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[Article Full Title]

Dose-finding and efficacy confirmation trial of the superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for locally advanced maxillary sinus cancer (JCOG1212): Results of the efficacy confirmation phase in patients with T4aN0M0

[Short Running Title]

RADPLAT for T4aN0M0 Maxillary Sinus Cancer

[Author Names]

Akihiro Homma, MD, PhD[1], Masashi Mikami, MS[2], Kazuto Matsuura, MD, PhD[3], Rikiya Onimaru, MD, PhD[4], Daisuke Yoshida, MD[5], Hirotaka Shinomiya, MD, PhD[6], Akira Ohkoshi, MD, PhD[7], Ryuichi Hayashi, MD[3], Yuki Saito, MD, PhD[8], Hiroyuki Tachibana, MD[9], Kiyoto Shiga, MD, PhD[10], Tsutomu Ueda, MD, PhD[11], Hirokazu Uemura, MD, PhD[12], Kenichi Nakamura, MD, PhD[2], Haruhiko Fukuda, MD[2], Head and Neck Cancer Study Group of the Japan Clinical Oncology Group (JCOG-HNCSG).

[Author Institutions]

1. Department of Otolaryngology-Head and Neck Surgery, Hokkaido University Hospital, Sapporo, Japan
2. Japan Clinical Oncology Group Data Center/Operations Office, National Cancer Center Hospital, Tokyo, Japan
3. Department of Head and Neck Surgery, National Cancer Center Hospital East, Kashiwa, Japan
4. Department of Radiation Oncology, Tonan Hospital, Sapporo, Japan
5. Department of Diagnostic and Interventional Radiology, Hokkaido University Hospital, Sapporo, Japan.
6. Department of Otolaryngology-Head and Neck Surgery, Kobe University Graduate School of Medicine, Kobe, Japan
7. Department of Otolaryngology, Head and Neck Surgery, Tohoku University Hospital, Sendai, Japan
8. Department of Otolaryngology, Head and Neck Surgery, The University of Tokyo Hospital, Tokyo, Japan
9. Department of Radiation Oncology, Aichi Cancer Center Hospital, Nagoya, Japan
10. Department of Head & Neck Surgery, Iwate Medical University, Shiwa, Japan
11. Department of Otorhinolaryngology, Head and Neck Surgery, Hiroshima University Hospital, Hiroshima, Japan
12. Department of Otolaryngology-Head and Neck Surgery, Nara Medical University, Kashihara, Japan

[Corresponding Author Name & Email Address]

Akihiro Homma
E-mail: ak-homma@med.hokudai.ac.jp

[Author Responsible for Statistical Analysis Name & Email Address]

Masashi Mikami
E-mail: mikamimsncchd@gmail.com

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[Data Availability Statement for this Work]

Anonymized individual participant data that underlie the results reported in this Article will not be shared because patient follow-up will be continued until December 2026. After publication of the final follow-up, using data as of December 2026, the individual participant data that underlie the results will be shared after deidentification to investigators whose proposed data use has been approved by investigators of the JCOG Head and Neck Cancer Study Group identified for that purpose. Proposals should be directed to ak-homma@med.hokudai.ac.jp.

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Abstract

Background: Locally advanced maxillary sinus cancers require radical surgery as a standard treatment. But this often results in significant disfigurement and impairment of function. XXXX seeks to evaluate the safety and efficacy of the superselective intra-arterial infusion of cisplatin and concomitant radiotherapy (RADPLAT) for T4aN0M0 and T4bN0M0 maxillary sinus squamous cell carcinomas (MS-SCC). We herein report the results of the efficacy confirmation phase in the T4a cohort.

Patients and methods: Patients received cisplatin 100 mg/m^2 intra-arterially weekly for 7 weeks with concomitant radiotherapy (total 70 Gy) as determined by the results of the preceding dose-finding phase. The trial aimed to evaluate the primary endpoint of 3-year overall survival (3yr OS), comparing RADPLAT with the historical control for 3yr OS in surgery (80%).

Results: From April 2014 to August 2018, 65 patients were registered in the T4a cohort from 18 institutions, consisting of 54 males and 11 females with a median age of 64 years (range, 40-78 years) and ECOG PS 0/1 (58/7). After excluding one ineligible patient, 64 patients were included in the primary analysis of efficacy and safety. The median follow-up was 4.5 years in all eligible patients, and the primary endpoint for 3yr-OS was 82.8% (90% CI, 73.4%-89.2%). With regard to acute adverse events, mucositis (≥ grade 3), neutropenia (≥ grade 3), increased creatinine (≥ grade 2), hearing impairment (≥ grade 2), and stroke (≥ grade 2) were observed in 20.3%, 14.1%, 3.1%,

3.1%, and 1.6% of patients, respectively. One treatment-related death due to a thromboembolic event was reported.

Conclusion: We demonstrated that RADPLAT showed favorable results for patients with T4aN0M0 MS-SCCs compared with the historical control for 3yr OS in surgery, which was from an earlier period, and showed some specific toxicities. Therefore, RADPLAT, as well as surgery, can be regarded as a possible treatment option for these patients.

Maxillary sinus cancers are mostly detected in the locally advanced stage due to the absence of symptoms in early-stage disease. Locally advanced maxillary sinus cancers require radical surgery with or without complete resection of the orbital contents as a standard treatment. This often results in significant disfigurement and impairment of function, and patient refusal of radical surgery. Minimally invasive endonasal endoscopic surgery has been applied to the management of sinonasal cancers based on recent advances in endoscopic surgical techniques and technologies. Unfortunately, it is not usually applied to locally advanced maxillary sinus cancer due to anatomical limitations. Therefore, the development of a new less-invasive therapy that is as effective as radical surgery is critical.

Intra-arterial (IA) chemotherapy has been applied to treat localized malignant neoplasms in patients with head and neck cancer for over 70 years based on the fact that the head and neck region is particularly well suited to regional chemotherapy as the blood supply to these tumors is primarily derived from branches of the external carotid artery [1,2]. IA chemotherapy has been utilized since the 1960s in Japan, mainly for the treatment of maxillary sinus cancer [3,4]. Despite decades of experience, the use of IA chemotherapy for the treatment of head and neck cancer has not been universally accepted as it has not shown clear benefits [5,6].

Eventually, Robbins et al. developed a specific concomitant chemotherapy protocol for head and neck cancer that used the pharmacologic principles of IA cisplatin while capitalizing on

the cisplatin-neutralizing activity of sodium thiosulfate [7]. As the next step, concomitant radiotherapy was added to the high-dose cisplatin infusion strategy [8]. The regimen, consisting of the combination of radiation therapy and IA cisplatin (hereafter RADPLAT), was mainly indicated for patients with locally advanced head and neck cancers such as oral cavity, laryngeal, oropharyngeal, and hypopharyngeal cancer in Western countries. Based on the promising results reported for RADPLAT by Robbins et al. [8,9], a randomized trial was conducted in the Netherlands comparing RADPLAT with i.v. chemoradiation therapy [10]. After a median follow-up of 33 months, no differences in locoregional control or overall survival were observed between the treatment arms. No follow-up on RADPLAT was undertaken worldwide due to the results of the Dutch trial.

However, RADPLAT has been performed for the patients with locally advanced sinonasal cancer in several institutions and has been reported to result in a favorable survival [11-14]. Therefore, we conducted a dose-finding and efficacy confirmation trial of the superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for locally advanced maxillary sinus squamous cell carcinoma (MS-SCC) (XXXX, Figure 1) [15,16]. We have already reported the results of the dose-finding phase and we herein report the results of the efficacy confirmation phase in the T4a cohort.

PATIENTS AND METHODS

Eligibility

Eligibility criteria in the T4a cohort included the following: primary lesion located at the maxillary sinus; histologically proven squamous cell carcinoma (SCC); clinical stage T4aN0M0; no severe carotid stenosis as evaluated by ultrasonography; aged between 20 and 75 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; no prior therapy for maxillary sinus cancer; no prior radiotherapy to the head and neck or brain; no prior chemotherapy for any other malignancies; sufficient organ function as shown by a peripheral blood white blood cell count of at least 4,000 cells per μL and 12,000 cells per μL or less; hemoglobin concentration of at least 9.5 g/dL; platelet count of at least 100 000 cells per μL; serum total bilirubin concentration of 2.0 mg/dL or less; aspartate aminotransferase of 100 IU/L or less; alanine aminotransferase of 100 IU/L or less; serum creatinine concentration of 1.2 mg/dL or less; normal electrocardiogram; the ability to reach the external carotid arteries from the femoral artery with a catheter; and satisfying the normal tissue radiation dose constraints for the ipsilateral eyeball and optic nerve, spinal cord, brainstem, and chiasma. Written informed consent was obtained from all patients before registration. The eligible criteria were changed as follows; from May 2017, white blood cell count of at least 4,000 cells per μL and no upper limit, and from May 2019, aged 20 years or older; hemoglobin concentration of at least 9.0 g/dL; and serum creatinine concentration of

1.3 mg/dL or less.

Patients were excluded if they had any of the following conditions: simultaneous or metachronous (within 5 years) double cancers other than in situ carcinoma or intramucosal tumors; active infection requiring systemic therapy; body temperature ≥ 38 °C; women during pregnancy, breastfeeding, or within 28 days after delivery; severe psychosis; need for systemic steroid medication or immunosuppressant medication; poorly controlled diabetes mellitus; poorly controlled hypertension; an angina pectoris attack within 3 weeks or myocardial infarction within 6 months; or were positive for serum hepatitis B antigen.

Study Design (Figure 1)

XXXX is a multi-institutional, single-arm, prospective interventional study of superselective intra-arterial infusion of high-dose cisplatin with concomitant radiotherapy for patients with T4aN0M0 and T4bN0M0 locally advanced MS-SCCs conducted in 18 institutions in XXXX. The trial consisted of a dose-finding phase and an efficacy confirmation phase. It was registered with the XXXX and approved by the XXXX [15].

The dose-finding phase was designed to determine the recommended number of cycles through the study of patients with either T4aN0M0 or T4bN0M0 tumors. In this phase, 100 mg/m^2 of cisplatin was administered intra-arterially weekly for 7 weeks with concomitant radiotherapy

(70 Gy/35 fractions) [16]. As a result, all 18 patients received a full dose of radiotherapy. The number of cycles of cisplatin was 7 in 13 patients and 6 in 5 patients. Dose-limiting toxicities were observed in 5 patients. These results indicated that this therapy is safe and well-tolerated at 7 cycles of cisplatin, which was determined to be the recommended number of cycles for locally advanced MS-SCC.

In the efficacy confirmation phase, the objective is to evaluate the efficacy and safety of RADPLAT for patients with locally advanced MS-SCC. The efficacy confirmation phase is being conducted separately for patients with T4aN0M0 and T4bN0M0 MS-SCC.

Per-protocol disease assessment (physical examination, magnetic resonance imaging of head and neck, and thoracoabdominal computed tomography) and adverse event data were required every 3 months for the first year, every 4 months for year 2 and 3, and then every 6 months for year 4 and 5. All patients who were enrolled in the study were to be followed for at least 5 years, while analysis of the primary endpoint of the efficacy confirmation phase was planned to be conducted 3 years after accrual completion.

Endpoints

The primary endpoint of the efficacy confirmation phase was the 3-year overall survival (OS), and the secondary endpoints were OS, event-free survival (EFS), local event-free survival

(LEFS), clinical complete response rate, incidence of adverse events, and serious adverse events. OS was computed from the date of registration to the time of death from any cause. EFS was computed from the date of registration to the death from any cause, any progression (including recurrence), and salvage surgery. LEFS was computed from the date of registration to the death from any cause, primary disease progression (including recurrence), and salvage surgery for the primary lesion. The clinical complete response rate was determined from the proportion of complete responses (CRs) and good partial responses (good PRs) among all eligible patients. Good PR was characterized as a secondary change unique to post CRT that was regarded as a remaining scar but not as a residual tumor. Good PR in this study was defined as lesions ≤10 mm in size or those not enhanced on contrast-enhanced MRI. This criterion was used in JCOG0706 by the same head and neck cancer group [17], and was applied in this study as well. Toxicities were evaluated according to the Common Toxicity Criteria for Adverse Events version 4.0.

Treatments

The protocol treatment consisted of weekly superselective intra-arterial infusion of cisplatin with concomitant radiotherapy and salvage surgery where necessary.

Chemotherapy

One hundred mg/m^2 of cisplatin was administered intra-arterially weekly for 7 weeks. At

the same time, sodium thiosulfate was administered at a dose of 20 g/m^2 intravenously to neutralize the cisplatin. Digital subtraction angiography and/or an IVR-CT system, which combines angiography and CT imaging with the patient remaining on the same table, was performed to accurately and carefully identify the arteries feeding the tumor and their perfusion. Tumors of the maxillary sinuses are usually fed by the internal maxillary artery, but for cases in which the facial artery, transverse facial artery, or so on fed the tumor, part of the dose was administered through these alternative arteries. The dose of cisplatin infused from each artery was determined as described in previous reports [13, 18]. Seven cycles, which was determined as the recommended number of cycles in the dose-finding phase, was applied in the efficacy confirmation phase. To control the quality of the interventional technique, central review of photographs and movies in arbitrarily selected patients was performed at a semiannual investigators' meeting. All interventional procedures were performed or directly supervised by interventional radiologists certified by the study chair.

Radiation therapy

Three-dimensional conformal radiation therapy (3D-CRT) or intensity-modulated radiation therapy (IMRT) was chosen at institutional discretion (this study began in April 2014 and IMRT became available after March 2016). For quality control and assurance of radiation therapy, compliance with protocol-specified radiation therapy planning was examined for all enrolled

patients at completion of radiation therapy.

Radiation therapy was administered with high-energy photons of 4–10 MV X-rays to a total dose of 70 Gy in 2 Gy fractions five times weekly. The gross tumor volume (GTV) included the volume of the primary tumor. The clinical target volume (CTV) included the GTV with a 0.5 cm margin and at least the entire ipsilateral maxillary sinus. The CTV did not include the area of potential lymph node metastasis in the neck. The planning target volume (PTV) for the CTV was defined as a 0.5 cm margin around the CTV to compensate for set-up variations and internal organ motion. To protect normal vital structures, such as the contralateral eye ball and/or optic nerve, chiasma, spinal cord and brain, a partial reduction in the PTV margin of 0.1 cm from the initial 0.5 cm was allowed. The protocol specified that any reduction in the PTV margin solely for the reason of lowering the dose to the affected eye was not acceptable, based on the idea that the risk of visual impairment in this patient group is deemed acceptable.

Statistical analysis

This trial aimed to evaluate the efficacy of RADPLAT for patients with T4aN0M0 in the efficacy confirmation phase.

For T4aN0M0, the primary endpoint of the 3-year survival was used to evaluate whether RADPLAT therapy is non-inferior to surgery, which is the current standard of care, and whether

it is superior to intravenous chemotherapy and radiotherapy (IV-CRT), which is used for patients who refuse surgery as a secondary hypothesis.

The historical control was based on data collected from 28 high-volume centers in Japan [19]. Among the cases of previously untreated T4 maxillary sinus squamous cell carcinoma that were treated at each center from 2006 to 2008, the 3-year OS of 30 patients that underwent curative surgery and 6 patients who received IV-CRT with T4aN0M0 was 81.8% and 66.7%, respectively. Based on the above, the historical control for the 3-year survival was set at 80% for surgery and 65% for IV-CRT [19]. Therefore, we test the null hypothesis that the RADPLAT would result in a true 3-year OS rate of 65% or less against the alternative hypothesis of a true 3-year OS rate of 80% or greater. As the hypothesis we sought to test in this study was one-sided, the level of significance was one-sided 5%. A sample size of 62 was required to achieve 80% power with a one-sided 5% significance level (https://support.sas.com/documentation/onlinedoc/stat/121/power.pdf). Patients who received less than or equal to the recommended number of doses in the dose-finding phase were considered to have a low risk of bias for overestimation of efficacy and were therefore included in the efficacy confirmation phase. In view of some ineligibility and lost to follow-up, the planned number of patients enrolled was 65 for T4aN0M0.

For all eligible patients, the 90% confidence interval for the 3-year survival estimated by the Kaplan-Meier method was calculated by the Greenwood formula to determine whether the

null hypothesis could be rejected. When the lower bound of the 90% confidence interval exceeded 65%, the threshold 3-year survival, the null hypothesis was rejected and judged to show non-inferiority to surgery as well as superiority to IV-CRT.

OS, EFS, LEFS were calculated by the Kaplan-Meier method. Hazard ratios (HRs) were computed using a univariable Cox proportional hazards model to compare the efficacy between subgroups, and two-sided Wald-type p-value were reported. Confidence interval for complete response rate was calculated by exact methods. All analyses were performed using SAS version 9.4.

RESULTS

Patient Characteristics

From April 2014 to August 2018, 65 patients were registered in the T4a cohort from 18 institutions, consisting of 54 males and 11 females with a median age of 64 years (range, 40-78 years) and an ECOG performance status of 0/1 (58/7) (Table 1). After the exclusion of one ineligible patient who did not fulfill the inclusion criteria because of moderate or greater stenosis of the common and internal carotid arteries, 64 patients were included in the primary analysis of efficacy and safety (Figure 2). Thirty-one patients received 3D-CRT and 33 received IMRT.

Efficacy

The complete clinical response rate among all eligible patients was 73.4% (47/64, 95% CI, 60.9%-83.7%), with 15 showing a CR and 32 showing a good PR. A case that achieved CR is presented in Supplementary Figure S1.

The median follow-up was 4.5 years in all eligible patients and the primary endpoint for 3yr OS was 82.8% (90% CI, 73.4%-89.2%), which met the prespecified hypothesis (Figure 3A). Regarding the cause of death, 12 patients died with the disease, while there was one treatment-related death and one death of other cause. The 3yr EFS and 3yr LEFS were 60.9% (95% CI, 47.9%-71.7%) and 65.6 % (95% CI, 52.5%-75.8%), respectively (Figure 3B, 3C). The 3yr OS,

EFS, and LEFS for all enrolled patients were 83.1% (95% CI, 71.5%-90.2%), 60.0% (95% CI, 47.1%-70.7%) and 64.5 % (95% CI, 51.6%-74.8%), respectively (Supplementary Figure S2). In an unplanned subgroup analysis, the OS, EFS, and LEFS curves by radiation technique are also shown in Supplementary Figure S3. Further, local event-free survival, regional lymph node event-free survival, and distant metastasis event-free survival are also shown in Supplementary Figure S4.

Safety

Median total dose and duration of radiotherapy was 70 Gy (interquartile range: 70-70 Gy) and 51 days (interquartile range: 50-52 days), respectively, with the median number of cycles of cisplatin being 7 (interquartile range: 6.5-7 cycles). The results of quality assurance for radiotherapy showed one unacceptable deviation in which a patient underwent IMRT in an uncertificated institution. There was one case of acceptable deviation in which only the brain exceeded the dose constraint. The case could have been corrected by prospective QA. With regard to acute adverse events, Grade 4 toxicities (neutropenia in 2 and anemia in 1) were observed, but they were not life-threatening. Mucositis (≥ grade 3), neutropenia (≥ grade 3), increased creatinine (≥ grade 2), hearing impairment (≥ grade 2), and stroke (≥ grade 2) were observed in 13 (20.3%), 9 (14.1%), 2 (3.1%), 2 (3.1%), and 1 (1.6%) patient, respectively (Table 2). Adverse events according to radiation techniques and maximum irradiated dose to both eye and chiasm are shown

in Supplementary Table S4 and S5, respectively. One treatment-related death due to a thromboembolic event was reported. The next morning after undergoing the 3rd session of IA chemotherapy at a dose of 20 Gy/10 fractions, the patient suddenly experienced a loss of consciousness and cardiac arrest while walking. The patient could not be revived despite resuscitation efforts and passed away. There were no previous special episodes or symptoms before this incident. Based on investigations conducted both internally and externally, the cause of death was determined to be pulmonary embolism. Myocardial infarction and cerebrovascular disorders were ruled out.

In terms of late adverse events (≥ grade 3), osteonecrosis of mandible, fatigue, and trismus were observed in 2 (3.2%), 1 (1.6%), and 1 (1.6%) patient, respectively. In addition, retinopathy in 11 (17.5%) and cataract in 8 (12.7%) patients were observed as affected-side eye disorders. Two patients had Grade 4 corneal ulceration. These patients received a maximum dose of 73.6 Gy and 73.8 Gy, respectively, to the eyeball on the affected side, and both were treated with IMRT.

Pattern of relapse and salvage surgery (Figure 4)

Twenty-five patients had residual or recurrent disease as follows: the primary site was involved in 17, regional lymph nodes involved in 6 and distant metastasis in 6 (some overlapping). In terms of the primary site, of the 8 patients with residual disease, 6 received salvage surgery, with 3 of them alive to date and 3 dead. On the other hand, none of the 9

patients with recurrent disease received salvage surgery.

Six patients had regional lymph node recurrence, with 4 of them undergoing neck dissection. As a result, 2 of the patients who received surgery are alive to date and the remaining 4 patients dead. These patients also had primary residual/recurrent disease or distant metastasis.

DISCUSSION

We demonstrated that RADPLAT showed favorable results for patients with T4aN0M0 MS-SCCs compared with the historical control for 3yr OS in surgery, which was from an earlier period. First of all, inclusion criteria in terms of clinical stage should be discussed. T4 disease is subdivided into T4a and T4b disease. In the 6th edition of the AJCC/UICC staging, T4a was classified as resectable, while T4b was classified as unresectable. However, the criteria for resectability or unresectability may vary depending on advancements in surgical techniques and the expertise of the facility and surgeon. In the 7th edition, although there were no changes in the classification itself, T4b was defined as "very advanced." However, T4b is still considered to consist of unresectable cases and cases on the border between surgical resectability and unresectability.

T4a disease is treated with total maxillectomy or extended total maxillectomy (including orbital content resection) as the standard treatment. These surgeries often result in significant changes in facial appearance and functional impairments, leading to a considerable number of patients refusing surgery. Therefore, the development of treatment approaches that improve prognosis while preserving aesthetics and function can be beneficial for patients, which is why T4a was chosen as the target in this study. On the other hand, T4b is not generally indicated for surgery and is commonly treated with chemoradiotherapy (IV-CRT). Moreover, the prognosis for

T4b is worse than that for T4a. Therefore, T4b was also included as a target in this study and analyzed separately from T4a disease. Our plan was to complete patient enrollment for both T4a and T4b simultaneously and also publish the results simultaneously. However, patient registration for T4a ended earlier than planned, while that for T4b experienced delays. Therefore, it was decided to publish the results separately. With regard to T3, the changes in facial appearance are not a significant concern even after surgery. Thus, the benefits of RADPLAT are considered limited in such cases and, therefore, patients with T3 tumors were excluded from the study.

Patients with maxillary sinus cancer who have lymph node metastasis have a poorer prognosis compared to those without lymph node metastasis [19, 20]. This trial aims to evaluate the effectiveness of RADPLAT, which is predicted to be highly effective against the primary tumor. Due to the complexity of the analysis that would arise from including patients with lymph node metastasis, such patients were also excluded from this study.

Ideally, this trial should have been planned as a randomized trial comparing RADPAT with surgery, which is the current standard of care for T4aN0M0 patients. However, in reality, we considered that it was impossible to recruit patients for a randomized trial comparing surgical interventions such as total maxillectomy, often with orbital content removal, in addition to the fact of the rarity of MS-SCC. Historical control was gathered from 28 high-volume centers in XXXX between 2006-2008. The 3yr OS was 81.9% and 66.7% for surgery and IV-CRT,

respectively [19]. Then we set the expected 3-year survival as 80% for surgery and 65% for IV-CRT. Previous reports did not focus on the results of T4aN0M0. However, Cantù et al. reported that the 2yr and 5yr overall survival for T4(a+b) were 60.2% and 35.9%, respectively, while the 2yr and 5yr OS for N0 were 70.3% and 50.6%, respectively [21]. Thus, we considered that the historical control was appropriate for comparison with the study treatment.

We would like to emphasize that RADPLAT is not a surgical approach. Further we do not consider this treatment to be minimally invasive; rather, we consider it to be a taxing alternative treatment to surgery. In addition, patients eligible for this study are patients with T4a and T4b tumors, where surgery would involve the removal of the orbital content, including the eyeball. Therefore, the radiotherapy treatment plan for the affected eye is based on the concept that the sacrifice of visual acuity is unavoidable, if necessary. Thus, it is significant that patients who need to receive total maxillectomy often with the orbital content removal expect similar survival from RADPLAT without surgery. As a result, the 3yr LEFS was 65.6%, but it was beneficial that more than half of patients did not receive surgery and remain alive.

As to the OTT, the protocol requires that the absence of severe hematologic toxicity is to be confirmed the day before or on the day of intra-arterial cisplatin administration. The protocol also prescribes that the start of radiation therapy is preferred to be the same day as the intra-arterial administration of CDDP. Therefore, the hematotoxicities should be evaluated on a weekday, and

radiotherapy started on the next day. Such a schedule would not allow radiotherapy to start on Monday, so the OTT of this study is longer than or equal to 49 days. Adding to that, as Japan has national holidays in every month except June, the OTT is sometimes longer due to the national holidays. Thus, the minimum OTT was longer than expected in this study.

With regard to management of the neck, the results of a survey conducted at JCOG participating facilities when making the protocol for this study revealed that no facility was administering elective nodal irradiation (ENI) for T4N0M0 patients. ENI along with the primary tumor inevitably causes mucositis during treatment and worsening of dry mouth after treatment. Consequently, it was decided not to administer ENI in this study. In contrast, in Western countries, ENI is frequently employed for sinonasal cancer, even in the absence of lymph node metastasis. Among patients without lymph node metastasis, the risk of subsequent lymph node recurrence has been found to range from 3 to approximately 30 percent in different series[22, 23]. There is an argument that while ENI can reduce the incidence of neck recurrence, most such relapses are associated with other sites of involvement, and it is not clear that there is an impact on overall survival. In the present study, 2 patients with lymph node recurrence only were successfully salvaged by surgery, whereas disease in the remaining 4 patients with other sites of involvement was not well controlled. Based on the above, we consider that our strategy of omitting ENI is acceptable. IA chemotherapy has been applied to head and neck cancer since 1960s [1-6].

However, it has not shown real benefits to date. The Dutch trial failed to show that RADPLAT had any positive effect on survival or locoregional control compared with IV-CRT [10]. However, good results obtained by RADPLAT for MS-SCC were reported from Japan, although such results were from a single center, retrospective study [12, 14, 18]. Furthermore, the low frequency of lymph node and distant metastasis at the first presentation as well as the fact local failure remains the most common site of failure and cause of death in this patient population compared with other head and neck cancers such as oral cavity and pharyngeal cancer were considered as additional reasons for RADPLAT, which targets the primary lesion, being suitable for maxillary sinus cancer [22, 24].

The angiographic technique is one of the keys to the success of RADPLAT. The training workshops before and during the study period together with semiannual investigator meetings are thought to have contributed to the safe performance of the procedure and the good treatment outcomes. Stroke is the main concern in relation to this therapy. It was reported to affect 3.3% (≥ grade 3) [25] 6.8% (≥ grade 2) [10], and 8.2% (≥ grade 3) of patients [26]. However, there was only two cases of stroke (3.1%, grade 1 and 2) observed in this study. We believe that this was due to the workshops and investigator meetings, the appropriateness of our certified system for interventional radiologists, exclusion criteria such as severe carotid stenosis, and the advances in vascular interventional radiology techniques. Based on our experience, RADPLAT could be

introduced in any institution across the globe as long as the treatment is performed in collaboration with interventional radiologists, even if they are not familiar with the head and neck area. At the start of this study, there were few hospitals with a lot of experience in RADPLAT, but it was successfully introduced and implemented in all hospitals without any problems.

Acute adverse events were generally equally frequent with the standard 3-weekly CDDP-RT regimen although high dose cisplatin was administered [27]. This is thought to have been due to the neutralization of cisplatin by sodium thiosulfate. However, it is necessary to carefully observe for the occurrence of late adverse events associated with RADPLAT such as brain necrosis, osteoradionecrosis, eye problems, and so on.

Our trial had some limitations. First, maxillary sinus cancers are a rare disease, so we considered that it was difficult to recruit patients for a randomized trial comparing our treatment regimen to surgery. In addition, a randomized controlled trial comparing highly invasive surgery with non-surgical treatment was considered difficult to conduct because of patient refusal. For this reason, we had to conduct the trial with a design that allowed comparison with a historical control. Despite this comparison with the standard of care; i.e., surgery, we understand that it cannot be claimed that the non-inferiority of RADPLAT to surgery has been demonstrated, given the fact that this comparison was with a historical control. Second, the disease stage that met the eligibility criteria was very limited. Patients with lymph node metastasis were excluded to

ensure homogeneity of the population and evaluate the efficacy of RADPLAT more clearly as they were reported to have a poorer prognosis than those without lymph node metastasis as mentioned earlier [18, 20]. In T3 stage, facial deformities after surgery are expected to be acceptable; thus, RADLAT is not considered to be necessary. In addition, for T4bN0M0, the primary endpoint of the 3-year survival is used to evaluate whether RADPLAT treatment is better than IV-CRT therapy, the current standard-of-care therapy. The primary endpoints differ between T4aN0M0 and T4bN0M0. As a result, the eligible stage was very limited in this study.

In addition, IMRT, particle radiotherapy and induction chemotherapy are promising approaches and have been applied to locally advanced maxillary sinus cancer in practice. They are also considered to contribute to improved treatment outcomes in such cancers [28]. As the study was designed in 2012, we set the historical control from this earlier period, which became one of the limitations of this study.

In conclusion, we demonstrated that RADPLAT showed favorable results for patients with T4aN0M0 MS-SCCs compared with the historical control for 3yr OS in surgery, which was from an earlier period, and had a specific toxicity profile. Therefore, RADPLAT should be considered the new standard treatment option in addition to surgery for these patients. This can be regarded as good news for patients who are hesitant to receive total maxillectomy with or without a complete resection of the orbital contents.

PRIOR PRESENTATION

Presented at the XXXX.

Declaration of Generative AI and AI-assisted technologies in the writing process

We did not use generative artificial intelligence (AI) and AI-assisted technologies in the writing process at all.

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15. XXXX

16. XXXX

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Figure Legends

Figure 1. Patient flow diagram of a dose-finding and efficacy confirmation trial of superselective intra-arterial infusion and concomitant radiotherapy for patients with locally advanced maxillary sinus squamous cell carcinoma. SCC, squamous cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status

Figure 2. CONSORT diagram

Figure 3. (A) The Kaplan-Meier curve for overall survival for all eligible patients. The symbols indicate censored observation. The 3yr OS was 82.8% (90% CI, 73.4%-89.2%). The lower boundary of the two-sided 90% confidence interval (CI) exceeded the threshold of 65% for the 3yr OS. (B) The Kaplan-Meier curve for event-free survival for all eligible patients. (C) The Kaplan-Meier curve for local event-free survival for all eligible patients.

Figure 4. Pattern of recurrence (A) and the timing and outcomes for patients with residual/recurrent primary disease (B) and those with recurrent neck disease (C).

Table 1. Baseline Characteristics of All Enrolled Patients (n=65)

Characteristic	
Age, years	
Median	64
Range	40-78
Sex	
Male	54
Female	11
ECOG performance status	
0	58
1	7
T classification	
T4a	65
Histology	
Well differentiated	7
Moderately differentiated	16
Poorly differentiated	13
Unknown	28
Missing	1

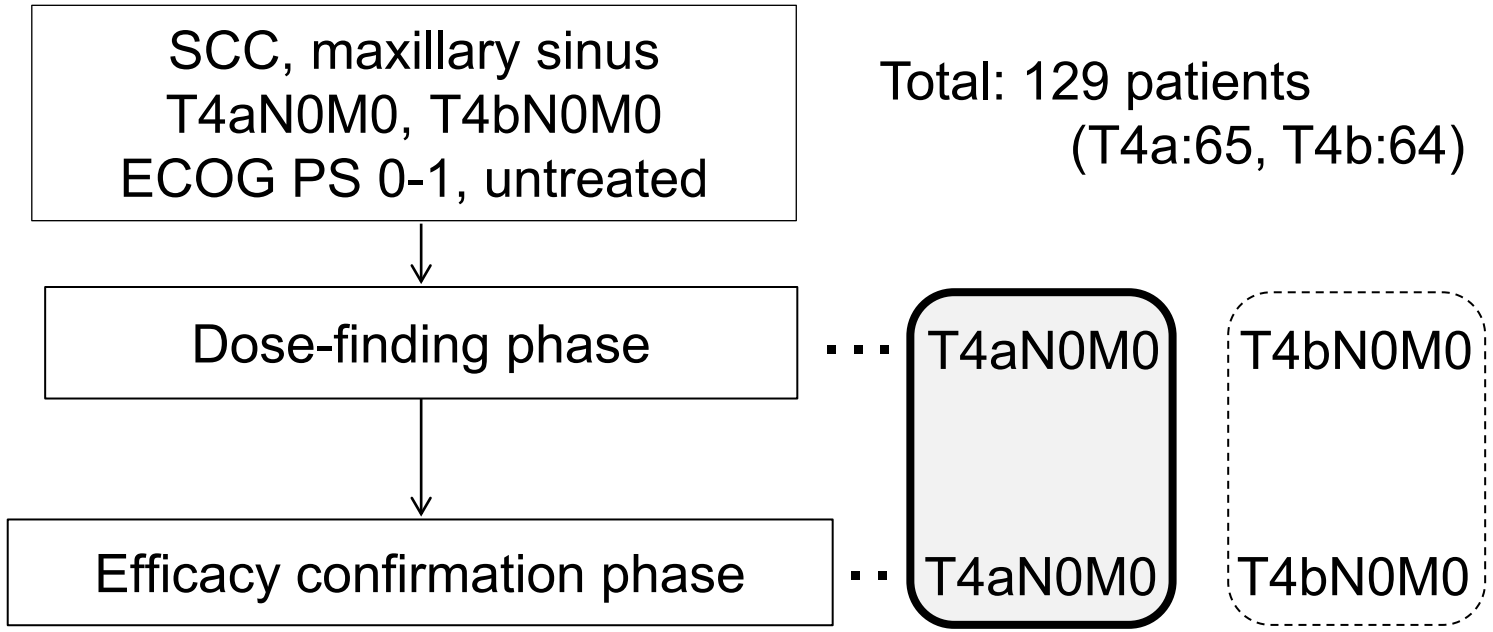
Abbreviations: ECOG, Eastern Cooperative Oncology Group

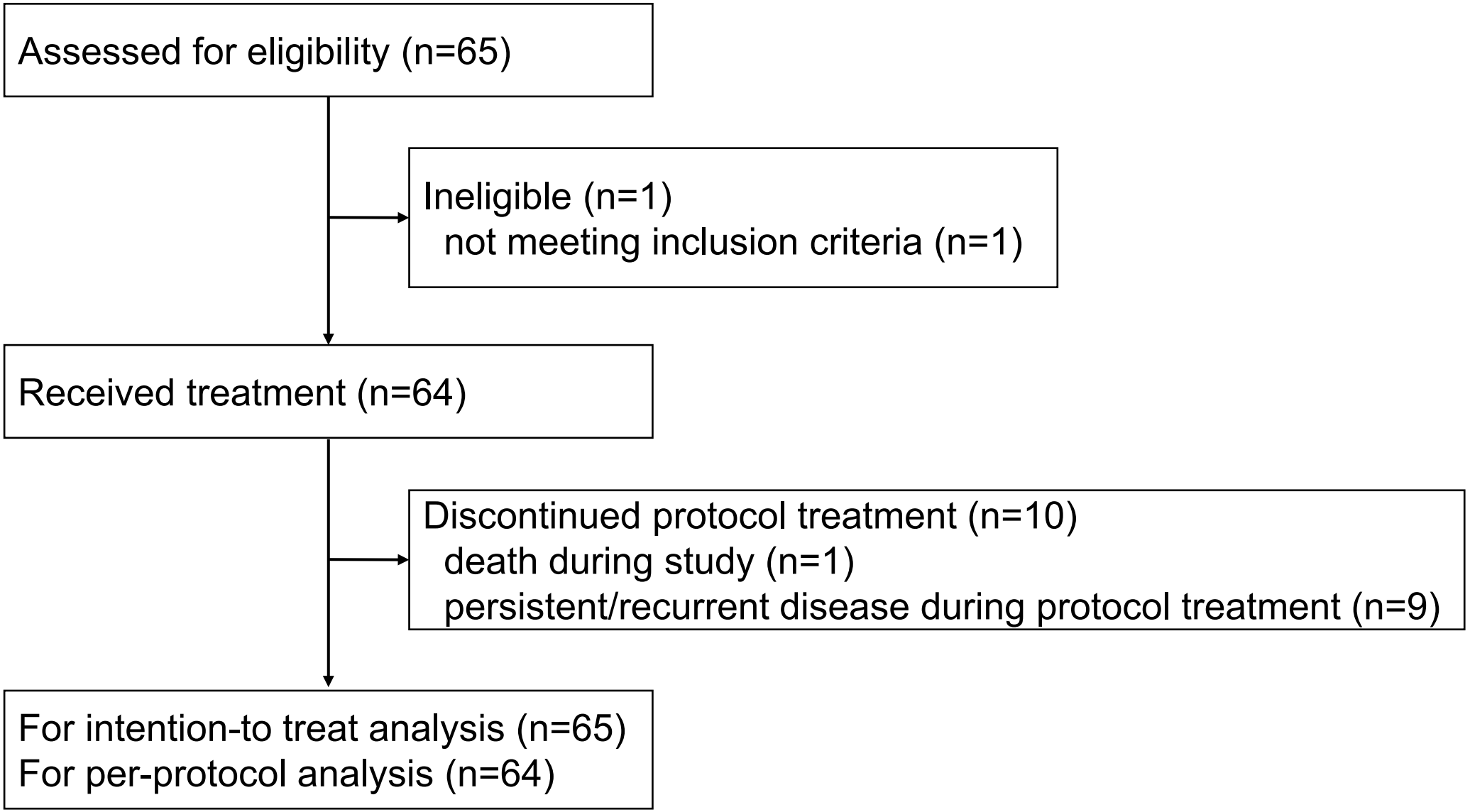
Table 2. Summary of Acute and Late Adverse Events

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	%G3-4
Acute (n=64)					
Leukocytopenia	6	19	12	0	18.8
Neutropenia	11	12	7	2	14.1
Thrombocytopenia	26	4	4	0	6.3
Febrile neutropenia	-	−	0	0	0
Fever	7	5	1	0	1.6
Creatinine increase	7	2	0	0	0
Anemia	23	18	5	1	9.4
Mucositis	10	39	13	0	20.3
Radiation dermatitis	31	28	4	0	6.3
Hearing disturbance	3	1	1	0	1.6
Fatigue	16	2	1	−	1.6
Dysphagia	2	3	0	0	0
Nausea	15	5	2	−	3.1
Stroke	1	1	0	0	0
Facial nerve disorder	0	0	0	0	0
Epistaxis	16	4	0	0	0
Watering eyes*	25	8	0	−	0
Cataract*	8	0	0	0	0
Corneal ulcer*	−	4	1	0	1.6
Retinopathy*	0	0	2	0	3.1
Glaucoma*	1	1	0	0	0
Late (n=63)					
Hearing impairment	8	4	0	0	0
Peripheral sensory neuropathy	1	2	0	0	0
Fatigue	1	3	1	-	1.6
Osteonecrosis of mandible	3	1	2	0	3.2
Trismus	8	2	1	-	1.6
Central nervous system necrosis	3	0	0	0	0
Stroke	1	0	0	0	0
Facial nerve disorder	2	0	0	-	0
Eyelid function disorder*	1	4	0	-	0

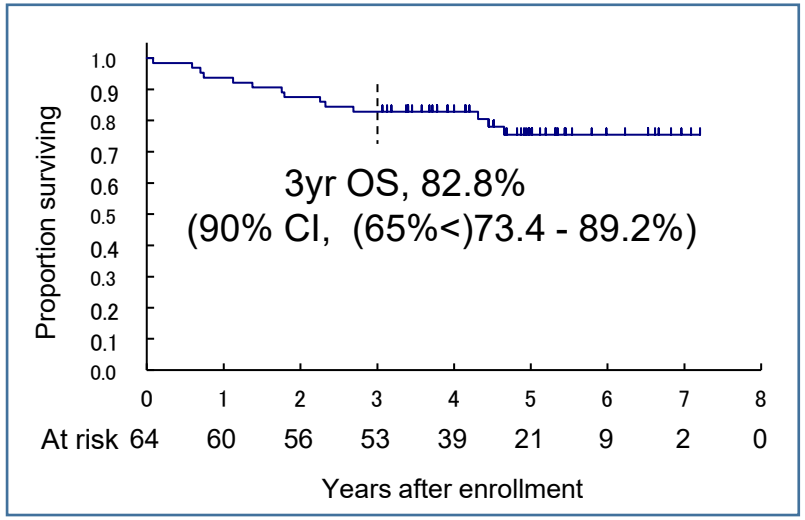
Watering eyes*	26	5	1	-	1.6
Cataract*	3	3	7	1	12.7
Corneal ulcer*	-	5	1	2	4.8
Retinopathy*	2	2	8	3	17.5
Glaucoma*	1	0	2	1	4.8
Periorbital infection*	-	2	0	0	0

*Affected side

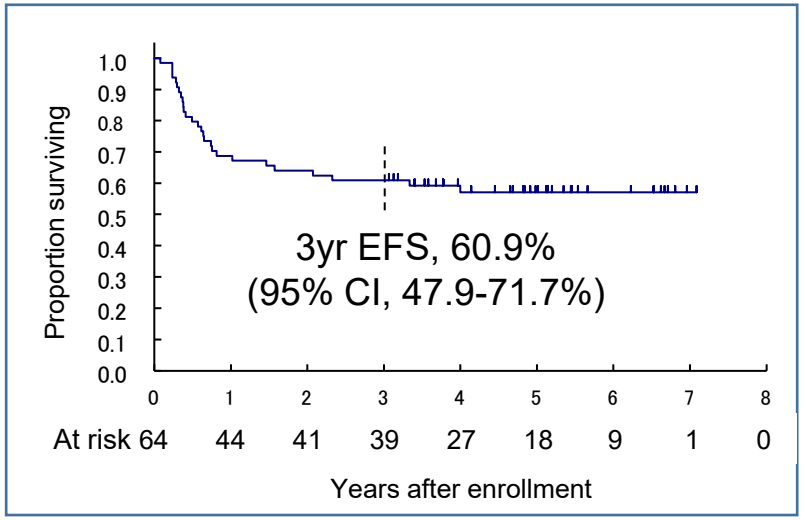

SCC, maxillary sinus
T4aN0M0, T4bN0M0
ECOG PS 0-1, untreated
Total: 129 patients
(T4a:65, T4b:64)
Dose-finding phase
Efficacy confirmation phase
T4aN0M0
T4aN0M0
T4bN0M0
T4bN0M0


Assessed for eligibility (n=65)
Ineligible (n=1)
not meeting inclusion criteria (n=1)
Received treatment (n=64)
Discontinued protocol treatment (n=10)
death during study (n=1)
persistent/recurrent disease during protocol treatment (n=9)
For intention-to treat analysis (n=65)
For per-protocol analysis (n=64)

(A)


Proportion surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
3yr OS, 82.8%
(90% CI, (65%<)73.4 - 89.2%)
0 1 2 3 4 5 6 7 8
At risk 64 60 56 53 39 21 9 2 0
Years after enrollment

(B)


Proportion surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
3yr EFS, 60.9%
(95% CI, 47.9-71.7%)
0 1 2 3 4 5 6 7 8
At risk 64 44 41 39 27 18 9 1 0
Years after enrollment

(C)

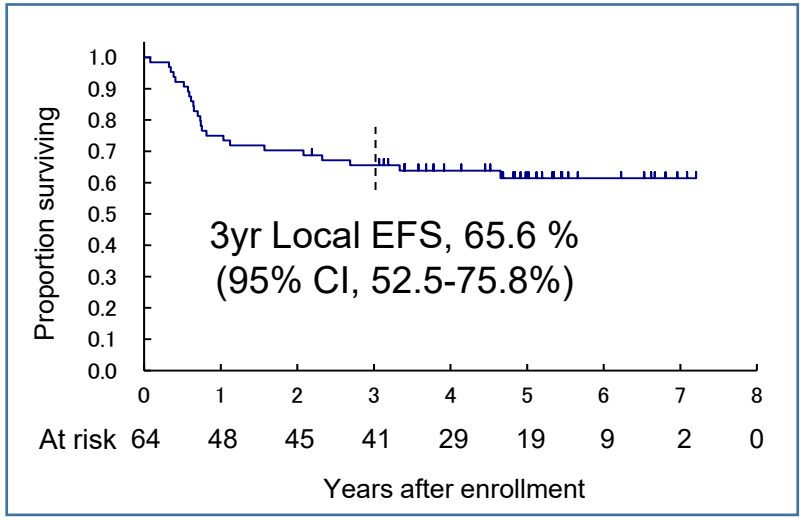
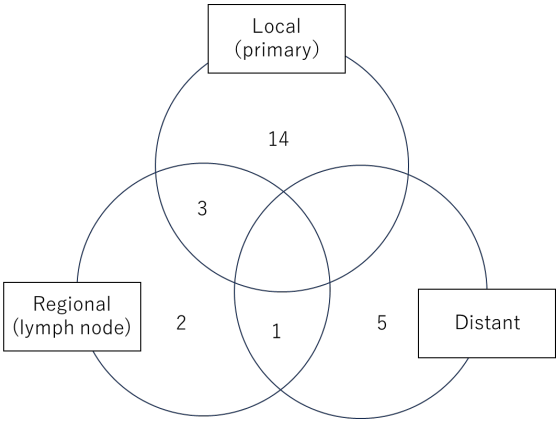
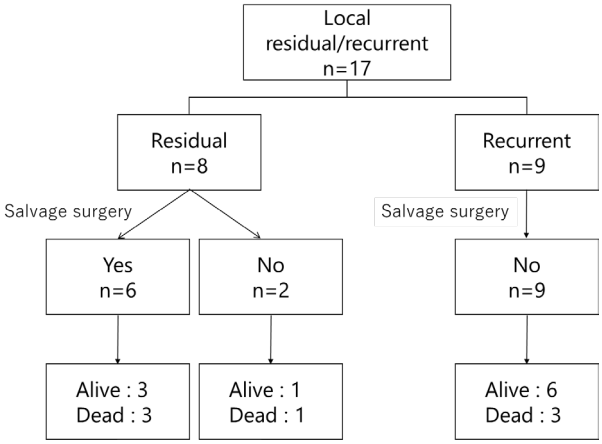

Proportion surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
3yr Local EFS, 65.6 %
(95% CI, 52.5-75.8%)
0 1 2 3 4 5 6 7 8
At risk 64 48 45 41 29 19 9 2 0
Years after enrollment

Figure 4.

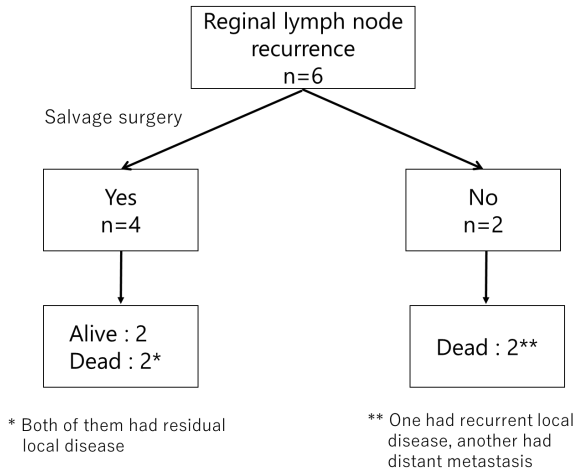
(A)


Local
(primary)
14
3
Regional
(lymph node)
2
1
5
Distant

(B)


Local
residual/recurrent
n=17
Residual
n=8
Recurrent
n=9
Salvage surgery
Salvage surgery
Yes
n=6
No
n=2
No
n=9
Alive : 3
Dead : 3
Alive : 1
Dead : 1
Alive : 6
Dead : 3

(C)


Reginal lymph node
recurrence
n=6
Salvage surgery
Yes
n=4
No
n=2
Alive : 2
Dead : 2*
Dead : 2**
* Both of them had residual
local disease
** One had recurrent local
disease, another had
distant metastasis