

## Maxillary sinus carcinoma outcomes over 60 years: experience at a single institution

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### ABSTRACT

Advances in the diagnosis and treatment of patients with maxillary sinus carcinoma have improved patient prognosis. This study investigated changes in demographic and clinical characteristics, treatment methods, and outcomes of patients with maxillary sinus carcinomas during three different 10-year periods spanning 60 years at our university hospital. Of the 233 patients with maxillary sinus carcinomas managed at Nagoya University Hospital, 135 were treated between 1951 and 1960 (first period), 35 between 1981 and 1990 (second period), and 63 between 2003 and 2012 (third period). Patient age, sex, TN classifications, treatment methods, and survival rates were compared among patients treated during these time periods. Of the 135, 35, and 63 patients with maxillary sinus carcinomas treated during these time periods, 86 (63.7%), 21 (51.4%), and 48 (76.2%), respectively, were men; 14 (10.4%), six (17.1%), and 14 (22.2%), respectively, were aged  $\geq 70$  years; and 135 (100%), 28 (80.0%), and 43 (68.3%), respectively, were treated surgically. The 5-year overall survival rates in patients treated during the first, second, and third periods were 29.7%, 44.3%, and 57.5%, respectively. These findings indicated that advances in the diagnosis and treatment of patients with maxillary sinus carcinoma, including computed tomography and craniofacial resection, have contributed to improvements in patient survival rates.

Keywords: maxillary sinus carcinoma, treatment, classification, craniofacial resection, computed tomography

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### INTRODUCTION

Malignant tumors of the nasal cavity and paranasal sinuses are uncommon, accounting for 0.2–0.5% of all cancers and 3% of malignant tumors of the head and neck.<sup>1,2)</sup> The maxillary sinus is the area most commonly affected by paranasal sinus carcinomas.<sup>3)</sup> Most maxillary sinus carcinomas present with few, if any, symptoms, increasing the likelihood of a delayed diagnosis. At the time of diagnosis, 70–80% of maxillary sinus carcinomas present with local extension and

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are classified as T3 or T4.<sup>4,5</sup> Craniofacial resection for sinonasal carcinoma was first described in 1963.<sup>6</sup> This procedure, however, was found to occasionally cause severe complications, as well as being a challenging operation. Craniofacial resections that include reconstruction methods, such as free flaps, have increased the safety of this procedure. Craniofacial resections of malignant skull base tumors have also yielded good results.<sup>7-10</sup> Computed tomography (CT) scans provide an excellent insight into the structural detail of bony and soft tissues and can reveal the exact extent of lesions, thereby optimizing pretreatment staging.<sup>11,12</sup> CT scans are essential for accurately diagnosing maxillary sinus carcinomas, especially in determining the locations of invasion into surrounding tissues and have been widely used in Japan since the 1980s.

Advances in the diagnosis and treatment of maxillary sinus carcinomas have contributed to better patient prognoses and low levels of complications. Maxillary sinus carcinomas have been actively treated at our hospital, mainly by surgical resection, since the 1950s. Few reports have described the outcomes of patients with maxillary sinus carcinomas over long periods of time. This study was designed to investigate changes in demographic and clinical characteristics, treatment methods, and outcomes of patients with maxillary sinus carcinoma who were treated at our hospital over three time periods spanning 60 years, and to verify improvements in the diagnosis and treatment of these lesions.

## METHODS

### *Patients*

Data were obtained from patients' medical records and two studies<sup>13</sup> of the management of maxillary sinus carcinoma at Nagoya University Hospital from 1951 to 2012. Patients were divided into three 10-year treatment periods: the period of introduction of radiation therapy (first period, between 1951 and 1960), the period after introduction of CT (second period, between 1981 and 1990), and the period following introduction craniofacial resection with microsurgery (third period, between 2003 and 2012). Clinical data, including patient age, sex, stage of maxillary sinus carcinoma, treatment methods, and survival rates were compared in the three periods. This study was approved by the ethics review committee of Nagoya University Hospital.

### *Stage Classification*

The TNM stages of the patients treated during the first (1951 to 1960) and second (1981 to 1990) periods were reclassified using the Union Internationale Contre le Cancer (UICC) 1987 staging system, whereas the TNM stages of patients treated during the third period (2003 to 2012) were classified using the American Joint Committee on Cancer (AJCC)/UICC 2009 staging system. Tumors were staged by examination plus tomography during the first period; by these methods plus CT evaluation during the second period; and by CT, magnetic resonance imaging (MRI), and ultrasonography during the third period.

### *Statistical Analysis*

All statistical analyses were performed using JMP software version 10 (SAS, Cary, NC, USA). Overall survival (OS) curves were estimated using the Kaplan-Meier method and compared using the log-rank test. OS was calculated from the date of the first visit to the date of death or last follow-up visit.

## RESULTS

A total of 233 patients presented with maxillary sinus carcinomas during the three time periods. Of these patients, 135, 35, and 63 underwent inpatient treatment at our center during the first, second, and third periods, respectively. Table 1 shows the demographic and clinical characteristics of these patients. Because the TN classifications of three patients during the first period were unclear, they were excluded from further analysis.

Table 2 shows the treatment modalities during each period. Of the 233 patients, 206 (88.4%) underwent surgery, including 135 (100%), 28 (80%), and 43 (68.3%) patients during the first, second, and third periods, respectively. Postoperative radiation therapy was performed using radium needles during the first period, x-rays or cobalt-60 during the second period, and x-rays during the third period. Chemotherapy agents included sarkomycin and carzinophilin during the first period; 5-fluorouracil (5-FU), cisplatin, peplomycin, and mitomycin during the second period; and 5-FU and cisplatin during the third period. Of the 35 patients diagnosed during the

**Table 1** Characteristics of patients with maxillary sinus carcinoma during the three study periods

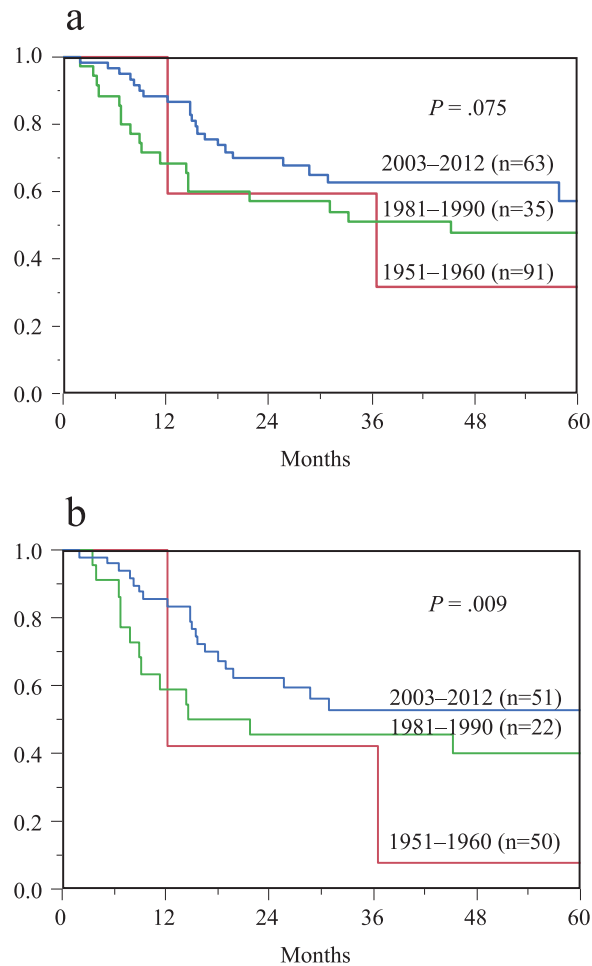
	Period		
	1951–1960 n (%)	1981–1990 n (%)	2003–2012 n (%)
Sex			
Men	86 (63.7)	18 (51.4)	48 (76.2)
Women	49 (36.3)	17 (48.6)	15 (23.8)
Total	135 (100)	35 (100)	63 (100)
Age (years)			
0–39	19 (14.1)	2 (5.7)	0 (0.0)
40–49	26 (19.3)	7 (20.0)	4 (6.3)
50–59	42 (31.1)	11 (31.4)	16 (25.4)
60–69	34 (25.2)	9 (25.7)	29 (46.0)
70–	14 (10.4)	6 (17.1)	14 (22.2)
Total	135 (100)	35 (100)	63 (100)
T classification			
T1	12 (9.1)	0 (0.0)	1 (1.6)
T2	33 (25.0)	3 (8.6)	4 (6.3)
T3	13 (9.8)	10 (28.6)	7 (11.1)
T4	74 (56.1)	22 (62.9)	32 (50.8)
T4a			19 (30.2)
T4b			
Total	132 <sup>a</sup> (100)	35 (100)	63 (100)
N classification			
N0	97 (73.5)	29 (82.9)	49 (77.8)
N1	35 (26.5)	6 (17.1)	9 (14.3)
N2		0 (0.0)	5 (7.9)
Total	132 <sup>a)</sup> (100)	35 (100)	63 (100)

<sup>a</sup>The TN classifications of 3 patients treated during the first period were unclear.

**Table 2** Treatment modalities during each period

		Period		
		1951–1960 n (%)	1981–1990 n (%)	2003–2012 n (%)
Surgery	Alone	4 (3.0)	1 (2.9)	8 (12.7)
	+ RT	108 (80.0)	13 (37.1)	8 (12.7)
	+ Chemo	3 (2.2)	0 (0.0)	7 (11.1)
	+ RT + Chemo	20 (14.8)	14 (40.0)	20 (31.7)
RT + Chemo		0 (0.0)	5 (14.3)	13 (20.6)
RT		0 (0.0)	2 (5.7)	7 (11.1)
Chemo		0 (0.0)	0 (0.0)	0 (0.0)
Total		135 (100)	35 (100)	63 (100)

Abbreviations: RT, radiotherapy; Chemo, chemotherapy



**Fig. 1** Kaplan-Meier analyses of overall survival in (a) 189 patients with maxillary sinus carcinomas and (b) 123 patients with T4 maxillary sinus carcinomas treated during the three study periods.

second period, 28 were histologically diagnosed with squamous cell carcinoma (SCC); three with adenoid cystic carcinoma; and one each with adenocarcinoma, mucoepidermoid carcinoma, undifferentiated carcinoma, and transitional carcinoma. Of the 63 patients diagnosed during the third period, 47 were histologically diagnosed with SCC; four with undifferentiated carcinoma; two each with adenocarcinoma, adenoid cystic carcinoma, transitional carcinoma, and small cell carcinoma; and one each with mucoepidermoid carcinoma, myoepithelial carcinoma, odontogenic ghost cell carcinoma, and carcinoma not otherwise specified.

During the first period, 44 of the 135 patients did not visit the hospital after their first treatment and did not receive their treatment results. These patients were therefore excluded from further analysis and OS rates during the first period were calculated based on the 91 remaining patients. Figure 1a shows the 1-, 3-, and 5-year OS rates for 189 patients with maxillary sinus carcinoma treated during the three time periods at our hospital. The 5-year OS rates of patients treated during the first, second, and third periods were 29.7%, 44.3%, and 57.5%, respectively ( $P = .075$ ). In addition, 148 patients were diagnosed with T3 and T4 maxillary sinus carcinomas; the 5-year OS rates of patients treated during the first, second, and third periods were 6.9%, 42.0%, and 59.1%, respectively, indicating a significant improvement over time ( $P = .001$ ). The 5-year OS rates among the 123 patients with T4 maxillary sinus carcinomas treated during the first, second, and third periods were 6.0%, 33.1%, and 52.7%, respectively, again demonstrating a significant improvement over time ( $P = .009$ ) (Fig. 1b)

## DISCUSSION

This study showed that the characteristics of patients with maxillary sinus carcinoma and their treatment outcomes at a single institution in Japan have changed over 60 years. During the first time period, from 1951 to 1960, tumors were staged by physical examination plus tomography. Surgical resection was the mainstay of treatment for any stage tumor, with surgery performed via the oral cavity or through a facial skin incision, and chemotherapy was not uncommon. Of 68 patients with maxillary sinus carcinoma who were managed at the same hospital from 1946 to 1954, all were treated with surgery alone, with these patients having 1- and 5-year OS rates of 25% and 7%, respectively.

Surgical resection, including partial, total, or extended maxillectomy, remained the mainstay of treatment for any stage tumor during the second time period, from 1981 to 1990. Routine use of CT scans during this period allowed the assessment of tumor invasion of surrounding tissues and the ability to choose a suitable surgical method according to tumor stage. However, it is difficult to completely remove tumors that have invaded the regions around the base of the skull, including the infratemporal fossa, pterygoid plate, cribriform plate, orbital apex, and dura, using facial and oral approaches alone. Tumors that had invaded the skull base were considered unresectable during the second period.

During the third period, from 2003 to 2012, craniofacial resection was the treatment of choice in our hospital for patients with maxillary sinus carcinomas, even those with locally advanced T4 tumors. Recent technological advances, including preoperative surgical simulation by 3-dimensional (3D) virtual imaging, have enabled a more accurate understanding of the complex anatomy of the skull base.<sup>14)</sup> These 3D surgical simulations have enabled radical operations to be performed safely, with en bloc craniofacial resection resulting in good survival rates, even for patients with locally advanced T4 maxillary sinus carcinomas.<sup>15)</sup> While maxillary sinus carcinomas often involve the surrounding tissues, including the orbit, nasal cavity, hard palate, skin, and skull base, the incidence of cervical lymph node metastases has been reported to be 10–20%.<sup>16–18)</sup> In

this study, the incidence of cervical lymph node metastases during the three study periods ranged from 15.8% to 26.5%, similar to previously reported rates. Our findings indicate that patients with “resectable” maxillary sinus carcinomas should undergo surgical resection, including craniofacial resection, followed by postoperative radiotherapy.

The number of patients treated during the first period was higher than those during the second and third periods. During the first period, from 1951 to 1960, the prefecture contained only two university hospitals and no cancer center. Thus, during the first period, most patients with maxillary sinus carcinoma were referred to our hospital. During the second and third periods, the prefecture contained four university hospitals and one cancer center, allowing patients to be treated at the nearest hospital. Moreover, the rate of severe complications and the need for challenging treatment have gradually increased as the average life span of Japanese people has increased. Indeed, the proportions of patients aged >70 years were higher during the second (24.1%) and third (22.2%) periods than during the first period (10.4%). Reports from the Ministry of Internal Affairs and Communications (MIC) showed that, in 1955, 1985, and 2005, 3.1%, 6.8%, and 14.3%, respectively of the Japanese population was aged  $\geq 70$  years (Ministry of Internal Affairs and Communications: <http://www.stat.go.jp/data/jinsui/index.htm>). Although the proportion of older people in Japan is increasing, the proportion of older patients with maxillary sinus carcinomas in this study was not higher during the third than during the second period. Craniofacial resection occasionally causes severe complications and can lead to death. Therefore, in our hospital, craniofacial resection is not recommended for patients aged >75 years or those with severe comorbidities. During the third period, many patients aged >75 years were not referred to our hospital; thus, the proportion of older patients who were treated in our hospital during the third period was similar to that during the second period.

Since the first description of the Ohngren line in 1933, many tumor staging methods have been proposed.<sup>19-21)</sup> Although the AJCC has long partially staged paranasal sinus carcinomas, the UICC did not stage paranasal sinus tumors in the first three editions of its manuals. Rather, maxillary sinus carcinomas were classified in the fourth edition in 1987 as a consequence of comparisons with the AJCC and Japanese Joint Committee proposal on TMN classification. Because the introduction of CT scanning and craniofacial resections has improved the diagnosis and treatment of maxillary sinus carcinomas, the tumor staging system has changed and been improved. Despite improvements in diagnostic imaging, the proportion of patients with T1 and T2 remained low in this study, suggesting the difficulties associated with the early detection of maxillary sinus carcinoma. Locally advanced maxillary sinus carcinomas have been classified as T3 or T4. The prognoses of our patients with T3 and T4 tumors reflect their actual treatment outcomes, regardless of staging system.

This study had several limitations. First, the number of patients was relatively small, with these patients showing heterogeneity in their pathologies and in types of adjuvant treatment. We also compared three 10-year non-consecutive time periods, which represents a key weakness of our study. Because a lack of accurate patient medical data from 1961 to 1980 and from 1991 to 2002, we could not provide consecutive data for 60 years. Although disease free survival rates are considered more important than overall survival rates, because the average life span increased about 10 years from the 1950s to the 2010s, the lack of accurate data allowed an investigation of only overall survival rates. Hence, the results of our study require confirmation in a larger series of patients and during consecutive time periods. Another limitation of our study was the use of different staging systems during the three time periods, with the UICC 1987 staging system used during the first and second periods and the AJCC/UICC 2009 during the third period. Better comparisons of patients treated during various study periods requires that the results be verified using the same staging system. A third limitation was our inability to determine detailed

histological diagnoses and to evaluate histological changes during the first period.

In conclusion, our study of patients with maxillary sinus carcinomas who were treated at a university hospital over a 60-year period showed that advances in diagnosis and treatment, including CT and craniofacial resection, have contributed to improved survival rates.

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#### CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

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