Significance of clinical stage, extent of surgery and outcome in cutaneous head and neck squamous cell carcinoma

Running heads short title: Novel staging system and outcome in CHNSCC

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Abstract

The authors analyzed a new clinical staging system and its correlation with pathologic findings and patient survival. Patients were eligible for inclusion in this longitudinal retrospective cohort study if they had cutaneous squamous cell carcinoma on the head or neck, underwent surgery and had a minimum 3 year follow-up. The primary study variable was using a new clinical staging system. Secondary variables included the parotid as a predictor of metastatic spread to the lymphatic nodes in the neck and primary lesion histopathologic traits. The outcome variable was patient survival. Associations between variables were assessed using Fisher's exact test, Mann-Whitney test, Kaplan-Meier method and Mantel log-rank test. $P<0.05$ was considered significant. The sample was composed of 103 patients. Regional metastatic disease was found in 24 patients. Histopathological analysis showed a higher frequency of neck metastatic disease if the parotid was positive for metastases ($p=0.022$). An extended staging system showed significant correlation between survival rate and substages ($p=0.0105$). Perineural invasion was a negative prognostic factor ($p=0.0151$) The results of this study suggest that combining curative parotidectomy and elective neck dissection could be beneficial in high risk patients. Both neck and parotid metastases should be included in the clinical and histological N classification.

Introduction

Cutaneous squamous cell carcinoma (CSCC) comprises nearly 20% of all non-melanoma malignant skin tumors and represents a significant global health issue. Most lesions (80-90%) occur in sun-exposed regions of the head and neck.[1,2] Although early stage cure rates are excellent, in some patients (5-10%) regional metastatic disease develops, lowering the survival rate by 50%.[3] The rate of distant metastatic disease remains low, even in those patients with regional metastases.[3,4] The inability to identify high risk lesions at the time of initial treatment is further aggravated by a lack of consensus on the appropriate management of regional metastases. Adequate surgical excision of the primary CSCC and an immediate curative lymphadenectomy remain essential in achieving control over disease progression and patient survival. There is no consensus on the indications for an elective neck dissection and extent of surgery, while further benefit can be expected from sentinel lymph node biopsy, selective neck dissection in high risk patients and adjuvant radiotherapy.[5,6,7] Only limited data exist on the relationship between clinical staging of advanced regional disease and patient survival rate.[8,9,10,11,12] The parotid gland is the first site for metastatic spread of head and neck CSCC, and parotid involvement poses a significant diagnostic and therapeutic challenge.[1,13,14] Therefore it is important to examine the relationship between patterns of metastatic spread in the parotid and the neck when planning surgical treatment.

Materials and Methods

This retrospective longitudinal cohort study and its protocol were approved by the University of Zagreb Medical School Bioethics Board, adhering to the Helsinki Declaration of 1983. All patients with head and neck CSCC who were surgically treated from September 1st, 1983 to October 31st, 2007 were eligible for inclusion in a comprehensive oncological database (tum-2). Patients were eligible for inclusion if they had a histopathologically confirmed CSCC on the head or neck, if they underwent primary surgical treatment in our institution, if the primary tumor measured >2 cm in its highest diameter and if they had a follow-up of minimum 3 years. The patients underwent extensive examinations and were treated according to standard clinical practices approved by a multidisciplinary oncological team. Clinical staging was carried out according to the current AJC staging system, but was revised using a new staging system (O'Brien's PN classification) shown in Table 1, which separates patients into groups according to the extent of parotid disease and presence or absence of clinical neck disease.[1,10,12] The patients were included consecutively, and follow-up lasted for a minimum of 3 years, until May 1st, 2010 or patient's death. Demographic information, prior history of skin malignancy, location, lesion size, previous therapy, surgical procedure and reconstruction method details, histopathologic findings (margin status, number of positive lymph nodes, number of examined lymph nodes, extracapsular spread and/or perineural invasion) and evidence of regional metastatic disease was collected. Histologic margins were defined as "clear" if there was a definitive healthy tissue margin of >5 mm around the cancer tissue, while "near" margins were defined with <5 mm of healthy tissue. Patients with a "near" or "positive" margin were evaluated by a multidisciplinary oncology team and underwent re-excision if necessary. The total number of surgically excised CSCC was well over a thousand patients, but due to strict study protocol criteria, the following patients were not eligible:

patients with primary tumors <2 cm in the highest diameter, incomplete documentation, incomplete follow-up or day clinic patients, or localization of CSCC on the lip, which is known to have clinical and histological characteristics and a poorer prognosis than other head and neck CSCC.[15] Patterns of metastatic involvement of cervical nodes were analyzed and correlated with primary lesion localizations. These primary lesions were divided into 5 different anatomic sublocalizations; 1. frontonasal, 2. auriculotemporal, 3. mental, submental and submandibular, 4. orbitozygomatic, 5. buccal and preauricular region (Figure 1). Localizations of regional metastatic disease were divided into the following anatomic regions: the parotid gland and neck regions I-VI, according to the recommendations proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery.[16]

Statistical analysis was performed using MedCalc software (Version 11.2.1 © 1993-2010. MedCalc Software bvba Software, Broekstraat 52, 9030 Mariakerke, Belgium), using standard descriptive statistics and frequency tabulation as indicated. The data for the n=24 cohort were expressed as ratios due to n<100. Associations between variables were assessed using Fisher's exact test, Mann-Whitney test and Kaplan-Meier method with Mantel log-rank test applied to endpoints to establish survival or recurrence probabilities. All tests of statistical significance were performed using a two-sided 5% type I error rate.[17]

Results

This study included 103 surgically treated patients from September 1st, 1983 to October 31st, 2007, while maintaining strict exclusion criteria. Among the patients that were eligible for inclusion, 56 were women and 47 were men. Average age was 74.5 years (69 in men and 79 in women) while ages ranged from 47 to 92 years. The highest incidence of head and neck CSCC was in the age group of 80-98 years, followed by the age group of 70-79 years. The average age of primary lesion occurrence was significantly greater in women (p<0.0012). Out of the 103 patients, a cohort of 24 patients with clinically apparent regional metastatic disease and neck dissection was formed. Data from the total cohort population (n=103) shows that the most frequent localization of the primary lesion was in the buccal and preauricular sublocalization (56,3%), followed by the frontonasal sublocalization (29,12%). Incomplete excision rate was 6.7%, and there was a significant positive statistical correlation with higher T stage in the cohort with regional metastatic disease (p=0.0018). Average lesion size ranged from 2.1 to 13.5 cm, with a median of 4.3 cm (n=103). There were 26 recurrences of the primary lesion both in the primary and metastatic disease localizations (25,2%), of which 15 patients with primary localization recurrence, 5 with recurring regional neck disease, 1 patient with recurring parotid disease after parotidectomy and 5 patients with new primary lesions in the follow up interval. Perineural invasion was recorded in 5 patients, while 2 patients had vascular invasion, all in the patient cohort with regional metastatic disease (n=24). Three patients with extensive primary lesions (8.1, 11.3 and 13,5 cm in diameter) were not submitted to skull base procedures upon review by a multidisciplinary oncological team. Regional metastatic disease rate was 23.3% (24/103) and the patients were singled out to form a separate cohort group. This group comprised of 12 men and 12 women with the highest incidence of CSCC in the 70-79 age group. The most common localization of primary lesions

was the auriculotemporal area (9/24), followed by the buccal and preauricular area (6/24). There were 10 patients with clinical N1 stage and 8 with clinical metastatic disease in the parotid gland only. There were 6 patients with clinical N2 stage. All 24 patients underwent curative neck dissection, whereas 19 patients underwent total parotidectomy sacrificing the facial nerve, and 3 patients underwent superficial parotidectomy. In the 3 remaining patients the parotid was not surgically treated.

There were 8 patients with clinical parotid disease and 16 patients with clinical neck disease, while there were no patients with a combined clinical finding. Histopathological analysis discovered 9 additional histopathologically positive metastases in the parotid gland that were clinically unrecognized. Histopathological analysis showed that there was a statistically significant higher frequency of neck metastatic disease if the parotid gland is also positive for metastases (p=0.022). A positive histopathological finding in the parotid gland is related with statistical significance to a higher frequency of neck metastases in all 5 regions (p=0.044), and a negative finding is related to a significantly higher frequency of metastatic spread in regions II and III (p=0.033). In the cohort with regional metastatic disease, primary lesions localized in the temporoauricular, buccal and preauricular areas have a statistically significant higher rate of metastatic spread into neck regions IV and V than primary lesions localized in the frontonasal, orbital and zygomatic, mental and submental areas (p=0.0299).

The survival rate calculated by Kaplan-Meier's method and using the standard AJC staging system is displayed in Figure 2. According to the most recent staging system, the N1 stage includes patients with a positive clinical finding in the parotid, neck or both. When an extended staging system was applied to the same group of patients, a statistically significant correlation between survival rate and substages of the PN classification is observed in Figure 3 (χ^2=9.1072, df=2, p=0.0105). Cumulative disease-specific survival was highest in N1 stage,

followed by P and N2 stages. Figure 4 shows a significant correlation between survival and P stage with cumulative disease-specific survival decreasing significantly with increasing P stage (χ^2=12.9407, df=3, p=0.0048).

In Figure 5, a significant correlation between histopathological findings and cumulative disease-specific survival was identified, with highest survival in the group that had histopathologically verified parotid disease only, and significantly lower survival rates in stages N1 and N2 (χ^2=12.7359, df=3, p=0.0052). Further data analysis yielded a significant correlation between survival rate in patients with isolated neck or parotid metastatic disease and those with metastatic disease in both the parotid and neck, as identified in Figure 6 (χ^2=10.2545, df=2, p=0.0059).

Perineural invasion proved to be a significant negative prognostic factor in the cohort with regional metastatic disease (χ^2=5.9011, df=1, p=0.0151) (Figure 7). Other analyzed variables (primary lesion size, margin status, extracapsular spread) did not yield any significant correlations in survival rate data distribution.

Discussion

The majority of head and neck CSCC patients are cured by timely surgical intervention, but some develop regional metastatic disease which adversely affects survival. Due to a small number of patients with regional metastases, their treatment algorhythms remain unstandardized, especially when extent of surgery is concerned. Although some authors consider sentinel lymph node biopsy techniques as standard of care, they still have no proven survival benefit in the management of head and neck CSCC, and their use remains unequivocally investigational.[18] It is important to note that metastatic head and neck CSCC comprise a heterogeneous group for diagnosing, treating and accurately assessing outcome. Due to these factors, the number of patients included in this study is comparable to earlier published results.

The aim of this study is to analyze clinical outcome in a group of patients surgically treated for metastatic cutaneous SCC and to document patterns of metastatic spread. We sought to confirm current clinical experience that outcome varies with lesion localization, metastatic disease and surgical treatment extent. We believe that the present head and neck CSCC staging system used in clinical work is inadequate and that an extended staging system of regional metastatic disease in the parotid and neck may significantly influence prognosis. The second question is whether there is a positive correlation between metastatic disease in the parotid gland and the lymphatic nodes in the neck. This information has potential implications to treat the clinically negative neck in patients with CSCC involving the parotid. In addition, we sought to determine the impact of histopathological parameters, nodal metastasis and surgery extent on disease control and patient survival.

The average age in the regional metastatic disease patient cohort was 73.1 years, with the average age in men being 69.8, and 76.4 in women. Male to female ratio was 1:1 (n=24). The

median 10-year survival rate for patients with regional metastatic disease was 12.1±9.8%, and for the entire patient cohort 45.5±10.2%, which is consistent with published results.[8] Analysis of the entire population with head and neck CSCC, including patients with regional disease (n=103) showed that women are affected significantly later (p<0.0012), probably due to a lesser degree of sun exposure and longer life expectancy.[19,20] Detailed histopathological analysis has identified perineural invasion as a risk factor for nodal metastasis. However, the analysis yielded no significant correlations between other tumor characteristics and metastatic disease rate, which can likely be attributed to a relatively small sample size, low inadequate excision rate and the lack of additional detailed histopatologic data gathered for analysis. Other authors have identified lesion size >2 cm, lesion localization, excision margins and depth >4 mm as risk factors for lymphatic metastases.[6,21] A large study conducted by Brantsch et al. with 615 patients designated tumor depth and histological differentiation as risk factors for metastatic disease, with 75% of lesions being <2 cm, confirming the opinion held by Veness et al, that even small lesions have a significant metastatic potential.[8,22] Lymphatic metastases were identified in 23.3% of the patients, which is slightly higher than previously reported rate, ranging from 0.3% to 20.7%. The incidence reflects the practice environment of the authors, since the patients referred to our comprehensive cancer center are more likely to suffer from aggressive or advanced disease.[6,9,12] According to our analysis, the number of patients with positive resection margins (6.7%) is consistent with previously published studies (6.3% to 15.9%), but shows no correlation to survival or local recurrence rates, although patients with T3 stage have a significantly higher rate of positive resection margins. Tumor size did not impact survival rates, which is consistent with existing results.[11] No correlation between incomplete excision and regional metastatic disease rates was found, most likely due to the consistent treatment protocol used in this study that mandated repeated

surgical treatment and adjuvant radiotherapy for all patients with positive resection margins. Cutaneous squamous cell carcinoma of the head and neck regions has a low metastatic rate to regional lymph nodes (5-10%) and the extraordinarily well developed neck lymphatic system poses a strong barrier to further metastatic spread.[1,8,13] Bearing that in mind, local and regional disease control is essential in improving survival. O'Brien et al have shown the importance of the parotid gland in the management and prognosis of CSCC, using a modification to current staging systems that includes parotid involvement. This study was conducted using O'Brien's modified PN system.[1] The majority of patients with regional metastatic disease (16/24) had clinically apparent metastatic disease, 7 patients were previously treated by primary tumor excision and had recurrent metastatic disease and one patient was primarily treated by radiotherapy. All of the patients with regional metastatic disease underwent a comprehensive excision of the primary lesion when present, neck dissection dictated by the location of the primary lesion or clinical metastases, and postoperative radiotherapy when indicated. Selective neck dissections were performed in the majority of cases; most commonly encompassing levels I, II and III (58,3%). The rate of recurrence was 11.9%, which confirms the validity of our treatment protocol in comparison to literature figures of 21% to 52%.[6]

In our study, isolated parotid metastatic disease was found in 8/24 patients, with 16/24 clinically presenting with isolated neck disease. Histopathologic findings revealed parotid involvement in 17/24 patients, and 16/24 had neck lymph node metastases. These results differ from data published by Veness et al, that identify the parotid gland as the primary clinically positive finding in regional metastatic disease.[11] Our study shows that there is a significantly higher incidence of clinically positive neck findings with an associated clinically negative parotid gland. However, histopathological analysis shows a statistically significant

number of false negative parotid clinical findings and a significantly higher rate of histopathologically verified regional metastatic disease associated with positive histopathological parotid involvement than that of a positive neck associated with a negative parotid gland. Although the clinical findings portend the neck as a principal metastatic site, the possibility of clinically occult parotid metastatic disease must not be discarded and surgery extent should be planned accordingly, as was previously discussed in a study by O'Brien et al.[11] Previous studies have shown that parotid metastatic involvement leads to a poorer prognosis when compared to patients that had regional metastatic disease in the neck alone, with the parotid gland free from disease.[21,23] Our results indicate that for patients with clinically positive parotid involvement and occult neck metastatic disease, an elective neck dissection might be beneficial without significant increase in surgery related comorbidity. However, the question of elective neck dissection extent remains open for debate. Furthermore, the results show that there is a statistically significant association between a positive histopathological parotid finding and regional neck metastatic disease. In turn, if the parotid is histopathologically negative, metastases are most frequently found in neck regions II and III. These results would ration elective neck dissection of neck regions II and III with accompanying parotidectomy in high-risk patients, which is supported by published data.[24] The lateral aspect of the head (auriculotemporal) was the most common primary localization site in our study. We found that primary lesion localization affects the pattern of metastatic distribution. The patients with primary lesions localized in the auriculotemporal, buccal and preauricular regions had a significantly higher incidence of metastatic spread into neck regions IV and V, which is consistent with a previous study by Veness, Palme and Morgan.[11] This finding supports the idea that primary lesions localized on the lateral side of the face have a determined direction of metastatic disease spread. The results speak in favor of

extending surgical treatment to a modified radical neck dissection in patients at risk, especially if there is clinically evident parotid disease present. The head and neck CSCC that have disseminated into the neck and/or parotid gland have a higher incidence of distant metastatic disease, are biologically more aggressive and histopathological findings show extracapsular spread in 70% of cases, which corresponds to our histopathological analysis (12/24 patients had extracapsular spread).[25] Better disease control could be achieved through encouraging more frequent use of ultrasound and/or MSCT diagnostics in the parotid region as a standard clinical practice.[26] Local extent of disease is the most important prognostic factor for primary head and neck CSCC, and the presence of regional metastases cuts the survival rate in half.[27] Our study discusses the correlation between clinical and histopathological findings and disease outcome using two different staging systems; the current AJC staging system, and a recently proposed PN staging system by O'Brien et al. The results show that both clinical and histopathological PN staging correlate well with disease outcome and survival, whereas the standard N status of the current AJC staging system has no significant correlation. Similar results confirm this finding.[1,11,12,16,21,23] Clinically evident metastatic neck disease staged by the PN system shows a statistically significant correlation with survival rate. The N1 group had the best outcome, while N2 had the worst outcome. The 2-year survival rates for group N1 was 85%, group P had 55% and group N2 had only 17% (Figure 3). Since only a small number of authors report a significant correlation (p=0,084) between an extended clinical neck and parotid status and survival, the results of this study warrant interest and further confirmation in larger patient cohorts.[1,11,12,14] Our study has also analyzed the relationship between clinical P stage (P1-3) and survival, with a significant correlation found (p=0.0048). The group P1 has the best prognosis, followed by P2 and P3 with the least favorable prognosis, which is consistent with clinical trends reported by

O'Brien et al.[1] Figure 5 displays that histopathologically positive regional metastatic disease adversely affects all PN staging groups with 2-year disease free survival for group P being 90%, and dropping to 70% and 32% for groups N1 and N2, respectively. This data correspond to that previously reported in literature.[1,12,13] When comparing the standard AJC N1 staging and the extended PN classification N group, a lack of prognostic capability of the AJC staging system is evident.

The results of this study suggest that combining curative parotidectomy and elective neck dissection (and vice versa) could be beneficial in high risk patients with CSCC of head and neck. In patients with regional metastatic disease, primary lesions localized in temporoauricular area, buccal and preauricular areas have a statistically significant higher rate of metastatic spread into neck regions IV and V than primary lesions localized in other areas of the head and neck. Histopathological analysis showed that there was a statistically significant higher frequency of neck metastatic disease if the parotid gland is also positive for metastases. Patients with regional metastatic involvement in both the parotid and the neck have a significantly worse prognosis than those with parotid involvement alone, regardless of primary lesion localization. Regional disease should not only involve metastases of the neck, but also metastases in the parotid region, and both should be included in the clinical and histological N classification, as is the case with the O'Brien's PN classification used in our study.

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Ethical approval: This retrospective longitudinal cohort study and its protocol were approved by the University of Zagreb Medical School Bioethics Board, adhering to the Helsinki Declaration of 1983.

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Table 1. Modified head and neck CSCC staging system (PN classification) as proposed by O'Brien et al.[1]

P	**Parotid**
P0	No clinical disease in the parotid
P1	Metastatic node up to 3 cm in diameter
P2	Metastatic node > 3 cm and up to 6 cm in diameter or multiple nodes
P3	Metastatic node > 6 cm in diameter or disease involving the facial nerve or skull base
N	**Neck**
N0	No clinical disease
N1	Single ipsilateral neck node up to 3 cm in diameter
N2	Single node > 3 cm in diameter or multiple nodes or contralateral nodes

Figure 1. Anatomic regions of the head and neck used in the present study: 1. frontonasal, 2. auriculotemporal, 3. mental, submental and submandibular, 4. orbitozygomatic, 5. buccal and preauricular region.

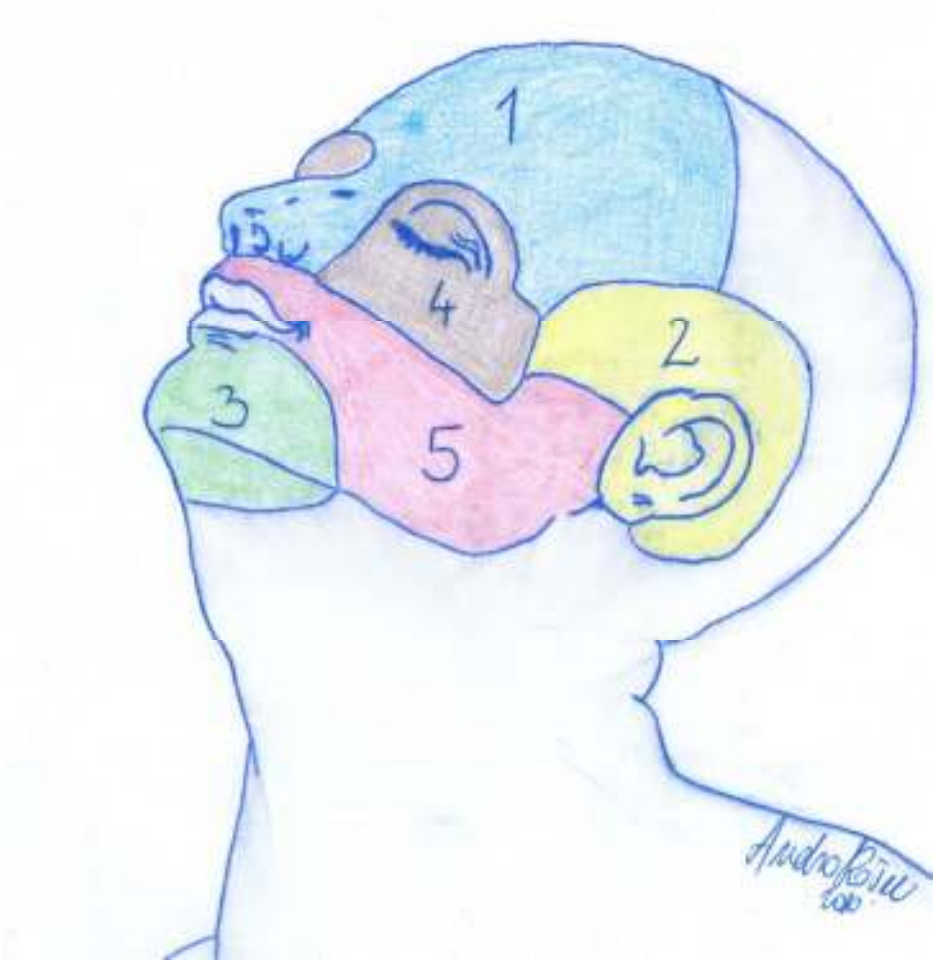

Figure 2. Patient survival rate displayed using the standard AJCC staging system. Solid line = all patients, male and female.

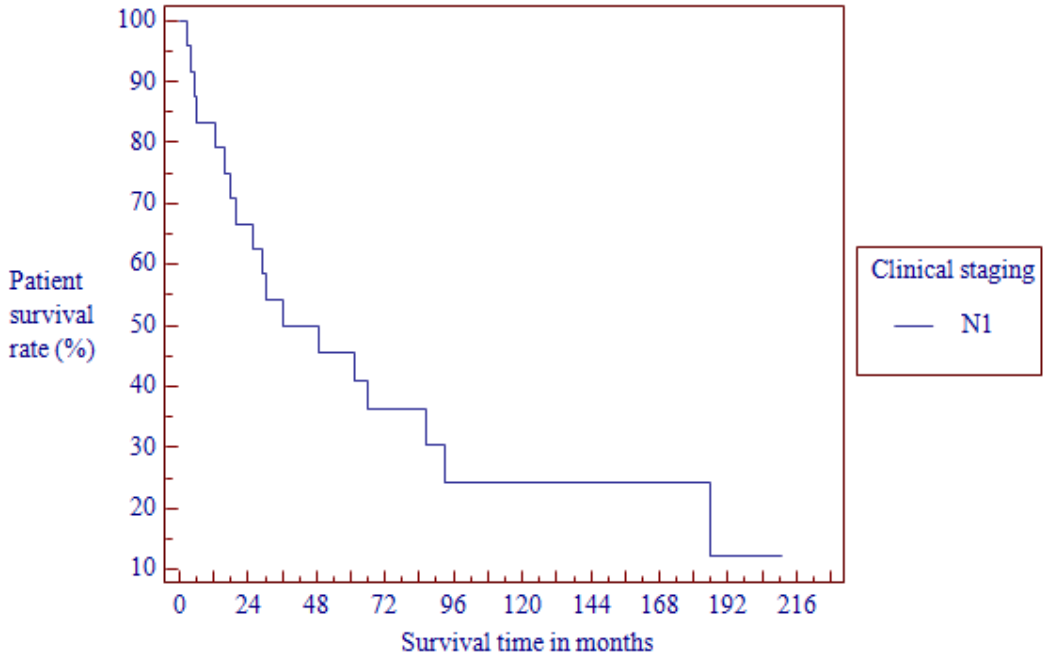

Figure 3. Correlation between patient survival rate and clinical N stage using an extended PN classification system (p=0.0105). Solid blue line = patients with N1 stage, solid orange line = patients with P stage, dashed red line = patients with N2 stage.

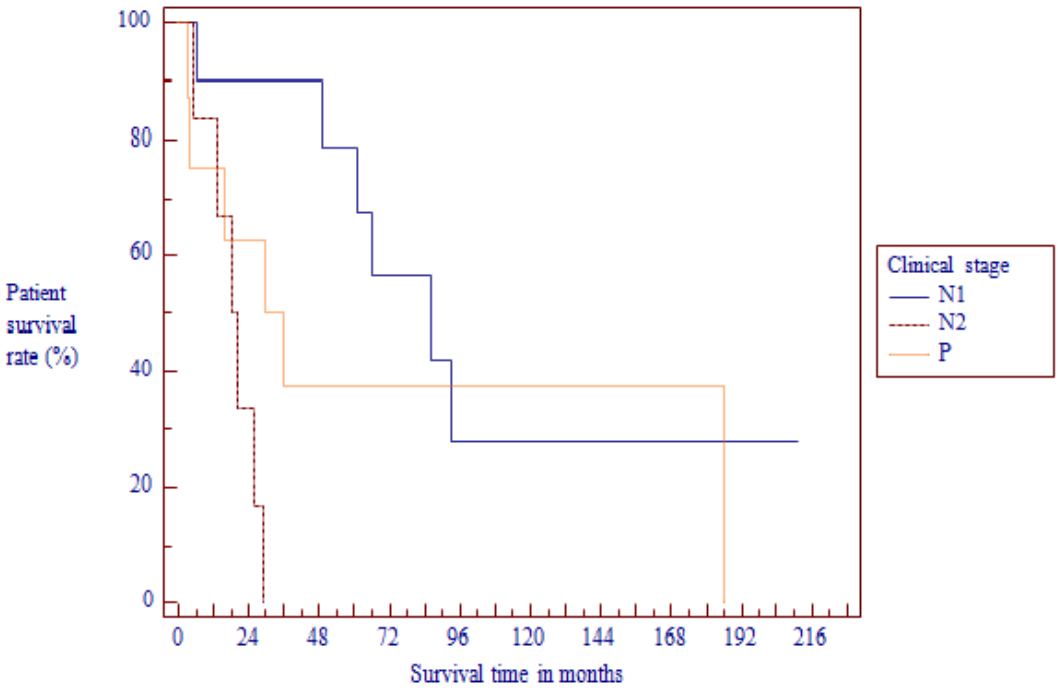

Figure 4. Correlation between survival rate and P stage (P1-3) (p=0.0048). Solid blue line = patients with N stage, dashed red line = patients with P1 stage, solid orange line = patients with P2 stage, dashed green line = patients with P3 stage.

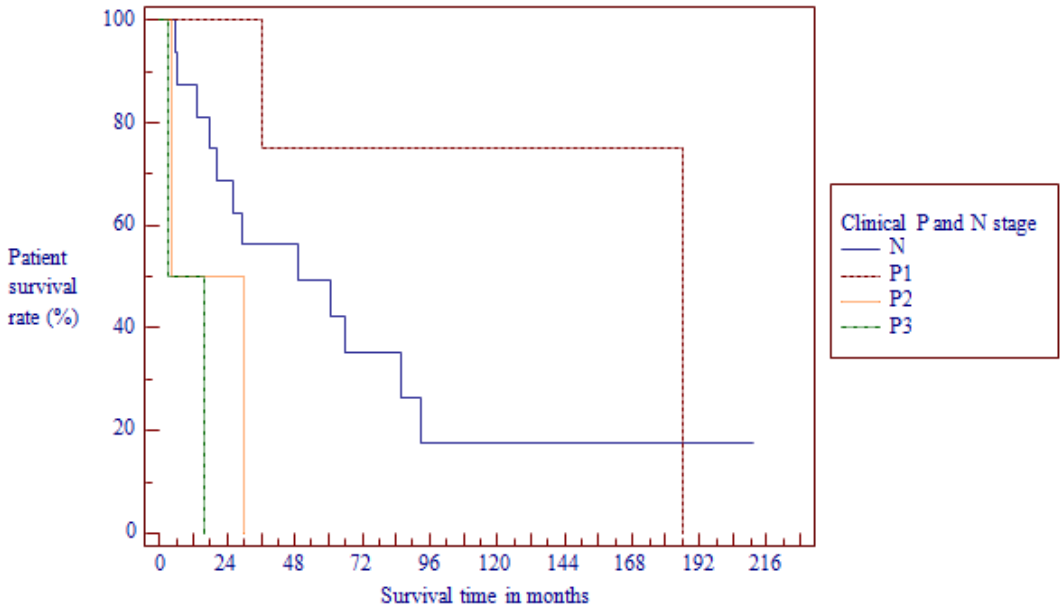

Figure 5. Correlation between histopathological PN classification stages and cumulative disease-specific survival (p=0.0052). Solid blue line = patients with N1 stage, dashed red line = patients with N2 stage, solid orange line = patients with P stage.

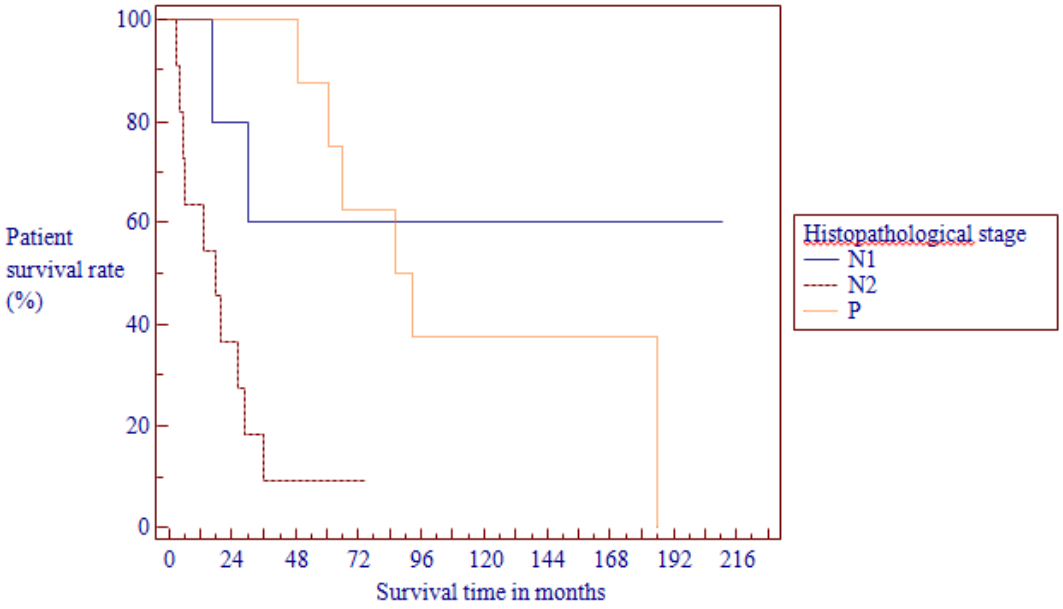

Figure 6. Correlation between cumulative disease-specific survival and histopathologically confirmed parotid and neck metastatic disease (p=0.0059). Solid blue line = patients with isolated parotid disease, dashed red line = patients with isolated neck disease, solid orange line = patients with both parotid and neck disease.

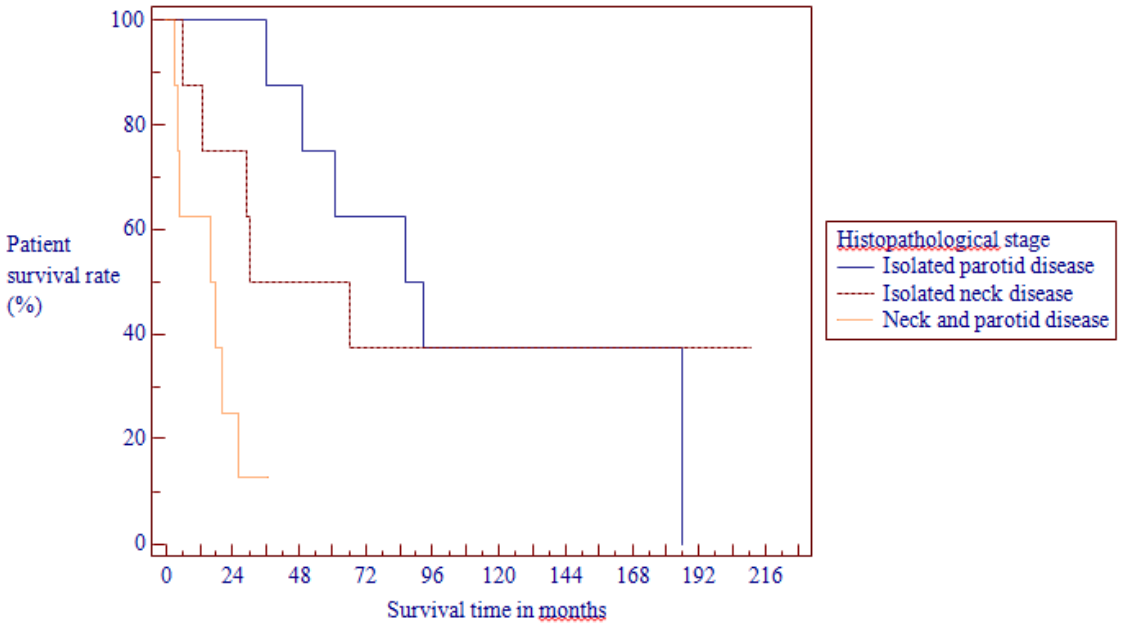

Figure 7. Perineural invasion and survival rate in the cohort with regional metastatic disease (p=0.0151) (n=24). Dashed line = positive perineural invasion, solid line = negative