cervical cancer, which is unfortunately still a relatively common cancer in our country, many institutions will need to update their accelerators with modern machines; this will contribute to improving the quality of radiation therapy in our country.

The valuable information reported here was derived from six leading institutions in the field of gynecological oncology. This information will be utilized for the improvement of a future prospective clinical trial.

ACKNOWLEDGEMENTS

This article was presented in the 73th Annual meeting of the Japan Radiology Society.

FUNDING

This study was partially supported by the Cancer Research Development Fund (23-A-13, 26-A-4 and 26-A-28). The name of the funding body was the National Cancer Center. Funding to pay the Open Access publication charges for this article was provided by the Cancer Research Development Fund (23-A-13, 26-A-4 and 26-A-28).

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Japanese Journal of Clinical Oncology Advance Access published October 23, 2015

JCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2015, 1–8
doi: 10.1093/jjco/hyv157
Original Article

Original Article

Clinical results of definitive intensity-modulated radiation therapy for oropharyngeal cancer: retrospective analysis of treatment efficacy and safety

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Received 12 August 2015; Accepted 25 September 2015

Abstract

Objective: To evaluate the clinical outcomes of intensity-modulated radiotherapy for patients with oropharyngeal carcinoma.

Methods: Ninety-three oropharyngeal carcinoma patients histopathologically diagnosed with squamous cell carcinoma and treated with definitive intensity-modulated radiotherapy using helical tomotherapy between January 2006 and December 2013 were analyzed. Planning target volume primary and involved nodes was delivered 66–70 Gy at 2 Gy per fraction, while planning target volume prophylactic was delivered 54 Gy using the simultaneous integrated boost technique.

Results: The median follow-up period among the surviving patients was 40 months (range, 13–96). There were 76 males and 17 females with a median age of 60 years (range, 34–80). The disease was Stage II in 13%, Stage III in 10% and Stage IV in 77% of patients. Ninety-two patients received chemotherapy (99%); 68 patients received induction chemotherapy (73%), while 21 received concurrent chemotherapy (23%). The 3-year overall survival, progression-free survival and locoregional control rates were 80, 68 and 79%, respectively. Multivariate analysis identified an advanced T-category (T3–4), having double cancer, and smoking habit as significantly unfavorable factors for overall survival, progression-free survival and both progression-free survival and locoregional control, respectively. Only two patients who achieved disease control required percutaneous endoscopic gastrostomy tubes in the last follow-up. The rate of Grade 2 xerostomia at 2 years was 23%.

Conclusions: Intensity-modulated radiotherapy using helical tomotherapy for patients with oropharyngeal carcinoma provided not only sufficient efficacy, but also preserved parotid function.

Key words: oropharyngeal cancer, squamous cell carcinoma, intensity-modulated radiotherapy, helical tomotherapy, prognostic factor, chemoradiotherapy, Japan

Introduction

Surgery and radiation therapy (RT) have traditionally been the standard treatments for oropharyngeal cancer (OPC) (1). Intensity-modulated radiation therapy (IMRT) was developed in the last decade of the 20th century, and is a system of radiation treatment planning and delivery that allows for more optimal radiation dose distributions (2). Many studies conducted in Western countries have described the application of IMRT to the treatment of OPC (3–7). However, IMRT is not commonly performed in daily clinical practice in Japan, and well-organized studies have not yet been published. The principle advantages of IMRT in the treatment of OPC are the ability to deliver not only a more conformal dose distribution, but also a lower dose to the parotid glands and minimize the incidence of severe xerostomia.

Helical tomotherapy (HT), a novel highly accurate apparatus for IMRT with an image-guided support using suited megavoltage computed tomography (MVCT) (8), is now clinically used at many institutions worldwide. A Tomotherapy Hi-Art system (TomoTherapy, Madison, WI) was installed in our institute, and IMRT for head and neck squamous cell carcinoma (HNSCC) patients was initiated in June 2006.

In the PARSPORT trial (9), a randomized trial conducted in the UK that compared 3D-CRT with IMRT, xerostomia rates were significantly lower in the IMRT group than in the 3D-CRT group. Furthermore, Marta et al. (10) demonstrated IMRT using a systemic review and meta-analysis that the incidence of Grade 2–4 xerostomia was reduced in patients with head and neck cancers. These findings supported the application of IMRT for the preservation of salivary gland function in the treatment of OPC.

We previously reported the outcomes of three-dimensional conformal radiotherapy (3D-CRT) for OPC (11); however, few studies have investigated the outcomes of IMRT for OPC in Japan. Thus, we consider it important to evaluate the clinical outcomes of IMRT for OPC in Japan. The aim of the present study was to investigate the clinical efficacy of IMRT for OPC.

Patients and methods

Patients

The records of 107 patients treated consecutively with IMRT using HT for OPC at Aichi Cancer Center Hospital between January 2006 and December 2013 were reviewed. Eligibility criteria were as follows: biopsy-proven squamous cell carcinoma, no distance metastases, Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0–2 and written informed consent before the treatment. Fourteen patients were excluded from the analysis because of the combined use of 3D-CRT and IMRT ($n = 5$), the postoperative setting ($n = 5$), a prior history of RT for head and neck cancer ($n = 2$), and other reasons ($n = 2$). The remaining 93 patients were entered into this analysis. The staging of OPC was based on the TNM system of the American Joint Committee on Cancer (AJCC) 7th edition. We defined former smokers as those who had not smoked within one year prior to the treatment and current smokers as those who were smoking at the start of the treatment.

Prior to initiation of the treatment, all patients provided a comprehensive medical history and underwent a physical examination and dental evaluation. The staging evaluation included an endoscopic evaluation, palpation of the neck, a complete blood count, positron emission tomography (PET)/CT and cervical magnetic resonance imaging (MRI). We defined simultaneous cancers as those diagnosed <1 year of the diagnosis of OPC and metachronous cancers as those diagnosed >1 year before or after the diagnosis of OPC.

The present study was approved by the Institutional Review Board of our hospital.

Chemotherapy

RT was administered to patients who achieved a partial response (PR) or complete response (CR) after induction chemotherapy (ICT). On the other hand, concurrent chemoradiotherapy (CCRT) was initiated immediately for patient refusal of surgery or inoperable cases. The most commonly used regimens of ICT were 5-fluorouracil (5-FU)/cisplatin (FP). As a general rule, the FP regimen consisted of 5-FU (700 mg/m^2 intravenously) on Days 1–5 and cisplatin (80 mg/m^2 intravenously) on Day 6. Patients without sufficient renal function (serum creatinine levels >1.2 mg/dl) were given carboplatin [area under the blood concentration–time curve: 5; intravenous administration; 5-FU/carboplatin (FB) regimen] instead of cisplatin. These regimens were typically given in a 28-day cycle in the concurrent phase and a 21-day cycle in the sequential phase, and two or three courses were administered. The concurrent chemotherapy regimens were a single agent of cisplatin (25 mg/m^2 weekly or 80 mg/m^2 tri-weekly intravenously) concurrently combined with RT. Other courses of chemotherapy consisting of the continuous intravenous administration of 5-FU at a dose of 800 mg/m^2/24 h for 5 days (Days 1–5) and nedaplatin at a dose of 130 mg/m^2 6 h for 1 day (Day 6) were given approximately every 4 weeks in the alternating setting (FN).

Radiotherapy

All patients were immobilized in a cast, and CT with a 2.5 mm slice thickness was taken for treatment planning. Target objects and normal structures were contoured on a Pinnacle workstation (Pinnacle Treatment System; Philips, Milpitas, CA) or MIM Maestro (MIM software, Inc., Cleveland, OH). MRI images were retrieved on a Pinnacle workstation or MIM Maestro and fused with CT images. The PET/CT images of most patients were evaluated, and were used as a guide for the contours of tumor volumes on workstations. The gross tumor volume (GTV) was defined by perception, palpitation and diagnostic imaging such as CT, MRI and FDG-PET or PET-CT images. The clinical target volume (CTV) primary included the GTV primary with an expansion of 10 mm, and the CTV node included the GTV node with an expansion of 5 mm. If a positive lymph node was >2 cm in diameter or had suspicious findings of extracapsular invasion, CTV1 was included in the GTV node with a minimum 10 mm margin.

Clinical target volume 1 (CTV1) was the sum of the CTV primary and CTV node. Planning target volume 1 (PTV1) was defined as CTV1 with a 5 mm margin in all dimensions. CTV prophylactic was designed to include the lymph node at Levels II–V and retropharyngeal node according to nodal regions as defined by the RTOG consensus guidelines (12,13). In the case of the base of tongue disease or lymphatic involvement on Level II, Level Ib was included in CTV prophylactic. In patients with positive nodes, the supraclavicular region was also included. We regarded CTV prophylactic as CTV2. PTV2 was defined as CTV2 with a 5 mm margin in every direction.

Optimization was performed using the following criteria for dose constraints. All cases were planned using the simultaneous integrated boost method. The planned dose at D95 was prescribed to PTV1 at 66–70 Gy and PTV2 at 54 Gy in 33–35 fractions. Dose constraints for organs at risk and other RT techniques were similar to those described in our previous study (8).

Surgery

Planned neck dissection was generally considered for patients with suspected residual neck disease 1–3 months after the completion of RT. In the case of locoregional recurrence, salvage surgery was performed. Planned neck dissection was not regarded as recurrence, and other surgery for salvage intent was defined as recurrence.

Study design and statistical analysis

Follow-up evaluations after the treatment were typically performed at intervals of 1 month for 1 year and at intervals of 3 months thereafter. When necessary, upper gastrointestinal fiberscopy and PET/CT were performed at least annually during the follow-up. Adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Late toxicity was scored according to the Radiation Therapy Oncology Group morbidity grading scale (14). Percutaneous endoscopic gastrostomy (PEG) tubes were placed at the start of or during the treatment period for 17 patients (18%).

Survival was measured from the start date of any treatment at our hospital to the date of the last follow-up or death from any cause. Locoregional control (LRC) was defined as local and/or regional progression as an event. Concurrent locoregional and distant failures were scored as locoregional failures for the first failure sites. Progression-free survival (PFS) was measured from the start date of any treatment at our hospital until the date of disease progression or death. The overall survival (OS) rates were included all patients including the patients who died of double cancers. OS, LRC and PFS rates were calculated using Kaplan–Meier estimates (15). In a univariate analysis (UVA), gender, age at diagnosis (>60 years vs. ≤60 years), subsite at the primary site (Tonsil vs. Others), disease stage (IV A/B vs. ≤III), T-stage (T3–4 vs. T1–2), N-stage (N2-3 vs. N0–1), concurrent chemotherapy (Yes vs. No), induction chemotherapy (ICT) (Yes vs. No) and smoking status (Ever vs. Never) were entered by the Log-rank test. Cox's proportional hazards model was used in a multivariate analysis (MVA). $P < 0.05$ was considered significant. Factors that showed significance with a P value <0.05 in UVA were entered into MVA. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 2.13.0). More precisely, it is a modified version of R commander (version 1.6-3) that was designed to add statistical functions frequently used in biostatistics (16).

Table 1. Patient characteristics

Factor	*n* (%)
Age (years)	60 (range, 34–80)
Gender	
Male	76 (81.7)
Female	17 (18.3)
Subsite	
Base of the tongue	24 (25.8)
Tonsils	54 (58.1)
Soft palate	5 (5.4)
Pharyngeal wall	2 (2.2)
Unclassifiable	8 (8.6)
T-stage	
1	2 (2.2)
2	54 (58.1)
3	20 (21.5)
4a	15 (16.1)
4b	2 (2.2)
N-stage	
0	13 (14.0)
1	11 (11.8)
2a	9 (9.7)
2b	40 (43.0)
2c	13 (14.0)
3	7 (7.5)
AJCC stage	
I	0
II	12 (12.9)
III	9 (9.7)
IV A	58 (62.4)
IV B	14 (15.1)
Chemotherapy	
Concurrent	21 (22.5)
Induction + concurrent	45 (48.4)
Induction + adjuvant	3 (3.2)
Induction only	16 (17.2)
Induction + concurrent + adjuvant	4 (4.3)
Alternating	3 (3.2)
None	1 (1.1)
Smoking	
Current	31 (33.3)
Former	35 (37.6)
Never	26 (28.0)
Unknown	1 (1.1)

Results

Patient and treatment characteristics

Seventy-five (80.6%) patients were alive at the time of this analysis (March 18, 2015), and the median follow-up period was 39.6 months (range, 13.2–96.3) for surviving patients and 34.7 months (range, 4.5–96.3) for all patients.

The characteristics of the 93 eligible patients are shown in Table 1. Ninety-two out of 93 patients (98.9%) received systemic chemotherapy, with most receiving cisplatin-based chemotherapy regimens. Sixty-eight out of all patients (73.1%) received ICT; the most commonly used regimen for ICT was FP for 64 patients, followed by FB for 3, and the docetaxel/5-FU/cisplatin regimen for 1. Twenty-one patients (22.5%) received CCRT, 20 patients received a high dose (tri-weekly, 80 mg/m^2), while 1 received a low dose (weekly, 20 mg/m^2) of cisplatin. Three patients (3.2%) received alternating chemotherapy; the regimen was FN. Seven patients received adjuvant chemotherapy; three patients received afatinib, three oral S-1 and 1 UFT.

The median total RT doses for PTV1 and PTV2 were 70 Gy (range, 52–70 Gy) and 54 Gy (range, 40–54 Gy), respectively. The median duration of RT was 51 days (range, 40–65 days). Planned neck dissection after definitive radiotherapy was performed on 13 patients (14%), with residual tumors being confirmed histologically in 4.

Treatment outcomes

Eighteen out of 93 patients, (19.4%) died at the time of this analysis. Twelve patients died of the disease, including one patient with treatment-related death; in this case, the patient developed interstitial pneumonia during the period of ICT using the FP regimen and died of respiratory failure. One patient died of double cancer (lung). The remaining five patients died of other causes [one: pneumonia; one: cancerous peritonitis; one: disseminated intravascular coagulation (DIC); and two: unknown].

Twenty-eight patients (30.1%) relapsed; 13 patients at the local site, 5 at the regional site, 3 at the local and regional sites and 7

Table 2. Univariate analysis of overall survival, progression-free survival and locoregional control according to prognostic factors

Variable	*n*	OS		PFS		LRC	
		3-year OS (95%CI)	*P* value	3-year PFS (95%CI)	*P* value	3-year LRC (95%CI)	*P* value
Gender			0.0994		0.11700		0.511
Male	76	0.766 (0.638–0.854)		0.643 (0.519–0.743)		0.781 (0.667–0.860)	
Female	17	0.941 (0.650–0.991)		0.824 (0.547–0.939)		0.824 (0.547–0.939)	
Age (years)			0.103		0.73700		0.947
>60	44	0.740 (0.568–0.852)		0.666 (0.499–0.789)		0.787 (0.629–0.884)	
≤60	49	0.855 (0.698–0.934)		0.691 (0.540–0.801)		0.789 (0.643–0.881)	
Overall stage (Stage IV vs. other)			0.55		0.13200		0.284
IV	72	0.774 (0.645–0.862)		0.643 (0.517–0.744)		0.773 (0.656–0.854)	
≤III	21	0.902 (0.662–0.975)		0.791 (0.528–0.918)		0.840 (0.576–0.947)	
T-stage (T3–4 vs. T1–2)			0.0101*		0.00195*		0.0159*
3, 4	37	0.671 (0.467–0.811)		0.498 (0.323–0.650)		0.668 (0.488–0.797)	
1, 2	56	0.886 (0.763–0.947)		0.800 (0.667–0.884)		0.872 (0.749–0.937)	
N-stage (N2–3 vs. N0–1)			0.366		0.303		0.738
2, 3	69	76.5 (63.1–85.6)		0.641 (0.512–0.745)		0.777 (0.658–0.859)	
0, 1	24	91.5 (70.0–97.8)		0.778 (0.541–0.902)		0.820 (0.585–0.929)	
Primary site (Others vs. tonsil)			0.791		0.279		0.041*
Others	39	0.847 (0.664–0.935)		0.619 (0.437–0.757)		0.683 (0.508–0.807)	
Tonsils	54	0.768 (0.616–0.866)		0.719 (0.578–0.820)		0.867 (0.742–0.935)	
Double cancer			0.00422*		0.323		0.91
Yes	26	0.636 (0.417–0.792)		0.564 (0.350–0.732)		0.760 (0.540–0.885)	
No	67	0.888 (0.779–0.945)		0.730 (0.607–0.821)		0.801 (0.682–0.879)	
Concurrent CHT (yes vs. no)			0.366		0.817		0.963
Yes	22	0.820 (0.685–0.901)		0.687 (0.556–0.786)		0.796 (0.679–0.874)	
No	71	0.718 (0.476–0.862)		0.636 (0.403–0.799)		0.764 (0.522–0.894)	
NAC (yes vs. no)							
Yes	68	0.792 (0.667–0.874)	0.413	0.659 (0.533–0.759)	0.273	0.757 (0.634–0.844)	0.186
No	25	0.805 (0.491–0.936)		0.709 (0.443–0.865)		0.880 (0.673–0.960)	
Smoking (ever vs. never)					0.000347*		0.00781*
Ever	67	Not calculated		0.569 (0.437–0.680)		0.721 (0.593–0.814)	
Never	26			0.962 (0.757–0.994)		0.962 (0.757–0.994)	

n, number of patients; CI, confidence interval; OS, overall survival rate; PFS, progression-free survival rate; LRC, locoregional control rate; CHT, chemotherapy; NAC, neoadjuvant chemotherapy; Not Calculated; because never smokers had no event of death.

*Significantly different ($P < 0.05$)

with distant metastases (lung: four; bone: three; brain, liver and skin: one, respectively). Sixteen patients developed local recurrence: 10 recurred at the same site and 6 at a different site. Of the 21 patients with locoregional recurrence, 17 underwent salvage surgery, including neck dissection and/or salvage surgery at the primary site, and 3 received systemic chemotherapy. Four out of the seven patients with distant metastases received palliative RT and three received systemic chemotherapy.

The 3-year OS, PFS and LRC rates were 80.1% [95% confidence interval (CI) 69.3–87.4%], 67.7% (95% CI: 56.8–76.4%) and 78.9% (95% CI 68.9–86.0%), respectively.

Univariate and multivariate analyses for endpoints

Table 2 shows the results of the UVA for OS, PFS and LRC rates. Patients with double cancer had a significantly poorer 3-year OS rate (63.6 vs. 88.8%, $P = 0.004$, Fig. 1). An advanced T-category (T3–4) was identified as an unfavorable factor for OS ($P = 0.01$), PFS ($P = 0.0016$, Fig. 2) and LRC ($P = 0.008$). The effect of the smoking status on OS could not be assessed because there was no event of death among never smokers. The 3-year LRC rate of patients with tonsillar lesions was higher than that of the other group (86.7 vs. 68.3%, $P = 0.04$).

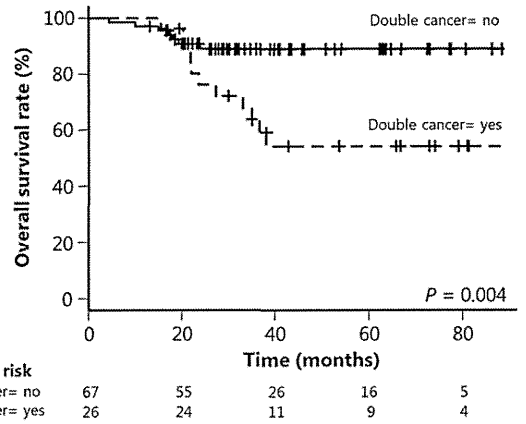

Figure 1. Kaplan–Meier estimates of overall survival in the group divided by double cancer.

Table 3 shows the results of the multivariate analysis for OS, PFS and LRC rates. Double cancer remained a significant predictor of OS ($P = 0.008$), while T-category ($P = 0.04$) and smoking history ($P = 0.014$) were significant predictors of PFS (Fig. 3). Only smoking history was identified as a prognostic factor of LRC ($P = 0.029$).

Double cancer

Twenty-six patients (28%) developed simultaneous or metachronous cancer. Five patients (5%) had two or more cancers other than OPC. The most frequent sites were the stomach and esophagus (nine patients), with the other sites being the colon in four patients, the lung and tongue in three patients each, the rectum in two patients and the hypopharynx, bladder, thyroid, prostate and testis in one patient, each. Of these patients, 14 received curative treatment, including surgery or endoscopic mucosal resection, with one received chemoradiotherapy (CRT) after surgery.

Toxicity

Acute Grade 3 skin and mucosal toxicities were detected in 19 (20.4%) and 42 patients (45.2%), respectively. Regarding hematological toxicities, Grade 3 leukopenia was noted in 21 patients (22.6%). Grade 5 pneumonia was observed with 1 patient. As discussed earlier, since this patient developed interstitial pneumonia during the period of ICT using the FP regimen and died of respiratory failure, we regarded this as a treatment-related death.

As for late toxicities, two patients who were without disease for >12 months after the completion of RT, still required the PEG tube in the last follow-up and were regarded as having Grade 3 dysphasia. We showed the rates of xerostomia among patients with available follow-ups in Table 4. The rate of Grade 2 xerostomia decreased gradually: Grade 2 xerostomia was observed in 44.7% of patients at 6 months, 35.9% at 12 months and 22.6% in 24 months. The mean dose delivered to the mean ipsilateral parotid was 32.2 Gy (range, 14.1–54.2 Gy), while that to the contralateral parotid was 24.1 Gy (range, 14.3–42.8 Gy). Other late toxicities were as follows: 2 with Grade 1 and 1 with Grade 2 hypothyroidism; 1 with Grades 1 and 4 with Grade 2 osteonecrosis of the jaw.

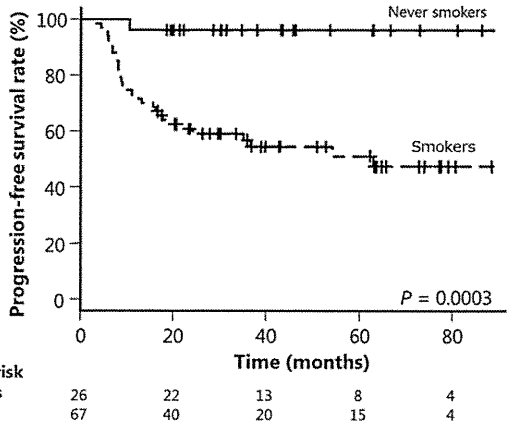

Figure 2. Kaplan–Meier estimates of progression-free survival in the group divided by smoking status.

Discussion

The standard treatment strategies for locally advanced OPC are CRT and surgery with or without postoperative radiotherapy (PORT) (1). Treatment strategies are determined based on treatment efficacy and functional preservation. In the case of bulky disease and unresectable lesions, CRT is typically preferred due to the benefit of organ preservation. In the case of CRT, CDDP is the most widely used. The concurrent use of CDDP has been shown to improve treatment efficacy, especially for local control; however, it is also associated with an increase in the incidence of severe toxicities.

A total of 141 patients from our study on 3D-CRT showed similar findings for survival and disease control (11) (Table 5). Differences between the two groups may have been due to the staging accuracy according to developing diagnostic imaging modalities such as PET and the increasing prevalence of Human papilloma virus (HPV) related to OPC is considered as a favorable prognostic factor. However, we did not obtain exact data for HPV statuses in our cohort. Regarding clinical findings on OPC in studies conducted in Japan, Kano et al. (17) compared the outcomes of surgery with those of CRT in 186 patients with locally advanced OPC gathered from 12 institutions participating in the Head and Neck Cancer Study Group of Japan Clinical Oncology Group (JCOG). No significant differences were observed in the 5-year OS, PFS or local control rates between the two groups (Table 5). Thus, in Japan, as in Western countries, CRT may be regarded as the standard treatment for advanced OPC.

Although there are some problems in terms of time consuming for planning, needs of man power and so on in the planning of IMRT treatment, IMRT has advantage to lead to many cases to radical cure, and IMRT is considered to provide better tumor coverage and minimize the incidence of late toxicities such as xerostomia. IMRT is the standard treatment for OPC and several studies reported that outcomes were similar to those achieved using conventional RT techniques (4). In the PARSPORT study (10), a multi-institutional randomized controlled trial, IMRT had the clear advantage over 2D- or 3D-CRT in that it reduced toxicities, and the same findings were confirmed in a meta-analysis (11). However, few prospective and retrospective studies have been conducted on IMRT for OPC in Japanese institutes. To the best of our knowledge, the outcomes of IMRT for OPC in a relatively large number of patients have not yet been determined in Japanese institutes. Thus, we considered our first study is to have a meaningful impact on the clinical practice of CCRT for OPC patients in Japan.

Table 3. Multivariate analysis of overall survival, progression-free survival and locoregional control according to selected factors

Variable	OS		PFS		LRC	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
T-stage (T3–4 vs. T1–2)	2.71 (0.99–7.40)	0.052	2.16 (1.05–4.45)	0.036*	1.91 (0.77–4.74)	0.17
Primary site (others vs. tonsils)	NA	NA	NA	NA	1.72 (0.71–4.16)	0.23
Double cancer (yes vs. no)	3.645 (1.412–9.41)	0.0075*	NA	NA	NA	NA
Smoking (ever vs. never)	NA	NA	12.20 (1.65–90.48)	0.014*	9.324 (1.251–69.52)	0.029*

NA, not available.
*Significantly different ($P < 0.05$).

The adverse events observed in our cohort appeared to be acceptable based on previously reported findings.

In studies published in Western countries, Garden et al. (2) performed a retrospective study on IMRT in 776 patients with a median follow-up of 54 months. They achieved 5-year OS and LRC rates of 84 and 90%, respectively. Daly et al. (4) also examined 107 patients with a median follow-up of 29 months, and the 3-year LRC and OS rates in their series were 92 and 83%, respectively. Other studies are summarized in Table 6. In the present study, 3-year LRC and OS rates were 79 and 80% with a median follow-up of 34.7 months; therefore, the results obtained in our cohort were consistent with previous findings. In the present study, the rate of Grade 2 xerostomia decreased gradually until 2 years (Table 4). IMRT avoids the delivery of excessive doses to the parotid glands, and thus, preserves parotid function and the quality of life of patients (3,8). In our study, the mean doses delivered to the contralateral and ipsilateral parotid glands were sufficiently decreased (32.2 Gy for the ipsilateral parotid and 24.1 Gy for the contralateral parotid), such that the rate of xerostomia was more manageable than those of previous studies (Table 6). The rate of Grade 2 xerostomia at 1 year in our study was 36%; however, our results may have been overestimated due to the lack of patient records ($n = 39$, 42%). Late dysphagia is another major contributing factor decreasing the quality of life of patients after RT (5,18). Setton et al. (5) reported that 7% of OPC patients treated with IMRT remained PEG-dependent 12 months after the completion of RT. They also identified several clinical factors for PEG-dependency as; an elderly age, female gender, poor performance status and advanced T stage. Since only two patients (2%) remained PEG dependent after the completion of RT in the present study, we achieved sufficient late toxicity regarding dysphagia.

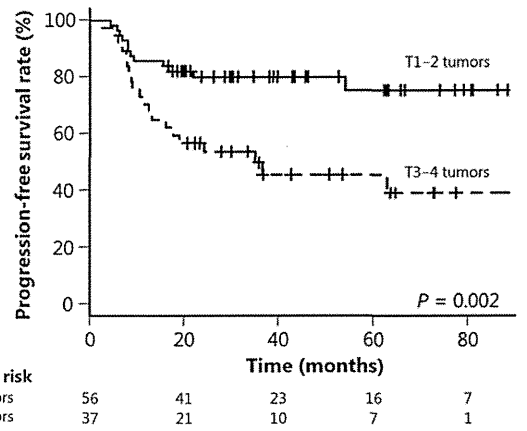

Figure 3. Kaplan–Meier estimates of progression-free survival in the group divided by T-category.

Table 4. Rate of xerostomia after IMRT

Grade	6 months ($n = 47$) (%)	12 months ($n = 39$) (%)	24 months ($n = 31$) (%)
0	1 (2.1)	1 (2.6)	5 (16.1)
1	25 (53.2)	24 (61.5)	19 (61.3)
2	21 (44.7)	14 (35.9)	7 (22.6)

n, number of patients assessable for xerostomia.

Double cancer was identified as a significant predictor of OS. Double cancer in the respiratory tract and upper parts of the digestive tract, so-called upper aero digestive tract (UADT), has also been identified as a poor prognostic factor. Selek et al. (19) previously reported the outcomes of patients with T1-2 OPC, 5-year OS rates were 65%/87% in patients with/ without double cancer of UADT, respectively, and the development of UADT malignancies had a significant impact on survival ($P = 0.018$). Although most patients presented with advanced stage disease in our cohort, 81 (87%) had Stage III or IV; therefore, our results were consistent with these findings. T-category and smoking history were significant predictors of PFS. Only smoking history was a prognostic factor of LRC. None of the never smokers died in our study. Regarding T-category and smoking history, Nichols et al. (20) reported similar findings among patients with an advanced T-category, smoking habit and HPV-16 negative. Kian et al. (21) classified OPC patients into a low-, intermediate- or high-risk group based on four factors: HPV status, pack-years of tobacco smoking, tumor stage and nodal stage. According to their classification, patients with HPV-positive tumors and ≤10 pack-years smoking, or HPV-positive tumors, >10 pack-years smoking and N0–N2a cancer were categorized into the low-risk group. Regarding the Japanese status regarding HPV-oriented OPC, Hama et al. (22) reported findings obtained in a nationwide study conducted to examine the HPV status in OPC patients from 21 institutes participating in the Basic Research Cooperative Group of Head and Neck Cancer. They showed that the prevalence of HPV in OPC markedly increased from 32% (from only one region) during the 2000s (23) to 50.0% during the 2010s. Although we did not have any distinct data regarding the presence of HPV infection in our cohort, the never-smoker group ($n = 26$) of our series may have included patients in the low-risk group (never smoker and N0–2a, $n = 12$, 13%). The number of HPV-positive patients in our cohort was expected to be higher than that in our previous study (9). Hama also reported that the features of HPV-positive OPC had a favorable outcome on definitive RT (21). Thus, the role of RT, especially IMRT, may become more essential in the future.

This study had several limitations, most of which were related to its retrospective nature. First, patients were treated by a consistent group

Table 5. Comparison of outcomes of oropharyngeal cancer patients in the present study those in Japanese institutes

Author	Year	Methods		OS		PFS		LRC	
			n	OS (%)	*P* value	PFS (%)	*P* value	LRC (%)	*P* value
Tomita et al (11)	1993–2008	3D-CRT	141	74.7 (3 years)	0.107	62.0 (3 years)	0.315	74.0 (3 years)	0.615
Present study	2006–13	IMRT	93	80.1 (3 years)		67.7 (3 years)		78.9 (3 years)	
Kano et al (17)	2005–07	CCRT	93	71.4 (5 years)	0.762	54.4 (5 years)	0.531	80.3 (5 years)	0.399
		Surgery	93	69.8 (5 years)		51.0 (5 years)		75.2 (5 years)	

3D-CRT, three-dimensional conformal radiation therapy; CCRT, concurrent chemoradiotherapy.

Table 6. Reported series of clinical outcomes of definitive IMRT for oropharyngeal cancer patients

Author (year)	Number of patients	Median F/U (months)	Definitive (%)	Clinical Stage (%)			Primary site (%)		CRT (%)	OS	LRC	Xerostomia
				IV	T3–4	N2–3	Tonsils	Base of the tongue				(≥Grade 2) (%)
Huang (2007) (3)	71	33	100	76	32	55	35	60	100	83% (3 years)	90% (3 years)	33 (at last F/U)[a]
Daly (2009) (4)	107	29[b]	79	85	47	83	44	51	87	83% (3 years)	92% (3 years)	–
Setton (2012) (5)	442	37[b]	93	73	31	69	50	46	91	84.9 (3 years)	LF 5.4% (3 years)[c]	13 (at 1 year)
Sher (2012) (6)	163	36	91	75	34	77	50	45	100	86% (3 years)	86% (3 years)	–
Garden (2013) (7)	776	54	100	74	26	71	48	46	54	84% (5 years)	90% (5 years)	–
Present study (2014)	93	35	100	77	40	77	55	25	99	80% (3 years)	79% (3 years)	36 at (1 year)

[a]62% (<2-year F/U).
[b]Surviving patients.
[c]Three-year cumulative incidence of local failure.

of radiation, surgical and medical oncologists, but were not selected or treated on a prospective protocol. Second, the distribution of disease stage was inconsistent and there were several kinds of chemotherapy regimens in this study, so this bias might make obscure the efficacy of definitive IMRT. Third, although the HPV status is essential for treatment evaluation of the OPC, it was not available for all patients. As examination of HPV status was not allowed by insurance inspection under the present conditions, there is no medical records in our hospital. Therefore, we were not able to analyze it this time, so we will consider examination in the future. Finally, the majority of our patients received ICT, for which the most commonly used regimen was FP. The standard treatment for organ preservation is considered to be CCRT; therefore, the results obtained in this study may decrease compared with that of CCRT. Nevertheless, our results were consistent with previous findings including those for CCRT; thus, ICT followed by definitive IMRT in our study showed acceptable efficacy with sufficiently low toxicity. Since ICT with docetaxel and FP was recently shown to achieve improvements over that with FP alone in locally advanced HNSCC patients (24,25), we will consider these regimens for ICT strategies in future studies.

Minimally invasive treatments adjusted to individual patient risks regarding T, N-stage, smoking status and HPV status may become more important. The JCOG Radiation Therapy Study Group recently conducted a non-randomized confirmatory study of definitive IMRT with a limited field for T1-2M0-1M0 OPC (JCOG1208) (26) in low-risk OPC patients. Reliable findings for definitive IMRT will greatly contribute to the refinement of Japanese practices of RT for head and neck cancer patients. Regarding intermediate-to-high-risk OPC patients, more intensive treatments, such as more intensive cytotoxic agents and molecular target agents with definitive RT, may be required; thus, IMRT may also greatly contribute to minimizing their toxicities.

Conclusions

We herein reported the initial results of definitive IMRT for OPC using IMRT with HT in Japan, which provided sufficiently better tumor control with markedly low toxicities, especially for xerostomia. Further improvements need to be considered in prospective multi-institutional trials in order to acquire reliable evidence for Japanese patients.

Funding

This research was partially supported by the Research for Innovative Cancer Control from Japan Agency for Medical Research and Development, AMED (15ck0106055h0102 and 15ck0106093h0102) and the National Cancer Center Research and Development Fund (25-B-2 and 26-A-4).

Conflict of interest statement

None declared.

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Appendix

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JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2015, 45(3) 235–243
doi: 10.1093/jjco/hyu209
Advance Access Publication Date: 9 December 2014
Review Article

OXFORD

Review Article

Definitive radiotherapy for head and neck squamous cell carcinoma: update and perspectives on the basis of EBM

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Received 29 October 2014; Accepted 19 November 2014

Abstract

Radiotherapy plays an essential role in the management of head and neck squamous cell carcinoma. Radiotherapy has a distinct advantage over surgical procedures in that it could achieve organ and function preservation with an efficacy similar to that of surgical series. To improve the clinical outcomes achievable by radiotherapy, altered fractionated radiotherapy has been prospectively tested for early and intermediate risk diseases, and was previously shown to be beneficial for local control and survival. Radiotherapy alone is insufficient for locally advanced disease; therefore, concurrent chemoradiotherapy is typically performed and plays an important role. A meta-analysis (Level Ia) revealed that the concurrent use of platinum agents appeared to improve tumor control and survival; however, this was accompanied by increases in the rates of both acute and late toxicities. Regarding radiation techniques, intensity modulated radiotherapy evolved in the 1990s, and has been globally used to treat head and neck squamous cell carcinoma patients. Intensity modulated radiotherapy reduces the exposure of normal tissue to radiation while preserving excellent dose coverage to the target volume; therefore, the rate of late toxicities especially xerostomia is minimized. Small size randomized studies and a meta-analysis have provided evidence to support the benefits of intensity modulated radiotherapy over two-dimensional or three-dimensional radiation therapy. Intensity modulated radiotherapy can also preserve quality of life following definitive chemoradiotherapy. Further improvements using intensity modulated proton therapy are warranted.

Key words: intensity modulated radiotherapy, chemoradiotherapy, altered fractionated radiotherapy

Introduction

Radiotherapy (RT) for head and neck squamous cell carcinoma (HNSCC) plays an important role in the preservation of organs and their functions. Small volume tumors, such as those of the T1–2 category, are expected to achieve 70–90% local control with RT (1–4); however, the efficacy of RT alone was shown to be reduced in cases of T3–4 category tumors (5–7). Controversy still surrounds the ability of RT to achieve tumor control and larynx preservation in locally advanced laryngeal and hypopharyngeal cancers. Although concurrent chemoradiotherapy (CCRT) appears to be the mainstay for successful

larynx preservation compared with surgery, increases in late morbidity and controversy in survival benefit with a longer follow-up are serious issues(8,9). Intensity modulated radiotherapy (IMRT) has rapidly evolved in the past two decades, and is considered the standard care of definitive RT for HNSCC (10). Previous studies reported that the rate of late morbidities especially xerostomia appeared to be lower following IMRT (11–16), and improved quality of life (QOL) after RT could be expected (17–20). Thus, the adaptation of IMRT for CCRT represents a reasonable combination to minimize the risk of the associated toxicities. Multi-agent induction chemotherapy containing taxanes and bioradiotherapy has been extensively researched in an attempt to balance treatment efficacy and safety (21–23).

Early stage

Optimal fractionation schedule

Prolonging the duration of RT for HNSCC is known to have a distinct negative impact on clinical outcomes (24–26), and has been attributed to a biological phenomenon, the so-called accelerated repopulation, which is accompanied by the development of radioresistance by tumor cells (27). To improve clinical outcomes, an altered fractionation (AF) schedule that minimizes the treatment duration, has been clinically tested on patients with low and intermediate risk diseases (28–31). A meta-analysis revealed that AF improved both local control and survival over those achieved by the standard fractionated schedule (32).

Early glottis cancer is considered to be an optimal model for presenting the advantages of AF. Definitive RT was previously reported to have acquired sufficient survival outcomes with excellent local control for patients with this cancer, even if salvage surgery for local recurrence was needed. Patients with T1–2N0 glottic cancer typically receive 66–70 Gy over 6.5 weeks on an outpatient basis. AF is expected to improve tumor control, thereby reducing the burden on patients and working staff, and ameliorating the cost of treatment for public insurance. Several retrospective studies have demonstrated the advantages of AF radiotherapy (>2.0 Gy per fraction) for glottis cancer (33,34); however, few prospective studies have been conducted in a multi-institutional setting (Table 1) (29–31). Yamazaki et al. (29) reported that the AF arm in a randomized controlled study from a single institute showed a significant advantage for local control. A total of 180 patients with T1 glottic tumors were entered into this trial; the AF arm ($N = 91$) received 56.25–63 Gy over 5–5.5 weeks with a 2.25 Gy fraction, while the SF arm received 60–66 Gy over 6–6.5 weeks with a 2 Gy fraction. The 5-year local control rate of the AF arm was significantly better than that of the standard fractionation (SF) arm (92 vs. 77% $P = 0.004$). Moon et al. (30) reported the findings of multi-institutional randomized controlled trial (RCT) for T1–2N0M0 glottic cancer. However, this trial was stopped due to poor accrual, because only 156 patients were ultimately registered against the planned 282 patients. The AF arm of 63–67.5 Gy with a 2.25 Gy fraction achieved slightly better local control than that of the SF arm of 66–70 Gy with a 2 Gy (93 vs. 76%; $P = 0.056$). The Radiation Therapy Study Group of the Japan Clinical Oncology Group (JCOG) conducted a multi-institutional RCT trial of the JCOG 0701 to demonstrate the non-inferiority of the efficacy of the AF arm with 2.4 Gy per fraction over the SF arm with 2 Gy per fraction (31). A total of 370 patients were registered in this study until January 2013, and a follow-up will be conducted on January 2016. It is the first multi-institutional RCT trial to investigate the advantage of AF radiotherapy for early glottic cancer, the findings of which are highly anticipated.

Intensity modulated radiotherapy

The incidence of oropharyngeal cancer (OPC) is gradually increasing, while that of human papilloma virus (HPV) infection is also high (35,36). Patients with OPC-related HPV infection have a favorable prognosis (37–39), and radiotherapy plays an important role among the treatment modalities available for these patients. The adaptation of IMRT could reduce the rate of late toxicity especially xerostomia; thus, it is considered a standard method in definitive RT for OPC (40,41). Several RCT have been conducted to demonstrate the advantages of IMRT for HNSCC patients including OPC (11,13). The RTOG 00-22 trial is a prospective single arm trial that tested the efficacy of IMRT using a slightly hypofractionated schedule with 2.2 Gy per fraction for early OPC patients with T1–2N0–1M0 diseases (42). The 2-year survival rate was reported to be 95.5%, with a loco-regional failure rate of only 9%. The 1- and 2-year rates of Grade 2 xerostomia were 25 and 16%, respectively. To further improve QOL, unilateral neck irradiation using IMRT for OPC, with a favorable prognostic factor, is expected to represent an attractive treatment option (43). Al-Mamgani et al. (44) retrospectively evaluated unilateral neck IMRT for early disease in this category in a relatively large series ($N = 185$). The 5-year local control rate was reported to be 91% with 7% Grade 2 xerostomia. Although this was a retrospective

Table 1. Reported series of definitive radiotherapy with altered fractionation for early glottic cancer

Author	Material	Number	Style	Total dose (Gy)	Fraction size (Gy)	LC (%)	OS (%)	Complication rate G3 or more
Robertson (33)	T1–4	118	Retrospective	60	2	55–70/39–62	NR	NR
		15		56.5	2.26	80/	NR	NR
		111		60	2.4	95/75	NR	NR
		37		54	3	81/37	NR	NR
		22		51	3.4	85/40	NR	NR
van der Voet (34)	T1	64	Retrospective	60–66	2	83–85		NR
		79		60, 61.6	2.4, 2.8	90–93		1.8–3.1
		142		62, 65	3.1, 3.25	93		10.9–12.5
Mendenhall (1)	T1–2	304	Retrospective	56.25/63 (T1/2)	2.25	93/75	NR	1.6
Yamazaki (29)	T1	180	Prospective Phase III	56.25/63 (S/L)	2.25	92	87	0
Moon (30)	T1–2	156	Prospective Phase III		2.25	88.5(LPFS)	86.6	0
RTOG 9512 (28)	T2	250	Prospective Phase III	79.6	1.2 bid	78	72	8.5
JCOG 0701 (31)	T1–2	370	Prospective Phase III	60/64.8 (T1/T2)	2.4			

S, small size; L, large size, bid, twice-a-day, LC, local control; LPFS, larynx progression-free survival; OS, overall survival; NR, not reported.

study, limited field IMRT was expected to successfully achieve high local control with a low incidence of xerostomia. The JCOG Radiation Therapy Study Group has now conducted the JCOG 1208 study to test the efficacy of IMRT using a limited target volume (TV) for patients with OPC of the T1–2N0–1 category. In this protocol, contralateral Level II–III area was excluded from prophylactic TV in the case of patients with tonsillar cancer. And only ipsilateral Level IV area was included in TV for patients with N1. This is the first multi-institutional prospective trial using this modified TV for early OPC.

Locally advanced stage

The efficacy of RT alone for locally advanced (LA) disease is lower than that of surgical series. The administration of cytotoxic agents to improve disease control has been practically considered for patients with certain medical conditions (5,23,45–47). CCRT was reported to significantly improve both disease control and survival in several RCTs, and these findings were also supported by meta-analyses (5,45,46,48). RT accompanied with platinum agents is considered the standard treatment for LA-HNSCC (45).

RT with cetuximab [CET; anti-epidermal growth factor receptor (EGFR)] also improved overall survival (OS) and LC over those with RT alone (47,49). In the Bonner trial, Stage III–IV patients were randomly assigned to a bioradiotherapy (BRT) arm or RT arm. The BRT arm showed significant improvements in loco-regional control and OS [hazard ratio (HR) 0.68; $P = 0.005$; HR = 0.74 $P = 0.03$]. No significant difference was observed in the rate of acute toxicities between both arms. Therefore, it is important to note that a direct comparison has not yet been conducted between the results achieved by BRT and CCRT, which is considered the standard treatment for LA-HNSCC (50).

AF has also been shown to increase local control for LA-HNSCC in several RCTs. A meta-analysis of 15 trials with 6515 patients revealed that AF was significantly advantageous for local control and OS (Level Ia) (32). The majority of cohorts were comprised of OPC patients (47.2%) and Stage III patients, who were expected to have relatively good prognoses, and these groups had slightly better OS in the subset analysis.

Although both chemical modulations by CCRT or BRT and dose modifications by AF increase tumor control, they are also accompanied by increased rates of acute and late toxicities due to definitive RT. The adaptation of IMRT should minimize the rates of these toxicities and, as such, is highly recommend for use in an intensive strategy for LA-HNSCC (13,16,20).

Optimal method of chemotherapy

The standard treatment for locally advanced HNSCC still remains concurrent chemoradiotherapy (CCRT) with cisplatin (45). Previous studies reported Level Ia evidence for the efficacy of CCRT (46,48).

MACH-NC trial comprised 93 trials with 17 346 patients, conducted between 1965 and 2000, revealed that the efficacy of CCRT was higher than that of induction or adjuvant chemotherapy (46). The administration of chemotherapy showed a 4.5% absolute benefit in survival and reduced the HR by 12% ($P < 0.0001$). Regarding the timing of chemotherapy, CCRT achieved a 6.5% absolute benefit in 5-year OS, and a 19% reduction in the HR of OS. In that study, induction chemotherapy (IC) led to moderate benefits in OS and had an apparent advantage by decreasing the rate of distant metastasis (46). This study also showed the benefits of CCRT were less in elderly patients ($P = 0.003$).

IC with taxanes containing multi-agents (ITM) was recently reported to be more advantageous for OS and disease control than cisplatin and 5-FU (PF) in RCTs (21,22), and these findings were confirmed by a meta-analysis (23). Several RCTs were previously conducted to compare the efficacy of ITM to that of PF; however, its apparent benefits over that of immediate CCRT have not been reported until now (51–53). One of the weaknesses of the ITM strategy was the significant increase in treatment-induced toxicities, which decreased compliance of following CCRT (54). Approximately half of the ITM cohorts could not receive chemotherapy during radiotherapy (21,22), which may have decreased the efficacy of CCRT. Several studies attempted to test ITM followed by BRT (55,56). In the Bonner trial, RT with CET was reported to induce similar acute toxicities to those of RT alone (49). ITM followed by BRT represents an attractive strategy for managing treatment toxicities without sacrificing efficacy. Ghi et al. (56) performed a randomized Phase II/III trial to test the efficacy of adding IC containing docetaxel, cisplatin and 5-FU. This trial had a 2 × 2 factorial design, in which second randomization of the CCRT arm or BRT arm occurred after first randomization of IC. They reported survival benefits in the ITM arm. Further modifications and optimization are required to balance the efficacies and morbidities of such intensive multidisciplinary treatments.

Role of bioradiotherapy

The Bonner trial reported the significant advantage of BRT toward RT alone in RCT with LA-HNSCC patients (47,49). Only one RCT has demonstrated the benefit of BRT; however, the control arm in this RCT was RT alone, which is not considered a standard treatment for LA-HNSCC. One of the expected merits of BRT is reduced toxicity. In the Bonner trial, acute toxicities were similar between the BRT arm and RT arm. Several randomized Phase II studies compared BRT with CCRT (55,56). The TREMPLIN trial was conducted to test larynx preservation rate of BRT compared with CCRT for patients treated with ITM for LA-HNSCC (55). Local control could not be achieved by 12 patients (21%) in the BRT arm and eight patients (13%) in the CCRT arm; however, this difference was not significant. BRT was shown to have superior compliance over CCRT (71 vs. 43%), and salvage surgery could be performed in six out of nine patients assessed as feasible for surgery in the BRT arm, but in none of the eight patients in the CCRT arm. Consequently, OS rates were similar in both arms. Ghi et al. (56) also conducted a Phase II/III study of randomization of BRT and CCRT arms. This trial also determined the efficacy of ITM with a 2 × 2 factorial design. No significant differences were observed in progression-free survival (PFS) or OS rates between the BRT and CCRT arms.

A systemic review was conducted on 15 trials comprising 1808 patients to compare BRT and CCRT (50). Only three trials were prospective, while the other 12 were retrospective. In this systemic review, CCRT achieved significantly better OS, PFS and LRR than BRT. RTOG 1016, a Phase III trial of BRT versus CCRT for HPV-associated OPC, is currently being conducted (57). This is the first trial to directly compare BRT and CCRT for a favorable risk group. The effectiveness and toxicity of BRT may be demonstrated in this trial, and its findings could also resolve the question as to whether the efficacy of BRT is similar to that of CCRT.

RTOG 0522 trial was designed to compare the CCRT with cetuximab (CET) arm to the CCRT arm (58). The 3-year OS, PFS and loco-regional relapse-free rate (LRF) were similar in both arms; however, the incidence of acute adverse events was higher in the combined arm. These findings suggest that CCRT with anti-EGFR should be tested in clinical trials, and special care should be taken for its clinical use.

To minimize the toxicity of definitive intensive RT, dose reductions using BRT for a favorable group is now being prospectively evaluated

(59). HPV-associated OPC patients are the main target in this trial. Reductions in toxicity are warranted after confirmation of its efficacy in the de-escalation trial.

Larynx preservation

Locally advanced laryngeal (LC) and hypopharyngeal cancers (HPC) have been treated with surgery, while laryngeal preservation (LP) with the aim of preserving the voice and swallowing function without sacrificing survival is considered a reasonable option in clinical practice (Table 2) (5–7,22,60–62). In the 1990s, several RCTs demonstrated the feasibility of the LP strategy (5–7,62,63). Two RCTs compared IC followed by RT with immediate surgery, the Veterans Affairs Laryngeal Cancer Study Group (VALCSG) trial for LC (7) and EORTC 24851 trial for HPC (6). The VALCSG study registered 322 patients with Stage III/IVLC. The IC group received two cycles of 5FU and cisplatin, then responders to chemotherapy were treated with definitive RT. Otherwise patients underwent laryngectomy with or without post-operative RT. In the IC arm, 107 patients (64%) preserved their larynx. The 2-year OS rate of both groups was 68%. In a subgroup analysis, 56% of patients with T4 category tumors and 29% of those with smaller lesions required salvage surgery. In the EORTC 24851 study, 194 patients with T2–4, N0–2b LA-HPC were randomized to an IC arm or immediate surgery arm (6). The DFS rates at 3 and 5 years were 43%/25% for the IC arm and 32%/27% for the surgery arm, respectively. The 3- and 5-year functional LP rates were 64 and 58% for patients with completed treatments from the IC arms. Responses to the LP protocol markedly varied according to the T category (T2 for 82%, T3 for 48% and T4 for 0%). In these two studies, approximately two-thirds of the IC group could preserve the larynxes without sacrificing survival against the surgical series.

RTOG 91-11 study was a RCT conducted to demonstrate the efficacy of three different RT arms including RT alone, IC followed by RT (identical to the VALCSG trial) and CCRT (5,62). A total of 547 patients with Stage III/IV LC were registered in this trial. Its findings were initially reported in 2003 (5), and then updated in 2012 (62). The rates of LP at a median follow-up of 3.8 years and 10.8 years were 83.6 and 81.7% for the CCRT arm, respectively, and were significantly higher than those from the other two arms (70.8 and 67.5% for the IC arm and 65.8 and 63.8% for the RT alone arm). The OS rates at 5 and 10 years did not differ among the treatment groups (55 and 27.5% for the CCRT arm, 59 and 39% for the IC arm and 54 and 31.5% for the RT alone arm). Although failure to achieve local control was lower in the CCRT arm, the rate of toxicity would have considerably increased with a longer follow-up. In this update series, the CCRT arm had better disease control and a higher rate of late toxicity. From the viewpoint of LP, ITM is expected to allow for feasible options, balancing its efficacy and lower toxicity. A multi-institutional consensus panel published guidelines for the conduct of RCTs for LP (64). They recommended the enrollment of patients with T2 or T3 LC or HPC. They also emphasized that clinical and instrumental assessments were essential, and also proposed the endpoint of disease free with a functional larynx, such as *laryngo-esophageal dysfunction-free survival*. Minimum invasive surgery has recently evolved, and objective and functional estimations are needed for comparisons between different treatment modalities including surgical series (60,65).

Role of intensity modulated radiotherapy

The use of IMRT has recently become more widespread, and this modality was supported by novel technological developments in the 1990s (10). Using this technique, conformal dose distributions to the clinical target volume could be achieved with identical dose reductions to the surrounding normal tissue. Several RCTs demonstrated that IMRT could reduce the rate of G2 xerostomia below that of the 2D or 3D technique (Table 3) (11–16). Two East-Asian RCTs were conducted using a small cohort ($N = 45$–56) of early nasopharyngeal

Table 2. Larynx preservation trials using induction chemotherapy for laryngeal and hypopharyngeal cancer

Study	Number	Site	Stage	IC	RT	LP (%)	OS (%)	Larynx toxicity %
VALCSG (7)	332	LC	III–IV	FP	RT	64	68	NR
EORTC24891 (6)	202	HPC	II–IV	FP	RT	22@5 years	38@5 years	NR
RTOG91-11 (62)	547	LC	III–IV	FP	RT/CRT	71/84@5 years	59/55@5 years	6–10/6–17
GORTEC2000-01 (60)	213	LC and HPC	III–IV	FP/TPF	RT	57/70@3 years	60/60@3 years	13.6/6.2
GETTEC (63)	68	LC	II–IV	FP	RT	42	69@2 years	NR
Posner (22)	166	LC and HPC	III–IV	FP/TPF	CRT	32/52@3 years	40/57@3 years	NR
TREMPLIN (55)	153	LC and HPC	III–IV	TPF	CRT/BRT	93/96@3 months	85/86@1.5 years	8.6/9
Prades (61)	71	HPC	III–IV	FP	RT/CRT	68/92@2 years	36/41@2 years	NR

VALCSG, Veterans Affairs Laryngeal Cancer Study Group; LC, laryngeal cancer; HPC, hypopharyngeal cancer; IC, induction chemotherapy; FP, 5FU and ccisplatin, TPF, docetaxel, 5FU and cisplatin, RT, radiotherapy; CRT, chemoradiotherapy; BRT, bioradiotherapy; LP, laryngeal preservation; NR, note reported.

Table 3. Reported series of randomized control trial comparing IMRT to conventional radiotherapy for head and neck carcinoma

Author	Site	Number	Control	Stage I/II (%)	Chemoradiotherapy	6 months–1 year xerostomia IMRT	6 months–1 year xerostomia conv.	LC (%)	OS (%)
Pow (12)	NPC	45	2D	100	No				
Kam (14)	NPC	54	2D	100	No	39.3	82.1		
Nutting (13)	H&N	94	2D	24	Yes	15	74	NS	NS
Gupta (11)	H&N	60	3D	20	Yes	28.8	76	NS	NS
Peng (15)	NPC	616	2D	31	Yes	28.1	57.4	F	F

NPC, nasopharyngeal carcinoma; H&N, head and neck carcinoma; 2D, two dimensional; 3D, three dimensional; IMRT, intensity modulated radiotherapy; conv., conventional radiotherapy; LC, local control; NS, not significantly different; F, IMRT group is favorable.

cancer (NPC) patients, and the findings obtained revealed that xerostomia was subjectively and/or objectively lower in the IMRT arm than in the 2D RT arm (12,14). Nutting et al. (13) reported the findings of a multi-institutional RCT that compared IMRT with 2D RT for OPC and HPC patients. The xerostomia rates at 1 and 2 years were significantly lower in the IMRT group (38 and 29%) than in the 2D RT group (74 and 83%). OS and loco-regional relapse-free survival LRPFS in both groups were not significantly different between both arms. These findings were also supported by a systematic review (16) (Level Ia). Marta et al. (16) conducted a meta-analysis on five trials comprising 871 patients, including 82% of NPC patients and 62% of patients with Stage III/IV disease. The rate of Grade 2–4 xerostomia was lower in the IMRT group [HR = 0.76, 95% confidence interval (CI) 0.66–0.87; $P < 0.00001$); however, no significant differences were observed in OS or LC between both groups. Over 80% of cohorts received concomitant chemotherapy during IMRT. CCRT is believed to increase the rates of both acute and late toxicities; thus, these findings could be extrapolated on to cases of chemo-IMRT.

IMRT is considered to improve QOL, and a previous systemic review chiefly assessed patient statuses (17,18,19,20) using questionnaires for EORTC C-30, EORTC QLQ H&N35 and SF-35 (Table 4). Tribius et al. (20) performed a systemic review using literature describing QOL assessments between 2005 and 2010. This review assessed 14 studies including five prospective trials with only one RCT. IMRT significantly improved QOL scores comprising xerostomia, dry mouth, sticky saliva, eating-related domains and global QOL over those achieved with 2D or 3D CRT. Klein et al. (19) also performed a systematic review on health-related QOL (HRQOL) scores between IMRT and 2D or 3D CRT. Eighteen studies having high-quality reports of the basis of quality assessment instrument were reviewed in this report. The HRQOL scores declined after RT and returned to baseline levels within 12 months in all groups. The HRQOL score achieved by IMRT was significantly higher than that of 2D or 3D CRT. The HRQOL score achieved by CCRT was slightly worse. These two reviews were considered to have the distinct weakness of strong biases due to the basis of a retrospective analysis. In addition, QOL was difficult to measure in patients with HNSCC, and global QOL is reflected by various factors relating to patient backgrounds and QOL instruments. The benefit of IMRT for dysphagia was also systematically reviewed from 16 studies (17); however, apparent evidence could not be derived in this review. This was attributed to the reported series being limited by both insufficient assessment methods and outcome descriptions of swallowing function. It was also caused by the lack of reliable measuring instruments for swallowing function including basement assessments, and the reported series also chiefly depended on retrospective analysis. A sophisticated RCT with a multi-institutional design is needed to accurately evaluate the advantages of IMRT regard for global QOL and late toxicities apart from xerostomia.

Optimal method for IMRT

IMRT for LA-HNSCC is routinely performed in a simultaneously integrated boost (SIB) method, in which variable doses are delivered to several CTVs for adjusted risk levels (66). Single-step optimization is typically performed during the radiation schedule, and reducing the time and labor required for treatment preparation appears to be feasible in clinical practice. A radiation dose with a lower risk level, 54–60 Gy over 6.5–7 weeks is often delivered in the SIB technique. Regarding 2D–3D CRT, 40–50 Gy is commonly delivered for prophylactic CTV; however, a slightly larger dose may be needed in the case

Table 4. Comparison of QOL score in IMRT group compared with that of conventional radiotherapy group in reported series

Author	Study design	Patient number	Site	EORTC QLQ-C30					EORTC QLQ-C30 HN&35					
				Global QOL	Physical function	Role function	Cognitive function	Social function	Pain	Swallowing	Speech	Social eating	Dry mouth	Sticky saliva
Pow (12)	Prospective	51	NPC			Y							Y	Y
Fang (80)	Prospective	203	NPC	Y									Y	
Vergeer (81)	Prospective	241	H&N	Y		Y	Y	Y	Y	Y	Y	Y	Y	Y
Fang (82)	Retrospective	356	NPC	Y	Y			Y	Y	Y	Y	Y	Y	Y
Graff (83)	Retrospective	134	H&N						Y	Y		Y	Y	
Huang (84)	Retrospective	307	H&N										Y	

NPC, nasopharyngeal cancer; QOL, quality of life; Y, significantly better for IMRT group.

of SIB due to the small fraction size (<1.8 Gy per fraction), which is expected to decrease the probability of disease control. An increased dose to the surrounding organ, such as the larynx and constrictor muscle, may lead to the development of dysphagia (8,67,68). Another weakness of the SIB technique is dose variations due to anatomical changes during the IMRT session. Several studies reported that anatomical changes may cause significant shortages in the dose on PTV and/or an excessive dose to the surrounding organ (69,70). A two-step method would resolve these problems by using the standard fraction size to all target volumes with a second boost IMRT plan (69,71,72). Although the burden on staff would increase due to additional optimization processes, dose variations resulting from anatomical changes due to tumor shrinkage and body weight loss could be adjusted for. The JCOG 1015 (UMIN000005448) is a Phase II trial that is being conducted to demonstrate the feasibility of two-step IMRT with CCRT for Stage II–IVB NPC patients. A total of 75 patients are planned to have registered by October 2014, and a follow-up will be conducted until 2017. The JCOG 1208 (UMIN000014274) is a Phase II trial conducted on patients with OPC of T1–2N0–1 category, and a two-step method is also used in this trial. These multi-institutional prospective trials are expected to demonstrate the original efficacy of the two-step IMRT method for HNSCC patients.

Japanese clinical trials for HNSCC

The JCOG Radiation Therapy Study Group developed a multi-institutional Phase II trial (JCOG 0403) on stereotactic body radiotherapy for Stage I non-small cell lung cancer in 2003. The group then expanded the trial to include several prospective trials including those for HNSCC. To date, the group has conducted a multi-institutional RCT trial to demonstrate the efficacy of AF for glottic cancer of the T1–2N0 category (JCOG 0701), a Phase II trial on chemo-IMRT for LA-NPC (JCOG 1015), and a Phase II trial on IMRT for early OPC (JCOG 1208). The Head and Neck Cancer Study Group of JCOG has conducted a Phase II/III study on post-operative chemoradiotherapy for LA-HNSCC, comparing the administration of cisplatin in a three weekly arm to a weekly arm (JCOG 1008) (73). This trial has made amendments for the use of IMRT in credentialed institutes in collaboration with the Radiation Therapy Study Group.

Apart from the JCOG group trial, a Phase II trial is being conducted on chemo-IMRT for cervical esophageal cancer (JROSG 12-1 UMIN000009880) and is supported by a National Grant Aid. The findings of these prospective trials will greatly impact on Japanese clinical practices and future trials.

Future perspective

Proton beam therapy (PBT) is expected to have the advantage of sparing normal tissue over photon beam. As for carbon-ion therapy, the high value of its relative biological effect may be beneficial for tumor control. A systemic review has discussed the benefits of particle therapy (74,75). Regarding carbon-ion therapy, survival advantages for mucosal malignant melanomas would be reported to some extent (75). The advantages of PBT for survival and tumor control in paranasal and sinonasal cancers have been reported previously (76). However, limited clinical data are available to demonstrate that toxicity is slightly lower for PBT than for photon therapy. Since the overall quantity and quality of data regarding particle therapy is poor, prospective multi-institutional data are needed in the future (75). Intensity modulated proton therapy (IMPT) is one of the promising methods that can improve the quality of definitive RT for HNSCC (75,77). IMPT has the distinct advantage of sparing normal tissue, especially with low dose exposure (77). IMPT is expected to have further advantages; thus, prospective trials on IMPT are warranted to demonstrate its benefits over IMRT.

Biomarkers play important roles in the selection of treatment modalities and/or estimation of treatment outcomes; however, reliable information has not yet been reported for HNSCC. Biomarkers to predict the outcome of CCRT and BRT are needed (78,79), and would be very helpful for both decision-making for optimal treatments and reduction of intensive multidisciplinary therapy.

Conclusion

AF, CCRT and BRT have advantages over standard fractionated radiotherapy; however, the management of both acute and late toxicities has become more important in clinical practice. Although CCRT using high dose cisplatin is the mainstay for LA-HNSCC, late toxicities were reported to increase in association with survival disadvantages. IMRT is believed to be useful for minimizing morbidity and mortality related to definitive RT, especially in the case of CCRT. Further improvements are warranted through the optimal use of adaptive radiotherapy and particle therapy.

Multi-agent induction chemotherapy with BRT represents on attractive option for balancing efficacy and toxicity, and is now being eagerly tested in prospective trials. In the future, customized therapy designed with biomarkers is desired to optimize definitive radiotherapy.

Acknowledgements

We wish to express our special appreciation to all the staff at the participating institutes of JCOG 0701, JCOG 1008, JCOG 1015 and JCOG 1208 trial, and JCOG Data Center.

Funding

The work was partially supported by Health Sciences Research Grants for a Grant-in-Aid for Cancer Research (20S-5, 20S-6, 17-17, 16-12, 17S-5 H21-018, H23-009, H24-007, H26-090) from the Ministry of Health, Labor and Welfare of Japan and the National Cancer Center Research and Development Funds (23-A-16, 23-A-21 and 26-A-4).

Conflict of interest statement

None declared.

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ORIGINAL PAPER

Nagoya J. Med. Sci. 77. 637 ~ 646, 2015

International prostate symptom score (IPSS) change and changing factor in intensity-modulated radiotherapy combined with androgen deprivation therapy for prostate cancer

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ABSTRACT

The purposes of this study on prostate cancer are to demonstrate the time course of International Prostate Symptom Score (IPSS) after intensity-modulated radiation therapy (IMRT) combined with androgen deprivation therapy (ADT) and to examine the factor associated with the IPSS change. This study included 216 patients treated with IMRT between 2006 and 2010. Patients were evaluated in three groups according to baseline IPSS as defined by the American Urological Association classification, where IPSSs of 0 to 7, 8 to 19, and 20 to 35 represent mild (n = 124), moderate (n = 70), and severe (n = 22) symptom groups, respectively. The average IPSSs ± standard deviation at baseline vs. those at 24 months after IMRT were 3.5 ± 2.1 vs. 5.1 ± 3.6 in the mild group ($P < 0.001$), 12.6 ± 3.4 vs. 10.0 ± 6.0 in the moderate group ($P = 0.0015$), and 23.8 ± 2.9 vs. 14.4 ± 9.1 in the severe group ($P < 0.001$). Among factors of patient and treatment characteristics, age, IPSS classification, pretreatment GU medications, and positive biopsy rates were associated with the IPSS difference between baseline and 24 months ($P = 0.023$, < 0.001, 0.044, and 0.028, respectively). In conclusion, patients with moderate to severe urinary symptoms can exhibit improvement in urinary function after IMRT, whereas patients with mild symptoms may have slightly worsened functions. Age, baseline IPSS, GU medications, and tumor burden in the prostate can have an effect on the IPSS changes.

Key Words: IPSS, prostate cancer, genitourinary toxicity, IMRT, ADT

INTRODUCTION

Major concerns associated with high-dose external beam radiotherapy (EBRT) for prostate cancer are rectal and urinary toxicities. Factors increasing the risk of rectal toxicity in this treatment approach are considered to be dose-volume parameters of the rectum in the radiotherapy planning and some clinical characteristics.[1)] Thus, intensity-modulated radiation therapy (IMRT)

Received: April 10, 2015; accepted: October 6, 2015

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has reduced rectal toxicity in this curative treatment.[2, 3] On the other hand, clinical factors related to genitourinary (GU) toxicities have not been fully elucidated. GU toxicities were enhanced by dose escalation with IMRT. We should pay more attention to detailed quality of life analysis, not only with respect to rectal bleeding but also other specific symptoms such as urinary incontinence.[4] Reliable dose–volume models of GU toxicity also remain unavailable because of the variable bladder filling occurring between computed tomography (CT) simulation and irradiation.[5]

In the case of brachytherapy, the pretreatment International Prostate Symptom Score (IPSS) has a high correlation with urinary function after treatment.[6] It is established that patients with pretreatment high IPSS and poor urinary function are typically not candidates for brachytherapy.[7] However, the significance of pretreatment IPSS and the time course of IPSS have not been clearly demonstrated in EBRT for prostate cancer. The purpose of this study was to demonstrate the IPSS course of prostate cancer patients after IMRT combined with androgen deprivation therapy (ADT) and to examine the relationship between the GU toxicity and the clinical characteristics with pretreatment IPSS.

MATERIALS AND METHODS

Patients

Of 241 patients treated with IMRT for clinically localized prostate cancer between June 2006 and December 2010 at our hospital, 216 who had continuous IPSSs were included in this retrospective study. Twenty-five patients excluded from this study lacked continuous IPSS data, mainly at the baseline. Informed consent was obtained for IMRT and data exploitation under adequate privacy control from all patients before treatment. This study was approved by the institutional review board.

Androgen deprivation therapy and radiotherapy

All patients were given neoadjuvant ADT consisting of a combination of a luteinizing hormone-releasing hormone (LHRH) analogue and anti-androgen treatment. The median time of neoadjuvant ADT was 10 months (range, 2–68 months). Most patients (96.8%) also received adjuvant ADT consisting of only the LHRH analogue. The median time of adjuvant ADT was 19 months (range, 1–37 months). The details of ADT are described in our previous report.[2]

The entire bladder was delineated on radiation planning CT as an organ at risk. The bladder V70, V40, and V20 means the percentage of the bladder covered by at least 70 Gy, 40 Gy, and 20 Gy, respectively. The definitions of the planning target volume (PTV) and other normal structures and other details for IMRT methods are described in our previous report.[2] Whole-pelvic radiotherapy was not used. Patients basically received 74 Gy in the low-risk group and 78 Gy in intermediate- and high-risk groups according to the National Comprehensive Cancer Network (NCCN) criteria.

Follow-up and data analysis

Follow-up evaluations were performed at 3-month intervals. IPSS consisting of seven domains, for evaluating incomplete emptying, frequency, weak stream, intermittency, urgency, straining, and nocturia, was measured on a 0 to 5 scale at each follow-up. The length of follow-up was calculated from the start date of IMRT. IPSSs at baseline (i.e., before the initiation of any therapy), and about 3, 6, 12, and 24 months after IMRT were reviewed. Patients were divided and evaluated in three groups according to baseline IPSS as defined by the American Urological Association (AUA) classification, where IPSSs of 0 to 7, 8 to 19, and 20 to 35 represent