development of chronic GI complications. Interestingly, patients with grade 2 or higher chronic GI complications featured significantly higher V15-V45 volumes and mean dose to the small bowel loops than did patients without this feature. In contrast, none of the parameters for the peritoneal cavity showed any association with chronic GI complications. Similarly, parameters for the large bowel did not correlate with radiation-induced chronic GI complications. These findings suggest that, compared to the peritoneal cavity, the small bowel loops may constitute a better predictor of chronic GI complications. However, it is also likely that the dose to the peritoneal cavity will be a predictor of acute GI complications (5), and Wedlake et al found that cumulative acute GI symptoms, measured using the questionnaire, are associated with consequential late symptoms (14). Collectively, these results suggest that our finding that parameters for the small bowel loops are better predictors of chronic GI complication, compared with those for the peritoneal cavity, requires verification in larger prospective studies.

The findings in this study should be interpreted with an understanding of the following limitations. First, the heterogeneity in the treatment planning approach over the period of the study (2D vs 3D), the low number of events, and the lack of a prespecified model or protocol are important limitations of the data and analysis. Second, our method resulted in large uniform doses to regions of the small bowel, which differ from the dose patterns produced by techniques such as IMRT, which is becoming more prevalent. Therefore, we cannot exclude the possibility that the optimal DVH parameter predictors found in this study may differ from those for IMRT.

Additionally, we used weekly nedaplatin as concurrent chemotherapy, whereas chemoradiation therapy with 40 mg/m^2 of weekly cisplatin is now accepted as a standard first-line treatment. We therefore cannot exclude the possibility that the optimal DVH parameter predictors found in the study may be chemotherapy-type specific. Furthermore, the small bowel DVH parameters were estimated based on only 1 radiation treatment planning CT before RT, while in fact daily variability of the distention or movement of the small bowels during the treatment course may have affected the dose-volume profile. Also, especially in the 2D era, radiation treatment planning CT performed with 5.0-mm slices without filling the bladder may not reflect the actual dose received. Han et al reported that the dose distribution in the small bowel as observed on CT varies significantly from week to week because of the interfractional variations of small-bowel positions (19). In addition, image guided RT is now widely used in many institutions (20). Therefore, further studies using image guided RT will be necessary to investigate the influence of intra- and interfraction motion of the small bowel loops on chronic GI complications.

Within these limitations, we conclude that DVH parameters of the small bowel loops may serve as predictors of chronic GI complications of grade 2 or higher after postoperative concurrent nedaplatin-based chemoradiation therapy in early-stage cervical cancer patients. For these patients, we recommend that V40 of the small bowel loops should be <340 mL to avoid chronic GI complications using a conventional 2D or 3D technique.

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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

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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

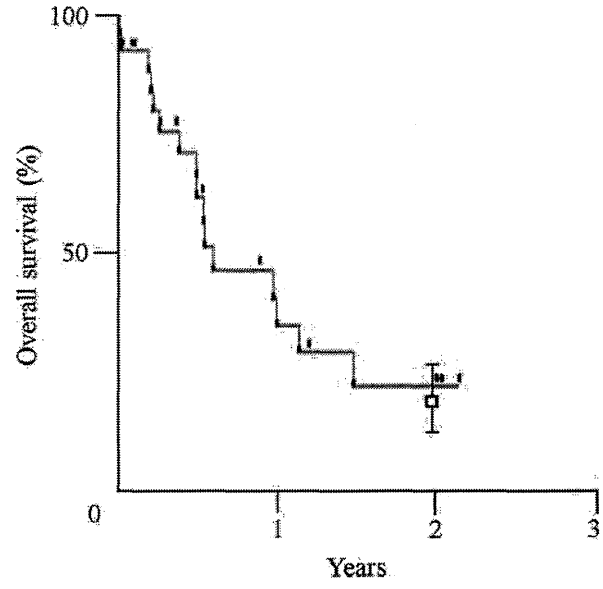

Figure 1. The overall survival curve (OS) of 28 patients with recurrent head and neck cancer (rHNC) was estimated using the Kaplan–Meier method. The white box shows the 2-year survival probability (16.8%) estimated using Tanvetyanon's nomogram. The vertical line indicates the 95% confidence interval 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.

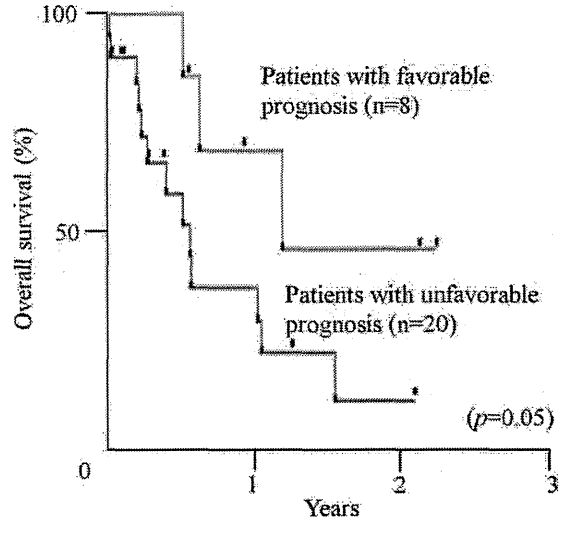

Figure 2. OS curves of patients with rHNC with favorable and unfavorable prognoses. The 2-year OS in 20 patients with unfavorable prognosis whose 2-year survival probability was <15% and the 2-year OS in eight patients with favorable prognosis whose 2-year survival probability was >15% were 11.0 and 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.

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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

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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

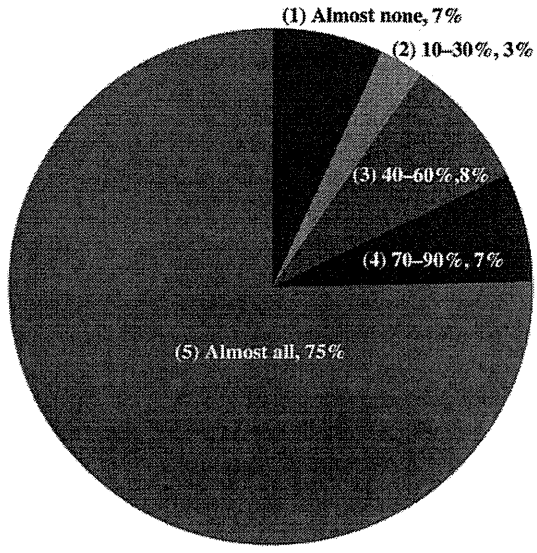

Figure 1. Proportion of the patients who are charged with the consultation fee for outpatient radiotherapy. Each questionee was asked to select from one of five options on the proportion of the patients who were charged with this consultation fee in his or her affiliated hospital: (1) almost none, (2) 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.

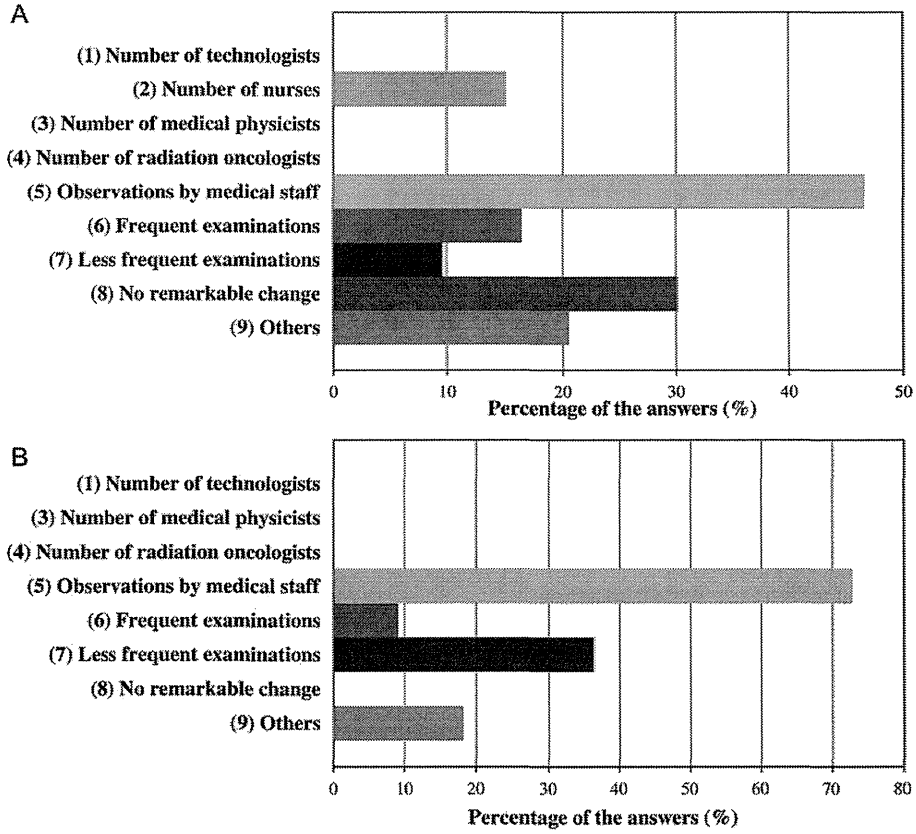

Figure 2. Changes after introduction of the consultation fee. The questionees were asked to select from nine options: (1) an increase in the number of radiotherapy technologists, (2) an increase in the number of full-time radiation oncology nurses, (3) an increase in the number of medical physicists, (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.

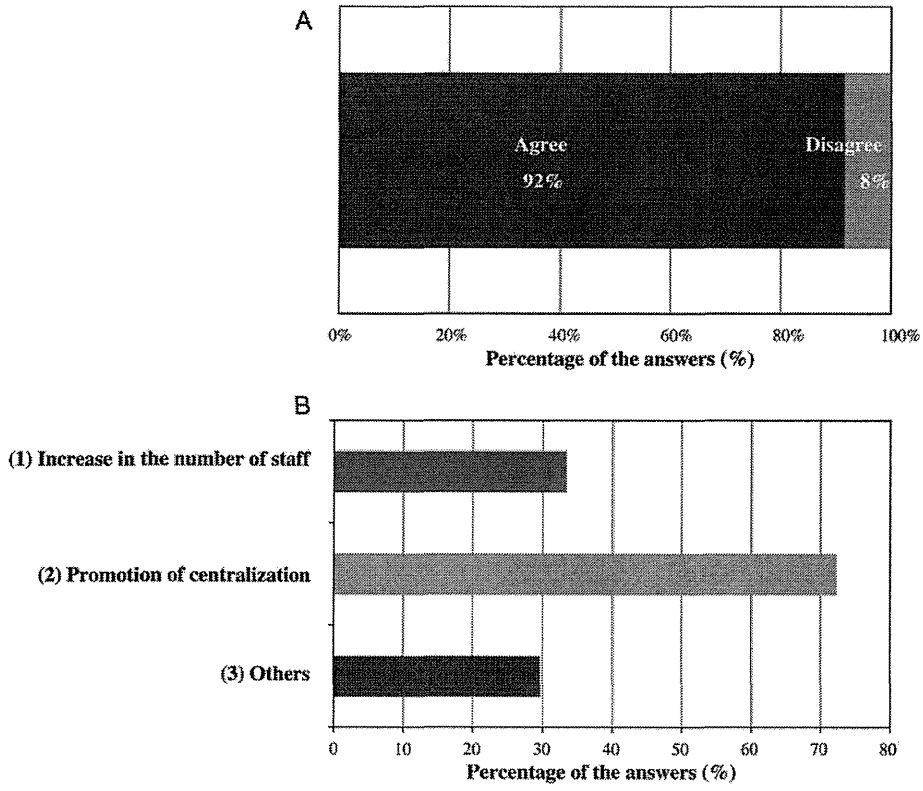

Figure 3. The influence of the consultation fee for outpatient radiotherapy on radiation oncology clinics in Japan. (A) The questionees were asked whether introduction of this consultation fee is expected to contribute to the future development of radiation oncology clinics in Japan. (B) Those who answered '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.

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JJCO Japanese Journal of Clinical Oncology

Review Article

Jpn J Clin Oncol 2013;43(4)345–350
doi:10.1093/jjco/hyt014
Advance Access Publication 21 February 2013

Stereotactic Body Radiation Therapy for Stage I Non-small-cell Lung Cancer: A Historical Overview of Clinical Studies

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Received August 2, 2012; accepted January 22, 2013

Because of difficulties with stabilization, breathing motion and dosimetry, stereotactic body radiotherapy for lung cancer has only been practiced for the past 15 years. However, a large amount of case data has rapidly been accumulated in recent years. Stereotactic body radiotherapy for Stage I non-small-cell lung cancer has been actively investigated in inoperable patients since around 1995, and a number of clinical trials have been undertaken. Early studies from 2001 presented a 3-year local control rate of 94% and a 3-year overall survival rate of 66% for patients receiving 50–60 Gy in 10 fractions. Another study in 2005, using 48 Gy in four fractions, presented a 3-year local control rate of 98% and 3-year overall survival rates of 83% for Stage IA patients and 72% for Stage IB patients. A multi-institutional study showed favorable local control and survival rates in a group receiving a biologically effective dose of 100 Gy. A dose-escalation study in the USA suggested a maximum tolerated dose of 60 Gy in three fractions. A Phase II clinical trial (RTOG0236) followed, with a reported 3-year local control rate of 98% and a 3-year overall survival rate of 56% for patients who received 60 Gy in three fractions. A Japanese Phase II clinical trial (JCOG0403) investigated a dose of 48 Gy in four fractions among 165 Stage IA patients, showing a 3-year survival rate of 76% and a 3-year locally progression-free survival rate of 69% for the operable group. An overview of past clinical trials in stereotactic body radiotherapy for Stage I non-small-cell lung cancer and current issues is presented and discussed.

Key words: stereotactic radiotherapy – non-small-cell lung cancer – Stage I – clinical study – review

INTRODUCTION

Lung cancer is one of the most prevalent cancers in the world and is the leading cause of cancer deaths in Japan for both men and women. In recent years, detection rates for early-stage lung cancer have improved as computed tomography (CT) examination has become more common. At present, the standard treatment for early-stage lung cancer is surgery. However, as the rapidly aging population increases the number of medically inoperable cases, the efficacy and safety of stereotactic radiotherapy, a less invasive treatment, have attained critical importance. This paper presents an overview of past clinical trials in stereotactic body radiotherapy (SBRT) for Stage I non-small-cell lung cancer (NSCLC) and current issues.

DEFINITION AND HISTORY OF SBRT

The use of stereotactic radiotherapy to treat extracranial tumors began with 40 years of using stereotactic radiosurgery with a gamma knife on cranial tumors. If stereotactic radiotherapy can be substituted for surgical resection of a solitary brain metastasis (1), then logically a similarly sized primary lesion could also be efficiently controlled using the same method. SBRT allows for the application of large

doses of radiation to the tumor with minimal exposure of surrounding organs. Rapid advances in the capabilities of radiotherapy equipment during the 1990s enabled three-dimensional irradiation. Stereotactic irradiation methods were gradually trialed for lung cancer from around 1995, with increases in stability and precision, and the development of related technologies such as image-guided navigation. Blomgren et al. (2) first reported how to perform stereotactic radiotherapy on body tumors. Uematsu et al. began clinical trials of stereotactic radiotherapy on body tumors in Japan with the development of a combined CT and linear accelerator unit (3) in 1996. Shirato et al. developed a method for tracing a fiducial marker placed near a tumor, installing a device that allowed real-time observation during irradiation in the irradiation room, and applied this method to SBRT (4). As a result of developments like these, SBRT is now showing promise as a radical treatment modality, mainly for lung cancers. Numerous clinical trials are currently underway. SBRT is being applied not only to lung cancers, but also to diverse other body tumors, including the liver, pancreatic, prostate and metastatic cancers, as well as to spinal arteriovenous malformations. Radiotherapy has recently achieved higher levels of accuracy in covering tumors, thanks to advances in respiratory motion management (5) and various image-guidance techniques (6). The cyberknife, originally designed for use on cranial lesions, is now good enough to also be applied to cervical and body lesions (7).

In 2004, Japanese health insurance policies began to cover SBRT using linear accelerators. Since then, the number of patients receiving SBRT has increased substantially. The specified treatment cost was 630 000 yen (~8000 USD), which covered medical services for the entire process, starting from treatment planning. The four conditions the radiotherapy must fulfill are as follows: (1) stability and reproducibility of the focal position of irradiation within 5 mm between treatment planning and actual treatment; (2) measures for preventing respiratory motion error (additionally approved for coverage by Japanese health insurance from 2012 in Japan); (3) dose concentration on the tumor by multi-directional, three-dimensional convergence of multiple beams and (4) short treatment period (generally <2 weeks) with a single high-dose treatment (generally ≥ 5 Gy). For lung cancer, coverage by the Japanese health insurance system is applied for: primary lung cancer with no metastatic lesions and diameter ≤ 5 cm; and up to three masses of metastatic lung cancer each ≤ 5 cm in diameter, with no other foci. According to a national survey conducted by Nagata et al., SBRT was being performed at 53 institutions in Japan as of 2005. Overall, 2104 patients had received treatment for lung cancer using stereotactic radiotherapy (including for primary lung cancer in 1111 patients, metastatic lung cancer in 702 patients and unknown histology in 291 patients) (8).

PHASE I (DOSE ESCALATION) STUDY

No rigorous Phase I clinical trial to identify the maximum tolerated dose of SBRT for lung cancer has been conducted in Japan. The results of retrospective study, discussed below, have suggested sufficient local control with biologically effective dose (BED) >100 Gy (9). The prescribed dose for clinical trials or medical practice was established with this trial in Japan. The most frequent SBRT dose fractionation for Stage I NSCLC in the previous survey by Nagata et al. was 12 Gy, administered four times (8).

However, in the USA, the maximum tolerated dose was set at 20 Gy, administered three times, based on a dose escalation study that started from 8 Gy, administered three times (10,11). The dose-limiting toxicities reported at the time included dermatitis, pericarditis, pneumonitis and bronchial necrosis. Some reports have described decreased local control using the Japanese standard SBRT dose for larger lesions (12,13), and a dose escalation study (JCOG0702) is being conducted in Japan for T2N0M0 NSCLC.

RETROSPECTIVE STUDY FOR MEDICALLY INOPERABLE PATIENTS

Needless to say, the standard treatment for Stage I NSCLC is surgery. SBRT was used only for inoperable patients in early phase. Table 1 shows the results of retrospective studies of SBRT for mostly inoperable patients (12,14–17). These studies showed variations in irradiation techniques and prescribed doses, but the results suggested that local control exceeded 90% when treatment doses were sufficient. However, the survival time was not long enough, as discussed below, and insufficient information was obtained regarding local control rates in the long-term follow-up. Survival rates appeared highly variable and were generally inferior to surgical outcomes. This may be partly attributable to a high number of deaths due to other causes, because of the poor health condition of inoperable elderly patients.

RETROSPECTIVE STUDY FOR OPERABLE PATIENTS

A certain proportion of patients are operable but choose to undergo SBRT. One retrospective study extracted operable cases from accumulated multi-institutional data in Japan (13,18). Doses achieving BED >100 Gy showed more favorable local control and survival rates than doses <100 Gy. The 87 operable cases in the group with BED >100 Gy (median age, 74 years) displayed 5-year locally progression-free and 5-year overall survival rates of 90% and 74% for Stage IA and 89% and 58% for Stage IB, respectively, at a median follow-up duration of 58 months. Other illnesses were a major cause of death. Grade 3 toxicity or above was found in only 2% of patients, but the true level of toxicity

Table 1. Results of retrospective studies of stereotactic body radiotherapy for mainly inoperable patients with T1-3N0M0 non-small-cell lung cancer

Author	Pt. no	Age min–max (median)	Dose Gy/fraction (fx)	Median follow-up (months)	Overall survival rate	Local control	Toxicity
Uematsu (14)	50	54–86 (71)	50–60 Gy/5–10 fx	36	66% (at 3 year)	94%	Rib fracture: 2%
Wulf (15)	20	58–82 (68)	26–37.5 Gy/1–3 fx	11	32% (at 2 year)	92%	No complications > RTOG grade 2
Onishi (16)	35	65–92 (71)	60 Gy/10 fx	13	64% (at 2 year)	88%	NCI-CTC (V2) grade 3 penumonia: 9%
Onimaru (12)	28	52–85 (76)	48 Gy/4 fx	27	IA 82% IB 32% (at 3 year)	64%	NCI-CTC (V3.0) grade 3 pneumonia: 4%
Takeda (17)	63	56–91 (78)	50 Gy/5 fx	31	IA 90% IB 63% (at 3 year)	95%	NCI-CTC (V3.0) grade 3 pneumonia: 3%

might not have been sufficiently evaluated due to the retrospective nature of the study.

PHASE II CLINICAL STUDY FOR MEDICALLY INOPERABLE PATIENTS

Many Phase II clinical trials for medically inoperable regular patients were conducted one after the other based on favorable local control results in early retrospective studies, as shown in Table 1. Table 2 shows the major results of various Phase II trials (19–25). Prescribed doses differ between Japan and the West, but variations in survival rates and local control rates were generally the same as those from retrospective research. A multi-institutional clinical trial undertaken in the USA (Radiation Therapy Oncology Group (RTOG)-0236) found a local control rate of 98%, a 3-year survival rate of 56% and grade 3 or 4 toxicity in 16.3% (24). Some studies showed a higher proportion of grade 3 toxicity and above than the retrospective research. This may be due to regular follow-ups with no missing values in prospective research. In particular, a study of SBRT with 60–66 Gy in three fractions for subjects including patients with centrally located lung tumors near the trachea or lobar bronchus found that 14 of 70 cases (20%) experienced toxicity of grade 3 or above, 6 cases showed grade 5 toxicity (pneumonia, 4 cases; pericarditis, 1 case; hemoptysis, 1 case) and 4 of these 6 cases had centrally located cancers (20). Accordingly, a dose escalation study has been conducted with the prescribed dose for centrally located lung cancer starting from 7.5 Gy administered eight times (JROSG10–1) in Japan and 10 Gy administered five times (RT0G0813) in the USA.

PHASE II STUDY FOR MEDICALLY OPERABLE PATIENTS

In 2004, a Japanese Radiation Treatment Group (representative: Masahiro Hiraoka) was first created in the Japan Clinical Oncology Group (JCOG) and a Phase II clinical trial of SBRT was initiated for NSCLC in clinical Stage IA (JCOG0403). All cases were pathologically confirmed, and two groups were registered, comprising patients with medially operable and inoperable tumors for standard surgery. The medically operable group reached the target number of registrations early and Nagata et al. presented preliminary results after a 3-year follow-up in 2010 at the annual meetings of the American Society for Therapeutic Radiology and Oncology (26) and the Japan Lung Cancer Society. This was the first Phase II clinical trial in the world for a medically operable case group. In JCOG0403, 48 Gy administered in four fractions was prescribed for the isocenter. Sixty-five patients were included between July 2004 and January 2007. The mean age of participants was 79 years (range, 50–91 years), with 45 men and 20 women. The mean tumor diameter was 21 mm (range, 10–30 mm), and histological examination revealed 40 adenocarcinomas, 21 squamous cell carcinomas and 4 others, with performance status (PS) 0 in 43, PS 1 in 20 and PS 2 in 2. The median observation period was 45 months, the 3-year overall survival rate was 76% and the 3-year locally progression-free rate was 69%. Treatment-related toxicities of grade 3 and above included one case of chest pain, two cases of dyspnea, one case of hypoxia and two cases of radiation pneumonitis. No cases of toxicity of grade 4 or above were identified.

PHASE III RANDOMIZED STUDY COMPARING SBRT WITH SURGERY

Two randomized multi-institutional studies comparing SBRT with surgery on operable patients preceded the announcement of JCOG0403. One was a randomized study comparing CyberKnife treatment to surgical resection for Stage I NSCLC (STARS) based in MD Anderson Cancer Center in the United States (27), while the other was a randomized Phase III trial, Radiosurgery or Surgery for operable Early-stage (Stage IA) non-small-cell Lung cancer (ROSEL) based in VU University Medical Center in Netherlands (28). These experimental studies did not have sufficient rationales affirming the randomization process between surgery and SBRT and the registration of patients has encountered difficulties.

Table 2. Results of prospective Phase II trials of stereotactic body radiotherapy for mainly inoperable patients with Stage I non-small-cell lung cancer

Author	Pt. no	Age min–max (median)	Dose Gy/fraction (fx) (prescription)	Median follow-up (months)	Three-year overall survival rate	Three-year local control	Toxicity
Nagata (19)	42	51–87 (77)	48/4 (tumor center)	30	IA 83%, IB 72%	98%	NCI-CTC (V2) grade 2 pneumonia: 4%
Timmerman (20)	70	51–86 (70)	60–66 Gy/3 fr	17	55% (at 2 year)	95% (at 2 year)	NCI-CTC (V2) grade 3–5: 20% grade 5: 8.5%
Zimmermann (21)	68	59–92 (76)	37.5 Gy/3–5 fx (60% isodose)	18	53%	94%	RTOG grade 3 pneumonia: 6% rib fracture: 3%
Fakiris (22)	70	not shown	T1: 60 Gy/3 fx T2: 66 Gy/3 fr (80% isodose)	50	43%	94%	peripheral; NCI-CTC (V2) grade 3–5: 10% central; NCI-CTC (V2) grade 3–5: 27%
Baumann (23)	57	59–87 (75)	45 Gy/3 fx (67% isodose)	35	60%	92%	NCI-CTC (V2) grade 3: 28%
Timmerman (24)	55	48–89 (72)	60 Gy/3 fx (D95)	34	56%	98%	grade 3 NCI-CTC (V3.0): 12.7% grade 4 NCI-CTC (V3.0): 3.6%
Ricardi (25)	62	53–83 (74)	45 Gy/3 fx (80% isodose)	28	57%	92%	pneumonia > RTOG grade 3: 3% rib fracture 2%

CURRENT CLINICAL TRIALS

Over 50 clinical trials on SBRT for early lung cancer are now underway around the world. The major studies are listed in Table 3. RTOG0618 is a Phase II study for medically operable patients with T1-3N0M0 NSCLC, RTOG0813 and JROSG10-1 are dose escalation studies regarding doses for centrally located lung cancer in close proximity to the trachea and lobar bronchus, RTOG0915 is an investigation into the safety and efficacy of single-fraction and four-fraction SBRT for Stage I NSCLC, and the American College of Surgeons Oncology Group (ACOSOG) Z4099/RTOG1021 is a randomized trial comparing SBRT with partial lung resection with or without brachytherapy in cases with a high risk for receiving lobectomy.

DISCUSSION

The processes used in radiation oncology can be divided into three successive steps: (1) treatment simulation, in which all relevant information on target definition is incorporated; (2) treatment planning, which involves selection of delivery technique and approach for optimizing target coverage and normal tissue avoidance; and (3) radiation delivery and treatment verification. Many technological developments have been made to enable SBRT for small lung tumor, including the following: (a) high precision and speed in calculation algorithms for treatment plans; (b) high dose rate and smaller size of irradiation equipment; and (c) increased precision in respiratory motion management.

Table 3. Major prospective studies of SBRT for lung cancer

Trial name	Protocol
RTOG0236 (closed)	Phase II study for inoperable T1-3N0M0 NSCLC (60 Gy/3 fx)
JCOG0403 (closed)	Phase II study for operable and inoperable T1N0M0 NSCLC (48 Gy/4 fx)
RTOG0618	Phase II study for operable T1-3N0M0 NSCLC (60 Gy/3 fx)
JCOG0702	Dose escalation study for T2N0M0 NSCLC (started from 40 Gy/4 fx)
RTOG0813	Dose escalation study for centrally located Stage I NSCLC (started from 50 Gy/5 fx)
JROSG10-1	Dose escalation study for centrally located Stage I NSCLC (started from 60 Gy/8 fx)
RTOG0915	Randomized study (34 Gy/1 fx versus 48 Gy/4 fx for inoperable Stage I NSCLC)
ACOSOG Z4099/RTOG1021	Randomized study (SBRT versus surgery ± brachytherapy) for high risk patients)
STARS	Randomized study (SBRT versus surgery) for operable Stage I NSCLC)
ROSEL	Randomized study (SBRT versus surgery) for operable Stage I NSCLC)

New dose-calculation programs more accurately predict the doses to which normal tissues are exposed, thereby overcoming the limitations of older software that over- or underestimated dose distributions in inhomogeneous tissues such as the lungs by more than 10% (29). Accurate dose estimation using these new algorithms will allow for better correlation of dose with toxicity, allowing higher doses to be delivered more safely (30).

Since 2003, four-dimensional (4D) CT scanners have become commercially available, and are increasingly replacing conventional CT for treatment simulation. The use of 4DCT allows organ motions to be observed and quantified (31). When 4DCT information is combined with daily patient position verification, safety margins around tumors can be significantly reduced, thereby decreasing target volumes. In addition, 4DCT allows for the evaluation of strategies such as respiration-gated radiation therapy to minimize target volumes in individual patients (32). When tumors show significant movement, enlargement of the planning target volume (PTV) can be circumvented by limiting treatment to only specific phases of respiration (33) or tracking the beam to the moving tumor (34).

Current approaches to image-guided radiation therapy aim to monitor patient and tumor positions during the course of treatment, an approach that is mandatory when using very small safety margins. Many commercial imaging systems are available for installation in treatment rooms, and are used to verify patient positioning using kilovoltage or megavoltage imaging devices, cameras, external markers or laser tracking systems. Tumor positions can be verified using kilovoltage or megavoltage imaging devices integrated into linear accelerator. The combined use of optimal pretreatment imaging with 4DCT-based target delineation, modern planning techniques and the use of linear accelerators equipped with cone-beam CT scanners allows for smaller safety margins around the tumor (35). In-room imaging in image-guided radiotherapy (IGRT) using CT-on rail (36) or cone-beam CT allows for variations in patient or tumor positions to be identified on a routine basis, and can identify trends in tumor volume and shape, increases or decreases in atelectasis, or changes in patient anatomy due to excessive weight loss.

Although there has been increasing evidence regarding the efficacy and safety of SBRT for patients with Stage I NSCLC, recruitment of further cases and sufficient follow-ups is currently required to create a fair evaluation of treatment outcomes for SBRT. We also have to pay special attention to patients with centrally located tumors or pulmonary fibrosis. SBRT is becoming established as a radical treatment strategy for medically inoperable Stage I NSCLC. Investigation of whether SBRT can also provide a surrogate treatment for surgery in medically operable patients would therefore be meaningful. It is necessary to both wait for progress in ongoing clinical trials and to formulate new clinical trials to more fully elucidate the position of SBRT among other treatment modalities for Stage I NSCLC. If the JCOG0403 study shows long-term, stable, positive outcomes for the operable group, a study of SBRT versus minimal surgery may be justified for patients who have some risks on standard lobectomy, such as due to poor pulmonary condition or overall physical state (the group for whom minimal surgery is considered). A major problem with SBRT is that it does not allow pathological diagnosis of resected subclinical lymph node metastases to determine the necessity of adjuvant chemotherapy. If subjects with a low risk of lymph node metastases can be clarified through the results of the trials currently underway by the lung cancer surgery group in Japan (JCOG0804/WJOG 4507L: case recruitment complete), then groups can be offered SBRT without adjuvant chemotherapy.

Table 4. Unsolved issues of SBRT

Tolerable dose of normal structures
Effect of pulmonary fibrosis on SBRT-induced pneumonitis
Justice of SBRT for histologically unproven lung tumors
Optimal dose fractionation
Adjuvant therapy
Salvage treatment after recurrence
Long-term prognosis (over 10 years)
Comparison with surgery

Furthermore, many issues (Table 4) remain unresolved and ought to be investigated through long-term follow-up of past clinical trials and the creation of new clinical trials.

CONCLUSION

Stereotactic radiotherapy administers a concentrated large dose in 3D, over a short time span, with precise targeting of the locations of small tumors. This treatment has been used more widely in recent years on a growing number of cases. Since 1995, SBRT for patients with Stage I NSCLC has mainly seen clinical use on inoperable patients. In addition, various clinical trials have been conducted and have found improved local control and survival rates compared with conventional radiation treatments. SBRT is considered the standard treatment for medically inoperable patients and is selected as a surrogate treatment for operable patients who reject surgery. However, the number of cases and observation periods remain insufficient and many uncertainties need to be clarified related to the tolerable dose to at-risk organs and appropriate dose-fractionation, and several issues related to oncology, such as adjuvant therapy or surgery, etc. It is hoped that SBRT will be used in clinics more properly through obtaining new clinical and long-term follow-up data for Stage I NSCLC.

Acknowledgement

We wish to express our special appreciation to Drs. Masahiro Hiraoka and Yasushi Nagata, primary investigators in the JCOG0403 trial who have provided a great deal of invaluable advice.

Funding

This work was partially supported by a Health and Labour Sciences Research Grant for Clinical Cancer Research (20S-5, 20S-6) from the Japanese Ministry of Health, Labour and Welfare.

Conflict of interest statement

None declared.

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