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Abstract

Background Elective neck dissection (END) in patients with salivary gland carcinoma is controversial and there are no universally accepted guidelines.

Methods Patients were identified from the Danish Head and Neck Cancer Group. Between 2006 and 2015, 259 patients with primary salivary gland carcinoma were treated with END. Variables potentially associated with regional metastases were analysed using logistic regression. Neck recurrence-free survival was calculated using the Kaplan–Meier method.

Results Occult metastases were found in 36 of the patients treated with END (14%) and were particularly frequent among patients with T3/T4 tumours and high-grade histology tumours. In multivariate analyses, high-grade histology and vascular invasion were associated with occult metastases.

Conclusion We recommend END of levels II and III for patients with high-grade or unknown histological grade tumours, and for T3/T4 tumours. Levels I, II, and III should be included in END in patients with submandibular, sublingual, or minor salivary gland carcinomas.

Introduction

Cervical lymph node metastasis is a negative prognostic factor in patients with salivary gland carcinoma (1-6), and therapeutic neck dissection (TND) is recommended in patients with clinically involved cervical lymph nodes (7-12). However, there are no universally accepted guidelines on the surgical treatment of patients with clinically negative neck. Salivary gland carcinoma is a heterogeneous disease, and treatment strategies depend on the histological subtypes and anatomical locations of tumours, as well as the stage of the disease.

Current practice in Denmark is TND in patients with clinically positive cervical lymph nodes, and elective neck dissection (END) is recommended in patients with T3/T4 tumours, high-grade histology tumours, or in cases of facial nerve palsy (13). This approach is supported by studies that recommend END in patients with high-grade histology tumours or advanced tumour classifications (8, 11, 12, 14-21). Other studies have recommended END in all patients with salivary gland carcinomas (22-26), because preoperative evaluations of histological tumour subtypes and grades are unreliable and there is a risk of regional metastases even for low-grade histology tumours. Occult regional metastases have been reported in 12%–45% of patients with salivary gland carcinomas (8, 16, 19, 23, 24, 26-30), with the highest incidence among patients with high-grade histological subtypes (4, 8, 16, 27, 29, 31). Preoperative characteristics such as large tumours, older age, facial palsy, and extra-parotid extension of the primary tumour have also been associated with regional metastases (1, 5, 11, 32, 33).

In this study, we evaluate results from all Danish patients diagnosed with salivary gland carcinomas over a period of 10 years. We identify clinical and pathological factors associated with regional metastases and occult metastases, and we recommend an approach to surgical treatment of the neck in patients with salivary gland carcinoma but no clinically suspected regional metastases.

Material and Methods

This was a retrospective study with inclusion of all patients diagnosed with previously untreated primary salivary gland carcinoma in Denmark between 1 January 2006 and 31 December 2015.

Patients were identified from the national Danish Head and Neck Cancer Group (DAHANCA) database. Completeness of the database was verified by cross referencing with two additional national databases: The Danish Cancer Register, and The Danish Pathology Register. We included patients treated with intended curative surgery of the primary site, with or without neck dissection. Information on diagnostic procedures, surgical treatments and follow-up data were obtained from medical records and pathology reports. All available pathological specimens of primary tumours were histologically revised by one of four experienced salivary gland pathologists (SRL, KK, BPU and TA). Histological subtypes were classified according to the World Health Organization (WHO) 2017 classification system for salivary gland carcinoma (34).

A total of 730 patients were diagnosed with salivary gland carcinoma during the inclusion period. Patients with distant metastases at the time of diagnosis (*n* = 42) and patients given primary radiotherapy, palliative treatment, or no treatment (*n* = 24) were excluded. Of the 664 patients treated with surgery, 81 had clinically suspicious lymph nodes (cN+) and 583 had clinically negative lymph nodes (cN0). Patients with cN+ were treated with TND. For patients with cN0, the primary tumour site was excised followed by either no neck dissection (noND) (*n* = 324) or END (*n* = 259). A flow chart showing inclusion is provided in Figure 1.

TND was defined as neck dissection in patients with clinically (including radiographically) suspected cervical lymph node metastases. END was defined as neck dissection in patients with cN0. Occult metastases were defined as histologically confirmed metastases (pN+) in clinically negative lymph nodes (i.e., cN0pN+). The proportion of occult metastases was defined as the ratio between patients with cN0pN+ and patients treated with END. Regional metastases were defined as metastases in cervical lymph nodes. Vascular invasion was equivalent to lymphovascular invasion.

Clinical N-classifications were determined by clinical examination and diagnostic imaging using ultrasonography (*n* = 389, 57%), computed tomopgraphy (CT) (*n* = 270, 40%), magnetic resonance imaging (MRI) (*n* = 342, 51%) and/or positron emission/computed tomography (PET/CT) (*n* = 193, 29%). If lymph node metastases were suspected from one of the diagnostic modalities, the clinical N-classification was defined as positive (cN+). Tumours were classified according to the Union for International Cancer Control (UICC) TNM 8th edition (35).

Preoperative decision on END was made by the patient and surgeon or a multidisciplinary team including a surgeon, oncologist, and radiologist. In accordance with the Danish treatment guidelines for salivary gland carcinoma, patients with T1/T2 tumours were offered END if fine needle aspiration from the primary tumour revealed malignant cells with high-grade or histologically undefined subtype, or in case of facial nerve palsy. Patients with T3/T4 tumours were offered END irrespective of histological grade or subtype (13). The criteria for postoperative radiotherapy were positive surgical margins, high-grade histology, T3/T4 tumour, cervical lymph node metastases, or perineural invasion.

Histological subtypes were categorised as high- or low-grade malignancies in accordance with Danish guidelines (13), as shown in Supplementary Table A.

Statistics

Variables potentially associated with histologically proven metastases (pN+) were analysed using univariate and multivariate logistic regression. These associations were evaluated by calculating odds ratios (OR). The test were two-sided, and a *p*-value < 0.05 was considered significant.

Estimates of neck recurrence-free survival (neck-RFS) were calculated using the Kaplan–Meier method. Follow-up time was calculated from the date of primary surgical treatment to the date of death or the end of data-collection (January 2018). Data were stored in a RedCap database provided by the Open Patient data Explorative Network (OPEN). Statistical analysis was performed using Stata ver. 16 (StataCorp LLC, College Station, Texas, USA).

Results

The study cohort consisted of 304 (46%) men and 360 (54%) women with a median age of 62 years (range, 6–94 years). Histological re-evaluation was performed in 639 (96.2%) cases.

A total of 259 patients were treated with surgery for the primary tumour and END. Occult metastases were histologically confirmed in 36 of the 259 patients (14%). The characteristics of patients treated with TND, END or noND are compared in Table 1.

Fifty of the 81 patients (62%) with cN+ (treated with TND) had histologically confirmed lymph node metastases (pN+). A total of 86 of the 340 patients (25%) treated with TND or END had pN+.

The median follow-up time for the entire cohort was 4.8 years (range, 0.1–12.5 years). For patients who remained alive at the end of data collection, the median follow-up time was 5.5 years (range, 2–12.5 years). For patients treated with END, the median follow-up time was 4.7 years (range, 0.1–12.3 years).

In univariate analyses of patients with pN+ versus those with no histological evidence of regional lymph node metastasis (pN0) (340 patients), all variables (i.e., male sex, age >60 years, T3/T4-classification, tumour size $\geq$ 4 cm, major glands, facial nerve impairment, high-grade histological subtype, involved surgical margins, perineural invasion, and perivascular invasion) were significantly associated with regional metastases. In the multivariate analyses, only high-grade histological subtypes, male sex, and vascular invasion were significantly associated with regional metastases. Information on perineural and vascular invasion were missing for 108 (32%) and 203 (60%) patients, respectively. Data from patients with pN+ and pN0, as well as the results from the regression analyses are compared in Table 2.

Occult metastases

Overall, the proportion of patients with histologically verified occult metastases among those treated with END was 14% (36/259). Among patients with high-grade histology tumours, the proportion of occult

metastases was 27% (20/74) and it was 9% (16/185) among patients with low-grade histology tumours. Similarly, the proportion of occult metastases was 22% (14/63) among patients with T3/T4 tumours and among those with T1/T2 tumours it was 11% (22/196). In total, 18% (21/115) of males and 10% (15/144) of females, treated with END, had occult metastases. The proportion of patients with occult metastases varied among those with a primary tumour in the parotid gland (15%), the submandibular gland (15%), the sublingual gland (25%), and the minor glands (5%). Univariate analyses of the END group showed that T3/T4 tumours, high-grade histological subtype, facial nerve impairment, as well as perineural and vascular invasion were all associated with occult metastases. In the multivariate analyses, only high-grade histological subtype and vascular invasion were significantly associated with occult metastases. The characteristics of patients with occult metastases and results from the regression analyses are summarised in Table 3.

Treatment at neck node levels

Regional metastases were observed in all neck node levels (I–V) in patients treated with either END or TND. Levels II and III were most frequently dissected. The numbers of patients treated with END and TND at each neck node level as well as the proportions of patients with metastases are summarised in Supplementary Table B. Figure 2 shows the distribution of occult metastases at different neck node levels. Occult metastases in level I were diagnosed in four patients with either submandibular gland carcinoma (*n* = 3, 75%) or sublingual gland carcinoma (*n* = 1, 25%). One patient with submandibular gland carcinoma had occult metastases in level III, but no metastases in levels I or II (after END of levels I–III). All other patients with occult metastases in levels III, IV, and V also had metastases in level II. Three patients had occult metastases in level IV, and all three had high-grade histology tumours with advanced T-classification (a T3 lymphoepithelial carcinoma, a T3 salivary duct carcinoma, and a T4a poorly differentiated carcinoma). Two patients had occult metastases in level V and also in levels III and IV; thus, there were no skip metastases in level V.

Recurrences

During follow-up, a total of 33 patients (5%) showed recurrence in cervical lymph nodes (i.e., regional recurrence). At the time of diagnosis, 16 of these patients (48%) had pN+, nine patients (27%) had pN0 and eight patients (24%) had noND. In total, 14 patients (42%) had been treated with TND, and 10 of these patients also received postoperative radiotherapy for the cervical lymph nodes (i.e., regional radiotherapy). Eleven patients (33%) had been treated with END, and one of them also had postoperative regional radiotherapy. A total of 21 patients (64%) with regional recurrence had not been treated with postoperative regional radiation. In five patients treated with neck dissection and postoperative radiotherapy (>50 Gy), recurrence was observed within the irradiated field. In seven patients treated with neck dissection and postoperative radiotherapy, recurrence occurred in cervical lymph nodes outside the area treated by surgery and radiotherapy.

Among the eight patients treated with noND, two had been given locoregional radiotherapy. Both patients had parotid gland carcinoma and high-grade histology tumours. Both recurrences occurred outside the irradiated field. Table 4 summarises information on patients with noND and regional recurrence.

Figure 3 shows Kaplan–Meier curves comparing neck-RFS in patients with pN+, pN0 and noND. The 5- and 10-year neck-RFS were 77% and 57% for patients with pN+, 98% and 94% for patients with pN0, and 98% and 96% for patients treated with noND, respectively. There were no differences in recurrence rates for patients with noND when stratified by radiotherapy (i.e., elective versus no neck radiotherapy) or histological tumour grade (i.e., high-grade versus low-grade).

Discussion

This is the largest national study on surgical treatment of the neck in patients with salivary gland carcinoma involving a complete cohort of unselected patients with re-evaluated histological diagnoses.

Our results support the current consensus on treating patients with cN+ with TND (12, 14, 20, 21, 36).

Achieving a consensus on guidelines for END in patients with cN0 is more difficult. Studies have found occult metastases in 6–45% of patients with salivary gland carcinomas (4, 8, 12, 14, 15, 17, 20, 21, 23, 26, 27, 30, 37-47). We found occult metastases in 14% of patients who had been treated with END. This proportion may be an overestimate because patients were selected for END based on known risk factors. If the proportion of patients with occult metastases were calculated using all cN0 patients, instead of only cN0 patients treated with END, there would be a risk of underestimating the true proportion of occult metastases due to unrecognised metastases in the NoND group.

Studies reporting the highest proportions of occult metastases selected those patients with advanced T-classifications (T3/T4) and high-grade histology tumours for END (8, 14, 17, 20, 30, 44). Variation in the staging procedures, preoperative diagnostic imaging methods, and histological grading definitions may have influenced the assessment of cervical lymph nodes in these studies and hence the proportions of occult metastases reported. In our study, only 12% of patients were cN+, presumably because we included the entire national cohort without selecting for aggressive tumours or particular anatomical subsites.

Our results showed that regional recurrence was significantly more frequent among patients with pN+ than among those with pN0 and those who had noND. However, the neck-RFS of patients with pN0 was similar to that of patients who had noND. Two patients (2/324, 0.6%) with noND had regional recurrence within the first year of follow-up. This relatively short time to recurrence may imply the presence of undiagnosed occult lymph node metastases. Considering the indications for END, all but one of the patients with noND and regional recurrence (Table 4) should have undergone END, but for various reasons they did not.

The proportions of patients with pN0 and noND who had elective radiotherapy of the neck were nearly identical. Regional recurrence occurred in 33 patients, and 12 (36%) of these patients had received radiotherapy with >50 Gy. In five of these 12 patients (42%), recurrence was observed within the irradiated field. Other studies have reported that elective neck radiotherapy decreased the risk of regional recurrence (1, 48) and that radiotherapy may be a better treatment option than neck dissection for patients receiving

adjuvant radiotherapy at primary tumour site (19). The proportion of patients with false-positive regional metastases after clinical evaluation was relatively high (31/81 patients, 38% of those with cN+). During follow-up, two of these patients were diagnosed with regional recurrence. Both patients had received postoperative radiotherapy at the primary tumour site but no elective neck radiotherapy. In both cases, recurrence occurred within the first year after the primary diagnosis and in neck node levels that had been included in the TND. This highlights a risk of false negative pathological evaluation and suggests that these patients would have benefitted from postoperative elective neck radiotherapy.

In this study, occult metastases occurred most frequently in patients with adenoid cystic carcinoma, followed by patients with salivary duct carcinoma. Several studies have reported a high frequency of occult metastases among patients with adenoid cystic carcinoma (37, 49, 50), whereas other studies have reported the highest rates of occult metastases among patients with adenocarcinoma, mucoepidermoid carcinoma, undifferentiated carcinoma, squamous cell carcinoma and salivary duct carcinoma (8, 17, 26, 27). Some studies recommend an individual assessment for END in patients with cN0 (38-40, 51), whereas other studies recommend END for all patients with high-grade histology or T3/T4 tumours (8, 14, 15, 17, 20, 21, 45). Several studies recommend END for all patients with salivary gland carcinomas (22, 23, 25), because preoperative diagnoses are inaccurate and occult metastases may occur in low-grade as well as high-grade histological subtypes. A previous recommendation that neck dissection was indicated for patients with squamous cell carcinoma if the risk of metastases was greater than 15-20% (52-54) has recently been challenged (55). The proportion of occult metastases observed in our study (14%), suggest that END should not be recommended for all patients with salivary gland carcinoma.

The decision for END as part of the primary surgical procedure is based on preoperatively known factors. Perineural invasion, vascular invasion, and surgical margins are preoperatively unknown and the same usually applies for histological grade or subtype as well. Preoperative diagnoses and surgical assessments are often based on fine needle biopsies from the primary tumour, but cytological classification of subtypes

and histological grade is inaccurate (56, 57). Consequently, reliable subtype and histological grade data may be unavailable prior to surgery, and we suggest that these cases should be treated as high-grade histology tumours. Here, high-grade histology tumours were significantly associated with metastases in analyses of all patients and analyses of patients with occult metastases. Therefore, we recommend END for patients with high-grade histological subtypes, irrespective of tumour classification. Importantly, if END is not performed during the primary surgical procedure and the histological examination reveals high-grade histology in tumours that were preoperatively assessed as low-grade, END may be performed as an additional surgical procedure. Elective neck radiotherapy may be used as an alternative to supplementary END for patients receiving postoperative radiotherapy due to characteristics of the primary tumour.

Tumour class was not a significant risk factor for occult metastases in the multivariate analyses, but the proportion of occult metastases in patients with T4/T4 was 22%, compared to 11% in patients with T1/T2 tumours. Therefore, we recommend END for patients with T3/T4 tumours. Several other studies have reported a significant association between regional metastases and advanced tumour size or classification (T3/T4 tumours) (8, 17, 20, 21, 58).

The likelihood of occult metastases was also influenced by the location of the primary tumour. Only 5% of patients with primary tumours in the minor salivary glands had occult metastases. Lee *et al*. (59) reported a high proportion of occult metastases (25%) among patients with carcinomas in the minor glands. Our data are not consistent with these results, probably because a relatively large proportion of patients with minor gland carcinomas were treated with END. The highest proportion of occult metastases by to subsite in our study (25%) was observed in patients with sublingual gland carcinomas. The large proportion of patients with sublingual gland carcinomas who had occult metastases justifies END in these patients, and this is consistent with other studies (41, 60). Regional metastases have been reported in 27–40% of patients with submandibular carcinomas (61-63), and occult metastases have been reported in up to 22% of patients with submandibular carcinomas who were treated with END (2). Considering that submandibular gland

carcinomas frequently are high-grade histological subtypes (61), END should be relevant for most of these patients.

Extent of elective neck dissection

Few studies have assessed recommendations for the extent of END. Occult metastases are most frequently reported in neck node levels II and III (8, 14, 20, 21, 44, 45). Our results are consistent with those studies, and we found most occult metastases in neck node levels II and III, regardless of the primary site. Importantly, these levels were also most frequently dissected. The proportions of occult metastases per dissected level were high in neck node levels IV and V, but these levels were only dissected in 19 and 18 selected patients, respectively. Lim *et al*. (64) studied the elective dissection of neck node level V in patients with parotid carcinomas and concluded that this was not obligate in patients with cN0. Stodulski *et al*. (45) reported that occult metastases occurred in neck node level V at a frequency of 30% in their group of patients and recommended including level Va in END of patients with T3/T4 tumours, but other studies have reported that occult metastases occur in level IV at a frequency of 0–11% and in level V at a frequency of 0–7% (8, 12, 14, 15, 20, 21, 27, 39). Consequently, we do not recommend including level V in the standard END procedure. In our study, occult metastases in level I were nearly almost found in patients with submandibular gland carcinoma, and nearly half of the patients with pN+ submandibular gland carcinomas had metastases in nock node level I (8/17, 47%). This supports the recommendation to include lymph nodes from levels I, II, and III in the primary surgical treatment of submandibular gland carcinomas, as suggested by other studies (38, 61).

Based on recommendations from other studies and our results, we suggest that END should include levels II and III in patients with parotid gland carcinomas, and levels I, II, and III in patients with submandibular gland carcinomas, sublingual gland carcinomas, or carcinomas in the minor oral salivary glands. If occult metastases are histologically diagnosed, levels IV and V should also be dissected. Alternatively, if these patients are receiving postoperative radiotherapy, the target field may be adjusted to include neck node levels IV and V, thereby avoiding a second surgical procedure. Intraoperative diagnosis with frozen section

of lymph nodes may enable an extension of the primary surgical procedure with END if regional metastases are identified peroperatively. Recent review studies by Vander Poorten *et al*. (65) and Lombardi *et al*. (66) suggested frozen section of lymph nodes from level II, and to proceed with the neck dissection if occult metastases are identified. In this study, only one patient had skip occult metastases to level III with no metastases in levels I and II. All other patients with metastases in levels III, IV and V also had metastases in level II. This observation supports using elective lymph node excision or selective dissection of level II for peroperative frozen sections. In this study, there was limited scope for evaluating the use of frozen section but this may be possible in future studies.

Limitations

This study had some limitations. Data collection was restricted by the retrospective study design. Different diagnostic imaging methods were used, and the quality of these methods may have influenced the clinical assessment of cervical lymph nodes and the evaluation of occult metastases. Pooling multiple subtypes in the analyses may have influenced outcomes, and the heterogeneity of salivary gland carcinomas restricts the generalisability of recommendations. Patients were selected for neck dissection, and the extent of the surgical procedure varied. Neck node levels II and III were most frequently dissected and occult metastases may have been present in other levels that were not dissected and histologically evaluated. In addition, these non-dissected levels may not reveal occult metastases if patients received postoperative neck radiation. A prospective study with uniform diagnostic and treatment methods would overcome these limitations.

Conclusion

In patients with salivary gland carcinoma and cN0, T-classification and histological grade are often used as indications for END. For patients with T3/T4 tumours, high-grade histological tumours, or unknown grade prior to surgery, we recommend END of neck node levels II and III. Levels I–III should be included in patients

with carcinoma in the submandibular gland, sublingual gland, or minor oral salivary glands. Selected patients with cN0 and low-grade histology T1/T2 tumours may be treated by observation and follow-up, but individual assessments are always necessary and should take patient preference and the location, size and clinical stage of the primary tumour into account.

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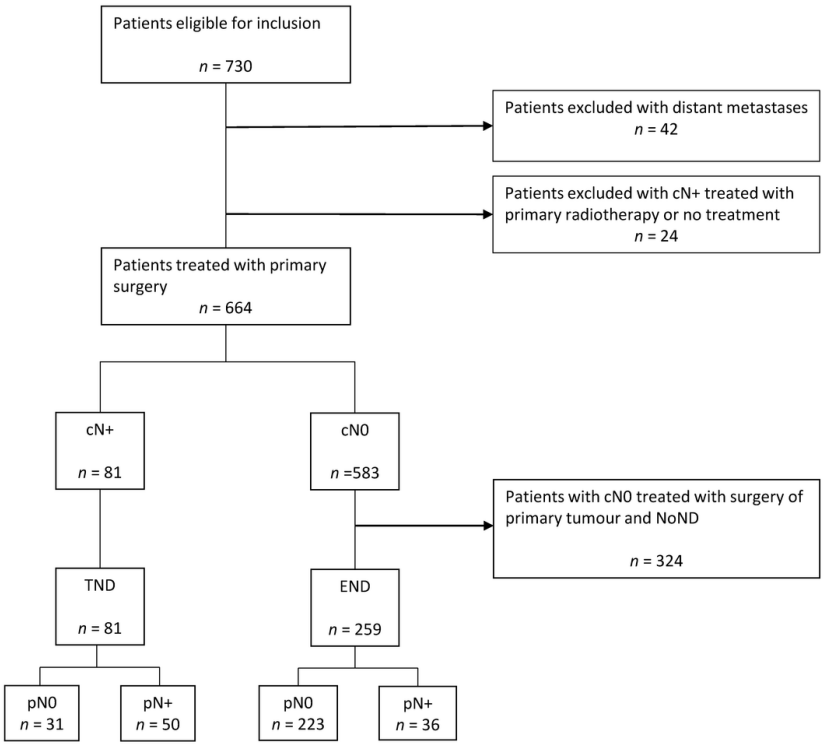

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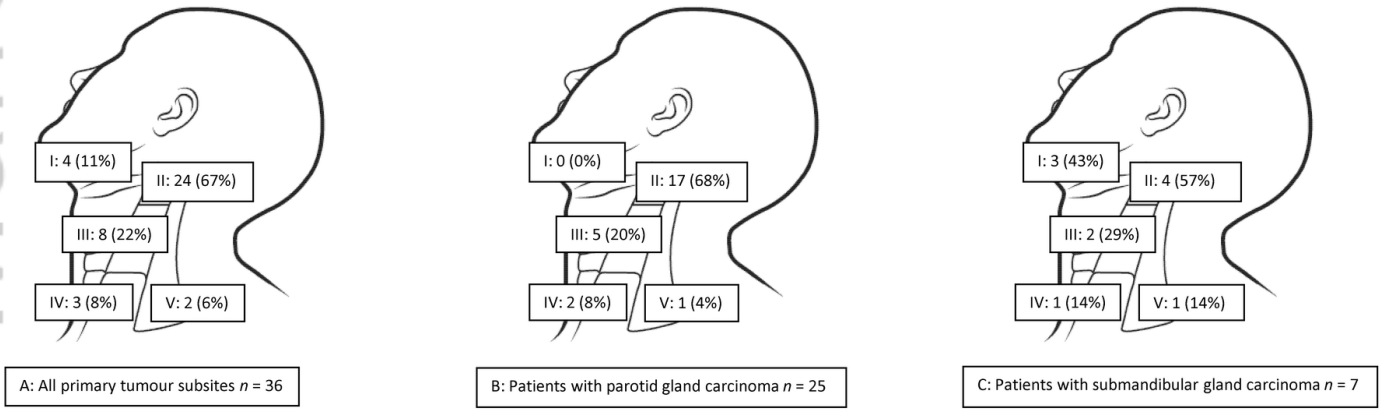

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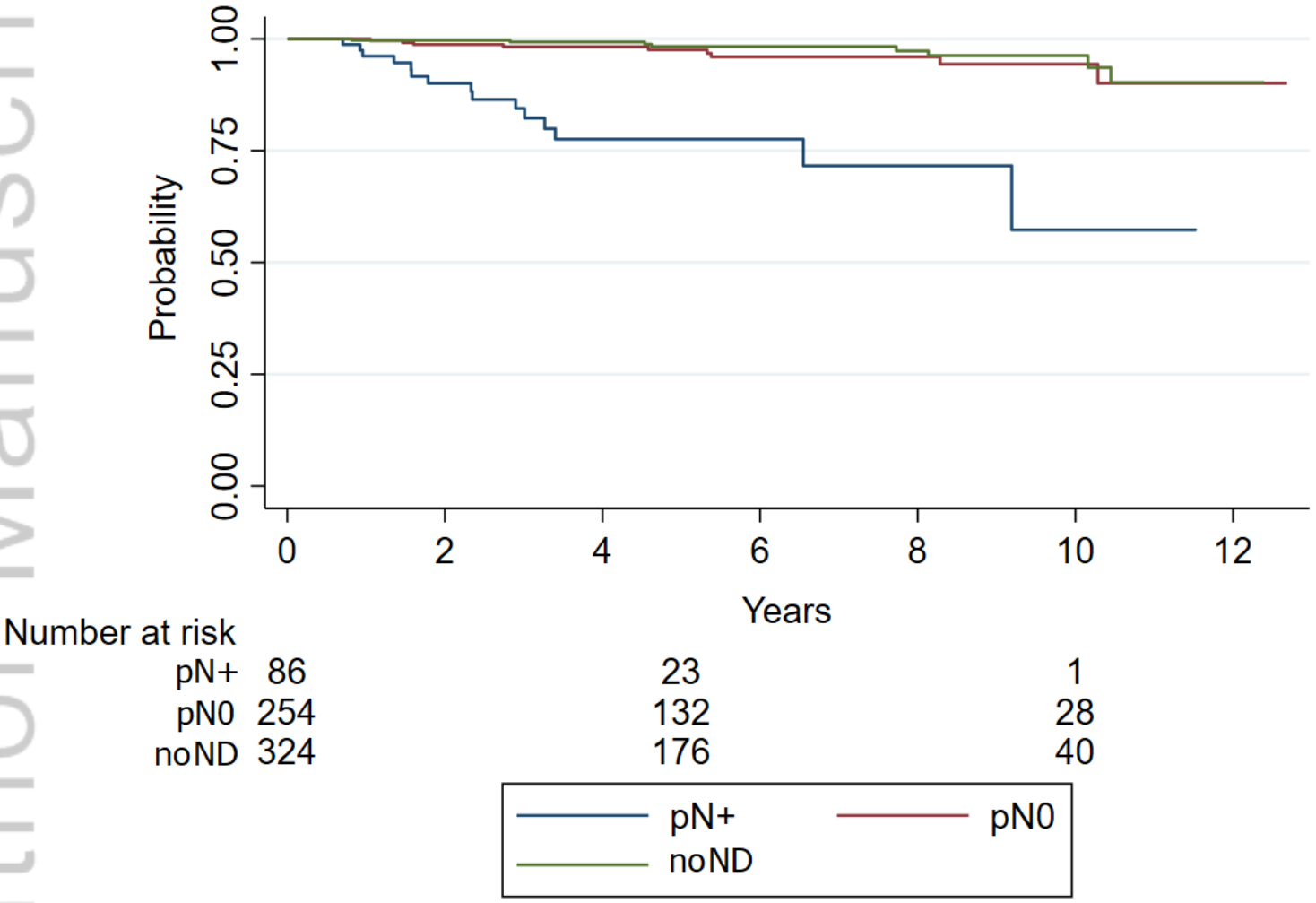

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Table 1. Patient and tumour characteristics related to surgical treatment of the neck.

Abbreviations: TND = Therapeutic neck dissection; END = Elective neck dissection; NoND = No neck dissection

Variable	TND (*n* = 81)	END (*n* = 259)	NoND (*n* = 324)
	Number of patients (%)	Number of patients (%)	Number of patients (%)
Sex			
Male	53 (65)	115 (44)	136 (42)
Female	28 (35)	144 (56)	188 (58)
Ratio (male:female)	1.9	0.8	0.7
Age			
≤60	33 (37)	116 (45)	133 (41)
>60	51 (63)	143 (55)	191 (59)
Median	63	61	63
Range	21-88	6-94	11-93
T-classification			
T1/T2	45 (56)	196 (76)	243 (75)
T3/T4	36 (44)	63 (24)	81 (25)
N-classification			
pN0	31 (38)	223 (86)	
pN+	50 (62)	36 (14)	
Metastatic rate	50/81=62%	36/259=14%	
Site			
Parotid gland	48 (59)	163 (63)	122 (37)
Submandibular gland	16 (20)	46 (18)	25 (8)
Sublingual gland	2 (2)	8 (3)	3 (1)
Minor salivary glands	15 (19)	41 (16)	174 (54)
Facial nerve impairment			
Yes	10 (12)	24 (9)	8 (2)
No	71 (88)	235 (91)	316 (98)
Histological grade			
Low-grade	40 (49)	185 (71)	277 (85)
High-grade	41 (51)	74 (29)	47 (15)
Histological subtypes			
Adenoid cystic carcinoma	11 (13.6)	66 (25.5)	75 (23.2)
Mucoepidermoid carcinoma	10 (12.4)	45 (17.4)	60 (18.5)
Polymorphous adenocarcinoma	3 (3.7)	7 (2.7)	57 (17.6)
Acinic cell carcinoma	6 (7.4)	33 (12.7)	22 (6.8)
Carcinoma ex pleomorphic adenoma	11 (13.6)	24 (9.3)	21 (6.5)
Salivary duct carcinoma	17 (21.0)	23 (8.9)	4 (1.2)
Epithelial-myoepithelial carcinoma	2 (2.5)	11 (4.3)	16 (4.9)
Basal cell adenocarcinoma	1 (1.2)	10 (3.9)	15 (4.6)
Squamous cell carcinoma	4 (4.9)	9 (3.5)	8 (2.5)
Adenocarcinoma	8 (9.9)	5 (1.9)	15 (4.6)
Clear cell adenocarcinoma	1 (1.2)	5 (1.9)	6 (1.9)
Secretory carcinoma	1 (1.2)	4 (1.5)	7 (2.2)
Poorly differentiated carcinoma	3 (3.7)	5 (1.9)	3 (0.9)
Myoepithelial carcinoma	0	3 (1.2)	6 (1.9)
Other subtypes	3 (3.7)	9 (3.5)	5 (1.6)
Surgical margins			
Involved	43 (53)	95 (37)	132 (41)
Close/free	38 (47)	164 (63)	192 (59)
Radiotherapy			
None	15 (19)	98 (38)	177 (55)
T-site	15 (19)	98 (38)	76 (23)
T- and N-site	51 (62)	63 (24)	71 (22)

Table 2. Regression analysis of factors associated with cervical lymph node metastases.

Abbreviations: OR = Odds Ratio

Variables	**pN+**	**pN0**	**Univariate regression**		**Multivariate regression**	
	***n* = 86 (%)**	***n* = 254 (%)**				
			OR	*p*-value	OR	*p*-value
Sex						
Female	29 (33)	111 (44)				
Male	57 (66)	143 (56)	2.5	<0.0001	2.4	0.016
Ratio (male:female)	2.0	0.8				
Age						
≤60	29 (34)	117 (46)				
>60	57 (66)	137 (54)	1.7	0.047	ns	
Median	64	61				
Range	24-88	6-94				
T-classification						
T1/T2	47 (55)	194 (76)				
T3/T4	39 (45)	60 (23)	2.7	<0.001	ns	
Tumour size						
<4 cm	60 (70)	210 (83)				
≥4 cm	26 (30)	44 (17)	2.1	0.011	ns	
Site						
Minor gland	8 (9)	49 (19)				
Major gland	78 (91)	205 (81)	2.3	0.036	ns	
Parotid gland	*57*	*154*				
Submandibular gland	*17*	*45*				
Sublingual gland	*4*	*6*				
Facial nerve impairment						
No	69 (80)	237 (93)				
Yes	17 (20)	17 (7)	3.4	0.001	ns	
Histological subtype						
Low-grade	35 (41)	190 (75)				
High-grade	51 (59)	64 (25)	4.3	<0.001	3.0	<0.001
Surgical margins						
Close/free	40 (47)	162 (64)				
Involved	46 (53)	92 (36)	2.0	0.005	ns	
Perineural invasion						
No (218)	14 (16)	90 (35)				
Yes (216)	46 (53)	82 (32)	3.6	<0.001	ns	
Unknown (230)	26 (30)	82 (32)				
Vascular invasion						
No (193)	17 (20)	87 (34)				
Yes (55)	22 (26)	11 (4)	10.2	<0.001	7.0	<0.001
Unknown (416)	47 (55)	156 (61)				

Table 3. Patient and tumour characteristics in patients with occult metastases (*n* = 33)
Abbreviations: ns = not significant; END = elective neck dissection; cN0pN+ = occult metastases

Variable	cN0pN+		Proportion of cN0pN+ in the total group of END patients (*n* = 259)	Univariate analyses	Multivariate analyses
	No of patients	%			
Sex					
Female	15	*42*	10% (15 of 144)		
Male	21	*58*	18% (21 of 115)	*ns*	*ns*
Ratio (male:female) 1.4					
Age					
≤60	15	*42*			
>60	21	*58*		*ns*	*ns*
Primary tumour					
Parotid gland	25	*69*	15% (25 of 163)		
Submandibular gland	7	*19*	15% (7 of 46)		
Sublingual gland	2	*6*	25% (2 of 8)		
Minor glands (palate)	2	*6*	5% (2 of 41)		
T-classification					
T1/T2	22	*61*	11% (22 of 196)		
T3/T4	14	*39*	22% (14 of 63)	OR 2.3, *p*=0.031	*ns*
Tumoursize					
Median 3.0 cm					
Range 1.2-5.5 cm					
Histological subtype					
Adenoid cystic carcinoma	11	*31*			
Tubulocribriform, n=7 (64%)					
Solid, n=4 (36%)					
Salivary duct carcinoma	8	*22*			
Acinic cell carcinoma	4	*11*			
Mucoepidermoide carcinoma	3	*8*			
Low-grade, n=1 (33%)					
High-grade, n=2 (67%)					
Lymphoepithelial carcinoma	3	*8*			
Adenocarcinoma (low-grade)	1	*3*			
Squamous cell carcinoma	1	*3*			
Carcinoma ex pleomorphic adenoma	2	*6*			
Poorly differentiated carcinoma	2	*6*			
small cell neuroendocrine, n=2 (100%)					
Clear cell carcinoma	1	*3*			
Histological subtype					
Low-grade	16	*44*	9% (16 of 185)		
High-grade	20	*56*	27% (20 of 74)	OR 3.9, *p*<0.001	OR 3.5, *p*=0.01
Facial nerve impairment					
No	27	*75*			
Yes	9	*25*		OR 4.6, *p*=0.001	*ns*
Surgical margins					
Close/free	20	*56*			
Involved	16	*44*		*ns*	*ns*
Perineural invasion					
No	4	*11*			
Yes	20	*56*		OR 5.4, *p*=0.003	*ns*
Unknown (*n* = 12, 33%)					
Vascular invasion					
No	6	*17*			
Yes	9	*25*		OR 14.6, *p*<0.001	OR 15.5, *p*<0.001
Unknown (*n* = 21, 58%)					

Table 4, Description of patients with recurrence in N-site in the group with cN0 and noND. Abbreviations: RT = radiotherapy; NO = no radiotherapy; pTNM = pathological tumour/node/metastasis classification

Tumour site	pTNM	Histological Subtype	Surgical margins	RT	Recurrence	Time to recurrence	Status at last follow-up
Minor gland (palate)	T4aN0M0	Carcinoma ex pleomorphic adenoma	Involved	T-site	N-site	1.1 year	Dead of disease
Parotid gland	T3N0M0	Carcinoma ex pleomorphic adenoma	Involved	T-site	N-site	7 months	Dead of disease
Submandibular gland	T2N0M0	Adenoid cystic carcinoma	Close	NO	N-site	1.5 year	Alive, treated for recurrence
Submandibular gland	T3N0M0	Carcinoma ex pleomorphic adenoma	Close	NO	N-site and T-site	4.1 years	Dead of disease
Minor gland (tongue)	T1N0M0	Polymorphous adenocarcinoma	Free	NO	N-site and T-site	7.9 years	Alive, treated for recurrence
Minor gland (sinus)	T4bN0M0	Epithelial-myoepithelial carcinoma	Involved	NO	N-site and T-site	6 months	Dead of disease
Parotid gland	T1N0M0	Oncocytic carcinoma	Involved	T- and N-site (50 Gy to levels II-III)	N-site and M-site	2.1 years	Alive, treated for recurrence
Parotid gland	T4bN1M0 (intraparotid metastasis)	Squamous cell carcinoma	Involved	T- and N-site (50 Gy to levels II, III and V)	N-site	2.4 years 3 months	Alive, treated for recurrence