JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2013;43(12)1233–1237
doi:10.1093/jjco/hyt147
Advance Access Publication 25 September 2013

A Newly Introduced Comprehensive Consultation Fee in the National Health Insurance System in Japan: A Promotive Effect of Multidisciplinary Medical Care in the Field of Radiation Oncology—Results from a Questionnaire Survey

Hiroshi Igaki[1,*], Hiroshi Onishi[2], Keiichi Nakagawa[1], Takushi Dokiya[3], Kenji Nemoto[4], Naoyuki Shigematsu[5], Yasumasa Nishimura[6], Masahiro Hiraoka[7] and Japanese Society for Therapeutic Radiology and Oncology Health Insurance Committee

[1]Department of Radiology, The University of Tokyo, Tokyo, [2]Department of Radiology, Yamanashi University, Yamanashi, [3]Department of Radiation Oncology, Saitama Medical University International Medical Center, Saitama, [4]Department of Radiation Oncology, Yamagata University, Yamagata, [5]Department of Radiology, Keio University, Tokyo, [6]Department of Radiation Oncology, Kinki University Faculty of Medicine, Osaka and [7]Department Radiation Oncology and Image-Applied Therapy, Kyoto University Graduate School of Medicine, Kyoto, Japan

*For reprints and all correspondence: Hiroshi Igaki, Department of Radiology, The University of Tokyo, 7-3-1, Hongo, Bunyo-ku, Tokyo 113-8655, Japan. E-mail: igaki-tky@umin.ac.jp

Received August 1, 2013; accepted September 2, 2013

Objective: The consultation fee for outpatient radiotherapy was newly introduced in the national health insurance system in Japan in April 2012. We conducted a survey on the use of this consultation fee and its effect on clinical practices.
Methods: The health insurance committee of the Japanese Society of Therapeutic Radiology and Oncology conducted a questionnaire survey. The questionnaire form was mailed to 160 councilors of the Society, the target questionees. A total of 94 answers (58% of the target questionees) sent back were used for analyses.
Results: The analyses revealed that 75% of the hospitals charged most of the patients who receive radiotherapy in an outpatient setting a consultation fee. The introduction of the consultation fee led to some changes in radiation oncology clinics, as evidenced by the response of 'more careful observations by medical staff' in 37% of questionees and a 12% increase in the number of full-time radiation oncology nurses. It was also shown that the vast majority (92%) of radiation oncologists expected a positive influence of the consultation fee on radiation oncology clinics in Japan.
Conclusions: Our questionnaire survey revealed the present status of the use of a newly introduced consultation fee for outpatient radiotherapy, and the results suggested its possible effect on promoting a multidisciplinary medical care system in radiation oncology departments in Japan.

Key words: consultation fee – outpatient radiotherapy – multidisciplinary medical care – questionnaire survey

INTRODUCTION

Under the Japanese national health insurance system, patients are generally charged a constant basic consultation fee for every hospital visit. This is because all medical interventions must be based on doctors' examinations and decisions on the day of the patient's hospital visit under the Japanese Medical

Practitioners' Act (1). But radiation oncologists have long been examining the patients once a week during the course of daily radiotherapy in Japanese hospitals since several decades ago, as is the case with other countries. Patients are irradiated by radiotherapy technologists five times per week according to the physician's comprehensive direction, which is provided on the day of the physician's weekly examination. The Ministry of Health, Labor and Welfare (MLHW) of Japan has long assumed that such a situation in Japanese radiation oncology clinics is illegal. In other words, four out of five irradiations per week are treatments that are not based on the physician's examination, according to the ministry's interpretation.

Because there was a big gap between the law and the real situations in radiation oncology clinics, the Japanese MLHW newly introduced a medical service fee, called a consultation fee for outpatient radiotherapy, in the Japanese national health insurance system in April 2012 (2). Under the rules of the new consultation fee, the situation of Japanese radiation oncology clinics described above is remedied if the hospital fulfills certain requirements of the structure of a multidisciplinary medical care team in the radiation oncology department (Table 1) and notifies the Regional Bureau of Health and Welfare. The patients are charged a new consultation fee once a week on the same day of the doctor's examination, instead of a daily basic consultation fee. Thus, the requirement of the Japanese Medical Practitioners' Act has changed to permit daily radiotherapy with once-a-week physician's examination in the Japanese health insurance system. This means that the introduction of this weekly comprehensive consultation system was a milestone change not only for Japanese radiation oncology clinics, but also for the Japanese medical community, because the Japanese Medical Practitioners' Act approved medical cares and treatments without a physician's examination for the first time in Japanese medical history.

A weekly comprehensive consultation system had long been sought in Japan because of the problem of workforce shortages of radiation oncologists to resolve 'illegal' situations in Japan. We report here the results of the questionnaire survey, as well as the present status of the consultation fee and its problems.

Table 1. Structural requirements of radiation oncology centers in charging a consultation fee for outpatient radiotherapy in Japan

1. At least one radiation oncologist with ≥5 years of experience in clinical radiation oncology is attending in the department when the patients receive radiotherapy.

2. At least one full-time radiation oncology nurse and one full-time radiotherapy technologist is in the department.

3. At least one medical physicist is attending in the department who is regularly in charge of quality assurance and control for radiotherapy machines.

4. There is an organization of communicating with radiation oncologists who can deal with the morbidities of the patients promptly, in case of an emergency.

The hospitals that fulfill the four requirements listed above can charge the outpatient who is receiving radiotherapy for this consultation fee after notifying the regional Bureau of Health and Welfare.

MATERIALS AND METHODS

The health insurance committee of the Japanese Society for Therapeutic Radiology and Oncology (JASTRO) carried out a questionnaire survey on the operations and the problems of a consultation fee for outpatient radiotherapy. The questionnaire consisted of 15 questions on the present status of the questionee's affiliation, changes in the clinics after introduction of this new consultation fee system and opinions on the rules of the cost accrual of the consultation fee (refer to the Supplementary data). The questionnaire form was mailed to the councilors of JASTRO on 5 September 2012. The questionees were asked to sign the form. As of 30 November 2012, 94 out of 160 councilors (59%) returned the form, including three anonymous questionees. Responses from all 94 questionees were used for the analyses.

RESULTS

Charging Status of the Consultation Fee for Outpatient Radiotherapy

We asked about the fulfillment of the requirements at the questionees' affiliated hospitals. Of the 94 questionees, 86 (91%) answered that their affiliated hospitals fulfilled all the requirements. Among these 86 questionees, 73 (85%) answered that their affiliated hospitals had notified the regional bureau about charging for the consultation fee. Of the 73 questionees whose affiliated hospitals had notified the bureau, 55 (75%) responded that the hospitals had charged almost all their patients a consultation fee for outpatient radiotherapy (Fig. 1).

Changes at the Clinics After Introduction of the Consultation Fee

The 73 questionees whose affiliated hospitals had notified the bureau were asked about the effects of introduction of the consultation fee for outpatient radiotherapy. Selecting from multiple options, the most frequent answer was 'more careful observations by medical staff' (34 answers, 47%) (Fig. 2A). In addition, 15% (11 out of 73 questionees whose affiliated hospitals had notified the bureau) reported institutional decisions to increase the number of full-time radiation oncology nurses. This is presumably because a significant portion of hospitals intended to meet the requirements for the cost accrual of the consultation fee to avoid an 'illegal' status. In contrast, there were no reports of increased numbers of radiation oncology physicians, radiotherapy technologists or medical physicists after introduction of the consultation fee (Fig. 2A).

Among 11 questionees who reported an increase in the number of full-time radiation oncology nurses, 8 (73%) also reported 'more careful observations by medical staff' (Fig. 2B), whereas only 26 answers of 'more careful observations by medical staff' were reported among the remaining 62

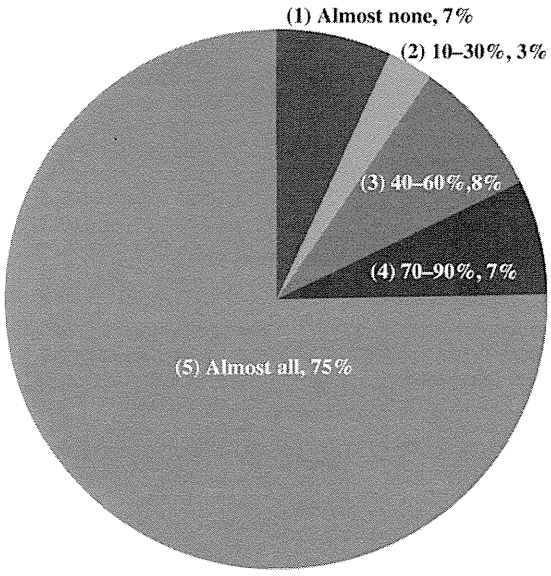

Figure 1. Proportion of the patients who are charged with the consultation fee for outpatient radiotherapy. Each questionee was asked to select from one of five options on the proportion of the patients who were charged with this consultation fee in his or her affiliated hospital: (1) almost none, (2) 10–30% of all outpatients, (3) 40–60% of all outpatients, (4) 70–90% of all outpatients and (5) almost all outpatients.

questionees whose affiliations had no increase in the number of full-time radiation oncology nurses (42%). The proportion of such answers appears to be higher among those who reported an increase in the number of full-time radiation oncology nurses than among other questionees, although the difference was marginally significant by a χ^2 test (73 vs. 42%, $P = 0.059$, Fig. 2B). In addition, the frequency of weekly examinations by radiation oncologists might has been slightly different between institutions with and without an increase in the number of full-time radiation oncology nurses. In the institutions with an increase in the number of nurses, the frequency of examinations by radiation oncologists was generally lower (Fig. 2B). In contrast, a considerable portion of the institutions reported an increase in the frequency of examinations (16%), which was greater than the response of less frequency of examinations among the whole questionees (Fig. 2A).

Perspective on the Consultation Fee

The questionees were asked whether introduction of the consultation fee for outpatient radiotherapy was presumed to contribute to the development of radiation oncology clinics in Japan. Among all the questionees, 35 had no distinct opinion.

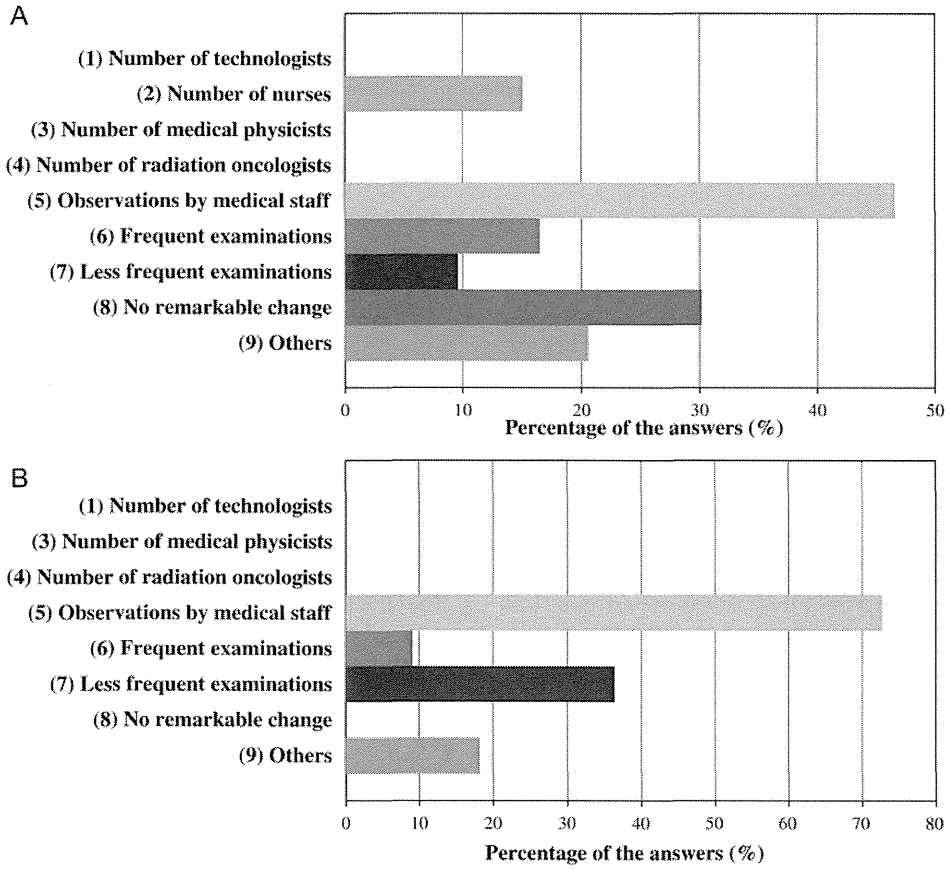

Figure 2. Changes after introduction of the consultation fee. The questionees were asked to select from nine options: (1) an increase in the number of radiotherapy technologists, (2) an increase in the number of full-time radiation oncology nurses, (3) an increase in the number of medical physicists, (4) an increase in the number of radiation oncologists, (5) more careful observations by medical staff, (6) more frequent examinations by radiation oncologists, (7) less frequent examinations by radiation oncologists, (8) no remarkable change and (9) others. Multiple selections were allowed. (A) Answers from all 73 questionees in whose affiliated hospitals the consultation fee can be charged from the outpatients. No increase in the numbers of radiotherapy technologists, medical physicists or radiation oncologists was reported. (B) Answers from 11 questionees who reported an increase in the number of full-time radiation oncology nurses.

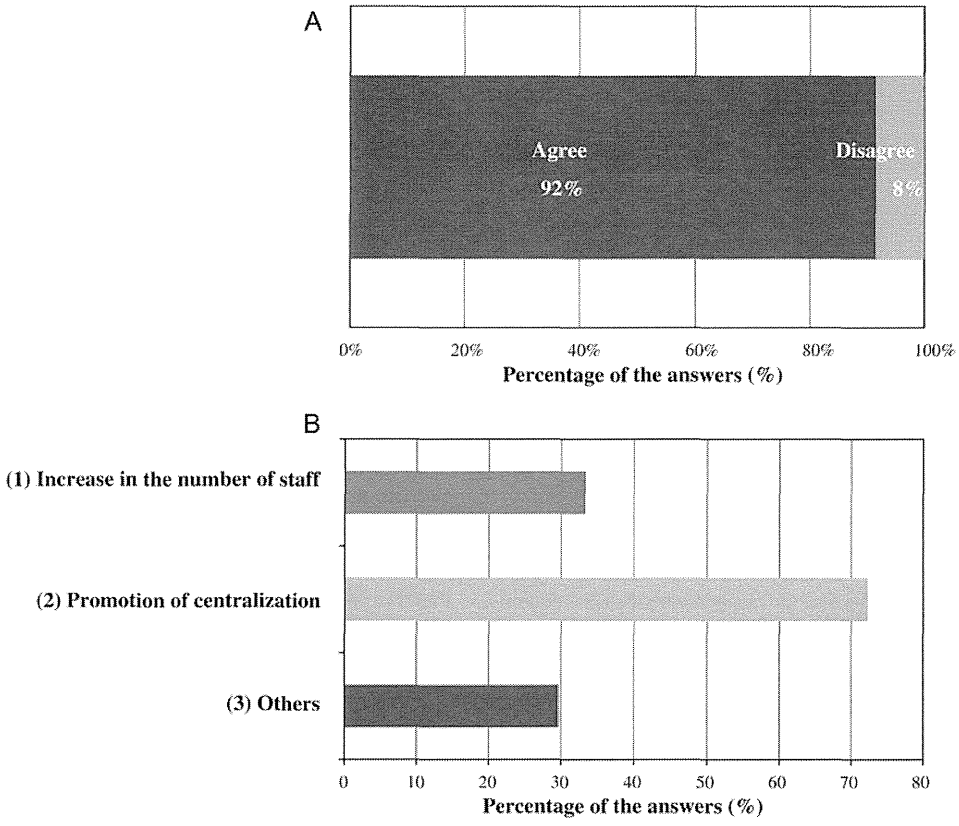

Figure 3. The influence of the consultation fee for outpatient radiotherapy on radiation oncology clinics in Japan. (A) The questionees were asked whether introduction of this consultation fee is expected to contribute to the future development of radiation oncology clinics in Japan. (B) Those who answered 'agree' in the above question were asked to select the reasons for their assumption from the following options: (1) compelling force to increase the number of staff in the radiation oncology department, (2) promotion of centralization of resources and staff in radiation oncology and (3) others. Multiple selections were allowed.

Of the remaining 59 questionees, 92% (54 out of 59) assumed that there was a positive influence of the consultation fee on radiation oncology clinics in Japan (Fig. 3A). The principal reason for this positive opinion was the compelling force to increase the numbers of staffs in the radiation oncology department (Fig. 3B).

DISCUSSION

In Japan, the consultation fee for outpatient radiotherapy was newly introduced in the national health insurance system in April 2012 (1). We assessed the effect of introduction of this consultation fee on radiation oncology clinics through a questionnaire survey. The results revealed that this consultation fee has prevailed in Japan, and most patients who receive radiotherapy in an outpatient setting in Japan are charged for this consultation fee (Fig. 1). The questionees of this survey were the councilors of JASTRO, whose affiliated hospitals were, in general, larger than those of average Japanese radiation oncology centers. Accordingly, the proportion of the patients who were charged a consultation fee might be overestimated in this survey.

Overall, an increased number of full-time radiation oncology nurses after introduction of the consultation fee for outpatient radiotherapy were reported by 15% of the questionees (Fig. 2A). A multidisciplinary medical care system was not common in Japan before the 1990s, but the Japanese MLHW introduced a multidisciplinary palliative care fee and a multidisciplinary nutrition support fee in 2002 and 2006, respectively, in the national health insurance system in Japan (3,4). These medical fees promoted multidisciplinary medical care teams for palliative care or nutrition support in Japan (4,5). A similar effect of promoting multidisciplinary radiation oncology teams is expected by introduction of the consultation fee for outpatient radiotherapy. In fact, more frequent observations of patients by medical staff were reported even from institutions where there was no increase in the number of medical staff for radiation oncology clinics.

JASTRO carries out national structure surveys in Japan every year, which include the number of personnel in each radiation oncology facility (6–8). The number of personnel is based on the answers from about 700 Japanese radiation oncology facilities (>90% of facilities at work in Japan), and these answers were provided by radiation oncologists at an administrative position of each facility. Compared with the JASTRO's national structure surveys, the targets for this questionnaire were a limited number of radiation oncologists, since there are about 1000 radiation oncologists in Japan (9). In addition, the data presented here were not based on the

administrative data of the hospital, but on the reports from the questionees. This was a major limitation of the study. However, because it was a small survey for a specific topic, our questionnaire could promptly detect a change in the number of personnel engaged in radiation oncology clinics in relation to this new consultation fee, compared with the JASTRO's national structure survey.

In conclusion, our questionnaire survey revealed that one reason for the workforce shortage in radiation oncology clinics might be attributable to poor reimbursement from the health insurance system in Japan, where there have long been smaller numbers of medical staff engaged in radiation oncology clinics than in the USA and European countries (10,11). A large proportion of the questionees were also expecting positive results on the development of radiation oncology clinics in Japan due to introduction of the consultation fee (Fig. 3A). The authors also assume that this consultation fee compels the development of radiation oncology clinics in Japan through an increase in the number of full-time radiation oncologists and other medical staff, and the prevalence of multidisciplinary medical care teams in radiation oncology.

Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org.

Funding

This work was supported in part by grants-in-aid for scientific research from the Japan Society for the Promotion of Science (grant number 23591835 to H.I.).

Conflict of interest statement

None declared.

References

1. Ministry of Justice. Japanese Law Translation: Medical Practitioners' Act. http://www.japaneselawtranslation.go.jp/law/detail/?ft=3&re=01&dn=1&x=46&y=16&bu=2048&ky=&page=19. (3 July 2013, date last accessed).
2. Ministry of Health, Labour and Welfare. Notice of revision of medical fee on April 2012. [In Japanese]. http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/iryouhoken/iryouhoken15/index.html. (3 July 2013, date last accessed).
3. Tsuneto S. Past, present, and future of palliative care in Japan. *Jpn J Clin Oncol* 2013;43:17–21.
4. Hirata K, Kawasaki K, Tatsumi H, et al. Present status and future prospects of nutritional support teams. [In Japanese]. *Nihon Geka Gakkai Zasshi* 2010;111:341–7.
5. Japan Hospice Palliative Care Foundation. Hospice Palliative Care White Book 2013. [In Japanese] http://www.hospat.org/white-book_2013-top.html. (3 July 2013, date last accessed).
6. 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.
7. Teshima T, Numasaki H, Shibuya H, et al. Japanese structure survey of radiation oncology in 2007 based on institutional stratification of patterns of care study. *Int J Radiat Oncol Biol Phys* 2010;78:1483–93.
8. Teshima T, Numasaki H, Shibuya H, et al. Japanese structure survey of radiation oncology in 2005 based on institutional stratification of patterns of care study. *Int J Radiat Oncol Biol Phys* 2008;72:144–52.
9. Japanese Society for Therapeutic Radiology and Oncology. List of physicians specializing in radiation oncology. [In Japanese] http://www.jastro.or.jp/doctorlist/. (3 July 2013, date last accessed).
10. Teshima T, Owen JB, Hanks GE, et al. A comparison of the structure of radiation oncology in the United States and Japan. *Int J Radiat Oncol Biol Phys* 1996;34:235–42.
11. 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.

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2013;43(2)154–160
doi:10.1093/jjco/hys210
Advance Access Publication 12 December 2012

Validation of Nomogram-based Prediction of Survival Probability after Salvage Re-irradiation of Head and Neck Cancer

Naoto Shikama[1,*], Yu Kumazaki[1], Nobuhiro Tsukamoto[2], Takeshi Ebara[1], Soichi Makino[1], Takanori Abe[1], Mitsuhiko Nakahira[3], Masashi Sugasawa[3] and Shingo Kato[1]

[1]Department of Radiation Oncology, Saitama Medical University International Medical Center, Hidaka, Saitama, [2]Department of Radiation Oncology, Saiseikai Yokohama-shi Tobu Hospital, Yokohama-shi and [3]Department of Head and Neck Surgery, Saitama Medical University International Medical Center, Hidaka, Saitama, Japan

*For reprints and all correspondence: Naoto Shikama, Department of Radiology Oncology, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka-City, Saitama 350-1298, Japan.
E-mail: nshikama0525@gmail.com

Received September 30, 2012; accepted November 17, 2012

Objective: Treatment outcomes after salvage re-irradiation in patients with recurrent head and neck cancer vary widely due to heterogeneous patient characteristics, and it is difficult to evaluate optimal re-irradiation schedules. This study aimed to validate a nomogram, originally developed by Tanvetyanon et al., used to predict the survival probability of patients with recurrent head and neck cancer after re-irradiation.

Methods: Twenty-eight patients with recurrent head and neck cancer who underwent salvage re-irradiation between June 2007 and November 2011 were evaluated. The median total dose used for initial radiotherapy was 60 Gy (range, 22–72). Re-irradiation sites included the nasopharynx or Rouviere's node ($n = 14$), external ear ($n = 4$), neck lymph node ($n = 3$) and other sites ($n = 7$). Overall survival after re-irradiation was calculated using the Kaplan–Meier method, and the 2-year survival probability was estimated using Tanvetyanon's nomogram.

Results: Twenty-two patients were treated with stereotactic body radiotherapy using a median total dose of 30 Gy (range, 15–40) in 1–7 fractions and six patients were treated with conventional external beam radiotherapy using 45 Gy (range, 23.4–60) in 10–30 fractions. The 2-year overall survival was 21.7% (95% confidence interval: 9.3–41.3), and the 2-year survival probability was 16.8% (95% confidence interval: 9.9–23.6). The 2-year overall survival in 20 patients with unfavorable prognosis (median 2-year survival probability, 5.5%) and in 8 patients with favorable prognosis (median 2-year survival probability, 45%) were 11.0 and 45.7%, respectively ($P = 0.05$).

Conclusions: Our findings show that Tanvetyanon's nomogram accurately estimates the survival probability in patients with recurrent head and neck cancer after re-irradiation.

Key words: salvage re-irradiation – head and neck cancer – nomogram – stereotactic body radiotherapy

INTRODUCTION

About 500 000 patients with head and neck cancer (HNC) are diagnosed each year worldwide (1). Despite comprehensive treatment strategies including surgery, radiotherapy and chemotherapy, approximately half of the patients with HNC die due to locoregional failure, distant metastases and second

primary neoplasms (2). Recurrent HNC (rHNC) and second primary neoplasms in the previously irradiated area represent a clinical challenge, and are normally treated with salvage surgical resection as this method offers the greatest probability for long-term survival (3–4). However, the population of candidates for curative salvage surgery is relatively small, and some patients require chemotherapy or re-irradiation in addition to surgery. The survival time after salvage chemotherapy has been estimated to be ~6 months (5). Re-irradiation using a full dose is associated with severe toxicities including tissue necrosis, bleeding and infection, and treatment-related deaths due to carotid hemorrhage (6–8). Recent studies using intensity modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT), twice-daily radiotherapy and concurrent chemotherapy reported the feasibility and effectiveness of re-irradiation in patients with rHNC (2,7,9). These studies also reported locoregional control rates after re-irradiation ranging from 19 to 64%, and median survival times (MST) ranging from 8.5 to 28 months (1,8,10–12). Treatment outcomes vary widely due to heterogeneous patient characteristics and diverse treatment schedules. Moreover, an optimal salvage re-irradiation schedule has not yet been established (1,8). Optimal sub-classification according to a confidential prognostic index is essential to rigorously compare treatment outcomes. Tanvetyanon et al. (13) developed a nomogram to predict 2-year survival probability in patients with rHNC after salvage re-irradiation. The nomogram includes the following: the presence of comorbidities, organ dysfunction, presence or absence of isolated neck recurrence, tumor bulk and time interval between the previous radiotherapy and start of re-irradiation. The overall goal of the present study was to validate this nomogram in patients with rHNC who were mainly treated with SBRT.

PATIENTS AND METHODS

Twenty-eight consecutive patients with local rHNC who underwent salvage re-irradiation between June 2007 and November 2011 were evaluated. The male-to-female ratio was 20:8, with a median age of 65 years (range, 43–90). Patients were treated for nasopharyngeal cancer ($n = 8$), external ear cancer ($n = 4$), hypopharyngeal cancer ($n = 3$) and other cancers ($n = 13$). Patient characteristics are shown in Table 1. Initial radiotherapy included treatment with definitive radiotherapy ($n = 22$), postoperative radiotherapy ($n = 5$) and salvage radiotherapy ($n = 1$) for recurrent disease after surgery. Twenty-three patients were treated with conventional three-dimensional external beam radiotherapy using Clinac iX or Trilogy (Varian Medical Systems, Inc., Palo Alto, CA) with a photon energy of 4 or 6 MV. Treatment plans included lateral opposed field, wedged pair field or multiple-field techniques. The radiation field covered the primary site, surrounding the lymph node area, and/or the prophylactic regional lymph node area. The prescribed dose was calculated at the center of the radiation field or from the planning target volume (PTV). The median total

Table 1. Patient characteristics

	Patient number	Median	Range
Age (years)		67	43–90
Gender			
Male	20		
Female	8		
Performance status			
0	20		
1	4		
2–4	4		
Initial diagnosis			
Nasopharyngeal cancer	8		
External ear cancer	4		
Hypopharyngeal cancer	3		
Tongue cancer	2		
Paranasal cavity cancer	2		
Others	9		
Pathology			
Squamous cell carcinoma	24		
Leiomyosarcoma	1		
Neuroblastoma	1		
Round cell sarcoma	1		
Salivary duct carcinoma	1		
Initial radiotherapy			
Total dose (Gy)		60	22–72
Fraction size (Gy)		2	1.8–22
Site of re-irradiation			
Nasopharynx or Rouviere's node	14		
External ear	4		
Neck lymph node	3		
Oropharynx	2		
Paranasal cavity	2		
Others	3		
Maximum diameter of recurrent disease			
Stereotactic radiotherapy (cm)		2.9	1.0–6.0
Conventional radiotherapy (cm)		3.8	2.5–10.0
Interval between initial treatment and salvage re-irradiation			
1–6 (months)	10		
Over 6 (months)	18		
Re-irradiation			
Stereotactic radiotherapy	22		
Total dose (Gy)		30	15–40
Fraction size (Gy)		8	5–23
Conventional radiotherapy	6		
Total dose (Gy)		45	23.4–60
Fraction size (Gy)		2	1.8–3

dose was 60 Gy (range, 48–72) in 24–36 fractions over a 5- to 7-week period. Five patients were treated with using robotic image-guided radiotherapy (Cyberknife Robotic Radiosurgery System; Accuracy, Inc., Sunnyvale, CA) with a median total dose of 38 Gy (range, 22–39) in one to six fractions over a 1- to 6-day period. The prescribed dose for SBRT was defined as the dose covering at least 80% of the PTV. Sixteen patients received systemic chemotherapy concurrently or sequentially, which included platinum-based or 5-fluorouracil (5-FU) regimens (Table 2).

The median interval from initial radiotherapy to salvage re-irradiation was 9 months (range, 3–40). Twenty-two patients had comorbidities and nine had organ dysfunction (e.g. tracheostomy and dysphagia) at the start of salvage re-irradiation. The median maximum diameter of recurrent disease was 3.4 cm (range, 1–10). Re-irradiation sites included the nasopharynx or Rouviere's node ($n = 14$), external ear ($n = 4$), neck lymph node ($n = 3$) and other sites ($n = 7$). Twenty-two patients were treated with SBRT and six were treated with conventional external beam radiotherapy. The median total dose administered during salvage re-irradiation using SBRT was 30 Gy (range, 15–40) in one to seven fractions over a 1- to 9-day period. The median total dose of salvage re-irradiation using conventional external beam radiotherapy was 45 Gy (range, 23.4–60) in 10–30 fractions over a 2- to 6-week period. Both re-irradiation techniques adopted narrow field margins without prophylactic regional lymph node irradiation. Three patients who were treated with conventional external beam radiotherapy received chemotherapy (i.e. platinum-based or 5-FU regimens) concurrently with radiotherapy.

The OS was calculated using the Kaplan–Meier method, and the median 2-year survival probability was estimated using the nomogram developed by Tanvetyanon et al. (13) The OS was measured from the start of re-irradiation and calculated using death due to any cause as an event. Tumor responses were classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) according to the revised Response Evaluation Criteria in Solid Tumors (revised RECIST guideline version 1.1) (14). In-field recurrence was defined as an increase in the tumor size or appearance of new lesions in the re-irradiation area from diagnostic images, and out-field recurrence was defined as an increase in the tumor size or appearance of new lesions in the non-irradiated head and neck area. Distant metastases were defined as the appearance of new lesions beyond the head and neck area. Toxicity was assessed using the Common Terminology Criteria Adverse Event (CTCAE version 4.0). Statistical analyses were performed using JMP version 5.1J (SAS Institute, Inc.).

Table 2. Patient characteristics in the favorable and unfavorable groups

	Favorable group	Unfavorable group
Age (years)	59.0 (44–72)	69.5 (43–90)
Gender		
Male	7	13
Female	1	7
Performance status		
0	8	12
1	0	4
2–4	0	4
Pathology		
Squamous cell carcinoma	8	16
Others	0	4
Initial radiotherapy		
Total dose (Gy)	60	57
Fraction size (Gy)	2	2
Site of re-irradiation		
Nasopharynx or Rouviere's node	5	9
External ear	1	3
Neck lymph node	1	2
Oropharynx	1	1
Paranasal cavity	0	2
Others	0	3
Maximum diameter of recurrent disease		
Stereotactic radiotherapy (cm)	1.6	3.6
Conventional radiotherapy (cm)	N/A	3.8
Interval between initial treatment and salvage re-irradiation		
1–6 (months)	3	7
Over 6 (months)	8	10
Organ dysfunction		
No	7	11
Yes	1	9
Re-irradiation		
Stereotactic radiotherapy	8	14
Total dose (Gy)	26	30
Fraction size (Gy)	9.4	8
Conventional radiotherapy	0	6
Total dose (Gy)	N/A	45
Fraction size (Gy)	N/A	2

RESULTS

The median follow-up time in the present study was 7.3 months (range, 1.7–25.3). After re-irradiation, 5 patients (18%) achieved CR, 8 (28%) achieved PR and 15 (54%) showed SD or PD. In addition, two patients achieving PR received salvage surgery and one patient achieving PR and three showing SD received systemic chemotherapy (i.e. Tegafur Gimeracil Oteracil Potassium, S-1). The other patients were carefully monitored and received supportive

care. The median progression-free survival time after re-irradiation was 5.5 months [95% confidential interval (CI), 3.3−7.2]. Among the patients with re-progressive disease after re-irradiation, 15 (83%) developed in-field recurrence with or without out-field recurrence and/or distant metastases, two (11%) developed distant metastases alone and one (6%) developed recurrence in the field margin. However, no patients developed regional recurrence alone. The sites of distant metastases included the lung and mediastinal lymph nodes. Thirteen patients (46%) achieved a relative response (RR), which included CR and PR, and had a median maximum tumor diameter of 2.7 cm (range, 1.0−6.0). In patients who did not achieve RR, the median maximum tumor diameter was 3.7 cm (range, 1.5−10.0; $P = 0.03$). MST after re-irradiation of patients who achieved RR was 13.3 months (95% CI, 6.0–N/A) and 7.3 months for those who did not achieve RR (95% CI, 3.8–14.9; $P = 0.03$).

Univariate analyses revealed that MST and 2-year OS of 19 patients with small recurrent disease <4 cm were 13.0 months (95% CI, 6.0–N/A) and 26.6%, and those of 9 patients with large recurrent disease 4 cm or larger were 7.3 months (95% CI, 1.7–N/A) and not applicable, respectively ($P = 0.39$). MST and 2-year OS of 8 patients who developed recurrence within 6 months from the initial treatment were 7.9 months (95% CI, 1.7–N/A) and 20.2%, and those of 18 patients who developed it beyond 6 months were 8.6 months (95% CI, 7.3–18.9) and not applicable, respectively ($P = 0.62$). MST and 2-year OS of 24 patients with good performance status (PS = 0–1) were 13.3 months (95% CI, 7.3–N/A) and 24.9%, and those of 4 patients with poor PS (PS = 2–4) were 3.9 months (95% CI, 1.7–N/A) and 0%, respectively ($P = 0.02$).

The 2-year OS estimated using the Kaplan–Meier method was 21.7% (95% CI, 9.3–41.3), and the MST was 8.6 months (95% CI, 6.0–14.9; Fig. 1). The median 2-year survival probability estimated by Tanvetyanon's nomogram was 16.8% (95% CI, 9.9–23.6). The 2-year OS in 20 patients with unfavorable prognosis whose 2-year survival probability was <15% (median, 5.5; range, 1−11) and the 2-year OS in eight patients with favorable prognosis whose 2-year survival probability was >15% (median, 45; range, 15−55) was 11.0 and 45.7%, respectively ($P = 0.05$; Fig. 2).

Two patients (7.1%) developed adverse events (Grades 2−3), which included tumor bleeding (Grade 2) and oral bleeding (Grade 3). In addition, three patients (10.7%) developed severe adverse events (Grade 5). All three patients developed local progression after re-irradiation, with two of them developing local infection and soft tissue necrosis in the submandibular area and paranasal cavity. These two patients died due to tumor progression and infection. The third patient was initially treated with whole neck conventional radiotherapy (60 Gy in 30 fractions) followed by adjuvant chemotherapy, and also received salvage SBRT (25.6 Gy in 5 fractions) to treat left-neck lymph node recurrence. Despite these treatments, the patient developed in-field recurrence 6 months later, which was treated with re-salvage SBRT (24 Gy in two fractions); however, recurrence was not controlled and the patient died eight months later due to a carotid artery rupture. Four patients who developed severe adverse events (Grades 3−5) were treated with

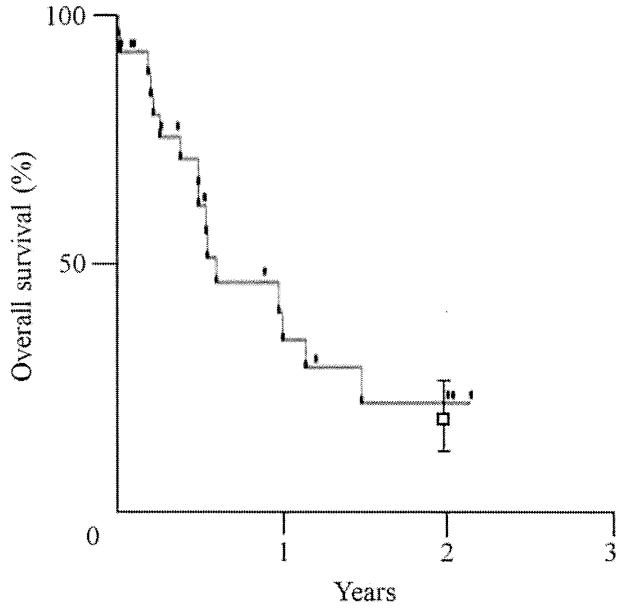

Figure 1. The overall survival curve (OS) of 28 patients with recurrent head and neck cancer (rHNC) was estimated using the Kaplan–Meier method. The white box shows the 2-year survival probability (16.8%) estimated using Tanvetyanon's nomogram. The vertical line indicates the 95% confidence interval of the 2-year OS rate (95% CI, 9.9–23.6%). This figure shows approximate values for the 2-year OS calculated by the Kaplan–Meier method and the 2-year survival probability estimated by Tanvetyanon's nomogram.

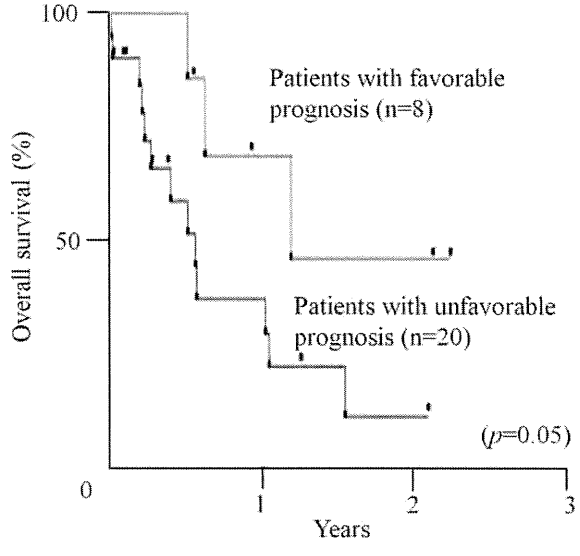

Figure 2. OS curves of patients with rHNC with favorable and unfavorable prognoses. The 2-year OS in 20 patients with unfavorable prognosis whose 2-year survival probability was <15% and the 2-year OS in eight patients with favorable prognosis whose 2-year survival probability was >15% were 11.0 and 45.7%, respectively ($P = 0.05$).

re-irradiation using SBRT; however, there was no difference between re-irradiation modalities ($P = 0.25$).

DISCUSSION

The American College of Radiology (ACR) Expert Panel on Head and Neck Cancer reviewed relevant literature on re-irradiation after definitive radiotherapy and evaluated its appropriateness, including radiation technique, treatment volume, doses and treatment schedule (3). The ACR Expert Panel emphasized the importance of patient selection and recommended careful evaluation and treatment by a comprehensive cancer team. Furthermore, they recommended considering re-irradiation with and without chemotherapy in patients with favorable prognosis and with relatively long estimated survival times. They also recommended performing a computed tomography (CT) scan of the chest and positron emission tomography/CT to determine the presence of metastatic disease, and evaluating patient conditions such as comorbidities, performance status, speech and swallowing function, and nutritional status. Moreover, a multi-disciplinary cancer care team should decide on the appropriate treatment strategy (e.g. salvage surgery, intensive re-irradiation with or without chemotherapy, chemotherapy alone and palliative care). The total absolute radiation dose to critical organs such as the spinal cord, carotid artery and optic pathways should be estimated using previous radiation dosimetry and latest patient images (8). Another important consideration is the interval between previous radiotherapy and start of salvage re-irradiation. One study showed that a longer interval was associated with a lower probability of severe adverse events due to re-irradiation and lower occurrence rates of distant metastases (15). In Tanvetyanon's nomogram, the interval is an important component used to estimate 2-year survival probabilities after re-irradiation (13). Previously published clinical trials have used intervals of >6 months to determine the eligibility for re-irradiation (6,7). Hoebers et al. (15) reported that an interval of over 3 years was associated with a favorable OS. However, the appropriate interval between previous radiotherapy and re-irradiation remains unknown.

The Fox Chase Cancer Center conducted a phase I study (FCCC 96-006) combining twice-daily radiotherapy (1.5 Gy per fraction bid; 5 days every other week; four cycles) with concurrent cisplatin and paclitaxel administration during salvage therapy (16). The MST was 9.5 months, and the 1- and 2-year OS were 41 and 27%, respectively. Hematologic toxicities were feasible, and grade 3 mucositis occurred in only 6% of patients. Given these encouraging results, the Radiation Therapy Oncology Group (RTOG) conducted a phase II study (RTOG 9911) to evaluate the efficacy and toxicity of twice-daily radiotherapy (1.5 Gy per fraction bid; 5 days every other week; four cycles) with concurrent cisplatin and paclitaxel administration (6). One-hundred and five patients were enrolled into the study, and 1- and 2-year OS were 50.2 and 25.9%, respectively. These findings suggest that this strategy is a promising treatment option; however, eight treatment-related deaths (8%), including acute neutropenic sepsis and late carotid hemorrhage, were noted. Spencer et al. (17) conducted a phase I study on previously irradiated patients with rHNC who received hydroxyurea and 5-FU in combination with daily radiotherapy (2 Gy per fraction) during a 2-week period followed by a 1-week break. These patients then received hyperfractionated radiotherapy on weeks 4 and 5 (total dose 50 Gy). The 1- and 2-year OS were 41 and 15%, respectively, and one patient died 3 weeks after the study due to pneumonia. Furthermore, two patients acquired soft tissue ulcers, and one developed trismus and a non-healing clavicular fracture. Therefore, concurrent chemoradiotherapy using twice-daily regimens are not considered ideal strategies for re-irradiation (18).

Hoebers et al. (15) evaluated 58 patients who had received re-irradiation at a median cumulative dose of 119 Gy (range, 76 − 140) with or without chemotherapy. The group reported a 2-year OS of 42%, and that higher re-irradiation doses and concurrent chemoradiation were associated with severe adverse events. They also reported that re-irradiation alone (compared with concurrent chemo-re-irradiation), a longer interval between initial radiotherapy and salvage re-irradiation, and a lower cumulative radiation dose were associated with better local control rates. Lee et al. (4) reported a study of 105 patients with rHNC who received re-irradiation with or without chemotherapy. The multivariate analyses revealed that non-nasopharynx and non-IMRT were associated with an increased risk of locoregional failure. Administration of chemotherapy could not be used to predict improved locoregional control rates and OS. The role of concurrent or sequential chemotherapy remains uncertain for re-irradiation in patients with rHNC. In the present study, 83% of patients with progressive disease after re-irradiation developed in-field recurrence with or without distant metastases. Lee et al. (4) reported the occurrence of locoregional failure with or without distant metastases in 65% of patients who developed progressive disease after re-irradiation. They also emphasized that future efforts for maximizing tumor control in a recurrent setting, including dose escalation with IMRT and effective chemotherapy, were warranted. The median re-irradiation dose of 45 Gy in our conventional radiotherapy is low compared with previously published doses. We could not use IMRT then for head and neck cancers in our institute, and thus relatively low re-irradiation doses were used to avoid the risk of high radiation exposure of organs. As it is now possible to use IMRT, more aggressive radiation therapy should be tried in the salvage setting.

Stereotactic radiotherapy, such as single fraction stereotactic radiosurgery (SRS) and fractionated SBRT using concave dose distributions, is useful since it protects critical organs (e.g. carotid artery, spinal cord, brain stem and optic pathway). The University of Pittsburgh conducted a phase I dose-escalation study in patients with rHNC. The results revealed that 44 Gy in five fractions over a 2-week period was

well tolerated (2). Vargo et al. (1) reported a retrospective study which included 34 patients with rHNC who received SBRT at a median dose of 40 Gy in five fractions (range, 30–44) as a strategy for salvage therapy. The report showed that local control was significantly improved for small tumors (i.e. <25 cc), and that late grade 3 adverse events occurred only in 6% of patients. Lee et al. (4) reported that IMRT was better suited to predict locoregional tumor control. New technologies such as stereotactic radiotherapy (SRT), SBRT and IMRT might be useful tools to increase the prescribed dose without incrementing the exposure to critical organs. In our study, 79% of patients received SRT/SBRT and the majority developed minor recurrent disease. The most frequent recurrence after re-irradiation occurred within the re-irradiation field. However, our findings did not highlight the superiority of SRT/SBRT, and it did not clarify what the appropriate modality and radiation schedule should be. Unger et al. (19) reported a study on 65 patients who received a median initial radiotherapy of 67 Gy and a median re-irradiation SBRT dose of 30 Gy (range, 21−35) in two to five fractions. They reported that the 2-year OS and locoregional control rates were 41 and 30%, respectively. In addition, they showed by multivariate analysis that a higher total dose, surgical resection and naopharynx site were significantly associated with an improved locoregional control rate. Surgical resection and non-squamous histology were also associated with an improved OS (19). However, 11% of patients in that study experienced severe toxicities due to re-irradiation. Lee et al. (4) reported that a nasopharyngeal site and IMRT technique were associated with a good locoregional progression-free survival (LRPFS) in patients with rHNC who received re-irradiation. Finally, they concluded that achieving locoregional control was crucial to improve OS and that radiation doses >50 Gy were associated with better LRPFS and OS.

The present study has a few limitations worth noting. First, this study is a retrospective review of patients from a single institution, and thus selection- and physician-based biases may exist. In addition, it is important to note that the results are based on a small number of patients who underwent diverse radiotherapy schedules. Secondly, a minority of patients received conventional external beam re-irradiation, whereas no patients received IMRT. Finally, the median follow-up time in the study was only 7.3 months (range, 1.7−25.3). Longer follow-up periods are needed to clarify the long-term complications associated with re-irradiation.

CONCLUSION

Our results suggest that Tanvetyanon's nomogram accurately estimates survival probability after salvage re-irradiation in patients with rHNC. This nomogram is a practical tool for optimal sub-classification of patients with rHNC to evaluate treatment outcomes. Future prospective studies using this nomogram should be performed to establish the appropriate re-irradiation schedule for these patients.

Funding

This study was supported by the Health and Labor Sciences Research Grant (H24-007, H22-001), Grants-in-Aid for Cancer Research (23-A-21) and Grants-in-Aid for Scientific Research: 'Third term comprehensive control research for cancer (H22-043, H23-007)' from the Ministry of Health, Labor and Welfare of Japan.

Conflict of interest statement

None declared.

References

1. Vargo JA, Wegner RE, Heron DE, et al. Stereotactic body radiation therapy for locally recurrent, previously irradiated nonsquamous cell cancers of the head and neck. *Head Neck* 2011;34:1153–61.
2. Heron DE, Ferris RL, Karamouzis M, et al. Stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck: results of a phase I dose-escalation trial. *Int J Radiat Oncol Biol Phys* 2009;75:1493–500.
3. McDonald MW, Lawson J, Garg MK, et al. ACR appropriateness criteria retreatment of recurrent head and neck cancer after prior definitive radiation expert panel on radiation oncology-head and neck cancer. *Int J Radiat Oncol Biol Phys* 2011;80:1292–8.
4. Lee N, Chan K, Bekelman JE, et al. Salvage re-irradiation for recurrent head and neck cancer. *Int J Radiat Oncol Biol Phys* 2007;68:731–40.
5. Forastiere AA, Metch B, Schuller DE, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. *J Clin Oncol* 1992;10:1245–51.
6. Langer CJ, Harris J, Horwitz EM, et al. Phase II study of low-dose paclitaxel and cisplatin in combination with split-course concomitant twice-daily reirradiation in recurrent squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Protocol 9911. *J Clin Oncol* 2007;25:4800–5.
7. Spencer SA, Harris J, Wheeler RH, et al. RTOG 96–10: reirradiation with concurrent hydroxyurea and 5-fluorouracil in patients with squamous cell cancer of the head and neck. *Int J Radiat Oncol Biol Phys* 2001;51:1299–304.
8. Chen AM, Phillips TL, Lee NY. Practical considerations in the re-irradiation of recurrent and second primary head-and-neck cancer: who, why, how, and how much? *Int J Radiat Oncol Biol Phys* 2011;81:1211–9.
9. Janot F, de Raucourt D, Benhamou E, et al. Randomized trial of postoperative reirradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinoma. *J Clin Oncol* 2008;26:5518–23.
10. Popovtzer A, Gluck I, Chepeha DB, et al. The pattern of failure after reirradiation of recurrent squamous cell head and neck cancer: implications for defining the targets. *Int J Radiat Oncol Biol Phys* 2009;74:1342–7.
11. Sulman EP, Schwartz DL, Le TT, et al. IMRT reirradiation of head and neck cancer-disease control and morbidity outcomes. *Int J Radiat Oncol Biol Phys* 2009;73:399–409.
12. Haraf DJ, Weichselbaum RR, Vokes EE. Re-irradiation with concomitant chemotherapy of unresectable recurrent head and neck cancer: a potentially curable disease. *Ann Oncol* 1996;7:913–8.
13. Tanvetyanon T, Padhya T, McCaffrey J, et al. Prognostic factors for survival after salvage reirradiation of head and neck cancer. *J Clin Oncol* 2009;27:1983–91.
14. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.

15. Hoebers F, Heemsbergen W, Moor S, et al. Reirradiation for head-and-neck cancer: delicate balance between effectiveness and toxicity. *Int J Radiat Oncol Biol Phys* 2011;81:e111–8.
16. Kramer NM, Horwitz EM, Cheng J, et al. Toxicity and outcome analysis of patients with recurrent head and neck cancer treated with hyperfractionated split-course reirradiation and concurrent cisplatin and paclitaxel chemotherapy from two prospective phase I and II studies. *Head Neck* 2005;27:406–14.
17. Spencer S, Wheeler R, Peters G, et al. Phase 1 trial of combined chemotherapy and reirradiation for recurrent unresectable head and neck cancer. *Head Neck* 2003;25:118–22.
18. McDonald MW, Moore MG, Johnstone PA. Risk of carotid blowout after reirradiation of the head and neck: a systematic review. *Int J Radiat Oncol Biol Phys* 2012;82:1083–9.
19. Unger KR, Lominska CE, Deeken JF, et al. Fractionated stereotactic radiosurgery for reirradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2010;77:1411–9.

Isohashi et al. Radiation Oncology 2013, 8:76
http://www.ro-journal.com/content/8/1/76

RADIATION ONCOLOGY

RESEARCH Open Access

Patterns of radiotherapy practice for biliary tract cancer in Japan: results of the Japanese radiation oncology study group (JROSG) survey

Fumiaki Isohashi[1], Kazuhiko Ogawa[1*], Hirobumi Oikawa[2], Hiroshi Onishi[3], Nobue Uchida[4,5], Toshiya Maebayashi[6], Naoto Kanesaka[7], Tetsuro Tamamoto[8], Hirofumi Asakura[9], Takashi Kosugi[10], Takashi Uno[11], Yoshinori Ito[12], Katsuyuki Karasawa[13], Makoto Takayama[14], Yoshihiko Manabe[15], Hideya Yamazaki[16], Mitsuhiro Takemoto[17], Yasuo Yoshioka[1], Kenji Nemoto[18], Yasumasa Nishimura[19] on behalf of the Japanese Radiation Oncology study Group (JROSG)

Abstract

Background: The patterns of radiotherapy (RT) practice for biliary tract cancer (BTC) in Japan are not clearly established.

Methods: A questionnaire-based national survey of RT used for BTC treatment between 2000 and 2011 was conducted by the Japanese Radiation Oncology Study Group. Detailed information was collected for 555 patients from 31 radiation oncology institutions.

Results: The median age of the patients was 69 years old (range, 33–90) and 81% had a good performance status (0–1). Regarding RT treatment, 78% of the patients were treated with external beam RT (EBRT) alone, 17% received intraluminal brachytherapy, and 5% were treated with intraoperative RT. There was no significant difference in the choice of treatment modality among the BTC subsites. Many patients with EBRT were treated with a total dose of 50 or 50.4 Gy (~40%) and only 13% received a total dose ≥60 Gy, even though most institutions (90%) were using CT-based treatment planning. The treatment field consisted of the primary tumor (bed) only in 75% of the patients. Chemotherapy was used for 260 patients (47%) and was most often administered during RT (64%, 167/260), followed by after RT (63%, 163/260). Gemcitabine was the most frequently used drug for chemotherapy.

Conclusions: This study established the general patterns of RT practice for BTC in Japan. Further surveys and comparisons with results from other countries are needed for development and optimization of RT for patients with BTC in Japan.

Keywords: Biliary tract cancer, Radiotherapy, Chemotherapy, Adjuvant, Palliative

Background

Biliary tract cancer (BTC) is a rare disease that is curable by surgery in fewer than 10% of all cases. Prognosis depends in part on the anatomic location of the tumor, which affects its resectability. Total resection is possible for 25% to 30% of lesions originating in the distal bile duct, a rate that is clearly better than that for lesions in more proximal sites. However, the rate of relapse is as high as 60-75%, even if clear resection (R0 resection) is possible [1]. In many patients with a tumor that cannot be completely removed by surgery, other treatments such as radiotherapy (RT) or stenting procedures may maintain adequate biliary drainage and improve survival. Optimal management is therefore essential for both postoperative and unresectable BTC.

In Japan, there were an estimated 20,734 new cases of BTC in 2007, with more than a 3-fold increase over the last three decades [2], while RT has become much more common because new methods and technology for treatment planning are now available. For these reasons,

* Correspondence: kogawa@radonc.med.osaka-u.ac.jp
[1]Department of Radiation Oncology, Osaka University Graduate School of Medicine, 2-2 (D-10) Yamadaoka, Suita, Osaka 565-0871, Japan
Full list of author information is available at the end of the article

optimal management of RT for BTC has become a major concern in Japan. For the study presented here, the Japanese Radiation Oncology Study Group (JROSG) conducted a nationwide questionnaire-based survey on BTC. The questionnaire elicited detailed information regarding patient characteristics, treatment characteristics, and outcomes of treatment. The primary goal of this study was to determine the patterns of RT practice for BTC in order to provide assistance with development of future randomized clinical trials. Therefore, factors influencing the treatment outcome are analyzed elsewhere (Yoshioka et al.: Factors influencing survival outcome in radiotherapy for biliary tract cancer, submitted). To the best of our knowledge, this is the first report to establish how RT is used nationally to treat BTC in Japan.

Methods

The JROSG conducted a nationwide survey of RT used for BTC treatment between 2000 and 2011 using a questionnaire requesting detailed information on patients and treatment characteristics. Patients were included if they met the following criteria: diagnosis of BTC without evidence of distant metastasis; treatment with RT between 2000 and 2011; no diagnosis of any other malignancy; and no previous RT. Diagnosis of BTC without pathologic verification was based on radiographic findings from contrast-enhanced computed tomography (CT), ultrasonography, endoscopic ultrasonography, and endoscopic retrograde/magnetic resonance cholangiopancreatography.

Of the 71 radiation oncology centers in Japan belonging to the JROSG, 31 (40%) agreed to participate in the survey. The other centers did not participate mostly because too few BTC patients had been treated with RT at the center in the study period. Each participating center provided a database of patients with BTC treated with RT between 2000 and 2011. The study was performed according to guidelines approved by the institutional review board of each institution whenever necessary.

The Mann–Whitney *U* test and Student's *t*-test were used to investigate relationships between variables. A p value of $< .05$ or a 95% confidence interval not including 1 was considered to be statistically significant. All statistical tests were 2-sided.

Results

Data collection

Detailed information was collected for 555 patients from 31 institutions with a median of 15 patients per institution (range: 1–56 patients). The distribution of the number of institutions based on the number of patients treated between 2000 and 2011 is shown in Figure 1. This indicates considerable variation among institutions in the number of patients treated during the 11-year period: ≤10 patients were treated at 13 institutions (42%), while over 30 patients were treated at only 6 institutions (19%).

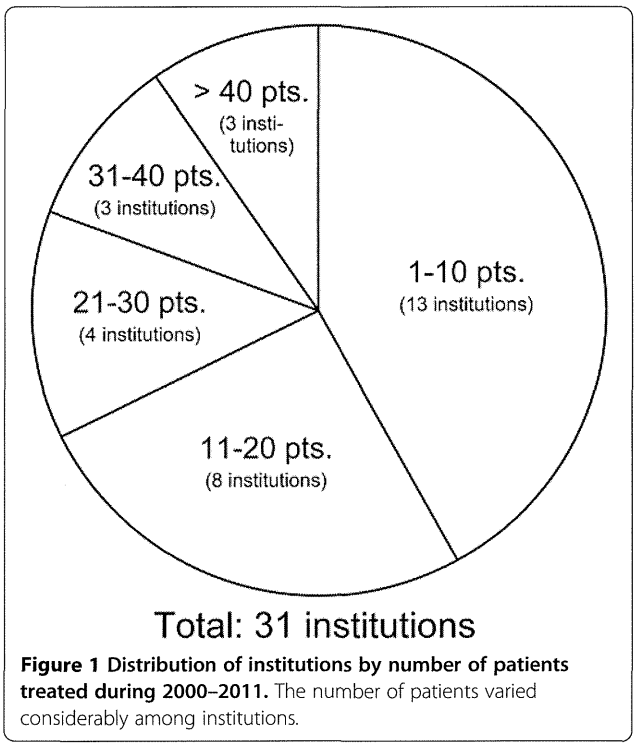

Figure 1 Distribution of institutions by number of patients treated during 2000–2011. The number of patients varied considerably among institutions.

Patient and disease characteristics

The background characteristics of all 555 patients are listed in Table 1. The median age was 69 years old (range, 33–90 years old) and 48% of the patients were ≥70 years old. Pre-therapeutic evaluations were performed by ultrasonography, CT, and magnetic resonance cholangiography in 81%, 93%, and 58% of the patients, respectively. Regarding the primary site, ~50% of BTC lesions arose in the perihilar regions of the extrahepatic bile duct, with distal regions of the extrahepatic bile duct being the second most common site (26%). Among all patients, >80% had an Eastern Cooperative Oncology Group performance status of 0–1, ~30% had a drinking or smoking habit, 52% had an unresectable tumor at diagnosis, and 53% had clinical stage T3-4 disease at diagnosis.

Characteristics of surgical procedures

Primary surgery before RT was performed in 242 patients (44%). Curative surgery was performed in 235 patients, but only 63 (26% of those who underwent surgery) had complete (R0) resection. R1 resection (microscopic positive margins) and R2 resection (macroscopic residual tumor) were performed in 142 (59%) and 37 (15%) patients, respectively. Note that surgeries included non-curative (R2) and curative-intent (R0 or R1) resections, because our cohort was based on a RT database. Lymph node dissection was performed on

Table 1 Patient and disease characteristics (n = 555)

Characteristic	Patients (%)
Age (median, 69 y)	
< 70 y	288 (51.9)
≥ 70 y	267 (48.1)
Gender	
Female	183 (33.0)
Male	372 (67.0)
Pathologic type, verified	
Yes, adenocarcinoma	417 (75.1)
Yes, other	5 (0.9)
No	133 (24.0)
Ultrasonography (before RT)	
Yes	451 (81.3)
No	21 (3.8)
Unknown	83 (14.9)
CT (before RT)	
Yes	515 (92.8)
No	5 (0.9)
Unknown	35 (6.3)
MRCP (before RT)	
Yes	324 (58.4)
No	152 (27.4)
Unknown	79 (14.2)
PTCD	
Yes	242 (43.6)
No	151 (27.2)
Unknown	162 (29.2)
Primary site	
Intrahepatic bile duct	71 (12.8)
Gallbladder	42 (7.6)
Extrahepatic bile duct	439 (79.1)
Perihilar	278 (50.0)
Distal	144 (25.9)
Unknown	17 (3.1)
Ampulla of Vater	3 (0.5)
Maximal tumor size (Median, 4.0 cm)	
< 4.0 cm	195 (35.1)
≥ 4.0 cm	198 (35.7)
Unknown	162 (29.2)
Tumor emboli	
Yes	32 (5.8)
No	292 (52.6)
Unknown	231 (41.6)
ECOG performance status	
0	223 (40.2)
1	226 (40.7)
2	77 (13.8)
3	17 (3.1)
4	1 (0.2)
Unknown	11 (2.0)
Jaundice	
Yes	355 (64.0)
No or unknown	200 (36.0)
CA19-9 (U/mL)	
< 37	102 (18.4)
37-1,000	253 (45.6)
≥ 1,000	81 (14.6)
Unknown	119 (21.4)
CEA (ng/ml)	
< 5	300 (54.1)
5-10	63 (11.3)
≥ 10	49 (8.8)
Unknown	143 (25.8)
Alcohol consumption	
Yes	193 (34.8)
No	223 (40.2)
Unknown	139 (25.0)
Smoking	
Yes	175 (31.5)
No	239 (43.1)
Unknown	141 (25.4)
Diabetes mellitus	
Yes	75 (13.5)
No	383 (69.0)
Unknown	97 (17.5)
Clinical T stage	
TX	11 (2.0)
T1	41 (7.4)
T2	147 (26.4)
T3	183 (33.0)
T4	112 (20.2)
Unknown	61 (11.0)
Clinical N stage	
N0	310 (55.9)
N1	165 (29.7)
Unknown	80 (14.4)
Clinical stage	
I	96 (17.3)
II	202 (36.4)

Table 1 Patient and disease characteristics (n = 555) *(Continued)*

III	146 (26.3)
IV	25 (4.5)
Unknown	86 (15.5)
Resectable at diagnosis	
Yes	254 (45.8)
No	288 (51.9)
Unknown	13 (2.3)
Investigational protocol	
Yes	0 (0)
No	555 (100)

Abbreviations: *RT* Radiotherapy; *CT* Computed tomography; *MRCP* Magnetic retrograde cholangiopancreatography; *PTCD* Percutaneous transhepatic cholangiodrainage; *ECOG* Eastern cooperative oncology group; *CEA* Carcinoembryonic antigen; *CA19-9* Carbohydrate antigen 19–9.

173 patients (71%) and a positive node was identified pathologically in 85 patients (35%).

Radiation treatment characteristics

The most common treatment modality was external beam radiotherapy (EBRT) alone (78% of the patients), followed by intraluminal brachytherapy (ILBT) with or without EBRT (17%) and intraoperative RT (IORT) with or without EBRT (5%). Chemotherapy before, during, or after RT was used for 260 patients (47%).

The patterns of RT practice or choice of treatment modality according to the BTC subsites are shown in Figure 2. Because the subsites of 17 patients were unknown, the patterns for 538 patients were analyzed. The rate of primary surgery varied according to the tumor subsite: primary surgery was performed for only 30% of tumors that originated in proximal regions (intrahepatic and perihilar), but for 67% of those that originated in more distal lesions (distal and gallbladder) ($p < .05$). However, there was no significant difference in the choice of treatment modality among the BTC subsites.

Table 2 shows the treatment modality choices according to purpose of RT, which was divided into four groups: RT after curative resection (R0-1) (n = 183), RT after non-curative resection (R2) (n = 33), curative RT for inoperable cases (n = 235), and palliative RT for inoperable cases (n = 78). The purpose of RT for inoperative cases (curative or palliative) was chosen by radiotherapists who answered the questionnaire. Twenty-six patients with IORT were excluded from this analysis based on a comparison of doses among the variables because strong bias was suspected when a parameter such as IORT was used, which involved a very large dose at one time. Over 90% of the patients who underwent surgery received EBRT alone. For the patients who did not undergo surgery, there was a tendency for ILBT with EBRT to be used for a curative purpose more often than for a palliative purpose, but the difference was not statistically significant (25% vs. 15%, $p = .08$). To compare the combined dose of ILBT and EBRT with a single modality dose (ILBT alone or EBRT alone), the total dose (ILBT + EBRT) was calculated as the biologically equivalent dose in 2-Gy fractions (EQD_2) using the linear quadratic model. The value used for assessing effects on tumors was $\alpha/\beta = 10$ Gy. The median EQD_2 for EBRT alone, ILBT alone and EBRT with ILBT was 50 $Gy_{\alpha/\beta 10}$, 36 $Gy_{\alpha/\beta 10}$, and 60$Gy_{\alpha/\beta 10}$, respectively, while that for ILBT with EBRT was significantly greater than EBRT alone or ILBT alone ($p = .001$). In terms of treatment purpose, however, there were no significant differences in the median EQD_2 among the groups (50$Gy_{\alpha/\beta 10}$ for all variables).

EBRT characteristics

The characteristics of the 521 patients who received EBRT are shown in Table 3. The median duration from

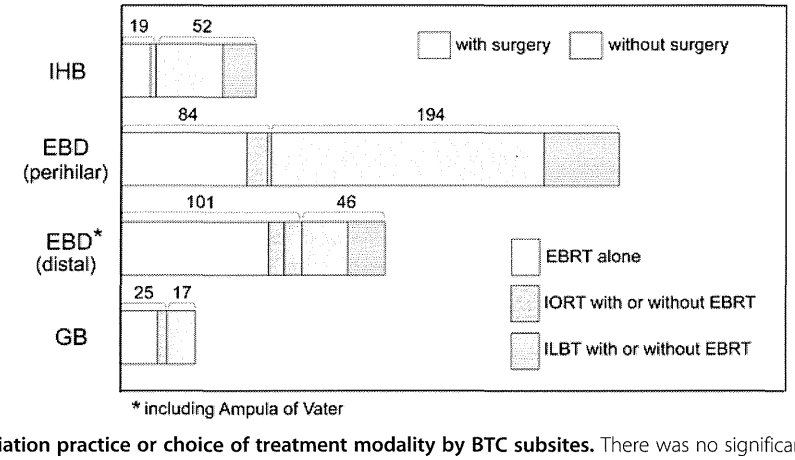

Figure 2 Patterns of radiation practice or choice of treatment modality by BTC subsites. There was no significant difference in the choice of treatment modality among the BTC subsites.

Table 2 Choices of treatment modality according to purpose of RT (n = 529)

	Purpose of RT	Actual patients	Treatment modality (%)			median EQD_2 (range) $Gy_{\alpha/\beta 10}$
			EBRT alone	ILBT alone	ILBT + EBRT	
Surgery+	Curative intent (R0-1)	183	170 (92.9)	8 (4.4)	5 (2.7)	50 (6–90)
	Non-curative intent (R2)	33	31 (93.9)	1 (3.0)	1 (3.0)	50 (4–74)
Surgery-	Curative	235	177 (75.3)	0 (0)	58 (24.7)	50 (9–68)
	Palliative	78	55 (70.5)	11 (14.1)	12 (15.4)	50 (39–74)
	median EQD_2 (range) $Gy_{\alpha/\beta 10}$		50 (4–90)	36 (14–44)	60 (33–82)	

Abbreviations: *RT* Radiotherapy; *EBRT* External beam radiotherapy; *ILBT* Intraluminal brachytherapy; *EQD2* The biologically equivalent dose in 2-gray fractions.

Table 3 EBRT characteristics (n = 521)

Characteristic	Patients (%)
EBRT Radiation portals	
2 portals	162 (31.1)
≥ 3 portals	359 (68.9)
EBRT beam energy (MV)	
< 10	24 (4.6)
≥ 10	491 (94.2)
Unknown	6 (1.2)
EBRT dose/fraction (Gy)	
< 1.8	7 (1.3)
1.8	131 (25.1)
2	352 (67.6)
> 2.0	31 (6.0)
EBRT total radiation dose (Gy)	
< 40	69 (13.2)
40 - < 50	129 (24.8)
50/50.4	206 (39.5)
> 50.4 - < 60	52 (10.0)
≥ 60	65 (12.5)
Radiation field	
primary only	388 (74.5)
primary plus regional LN	119 (22.8)
LN only	5 (1.0)
Unknown	9 (1.7)
CT-based treatment planning	
Yes	468 (89.8)
No	53 (10.2)
Conformal therapy	
Yes	333 (63.9)
No	75 (14.4)
Unknown	113 (21.7)
IMRT	2 (0.38)

Abbreviations: *EBRT* External beam radiotherapy; *MV* Megavolt; *Gy* Gray; *LN* Lymph node; *CT* Computed tomography; *IMRT* Intensity-modulated radiotherapy.

surgery to EBRT was 34 days (range, 9–88 days). EBRT was administered with ≥3 portals to 69% of the patients, at ≥10-megavolt beam energy for >90%, and at 1.8 Gy or 2.0 Gy per fraction; and with a total dose of ≥40 Gy for ~90%. CT-based treatment planning and conformal RT were used for 90% and 64%, respectively, of patients treated with EBRT, but only two of these patients received intensity-modulated RT (IMRT).

A summary of the EBRT field based on performance of surgery and nodal status is shown in Table 4. The treatment field consisted of the primary tumor only in 388 (75%) of 521 patients and the primary tumor plus regional lymph nodes in 119 (23%). Patients who underwent surgery received RT for the primary tumor (bed) plus regional lymph nodes more frequently than patients who did not undergo surgery (29% vs. 19%, $p < .01$). Additionally, among the patients who underwent surgery, RT for the primary tumor (bed) plus regional

Table 4 EBRT field according to performance of surgery and N stage (n = 521)

Group	Patients (n)	Radiation field (%)		
		Primary	Primary plus LN	Others
Surgery +				
Total	219	151 (68.9)	63 (28.8)	5 (2.2)
pN0	75	54 (72.0)	20 (26.7)	1 (1.3)
pN1	78	49 (62.8)	29 (37.2)	0 (0)
Unknown	66	48 (72.7)	14 (21.2)	4 (6.1)
cN0	111	95 (85.6)	13 (11.7)	3 (2.7)
cN1	65	43 (66.2)	20 (30.8)	2 (3.0)
Unknown	43	13 (30.2)	30 (69.8)	0 (0)
Surgery -				
Total	302	237 (78.5)	56 (18.5)	9 (3.0)
cN0	189	171 (90.5)	11 (5.8)	7 (3.7)
cN1	79	34 (43.0)	44 (55.7)	1 (1.3)
Unknown	34	32 (94.2)	1 (2.9)	1 (2.9)
Total	521	388 (74.5)	119 (22.8)	14 (2.7)

Abbreviation: *EBRT* External beam radiotherapy; *LN* Lymph node.

lymph nodes of those with clinically positive nodes was more frequently performed than in patients with clinically negative nodes (31% vs. 12%, $p < .01$). However, patients with pathologically positive nodes tended to receive RT for the primary tumor (bed) plus regional lymph nodes more frequently than patients with pathologically negative nodes, but the difference was not statistically significant (37% vs. 27%, $p = .16$). Among patients who did not undergo surgery, RT for the primary tumor and regional lymph nodes of those with clinically positive nodes was more frequently performed compared to patients with clinically negative nodes (56% vs. 6%, $p < .01$). However, some patients with clinically positive nodes also underwent EBRT for the primary tumor only (43%).

Analyses of practice patterns of EBRT were performed according to caseload of institutions (Figure 3a-d) and patient age (Figure 3e-h). Caseloads were divided into three categories based on the number of patients treated within the study period at each institution (≤10, 11–29, and ≥30 patients). In institutions with ≥30 patients, the rates of postoperative RT (compared to inoperable cases) (Figure 3A), EBRT for the field of the tumor (bed) plus regional LN (compared to tumor only) (Figure 3B),

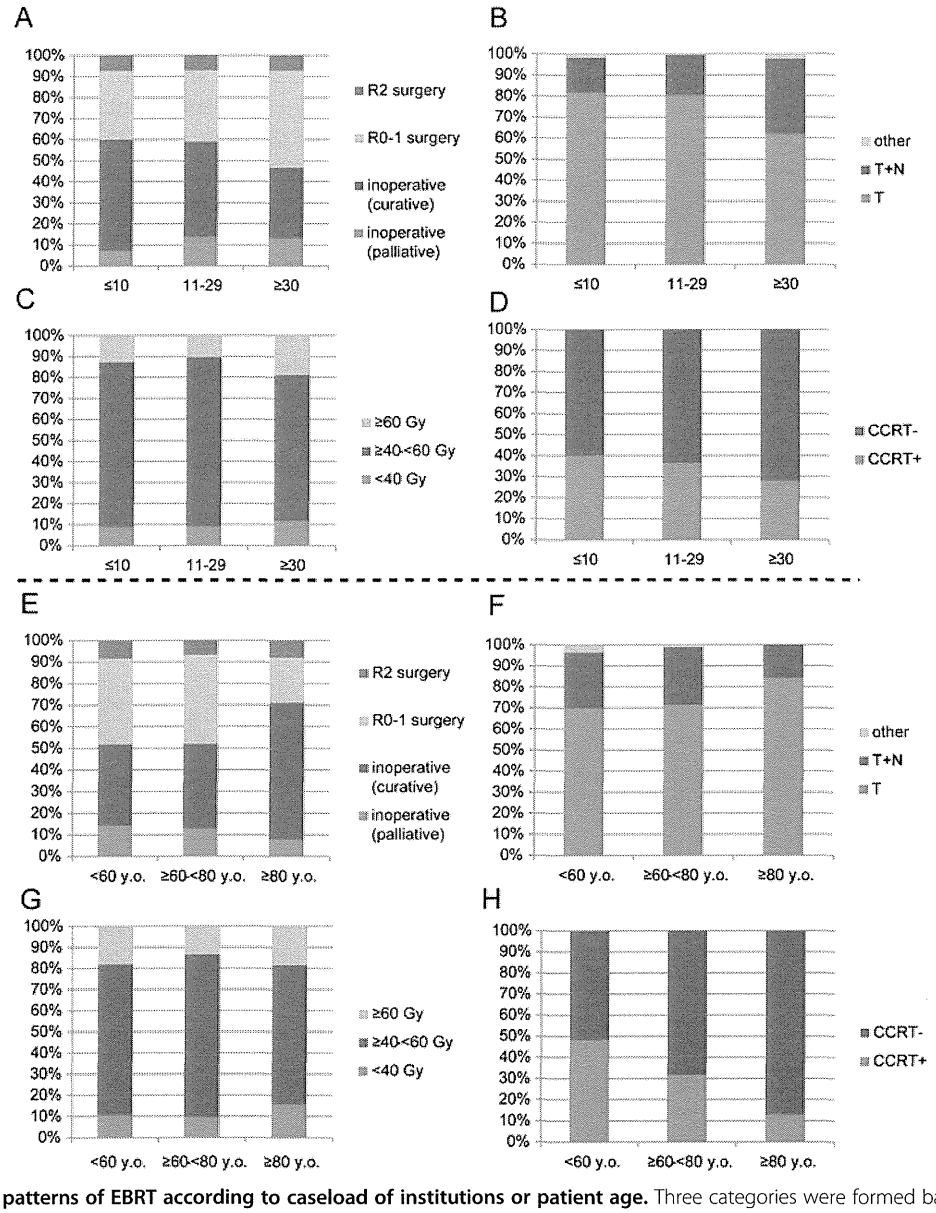

Figure 3 Practice patterns of EBRT according to caseload of institutions or patient age. Three categories were formed based on the number of patients treated at each institution (≤10, 11–29 and ≥30 patients) (**A-D**) or age (<60, ≥60- < 80, and ≥80 years old) (**E-H**) and evaluated based on treatment intent (**A, E**), EBRT field size (**B, F**), EBRT total dose (**C, G**), and concurrent chemotherapy (**D, H**).

and patients receiving ≥60 Gy (Figure 3C) were significantly higher than those in institutions with <30 patients. Age was also divided into three categories (<60, ≥60- < 80, and ≥80 years old). The use of CCRT was significantly higher in patients <60 years old compared to those ≥60- <80 years old, and in those ≥60- < 80 years old compared to those ≥80 years old (Figure 3H).

ILBT and IORT characteristics

A total of 96 patients (17%) received ILBT at 13 institutions (42%). The characteristics of these cases are listed in Table 5. All 96 patients were treated with ILBT using an iridium-192 source and at 5 or 6 Gy per fraction in 55% of cases and with a total dose of ≥15 Gy in 85%, 76 (79%) of whom received ILBT with EBRT at a median EBRT dose of 40 Gy (range, 20–60 Gy). The most common prescription point was 10 mm from the source (75%).

IORT was used for only 26 patients (5%) at four institutions (13%, 4/31), 12 (2%) of whom received IORT with EBRT and 14 (3%) received IORT alone. The median dose for IORT was 25 Gy (range, 20–30 Gy), with a median beam energy of 12 mega-electron volts (range, 4–25 mega-electron volts).

Chemotherapy

Chemotherapy was used for 260 patients (46%), including 167 concurrently with RT (78 concurrently alone; 7 pre-RT and concurrently; 67 concurrently and post-RT; and 15 pre-RT, concurrently, and post-RT), 4 pre- and post-RT, 12 pre-RT alone, and 77 post-RT alone. The drugs and timing of chemotherapy for these patients are listed in Table 6. Chemotherapy was most often given during RT (64%, 167/260) followed by after RT (63%, 163/260), while the most frequently used drug for chemotherapy was gemcitabine (47%) followed by 5-FU (37%). TS-1 and UFT were especially frequently used after RT.

The 167 patients who received chemotherapy during RT (concurrent chemoradiation (CCRT)) were analyzed further because this method has been shown to be efficacious for treatment of patients with BTC with or without surgery. The patients were divided into four groups according to performance of surgery and timing during the study period: Group A, surgery, 2000–2005 (n = 24); Group B, surgery, 2006–2011 (n = 30); Group C, no surgery, 2000–2005 (n = 65); and Group D, no surgery, 2006–2011 (n = 48). There was a significant difference in the use of gemcitabine-containing regimens between Groups A and B and between Groups C and D (Figure 4). This suggests a trend away from the use of 5-FU towards a more frequent use of gemcitabine concurrently with RT for patients with BTC treated with or without surgery.

Table 5 Intraluminal brachytherapy (n = 96)

Characteristic	Patients (n)
Source	
Ir-192	96 (100)
ILBT single dose/fraction (Gy)	
< 5	16 (16.7)
5	33 (34.4)
6	20 (20.8)
> 6	27 (28.1)
Total dose (Gy)	
< 15	14 (14.6)
15 - 25	41 (42.7)
≥ 25	41 (42.7)
Prescription point (from the source)	
5 mm	4 (4.2)
7 mm	4 (4.2)
10 mm	72 (75.0)
12 mm	14 (14.6)
Unknown	2 (2.1)
With EBRT (Median EQD_2, 60.4 Gy)	76 (79.2)
Without EBRT (Median EQD_2, 35.8 Gy)	20 (20.8)

Abbreviations: *Ir* Iridium; *Gy* Gray; *EBRT* External beam radiotherapy; *EQD_2* The biologically equivalent dose in 2-gray fractions.

Discussion

RT for BTC can be classified into adjuvant therapy after surgery or therapy for inoperable cases. While no randomized control trial has been conducted, a meta-analysis revealed that patients with extrahepatic cholangiocarcinoma treated with adjuvant RT show a significantly lower mortality rate than patients treated with surgery alone [3]. Data in the Surveillance Epidemiology and End Result database also suggest that palliative RT prolongs survival in patients with extrahepatic cholangiocarcinoma [4]. In these reports, the outcomes of the treatment were

Table 6 Drugs used and timing of chemotherapy (n = 260)

Variable	Actual patients (%)	Chemotherapy timing (%)		
		Before RT	During RT	After RT
Actual patients (n)	260	38	167	163
Drugs				
GEM	122 (46.9)	24 (63.2)	72 (43.1)	78 (47.9)
5-FU	97 (37.3)	9 (23.7)	74 (44.3)	43 (26.4)
Cisplatin	40 (15.4)	9 (23.7)	22 (13.2)	15 (9.2)
TS-1	45 (17.3)	6 (15.8)	5 (3.0)	42 (25.8)
UFT	34 (13.1)	3 (7.9)	12 (7.2)	24 (14.8)
Other	9(3.4)	3 (7.9)	4 (2.4)	2 (1.2)

Abbreviations: *RT* Radiotherapy; *GEM* Gemcitabine; *5-FU* 5-Fluorouracil; *TS-1* Tegafur-gimeracil-oteracil potassium; UFT Tegafur-uracil.

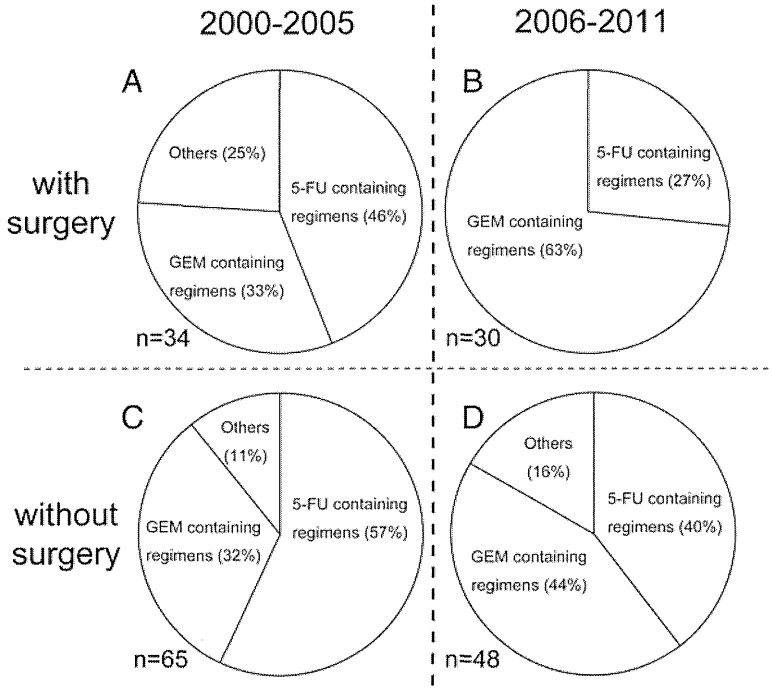

Figure 4 Changes in chemotherapy regime combined with radiotherapy during 2000–2011 based on prior therapy. The patients were divided into four groups according to performance of surgery and the timing during the study period. **A**: Surgery, 2000–2005 (n = 24); **B**: Surgery, 2006–2011 (n = 30); **C**: No surgery, 2000–2005 (n = 65); **D**: No surgery, 2006–2011 (n = 48).

reported in detail, but detailed information on RT use has not been provided and there are few reports on patterns of RT practice. We therefore decided to evaluate the practice of RT for BTC at Japanese radiation oncology centers, with the goal of assisting with development of randomized clinical trials. JROSG has conducted similar surveys and successfully determined the general patterns of RT practice for several other cancers in Japan [5,6]. Of the 31 responding institutions, 43% treated fewer than 10 patients over the period covered by the survey. Surprisingly, none of the patients were treated with an investigational protocol, clearly indicating a need for a prospective multicenter study to determine a standard therapeutic approach.

The results of the study showed that CT-based treatment planning was used for approximately 90% of the patients. Previous nationwide surveys of the structural characteristics of radiation oncology in Japan found that only 329 (45%) of 726 facilities in 2003 and 407 (57%) of 712 facilities in 2005 used CT-based treatment planning [7,8]. These results suggest that three-dimensional conformal RT planning became mainstream during the survey period or that patients with BTC received RT more frequently in facilities with advanced equipment.

We examined the variations in RT use (modality, total dose, or RT fields) according to the purpose of RT or BTC subsites. Some analyses have suggested that there is a dose–response relationship for treatment of BTC and have stressed the importance of dose escalation [9,10]. However, many patients with EBRT included in this survey were treated with a total dose of 50 or 50.4 Gy (~40%) and only 13% of the patients received a total dose ≥60 Gy. These data indicate that use of sufficient doses for EBRT for tumors in the hepatic hilum and liver regions was severely restricted by technical difficulties with the delivery of high doses to these regions while sparing surrounding organs, including the liver, duodenum, stomach, and spinal cord, even though most institutions used CT-based treatment planning. Recently, IMRT has emerged as a sophisticated technique for treatment of tumors, including BTC, in areas at risk of recurrence, while sparing adjacent normal tissue from high-dose irradiation [11]. However, only two patients were treated with IMRT for EBRT during the survey period.

ILBT can also be used for dose escalation in a region at risk [9,12] since it has the advantage of allowing delivery of a sufficient dosage to a target focus while reducing the effect of irradiation on surrounding tissues. Theoretically, a combination of ILBT and EBRT can enhance the beneficial effects of RT, with fewer adverse effects than those incurred with EBRT alone. In fact, ILBT with EBRT entailed a significantly higher EQD_2 dose than EBRT alone in our study cohort. While 42% of the