Invasion of Pterygoid Plates; an Indicator for Regional Lymph Node Failure in Maxillary Sinus Cancer

Yasuo Kosugi (ykosugi@juntendo.ac.jp)
Juntendo Daigaku https://orcid.org/0000-0002-7974-2060
Terufumi Kawamoto
Juntendo Daigaku
Masaki Oshima
Juntendo Daigaku
Mitsuhisa Fujimaki
Juntendo Daigaku
Shinichi Ohba
Juntendo Daigaku
Fumihiko Matsumoto
Juntendo Daigaku
Naoto Shikama
Juntendo Daigaku
Keisuke Sasai
Juntendo Daigaku

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Abstract

Purpose: The aim of this study was to evaluate the long-term treatment results of combined superselective intraarterial chemotherapy and radiation therapy for advanced maxillary sinus cancer (MSC) and the incidence of regional lymph node failure, and to reveal the clinical and anatomical predictive factors for metastasis.

Methods: We retrospectively evaluated 55 consecutive patients with locally advanced squamous cell carcinoma of the maxillary sinus who were treated with external radiotherapy and superselective intraarterial chemotherapy. Elective nodal irradiation (ENI) was performed only in the clinical node-positive (cN+) cases and not in the clinical node-negative (cN0) cases.

Results: Thirty-eight patients were cN0, and 17 were cN+ at diagnosis. Regional lymph node metastases occurred in 7 of 38 patients with cN0, and 2 of 17 with cN+ during the median follow-up period of 36 months. There were more cases of high-grade (3 or 4) late adverse events in the ENI group than in the non-ENI group (13% vs. 41%, respectively; $p = 0.03$). In cN0 cases without ENI, invasion of the pterygoid plates (57% vs. 90%; $p < 0.01$) and oral cavity (35% vs. 92%; $p = 0.02$) was significantly correlated with a low 5-year regional recurrence-free rate.

Conclusions: Patients with MCS and invasion of the pterygoid plates and oral cavity can be considered appropriate candidates for ENI.

Introduction

Maxillary sinus cancer (MSC) is a relatively rare disease, with an incidence of 1 per 100,000 person-years, accounting for 3% of all head and neck cancers [1]. There is a paucity of prospective randomized studies to lead clinical practice because of the rarity of this disease. The combination of resection, external beam radiotherapy, and systemic chemotherapy is an international standard treatment [2, 3]. The National Comprehensive Cancer Network (NCCN) guidelines recommend elective nodal irradiation (ENI) for patients with T3 or T4 MSC, even in clinical node-negative (cN0) cases [2]. A meta-analysis indicated that ENI can significantly reduce the incidence of regional failure in cN0 cases. However, the use of ENI for MSC is controversial because of the variability in the frequency of regional failure of 3–33% [1], and the lack of reliable evidence. Furthermore, the long-term safety of ENI as a treatment for patients with advanced MSC is unknown due to its poor prognosis [3, 4].

The combination of radiation therapy and intraarterial (IA) chemotherapy is a promising treatment for unresectable or surgery-refused MSC because of its high local control rate and overall survival [5, 6]. This is a popular treatment in Japan, and although it is not a standard method, we have treated patients with locally advanced MSC using this combination, and reported good results [7]. In this setting, we have performed ENI only for patients with regional lymph node metastasis (cN+). The aim of this study was to evaluate the long-term treatment results of advanced MSC and to clarify the incidence of regional lymph node failure and its predictive factors.

Materials And Methods

Study design and data collection

We retrospectively analyzed data for 55 consecutive patients with locally advanced squamous cell carcinoma of the maxillary sinus who were treated with external beam radiotherapy and IA chemotherapy from April 2009 to August 2017 at our institution. All patients had unresectable MSC or refused surgery. The ethics committee of our hospital approved the study protocol (approval number: 19-173), and the study was conducted in accordance with the principles of the Declaration of Helsinki. In accordance with the Union for International Cancer Control (UICC, 7^{th} edition) [8], staging was performed based on physical examination, computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography-CT (PET-CT) findings.

Treatment

External beam radiotherapy was provided using three-dimensional conformal radiotherapy (3DCRT) in 44 patients until June 2015 and intensity-modulated radiation therapy (IMRT) in 11 patients after July 2015. The patients were immobilized using a thermoplastic mask, and radiotherapy and IA chemotherapy were performed simultaneously. The primary sites and lymph node (LN) metastases were irradiated with 60–70 Gy (median, 60 Gy) in 30–35 fractions over 6–7 weeks. The dose of ENI was 46 Gy in 23 fractions by 3DCRT or 50 Gy in 25 fractions by IMRT (median, 46 Gy) for cN+ cases; ENI was not performed in cN0 cases. Ipsilateral levels I, II, and III were set for regional irradiation, and contralateral levels II and III were additionally included in cases of bilateral LN metastases at presentation. We provided 3DCRT with 4- or 10-MV photons produced by the Clinac 21EX or TrueBeam (Varian Medical Systems, Palo Alto, CA) systems and IMRT with 6-MV photons produced by a TomoTherapy HD unit (Accuray; Sunnyvale, CA).

Cisplatin at a dose of 150 mg/m^2 was superselectively administered to mainly the maxillary artery and branches of the external carotid artery, which perfuse the primary and lymph node lesions, and the procedures were repeated 4–5 times during treatment. During infusion of the agent, 200-fold sodium thiosulphate was additionally injected via a catheter in the brachiocephalic vein introduced via the subclavian vein to neutralize the adverse effects of the drug.

Anatomic considerations

Previous reports suggest that the anatomical sites of tumor invasion are particularly important for regional failure [9–11]. Therefore, we classified tumor invasion into six directions (Fig. 1) based on a study by Jeon et al. [11], with some modifications. The anterior, posterior, medial, lateral, cranial, and caudal extent were defined as the cheek, pterygoid plates, nasal cavity, masticator space, orbit or skull base, and oral cavity, respectively. Additionally, we analyzed the nasopharyngeal extent separately because other investigators reported that this is an important prognostic factor [9, 10]. Invasion was judged according to the bone destruction on CT, and that into the nasopharynx was judged when the

mass was clearly protruding into the nasopharyngeal cavity. The destruction of the posterior wall in a previous study was approximately equal to the combined posterior and lateral extent in this study.

Statistical analysis

Factors associated with regional failure, local failure, distant metastases, and overall survival (OS), namely invasion direction, sex, age, Eastern Cooperative Oncology Group performance status (PS), and T-stage, were analyzed. Pearson's chi-squared test, Fisher's exact test, the log-rank test, and Cox proportional-hazards models were used to analyze the correlation between the factors and regional failures or LN metastases at presentation. Regional control and survival outcomes were calculated using the Kaplan–Meier method. Adverse events (AEs) were assessed and documented according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 [12]. Adverse events occurring within 3 months after treatment were defined as acute, and those occurring ≥ 3 months after treatment were defined as late. All statistical analyses were assessed at a significance level of 0.05 using JMP 12 (SAS Institute; Minato-ku, Tokyo, Japan).

Results

Patients' characteristics and lymph node metastases at presentation

Table 1 presents the patients' characteristics. The median age was 70 years (range, 38–91 years). For staging, CT was performed in all cases, and MRI or PET-CT was performed in select cases. Most patients had cT4 disease. In the 17 cN+ cases at diagnosis, ipsilateral levels I and II were the most prevalent regions of metastases. Figure 2A shows the distribution of LN metastases at diagnosis.

Regional failure

After a median follow-up period of 36 months, 24 patients died, 21 were alive, and 10 were lost to follow-up at 6, 10, 16, 17, 19, 31, 62, 65, 89, and 95 months, respectively. The median follow-up period for the 21 surviving and 10 censored patients was 63 months (range, 5–113 months). Of the 10 patients lost to follow-up, 4 developed disease progression and were considered dead as of the day of the last visit (at 6, 16, 19, and 65 months, respectively) in subsequent survival analyses. The analyses were censored as of the last visit day for 6 other patients without tumor recurrence. The 1-, 3-, and 5-year OS rates were 78%, 53%, and 50%, respectively, and there were 14 local failures, 9 regional, and 10 distant. The 5-year local control (LC) and distant metastatic recurrence-free survival (DMFS) rates were 67% and 47%, respectively. The 5-year OS, LC, and DMFS rates for all cases or cN0 cases for each patient characteristic are shown in Table 2 and Table 3.

In the 9 cases of regional failure after treatment (median, 4 months; range, 3–49 months), 7 cases (18%) were cN0, and 2 (12%) were cN+. Of the 9 regional failures, 1 was local and regional, and 8 were regional only (3 were after local failures). Salvage surgery was performed in 8 of 9 cases, 1 died from surgical complications (brain abscess), 5 died due to disease progression, and 2 survived. Figure 2B and C show

the distribution of regional failure in cN0 and cN+ cases. Figure 3 demonstrates the regional recurrence-free survival rates according to LN status at the start of treatment.

Risk factors for regional failure in cN0 cases

For 38 patients with cN0, we analyzed the factors associated with regional failure, which was seen in 7 cases. In the univariate analysis, posterior ($p < 0.01$) and caudal extension ($p = 0.02$) were significantly correlated with the 5-year regional recurrence-free rates (Table 1). Other clinical factors, namely age, PS, and T-stage, showed no correlations. The multivariate analysis showed a significant correlation between posterior extension and regional failure (hazard ratio, 10.5; $p < 0.01$).

Risk factors for LN metastases at diagnosis

Table 1 demonstrates the frequency of LN metastasis at diagnosis classified according to patients' clinical and anatomic characteristics. In the univariate analysis, LN metastases were significantly associated with posterior extension (41% vs. 13%, respectively; p = 0.02) but not with other factors.

Adverse events

Table 4 summarizes the adverse events (AEs) associated with external radiotherapy and IA chemotherapy. In the non-ENI group, one patient suffered an early death 8 days after the end of treatment because of aspiration pneumonitis, which appeared to be due to treatment-related mucositis and dysphagia. There were no significant differences between the two groups in the incidence of acute high-grade (3 or 4) AEs. There were significantly more cases of high-grade late AEs in the ENI group than in the non-ENI group (41% vs. 13%, respectively; p = 0.03).

In 11 cases in the IMRT group (ENI = 5, non-ENI = 6), there were 7 acute and 4 late high-grade AEs. Three of the late high-grade AEs were in the ENI group, and all affected patients received 70-Gy radiation doses.

Discussion

In this study, we treated patients with locally advanced MSC using external beam irradiation combined with superselective IA chemotherapy, and the 5-year LC and OS were 67% and 50%, respectively. Our results were similar to results in other studies [5, 6]. The combination of IA chemotherapy and external radiation therapy or proton therapy can improve LC and OS [7, 13]. Homma et al. reported good results for 5-year LC (66%) and 5-year OS for stage cT4a (67%) and cT4b (57%) after external radiotherapy and IA chemotherapy [6]. Zenda et al. reported a 1-year LC of 77% and a 5-year OS of 55% for unresectable paranasal sinus and nasal cavity cancers after proton therapy [13]. ENI was not conducted in these studies, including ours, for cN0 cases.

Two of 17 patients with pN + who received ENI in this study developed regional node failure. This incidence was similar to that of patients with cN0, who did not receive ENI. In addition, the 5-year DMFS and 5-year OS in both groups were similar (Table 3). However, there were more patients with high-grade

late AEs in the cN + and ENI group than in the cN0 and non-ENI group (41% vs. 13%, respectively; p = 0.03). Feng et al. reported grade 3 dysphagia in 8% of cases and aspiration on videofluoroscopy in 44% of cases 3 months after irradiation with a high radiation dose (mean, 64 Gy) to the pharyngeal constrictor muscle [14]. If ENI is performed for all patients with T3 and T4 disease, the incidence of late high-grade adverse events may increase with prolonged survival [15]. Therefore, it is necessary to select appropriate candidates for ENI to maximize the clinical benefit in locally advanced MSC.

We divided tumor invasion into six directions, and found that only posterior and caudal extension correlated significantly with regional failure. Jeon et al. divided extra-maxillary sinus involvement of the tumor into four directions, and in their definition, destruction of the posterior wall meant infratemporal fossa involvement. The authors reported that this destruction was a significant risk factor for regional failure in cN0 MSC [11]. The categorized destruction of the posterior wall in Jeon et al.'s study meant a wide range of extensions, including T3 and T4 tumors. We attempted to analyze the relationship between the incidence of regional recurrence and the direction of the tumor invasion according to Jeon et al.'s classification. We identified 33 patients with destruction of the posterior wall; however, we found that this was not a significant predictive factor (P = 0.3). Therefore, we divided Jeon et al.'s classification of the posterior wall destruction into two categories: lateral extension (to the masticator space) and posterior extension (to the pterygoid plates) to identify more appropriate risk factors for regional failure. Previous studies reported that ENI for cN0 cases is necessary only if the tumor extends to a contiguous area, such as the nasopharynx or oral cavity, where lymphatic flow is rich [9, 10]. In those studies, regional failure occurred in only T4b cases of nasopharyngeal invasion; only two cases showed nasopharyngeal extension in our series. Invasion of the pterygoid plates is categorized as T4a. All nasopharyngeal invasions were included in the classification of posterior extension, in our study, because tumors reach this region via the pterygoid plates. In this study, the incidences of posterior wall destruction, invasion of the pterygoid plates, and nasopharyngeal invasion were 33 (87%), 20 (53%), and 2 (5%) of 38 cN0 cases, respectively. In our study of advanced MSC (91% of patients were cT4), most cases had destruction of the posterior wall.. Therefore, invasion of the pterygoid plates and oral cavity were considered more appropriate risk factors for regional recurrence. We were able to identify patients with a higher risk of regional recurrence more precisely using our new categorization of tumor extension. Regional failure affects distant metastases and OS [4, 11, 16, 17]. We did not perform ENI for cN0 patients, so its usefulness is still unknown. However, according to our analysis of the risk factors for regional recurrence and OS in cN0 cases (Table 4), these patients were considered good candidates for ENI.

To confirm our results, we also examined the risk factors for LN metastases present at diagnosis in the cN + group. Invasion of the pterygoid plates was the only factor correlated with LN metastases, which supported the results in the cN0 cases. In a multi-center retrospective study by Homma et al., the incidence of LN metastases was significantly higher in cases of nasopharyngeal or oral invasion at presentation among 128 cases of T4 MSC [18]. In all cases of nasopharyngeal invasion, invasion of the pterygoid plates was also observed, which is consistent with our results. Other factors, such as T-stage, PS, or age, showed no association with regional failure.

Regional failure occurred mainly at levels I and II in this study, as reported previously [1]. However, recurrence was also observed in level III in both cN0 and cN + cases. This may be due to differences between IA chemotherapy and systemic chemotherapy. IA chemotherapy is effective only in the arterial perfusion territory; therefore, this method cannot eradicate tumor cells located in the regions far from the primary tumor.

The median irradiation dose to the primary site and LN metastases in our study was 60 Gy, which is lower than the dose in other studies [3, 5, 6]. Previous studies reported high frequencies of the high-grade late adverse event of optic neuropathy (35%) when combining irradiation therapy with IA chemotherapy. Compared with these results, the frequency in our study was relatively low (2/55), and this may be due to the lower radiation dose. Further evidence of the usefulness and optimal procedure for IA chemotherapy will be obtained by an ongoing Phase III clinical trial (University Hospital Medical Information Network (UMIN) Clinical Trials Registry number: UMIN000013706).

This study has several limitations associated with its retrospective design. First, the diagnostic imaging modalities performed before and after treatment were not standardized. Second, when regional failure was suspected, pathological examination was not performed in all cases; 3/9 cases were diagnosed according to imaging findings. Third, differences between IA and intravenous chemotherapy might have affected regional control.

In conclusion, ENI for advanced MSC increased the incidence of severe late toxicities. Invasion of the pterygoid plates and oral cavity were high-risk factors for regional failure in cN0 cases, and these patients may be suitable candidates for ENI.

Declarations

Funding

No funding was received for this study.

Conflicts of interest/Competing interests

Y Kosugi, T Kawamoto, M Oshima, M Fujimaki, S Ohba, F Matsumoto, N Shikama, and K Sasai declare that they have no competing interests.

Ethics approval

This retrospective analysis was approved by the ethics committee of Juntendo University (approval number: 19-173).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Informed consent was obtained from all individual participants included in the study.

Availability of data and material

The data that support the findings of this study are available on request from the corresponding author

Code availability

Not applicable

Authors' contributions

YK prepared the manuscript, conducted the literature search, and reviewed and edited the manuscript. YK, TK, MO, MF, SO, FM, NS, and KS reviewed the manuscript. All authors have read and approved the final manuscript.

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Tables

Due to technical limitations, table 1, 2, 3, 4 is only available as a download in the Supplemental Files section.

Figures

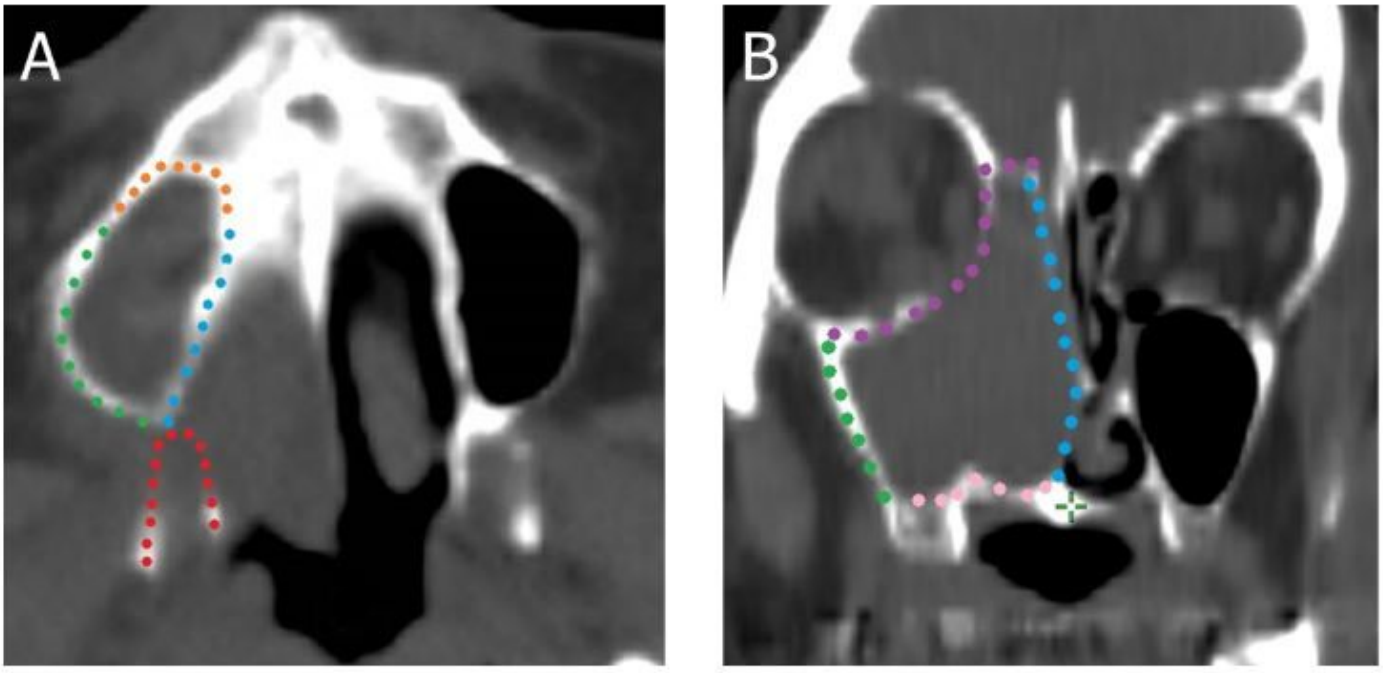

Figure 1

Anatomical direction of invasion of the primary lesion Tumors with posterior (A) and cranial and medial extension (B) in the present study. Orange: anterior side; Red: posterior side; Blue: medial side; Green: lateral side; Purple: cranial side; and Pink: caudal side. +, Combined posterior and lateral extension

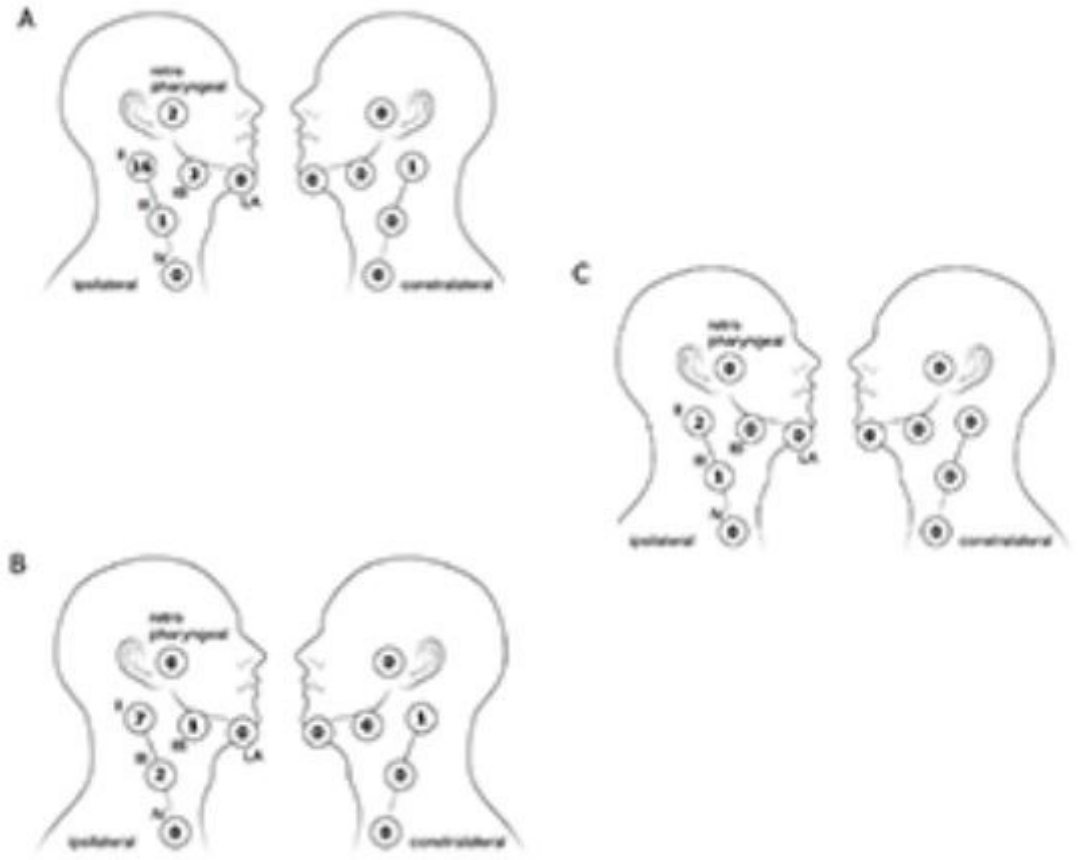

Figure 2

Number of cases of lymph node metastases at each level at presentation (A) and regional failures in cN0 (B) and cN+ (C) cases

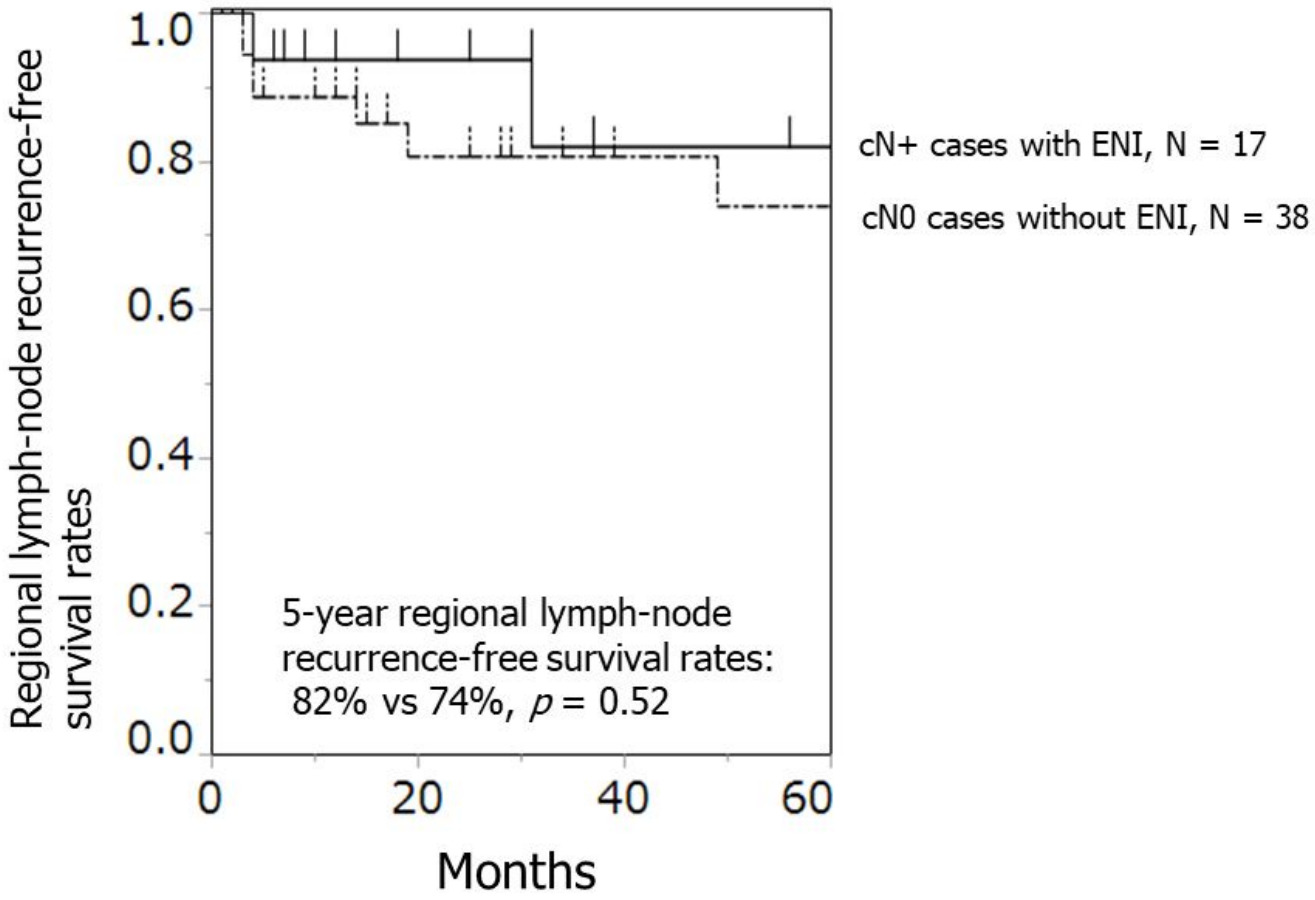

Figure 3

Regional recurrence-free survival rates according to lymph node (LN) status upon commencement of treatment

Supplementary Files

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