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# Treatment outcomes of (chemo) radiotherapy for oropharyngeal cancers: influence of the use of 15 MV X-rays in radiation boost

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► ***Original article***

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## ABSTRACT

***Background*:** Using high energy X-rays (>10 MV) as a radiotherapy boost in treating oropharyngeal cancers (OPC) to reduce mandible radiation exposure may result in deterioration of disease control rates due to re-build-up of X-rays at the tumor surface. Therefore, we retrospectively compared the treatment outcomes and toxicities in OPC patients treated with radiotherapy using 15 MV and/or 4–6 MV X-rays as a boost. ***Materials and Methods*:** Between 2008 and 2014, 63 OPC patients received definitive 3-dimensional conformal radiotherapy. The median total dose was 70.2 (range, 46.8–75.6) Gy. The median follow-up period for surviving patients was 48 (range, 9–88) months. Twenty-one patients (33.3%) received a boost employing 15 MV X-ray in at least one beam during treatment, and 42 patients (66.7%) received only 4–6 MV X-rays. Local control (LC), locoregional control (LRC), disease-free survival (DFS), overall survival (OS) rates and the incidence of osteoradionecrosis (ORN) in the mandible for the two cohorts were estimated using the Kaplan-Meier method and compared using the log-rank test. ***Results:*** There were no statistically significant differences between the two cohorts in either treatment outcomes (3-year LC, 81% versus 75% [p=0.742]; 3-year LRC, 71% versus 71% [p=0.925]; 3-year DFS, 66% versus 66% [p=0.934]; 3-year OS, 65% versus 78% [p=0.321]) or incidence of grade >2 ORN in the mandible (9.5% versus 11.9% [p=0.883]). ***Conclusion:*** Employing 15 MV X-rays in a boost may provide comparable treatment outcomes to 4–6 MV X-rays. However, reduction in the incidence of ORN in the mandible was not demonstrated.

***Keywords:*** *Oropharyngeal cancer, osteoradionecrosis, radiotherapy.*

## INTRODUCTION

The incidence of oropharyngeal cancer (OPC) has increased over the last 20 years in several countries including Japan [1, 2]. According to Simard *et al.*, the age-standardized 5-year average annual incidence rate for OPC per 100,000 in the Japanese population was 1.33 for males and 0.18 for females during the period 1998–2002 [3]. Definitive radiotherapy (RT) is currently the mainstay of treatment because of the significant functional impairment associated with classical surgical resection in this location [4]. Osteoradionecrosis (ORN) in the mandible is a well-documented complication of RT for head and neck cancers [5]. The incidence of ORN in the mandible has been reported to be between 2% and 22% [6]. To reduce radiation exposure to the mandible, some clinicians often employ high energy X-rays exceeding 10 MV as an RT boost, with the expectation that it may reduce the rate of development of ORN in the mandible. However, there is concern that disease control rates may deteriorate because of re-build-up of X-rays at the tumor surface. Specific guidelines recommend that X-rays with energies exceeding

10 MV should not be used in the treatment of lung cancers for the similar reason [7]. Regarding head and neck cancers, Izuno *et al*. compared the outcomes of vocal cord carcinoma patients treated with RT using 8 MV/10 MV X-rays or $^{60}$Co. They reported that the patients treated with 8 MV/10 MV X-rays exhibited significantly inferior 5-year local control (LC) rates [8]. Therefore, we retrospectively compared the treatment outcomes and the development rates of ORN in the mandible among OPC patients treated with RT using 15 MV and/or 4–6 MV X-rays as an RT boost.

## MATERIALS AND METHODS

### *Patient characteristics*

Sixty-three OPC patients treated with definitive RT with curative intent between April 2008 and April 2014 at a single institution were included. The medical records were retrospectively reviewed. Tumor stages were classified using the Union for International Cancer Control (UICC) TNM classification for head-and-neck tumors, seventh edition [9]. All patients underwent computed tomography (CT) (Siemens, SOMATOM Definition AS+, Germany) and positron emission tomography (PET)-CT (Toshiba Medical Systems, Aquiduo16, Japan) before treatment. The majority of patients also underwent magnetic resonance imaging (MRI) (Siemens, MAGNETOM Symphony, Germany) and endoscopy of the upper digestive tract prior to treatment. The current study was approved by the Yokohama City University Review-board of Research Ethics (approved January 7, 2016; registration number B151201006). All patients provided written informed consent before the initiation of treatment.

Patient characteristics are summarized in table 1. No patient with clinical stage I disease was included in our cohort, because they usually underwent surgical treatment. All patients had histologically confirmed carcinomas. Besides the 61 (96.8%) patients with SCCs, 1 (1.6%) had an adenosquamous cell carcinoma, and 1 (1.6%) patient had a sarcomatoid carcinoma. Twenty two (34.9%) patients had developed double cancer, which is defined as the diagnosis of another cancer at their primary evaluation for OPC (synchronous), or during their follow-up period (metachronous). Only 12 patients (19%) had available information regarding their human papilloma virus (HPV) status. Among them, two patients were positive for HPV infection. All patients underwent dental examination before RT and extraction was performed at least one week before initiation of RT when required. Extraction was generally prohibited after RT.

**Table 1.** Patient characteristics.

| | |
|---|---|
| Age (years) | |
| Median | 65 |
| Range | 91–39 |
| Sex | |
| Male | (%81) 51 |
| Female | (%19) 12 |
| Performance status (ECOG) | |
| 0 | (%17.5) 11 |
| 2–1 | (%82.5) 52 |
| Subsite | |
| lateral wall | (%61.9) 39 |
| anterior wall | (%19.0) 12 |
| superior wall | (%15.9) 10 |
| posterior wall | (%3.2) 2 |
| T-category | |
| T1 | (%1.6) 1 |
| T2 | (%42.9) 27 |
| T3 | (%22.2) 14 |
| T4a | (%31.7) 20 |
| T4b | (%1.6) 1 |
| N-category | |
| N0 | (%25.4) 16 |
| N1 | (%15.9) 10 |
| N2a | (%6.3) 4 |
| N2b | (%33.3) 21 |
| N2c | (%12.7) 8 |
| N3 | (%6.3) 4 |
| Stage | |
| I | (%0) 0 |
| II | (%12.7) 8 |
| III | (%20.6) 13 |
| IVA | (%57.1) 36 |
| IVB | (%9.5) 6 |
| Histology | |
| squamous cell carcinoma | (%96.8) 61 |
| adenosquamous cell carcinoma | (%1.6) 1 |
| sarcomatoid carcinoma | (%1.6) 1 |
| Double cancer | |
| Yes | (%34.9) 22 |
| No | (%65.1) 41 |
| Pretreatment hemoglobin level (g/dL) | |
| Median | 12.7 |
| Range | 17.2–7.7 |
| Total RT dose (Gy) | |
| Median | 70.2 |
| Range | 75.6–46.8 |
| Duration of RT (days) | |
| Median | 57 |
| Range | 71–36 |

ECOG: Eastern Cooperative Oncology Group, RT: radiotherapy.

***Radiation therapy***

All patients received definitive CT-based 3-dimensional conformal RT (3DCRT) which was performed 5 days per week, using a conventional fractionation regimen (1.8–2.0 Gy per fraction). To generate radiation, a linear accelerator was used which was either PRIMUS High Energy (Toshiba Medical Systems, Japan) or Clinac iX (Varian Medical Systems, USA). Intensity-modulated radiation therapy (IMRT) was not performed. The median total dose was 70.2 (range, 46.8–75.6) Gy in median fractions of 39 (range, 25–42). The median duration of RT was 57 (range, 36–71) days. Generally, the initial RT field encompassed the bilateral level 1–5 lymph node areas and the retropharyngeal lymph nodes using 4–6 MV X-rays. Prophylactic irradiation at total doses of 40–50 Gy was administered followed by a radiation boost to the gross tumor volume. Three patients with no clinical lymph node metastasis had their prophylactic irradiation omitted because of past histories of neck dissection or RT to the neck for distinct malignancies. Another patient with stage II disease also did not receive prophylactic RT with administration of superselective intra-arterial chemotherapy. Another stage II case, with the primary tumor located in the lateral wall, underwent prophylactic RT against the ipsilateral neck alone. One patient experienced a cessation of treatment as a result of disseminated intravascular coagulation during RT, which was probably caused by OPC. Another patient also experienced a treatment cessation due to severe delirium. Twenty one (33%) patients received a boost using 15 MV X-ray in at least one beam during their treatment course, and 42 (66.7%) patients received a boost using only 4–6 MV. In 11 (17.5%) patients, 9 MeV electrons were also used in the boost. The patient characteristics of the cohorts receiving the 15 MV-X-ray boost and the 4–6 MV-X-ray boost are detailed in table 2. There were no significant differences between the two cohorts.

***Chemotherapy***

All patients except for one (62 of 63 patients) received chemotherapy, which was generally administered concomitantly (60/63 patients; 95.2%). Various regimens were used in the concurrent chemotherapy. Thirty-three were cisplatin (Nichi-iko, Japan) and 5-fluorouracil (Kyowa Hakko Kirin, Japan) based; docetaxel (Sawai, Japan) or methotrexate (Pfizer, USA) and leucovorin (Pfizer, USA) were added. Sixteen received S-1 (Taiho Pharmaceutical, Japan) based, 5 received carboplatin (Nippon Kayaku, Japan) and tegafur-uracil (Taiho Pharmaceutical, Japan) based chemotherapy, 4 received docetaxel alone, and one received cetuximab (Merck Serono, Germany) alone. In the remaining patient, selective intra-arterial infusion was combined with cisplatin and docetaxel. Forty-three (68.3%) patients received adjuvant chemotherapy predominantly consisting of tegafur-uracil or S-1.

**Follow up, toxicity assessment, and statistics**

Patients were typically followed up every 2–4 weeks during the first year after RT, every 1–3 months during the following 2 years, and every 2–6 months thereafter. PET-CT was performed every 6 months or annually. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1 [10]. All actuarial survival, control, and toxicity development rates were calculated from the beginning of RT, using the Kaplan-Meier method. Overall survival (OS) was defined as death from any cause. Disease-free survival (DFS) was defined as the time to the first failure, locoregional control (LRC) was defined as the time to the first in-field relapse, and LC was defined as the time to the first relapse of the primary lesion. Freedom from ORN in the mandible (FOM) was defined as the time to the development of ORN in the mandible. Toxicities were assessed according to the Common Terminology Criteria for Adverse Events version 4.0 [11]. Acute toxicities were defined as toxicities occurring within 3 months from the beginning of RT, and late toxicities as those occurring later.

*All statistical analyses were performed using SPSS statistical* software (version 23.0; IBM Corp., Armonk, NY, USA). Differences in the distribution of variables across the 15 MV X-ray

and the 4–6 MV X-ray boost cohorts were compared using the chi-square test or Fisher's exact test for categorical variables, and the Mann-Whitney U test for continuous variables. The log-rank test was used for univariate analysis. The factors which had been considered significant in the log-rank test were included in the Cox proportional hazards model for multivariate analysis to identify prognostic factors which predicted treatment outcomes. A *p*-value of <0.05 was considered statistically significant. Pre-treatment hemoglobin levels were also analyzed to assess their prognostic value in accordance with previous studies [12, 13].

**Table 2.** Patient and treatment characteristics on the basis of the X-ray energy in boost.

| Characteristic | | 15 MV using | 4–6 MV only | *p* value |
|---|---|---|---|---|
| Follow up period (months) | Median | 40 | 42 | 0.184 |
| | Range | 6–87 | 1–93 | |
| Age (years) | Median | 60 | 66 | 0.089 |
| | Range | 39–82 | 39–91 | |
| Sex | Male | 17(81%) | 34(81%) | 1.00 |
| | Female | 4(19%) | 8(19%) | |
| Performance status (ECOG) | 0 | 2(9.5%) | 9(21.4%) | 0.310 |
| | 1–2 | 19(90.5%) | 33(78.6%) | |
| Disease subsite | lateral wall | 12 (57.1%) | 27 (64.3%) | 0.582 |
| | Others | 9(42.9%) | 15(35.7%) | |
| Stage | I | 0 (0%) | 0 (0%) | - |
| | II | 3 (14.3%) | 5 (11.9%) | 1.00 |
| | III | 5 (23.8%) | 8 (19.0%) | 0.745 |
| | IVA/B | 13 (61.9%) | 29 (69.0%) | 0.571 |
| Histology | squamous cell carcinoma | 21 (100%) | 40 (95.2%) | 0.548 |
| | Others | 0(0%) | 2(4.8%) | |
| Double cancer | Yes | 9 (42.9%) | 13 (31.0%) | 0.350 |
| | No | 12(57.1%) | 29(69.0%) | |
| Pretreatment hemoglobin level (g/dL) | Median | 13.4 | 12.6 | 0.656 |
| | Range | 10.0–16.7 | 7.7–17.2 | |
| Duration of RT (days) | Median | 57 | 57 | 0.675 |
| | Range | 50–64 | 36–71 | |
| Total RT dose (Gy) | Median | 70.2 | 70.2 | 0.390 |
| | Range | 66.6–72.0 | 46.8–75.6 | |
| Concurrent chemotherapy | Yes | 21 (100%) | 39 (92.9%) | 0.545 |
| | No | 0 (0%) | 3(7.1%) | |
| Adjuvant chemotherapy | Yes | 15 (71.4%) | 28 (66.7%) | 0.702 |
| | No | 6(28.6%) | 14(33.3%) | |
| Use of electron | Yes | 3 (14.3%) | 8 (19.0%) | 0.738 |
| | No | 18(85.7%) | 34(81.0%) | |

ECOG: Eastern Cooperative Oncology Group, RT: radiotherapy.

## RESULTS

### *Local control and failure patterns*

After the initial treatment, 54 (85.7%) patients achieved complete response, whereas one (1.6%) showed progressive disease, and 8 (12.7%) partial response.

The median follow-up period for surviving patients was 48 (range, 9–88) months. The 3- and 5- year LC rates for the entire cohort were 77% and 77%, respectively, whereas the LRC rates were 71% and 71%, respectively (Figure

1A). During the follow-up period, disease recurrences were observed in 21 (33.3%) patients. Tumor recurrence developed inside the radiation field in 17 patients (13 at the site of the primary lesion, 6 in the cervical lymph nodes, and 2 in both locations), and 7 patients developed distant metastases including 3 lung metastases. Three patients showed both in-field relapse and distant metastasis. Eight patients underwent salvage surgery after the initial treatment. Three patients underwent tumorectomy for the locally recurrent tumor, two received neck dissection, two underwent excision of the metastatic disease of the lung, and one underwent both tumor resection of the primary lesion and partial resection of the lung.

Among the 22 patients who developed double cancers (simultaneously or during follow -up), the most frequent site was the esophagus (n=12), followed by the head and neck (n=7), the stomach (n=4), and the colon (n=2). Other sites included the prostate, bile duct, breast, liver, cervix, and the renal pelvis. Seven patients developed multiple cancers in two or more sites other than OPC.

### *Survival*

The 3-year DFS and OS rates for the entire cohort were 66%, and 74%, respectively. The 5-year DFS and OS rates for the entire cohort were 56% and 62%, respectively (figure 1B). Considered overall, 21 deaths were observed. Thirteen patients died from disease progression, including one death caused by liver metastasis. Four patients died from pneumonia, one from esophageal cancer, and one from cancer of the tongue. Two patients died from unknown causes.

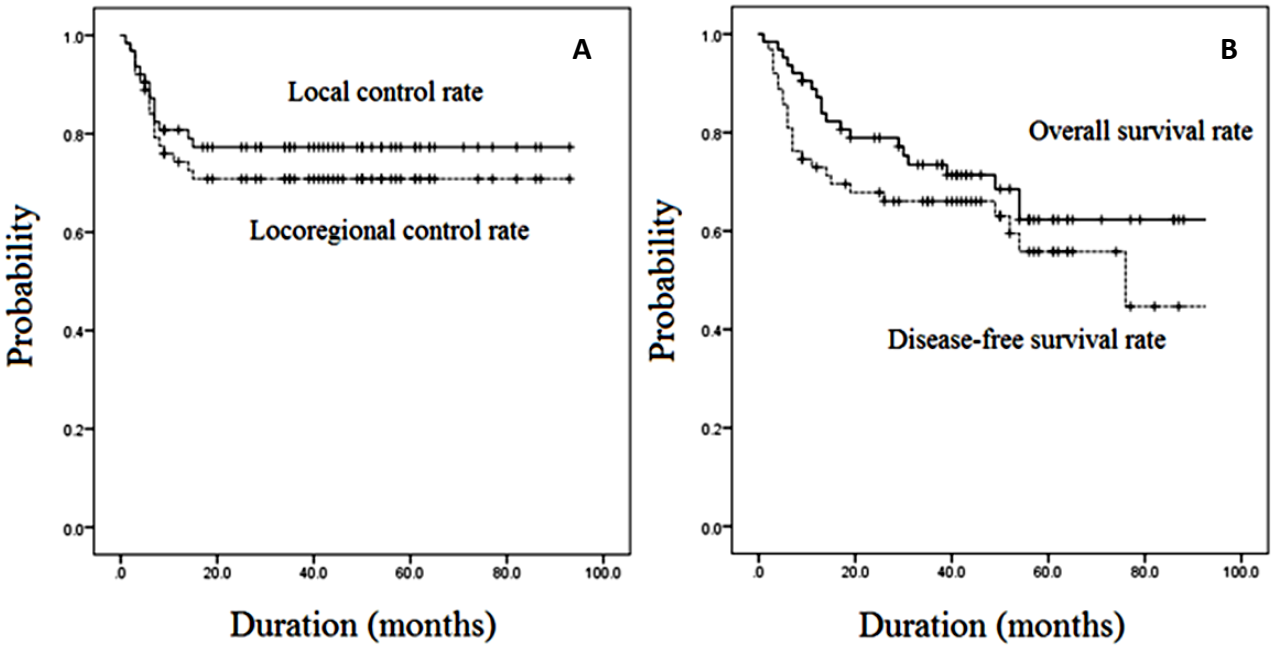


**Figure 1.** Local control and locoregional control (**A**), overall survival and disease-free survival (**B**) rates in patients with oropharyngeal cancer treated with radiotherapy.

### *Prognostic factors*

The results of the Kaplan-Meier analysis and the log-rank tests for LC, LRC, DFS, and OS are summarized in table 3. Using univariate analysis, a higher T-category ($p$=0.023) and lower pretreatment hemoglobin level ($p$=0.033) were identified as significant prognostic factors for inferior LC. Similarly, a lower performance status (PS; $p$=0.028) and higher T-category ($p$>4.446) were significant prognostic factors for inferior LRC. A lower PS ($p$=0.006), primary tumor subsite (not located in the lateral wall; $p$>4.465), higher T-category ($p$<0.001), and lower pretreatment hemoglobin level ($p$=0.008)

were significant prognostic factors for inferior DFS. A lower PS ($p$=0.016), subsite (not located in the lateral wall; $p$=0.013), higher T-category ($p$<0.001), lower total RT dose ($p$=0.037), and lower pretreatment hemoglobin level ($p$=0.003) were significant prognostic factors for inferior OS. There were no statistically significant differences in treatment outcomes between the 15 MV X-ray boost cohort and the 4–6 MV X-ray boost cohort (3-year LC, 81% versus 75% [$p$=0.742]; 3-year LRC, 71% versus 71% [$p$=0.925]; 3-year DFS, 66% versus 66% [$p$=0.934]; 3-year OS, 65% versus 78%, [$p$=0.321]). The LC and the OS curves for each cohort are shown in figures 2A and 2B.

On multivariate analysis, a higher T-category remained significantly prognostic for inferior LRC ($p$=0.009), DFS ($p$=0.014), and OS ($p$>4.446). A lower total RT dose also remained significantly prognostic for inferior OS ($p$=0.019). Conversely, there were no significant prognostic factors for LC. Although a higher T-category showed a trend towards being prognostic for inferior LC ($p$=0.090) and subsite (not located in the lateral wall) towards being prognostic for inferior DFS ($p$=0.060), they were not statistically significant. The results are summarized in table 4.

**Table 3.** Results of Kaplan-Meier analysis and log-rank tests of prognostic factors for local control, locoregional control, disease-free survival and overall survival.

| Prognostic factor | No. of patients | 3 year-LC rate (%) | *p* value | 3 year-LRC rate (%) | *p* value | 3 year-DFS rate (%) | *p* value | 3 year-OS rate (%) | *p* value |
|---|---|---|---|---|---|---|---|---|---|
| Sex | | | | | | | | | |
| Male | 51 | 82.0% | | 74.0% | | 68.1% | | 75.8% | |
| Female | 12 | 57.1% | 0.074 | 57.1% | 0.274 | 57.1% | 0.303 | 62.9% | 0.574 |
| Age | | | | | | | | | |
| <65 | 31 | 86.8% | | 80.1% | | 70.8% | | 80.5% | |
| ≥65 | 32 | 67.5% | 0.074 | 61.2% | 0.102 | 61.2% | 0.417 | 66.5% | 0.131 |
| Performance status (ECOG) | | | | | | | | | |
| 0 | 11 | 100.0% | | 100.0% | | 100.0% | | 100% | |
| 1–2 | 52 | 72.3% | 0.060 | 64.4% | 0.028 | 58.7% | 0.006 | 67.6% | 0.016 |
| Primary tumor subsite | | | | | | | | | |
| lateral wall | 39 | 84.2% | | 79.1% | | 76.7% | | 83.9% | |
| others | 24 | 66.4% | 0.121 | 57.8% | 0.106 | 48.9% | 0.021 | 56.9% | 0.013 |
| T-category | | | | | | | | | |
| 1–3 | 42 | 85.7% | | 83.3% | | 80.8% | | 90.4% | |
| 4 | 21 | 58.0% | 0.023 | 42.7% | 0.002 | 34.3% | <0.001 | 37.8% | <0.001 |
| N-category | | | | | | | | | |
| 0–1 | 26 | 80.8% | | 80.8% | | 72.7% | | 84.4% | |
| 2–3 | 37 | 74.9% | 0.535 | 63.6% | 0.133 | 61.6% | 0.144 | 65.5% | 0.108 |
| RT dose (Gy) | | | | | | | | | |
| <70 | 7 | 57.1% | | 57.1% | | 57.1% | | 57.1% | |
| ≥70 | 56 | 79.9% | 0.086 | 72.6% | 0.224 | 67.3% | 0.269 | 75.8% | 0.037 |
| Duration of RT (days) | | | | | | | | | |
| <57 | 28 | 74.8% | | 71.1% | | 66.9% | | 76.8% | |
| ≥57 | 35 | 79.3% | 0.643 | 70.6% | 0.974 | 65.2% | 0.419 | 70.7% | 0.174 |
| Pretreatment hemoglobin level (g/dL) | | | | | | | | | |
| ≤13 | 34 | 66.1% | | 63.5% | | 57.8% | | 62.7% | |
| >13 | 29 | 89.7% | 0.033 | 79.3% | 0.157 | 75.5% | 0.008 | 85.8% | 0.003 |
| Double cancer | | | | | | | | | |
| Yes | 22 | 80.7% | | 76.5% | | 67.3% | | 75.5% | |
| No | 41 | 75.4% | 0.617 | 68.0% | 0.533 | 65.3% | 0.999 | 72.3% | 0.879 |
| Use of 15 MV X-ray | | | | | | | | | |
| Yes | 21 | 81.0% | | 71.1% | | 66.0% | | 65.0% | |
| No | 42 | 75.4% | 0.742 | 70.5% | 0.925 | 66.1% | 0.934 | 77.8% | 0.321 |

No.: Number, LC: local control, LRC: locoregional control, DFS: disease-free survival, OS: overall survival, ECOG: Eastern Cooperative Oncology Group, RT: radiotherapy.

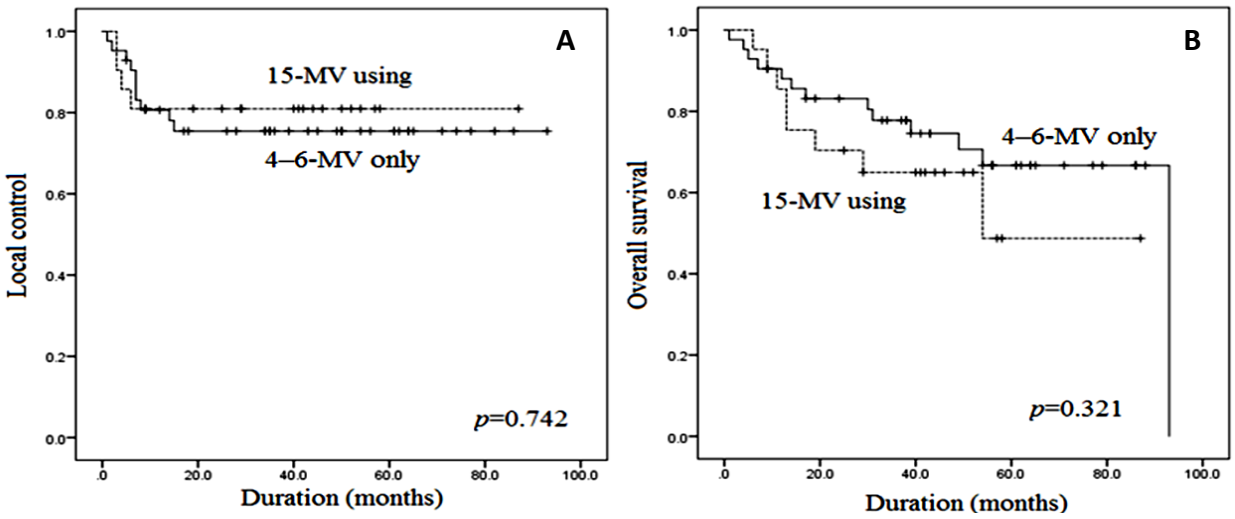


**Figure 2.** Local control (**A**) and overall survival (**B**) rates with regard to the X-ray energy used in the boost of radiotherapy. The two cohorts exhibited comparable outcomes.

**Table 4.** Probable prognostic factors for locoregional control, disease-free survival and overall survival obtained from multivariate analysis.

| | Variable | Hazard ratio | 95% confidence interval | *p* value |
|---|---|---|---|---|
| *Locoregional control* | | | | |
| | T-category | 0.28 | 0.11–0.72 | 0.009 |
| *Disease-free survival* | | | | |
| | T-category | 0.34 | 0.14–0.81 | 0.014 |
| *Overall survival* | | | | |
| | T-category | 0.19 | 0.07–0.53 | 0.002 |
| | RT dose | 4.50 | 1.28–15.90 | 0.019 |

RT: radiotherapy.

### *Toxicities*

Treatment-related deaths were not recorded. The most commonly observed acute non-hematological grade 3/4 toxicity was mucositis which was observed in 33 (52%) patients, followed by dysphagia (51%) and dermatitis (24%). The most commonly occurring acute grade 3/4 hematological toxicity was lymphocytopenia, which was observed in 59 (94%) patients, followed by leukocytopenia (56%) and neutropenia (35%). Acute toxicities were all manageable and temporary.

Overall, development of grade ≥2 ORN in the mandible were observed in seven patients (11.1%; 4 were grade 2 and 3 were grade 3). Among these patients, 2 (9.5%) were in the 15 MV X-ray boost cohort, and 5 (11.9%) were in the 4–6 MV X-ray boost cohort. The difference in the FOM rates between the two cohorts was not statistically significant ($p$=0.883). The FOM curves for each cohort are shown in figure 3.

Other grade ≥3 late toxicities consisted of dysphagia (n=5), mucositis (n=3), hearing impairments (n=3), and vertigo (n=1). In addition, 16 (25%) patients complained of grade 2 xerostomia, and 14 (22%) suffered from grade 2 hypothyroidism.

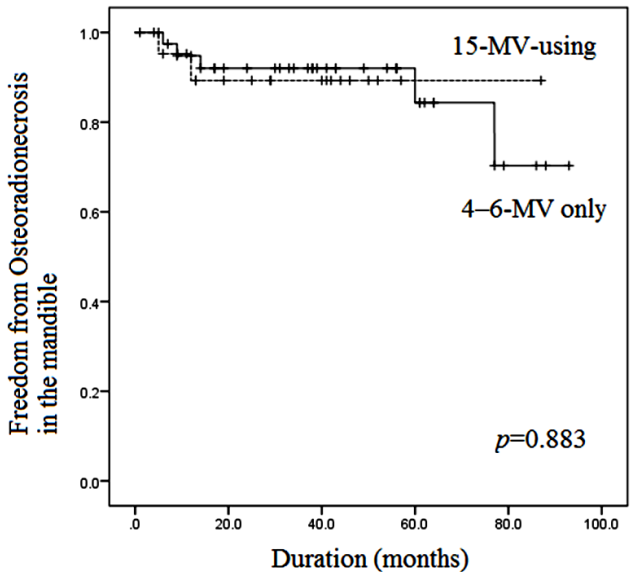


**Figure 3.** Rates of freedom from osteoradionecrosis in the mandible with regard to the X-ray energy used in the boost of radiotherapy. The 15 MV X-ray boost cohort and the 4–6 MV X-ray boost cohort exhibited no significant difference.

## DISCUSSION

To preserve the swallowing function after treatment which is essential in maintaining the patient's quality of life, RT plays a critical role in the treatment of OPC. Clinicians are endeavoring to reduce radiation exposure to the mandible, which may potentially reduce the incidence of ORN in the mandible. One of the potential modalities used to achieve this is IMRT. Tsai *et al.* reported the incidence of ORN in the mandible among OPC patients treated with RT, and saw a trend toward lower levels of ORN in the mandible in patients treated with IMRT as compared with 3DCRT (6% versus 13%) [14]. However, despite numerous reports recommending IMRT in the treatment of head and neck cancers, some institutions have not adopted this modality yet. In such institutions, clinicians may consider reducing radiation exposure to the mandible by employing high energy X-rays exceeding 10 MV in boost. Nevertheless, there is concern that employing such high energy X-rays may result in deterioration of tumor control rates because of re-build up effects at the tumor surface. Our series indicated there the X-ray energy of the RT boost had no effect on treatment outcomes; in addition, there was no difference in the development rates of ORN in the mandible between the two boost cohorts. It may be concluded that although 15 MV X-rays could be used clinically for the radiation boost in OPC treatment without compromising treatment outcomes, the effect regarding the reduction of the incidence of ORN in the mandible is not clear.

One limitation of the current study was that because it was retrospective, selection bias in terms of treatment was unavoidable. Clinicians may have chosen the X-ray energies according to their considered risk of ORN in the mandible, such as the proportional volume of the irradiated mandible. To address such issues, a prospective randomized trial with a longer follow-up period is warranted.

The treatment outcomes of the whole cohort in the present study seemed comparable to those previously reported. Fein et al. presented the treatment results from 490 OPC patients with stage I–IVB disease, treated with RT. In their study, the LRC and the OS rates at 5 years were 67% and 44%, respectively [15]. According to an analysis including 627 OPC cases by Agarwal *et al*., the 3-year LRC, DFS and OS rates were 41%, 39%, and 36%, respectively [16]. Similarly, Tomita *et al*. retrospectively analyzed the results of 141 OPC patients treated with RT

with stage I–IVB disease. They reported that their 5-year progression-free survival, LRC, and OS rates were 66%, 73%, and 65%, respectively [12]. In addition, Setton *et al*. reported achieving a 3-year OS rate of 85% in patients with stage I–IV OPC using IMRT [4]. The promising results of this modality suggest the potential for further improvement in treatment outcome, in addition to reducing the incidence of ORN in the mandible.

The development rate of ORN in the mandible seen in the current study also seemed consistent with those reported in other series. Reuther et al. showed an overall incidence of 8.2% among a group of 830 head and neck tumor patients who had received RT [17]. A review of 402 OPC patients treated with definitive RT by Tsai *et al*., found that ORN in the mandible developed in 30 (7.5%) of these patients; when limited to patients treated with 3DCRT, the incidence was 13% [14].

Regarding prognostic factors, the current study demonstrated that a higher T-category was a significant factor for inferior LRC, DFS, and OS whereas a lower total RT dose was significantly associated with inferior OS. In terms of T-category, our results are consistent with previous reports. Sedaghat et al. analyzed 49 oropharyngeal SCC patients and demonstrated that advanced T-category (T4) was a significant risk factor for recurrence and death [18]. Similarly, Tomita *et al*. reported the results of their detailed prognostic analysis involving 141 OPC patients; they found that T-category and age were significantly associated with OS in multivariate analysis [12]. Regarding RT dose, Agarwal *et al*. demonstrated in their multivariate analysis of 627 OPC cases that a total dose of <66 Gy was an independent prognostic factor for inferior LC, LRC, and DFS [16]. Our results indicated that patients who had received a total RT dose of $\geq$70 Gy achieved superior OS relative to those who had received lower doses. However, we consider that this finding does not suggest the preferred dose for tumor control, because there were few patients who had received $\geq$60 Gy but <70 Gy in our series. In addition, the cohort that received lower doses contained two patients who had ceased treatment; this may have resulted in bias as a consequence of undertreatment. Agarwal et al. excluded patients receiving <60 Gy (usually because of poor tolerance or noncompliance) from the analysis for similar reasons [16]. It is appropriate to conclude that completion of the planned treatment provides more favorable outcomes. Pretreatment hemoglobin level has also been reported to be a significant prognostic factor in previous studies [19, 20]. In our series, although pretreatment hemoglobin level indeed proved to be a significant prognostic factor in univariate analysis, it did not remain statistically significant in multivariate analysis. Similarly, age, PS, disease subsite and N-category were not found to be significant predictors in the multivariate analysis of our series. The inconsistency in the findings between the current study and previous studies might potentially due to the smaller number of patients and relatively short follow-up periods in the current study.

HPV status was not included in the present analysis because there were only 12 (19%) patients with available information. Recently, HPV has been established as a causative agent in OPC and its positive status has been demonstrated as a favorable prognostic factor for survival [21, 22]. We aim to include information on HPV status in the future analysis to establish an optimal, tailor-made treatment strategy.

In the current study, 34.9% (n=22) of patients exhibited double primary cancers, which seems to be a substantially higher rate than previously reported [23]. One possible reason for this is the use of narrow-band imaging endoscopy, which has been reported to provide high sensitivity in detecting early-stage lesions in the upper aero-digestive tract. [24, 25] This technique had recently been introduced in our institution, and may potentially have contributed to the improvement in the accuracy of screening for double primaries.

In conclusion, the employment of 15 MV X-rays in a radiation boost may provide comparable treatment outcomes to a boost employing 4–6 MV X-rays only. However, reduction in the development rate of ORN in the mandible was not demonstrated, and

consequently the usefulness of 15 MV X-rays in a boost remains unclear. Further investigation in a larger population is required.

***Conflicts of interest*:** *Declared none.*

## REFERENCES


1. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, Rosenberg PS, Bray F, Gillison ML (2013) Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. *J Clin Oncol, **31**: 4550-4559*.
2. Hama T, Tokumaru Y, Fujii M, Yane K, Okami K, Kato K, Masuda M, Mineta H, Nakashima T, Sugasawa M, Sakihama N, Yoshizaki T, Hanazawa T, Kato H,Hirano S, Imanishi Y, Kuratomi Y, Otsuki N, Ota I, Sugimoto T, Suzuki S (2014) Prevalence of human papillomavirus in oropharyngeal cancer: a multicenter study in Japan. *Oncology, **87**: 173-182*.
3. Simard EP, Torre LA, Jemal A (2014) International trends in head and neck cancer incidence rates: differences by country, sex and anatomic site. *Oral Oncol, **50**:* 387-403.
4. Setton J, Caria N, Romanyshyn J, Koutcher L, Wolden SL, Zelefsky MJ, Rowan N, Sherman EJ, Fury MG, Pfister DG, Wong RJ, Shah JP, Kraus DH, Shi W,Zhang Z, Schupak KD, Gelblum DY, Rao SD, Lee NY (2012) Intensity-modulated radiotherapy in the treatment of oropharyngeal cancer: an update of the Memorial Sloan-Kettering Cancer Center experience. *Int J Radiat Oncol Biol Phys, **82**:* 291 -298.
5. Ben-David MA, Diamante M, Radawski JD, Vineberg KA, Stroup C, Murdoch-Kinch CA, Zwetchkenbaum SR (2007) Eisbruch A Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: likely contributions of both dental care and improved dose distributions. *Int J Radiat Oncol Biol Phys, **68**:* 396-402.
6. Rathy R, Sunil S, Nivia M (2013) Osteoradionecrosis of mandible: Case report with review of literature. *Contemp Clin Dent, **4**:* 251-253.
7. Radiotherapy Treatment Planning Guidelines 2012, Japanese Society for Radiation Oncology. Accessed Jul 16 2015. Available from: http://www.jastro.or.jp/guideline/child.php?eid=00007.
8. Izuno I, Sone S, Oguchi M, Kiyono K, Takei K (1990) Treatment of early vocal cord carcinoma with $^{60}$Co gamma rays, 8/10 MV x-rays, or 4 MV x-rays--are the results different? *Acta Oncol, **29**:* 637-639.
9. Sobin LH, Gospodarowicz MK, Wittekind Ch (2009) International Union against Cancer (UICC) TNM Classification of Malignant Tumours. 7th ed. Wiley-Blackwell, the United States of America.
10. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer, **45**:* 228-247.
11. NCI Common Terminology Criteria for Adverse Events v4.0 (CTCAE). National Cancer Institute, USA. Accessed Jul 17 2015. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.
12. Tomita N, Kodaira T, Furutani K, Tachibana H, Hasegawa Y, Terada A, Hanai K, Ozawa T, Nakamura T, Fuwa N (2010) Long-term follow-up and a detailed prognostic analysis of patients with oropharyngeal cancer treated with radiotherapy. *J Cancer Res Clin Oncol, **136**:* 617-623.
13. Fukada J, Shigematsu N, Takeda A, Ohashi T, Tomita T, Shiotani A, Kunieda E, Kawaguchi O, Fujii M, Kubo A (2010) Weekly low-dose docetaxel-based chemoradiotherapy for locally advanced oropharyngeal or hypopharyngeal carcinoma: a retrospective, single-institution study. *Int J Radiat Oncol Biol Phys, **76**:* 417-424.
14. Tsai CJ, Hofstede TM, Sturgis EM, Garden AS, Lindberg ME, Wei Q, Tucker SL, Dong L (2013) Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer. *Int J Radiat Oncol Biol Phys, **85**:* 415 -420.
15. Fein DA, Lee WR, Amos WR, Hinerman RW, Parsons JT, Mendenhall WM, Stringer SP, Cassisi NJ, Million RR (1996) Oropharyngeal carcinoma treated with radiotherapy: a 30-year experience. *Int J Radiat Oncol Biol Phys,* **34**: 289-296.
16. Agarwal JP, Mallick I, Bhutani R, Ghosh-Laskar S, Gupta T, Budrukkar A, Murthy V, Sengar M, Dinshaw KA (2009) Prognostic factors in oropharyngeal cancer--analysis of 627 cases receiving definitive radiotherapy. *Acta Oncol, **48**:* 1026-1033.
17. Reuther T, Schuster T, Mende U, Kübler A (2003) Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients--a report of a thirty year retrospective review. *Int J Oral Maxillofac Surg, **32**:* 289-295.
18. Sedaghat AR, Zhang Z, Begum S, Palermo R, Best S, Ulmer KM, Levine M, Zinreich E,Messing BP, Gold D, Wu AA, Niparko KJ, Kowalski J, Hirata RM, Saunders JR, Westra WH, Pai SI (2009) Prognostic significance of human papillomavirus in oropharyngeal squamous cell carcinomas. *Laryngoscope, **119**:* 1542-1549.
19. Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, Bergerot P, Rhein B, Tortochaux J, Calais G (2004) Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol, **22**:* 69-76.
20. Oblak I, Strojan P, Zakotnik B, Budihna M, Smid L (2003) Hemoglobin as a factor influencing the outcome in inoperable oropharyngeal carcinoma treated by concomitant radiochemotherapy. *Neoplasma, **50**:* 452-458.
21. Woods R Sr, O'Regan EM, Kennedy S, Martin C, O'Leary JJ, Timon C (2014) Role of human papillomavirus in oropha-

ryngeal squamous cell carcinoma: A review. *World J Clin Cases, **2**:* 172-193.
22. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML (2010) Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med, **363**:* 24-35.
23. Jones AS, Morar P, Phillips DE, Field JK, Husband D, Helliwell TR (1995) Second primary tumors in patients with head and neck squamous cell carcinoma. *Cancer, **75**:* 1343-1353.
24. Yoshida T, Inoue H, Usui S, Satodate H, Fukami N, Kudo SE (2004) Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. *Gastrointest Endosc, **59**:* 288-295.
25. Watanabe A, Taniguchi M, Tsujie H, Hosokawa M, Fujita M, Sasaki S (2008) The value of narrow band imaging endoscope for early head and neck cancers. *Otolaryngol Head Neck Surg, **138**:* 446-451.