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Eleven secondary cancers after hematopoietic stem cell transplantation using a total body irradiation-based regimen in 370 consecutive pediatric and adult patients

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Abstract

Go to:

About the bone marrow transplantation that high dose chemotherapy and total-body irradiation (TBI) are used for as conditioning regimen, a late toxicity may become the problem in the long-term survival patient. One of the toxicities which has been implied to be associated with TBI is secondary cacinogenesis. Between June 1995 and December 2010, 370 patients who were undergoing allogeneic hematopoietic stem cell transplantation using a TBI-based regimen at our department, were the subjects of this study. Eleven secondary cancers occurred in 10 patients. The median time from transplantation to diagnosis of a secondary cancer was 6.8 years. In this analysis, the cumulative incidence rate of secondary cancer at 5 and 10 years was 2.15% and 6.46%, respectively after TBI in our institution.

Keywords: Total body irradiation, Secondary cancer, Bone marrow transplantation

Introduction

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The conditioning regimen before allogeneic hematopoietic stem cell transplantation is intended to eradicate tumor cells and to promote immunosuppression to prevent graft rejection. A combination of cyclophosphamide and total body irradiation (TBI) is the most widely used regimen in transplantation for leukemia.

Patients who receive bone marrow transplantation underlie an increased risk for secondary cancers because of several risk factors, including radiation, chemotherapy, and immune stimulation. Several studies (Schneider et al. 2007; Bhatia et al. 1996; Witherspoon et al. 1989; Deeg & Witherspoon 1993; Witherspoon et al. 1992; Deeg et al. 1984) described the risk factors and incidence of secondary malignancy after transplantation.

We here report our single-center experience regarding second malignancy in patients treated with TBI-based regimen. This paper focuses on the occurrence of second solid cancer.

Materials and methods

Go to:

Patients

Between June 1995 and December 2010, 370 patients who were undergoing allogeneic hematopoietic stem cell transplantation using a TBI-based regimen at our department, were the subjects of this study. Data were obtained from our bone marrow transplantation (BMT) database.

Transplantation procedure

The first choice of the preparative regimen is cyclophosphamide (Endoxan) 60 mg/kg div day −3, -2 and full TBI 2 Gy x2/day day −6, -5, -4 for acute myeloblastic leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), chronic myeloblastic leukemia (CML). Calcineurin inhibitor [Cyclosporine A (Sandimmun) 3 mg/kg/day, cdiv day-1~ or FK506 (Tacrolimus) 0.03 mg/kg/day, cdiv day-1~] plus Methotrexate (MTX) day 1, 3, 6, 11 were administered to prevent GVHD.

A purpose of use of the immunosuppressive drugs in pediatric stem cell transplant is to control GVHD not to become severe. About the duration of administration, we reduce and cancel the immunosuppressive drug when GVHD becomes the minor degree not to affect everyday life. The period until coming to become able to control is not fixed because there is individual difference. In other words, we continue using an immunosuppressive drug for years for the case that GVHD aggravates when dose reduction. The kind of the immunosuppressive drug uses cyclosporine in the case of transplant between blood relatives and tacrolimus in the case of between unrelated blood relatives interval like the transplant of the adult.

Total body irradiation

Patients were treated in a mobile box made of 10 mm thick polymethyl methacrylate 600 mm wide by 2000 mm long by 400 mm high. The box is capable of moving up to 250 cm forward and backward on the rails with a constant speed. Beam intensity and moving velocity defined dose rate in TBI (Ban et al. 2001). Normally, beam opening of the linac is 400 cm × 10 cm. Leukemia patients were usually treated in the supine position for three fractions in the morning and in the prone position for three fractions in the evening. The center of the mobile box was selected to be a reference point to attain the prescribed dose. Beam intensity and moving velocity were determined based on the measurement of the doses in Mix-DP slab phantoms with an ionization chamber, but no corrections for patient body size were required due to the use of the mobile box. Dose rate was 150 MU/min in all cases. Most commonly, a pair of customized metal blocks was placed on the mobile box for lung shielding. The blocks were fabricated according to the lung shape, which was obtained by use of the X-ray film taken in the box. Lung shielding was performed in a fraction of TBI out of six fractions for three consecutive days in most cases.

Statistical analysis

The probability of the incidence of secondary cancer was estimated using the Kaplan-Meier method.

Patients

The patients were 236 males and 134 females. The median age at transplantation was 36 years old (range; 1–72). The median follow-up time for only survivors was 10.5 years (max; 16.4). A hundred thirteen patients (31%) received transplantation for acute AML, 117 patients (32%) for ALL, 39 patients (11%) for lymphoma, 34 patients (9%) for MDS, 41 patients (11%) for CML, and six patients (1.6%) for dyshematopoiesis. Two hundred forty patients (65%) survived at least 1 year after TBI.

The conditioning regimens included TBI with cyclophosphamide (CY) alone (72%), etoposide (VP-16) alone (10%), or a combination of CY and VP-16 (18%). For pediatric case, melphalan (L-PAM), antithymocyte globulin (ATG), thiotepa (TESPA), or fludarabine were administered for ten, one, one, and two patients, respectively. Graft-versus-host disease (GVHD) prophylaxis consisted in the majority of patients of cyclosporine-A associated to methotrexate, and FK506 associated to methotrexate in some patients.

Results

Go to:

Secondary cancers

Eleven secondary cancers occurred in 10 patients. One patient presented both esophageal and gastric cancer. The median time from transplantation to diagnosis of a secondary cancer was 6.8 years. The probability of incidence of secondary cancers at 5 and 10 years after transplantation was 2.15% (+/− 1.22%) and 6.46% (+/− 2.82%), respectively (Figure 1).

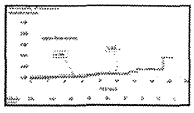

Figure 1

The probability of incidence of secondary cancers after transplantation.

Secondary cancers were thyroid papillary carcinoma in one patient (7.8 years after TBI), sub-maxillary gland tumor in one patient (1.4 years), esophageal cancer in 2 patients (7.1 and 12.2 years), oral cavity carcinoma in 1 patient (15.2 years), gastric cancer in 2 patients (1.9 and 7.1 years), and ureteral cancer in 1 patient (6.4 years), border malignant ovarian tumor in 1 patient (11.3 years), extragonadal germ cell tumor in 1 patient (3 years), the head and neck cancer in 1 patient (3 years). Table 1 shows the clinical characteristics of the patients with a secondary cancer.

Table 1

Clinical characteristics of the patients with a secondary cancer

Among 10 patients with secondary cancer, six are alive at last follow-up. One patient with secondary gastric cancer had a recurrence of leukemia, and died on the primary disease 2.8 years after TBI. Three patients died from a reason due to secondary cancer.

Discussion

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This is a report about 10 patients with secondary malignancies after TBI. The study population includes 370 patients after undergoing TBI between 1995 and 2010 as a single center experience. Secondary solid cancers are seen after a latency period of 3 to 5 years after hematopoietic cell transplantation, subsequently, their incidence continues to rise with time. Several series (Schneider et al. 2007; Bhatia et al. 1996; Witherspoon et al. 1989; Deeg & Witherspoon 1993; Witherspoon et al. 1992; Deeg et al. 1984) have described the increased risk of secondary cancer after hematopoietic cell transplantation.

The Collaborative study between the CIBMTR and Fred Hutchinson Cancer Research Center (FHCRC) conducted a study among 19,229 recipients of allogeneic and syngeneic transplantation (Curtis et al. 1997). 72.8% of patients received TBI as the conditioning regimen. The cumulative incidence of secondary cancers at 5, 10, and 15 years after transplantation was 0.7%, 2.2% and 6.7%, respectively, compared to the general population rates of 0.3%, 0.6% and 0.8% (Curtis et al. 1997). In a similar report of the Late Effects Working Party in the European Cooperative Group for Blood and Marrow Transplantation, 1,036 consecutive patients surviving more than 5 years post transplants were recorded (Kolb et al. 1999). With a median follow-up of 10.7 years, the actuarial incidence of a solid tumor post-BMT was 3.5% +/− 0.6% at 10 years and 12.8% +/− 2.6% at 15 years and this incidence is 3.8-fold higher than that in an age-matched control population ($p < 0.001$) (Kolb et al. 1999). The University of Minnesota reported a series of 3,372 recipients of BMT (Baker et al. 2003). The majority of patients in this study (78%) received a regimen that contained radiation, delivered as a fractionated TBI (12.0 to 13.2 Gy) in most patients or as a single-fraction TBI (7.5 Gy), given in combination with cyclophosphamide or with other chemotherapy agents. After a median follow-up of 5 years 137 patients developed 147 second malignancies, compared with 4.3 expected from general population and the estimated actuarial incidence of any post-BMT malignancy was 9.9% +/− 2.3% at 13 years (Baker et al. 2003). The City of Hope National Medical Center reported 2,129 patients who had undergone BMT for

hematologic malignancies (Bhatia et al. 2001). The conditioning regimens for patients with leukemia included TBI. The estimated cumulative probability for development of a solid cancer was 6.1% +/− 1.6% at 10 year which represents a two-fold increase in risk compared with general population (Bhatia et al. 2001). In this report, 11 solid secondary cancers occurred in 10 patients, and the cumulative incidence rate of secondary cancers at 5 and 10 years after transplantation was 2.2% and 6.5%, respectively, which is comparable with published studies evaluating the rate of secondary cancer after transplantation. According to the 2013 Annual Report of Nationwide Survey of HSCT by the Japan Society for HSCT, the incident probability of second cancer after CY+TBI and FL+TBI was 1.1% (CI: 0.7-1.6, N=1067) and 3.0% (CI: 2.2-4.1, N=509) at 3 years and 2.1% (CI: 1.4-3.3, N=198) and 5.2% (CI: 3.3-8.0, N=96) at 5 years after transplant, respectively.

In the pediatric experience reported by Socie et al. (2000), the Kaplan-Meier estimates of the probability of new invasive solid tumors at 5, 10, and 15 years after transplantation were 0.9% (+/− 0.6%), 4.3% (+/− 2.1%), and 11.0% (+/− 8.8%). Younger age at transplantation is a major risk factor of secondary solid cancers. Children less than 10 years of age also had a 33 to 36.6 fold higher risk of solid tumors than that expected in the general population. For Baker et al. (2003), children who had undergone transplantation when younger than 10 years had the highest risk (36.6 times as high as expected); the risk was 4.6 times as high as expected for those who were 10 to 29 year old at the time of transplantation and nearly normal for those who were 30 years or older ($p < 0.001$). 86.5% of patients received TBI in the conditioning regimen. In this report, there was not the secondary solid carcinoma among 50 pediatric patients. It is cited in the reason that there are few numbers of people and that an observation period is short.

The risk factors for the development of post-transplant solid tumors included the use of radiation or the radiation dose in the conditioning regimen. TBI significantly increases the risk of second cancer especially if higher dose are delivered (Deeg & Witherspoon 1993). All patients with secondary cancer were performed TBI of 12 Gy in this report, but it is unknown whether a higher dose of TBI contributed to secondary cancer because almost all patients received 12 Gy.

Unusual cancers were frequently diagnosed as post transplantation secondary cancer. Cancers of the buccal cavity, liver, brain and central nervous system, thyroid, bone, connective tissue, salivary gland plus melanoma were significantly elevated compared to the general population for most authors (Curtis et al. 1997; Kolb et al. 1999; Baker et al. 2003; Bhatia et al. 2001). Although the risk of common adult cancer was little increased, TBI has been reported to increase the risk of breast cancer. In a cohort of 3,337 female 5-year survivors, the 25-year cumulative incidence of breast cancer was 17% in recipients of TBI compared to 3% in those who did not receive TBI as a part of their conditioning regime (Majhail 2008). In the results published by Socie et al. (2000), half the excess solid tumors in the youngest age group were cancers of the brain (observed cases, 9; expected cases, 0.22) or thyroid (observed cases, 4; expected cases, 0.02). In this report, a relative rare solid cancer like maxillary gland tumor or extragonadal germ cell tumor was seen and the carcinogenesis of secondary breast cancer and brain tumor was not observed. This fact will be a cause that we had few long-term observation cases.

From the epidemiologic data of atomic bomb survivors from Hiroshima and Nagasaki, radiation induced solid cancer is gradually increasing after 10 years from exposure. However, as shown in our and other reference research, it seems to be induced little earlier than atomic bomb survivor. We may have to follow the patients at least 10 years in order to focus our subject to the incidence of second solid malignancy. A larger number of irradiated patients with adequate longer follow-up periods are necessary to calculate a radiation carcinogenesis risk with reasonable accuracy.

Additionally, the definition of secondary cancer is too difficult. Some of cancer patients with surgery and without chemotherapy are suffered from another metachronous cancer. Although these cancers are so called secondary cancer or double cancer, they are not treatment-related cancer. The cause of treatment-not-related metachronous cancer may be related to hereditary and/or environment etc. From our research, some of patients seem to become secondary cancer very early from TBI compared with atomic bomb survivor or HD irradiated patients. In this study, we defined second cancer as the all new diagnosed cancers after TBI.

Secondary primary cancer may also be induced by agents other than radiation; chemotherapeutic agents such as especially alkalylators, immunosuppressive agents, environmental exposures such as smoking and alcohol, hereditary disposition and so on.

We were not able to analyze statistically on the relationship between 11 secondary malignancies and TBI. It would be better to compare this study population to an age-matched control population, because age is a critical factor in determining radiation risk.

The number of enrolled patients (370 cases) may be substantially small for such an epidemiologic study. Many previously published reports involved several thousands of patients, such as Yokota's report (2062 cases) (Yokota et al. 2012) and other reports (Curtis et al. 1997; Kolb et al. 1999; Baker et al. 2003; Bhatia et al. 2001; Socie et al. 2000; Majhail 2008).

Conclusion

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Various factors such as GVHD, high dose chemotherapy, or the use of CY have been nominated for risk factor of the secondary carcinoma other than TBI. The influence that TBI gives secondary cancer is hard to evaluate because a regimen including TBI is performed for all patients in this study. However, it is shown by the analysis of our institution that the risk of the secondary cancer rises by BMT including TBI just like the past reports and may not ignore the influence that TBI gives secondary cancer.

Footnotes

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MO carried out the conception and design of the study and the analysis & interpretation of data and the drafting of the article as the first author. HY carried out the critical revision of the article for important intellectual content as a corresponding author. AS & MK carried out the collection and assembly of BMT data of adult and JT & MH BMT data of child and KN radiotherapy data. All authors read and approved the final manuscript.

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Non-invasive objective evaluation of radiotherapy-induced dry mouth

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BACKGROUND: Dry mouth is a common complaint in patients undergoing radiotherapy. Here, we employed the oral moisture meter Mucus III to evaluate dry mouth in head and neck tumor patients before and after they underwent radiotherapy.

METHODS: We recruited 17 newly diagnosed patients with pharyngeal squamous cell carcinoma or unknown primary squamous cell carcinoma, who received head and neck radiation therapy at Tokyo University Hospital in 2008–2010. The primary sites were the epipharynx (n = 1), oropharynx (n = 6), or hypopharynx (n = 5); it was unknown in five cases. Salivary function was assessed by a dry mouth questionnaire, resting saliva test, chewing gum test, and Mucus III, before (n = 17), immediately after radiotherapy (n = 10), and at 3 (n = 9) and 12 months after radiotherapy (n = 11).

RESULTS: The questionnaire, resting saliva test, and chewing gum test at 3 and 12 months after radiotherapy indicated a significantly decreased resting and stimulated whole saliva flow rate than prior radiotherapy ($P < 0.05$ and $P < 0.001$). In contrast, Mucus III results showed significant worsening of xerostomia at 12 months after radiotherapy ($P < 0.05$).

CONCLUSION: Mucus III has been proven to be an objective diagnostic tool for patients with serious dry mouth, such as in patients with Sjogren's syndrome. However, we did not find a perfect correlation between Mucus III and other objective (resting saliva and chewing gum) and subjective (questionnaire) measures of dry mouth. To precisely diagnose radiotherapy-induced dry mouth, further improvement to the method is needed.

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Keywords: head and neck cancer; xerostomia

Introduction

Dry mouth can be caused by various conditions such as hyposalivation due to Sjögren's syndrome, inflammation of the salivary gland and atrophy due to irradiation of head and neck tumors, mouth breathing due to nasal sinus disease and sleep apnea syndrome, and reduction in saliva secretion due to consumption of certain drugs (1–8). Dry mouth can lead to oral mucosal diseases, causing oral and oropharyngeal pain, oropharyngeal infections, dysphagia, cacogeusia, and difficulty in speaking (3).

Mouth dryness can be measured by several tests. Salivary secretion tests such as the chewing gum test, the Saxon test, and the paraffin test apply stimuli of variable intensities (9–16). They are useful for evaluating the amount of stimulated saliva, but not mucosal wetness in resting conditions (16). This is a problem for bed-ridden patients, dementia patients, and patients with dental prosthesis, in whom stimulated saliva tests are difficult to perform. Therefore, an objective evaluation method that did not depend on the patient's function was needed.

To take care of this need, an oral moisture meter (Mucus) was developed by Life Co. Ltd (Saitama, Japan) in 2001, based on the improved design of an original skin wetness meter (17). The tool works according to the principle of a condenser, which measures impedance with capacitive sensors, using the resonant frequency of the alternating current. The displayed number is not the actual value of the amount of water, but it is a relative value that reflects it. Therefore, units are not indicated. Thus, the moisture content of the mouth and tongue mucosae can be evaluated with this device (Fig. 1). The probe is placed against the oral and tongue mucosae for approximately within 5 s, and an alarm sounds at the end of the measurement. The probe tip (1 cm^2) touches the oral mucosa and tongue with a

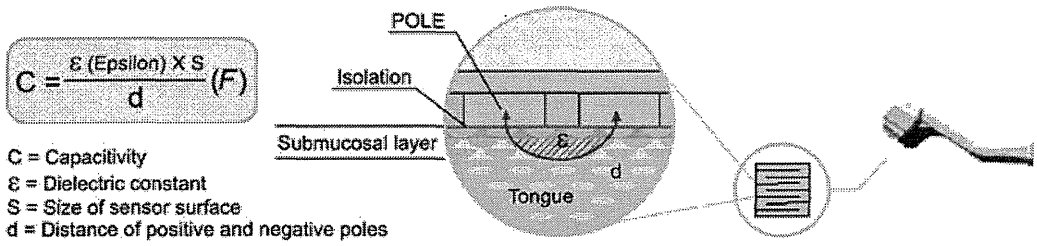

Figure 1 Measurement of the moisture content of the submucosal layer (about 50 μm under the mucosal surface) of the tongue was based on the principle of a condenser. The formula shown was used for calculation. As the value of '*S*' and '*d*' is constant, changes in '*C*' depend solely on '*ε*'. When the sensor is placed against the tongue, '*ε*' changes with the amount of moisture. In general, high moisture content gives high '*ε*' and '*C*' values, while low moisture content gives low '*ε*' and '*C*' values. Adapted from (18).

pressure of about 200 g/cm^2. After 27 mA (80 mW) of microelectrical current is delivered to the probe, the capacitance at the mucosal depth of 50 μm of the oral mucosa is quantified. Because the probe tip is covered with a sterile sensor cover (thickness, 12 μm), there is no risk of bacterial or viral infection. The tool is non-invasive and easy to operate. A digital display provides objective data.

However, this earlier model of Mucus had low reliability. To improve this, Ishimoto et al. pointed out the problems and came up with possible solutions to the manufacturer (18). This has led to the development of an improved version, the so-called Mucus III (Fig. 2). In an animal study, Ishimoto et al. established the reliability and usefulness of Mucus III (18). Later, Ishimoto et al. confirmed the reliability of Mucus III in healthy volunteers (standard value of the tongue's moisture content: 30.9 ± 1.8) and its usefulness in comparing the oral mucosa of patients with Sjogren's syndrome with that of controls (19). Currently, Mucus III is commercially marketed as MUCUS®.

To date, subjective questionnaire-based measures have been mainly used for the study of radiotherapy-induced dry mouth (20–24). We hypothesized that Mucus III could be as useful in the evaluation of radiotherapy-induced dry mouth as it was in the case of patients with Sjogren's syndrome.

The purpose of this study was to evaluate Mucus III for the assessment of oral dryness in head and neck cancer patients who have undergone radiation treatment. We also show the results of subjective (questionnaire) and objective (resting saliva and chewing gum) tests for comparison with the results of Mucus III.

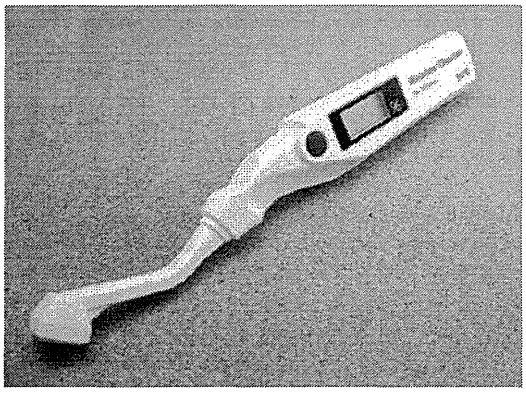

Figure 2 Mucus III device. Mucus III device measures 21.5 mm (width), 238 mm (length), and 41 mm (height), and weights 60 g.

Materials and methods

Subjects

From August 2008 to July 2010, 17 newly diagnosed patients with pharyngeal squamous cell carcinoma and unknown primary squamous cell carcinoma were recruited (Table 1).

All these patients underwent conventional radiotherapy (CRT) of the head and neck region at the Department of Otolaryngology, Tokyo University Hospital. The primary tumor site was classified into the epipharynx (n = 1), oropharynx (n = 6), hypopharynx (n = 5), or unknown (n = 5). Sixteen patients received a radiotherapy dose of 70 Gy, and one patient whose primary tumor site was unknown received a radiotherapy dose of 60 Gy. Fourteen patients received no medication (oral tablets or gel) during the follow-up period. Three patients were given a dose of pilocarpine hydrochloride to increase salivary secretion, but administration was stopped because of its side effects. The study was conducted in accordance with the Declaration of Helsinki and approved by the appropriate ethical committee. Informed consent was obtained from all the participants.

Assessment of mouth dryness

Four different tests (A–D) were applied to the enrolled participants before and after they underwent radiotherapy. Ten patients (9 men, 1 woman, age: 44–77 years, mean age: 61.1 years) were successfully evaluated before and immediately after the radiotherapy (within a maximum period of 11 days). The primary sites were the oropharynx (n = 3) and hypopharynx (n = 4); the site was unknown in three cases. The average radiation dose for the parotid glands was 45.4 ± 2.2 Gy. Nine cases (7 men, 2 women, age: 44–77 years, mean age: 60.2 years) were successfully evaluated before and 3 months after radiotherapy. The primary sites were the oropharynx (n = 4) and hypopharynx (n = 4), while it was unknown in one case. The average radiation dose for the parotid glands was 48.5 ± 4.2 Gy. Eleven cases (8 men, 3 women, age: 44–74 years, mean age: 58.8 years) were successfully evaluated before and 12 months after the radiotherapy; the primary sites were the nasopharynx (n = 1), oropharynx (n = 4), and hypopharynx (n = 3), while it was unknown in the three cases. The average radiation dose for the parotid glands was 43.3 ± 2.7 Gy.

Table 1 Clinical characteristics of the 17 patients enrolled in this study

No	*Sex*	*Age*	*Tumor site*	*TNM*	*Total radiation (Gy)*	*Chemotherapy*	*Immediately after*	*At 3 months*	*At 12 months*
1	M	65	OPX	T2N0M0	70	Yes	Yes	Yes	Yes
2	F	74	OPX	T2N0M0	70	Yes		Yes	Yes
3	F	67	OPX	T4aN0M1	70	Yes	Yes	Yes	Yes
4	M	59	OPX	T4aN1M0	70	Yes	Yes		
5	M	54	OPX	T4aN3	70	Yes			Yes
6	M	50	OPX	T4N2cMo	70	Yes		Yes	
7	M	77	HPX	T3N2aM1	70	Yes	Yes	Yes	
8	M	50	HPX	T2N1M0	70	Yes	Yes	Yes	Yes
9	M	62	HPX	T2N2M0	70	Yes			Yes
10	M	44	HPX	T4N2bM0	70	Yes	Yes	Yes	Yes
11	M	76	HPX	T2N3M0	70	Yes	Yes		
12	M	67	HPX	T3N0M0	70	Yes		Yes	
13	M	63	UP		60	Yes	Yes		Yes
14	M	59	UP		70	Yes	Yes		Yes
15	M	51	UP		70	Yes	Yes		Yes
16	M	48	UP		70	Yes		Yes	
17	F	58	EPX	T2bN1M0	70	Yes			Yes

EPX, epipharynx; HPX, hypopharynx; OPX, oropharynx; TNM, tumor, node, metastasis classification; UP, unknown primary.

Five cases (3 men, 2 women, age: 44–74 years, mean age: 60.0 years) were successfully evaluated before, 3 months, and 12 months after radiotherapy; the primary sites were the oropharynx (n = 3) and hypopharynx (n = 2), and it was unknown in three cases; the average radiation dose for the parotid glands was 42.4 ± 4.9 Gy.

A: Dry mouth questionnaire

A questionnaire for the subjective assessment of salivary dysfunction was designed based on the 8-item xerostomia questionnaire (20). The questionnaire consisted of eight questions regarding the sensation of mouth dryness and its influence on conversation and swallowing (Table 2). The participants were asked to grade each aspect with a score that ranged from 1 to 3, with a higher score denoting worse salivary function (21). The mean of the eight scores was calculated.

B: Resting saliva test

To evaluate resting salivary secretion, the patients were requested to keep spitting out saliva into a beaker during a period of 10 min, after which the total amount of saliva was measured (25).

C: Chewing gum test

To evaluate salivation upon stimulation, the patients were requested to chew gum (Free Zone; Lotte Co. Ltd, Tokyo, Japan) and keep spitting out saliva into a beaker during a period of 10 min, after which the total amount of saliva was measured (9–14). This mint-flavor, plate-like gum can also be used in patients with dentures, because it seldom sticks to the teeth.

Table 2 Questionnaire for subjective assessment of salivary dysfunction (20, 21)

1. Rate the difficulty you experience in speaking due to dryness
2. Rate the difficulty you experience in swallowing due to dryness
3. Rate the dryness of your mouth
4. Rate the dryness of your lips
5. Rate the dryness of your tongue
6. Rate the level of your thirst
7. Rate the stickiness you experience due to dryness
8. Rate how frequently you drink water for dryness

D: Measurement of oral moisture with Mucus III

The oral moisture meter Mucus III (Life Co. Ltd) was employed to measure the moisture content of the oral mucosa in resting conditions. The probe which was covered with a sterile sensor cover (thickness, 12 μm) was placed on the central part of the dorsal surface of the tongue about 10 mm from the tip for approximately 5 s. An alarm rang to provide the signal for the end of the measurement. A digital display provided objective data.

The measurements were carried out in the afternoon, 1–2 h after lunch at each time point, and in the following order: A: Dry mouth questionnaire, D: Measurement of oral moisture with Mucus III, B: Resting saliva test, C: Chewing gum test. Patients did not eat or drink for at least 60 min before measurements, nor did they smoke after diagnosis.

Statistical analysis

All data are expressed as the mean ± standard deviation (SD). Differences between two time points (before and immediately after, before and 3 months after, before and 12 months after, or 3 months and 12 months after radiotherapy) were examined for statistical significance using a paired t-test. A P-value of <0.05 was considered as significance thresholds.

Results

The dry mouth questionnaire (A), resting saliva test (B), and chewing gum test (C) showed that dry mouth symptoms were worsened immediately after radiotherapy as compared to before (2.47 ± 0.52 vs. 1.07 ± 0.10 [$P < 0.001$], 1.86 ± 1.38 vs. 5.51 ± 4.64 ml/10 min [$P < 0.05$], and 4.80 ± 5.35 vs. 24.15 ± 11.98 ml/10 min [$P < 0.001$], respectively). In the case of the Mucus III test (D), the reduction in oral moisture was not significantly different (30.00 ± 4.63 vs. 31.39 ± 1.27 [$P = 0.412$]) (Fig. 3).

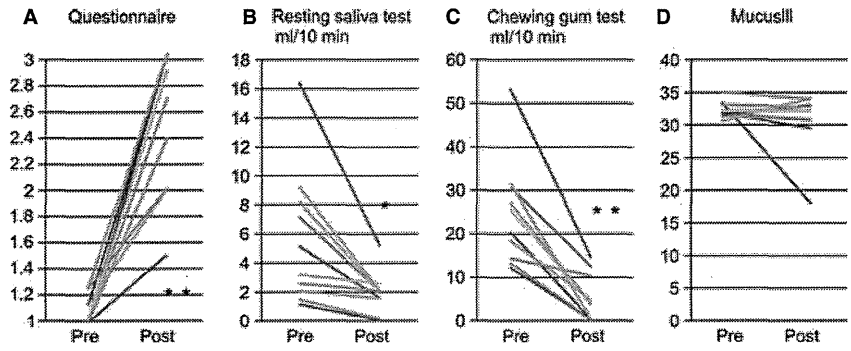

Figure 3 Results of the dry mouth questionnaire (A), resting saliva test (B), chewing gum test (C), and Mucus III test (D) before and immediately after radiotherapy ($n = 10$). *$P < 0.05$, **$P < 0.001$.

A similar trend in the results of the dry mouth questionnaire, resting saliva test, and chewing gum test was observed at 3 months after radiotherapy (2.68 ± 0.48 vs. 1.06 ± 0.12 [$P < 0.001$], 0.44 ± 0.53 vs. 7.04 ± 4.92 ml/10 min [$P < 0.05$], and 4.62 ± 4.64 vs. 22.66 ± 12.69 ml/10 min [$P < 0.001$], respectively). Again, the reduction in oral moisture was not significantly different in the case of the Mucus III test (26.69 ± 8.86 vs. 32.21 ± 1.91 [$P = 0.096$]) (Fig. 4). However, the decreasing trend was in accordance with the results of the other three tests.

At 12 months after radiotherapy, all four tests showed significant worsening of dry mouth symptoms, suggesting that subjective and objective reduction in salivation persisted for as long as 1 year (2.50 ± 0.42 vs. 1.06 ± 0.12 [$P < 0.001$], 0.72 ± 0.69 vs. 5.42 ± 4.39 ml/10 min [$P < 0.05$], 9.39 ± 4.81 vs. 23.86 ± 12.64 ml/10 min [$P < 0.001$], and 30.07 ± 1.73 vs. 31.94 ± 1.16 [$P < 0.05$], respectively) (Fig. 5).

Confirming the previous results, the five cases that were successfully evaluated before, 3 months, and 12 months after radiotherapy revealed significant differences in the dry mouth questionnaire results before radiotherapy and after 3 months, and before radiotherapy and after 12 months (1.10 ± 0.16 vs. 2.47 ± 0.58 [$P < 0.05$] and 1.10 ± 0.16

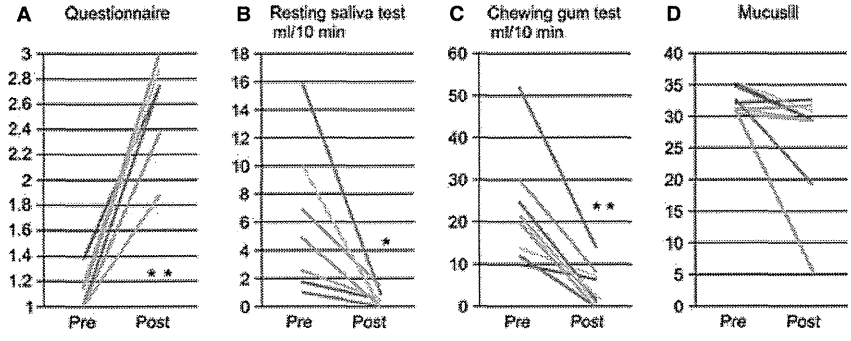

Figure 4 Results of the dry mouth questionnaire (A), resting saliva test (B), chewing gum test (C), and Mucus III test (D) before and 3 months after radiotherapy ($n = 9$). *$P < 0.05$, **$P < 0.001$.

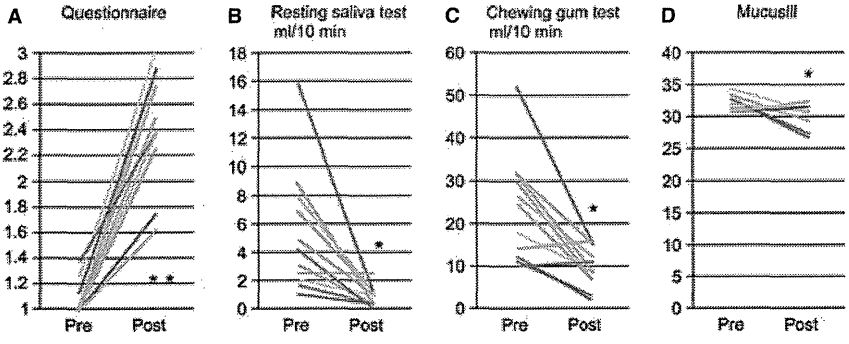

Figure 5 Results of the dry mouth questionnaire (A), resting saliva test (B), chewing gum test (C), and Mucus III test (D) before and 12 months after radiotherapy ($n = 11$).*$P < 0.05$, **$P < 0.001$.

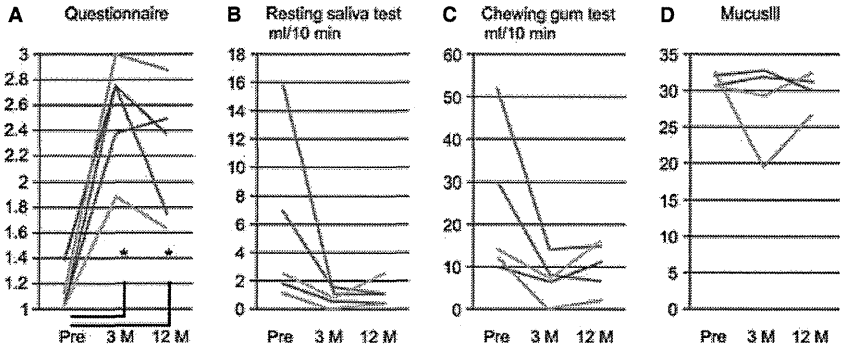

Figure 6 Results of the dry mouth questionnaire (A), resting saliva test (B), chewing gum test (C), and Mucus III test (D) before and 3 and 12 months after radiotherapy ($n = 5$). *$P < 0.05$.

vs. 2.27 ± 0.46 [$P < 0.05$], respectively). Comparison between the results at 3 months and 12 months after radiotherapy did not show a significant difference (2.47 ± 0.58 vs. 2.27 ± 0.46 [$P = 0.44$]); however, compared to 3 months after radiotherapy, 4 of 5 cases had improved mean scores at 12 months after radiotherapy. The resting saliva test, the chewing gum test, and Mucus III did not show significant differences between the same time points (Fig. 6). However, in the three tests, improvements in the mean scores at 12 months compared to 3 months after radiotherapy were observed (resting saliva test: 1.02 ± 0.89 vs. 0.74 ± 0.55 ml/10 min [$P = 0.52$]; chewing gum test: 10.10 ± 5.87 vs. 7.10 ± 4.98 ml/10 min [$P = 0.16$]; and Mucus III: 30.33 ± 2.17 vs. 29.04 ± 5.55 [$P = 0.50$]).

Discussion

Radiotherapy-induced dry mouth markedly reduces a patient's quality of life, and non-invasive objective evaluation tools are needed to help improve the management of radiotherapy side effects. Here, we tested the usefulness of the novel Mucus III in assessing mouth dryness in head and neck cancer patients who underwent radiotherapy. However, we found that Mucus III did not perform sufficiently well in reflecting dry mouth symptoms.

In this study, radiotherapy-induced dry mouth symptoms were identified subjectively and objectively by means of three different tests: a questionnaire, resting saliva test, and chewing gum test, immediately, 3 and 12 months after radiotherapy. Objective evaluation of oral moisture was obtained using Mucus III 12 months after radiotherapy. There was no significant difference seen immediately after the radiotherapy and 3 months after the radiotherapy. Unfortunately, because of the patients' physical and mental conditions and the difficulty with matching evaluation time points, we were unable to evaluate all 17 patients at each time point. Employing Mucus III to evaluate radiotherapy-induced dry mouth immediately after radiotherapy might not be the best option because inflammation of the oral mucosa is severe. On the other hand, 3 months after treatment, when the oral mucosa almost recovered from inflammation, application of Mucus III might be preferable. However, at 3 months after radiotherapy, Mucus III results showed a similar trend to the results of the other three tests, but the changes shown by Mucus III were not statistically significant. At 12 months after radiotherapy, dry mouth symptoms were evident in all four tests conducted, indicating that dry mouth was a long-term condition in these patients.

However, evaluating the data of 5 patients in a period of 1 year (Fig. 6), measurements at 12 months showed better improvement compared to the measurements obtained at 3 months after radiotherapy. Even though complete recovery from dry mouth symptoms is thought to be difficult or even almost impossible, the present results show that the process might not be entirely irreversible. This is consistent with the published literature (23, 24). To confirm this observation, a future study with a larger number of subjects and a longer follow-up period is necessary.

The results also indicate that Mucus III might not show consistent results across patients and/or time points. In case dry mouth is severe, and the absolute amount of saliva is reduced markedly, the value measured by Mucus III is also significantly lower, indicating its capacity to evaluate dry mouth precisely. However, when some degree of saliva secretion capacity remains, the measured value does not decrease significantly; in fact, it remains around normal values. Even if the relative value measured by Mucus III is lowered after irradiation, the absolute value is not significantly below the normal range. In short, the remaining saliva secretion capacity may not be sufficiently small to lower the absolute values measured by Mucus III; this might explain discrepancies in values compared to the other three tests.

Mucus III has proved its usefulness in the evaluation of hyposalivation in Sjogren's syndrome (6). However, in the present study, Mucus III did not perform sufficiently well in reflecting dry mouth symptoms resulting from radiation therapy. Importantly, in this study, there were no complaints of pain or discomfort associated with the probe. If this tool is revised and improved, it might help in the management of radiotherapy side effects, ultimately improving the quality of life after radiotherapy.

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Conflict of interests

The authors have no conflict of interests to declare.

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ORIGINAL ARTICLE

Japanese structure survey of radiation oncology in 2009 with special reference to designated cancer care hospitals

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Abstract
Background The structure of radiation oncology in designated cancer care hospitals in Japan was surveyed in terms of equipment, personnel, patient load, and geographic distribution, and compared with the structure in other radiotherapy facilities and the previous survey.

Methods The Japanese Society for Therapeutic Radiology and Oncology surveyed the national structure of radiation oncology in 2009. The structures of 365 designated cancer care hospitals and 335 other radiotherapy facilities were compared.

Results Designated cancer care hospitals accounted for 50.0 % of all the radiotherapy facilities in Japan. The patterns of equipment and personnel in designated cancer

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care hospitals and the other radiotherapy facilities were, respectively, as follows: linear accelerators per facility: 1.4 and 1.0; dual-energy function: 78.6 and 61.3 %; three-dimensional conformal radiotherapy function: 88.5 and 70.0 %; intensity-modulated radiotherapy function: 51.6 and 25.3 %; annual number of patients per linear accelerator: 301.3 and 185.2; Ir-192 remote-controlled afterloading systems: 31.8 and 4.2 %; and average number of full-time equivalent radiation oncologists per facility: 1.8 and 0.8. Compared with the previous survey, the ownership ratio of equipment and personnel improved in both designated cancer care hospitals and the other radiotherapy facilities. Annual patient loads per full-time equivalent radiation oncologist in the designated cancer care hospitals and the other radiotherapy facilities were 225.5 and 247.6, respectively. These values exceeded the standard guidelines level of 200.

Conclusions The structure of radiation oncology in designated Japanese cancer care hospitals was more mature than that in the other radiotherapy facilities. There is still a shortage of personnel. The serious understaffing problem in radiation oncology should be corrected in the future.

Keywords Radiotherapy · Medical engineering · Epidemiology

Introduction

In Japan, the current utilization rate of radiotherapy (RT) for new cancer patients in Japan is only 27.7 % and surgery remains predominant [1]. This rate is very low when compared to those for western developed countries. The main reason for this is that there is not enough personnel, such as radiation oncologists (ROs), medical physicists (MPs), and radiotherapy technologists (RTTs) [2, 3]. The Cancer Control Act was implemented in 2007 in response to patients' urgent petitions to the Japanese government [4]. This law strongly advocates the promotion of RT and an increase in the number of ROs and MPs. At the same time, the Ministry of Health, Labour and Welfare began the accreditation of "designated cancer care hospitals (DCCHs)" with the aim of correcting regional differences in the quality of cancer care and strengthening cooperation among regional cancer care hospitals [5, 6]. The Japanese Society for Therapeutic Radiology and Oncology (JASTRO) has conducted national structure surveys of RT facilities in Japan every 2 years since 1990 [7]. Findings of these surveys indicate that the structure of radiation oncology in Japan has improved in terms of equipment and functioning in response to the increasing numbers of cancer patients who require RT.

In the study presented here, the structure of radiation oncology in DCCHs in Japan was analyzed in terms of equipment, personnel, patient load, and geographic distribution, and compared with these features in other RT facilities in Japan. In addition, the recent structure of RT facilities was compared with that surveyed in 2007 [2] and the medical care situation in Japan was compared with that in European countries and the USA.

Methods and materials

A national survey in the form of a questionnaire on the structure of radiation oncology in Japan in 2009 was conducted by JASTRO from March 2010 to January 2011 [1]. The questionnaire consisted of items related to the number of treatment machines and type of modality, the number of personnel by job category, and the number of patients by type and disease site. The response rate was 90.9 % (700 out of 770) from all actual RT facilities in Japan. The number of DCCHs certified by the Ministry of Health, Labor and Welfare was 375 as of April 1, 2011 [8]. Of this total, 51 were designated prefectural and 324 were designated regional cancer care hospitals. The surveys were not returned by 20 facilities, and 3 facilities did not have departments of RT at the time of the survey, so that the structures of 365 DCCHs and 335 other RT facilities were analyzed. In this survey, full-time equivalent (FTE) (40 h/week for radiation oncology work only) data were surveyed in terms of the clinical working hours for RT of each staff member. SAS® 8.02 (SAS Institute Inc., Cary, NC, USA) [9] was used for the statistical analysis and statistical significance was determined by means of the χ^2 test and Student's t test.

The Japanese Blue Book Guidelines (JBBG) [10, 11] were used for comparison with the results of this study. These guidelines pertain to the structure of radiation oncology in Japan based on Patterns of Care Study (PCS) [12, 13] data. The standard guidelines for annual patient load per external beam equipment were set at 250–300 (warning level 400), those for annual patient load per FTE RO at 200 (warning level 300), and those for annual patient load per FTE RT technologists at 120 (warning level 200).

Results

Current situation of radiation oncology

Table 1 shows the current situation of radiation oncology in Japan. DCCHs accounted for 50.0 % (385/770) of all the RT facilities in Japan. The numbers of new patients and total patients in all RT facilities in Japan were estimated at approximately 201,000 (182,390 × 770/700) and 240,000 (205,087 × 770/700), respectively. For DCCHs,

Table 1 Numbers of new patients and total patients (new plus repeat) requiring radiotherapy in designated cancer care hospitals and other radiotherapy hospitals

	DCCHs	Other RT facilities	*p* value (95 % CI)[a]	Total
Facilities	365	335	–	700
New patients	126,123[b]	56,267	–	182,390[c]
Average new patients/facility	345.5	168.0	<0.0001 (146.7, 208.4)	260.6
Total patients (new + repeat)	150,215[b]	67,614	–	217,829[c]
Average total patients per facility	411.5	201.8	<0.0001 (171.6, 247.8)	311.2

DCCH designated cancer care hospital, *RT* radiotherapy, *CI* confidence interval

[a] Student's *t* test

[b] The number of designated cancer care hospitals with RT was 385, and the number of new patients in DCCHs was estimated at approximately 134,000; the corresponding number of total patients (new plus repeat) was 159,000

[c] The number of radiotherapy facilities was 770 in 2009, and the number of new patients was estimated at approximately 201,000; the corresponding number of total patients (new plus repeat) was 240,000

the corresponding numbers were approximately 134,000 (126,123 × 385/365) and 159,000 (150,215 × 385/365). The number of new patients and total patients in DCCHs thus accounted for approximately 66.7 % (134,000/201,000) and 66.3 % (134,000/201,000 and 159,000/240,000) of the number of new patients and total patients in all RT facilities. The average numbers of new patients per facility were 345.5 for DCCHs and 168.0 for the other RT facilities, and for the average numbers of total patients per facility the corresponding figures were 411.5 and 201.8, respectively.

Facility and equipment patterns and patient load per linear accelerator

The RT equipment patterns and related functions in Japan are shown in Table 2. In DCCHs, 496 linear accelerators (linacs) and 116 ^{192}Ir remote-controlled after-loading systems (RALSs) were in current use, while the corresponding data for the other RT facilities were 320 and 14, respectively. The rate of equipment ownership at DCCHs was significantly higher than at the other RT facilities. As for the linac systems in DCCHs, the dual-energy function was used in 390 (78.6 %), the three-dimensional conformal radiotherapy (3D-CRT) function in 439 (88.5 %), and the IMRT function in 256 (51.6 %). For the other RT facilities, the corresponding figures were 196 (61.3 %), 224 (70.0 %), and 81 (25.3 %). The patient load per linac was 301.3 at DCCHs and 185.2 at the other RT facilities. Compared with the data for DCCHs in 2007 [2], the rate of linac ownership increased by 0.6 % while the rates of increase for installation of the various functions used with linacs were 3.8 % for dual-energy, 13.2 % for 3D-CRT, and 15.2 % for IMRT function. At the other RT facilities, the rate of linac ownership decreased by 0.4 %, while the rates of installation corresponding to those for DCCHs increased by 4.8, 9.5, and 5.5 %. The patterns for radiotherapy planning systems (RTPs) and other equipment are shown in Table 2. X-ray simulators were installed in 56.7 %, computed tomography (CT) simulators in 83.3 %, and RTPs in 97.3 % of the DCCHs, while the corresponding percentages for the other RT facilities were 44.2, 70.4, and 94.6 %. A noteworthy difference between the two types of facilities was found in the rates of X-ray simulator and CT simulator installation. Compared with the data for 2007 [3], X-ray simulator ownership at DCCHs decreased by 12.6 %, while CT simulator and RTP ownership increased by 8.2 and 0.5 %, respectively. At the other RT facilities, X-ray simulator ownership decreased by 8.8 % while CT simulator and RTP ownership increased by 13.7 and 0.8 %, respectively.

The distribution of annual patient load per linac in Japan is shown in Fig. 1. The patient load at 19.4 % of DCCHs and 4.6 % of the other RT hospitals exceeded the JBBG warning level of 400 patients per linac, but the average patient load per linac at the other facilities was below that level. Compared with the data for 2007 [2], the rate of facilities exceeding the JBBG warning level (400 patients per linac) decreased at both DCCHs (−0.8 %) and the other RT facilities (−0.7 %). However, the average number of total patients per facility increased at both DCCHs (1.6 %) and the other RT facilities (5.9 %).

Staffing patterns and patient loads

Staffing patterns and patient loads in Japan are detailed in Table 3. The figures for total FTE ROs were 666.3 for DCCHs and 273.1 for the other RT facilities, while the corresponding average numbers of FTE ROs per facility were 1.8 and 0.8 and for patient load per FTE RO 225.5 and 247.6. The distribution of annual patient load per FTE RO in Japan is illustrated in Fig. 2. More than 300 patients per RO (JBBG warning level) were treated in 23.3 % of DCCHs and in 10.7 % of the other facilities. Figure 3 shows the distribution of facilities by patient load per FTE RO, with the largest number featuring a patient per FTE RO level in the 100–149 range for DCCHs and the other

Table 2 Items of equipment, their function and patient load per unit of equipment in designated cancer care hospitals and other radiotherapy hospitals

	DCCHs (n = 365)		Comparison with 2007	Other RT facilities (n = 335)		Comparison with 2007	p value (95 % CI)	Total (n = 700)	
	n	%	%	n	%	%		n	%
Linac	496	98.6[a]	0.6[c]	320	90.4[a]	−0.4[c]	<0.0001[f]	816	94.7[a]
With dual energy function	390	78.6[b]	3.8[c]	196	61.3[b]	4.8[c]	<0.0001[f]	586	71.8[b]
With 3D-CRT function (MLC width ≤1.0 cm)	439	88.5[b]	13.2[c]	224	70.0[b]	9.5[c]	<0.0001[f]	663	81.3[b]
With IMRT function	256	51.6[b]	15.2[c]	81	25.3[b]	5.5[c]	<0.0001[f]	337	41.3[b]
Average no. linac per facility	1.4	–	4.7[e]	1.0	–	0.4[e]	<0.0001 (0.3, 0.4)[g]	1.2	–
Annual no. patients per linac	301.3[d]	–	1.6[e]	185.2[d]	–	5.9[e]	<0.0001 (86.8, 133.9)[g]	255.8[d]	–
^{192}Ir RALS (actual use)	116	31.8[a]	2.3[c]	14	4.2[a]	−1.2[c]	<0.0001[f]	130	18.6[a]
X-ray simulator	211	56.7[a]	−12.6[c]	150	44.2[a]	−8.8[c]	0.0009[f]	361	50.7[a]
CT simulator	324	83.3[a]	8.2[c]	251	70.4[a]	13.7[c]	<0.0001[f]	575	77.1[a]
RTP computer	854	97.3[a]	0.4[c]	417	94.6[a]	0.8[c]	0.0757[f]	1,271	96.0[a]

DCCH designated cancer care hospital, *RT* radiotherapy, *CI* confidence interval, *Linac* linear accelerator, *IMRT* intensity-modulated radiotherapy, *RALS* remote-controlled after-loading system, *CT* computed tomography, *3D-CRT* three-dimensional conformal radiotherapy, *RTP* radiotherapy planning

[a] Percentage of facilities which have this equipment

[b] Percentage calculated from the number of systems using this function and the total number of linac systems

[c] Comparison with the data of 2007, calculated using the formula: data of 2009 (%) − data of 2007 (%)

[d] Percentage calculated from the number of patients and the number of linac units. Facilities without linacs were excluded from the calculation

[e] Rate of increase compared with the data of 2007, calculated using the formula: $\frac{\text{data of 2009 } (n) - \text{data of 2007 } (n)}{\text{data of 2007 } (n)} \times 100$ (%)

[f] χ^2 test

[g] Student's t test

RT facilities. Facilities with less than 1 FTE RO still account for about 31.2 % of DCCHs and 65.7 % of the other RT facilities. The average numbers of FTE ROs per facility and full-time JASTRO-certified ROs per facility at DCCHs increased by 11.5 and 6.7 %, respectively, compared with 2007 data, and for the other RT facilities, those numbers increased by 18.9 and 22.3 %. The annual patient load per FTE RO, on the other hand, decreased by 4.9 % at DCCHs and 9.4 % at the other RT facilities.

The total numbers of FTE RTTs were 1175.7 for DCCHs and 660.2 for the other RT facilities, and the corresponding average numbers of RTTs per facility were 3.2 and 2.0, while the patient loads per FTE RTT were 127.8 and 102.4. The distribution of annual patient load per FTE RTT in Japan is shown in Fig. 4. More than 200 patients per RTT (JBBG warning level) were treated in 11.0 % of DCCHs and in 7.5 % of the other RT facilities, while Fig. 5 shows the distribution of facilities by patient load per FTE RTT. The largest number of facilities featured a patient per FTE RTT level in the 100–119 range for DCCHs and the other RT facilities. The total numbers of FTE MPs and FTE RT nurses were 74.6 and 392.8, respectively, for DCCHs and 43.0 and 228.4 for the other RT facilities.

Distribution of primary disease sites and palliative treatment

Table 4 shows the distribution of primary disease sites and palliative treatment at DCCHs and the other RT facilities. The most common disease site at DCCHs and the other RT facilities was the breast. Head/neck, esophagus, liver/biliary tract/pancreas, gynecologic, urogenital, prostate, hematopoietic/lymphatic, and skin/bone/soft tissue cancers were treated at higher rates at DCCHs than at the other RT facilities. The rates for other cancers were the reverse. Compared with the data for 2007, the percentage of breast cancers increased the most at DCCHs (1.4 %), and at the other RT facilities the percentage of head/neck and breast cancers increased significantly (2.4 and 2.3 %).

Brain metastasis was treated at higher rates at the other RT facilities (14.7 % of total patients) than at DCCHs (6.9 % of total patients), while the reverse was true for

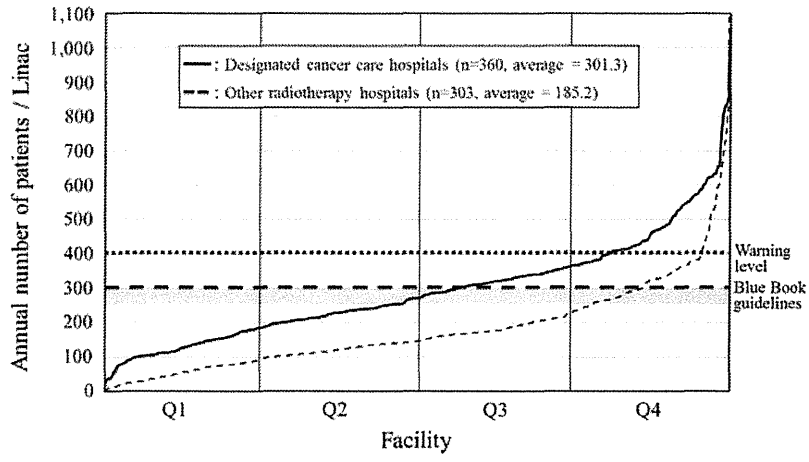

Fig. 1 Distribution of annual patient loads per linear accelerator in designated cancer care hospitals and the other radiotherapy facilities. *Horizontal axis* represents facilities arranged in order of increasing value of annual number of patients per treated equipment within facilities. *Q1* 0–25 %, *Q2* 26–50 %, *Q3* 51–75 %, *Q4* 76–100 %

Table 3 Structure and personnel of designated cancer care hospitals and other radiotherapy hospitals

	DCCHs ($n = 365$)	Comparison with 2007[a] (%)	Other RT facilities ($n = 335$)	Comparison with 2007[a] (%)	p value[b]	Total ($n = 700$)
Facilities with RT beds	190	–	108	–	–	298 (42.6)
Average no. RT beds per facility	4.2	−1.5	2.2	11.5	–	3.3
Total (full + part-time) RO FTE	666.3	–	273.1	–	–	939.4
Average no. FTE ROs per facility	1.8	11.5	0.8	18.9	<0.0001	1.3
JASTRO-certified RO (full-time)	422	–	109	–	–	531
Average no. JASTRO-certified ROs per facility	1.2	6.7	0.3	22.3	<0.0001	0.8
Annual no. patients per FTE RO	225.5	−4.9	247.6	−9.4	<0.0001	231.9
Total (full + part-time) RT technologist FTE	1175.7	–	660.2	–	–	1836.0
Average no. FTE RT technologists per facility	3.2	16.8	2.0	9.1	<0.0001	2.6
Annual no. patients per FTE RT technologist	127.8	−9.2	102.4	−1.3	<0.0001	118.7
Total (full + part-time) medical physicist FTE	74.6	77.7	43.0	62.9	–	117.6
Total (full + part-time) RT nurse FTE	392.8	29.1	228.4	20.1	–	621.2

DCCH designated cancer care hospital, *RT* radiotherapy, *RO* radiation oncologist, *FTE* full-time equivalent (40 h/week only for RT practise), *JASTRO* Japanese Society for Therapeutic Radiology and Oncology

[a] Rate of increase compared with the data of 2007, calculated using the formula: $\frac{\text{data of 2009 } (n) - \text{data of 2007 } (n)}{\text{data of 2007 } (n)} \times 100\ (\%)$

[b] Student's t test

bone metastasis (11.3 and 12.8 %, respectively). Compared with the data for 2007, the rate of brain and bone metastasis decreased in both DCCHs (−0.7 and −0.9 %) and the other RT facilities (−1.0 and −2.3 %).

Discussion

The utilization rate of RT for new cancer patients in Japan is less than half of that in developed countries in Europe and in the USA [14]. However, RT is expected to play an increasingly important role in Japan because the increase in the elderly population is the highest among developed countries. The distribution of facilities by patient load per RO for DCCHs proved to be largely similar to that of the USA in 1989 [15]. While the numbers of ROs in both DCCHs and the other RT hospitals in Japan has increased, the facilities which have less than one FTE RO still account for 31.2 % of DCCHs and 65.7 % of the other RT facilities. In Japan, the majority of facilities still rely on

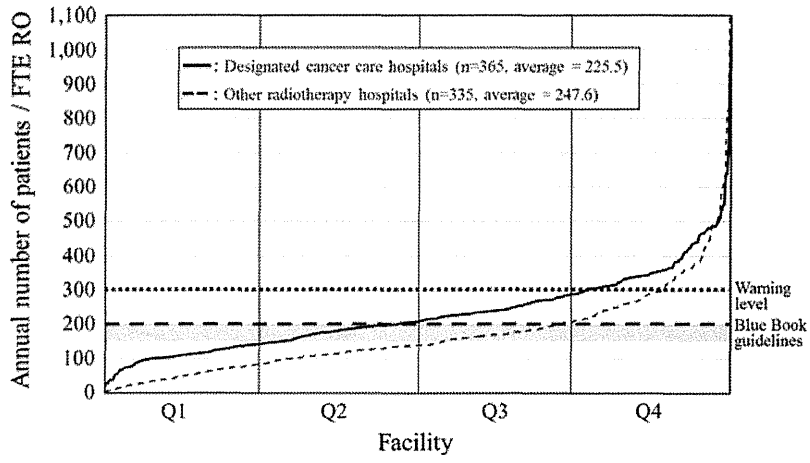

Fig. 2 Distribution of annual patient loads per FTE RO in designated cancer care hospitals and the other radiotherapy facilities. *Horizontal axis* represents facilities arranged in order of increasing value of annual number of patients per FTE RO within facilities. *Q1* 0–25 %, *Q2* 26–50 %, *Q3* 51–75 %, *Q4* 76–100 %. Number of FTE RO for facilities with FTE <1 was calculated as FTE = 1 to avoid overestimating patient loads per FTE RO

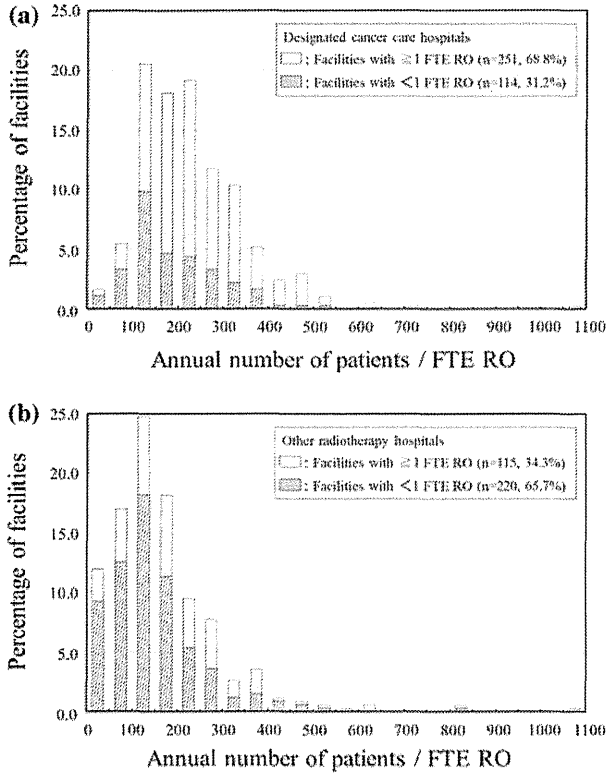

Fig. 3 Percentage of facilities by patient loads per FTE RO in designated cancer care hospitals (**a**) and in the other radiotherapy hospitals (**b**). *Each bar* represents an interval of 50 patients per FTE RO. Number of FTE RO for facilities with FTE <1 was calculated as FTE = 1 to avoid overestimating patient loads per FTE RO

part-time ROs, especially in facilities other than DCCHs, but in western developed countries, most facilities have at least 1 full-time RO. The distribution in Japan of facilities by patient load per RO for the other RT facilities in this study was similar to that in 1990 [15], so that a shortage of ROs has remained a major concern. More than 300 patients per RO (JBBG warning level) were treated in 17.6 % of all RT facilities. This is a matter of critical importance to the quality of radiotherapy.

A new educational system called "Cancer Professional Training Plan" by the Ministry of Education, Culture, Sports, Science and Technology, Japan is being developed in Japan to train specialists for cancer care, including ROs, MPs, medical oncologists, oncology nurses, and palliative care doctors. The average number of RT staff members at DCCHs was greater than that in the other RT hospitals. As noted above, there is still a shortage of Ros, although the numbers have increased. In Japan, many RT hospitals do not have an independent department for RT. One way to increase the number of ROs is to create an independent department for RT. The numbers of MPs in Japan are still smaller than those in western developed countries, and they work mainly in metropolitan areas or academic facilities, such as university hospitals or cancer centers. At present, no national license is available for MPs in Japan, but those with a master's degree in radiation technology or science and engineering can take the accreditation test for MPs administered by the Japanese Board of Medical Physics (JBMP). Compared with ROs and MPs, a sufficient number of RTTs is ensured in Japan. However, there is a significant number of hospitals with less than 1 FTE RTT in both DCCHs ($n = 13$) and the other RT hospitals ($n = 50$). In addition, many RTTs are extremely busy because they must also partially act as MPs. As for equipment, the ownership of equipment for advanced high-precision radiation therapy machines increased compared with 2007 at all RT facilities, especially DCCHs, indicating that the accreditation of DCCHs closely correlates with the maturity of the radiation oncology structure. Further accreditation of DCCHs by the Ministry of Health, Labor, and Welfare would be a move in the right direction towards a more balanced geographic consolidation of RT facilities in Japan.

The findings of this study show that, on a regional basis, DCCHs were located in the most suitable areas. There were

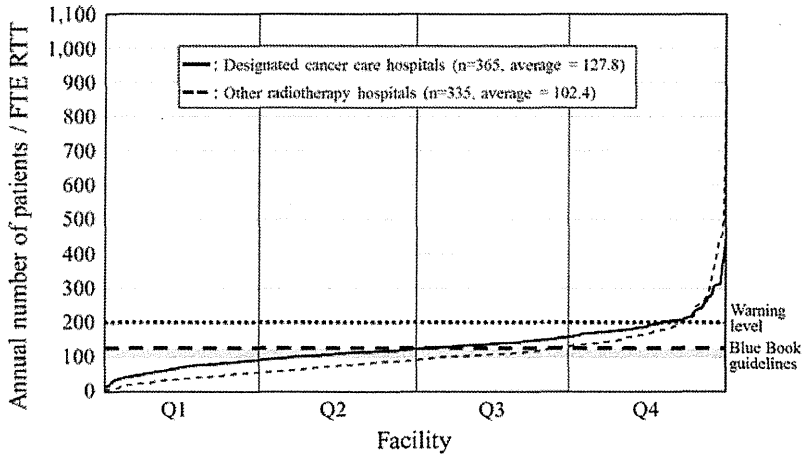

Fig. 4 Distribution of annual patient loads per FTE RTT in designated cancer care hospitals and the other radiotherapy facilities. *Horizontal axis* represents facilities arranged in order of increasing value of annual number of patients per FTE RTT within facilities. *Q1* 0–25 %, *Q2* 26–50 %, *Q3* 51–75 %, *Q4* 76–100 %. Number of FTE RTT for facilities with FTE <1 was calculated as FTE = 1 to avoid overestimating patient loads per FTE RTT

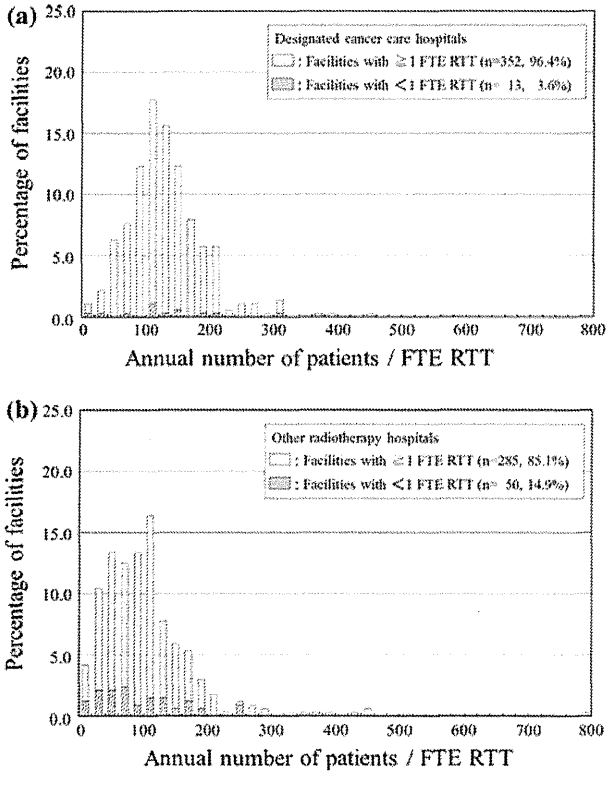

Fig. 5 Percentage of facilities by patient loads per FTE RTT in designated cancer care hospitals (**a**) and in the other radiotherapy hospitals (**b**). *Each bar* represents an interval of 20 patients per FTE RTT. Number of FTE RTT for facilities with FTE <1 was calculated as FTE = 1 to avoid overestimating patient loads per FTE RTT

388 DCCH facilities by the end of fiscal year 2011 because some further university facilities with many patients undergoing RT had been certified as DCCHs since the previous survey, while some small-scale facilities were not certified as DCCHs by the Ministry of Health, Labor, and Welfare. In terms of nationwide distribution, there seem to be enough RT facilities in Japan. On the other hand, the RT potential of RT facilities other than DCCHs in Japan remains unrealized because of personnel shortages. The most frequent primary disease site treated with RT at the other RT facilities changed from lung/trachea/mediastinum to breast, compared with the data for 2007, while at DCCHs, the most frequently treated primary disease site, the breast, remained unchanged from 2007. Finally, the number of patients with brain and bone metastasis did not increase since 2007.

To evaluate medical care systems for cancer at regular intervals, it is very important to collect detailed information on all cancer care facilities. In Japan, the structural data for all RT facilities is regularly surveyed by JASTRO. In addition, the procedures and the outcome data of cancer care for patients undergoing RT have been conducted by PCS every 4 years, but insufficient outcome data is collected. In the USA, a National Cancer Data Base was established in 1989 and since then has been collecting comprehensive data on cancer care, and this database is used as the quality indicator for improvements in the processes and outcomes of cancer care [16, 17]. We have established a Japanese National Cancer Database based on the RT data in Japan and we are preparing to use this system for the collection of cancer care data.

In conclusion, the RT structure of DCCHs in Japan showed more maturity than that of other RT facilities in terms of equipment, functions, and staff. However, there is still a shortage of personnel (ROs, RTTs, MPs, RT nurses, and so on) in radiation oncology in Japan. The structure survey data presented and discussed here seemed to be both fundamental and important for a clear and accurate understanding of the medical care system for radiation oncology in Japan. As this survey data makes clear, a

Table 4 Primary sites of cancer, brain metastasis, and bone metastasis treated with RT in designated cancer care hospitals and the other radiotherapy hospitals

Primary site	DCCHs ($n = 344$)		Comparison with 2007[a]	Others ($n = 300$)		Comparison with 2007[a]	p value[b]	Total ($n = 644$)	
	n	%	%	n	%	%		n	%
Cerebrospinal	4,719	3.9	0.2	4,342	8.5	−1.1	<0.0001	9,061	5.8
Head and neck (including thyroid)	13,084	10.9	−0.2	5,021	9.8	2.4	<0.0001	18,105	9.8
Esophagus	7,306	6.1	−0.4	2,288	4.5	−0.6	<0.0001	9,594	6.0
Lung, trachea, and mediastinum	21,600	18.0	−0.6	10,707	21.0	−0.5	<0.0001	32,307	19.5
Lung	19,532	16.2	−0.6	9,659	18.9	0.7	<0.0001	29,191	17.3
Breast	27,706	23.0	1.4	12,128	23.8	2.3	0.0008	39,834	21.5
Liver, biliary, tract, and pancreas	4,733	3.9	−0.1	1,908	3.7	0.3	0.0577	6,641	3.8
Gastric, small intestine, and colorectal	5,693	4.7	−0.2	2,586	5.1	−0.4	0.0029	8,279	5.1
Gynecologic	6,851	5.7	0.0	1,365	2.7	−0.6	<0.0001	8,216	4.9
Urogenital	16,641	13.8	0.7	6,409	12.6	−0.2	<0.0001	23,050	13.0
Prostate	12,830	10.7	0.9	5,089	10.0	0.6	<0.0001	17,919	9.6
Hematopoietic and lymphatic	6,176	5.1	−0.3	1,773	3.5	−0.1	<0.0001	7,949	4.8
Skin, bone, and soft tissue	3,014	2.5	−0.1	1,079	2.1	−0.7	<0.0001	4,093	2.7
Other (malignant)	1,359	1.1	−0.2	582	1.1	−0.3	0.8388	1,941	1.4
Benign tumors	1,407	1.2	−0.3	813	1.6	−0.4	<0.0001	2,220	1.6
Pediatric < 15 years (included in totals above)	900	0.7	0.0	192	0.4	−0.1	<0.0001	1,092	0.6
Total	120,289	100.0	0.0	51,001	100.0	0.0		171,290[c]	100.0
Metastasis	($n = 365$)			($n = 335$)				($n = 700$)	
Brain	10,361	6.9	−0.7	9,973	14.7	−1.0	<0.0001	20,334	10.4
Bone	19,293	12.8	−0.9	7,613	11.3	−2.3	<0.0001	26,906	13.6

[a] Comparison with the data of 2007, calculated using the formula: data of 2009 (%) − data of 2007 (%)

[b] χ^2 test

[c] Number of total new patients is different with these data, because no data on primary sites were reported by some facilities

national policy is needed to improve the establishment of DCCHs and overcome the shortage of personnel for cancer care.

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Conflict of interest The authors declare that they have no conflict of interest.

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