biologically equivalent dose (BED; 68.5%) were taken into account during Re-RT planning. These factors were similar to those considered in the Canadian survey; however, the present study did not consider age. In eight site-specific scenarios, barring central nervous system recurrence, more than 90% of ROs agreed to perform Re-RT, which was higher than the percentage observed in the Canadian survey. Re-RT cases have increased in number and aroused interest among ROs in this decade of advanced technology. However, consensus building to establish guidelines for the practice and prospective evaluation of Re-RT is required.

KEYWORDS: reirradiation, questionnaire

INTRODUCTION

The advancement of treatment modalities in surgery, chemotherapy and radiotherapy (RT) has improved survival rate and loco-regional control at many sites of cancer occurrence. However, in-field cancer recurrence after RT remains an obstacle to cure [1]. Treatment options for in-field cancer recurrence after RT include surgery, systemic chemotherapy, and reirradiation (Re-RT) [2–7]. With the advancement of modern radiation techniques, Re-RT has become a promising optional therapy that uses state-of-the-art advanced technologies, including intensity-modulated radiation therapy (IMRT), stereotactic RT (SRT), and particle therapy [5–10]. However, there is little evidence in support of Re-RT therapy; therefore, radiation oncologists (ROs) should make clinical decisions on their own experiences, either with palliative or radical intention. In other words, Re-RT is still in the experimental phase and requires further exploration. The objective of this study was to survey the present state of Re-RT and to determine its patterns of practice for in-field cancer recurrence after previous RT. In addition, we compared the present results with those of the Canadian survey to examine changes across decades and between countries [11].

MATERIALS AND METHODS

A survey questionnaire (refer to supplement) was emailed to ROs registered in the Kansai Cancer Therapist Group directory as of 2015. At the time of correspondence, all the respondents were actively practicing in Japan. Part I of the survey questionnaire investigated the following: the actual number of Re-RT cases in 2014, 2005–2009 and 2010–2014, both in total and sub-grouped by location. Part II investigated the indications for Re-RT, Re-RT treatment planning, and eight case scenarios selected from the most common tumor types (head and neck, chest, colorectal, genitourinary, gynecologic and gastrointestinal) reported in the Canadian survey [11]. The completed questionnaires were received via email. Comparisons were made between patients treated in 2004–2009 and those treated in 2010–2014, and between the Canadian survey and the present Japanese survey. This study defined Re-RT as RT performed after previous RT of 30 Gy/10 fractions (= EQD2 36 Gy, using $\alpha/\beta = 3$, where EQD2 = equivalent 2-Gy fractions) or more. A biologically equivalent dose (BED) was calculated into EQD2 using the linear quadratic model: EQD2 = prescription dose × $(\alpha/\beta + \text{dose per fraction})/(\alpha/\beta + 2)$, where $\alpha/\beta = 10$ for tumors and 3 for organs at risk.

Statistical analysis

All statistical analyses were performed using Stat-view 5.0 statistical software (SAS Institute, Inc., Cary, NC, USA). The percentage values were analyzed using the χ^2 test, and values were compared using Mann–Whitney U analysis. All analyses used the $P < 0.05$ level of significance.

RESULTS

A total of 34 ROs from 28 institutions returned the survey. All 28 institutions experienced Re-RT cases in 2014. However 26 institutions (93%) had difficulty in obtaining individual Re-RT case details from their respective databases, primarily because there were no accompanying details, such as 'second RT course' or 'in-field cancer recurrence after initial RT'. Only 19 institutions provided detailed information for Re-RT cases (Table 1). Of these, 193 Re-RT cases (institution median = 6; 1–51) occurred in 2014 (Table 1). The most common Re-RT sites were the brain ($n = 55$, 28.9%), vertebral body ($n = 30$, 15.8%), chest ($n = 30$, 15.8%), and head or neck ($n = 28$, 14.7%) in 2014. These figures showed a similar distribution in 2005–2009 (brain = 18%, vertebral body = 19.7%, chest = 24%, head and neck = 19.7%) and in 2010–2014 (brain = 30%, vertebral body = 17.4%, chest = 18.3%, head and neck = 15.3%) except those for the brain ($P = 0.037$; Table 1). The number of Re-RT cases increased from 183 in 2005–2009 (institution median = 4; 2–129) to 562 in 2010–2014 (institution median = 26; 2–225). It should be noted that one new institution was included in 2010–2014 as it received sophisticated equipment after 2010.

Table 1. Patient numbers treated by reirradiation in responding institutes

	2004–2009 (5 years)	(%)	2010–2014 (5 years)	(%)	*P*-value	2014 (Single year)	(%)
Total number	183		562			193	
Brain	33	(18%)	171	(30%)	0.037	55	(28%)
Head and neck	36	(20%)	86	(15%)		28	(15%)
Chest	44	(24%)	103	(18%)		30	(16%)
Abdomen	17	(9%)	41	(7%)		10	(5%)
Pelvis	9	(5%)	23	(4%)		19	(10%)
Bone mets	6	(3%)	25	(4%)		12	(6%)
Vertebrae mets	36	(20%)	98	(17%)		30	(16%)
Other	2	(1%)	15	(3%)		9	(5%)

Table 2. Demographic data for radiation oncologists (ROs)

		No. of ROs	(%) of ROs	No. of Canadian ROs [11]	(%) of Canadian ROs [11]	*P*-value
Experience (years in RO practice)	<5 years	7	(21%)	35	(19%)	n.s.
	5–10 years	8	(24%)	42	(23%)	
	11–20 years	11	(32%)	69	(38%)	
	>20 years	8	(24%)	38	(21%)	

Respondent demographics and Re-RT eligibility and exclusion criteria

Of the total respondents, 24% had been in practice for > 20 years, whereas 21% had been in practice for < 5 years; these respondent demographics resembled those of the Canadian survey (Table 2) [11]. Respondents were asked to comment on patient factors that would influence their decision to recommend Re-RT. Important factors included age (65%), performance status (PS) (83%), life

Table 3. Factors affecting indication of reirradiation

Factor		No. of ROs	(%)	No. of Canadian ROs [11]	(%) of Canadian ROs [11]	*P*-value	Additional comments: Detailed factor	No. of ROs	(%)	No. of Canadian ROs [11]	(%) of Canadian ROs [11]	*P*-value
Age	No	12	(35%)	133	(73%)	<0.0001						
	Yes	22	(65%)	35	(19%)							
	Unc.	0	(0%)	15	(8%)							
Performance status	Yes	25	(83%)	128	(70%)	n.s.	ECOG 1≥	1	(4%)	58	(45%)	<0.0001
	No	6	(20%)	39	(21%)		ECOG 2≥	13	(50%)	51	(40%)	
	Unc.	0	(0%)	16	(9%)		ECOG 3≥	6	(23%)	13	(10%)	
							ECOG 4≥	0	(0%)	6	(5%)	
							Unc.[a]	6	(23%)	0	(0%)	
Life expectancy	Yes	21	(70%)	109	(60%)	n.s.	1–3 months	2	(8%)	17	(18%)	n.s.
	No	9	(30%)	59	(32%)		3–6 months	9	(38%)	33	(36%)	
	Unc.[b]	1	(4%)	15	(8%)		6–12 months	7	(29%)	20	(22%)	
							1–2 years	4	(17%)	14	(15%)	
							≥2 years	1	(4%)	8	(9%)	
							Unc.[c]	1	(4%)	8	(9%)	
Distant metastasis	Yes[d]	22	(67%)	99	(54%)	n.s. (0.08)						
	No	11	(33%)	60	(33%)							
	Unc.	0	(0%)	23	(13%)							
Disease-free interval after initial RT	Yes	22	(73%)	144	(79%)	n.s.	1–3 months	0	(0%)	18	(13%)	0.03
	No	8	(27%)	25	(14%)		3–6 months	4	(15%)	43	(30%)	
	Unc.	1	(4%)	14	(8%)		6–12 months	12	(46%)	36	(25%)	
							1–2 years	3	(12%)	14	(10%)	
							≥2 years	0	(0%)	12	(8%)	
							Unc.	7	(27%)	21	(15%)	

Summation of % does not equal 100% because of duplicated answers. 'Other' included distance from OAR, patient will. Unc. = uncertain, RO = radiation oncologist, ECOG = Eastern Cooperative Oncology Group.

[a]One RO replied: ECOG 2≥ for curative Re-RT, ECOG 4≥ for palliation.

[b]One RO replied: It is case sensitive.

[c]One RO replied: >2 months for palliative and >6 months for curative Re-RT.

[d]Six ROs replied: Yes for curative Re-RT.

expectancy (70%), absence of distant metastases (67%), and interval since initial treatment (73%; Tables 2 and 3). Most respondents believed that patients should have a minimum Eastern Cooperative Oncology Group (ECOG) PS of 2–3, a minimum life expectancy of 6–12 months, and an interval of 6 months or more from initial treatment to be considered for Re-RT (Table 3). These figures were similar to those in the Canadian survey, except those for age, detailed ECOG PS, and time interval since initial therapy. The Canadian survey reported that age did not influence the likelihood of an RO prescribing Re-RT (Table 3) [11].

Factors affecting Re-RT treatment planning

Most ROs suggested that factors such as metastatic work-up (69%), previous total radiation dose (91%) and the BED (68%) were significant considerations when deciding the amount of residual normal tissue tolerance, the Re-RT dose and Re-RT feasibility (Table 4). Significant factors in deciding Re-RT dose were previous dose (74%), clinical judgment (79%) and BED (79%). Only 16% of ROs simultaneously used chemotherapy and Re-RT. Similar respondent attitudes were observed in the present survey and the Canadian survey.

Responses for site-specific case scenarios

Responses to the site-specific questions are summarized in Table 5. In this study, 94% of ROs recommended Re-RT for central nervous system cases, as compared with 34% of ROs in the Canadian survey. Most ROs (18/24 = 75%) recommended SRT, and one recommended stereotactic radiosurgery (SRS) after debulking surgery. In general, > 60% of ROs recommended Re-RT for every scenario, which seems to be higher than the percentage observed in the Canadian survey (34.8–78.8%); however, the opposite trend was observed for cervical cancer recurrence cases (Table 5). Ninety-six percent of Canadian ROs recommended Re-RT in recurrent cervical cancer scenarios, as compared with 82% of Japanese ROs. Japanese ROs recommended only brachytherapy, whereas Canadian ROs recommended external beam radiotherapy (EBRT) + BT.

DISCUSSION

The aim of this study was to survey the present state of Re-RT; this included comparing the attitude towards Re-RT between Japanese ROs in 2015 and Canadian ROs in 2008. The widely prevailing notion that Re-RT cannot be used after a radical course of RT continues to hinder the active management and treatment of patients with in-field cancer recurrence. Factors determining the safe and effective use of Re-RT include primary tumor site, the initial cancer stage, type of initial treatment (radiation dose, technique, dose per fraction, use of concurrent chemotherapy), response to initial treatments, clinically apparent late effects from initial RT, residual radiation tolerance of the normal tissues (including BED calculation), the duration of the relapse-free interval, and the existing literature. Re-RT purpose (radical or palliative) is also an important

Table 4. Factors affecting reirradiation planning

		No. of ROs	(%)	(%) of Canadian ROs [11]
Metastatic work-up	Yes	22	(69%)	(72%)
	No	4	(13%)	
	Unc.	6	(19%)	
Normal tissue tolerance[a]	Previous dose	31	(91%)	(90%)
	Clinical decision	21	(62%)	
	BED	23	(68%)	(69%)
	Irradiated volume	13	(38%)	(90%)
Factor to decide Re-RT dose[a]	Previous dose	25	(74%)	
	Clinical decision	27	(79%)	(83%)
	BED	27	(79%)	(53%)
	Irradiated volume	13	(38%)	
	Other[b]	1	(3%)	
Chemotherapy use	Yes	5	(16%)	(28%)
	No	16	(50%)	
	Unc.	11	(34%)	

[a]Summation of % does not equal 100% because of duplicated answers.
[b]'Other' included distance from organs at risk, patient will. Unc. = uncertain, RO = radiation oncologist.

Table 5. Attitude to reirradiation for site-specific case scenarios

Case No.		RO's answer				(%) of Canadian ROs [11]	Initial indication	Reason for Re-RT decision (in descending order)	Methods and dose fractionation (in descending order)	
		Yes	No	Unc.	(%) 'Yes'	(%) 'Yes'			RO's answer	Canadian ROs [11]
1	Central nervous system	30	2	0	(94%)	(34.8%)	Curative	Yes (No other option left) (For QOL maintenance) (Modern technology: SRT and IMRT available) (Young age) No (Risk of brain necrosis) (Surgery preferred)	SRT (25–48 Gy/3–8 fr), IMRT (20–40 Gy/ 7–15 fr), SRS, BT (25–30 Gy/5–10 fr)	SRS (15 Gy or 18 Gy/1 fr), 3D-CRT EBRT (20 Gy/10 fr, 25–40 Gy/20 fr, 30 Gy/5 fr[a])
2	Head and neck ca. (nasopharyngeal cancer)	27	4	0	(87%)	(78.8%)	Curative	Yes (No other option left) (More effective than chemotherapy) No (Surgery preferred) (Chemotherapy preferred) (Risk of visual disturbance)	IMRT (40–70 Gy/20–35 fr), SBRT (20–40 Gy/ 5–10 fr), 3D-CRT, BT (18–48 Gy/6–12 fr bid)	3D-CRT, IMRT, SRS (18 Gy/ 1 fr), BT,EBRT (50–70 Gy/ 25–35 fr, 60 Gy/25 fr, 50 Gy/ 20 fr, bid 50 or 60 Gy/40 fr/ 4 weeks)
3	Non–small cell lung ca.	23	7	2	(72%)	(65%)	Curative	Yes (Useful for palliation more than CTX) (QOL maintenance; hemosputum prophylaxis) (Yes for peripheral lesion, but no for central lesion) (SBRT, IMRT, Particle radiotherapy preferred) (Long interval) No (Depend on place and recurrent pattern) (Primary and lymph node area could be too large to Re-RT) (Difficult to identify the lesion from radiation fibrosis) Unc. (Yes for peripheral tumor, but no for central tumor)	3D-CRT (30–50 Gy/ 10–25 fr), IMRT (30 Gy/10 fr, 48–60 Gy/ 20 fr, 50–56 Gy/ 25–33 fr), SBRT (40–60 Gy/4–10 fr, 25 Gy/5 fr)	3D-CRT, conventional RT, endobronchial BT (8 Gy/1 fr, 14–15 Gy/ 2–3 fr/ 2–3 weeks), IMRT EBRT (30 Gy/10–15 fr, 36 Gy/12 fr, 25 Gy/10 fr, 20 Gy/5 fr)
4	Breast ca.	21	11	0	(66%)	(51.9%)	Curative	Yes (Long interval from initial RT) (Curative potential for oligo recurrence) (Skin could tolerable) (No serious OAR involved except skin) (There was a reference for this case)	3D-CRT (40–60 Gy/ 20–30 fr), Electron (50–60 Gy/25–30 fr), IMRT (40–56 Gy/ 20–33 fr)	Electron therapy, 2D RT, BT (50 Gy LDR or 20–25 Gy HDR/4–5 fr bid/2–2.5 days), 3D-CRT, IMRT EBRT (30–50 Gy/15–25 r, 30–50 Gy/ 30 fr bid/2 weeks)

Continued

Table 5. Continued

Case No.		RO's answer				(%) of Canadian ROs [11]	Initial indication	Reason for Re-RT decision (in descending order)	Methods and dose fractionation (in descending order)	
		Yes	No	Unc.	(%) 'Yes'	(%) 'Yes'			RO's answer	Canadian ROs [11]
								No (Hormonal Tx preferred) (Prophylaxis Re-RT may be overtreatment) (No symptom) (Retained to recurrence) (Toxicity concern)		
5	Brain metastasis (breast)	19	12	0	(61%)	Not available	Palliative	Yes (No other option left) (Small lesion) (Palliative merit) (According to patient's will) (Brain could be tolerated up to 60 Gy) No (Too many lesions) (Symptom could not be related to lesions) (Multiple small lesions indicated meningitis carcinomatosa) (Toxicity concern) (Wait for steroid refractory)	SBRT (18–25 Gy/1 fr, 30–36 Gy/3 fr), 3D-CRT (30–40 Gy/5–10 fr), IMRT (45–60 Gy/15 fr, 35 Gy/5 fr)	Not available
6	Cervical ca.	28	3	3	(82%)	(95.5%)	Curative	Yes (No other option left) (Curative possibility) (Brachytherapy could avoid severe toxicity) No (Surgery preferred) (Toxicity concern)	BT (HDR 18–25 Gy/ 4–5 fr, 36–42 Gy/6–5 fr), SBRT and IMRT (20 Gy/5 fr – 48 Gy/ 8 fr)	3D-CRT, IMRT, 2D EBRT followed by BT (40–50 Gy/ 20–25 fr/4–5 weeks followed by BT (LDR) 60–65 Gy) EBRT alone (45 Gy/25 fr, 40 Gy/20 fr, 30 Gy/20 fr) BT alone (35–50 Gy LDR/4–6 days or 20–25 Gy HDR/4–5 fr bid/ 2–2.5 days)
7	Rectal ca.	22	7	5	(65%)	(61.1%)	Curative	Yes (No other option left) (Particle therapy preferred) (Palliative merit: pain relief) (BT possible) No (Re-RT is not routine protocol) (Toxicity concern)	IMRT (30–40 Gy/50 fr, 50–66 Gy/20–25 fr, 30 Gy/10 fr), 3D-CRT (30 Gy/10 fr, 20 Gy/5 fr, 8 Gy/1 fr, 40 Gy/20 fr), Charged particle, BT (8 Gy/1 fr, 20–30 Gy, 66 Gy/33 fr; SIB)	3D-CRT, conventional RT, SRS, IMRT EBRT (30 Gy/10 fr, 20 Gy/5 fr, 20 Gy/10 fr, 5–8 Gy/1 fr)

8	Prostate ca.	26	5	0	(84%)	Not available	Palliative	Yes (No other option left) (Small lesion) (Palliative merit) (IMRT could avoid cord) (According to patient's will) (Already symptom occurring) No (Too many lesions) (OAR tolerance: cord) (Little hope for cure) (Large RT field) Unc. (Yes for palliation, but no for tumor control)	3D-CRT (20–30 Gy/10 fr, 8 Gy/1 fr, 40 Gy/16 fr), IMRT (30–40 Gy/ 10–20 fr, 20–25 Gy/ 4–5 fr), 2D, SRT (8 Gy/ 1 fr, 20–30 Gy/5–15 fr, 57–60 Gy/15–20 fr)	Not available

Summation of % does not equal 100% because of duplicated answers. fr = fractions, SRT = stereotactic radiotherapy, 3D-CRT = 3D radiotherapy, BT = brachytherapy, Unc. = uncertain, bid = twice in a day, SIB = simultaneous-integrated boost, IMRT = intensity-modulated radiotherapy, QOL = quality of life, OAR = organ at risk, TX = therapy, EBRT = external beam radiation therapy (includes electron, 2D, 3D-CRT, IMRT).
[a]Equal daily dose given once weekly.

determinant, which is influenced by the presence of distant metastases (other active lesions), PS and age. Although age and PS were important factors in Japan, the Canadian survey showed that those were not limiting factors when deciding whether Re-RT was needed (Tables 1, 2), possibly reflecting the attitudes changing from palliative to curative intentions with current challenges with using advanced technology today [11].

Re-RT cases increased in number from 2005–2009 to 2010–2014, indicating that ROs are becoming more familiar with Re-RT; this was also true in the comparison between the present survey and the Canadian survey [11]. This may have been because RT technology has considerably improved during this decade, and more patients are receiving Re-RT therapy using state-of-the-art equipment. Re-RT has been successfully used with acceptable morbidity for a variety of locally recurrent tumors, including tumors of the breast, head and neck, brain, pelvis, bone and lung [6]. However, occasionally lethal side effects such as carotid blow-out syndrome may occur [12]. The risks of normal tissue complications and the lack of adequate data on recovery from radiation injury were the common barriers to using Re-RT as a salvage treatment modality. Acutely responding tissues fully recover within a few months, and these tissues can tolerate retreatment as well as untreated tissue [13]. On the other hand, the pattern of recovery from radiation injury varied considerably in late-responding tissues. Late-responding tissues (the heart, bladder and kidney) do not exhibit long-term recovery, whereas the skin, mucosa, lung, and spinal cord do recover from occult injury of varying magnitudes [9]. Several studies have analyzed the suitability of Re-RT for in-field cancer recurrence and reported that Re-RT (with or without chemotherapy) results in adequate loco-regional tumor and symptom control [5–7, 14–17].

An additional barrier to the use of Re-RT is the paucity of data available to determine the Re-RT schedule and dose fractionation–volume relationships, although hyperfractionated schedules or day-after-day schedules were suggested as a means of limiting retreatment toxicity [18, 19]. In addition, newly installed technology (SRT, IMRT, IGRT, particle therapy and image-guided brachytherapy) increased the Re-RT potential, which simultaneously made it more difficult to establish a clear consensus on Re-RT. For example, charged particle therapy was recommended for several recurrence sites in this survey (Table 5); this was not observed in the Canadian survey [11]. Recently, newer technologies, such as 3D conformal radiotherapy (3D-CRT), IMRT, SRS, SRT and charged particle therapy, have influenced Re-RT planning and delivery to facilitate normal tissue tolerance. For example, in this survey three ROs recommended charged particle radiotherapy for rectal cancer.

The consensus on palliative or curative intention has also been changing recently; the oligometastasis concept illustrates this [20]. Furthermore, the presently available database systems do not facilitate the easy retrieval of Re-RT cases. Most institutions reported difficulty in retrieving Re-RT case information. Some institutions examined the data for all patients that received RT twice or more, to identify the overlap between initial RT fields and the Re-RT field. An easy system for Re-RT case information retrieval from databases is essential for the future exploration of Re-RT utility. Finally, future studies should also take into account the quality of life for patients who undergo Re-RT.

In conclusion, this decade saw an increase in the number of Re-RT cases and RO interest in Re-RT as a viable therapeutic option.

However, further consensus building is required, to establish guidelines for practice and prospective evaluation.

ACKNOWLEDGEMENTS

We are very grateful to Dr Joseph for allowing us to use the Canadian survey [11]. The authors would also like to thank Enago for the English language review, and Kansai Cancer Therapist Group Responders: Kengo Ogura, Gen Suzuki, Hiroya Siomi, Satoaki Nakamura, Tadayuki Kotsuma, Ken Yoshida, Yasuo Yoshioka, Shuichi Kanamori, Hideki Nishimura, Masasuke Matsui, Yasuo Ejima, Toshiyuki Nishita, Shigetoshi Shimamoto, Hitoshi Tatebe, Ryoongjin Oh, koji Konishi, Yoshiharu Negoro, Yo Ushijima, Tomomi Tsujimoto, Takayuki Kotsuma, Norihiro Aibe, Akihiro Nakajima, Takuya Kimoto, Masahiko Koizumi, Naohiro Kodani, Tomoaki Okimoto, Koji Masui, Kotoha Tatekawa and Nishimura Takuya.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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