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Lymph node metastasis in T4 maxillary sinus squamous cell carcinoma: Incidence and treatment outcome

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Running title: Node metastasis in T4 maxillary sinus SCC

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SYNOPSIS

This study identified the incidence of lymph node metastasis among patients with T4 maxillary sinus squamous cell carcinoma (MS-SCC) as well as the delayed metastasis rate and the treatment outcome for untreated N0 neck in patients with T4 MS-SCC.

ABSTRACT

PURPOSE

To evaluate the incidence of lymph node metastasis among patients with T4 maxillary sinus squamous cell carcinoma (MS-SCC) as well as the delayed metastasis rate and the treatment outcome for untreated N0 neck in patients with T4 MS-SCC.

PATIENTS AND METHODS

Consecutive series of all patients (n=128) with previously untreated T4 maxillary sinus SCC between 2006 and 2007 were obtained from 28 institutions belonging to or cooperating in the Head and Neck Cancer Study Group of the Japan Clinical Oncology Group.

RESULTS

Twenty-eight (21.9%) of the 128 patients had lymph node metastasis, and 6 patients (4.7%) had distant metastasis at diagnosis. Among the 111 patients who were treated with curative intent, 98 had clinically N0 neck disease and did not receive prophylactic neck irradiation. A total of 11 patients (11.2%) subsequently developed evidence of lymph node metastasis, of whom 8 were among the 83 patients with an N0 neck and had not received elective neck treatment. There were 15 patients who received an elective neck dissection as part of the initial treatment, of whom 3 had pathologically positive for lymph node metastases. Of 11 patients, 6 patients with non-lateral retropharyngeal

lymph node metastasis without primary or distant disease were successfully salvaged.

CONCLUSION

This study identified the incidence of lymph node metastasis among patients with T4 MS-SCC as well as the delayed metastasis rate and the treatment outcome for untreated N0 neck in patients with T4 MS-SCC. These results will be of assistance in selecting treatment strategy for T4 MS-SCC in the future.

Maxillary sinus cancer is the most common form is sinonasal cancer. But the incidence of it has been considered to be decreasing gradually. According to vital statistics obtained from the Ministry of Health, Labour and Welfare, Japan, the number of deaths due to the maxillary sinus cancer was 1,051, 643, and 175, in 1971, 1991, and 2011, respectively. Some investigators in Japan consider this decrease to be correlated with the decrease in sinusitis, which is considered to be one of the risk factors of maxillary sinus cancer.

The Japanese head and neck community has been gaining experience in the treatment of patients with maxillary sinus cancer due to the many opportunities we have to treat them, and most head and neck surgeons and radiation oncologists in Japan prefer to take a common sense “wait-and-see” approach in the management of patients with clinically negative neck as the incidence of delayed neck metastasis is considered to be low. However, whether clinically negative neck in patients with the maxillary sinus cancer should be irradiated prophylactically or not is controversial in Europe and the United States[1, 2].

In addition, the incidence of neck metastasis in cases of maxillary sinus cancer has not been well defined, although it is currently believed to be low. To help clarify the situation, a multi-institutional joint research program for maxillary sinus cancer was undertaken in Japan[3]. This study was aimed at evaluating the incidence of lymph node metastasis among patients with T4 maxillary sinus squamous cell carcinoma (MS-SCC)

as well as the delayed metastasis rate and the treatment outcome for untreated N0 neck in patients with T4 MS-SCC.

MATERIALS AND METHODS

Consecutive series of all patients with previously untreated T4 MS-SCC between January 2006 and December 2007 were obtained from 28 institutions belonging to or cooperating in the Head and Neck Cancer Study Group of the Japan Clinical Oncology Group. This study was a retrospective analysis. Therefore, the selection criteria for therapeutic modality were decided according to the policy of each institution or individual patient preference. This multi-institutional joint research has been representatively approved by the appropriate ethical committee in the National Hospital Organization Tokyo Medical Center, Tokyo, Japan.

Initial treatment of the primary tumor

The initial therapeutic strategy was classified in the treatment for primary tumor. Surgical treatment was classified into total maxillectomy and partial maxillectomy. The classification of total maxillectomy included extended total maxillectomy simultaneously orbital exenteration and skull base surgery. “Trimodality therapy”, consisting of partial maxillectomy, intra-arterial chemotherapy and radiotherapy, was classified as partial maxillectomy. Surgery in which the anterior wall of the maxillary

sinus was opened and the necrotic tumor tissue therein was curetted was also classified as partial maxillectomy. The superselective intra-arterial infusion of high-dose cisplatin with concomitant radiotherapy was defined as RADPLAT, while intravenous chemotherapy with concomitant radiotherapy was defined as IV-CRT. All patients undergoing any form of surgical intervention as part of the initial treatment were classified into either the total or partial maxillectomy group, even if radiotherapy and/or chemotherapy was performed as pre- or post-surgical therapy. No patients with clinically N0 received elective radiation therapy to the neck lymph nodes.

Local extension sites

In this study, the anatomical sites of the primary tumor has developed were evaluated in detail using CT and/or MR imaging. The local extension sites were classified according to the 7th Edition of the Union for International Cancer Control staging system (Table 1). As only 2 cases had invasion into the brain, with both involving the dura, they were included as extension into the dura/brain. No cases showed involvement of the clivus.

Statistical analysis

The median follow-up period for the survivors was 4.3 years (range 0.2-5.9 years). Correlations between neck metastasis and variables including age, sex, T-stage, tumor

differentiation and local extension site were tested using Pearson's Chi-square test or Fisher's exact test using JMP Pro 10.0.0 statistical software (SAS Institute, Cary, NC). A 2-tailed *p* value <0.05 was considered to be statistically significant.

RESULTS

A total of 128 patients enrolled. T and N classifications of the 128 patients are shown in Table 2. Ninety-six patients were male and 32 were female. The median age was 64 years (range 30-84 years). Seventy-seven patients (60.1%) had T4a disease, and 51(39.8%) had T4b disease. Twenty-eight patients (21.9%) had lymph node metastasis and 6 patients (4.7%) had distant metastasis at diagnosis. The distribution of clinically diagnosed lymph node metastasis is shown in Figure 1. All patients showed clinically N positive but one patient had ipsilateral level Ib or II metastasis. One patient had a solitary metastasis in his contralateral level II node. Apart from this patient, all patients with metastasis to other sites had level Ib and/or II metastasis. Regarding correlations between neck metastasis and variables such as age, sex, T-stage, tumor differentiation and local extension site at diagnosis, the nasopharynx ($p= 0.046$) and the hard palate ($p<0.001$) were the only sites that was correlated with neck lymph node metastasis.

Of the 128 patients, 6 patients underwent palliative therapy due to distant metastasis. Three patients chose to be treated at other institutions, and one patient refused any therapy. The initial treatment for the remaining 118 patients was classified

by treatment for primary tumor. A total of 39 (33%) of the 118 patients were categorized into the total maxillectomy group, while 25 patients (21%) underwent partial maxillectomy, 22 patients (19%) underwent RADPLAT, 19 patients (16%) underwent IV-CRT, and 13 patients (11%) underwent other therapies, such as radiation alone.

Among the 111 patients who were treated with curative intent, 98 had clinically N0 neck disease and did not receive prophylactic neck irradiation (Figure 2). A total of 11 patients (11.2%) subsequently developed evidence of lymph node metastasis, of whom 8 were among the 83 patients with an N0 neck and had not received elective neck treatment. There were 15 patients who received an elective neck dissection as part of the initial treatment, of whom 3 had pathologically positive for lymph node metastases. Delayed neck recurrence was observed at a median 6 months (average; 10 months, range: 1-39 months) after the completion of RADPLAT.

Among the 8 patients who had no elective neck treatment and developed delayed neck metastasis, 3 patients were successfully salvaged by neck dissection. But neck disease could not be controlled in 2 patients with lateral retropharyngeal lymph node (RPLN) metastasis and 3 patients with residual or recurrence of primary or distant disease. And neck disease was successfully controlled in 3 patients who had pathologically positive for lymph node metastasis after elective neck dissection.

Sixty-three patients with N0 neck disease at diagnosis and who were monitored for neck disease for more than 2 years were analyzed for late neck metastasis. Of the

initial 128 patients, 28 patients with clinical neck metastasis at diagnosis, 35 patients with N0 neck disease at diagnosis who died within 2 years due to primary and/or distant disease without neck recurrence, and 2 patients who died of other causes without neck recurrence were excluded. Of the remaining 63 patients, 11 (17.5%) had late neck metastasis, as mentioned above. With regard to correlations between delayed neck metastasis and variables such as age, sex, T-stage, tumor differentiation and local extension sites among the 63 patients, no factor was found to be correlated with neck lymph node metastasis. Moreover, the factors related to a delayed neck metastasis rate of more than 25 % were female gender (4/16=25%), T4b (6/23=26.1%), low-grade tumor (6/17=35.3%), nasopharyngeal invasion (2/5=40%), middle cranial fossa invasion (3/10=30%), and invasion of a cranial nerve other than V2 (2/4=50%).

DISCUSSION

The prognosis for MS-SCC is significantly related to local tumor control. Therefore, lymph node metastasis in MS-SCC has received little attention to date. The incidence and distribution of lymph node metastasis and the percentage of delayed metastasis in cases of maxillary sinus SCC are reported to range widely (Table 3)[4-9] as MS-SCC is a rare neoplasm and the number of patients treated at a single center is small. In addition, some reports have included patients from several decades ago. Time factor must have influence on pretreatment diagnosis and treatment outcome.

The retrospective data in this study were limited to patients with T4 MS-SCC who were treated between 2006 and 2007. Thus, the cases represent a very limited stage treated within a limited period, affording homogeneity to the data. The modality for diagnosis was not checked, but most of the patients were examined by physical examination as well as CT scan and/or MRI at that time. FDG-PET, ultrasound, and fine needle aspiration cytology were used at the attending physician's discretion.

Regarding the correlation between local extension site and neck lymph node metastasis at diagnosis, the nasopharynx and hard palate were both correlated with lymph node metastasis. There was a report that the rate of neck metastasis is much higher in T2 tumors than in T3 or T4 tumors[10]. The reason for this was suspected to be that cases with extension to the hard palate diagnosed as T2 are more likely to develop lymph node metastasis. This study supports this speculation. Cases with invasion to areas known to be rich in lymphatics, such as the nasopharynx and hard palate, are considered more likely to develop lymph node metastasis[11].

The risk of RPLN metastasis in cases of MS-SCC has been discussed previously[1,12, 13]. In 1993, in a series of 25 patients with maxillary sinus cancer, Watarai *et al*. found that RPLNs were involved in 16% of the patients[12]. In this study, only 3 patients had RPLN metastasis at diagnosis (one patient had bilateral RPLN metastasis) (Figure 1). And 2 patients who received en bloc tumor resection and radiotherapy as an initial treatment showed delayed RPLN metastasis. The incidence of delayed RPLN

metastasis is considered to be low. Therefore, whether the radiotherapy plan should include the RPLN area or not needs to be discussed carefully.

Delayed neck metastasis developed in 11 patients with clinically N0. The possibility of delayed neck metastasis was calculated to be 11.2%, based on the 98 patients with clinically N0 neck disease among the 118 patients treated with curative intent. This result was comparable with those of previous reports[4-9]. In addition, the delayed neck metastasis rate was 17.5%, based on the 63 patients with N0 neck disease at diagnosis who were monitored for neck disease for more than 2 years.

The reason why elective neck irradiation was not done for patients with clinically N0 neck in this retrospective multi-institutional study was that we could identify neck metastasis at an early stage and control it effectively as patients were followed up closely. Indeed, all 3 patients with non-RPLN delayed neck metastasis without residual or recurrent primary or distant disease were successfully salvaged.

Delayed neck metastasis is an unfavorable prognostic factor; therefore, some investigators have recommended prophylactic neck irradiation[7,5,9,14]. In general, elective treatment of the neck is recommended for patients with squamous cell carcinoma of the upper aerodigestive tract when the anticipated risk of occult metastasis is greater than 15-20%[15,16]. According to this idea, patients with T4N0 MS-SCC should be candidates for elective neck irradiation. However, if close follow-up is possible, we consider that prophylactic neck irradiation is unnecessary, particularly due to the risk of adverse effects of elective

neck irradiation, such as mucositis and osteoradionecrosis of the mandible.

In conclusion, this study revealed the incidence of lymph node metastasis among patients with T4 MS-SCC as well as the proportion of cases with delayed metastasis and the treatment outcome for untreated N0 neck disease in patients with T4 MS-SCC. We expect these result to be of assistance in selecting treatment strategies for T4 MS-SCC in the future.

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APPENDIX

In addition to the authors, the following investigators participated in this study: *National Cancer Center Hospital East, Kashiwa* - T. Shinohara; *Miyagi Cancer Center, Sendai* - Y. Asada; *Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo* - T. Sasaki; *Aichi Cancer Center, Nagoya* - H. Hirakawa; *Osaka Medical Center for*

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FIGURE LEGEND

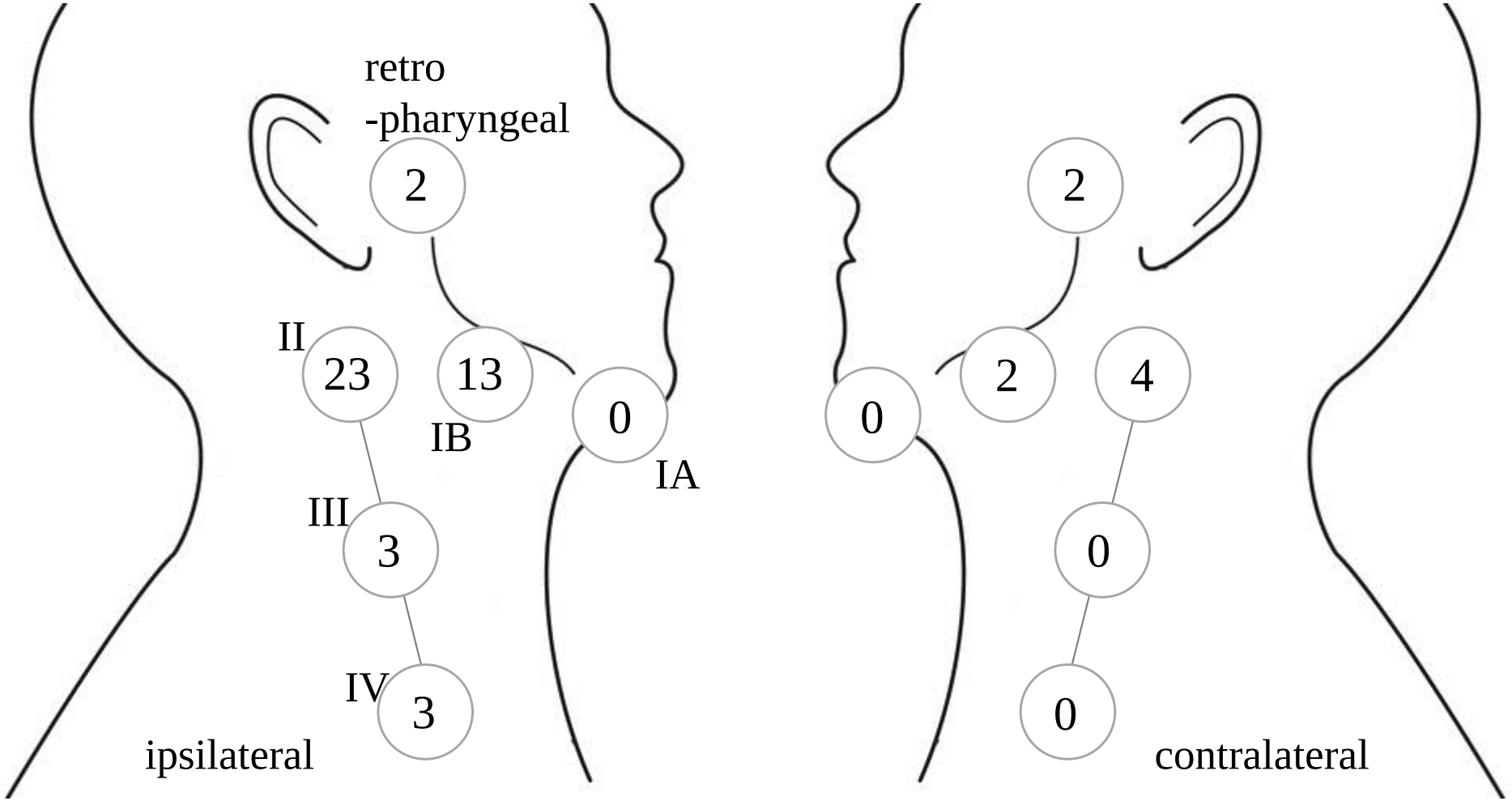
Figure 1

Nodal distribution at diagnosis (n=28)

Figure 2

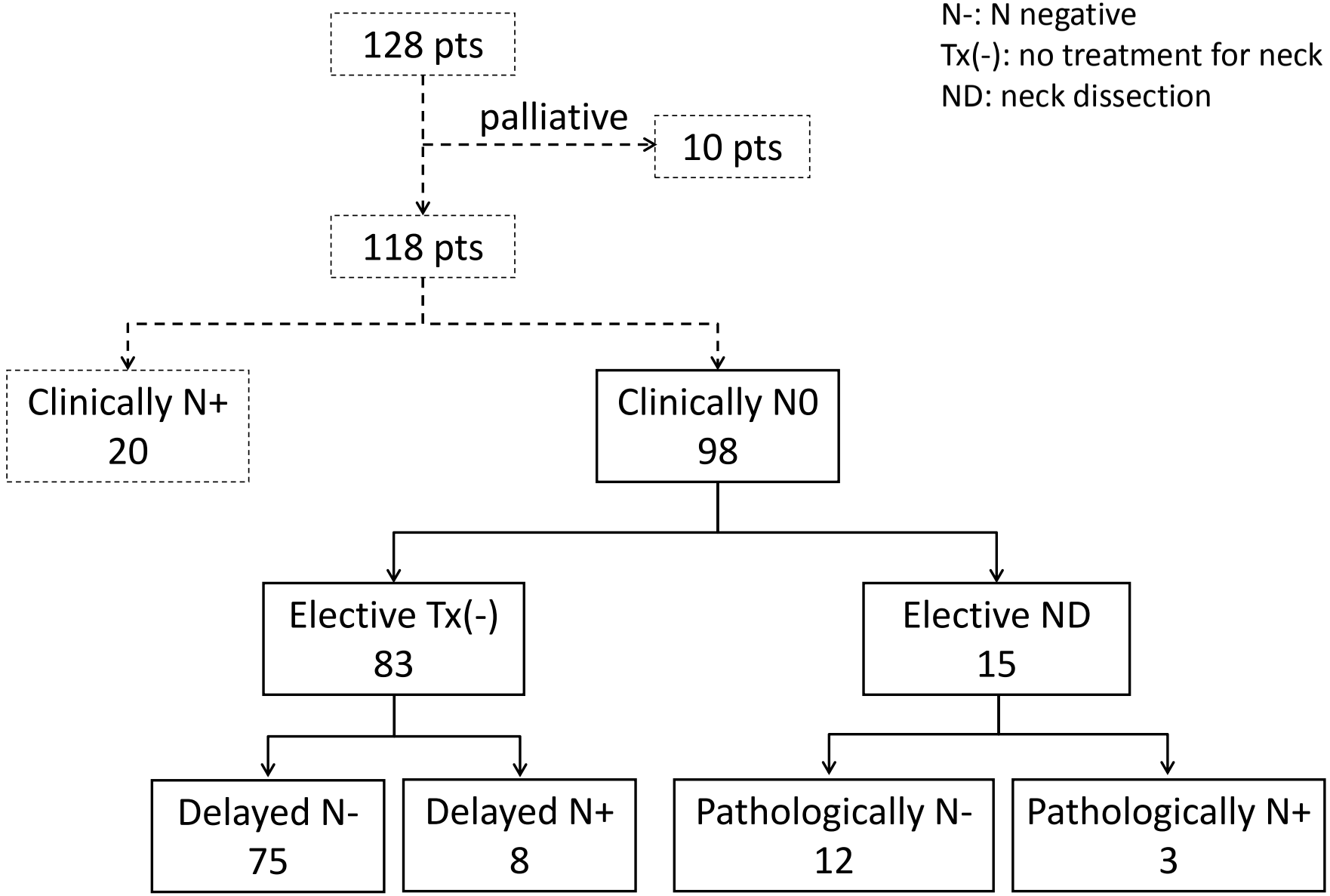
Clinical course in 98 patients with Clinically N0 neck disease.

Figure 1. Nodal distribution at diagnosis (n=28)



* 1 patient: data unavailable

N+: N positive
N-: N negative
Tx(-): no treatment for neck
ND: neck dissection



Number of patients controlled neck disease	75	3	12	3

Table 1　Local extension sites

	T2	T3	T4a	T4b
Superomedial	Middle nasal meatus	Ethmoid sinuses	Cribriform plate Frontal sinus	Dura/Brain
Superior			Anterior orbital contents	Orbital apex
Posterior		Posterior wall Pterygoid fossa	Pterygoid plates Sphenoid sinus	Nasopharynx Middle cranial fossa
Lateral			Infratemporal fossa	
Inferior	Hard palate			
Anterior		Subcutaneous tissue	Skin of cheek	
Cranial nerve				Other than V2

Table 2 T and N classification (n = 128)

T classification	Number of patients by N classification						Total
	0	1	2a	2b	2c	3	
T4a	62	2(1)	1	10(1)	2	0	77(2)
T4b	38(1)	5(1)	0	3	4(1)	1(1)	51(4)
Total	100(1)	7(2)	1	13(1)	6(1)	1(1)	128(6)

* number of distant metastasis are shown in parentheses.

Table 3 Incidence of lymph node metastases in patients with MS-SCC reported in the literature

First author	period	Number of patients	lymph node metastasis at diagnosis	delayed lymph node metastais	Total lymph node metastasis	Institution
Jiang GL[4]	1969–85	36	5 (13.8%)	6 (19.3%)	11 (30.6%)	M.D. Anderson Cancer Center
Paulino AC[5]	1971–95	42	4 (9.5%)	11 (28.9%)	15 (35.7%)	Loyola University Medical Center
Kim GE[6]	1984–93	116	12 (10.3%)	14 (13.5%)	26 (22.4%)	Yonsei Cancer Center, Seoul
Le QT[7]	1959–96	58	9 (15.5%)	6 (12.2%)	15 (25.9%)	Stanford University and University of California
Yagi K[8]	1982–97	104	9 (8.6%)	7 (7.4%)	16 (15.3%)	Hokkaido University
Hinerman RW[9]	1969-2006	54	9 (16.6%)	3 (6.7%)	12 (22.2%)	University of Florida
Present series	2006-7	128	28 (21.9%)	11 (11.2%)	39 (30.5%)	Japan Clinical Oncology Group