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).

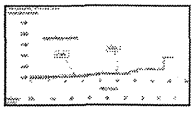

Figure 1

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.

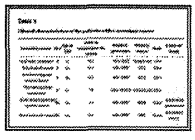

Table 1

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

Go to:

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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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

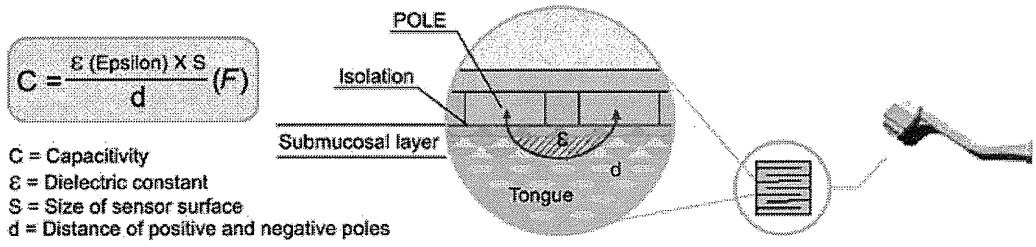

Figure 1 Measurement of the moisture content of the submucosal layer (about 50 μm under the mucosal surface) of the tongue was based on the principle of a condenser. The formula shown was used for calculation. As the value of '*S*' and '*d*' is constant, changes in '*C*' depend solely on '*ε*'. When 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.

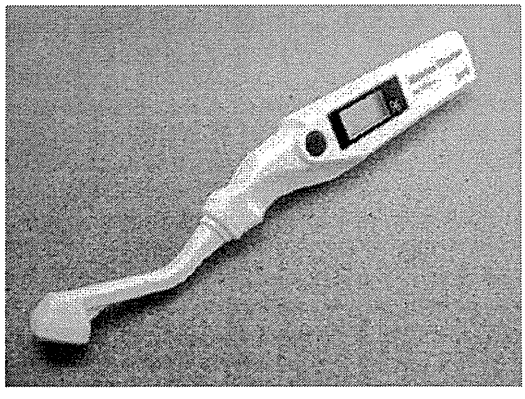

Figure 2 Mucus III device. Mucus III device measures 21.5 mm (width), 238 mm (length), and 41 mm (height), and weights 60 g.

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).

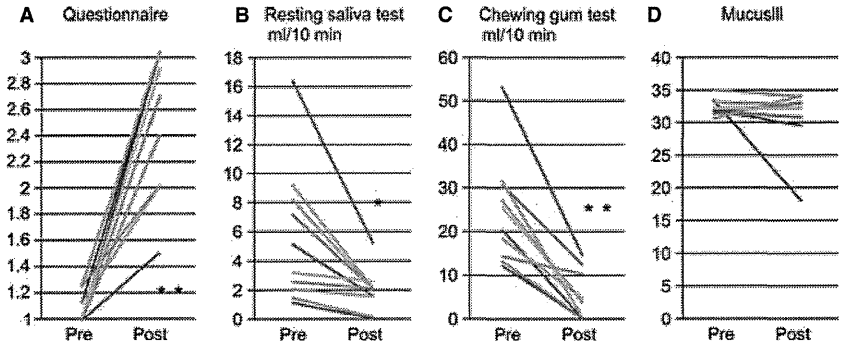

Figure 3 Results of the dry mouth questionnaire (A), resting saliva test (B), chewing gum test (C), and Mucus III test (D) before and immediately after radiotherapy ($n = 10$). *$P < 0.05$, **$P < 0.001$.

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

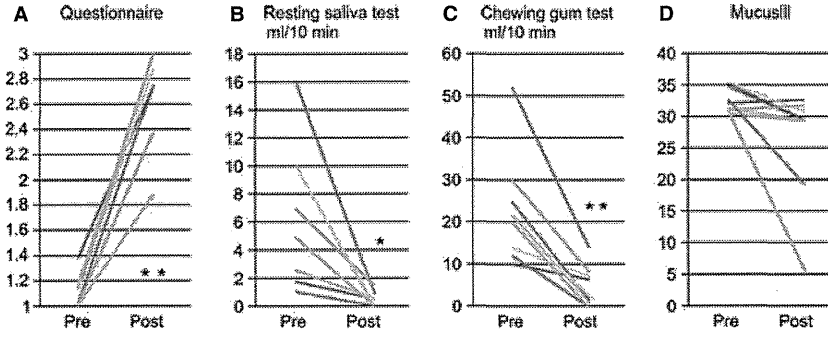

Figure 4 Results of the dry mouth questionnaire (A), resting saliva test (B), chewing gum test (C), and Mucus III test (D) before and 3 months after radiotherapy ($n = 9$). *$P < 0.05$, **$P < 0.001$.

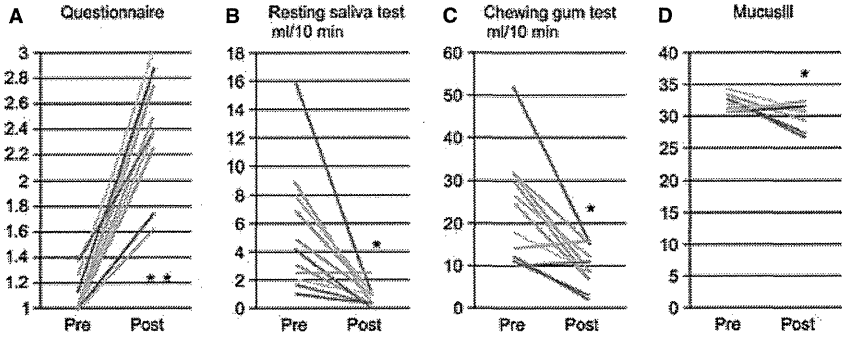

Figure 5 Results of the dry mouth questionnaire (A), resting saliva test (B), chewing gum test (C), and Mucus III test (D) before and 12 months after radiotherapy ($n = 11$).*$P < 0.05$, **$P < 0.001$.

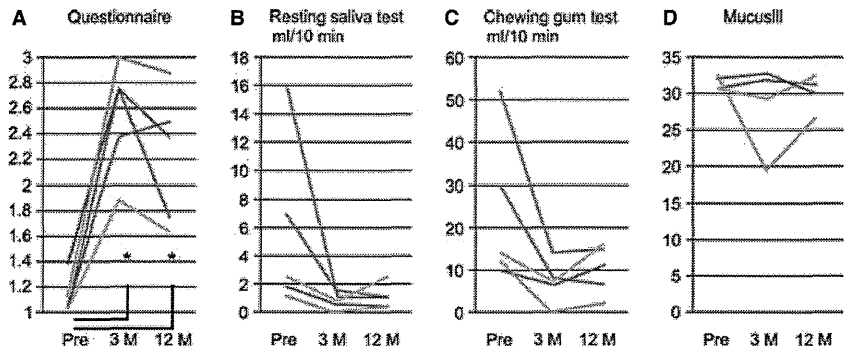

Figure 6 Results of the dry mouth questionnaire (A), resting saliva test (B), chewing gum test (C), and Mucus III test (D) before and 3 and 12 months after radiotherapy ($n = 5$). $^*P < 0.05$.

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.

● 特 集 ● 脳腫瘍に対する治療の現状と展望

悪性グリオーマに対する放射線治療の現状と展望

寺原 敦朗*

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Current Situation and Future Prospects of Radiotherapy for Malignant Gliomas: Atsuro Terahara (*Dept. of Radiology, Toho University Omori Medical Center*)

Summary

Prognosis of malignant gliomas remains poor, although adjuvant radiotherapy increases survival time. To improve treatment outcomes, high-precision radiotherapy techniques such as three-dimensional conformal radiotherapy, stereotactic irradiation, intensity modulated radiotherapy, and charged particle radiotherapy have been developed for dose distribution optimization and dose escalation. Improvements in clinical outcomes with these new treatment strategies have been reported; however, the efficacy of these treatment strategies has not yet been verified in randomized trials. Further development of radiation delivery techniques, including boron neutron capture therapy, and ways of achieving more adequate target volume delineation using modern multimodality imaging technology are currently being intensively investigated to further improve patient outcomes. Key words: Malignant glioma, Radiotherapy, Dose escalation, High-precision radiotherapy, Corresponding author: Atsuro Terahara, Department of Radiology, Toho University Omori Medical Center, 6-11-1 Omori-nishi, Ota-ku, Tokyo 143-8541, Japan

要旨 悪性グリオーマに対して，放射線治療により生存期間の延長は得られているものの，生存率はまだ低く，そのさらなる向上をめざした試みが行われてきた。三次元原体照射や定位放射線照射，強度変調放射線治療，粒子線治療といった高精度照射技術を用いた線量分布の改善および線量増加がその一つの手段として試みられており，期待される結果はでてきているものの，明らかな有用性を証明するには至っていないのが現状である。さらなる照射技術の改善や画像診断の進歩による照射範囲設定や線量分布の最適化，また一方で中性子捕捉療法の発展に期待がもたれる。

はじめに

グリオーマの治療において放射線治療は手術および化学療法と並んで，重要な役割を果たしている。グリオーマのなかでも，今回は特に悪性グリオーマ［退形成性星細胞腫: anaplastic astrocytoma (AA) および神経膠芽腫: glioblastoma multiforme (GBM)］に対する放射線治療のこれまでと現状，展望について概説する。

悪性グリオーマに対する放射線治療は，主に術後の補助療法として用いられてきた。1970年代に術後照射の有用性が示されたが，当時は画像診断が発達していなかったこともあり，全脳照射が主に使用されていた[1,2]。非照射群では4〜5か月であった中間生存期間が，照射群では9〜10か月程度に延長していた。その後，CT，MRIといった画像診断の発達により，腫瘍の存在部位や範囲を特定しやすくなったことと，腫瘍の浸潤範囲や再発部位の検討により，全脳照射は必ずしも必要ないことがわかってきたこと[3,4]，さらにShapiroらが報告したBTCG 80-01試験の結果，全脳照射60 Gyと全脳に43 Gy照射後，腫瘍部に縮小して60 Gyまで追加照射した場合とで成績に差が認められなかったことなどから[5]，拡大局所照射40〜50 Gy＋局所への追加照射による計60 Gyが広く用いられる標準的な照射方法となっている。化学療法の併用については，現在は経口投与も可能なテモゾロマイドの併用が標準となっている[6]。しかし，その有用性を示したStuppらのEORTC-NCIC試験でも，GBMに対するテモゾロマイド併用群の中間生存期間は14.6か月にすぎない。

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このように，放射線治療を加えることにより生存期間の延長は得られたものの，未だに生存率は低く，そのさらなる向上をめざす試みが行われてきた。放射線治療のめざすところは，腫瘍に対してできるだけ多くの線量を照射することにより腫瘍の制御率を上昇させつつ，周囲の正常脳組織に対しては悪影響を起こさないことである。悪性グリオーマの放射線治療において課題となっている問題点は，①どの範囲に照射のターゲット（clinical target volume: CTV）を設定するべきか，②どのような方法を用いて照射を行うのか，③線量（および分割法）はどうするのがよいのか，④周囲の正常脳組織にはどこまで照射が許されるのかといったところであろう。

局所への線量増加を直接的にめざして術中照射や組織内照射が行われたが，明らかな治療成績の向上は確認されておらず，また適応症例が限られ，手技的な問題もあり，広く行われるには至っていない[7-10]。そこで本稿では，外照射による放射線照射技術を中心に解説したい。

Ⅰ．三次元原体照射

外照射の総線量は60 Gyが標準的な線量と考えられ，広く用いられているが，その根拠としては1970年代に施行された臨床試験の結果が未だに引用されている。Walkerらの報告したBTSG試験において，全脳照射45～60 Gyの範囲では，4～10か月と線量が高いほど生存期間が延長する傾向が認められた[11]。この報告は無作為比較試験ではなかったことから，1980年代半ばに無作為比較試験MRC/BR2が行われた。45 Gy/20 Frと60 Gy/30 Frを比較したものである。これらは全脳照射ではなく，拡大局所照射（45 Gy群）と拡大局所照射＋局所照射（60 Gy群）が用いられ，中間生存期間がそれぞれ9か月と12か月であり，60 Gy群で有意に延長していた[12]。これらの結果から，60 Gyまでの線量増加は生存期間延長に寄与していると考えられた。

Nelsonらによって報告されたRTOG7401/ECOG1374試験においては，全脳照射60 Gyとそれに10 Gyのboostを行った群との比較も行われている。両群間で生存期間に差は認められず，60 Gy以上の線量増加の有効性は否定されているが，これは1970年代のデータである[13]。

1980年代の後半ごろから，CTを用いた治療計画による三次元原体照射法が行われるようになり，二次元治療計画の時代に比較してターゲットへの線量集中性が改善してきた。この技術を用いた80～90 Gy程度までの線量増加が試みられてきた。東京大学の中川らは，1998年にGBMに対して線量増加を行った治療結果を報告している。1991年以降の90 Gyまで照射した群では，局所再発は減少したものの播種が多く認められ，結果的に生存率の向上には結び付いていない[14]。その後，同じ東京大学における治療成績を田中らが2005年に報告している。1990年以降の80～90 Gyまで照射を行った高線量群で，それ以前の通常線量である60 Gy群に比較して生存期間の有意な延長が認められており，GBMでは通常線量群の中間生存期間が12.4か月であったのに対して，高線量群では16.2か月，AAでは通常線量群で22.3か月，高線量群では中間生存期間に達していなかった[15]。Chanらの2002年の報告では，90 Gyまで線量増加を行ったが中間生存期間は11.7か月と通常線量照射での成績と変わりなく，また再発部位も91％は照射野内であった[16]。MRIのT2強調画像における高信号域は必ずしもターゲットには含めておらず，90 Gy照射したplanning target volume（PTV）はgross tumor volume（GTV）＋0.5 cmの範囲と照射野を絞っているにもかかわらず，照射野辺縁や外からの再発が増えていないことから，さらなる線量増加により成績向上が期待できる可能性もあると考察している。

現時点では，三次元原体照射による線量増加の有効性は明らかに確認されたとはいえない。

Ⅱ．定位放射線照射

1990年代から急速に普及していった定位放射線照射を，悪性グリオーマの腫瘍制御率向上をめざして応用する試みもなされてきた。再発病変に対して定位放射線照射を施行することにより，照射部位の局所制御が得られることが多いのは実地臨床においてしばしば経験することである[17]。

定位手術的照射（SRS）に関する第Ⅲ相試験であるRTOG9305の結果が2004年に報告されている[18]。GBMに対して，外照射60 Gyと外照射の前に15～24 GyのSRSを行う群との比較試験である。両群の生存率には差は認められず，再発様式も局所からの再発が多いパターンに変わりはなかったことから，SRSの有用性は確認されなかった。ただし，この試験ではSRSを外照射の前に施行しており，通常と逆の順番であることについての批判もある。2005年に報告されたASTROのevidence-based reviewでもSRSおよび定位放射線治療（SRT）の有用性を示す根拠はないとされているが[19]，後ろ向き試験ではSRSが有用であるとする報告や[20]，再発に対しては局所制御，延命に意義があるとの報告もある[21]。

Ⅲ．強度変調放射線治療（IMRT）

現在，期待されている放射線照射技術の一つである強度変調放射線治療（intensity modulated radiotherapy: IMRT）では，照射野内の強度を変調したビームを多方

向から組み合わせることにより，ターゲットの形に合わせた高線量域を作成しつつ，リスク臓器への線量低減が可能となる。さらに標的体積内同時ブースト（simultaneous integrated boost: SIB）法を用いることで，ターゲット内の残存腫瘍部および再発リスクの高い部位により高い1回線量を与えることが可能となり，途中で照射方法を変更する必要がなく，照射期間を短縮することも可能となり，その効果が期待されている[22,23]。Tsienらは GBM に対するテモゾロマイドを併用した放射線治療において，SIB 法を用いた IMRT による線量増加試験の結果を報告している。その結果，75 Gy/30 回までであれば安全に照射可能であり，中間生存期間 20 か月と良好な成績を報告している[24]。また，この報告ではターゲット設定，特に SIB 法を用いた高線量照射容積の設定におけるメチオニン PET の有用性についても言及されており，他にも MR spectroscopy を用いる方法も報告されている[25]。このように，この技術を用いることによりある程度の線量増加は比較的安全に施行可能と思われ，線量分布の最適化とその結果としての治療成績向上が期待されているが，その有用性を示す無作為比較試験の報告はまだないのが現状である。

Ⅳ．粒子線治療

陽子線や重粒子線（炭素線）などを用いた粒子線治療も試みられており，IMRT よりもさらに良好な線量分布，およびより高い生物学的効果（重粒子線のみ）による腫瘍制御ならびに治療成績の向上が期待されている。Mizoe らは，放射線医学総合研究所で行われた GBM に対する X 線 50 Gy に加える炭素線を用いた boost 線量の増加試験（16.8～24.8 Gy）の結果を報告している。その結果，全体で中間生存期間 17 か月であり，炭素線の線量が高い群で生存率が有意に良好である傾向が認められていた[26]。この結果を踏まえて炭素線単独の線量増加試験が行われ，高線量群で局所制御率は向上したが，照射野が狭いと辺縁再発が発生し，照射野が広いと脳壊死の範囲が増大する傾向がみられ，生存期間の延長は得られてない。Rieken らはハイデルベルクにおける粒子線治療の初期治療効果を報告している[27]。GBM を対象とした phase Ⅱ study である CLEOPATRA trial[28]および再発グリオーマに対する phase Ⅰ/Ⅱ trial である CINDERELLA trial[29]が進行中で，有害事象は少なく安全に治療が行われているが，効果の評価については今後のさらなる症例登録および結果の解析が必要である。

Fitzek らは，GBM に対して X 線および陽子線を用いて accelerated fractionation にて 90 GyE を照射することにより，中間生存期間が 20 か月と良好な成績を報告している[30]。また，Mizumoto らは，筑波大学における GBM に対する陽子線治療において hyperfractionated concomitant boost 法にて 96.6 GyE まで照射した治療成績を報告しており，こちらも中間生存期間 21.6 か月という良好な結果であった[31]が，これらは比較試験ではない。また，外照射技術のなかでは最も良好な線量分布が得られる粒子線を用いた場合でも，照射野辺縁部からの再発や高線量域の拡大による脳壊死リスク増加の問題は解決できておらず，粒子線治療もグリオーマの治療において明らかに有用であることを証明はできていないのが現状である。

Ⅴ．中性子捕捉療法

最後に中性子捕捉療法（Boron neutron capture therapy: BNCT）について触れたい。腫瘍細胞に正常細胞よりも高い濃度のホウ素を取り込ませ，中性子線を照射することで生じるα線とリチウム反跳核によって，腫瘍細胞を比較的選択的に照射する治療法である。この原理を最大限に生かすことが可能となれば，細胞レベルで最も線量分布がよく，また高 LET であることによる生物効果の高さも期待され，最も理想的な治療方法ともいえるものである。

Yamamoto らは 15 例の GBM に対する BNCT の成績として，中間生存期間 25.7 か月という良好な結果を報告しており[32]，臨床的にもその有用性が期待されている。これまでは中性子線が十分に脳深部まで届かないことにより，治療対象が比較的浅い部分に存在している腫瘍に限定され，開頭術が必要であった点（この点は熱中性子よりもややエネルギーの高い熱外中性子を用いることで改善可能）や，ホウ素を腫瘍細胞により選択的に取り込ませる方法などの問題点に加えて，中性子線源として原子炉が必要であり，治療に用いることが必ずしも容易でなかったことから，まだ試験段階の治療法にとどまっていた。そこで，加速器を用いて発生させた中性子を使った BNCT を実現するプロジェクトが各地で進んでおり，京都大学原子炉実験所においてはサイクロトロン中性子源が開発され，2012 年 10 月から臨床試験が開始されている。また，腫瘍細胞に効率的にホウ素を取り込ませるなど他の技術開発も進められており，今後は広く臨床に応用される段階に進むことが期待されている。

ま と め

悪性グリオーマに対して放射線治療により生存期間の延長は得られているものの，生存率はまだ低く，その向上をめざした試みが行われてきた。高精度照射技術を用いた線量増加がその一つの手段として試みられており，

期待される結果はでているが，明らかな有用性を証明するには至っていないのが現状である。さらなる照射技術の改善やそれによる線量分布の最適化，画像診断の進歩による照射範囲設定の最適化，また一方でBNCTの発展に期待がもたれる。

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