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Title	The role of endoscopic resection for selected patients with sinonasal squamous cell carcinoma
Author(s)	Nakamaru, Yuji; Suzuki, Masanobu; Kano, Satoshi et al.
Citation	Auris nasus larynx, 48(1), 131-137 https://doi.org/10.1016/j.anl.2020.06.014
Issue Date	2021-02-01
Doc URL	https://hdl.handle.net/2115/84040
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Rights(URL)	https://creativecommons.org/licenses/by-nc-nd/4.0/
Type	journal article
File Information	ANL 48(1) 131-137.pdf



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The role of endoscopic resection for selected patients with sinonasal squamous cell carcinoma

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Abstract

Objective: Despite of rapid advances in endoscopic surgery, the gold standard for sinonasal squamous cell carcinoma (SNSCC) surgery has remained the open approach with en-block resection due to the aggressive nature of SNSCC, including frequent recurrence and high mortality rate. For that reason, few studies have focused on SNSCC treated by endoscopic surgery alone. The objective of this study was to evaluate the usefulness of endoscopic surgery for patients with SNSCC.

Methods: A retrospective analysis was performed for 15 consecutive SNSCC patients who underwent endoscopic surgery without an open approach. We carefully selected patients whose tumor attachment sites could be fully visualized and completely resected through an endonasal approach.

Results: Of the fifteen patients, 4 patients (27%) were diagnosed with T1, 7 (47%) with T2, 4 (27%) with T3, and no patients with T4a or T4b disease. Four of the 15 (27%) patients showed positive surgical margins. The 5-yr overall survival, disease-specific survival, and local control rate was 72.4%, 79.6%, and 92.9%, respectively. The 5-yr

disease-specific survival for T1, T2, and T3 disease was 100% and 75% and 75%, respectively. Patients with negative surgical margins had a better disease-specific survival rate than did those with positive surgical margins (p=0.0253).

Conclusion: Endoscopic surgery for patients with SNSCC appears to afford an effective method in selected cases. The achievement of negative surgical margins with a good view of the tumor attachment site was considered to be critical to the management of SNSCC.

Key words

Squamous cell carcinoma, Endoscopic sinus surgery, Nasal cavity, Paranasal sinus, Surgical margin

Introduction

Malignant tumors of the nasal cavity and paranasal sinuses are rare neoplasms that constitute fewer than 1% of all cancers and 3% of head and neck cancers [1]. There are many histological types of malignant tumor occurring in the nasal cavity and paranasal sinus, such as squamous cell carcinoma (SCC), adenoid cystic carcinoma, mucoepidermoid carcinoma, olfactory neuroblastoma, and malignant melanoma. Therefore, the number of patients with sinonasal SCC (SNSCC) at a single center is small, despite SCC being the most common histological type among sinonasal malignancies [2, 3].

Recent advances in instruments and endoscopic surgical techniques have enabled endoscopic surgery to be adopted for malignant sinonasal tumors. However, due to the aggressive nature of SNSCC, including its frequent recurrence and high mortality rate, it was thought that surgical treatments for SNSCC using open surgery require wide surgical margins. Further, because of the rarity and aggressive nature of SNSCC, most previous studies of endoscopic surgery for sinonasal malignant tumors included many different histologies, particularly slow growing and less aggressive tumors

such as olfactory neuroblastoma or adenocarcinoma [4, 5]. There have been few studies focused on the role of the endoscopic surgery for the typically rapid growing and aggressive SNSCC [6-8]. Therefore, the role of endoscopic surgery for SNSCC had not yet been thoroughly studied.

The purpose of this study was to report our experience with patients diagnosed with SNSCC that were treated with endoscopic surgery together with an analysis of treatment outcomes.

Materials and Methods

Patients

A retrospective analysis was performed on data for all patients who underwent endoscopic resection of SNSCC between March 2005 and April 2019 at Hokkaido University Hospital, a tertiary care comprehensive cancer center. Patients were excluded if the operative plan was for palliative surgery instead of complete resection.

All patients were initially evaluated by a multidisciplinary team consisting of head and neck surgeons, radiation oncologists, and medical oncologists. The primary tumor extension sited were classified based on the 7th Union for International Cancer Control (UICC) criteria. The tumor stage was determined from patient history, physical examination, chest X-rays, computed tomography (CT), and/or magnetic resonance imaging (MRI). This study was approved by the Institutional Review Board at Hokkaido University Hospital (No.019-0218) and the study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the

study.

Selection criteria for endoscopic endonasal surgery

Our policy for the treatment of SNSCC was as follows. Patients with limited disease (T1-2, N0) were treated by surgery or radiotherapy alone. Adjuvant radiotherapy after surgery was recommended if positive or close margins were confirmed pathologically. Positive surgical margin means positive of the surgical margin at the final pathological diagnosis. We set the definition of a close margin as malignant cells existing within 5 mm of the resected margin. Patients with locally advanced disease (T3-T4a) were treated by a combination of surgery followed by postoperative radiotherapy with intravenous chemotherapy (IV-CRT) or intra-arterial chemotherapy (RADPLAT). IV-CRT consisted of weekly cisplatin (40 mg/m2) together with radiotherapy (70Gy) over 7 weeks [9]. RADPLAT consisted of super selective intra-arterial infusions of cisplatin (100–120 mg/m2/week, 4 times) with simultaneous intravenous infusions of thiosulfate to neutralize cisplatin toxicity and conventional radiotherapy (65-70Gy) [10]. IV-CRT or RADPLAT is recommended for the treatment of unresectable tumors (T4b) or patients who refuse surgery [11].

In this study, we performed endoscopic surgery for tumors for which the attachment sites could be fully seen and could be completely resected through an endonasal approach. Therefore, patients included this study were mainly those with T1-2 SNSCC and some patients with locally advanced (T3) disease. Patients were not indicated for the endoscopic surgery if the tumor attachment site was located at the orbit, lacrimal pathway, bony wall of the maxillary sinus (with exception of the medial wall), or showed extension into the frontal sinus, intracranial space, pterygopalatine fossa, or infratemporal fossa.

All patients were closely observed during the follow-up period. Patients treated by a combined approach such as endonasal approach plus craniotomy and/or lateral rhinotomy were excluded from this study.

Surgical procedure

We referred to the "attachment-oriented endoscopic surgical technique" [12] and "multilayer centripetal technique" [13] for resecting SNSCC with some

modifications. A detailed description of this surgery was described in previous reports [4, 12, 13]. The surgery begins with debulking of the tumor with a microdebrider to identify the area in which the tumor originated. The surrounding structures that obstruct a clear view of the tumor, such as the uncinate plate, middle turbinate, and inferior turbinate, are also resected if necessary. If the tumor origin is located in the anterior portion of the sinus, we use the "outside-in approach" of the Draf III procedure [14]. In the Draf III procedure, a septal window is made in the anterior portion of the nasal septum and the bilateral frontal sinus is opened. This method enables access to the nasal cavity through the septal window and allows extensive visualization and working space. As the "outside-in approach" directly opens the frontal sinus without opening the ethmoid sinus, this method can be used without touching the origin of the tumor. After opening the frontal sinus, the anterior margin of the tumor can be identified. If the tumor invades the maxillary sinus, we use endoscopic medial maxillectomy with a prelacrimal duct approach [15]. This method allows access to all areas of the maxillary sinus without sacrificing the nasolacrimal duct. After identifying the entire attachment area of the tumor, a 6-8 point biopsy is performed at 1.0 cm from the macroscopic tumor margins and the

tissue sent to the pathologist for rapid intraoperative diagnosis. The mucosal incision is performed at a pathologically confirmed tumor-negative area. We use a Colorado Microdissection Needle (Stryker, Wien, Austria) to incise the nasal mucosa. As this instrument has a very thin needle tip and can be bent, we are able to make precise incisions in the mucosa in a very narrow area. The tumor attachment site is then dissected and excised subperiosteally. If the underlining bone of the tumor attachment sites is eroded, the bone is resected with a diamond bar at a safety margin of 1.0cm from the erosive site. The bone is resected from the underling periosteum with the tumor. The periosteum is resected when the tumor is suspected to have spread to the underling periosteum. (Figure 1)

Statistical analysis

Overall survival was calculated from the beginning of treatment to the time of death from any cause or the date of the last follow-up contact for surviving patients, disease-specific survival was calculated to death from disease or the date of last follow-

up contact for surviving patients, and local control was calculated to the time of local recurrence or the date of last follow-up contact for surviving patients. All parameters were calculated by the Kaplan-Meier method and compared using the log-rank test. P values <0.05 were considered statistically significant. Statistical analysis was performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

Fifteen patients were enrolled in this study. Patients consisted of 8 males and 7 females, with a median age of 68 years (range 47-81 years). Six patients (40%) had tumors arising in the nasal cavity, 4 (27%) in the ethmoid sinus (the number of patients for whom the tumor occupied the anterior ethmoid sinus, the posterior ethmoid sinus, or both ethmoid sinuses was 1, 1 and 2, respectively) and 5 (33%) in the maxillary sinus. No patients had tumors originating in the sphenoid sinus or frontal sinus. Four patients (27%) were diagnosed with T1, 7 (47%) with T2, 4 (27%) with T3, and no patients with T4a or T4b disease. No lymph node involvement or distant metastasis was noted in any patient. The median follow-up period for surviving patients was 26 months (range, 7 to 123 months. Of the 15 patients, 13 (87%) had previously untreated disease, 2 (13%) had recurrent disease after prior treatment (one patient experienced recurrence after a Caldwell-Luc operation and the other experienced recurrence after IV-CRT). Two patients were diagnosed as IP preoperatively.

Treatment modalities

Treatment according to T stage is shown in Table 1. All fifteen patients were treated with ESS. No patients underwent an additional external approach. Of these, 8 (53%) were treated with surgery alone, 5 (33%) with surgery and postoperative radiotherapy, and 2 patients (13%) in whom the tumor was fond to invade the nasopharynx or orbital tissue during surgery were treated with IV-CRT or RADPLAT. Four of the 15 (27%) patients showed positive surgical margins. The postoperative course was uneventful in all 15 patients.

Outcomes

Two patients died of disease. One T2 patient was treated by CRT after surgery as the tumor extended into the nasopharynx. As the extension of the tumor was not detected before surgery, this patient was categorized as cT2. Although the primary site in this patient was well controlled, the patient died due to liver metastasis. The other patient

with T3 maxillary cancer died due to local relapse and distant metastasis. Although his tumor invaded the cribriform plate and endoscopic surgery was not indicated, he refused craniotomy because of his advanced age and many comorbidities. He also refused adjuvant radiotherapy, so that we followed up this patient without adjuvant therapy in spite of positive surgical margins at the cribriform plate. Eleven months after surgery the tumor recurred and he was treated by palliative radiotherapy. He later died of local disease and lung metastasis. We had two patients with inverted papilloma-transformed SCC. One patient had T1 maxillary sinus tumor treated with ESS alone and the others had T4 ethmoid sinus tumors treated with ESS+R/T. Both patients are alive and well without recurrence.

Overall Survival and Disease-specific Survival Rates

The 5-year overall survival, disease-specific survival and local control rates, as calculated by the Kaplan-Meier method, were 72.4%, 79.6% and 92.9%, respectively (Figure 2). One patient died of primary site recurrence and 1 patient of distant metastasis without

primary site recurrence. Two patients with T1 and T2 tumors died of other causes: one patient died of heart failure and the other of middle ear carcinoma. The 5-yr overall survival for T1, T2, and T3 disease was 66.7%, 75.0%, and 75.0%, respectively. The 5-yr disease-specific survival for T1, T2, and T3 disease was 100% and 75% and 75%, respectively (Figure 3).

The 5-year disease-specific survival for positive and negative surgical margins was 37.5% and 100%, respectively. Patients with negative surgical margins had a better disease-specific survival rate than did those with positive surgical margins (p=0.0253; Figure 4). Age, sex, T-stage, and tumor site did not affect disease-specific or overall survival (Table 2).

Discussion

In this study, endoscopic surgery for patients with highly selected early-stage SNSCC show feasible results. We resected the tumor endonasally with reference to "attachment-oriented surgery" and the "multilayer centripetal technique" with slight modifications [12]. Attachment-oriented surgery was originally designed for sinonasal inverted papillomas and showed good oncological results [16]. The original version of this surgery begins with debulking of the tumor using a microdebrider to precisely identify the site of origin of the tumor. The mucosa is then resected far enough from the tumor to ensure safe margins. Finally, the tumor attachment site is drilled out with a diamond bar and the absence of cancer cells at the margins of the resected tumor confirmed by frozen sections. As SNSCC is more aggressive than inverted papillomas, we set wider surgical margins than those used in IP surgery and used frozen section biopsy before the mucosa around the tumor was incised. Moreover, we resected eroded bone instead of drilling, as drilling of tumor attachment site has a risk of tumor dissemination. The "multilayer centripetal technique" reported by Castelnuovo et al. involves similar debulking of the tumor and management of the tumor attachment site. This surgical

method is applicable for all sinonasal malignant tumors and they reported excellent results [13]. Although Castelnuovo et al. open the nasal septal window at the posterior portion of the nasal septum, we open the anterior portion of the nasal septum. Further, while the posterior septal window has advantages in allowing four hands to be used for tumor resection, the opening of this window requires the sacrifice of olfaction. For that reason, we use an anterior septal window, which is a little larger than that used for normal Draf III procedures, instead. We consider that the precise management of the tumor attachment site with tumor debulking enables complete resection of the tumor even without en-bloc resection.

There are very few studies focusing on endoscopic surgery for SNSCC. Shipchandler et al. reported preliminary data for 11 patients with SNSCC treated by endoscopic surgery [7]. The overall survival and disease-free survival with a mean follow-up of 31.5 months were both 91%. Although these results were excellent, the follow-up period was too short to ascertain the 5-year survival rate. Moreover, they included 4 patients who underwent craniotomy with endoscopic surgery, with only 7 patient undergoing purely endoscopic surgery. Kilic et al. reported a large study based

on data from the national cancer data base. They identified a total of 1483 patients (353 patients received endoscopic surgery and 1130 patients underwent open surgery) with SNSCC. The 5-year overall survival rates for the two groups were 56.5 and 46.0 %, respectively, and there was no significant difference between the two groups [6].

The 5-year overall survival, disease-specific survival and local control rates in this study were 72.4%, 79.6% and 92.9%, respectively, which are better than those reported by Kilic et al. One possible reason for this difference is patient selection. In contrast to our study which did not include any T4 patients, Kilic et al. included patients with clinical stage T4a (22%) and T4b (5.9%). As previously stated, we selected patients in strict accordance with our institutional policy [11]. Therefore, eligible patients for surgery were patients with T1-2 disease and slightly resected T3-T4a disease. Of these patients, the indication for purely endoscopic surgery is even more limited due to the rapid advancements in endoscopic surgery. Indeed, although we treated 154 cases of SNSCC in our hospital during the study period, only 15 patients were treated with endoscopic surgery. Nicolai et al. reported their indications for endoscopic surgery for sinonasal malignancies [4] as excluding patients with extension into the frontal sinus,

orbit, lacrimal pathway, bony wall of the maxillary sinus (except the medial wall), pterygopalatine or infratemporal fossa, and erosion of the skull base. The United Kingdom guidelines for sinonasal malignancies shows similar indications for endoscopic surgery except for erosion of the skull base [17]. These guidelines for endoscopic surgery include patients with skull base bone erosion and dura or brain involvement medial to the mid orbital roof. These guidelines are suitable for less aggressive sinonasal carcinomas; however, as SNSCC has more aggressive features than other histologies such as olfactory neuroblastoma or adenocarcinoma [2], we selected patients more strictly than required under the United Kingdom guidelines and followed Nicolai's indications. As a result, our patients had relatively limited disease such as T1-2 nasal cavity/ethmoid tumors and some T3 disease without boney destruction of the sinus walls.

In our study, 4 of the 15 patients (27%) had positive surgical margins. None of the surgical margin-negative patients (n=11) experienced any recurrence. On the contrary, the 5-year disease-specific survival of the patients with positive surgical margins was 38%, which was significantly lower than that in patients with negative surgical margins. This result suggests that negative surgical margins are also important in cases

treated using the multilayer centripetal technique. Our rate of positive surgical margins was equivalent to those in previous studies (21-33%) [6, 18]. It was reported that positive surgical margins was one of the poor prognostic factors [19]. It was also reported that there was no difference in the rate of positive margins between the endoscopic and open approach groups [6, 18, 20, 21]. This suggests that the ability to achieve histologically complete resection was comparable between the two approaches.

These data suggest that the most important factors for improving surgical results is the attainment of negative surgical margins with good visualization regardless of the surgical approach used. To achieve negative surgical margins, patient selection for endoscopic surgery is very important. As SCC as well as malignant melanoma and undifferentiated carcinoma are more aggressive than other malignant sinonasal tumors [2], wider surgical margins are considered necessary. The surgical approach should be selected in consideration of achieving wide negative surgical margin with good surgical visualization.

The merit in undertaking precise surgery for SNSCC is that it enables the assessment of the true local extent of the disease and affords information valuable for

choosing appropriate adjuvant therapy. Such information is critical to the management of aggressive diseases such as SNSCC. In our study, 7 of the 15 patients were treated with adjuvant therapy, with the remaining 8 patients without undergoing adjuvant therapy. As a result, the 5-year local control rate was high at 92.9%. This result shows that we could appropriately determine the indications for adjuvant therapy based on the preceding surgery.

In conclusion, endoscopic surgery showed excellent results for patients with highly selected early-stage SNSCC. The most important factor for attaining good surgical results is the achievement of negative surgical margins with good visualization of the tumor attachment site regardless of the surgical approach -- open or endoscopic. We consider, at this time, that the indications for endoscopic surgery for SNSCC include T1-2 nasal cavity/ethmoid tumors and some T3 disease without any boney destruction of the sinus walls.

Conflict of Interest

We declare that we have no conflicts of interest.

Funding

We declare that we have no funding.

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Figure legends

Figure 1: Surgical concept of the attachment-oriented surgery.

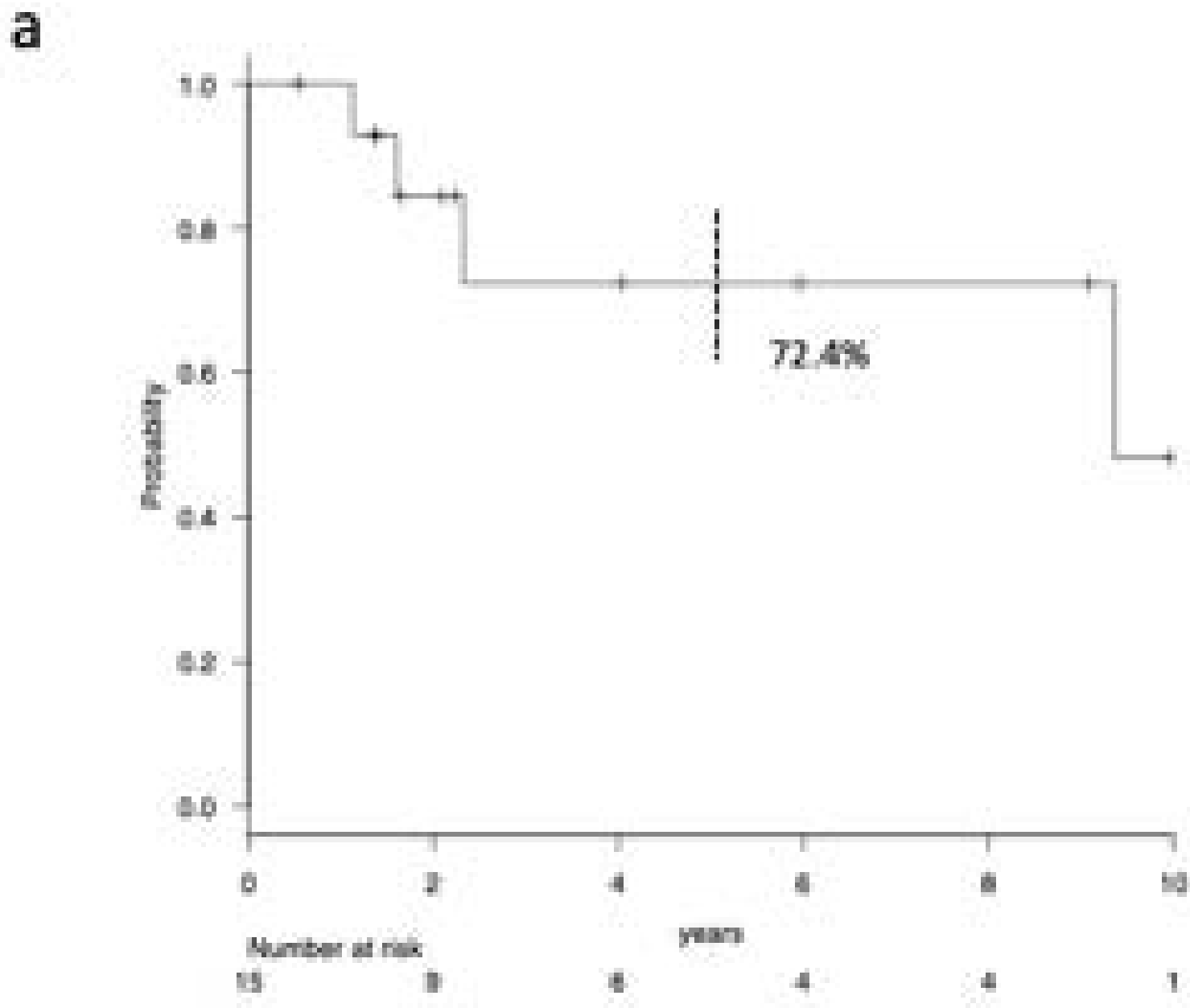
a. The surgery begins with debulking of the tumor with a microdebrider to identify the origin of the tumor. b. A 6-8 point biopsy is taken and frozen sections sent to the pathologist. The mucosal incision is performed with pathologically confirmed tumor-negative margins. c. and d. The tumor attachment site is dissected and excised subperiosteally. If the underlying bone is eroded, the bone is resected with the tumor.

Figure 2: Overall survival rate (a), disease-specific survival rate (b), and local control rate (c) for all patients

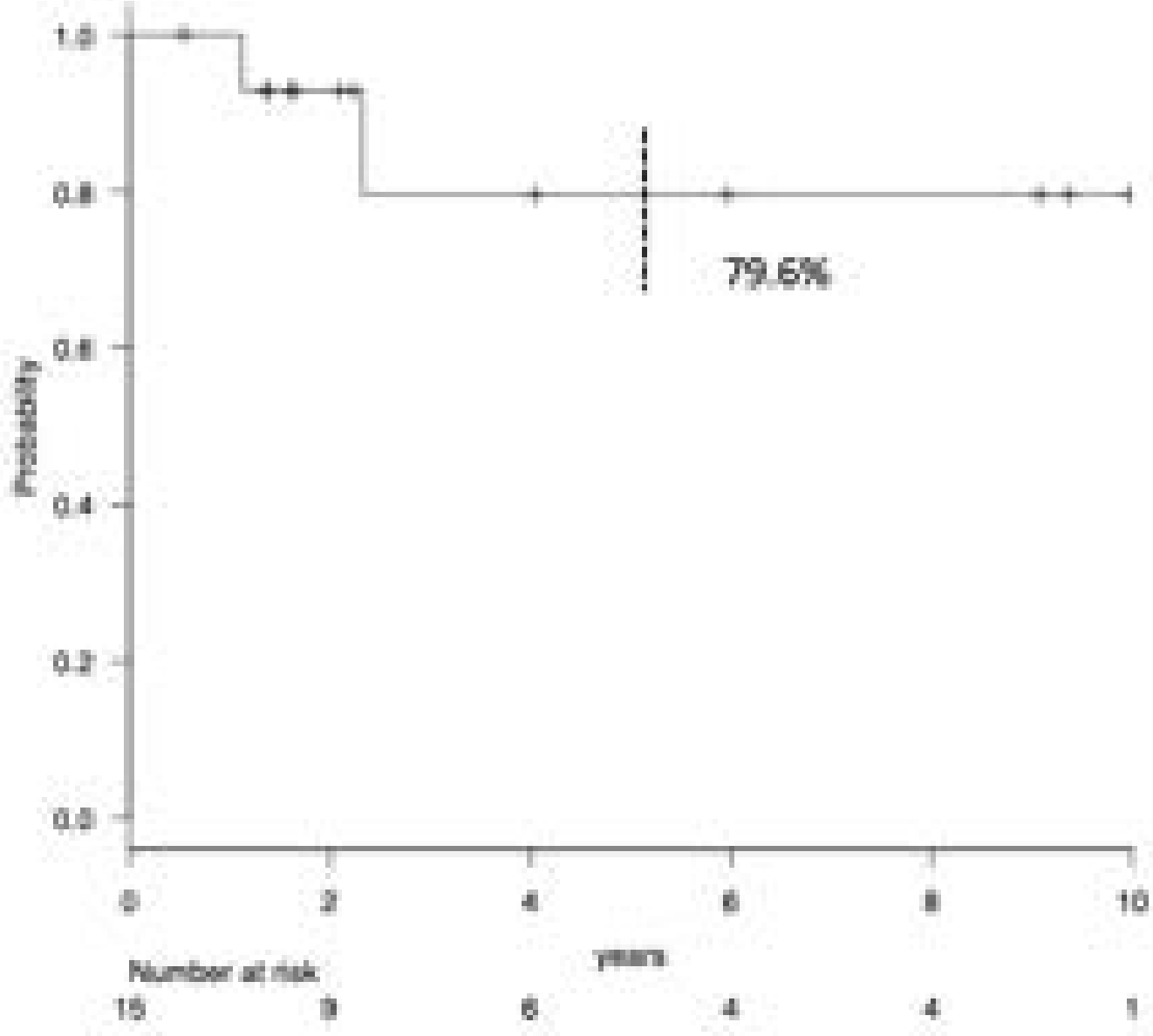
Figure 3 Disease-specific survival rate according to T classification.

Figure 4 Disease-specific survival rate according to surgical margins.

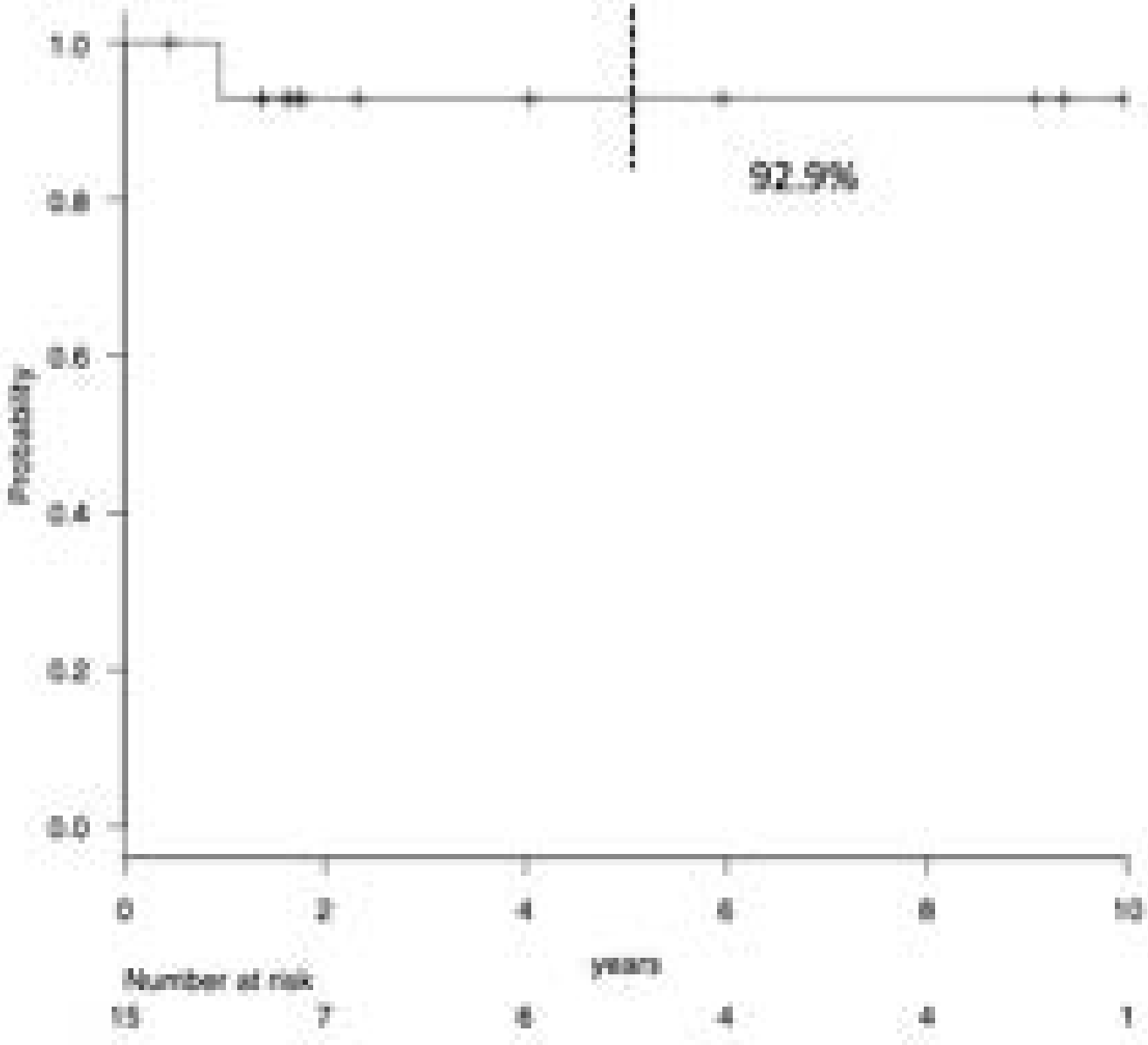


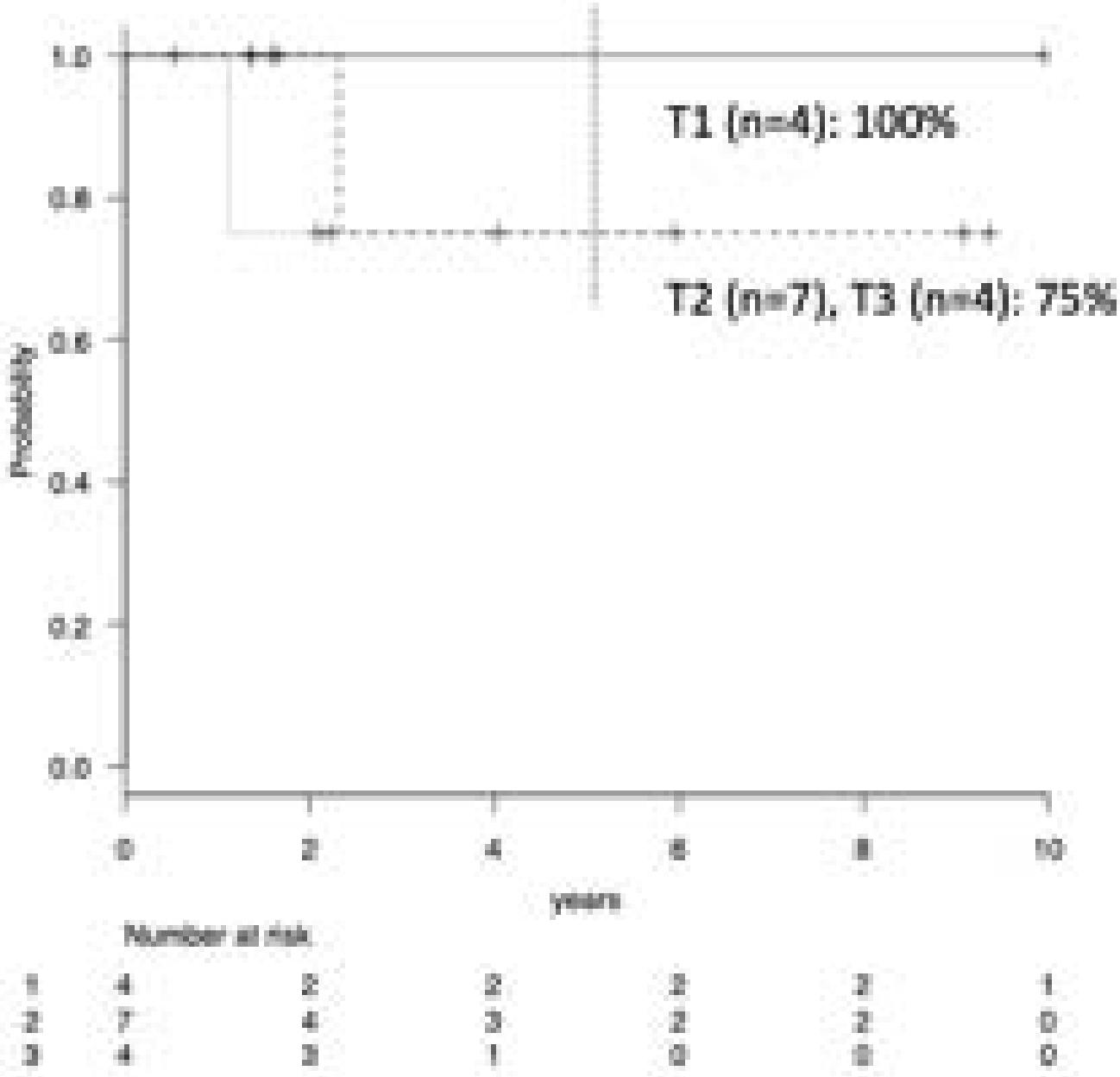

a
1.0
0.8
0.6
0.4
0.2
0.0
Probability
72.4%
0
2
4
6
8
10
years
Number at risk
15
9
6
4
4
1

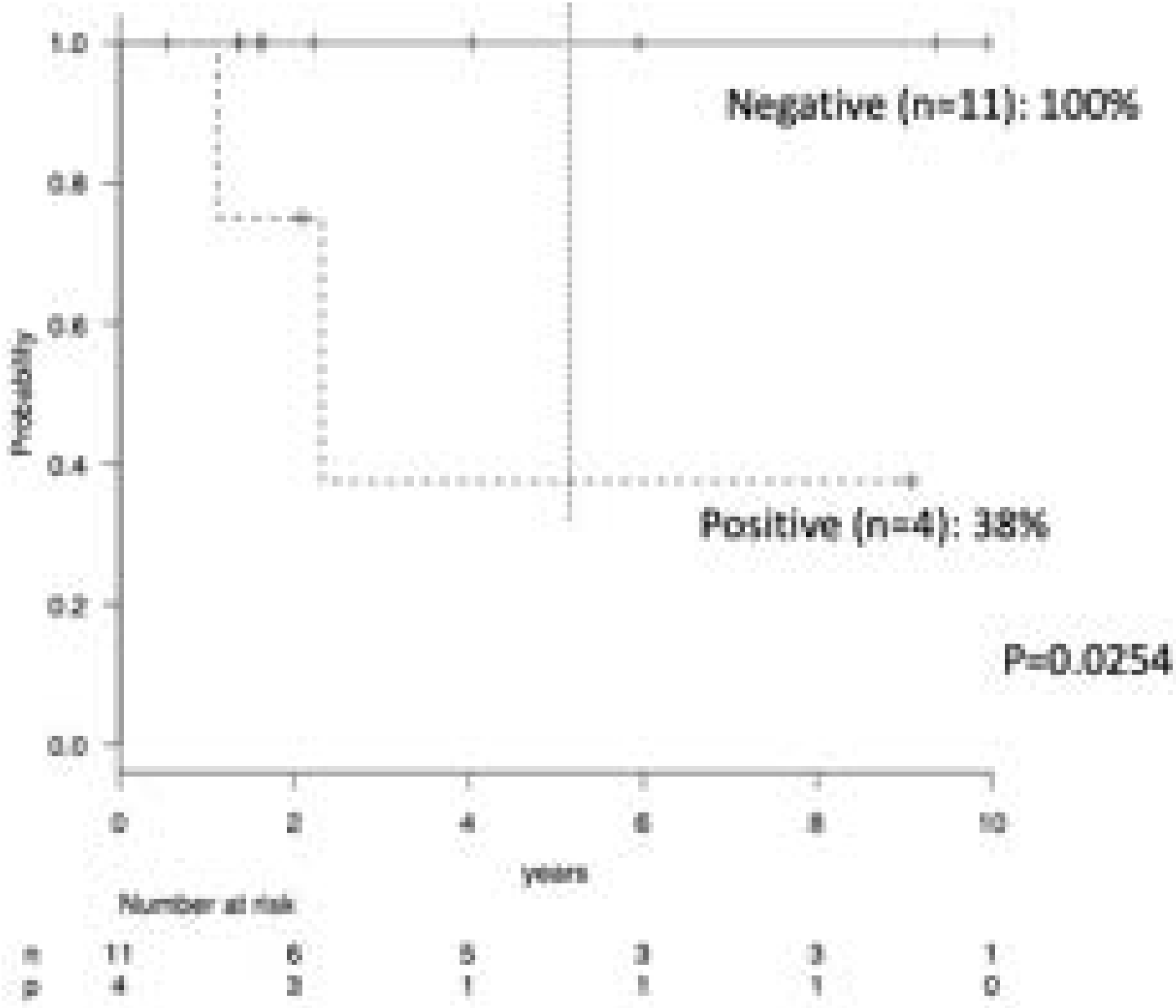
b


1.0
0.8
0.6
0.4
0.2
0.0
Probability
79.6%
0
2
4
6
8
10
years
Number at risk
15
9
6
4
4
1

C


1.0
0.8
0.6
0.4
0.2
0.0
Probability
92.9%
0
2
4
6
8
10
years
Number at risk
15
7
6
4
4
1


T1 (n=4): 100%
T2 (n=7), T3 (n=4): 75%
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
years
Number at risk
1 4 3 2 2 2 1
2 7 4 3 2 2 0
3 4 3 1 0 0 0


Negative (n=11): 100%
Positive (n=4): 38%
P=0.0254
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
years
Number at risk
n 11 6 5 3 3 1
p 4 3 1 1 1 0

T (n)	treatment	n	margin positive	outcome
T1 (4)	ESS	4	0	3:NED, 1DOC
T2 (7)	ESS	3	0	2:NED, 1:DOC
	ESS, RT	3	1	1:NED
	ESS, IV-CRT	1	1	1:DOD(D)
T3 (4)	ESS	1	0	1:NED
	ESS, RT	2	1	1:NED, 1:DOD(P, D)
	ESS, RADPLAT	1	1	1:NED
total		15	4	

Table 1. Treatment according to T stage (n=15)

Abbreviations: ESS=endoscpic sinus surgery; RT=radiotherapy;

RADPLAT=radiotherapy with intra-arterial chemotherapy;

IV-CRT=radiotherapy with intravenous chemotherapy,

NED=no evidence of disease, DOD=dead of disease, DOC=dead of other cause,

DOC=dead of other cause, P=primary disease, D=distant disease

Variables		n	5y OS	p-value	5y DSS	p-value
all		15	72.4		79.4	
age	<70	8	65.6	0.876	75	0.838
	≥70	7	83.3		83.3	
sex	male	8	71.4	0.902	71.4	0.292
	female	7	NA		NA	
histoloical gra	well, moderate	6	100	0.397	100	0.254
	poor	9	0.571		66.7	
site	NC, ethmoid	10	55.6	0.105	66.7	0.254
	maxllary	5	100		100	
T stage	T1and T2	11	72.9	0.680	83.3	0.317
	T3	4	75.0		75	
margin	negative	11	0.875	0.138	100	0.0253
	positive	4	0.375		37.5	

Table 2. Factors associated with patients survival

Abbreviations: well=well differentiated; moderate=moderatly differentiated; poor: poorly differentiated 5y OS=5-year over all survival; 5y DSS=5-year disease specific survival; NA=not available