# Cancer-specific and overall survival of patients with primary and metastatic malignancies of the parotid gland - A retrospective study

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## 1. Introduction

Malignancy of the parotid gland is rare as lesions of the salivary glands only represent 3% of all tumors found in the head and neck region (Maahs et al., 2015; Lin et al., 2008; Eveson and Cawson 1985; Keller et al., 2017). Due to their rarity adequate treatment of different cancer subtypes remains a constant challenge. Recently, 22 different subtypes of primary parotid gland tumors have been described by El-Naggar et al., (2017). The most frequent entity of malignancies within the parotid gland identified were metastases of cutaneous squamous cell carcinoma (cSCC) of the head and neck (Mayer et al., 2021). In the current literature mucoepidermoid carcinoma is reported to be the most common entity of a primary parotid gland malignancy (Maahs et al., 2015; Shashinder et al., 2009; Boukheris et al., 2009; Wahlberg et al., 2002).

In clinical practice, first-line therapy consists of complete resection of the tumor, which is defined as at least 5 mm of tumor free tissue (R0) surrounding the lesion, and at least a unilateral neck dissection, when cervical lymph node metastases are suspected. Adjuvant radiotherapy is recommended in patients with certain high-risk features such as cervical lymph node metastases, positive margins, adenoid cystic histology, and intermediate/high grade (Terhaard et al., 2004). Primary chemoradiation is only performed in patients who decline a surgical intervention or who have an unresectable mass (Wang et al., 2017).

The different tumor entities are associated with different survival rates and therefore varying prognosis (Castle et al., 1999; Clode et al., 1991). Additionally, the prognosis is dependent on the cervical lymph node status (Meyer et al., 2017). A recent study from central Europe showed that the five-year overall survival of patients with metastatic cSCC of the parotid gland was significantly

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worse than among patients with primary parotid malignancies (Meyer et al., 2021a). However, the mean age of the two groups in this study differed significantly.

Therefore, the aim of this study was to investigate the cancer-specific survival of patients with metastatic cSCC of the parotid gland and of patients with primary malignant tumors of the parotid gland and to identify independent predictors for a better outcome.

## 2. Materials and methods

A retrospective study was performed at the Department of Head and Neck Surgery of the University Hospital of Augsburg between March 2014 and May 2019. Inclusion criteria were histological evidence of first diagnosis of a primary parotid malignancy or first diagnosis of a metastatic cSCC to the parotid gland from a cSCC of the head and neck and a parotidectomy with curative intent. Exclusion criteria were a distant metastasis to the parotid gland from a cSCC not located in the head and neck and recurrent disease. The study was approved by the local ethics committee (BKF: 2018−15) and written informed consent was obtained from all patients included in this study.

Demographic and histological data were extracted from the local electronic health record and all patients as well as their attending physicians were contacted concerning the oncological outcome and tumor status via phone in April 2021.

All patients with a malignancy of the parotid gland were presented in the interdisciplinary tumor board and the treatment was discussed. A neck dissection was recommended by the tumor board in case of a metastatic cSCC to the parotid gland. In primary parotid gland malignancy without clinical neck involvement an ipsilateral neck dissection was performed in T3/T4 and in high-grade carcinomas.

Adjuvant radiation was performed in cases of intermediate/high-grade malignancy, in case of a histological finding of an adenoid cystic carcinoma, advanced T-stadium (T3/T4) locoregional lymph node metastasis, and positive margins.

All patients underwent clinical and diagnostic imaging on a regular basis as part of routine tumor follow-up. Complications of therapy, need for adjuvant therapy, recurrence, and death were extracted from the patient's medical record. The observation period in this study population was at least 24 months.

Overall and cancer-specific survival were graphically displayed with Kaplan-Meier survival curves. The overall survival was defined as the time interval between the end of treatment and the date of death from any cause. Cancer-specific survival was defined as the time interval between the end of treatment and the date of death from this specific disease. The log-rank test was used to compare survival between patients with a primary parotid malignancy and patients with cSCC of the parotid gland. Cox proportional hazard regression models were fit to investigate the association between tumor type, patient demographics, and oncologic outcome. The proportional hazard assumption was checked with Schoenfeld residuals test. For categorical variables chi-square test or alternatively fisher test were used. Statistical significance was assessed using a two-sided alpha level of 0.05 without adjustment for multiplicity. Statistical analyses were performed using R software (version 4.0.2, Vienna, Austria).

## 3. Results

### 3.1. Baseline characteristics

A total of 94 patients was included in this study. Of these, 51 patients (54.3%) had metastatic cSCC of the parotid gland and 43 patients (45.7%) had a primary parotid malignancy (Table 1). Patients with metastatic cSCC were significantly older ($p = 0.001$) and more frequently male ($p = 0.002$) than those with a primary parotid malignancy. Cervical lymph nodes were involved in 47.1% of patients with metastatic cSCC and in 25.6% of patients with primary parotid gland malignancies ($p = 0.054$). Adjuvant therapy was more frequently performed in patients with metastatic cSCC (76.5%) as compared to patients with primary parotid malignancy (48.8%; $p = 0.01$). Surgical approaches (type of parotidectomy) did not differ significantly between patients with metastatic cSCC and patients with primary parotid gland malignancies ($p = 0.49$). Neck dissection was more commonly performed among patients with metastatic cSCC of the parotid gland (100.0%) than among those with primary parotid malignancy (88.4%; $p = 0.01$).

Fig. 1 displays the distribution of primary malignancies of the parotid gland included in this study. Overall, patients with ten different histopathological subtypes were included. The most common subtype was acinic cell carcinoma (23.3%), followed by mucoepidermoid carcinoma (16.3%) and salivary duct carcinoma (14.0%).

**Table 1**
Demographic, histopathological, therapy-specific and survival data of patients with metastatic cutaneous squamous cell carcinoma (cSCC) and primary malignancy of the parotid gland.

| | All (N = 94) | Metastatic cSCC (N = 51) | Primary parotid malignancy (N = 43) | p-value | |
|---|---|---|---|---|---|
| Mean age in years (SD) | 73.7 (13.8) | 79.7 (9.6) | 66.6 (14.7) | 0.001* | Wilcoxon rank sum test |
| Sex, n (%) | | | | 0.002* | Chi-squared test |
| Female | 26 (27.7) | 7 (13.7) | 19 (44.2) | | |
| Male | 68 (72.3) | 44 (86.3) | 24 (55.8) | | |
| Cervical nodal involvement (N+) | 35 (37.2) | 24 (47.1) | 11 (25.6) | 0.054 | Chi-squared test |
| Adjuvant therapy | 60 (63.8) | 39 (76.5) | 21 (48.8) | 0.01 * | Chi-squared test |
| Type of Parotidectomy | | | | 0.49 | Fisher's exact test |
| Partial | 5 (5.3) | 2 (3.9) | 3 (7.0) | | |
| Lateral | 2 (2.1) | 0 (0.0) | 2 (4.7) | | |
| Total | 57 (60.6) | 32 (62.7) | 25 (58.1) | | |
| Radical | 30 (31.9) | 17 (33.3) | 13 (30.2) | | |
| 5 year-Cancer-Specific-Survival, n (%) | 71.8% | 54.5% | 87.3% | 0.006* | Comparison of proportions with z-Test |
| Neck dissection | | | | 0.009 * | Fisher's exact test |
| None | 5 (5.3) | 0 (0.0) | 5 (11.6) | | |
| Ipsilateral | 87 (92.6) | 49 (96.1) | 38 (88.4) | | |
| Bilateral | 2 (2.1) | 2 (3.9) | 0 (0.0) | | |

*SD* standard deviation, *n* number of patients, * Statistically significant result.

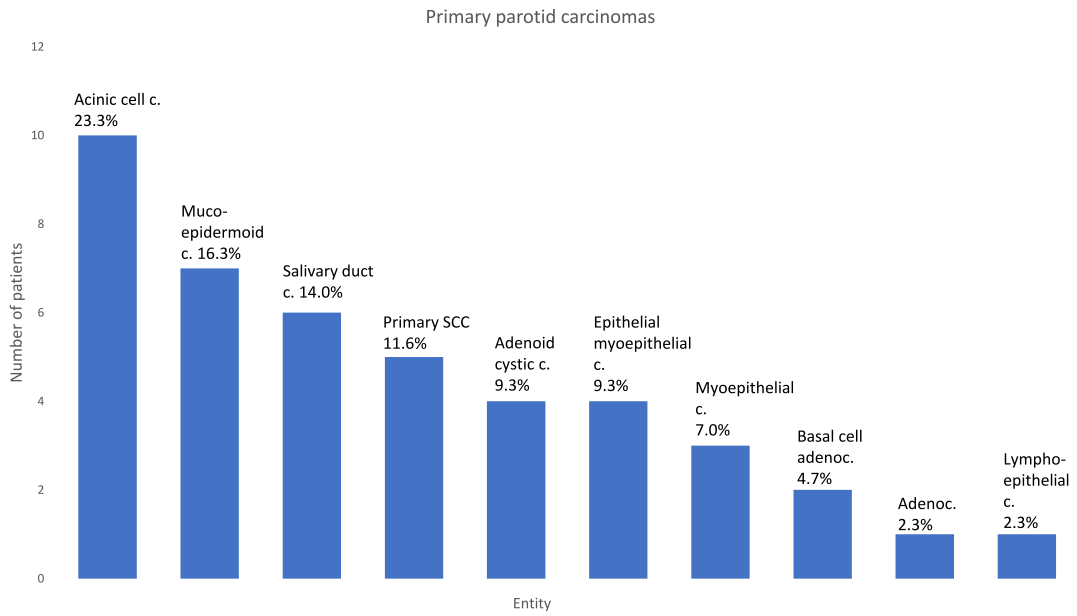


**Fig. 1.** Distribution of histopathological entities of primary parotid malignancies. c. = Carcinoma. SCC = Squamous cell carcinoma.

### 3.2. Overall survival

The mean follow-up was 50 (95% CI:40–65) months. Fig. 2 illustrates the overall survival of patients with primary parotid malignancies and of patients with metastatic cSCC of the parotid gland. Overall survival was significantly worse among patients with metastatic cSCC of the parotid gland as compared to patients with primary malignancy of the parotid gland ($p < 0.001$). Specifically, two-year overall survival was 79.1% (95%-CI: 67.8%–92.2%) among patients with primary parotid malignancies and 49.0% (95%-CI: 37.1%–64.9%) among patients with metastatic cSCC of the parotid gland. Five-year overall survival was 70.2% (95%-CI: 57.1%–86.2%) among patients with primary parotid malignancies and 27.4% (15.6%–48.1%) among patients with metastatic cSCC of the parotid gland.

Fig. 3 shows the overall survival of patients with metastatic cSCC of the parotid gland and for patients with primary parotid malignancy according to cervical lymph node status. Two-year overall survival was 87.5% (95%-CI: 76.8%–99.7%) among patients with primary parotid malignancies N- and 54.5% (95%-CI: 31.8%–93.6%) among patients with primary parotid malignancies N+. Two-year overall survival was 51.9% (95%-CI: 36.1%–74.6%) among patients with metastatic cSCC P + N-, and 45.8% (95%-CI: 29.7%–70.8%) among patients with metastatic cSCC P + N+. Five-year overall survival was 79.3% (95%-CI: 65.6%–95.9%) among patients with primary parotid malignancies N-, and 45.5% (95%-CI: 23.8%–86.8%) among patients with primary parotid malignancies N+. Five-year overall survival was 32.4% (95%-CI: 15.1%–69.4%) among patients with metastatic cSCC P + N-, and 21.8% (95%-CI: 9.0%–52.9%) among patients with metastatic cSCC P + N+ ($p < 0.001$).

### 3.3. Cancer-specific survival

Five-year cancer-specific survival was significantly higher among patients with primary parotid malignancies than among

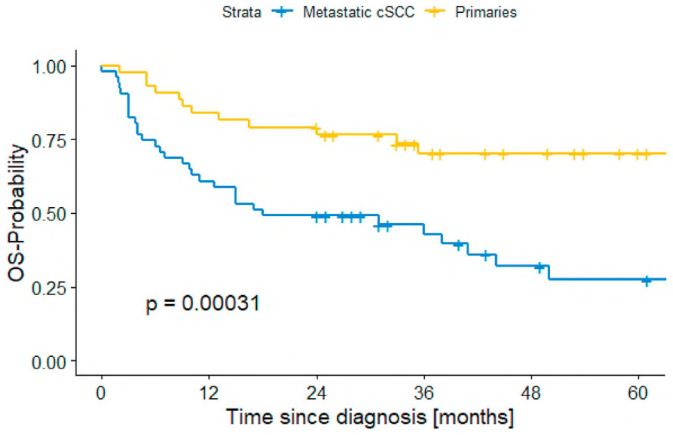


**Fig. 2.** Overall survival among patients with metastatic cutaneous squamous cell carcinomas of the parotid gland and among patients with primary malignancies of the parotid gland (generated according to the method of Kaplan and Meier). cSCC: cutaneous squamous cell carcinoma.

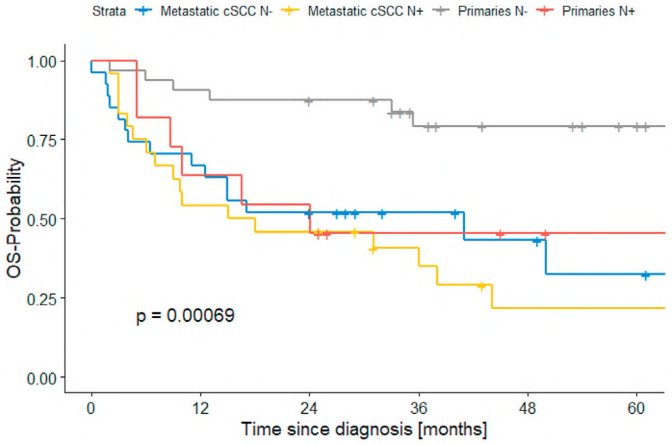


**Fig. 3.** Overall survival of patients with metastatic cutaneous squamous cell carcinomas of the parotid gland with (N+) and without (N-) cervical lymph node involvement and of patients with primary parotid malignancies of the parotid gland with (N+) and without (N-) cervical lymph node involvement (Kaplan-Meier analysis). cSCC: cutaneous squamous cell carcinoma.

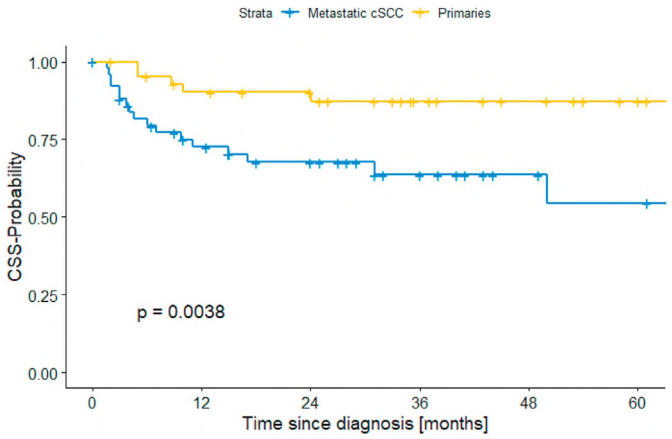


**Fig. 4.** Cancer-specific survival (CSS) of patients with metastatic cutaneous squamous cell carcinomas of the parotid gland and of patients with primary malignancies of the parotid gland. cSCC: cutaneous squamous cell carcinoma.

patients with metastatic cSCC of the parotid gland (87.3 vs. 54.5%, p = 0.006). Cancer-specific survival of patients with primary parotid malignancy and of patients with metastatic cSCC of the parotid gland is shown in Fig. 4. Two-year cancer-specific survival was 90.3% (95%-CI: 81.7%–99.8%) among patients with primary parotid malignancies and 67.6% (95%-CI: 55.3%–82.7%) among patients with metastatic cutaneous squamous cell carcinoma of the parotid gland (p = 0.004).

Cancer-specific survival of patients with metastatic cSCC and of patients with primary parotid malignancies according to cervical lymph node involvement is illustrated in Fig. 5. Two-year cancer-specific survival was 100.0% (95%-CI: 100%–100%) among patients with primary parotid malignancies N-, and 63.6% (95%-CI: 40.7%–99.5%) among patients with primary parotid malignancies N+. Two-year cancer-specific survival was 66.9% (95%-CI: 50.4%–88.9%) among patients with metastatic cSCC P + N-, and 68.8% (95%-CI: 51.9%–91.1%) among patients with metastatic cSCC P + N+. Five-year cancer-specific survival was 100.0% (95%-CI: 100%–100%) among patients with primary parotid malignancies N-, and 53.0% (95%-CI: 29.9%–94.0%) among patients with primary parotid malignancies N+. During follow-up two patients with a primary

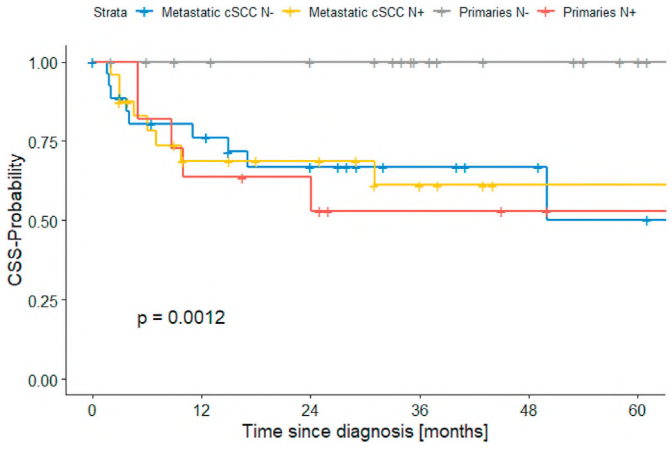


**Fig. 5.** Cancer-specific survival (CSS) of patients with metastatic cutaneous squamous cell carcinomas of the parotid gland with (N+) and without (N-) cervical lymph node involvement and of patients with primary malignancies of the parotid gland with (N+) and without (N-) cervical lymph node involvement (Kaplan-Meier analysis). cSCC: cutaneous squamous cell carcinoma.

**Table 2**
Association between locoregional nodal status/adjuvant therapy/age, and cancer-specific survival among patients with metastatic cutaneous squamous cell carcinoma of the parotid gland.

| Characteristic | HR (95% CI) | p-value |
|---|---|---|
| N-Status positive vs. negative | 1.00 (0.38–2.59) | 0.99 |
| Adjuvant therapy yes vs. no | 0.81 (0.26–2.49) | 0.71 |
| Age >75 years vs. ≤75 years | 0.69 (0.27–1.79) | 0.45 |

HR: Hazard ratio, CI: confidence interval.

**Table 3**
Association between locoregional nodal status/adjuvant therapy/age, and cancer-specific survival among patients with primary parotid malignancies.

| Characteristic | HR (95% CI) | p-value |
|---|---|---|
| N-Status positive vs. negative | 21.36 (2.40–189.90) | 0.006 |
| Adjuvant therapy yes vs. no | 1.41 (0.32–6.31) | 0.652 |
| Age >75 years vs. ≤75 years | 8.01 (1.45–44.21) | 0.017 |

HR: Hazard ratio, CI: confidence interval.

parotid malignancy N- died from recurrent disease 75 and 91 months after the initial diagnosis, respectively. Five-year cancer-specific survival was 50.2% (95%-CI: 26.7%–94.5%) among patients with metastatic cSCC P + N- and 61.1% (95%-CI: 42.5%–88.0%) among patients with metastatic cSCC P + N+ (p = 0.001).

One patient with metastatic cSCC of the parotid gland P+N+ died from recurrent disease 82 months after the initial diagnosis.

As found in cox regression analysis, cervical lymph node status, adjuvant therapy or age were not statistically significant prognostic factors in terms of cancer-specific survival among patients with metastatic cSCC of the parotid gland (Table 2).

Adjuvant therapy was not a statistically significant prognostic factors in terms of cancer-specific survival among patients with primary parotid malignancies. (Table 3). Cervical lymph node involvement was a statistically significant prognostic factor in terms of cancer-specific survival among patients with primary parotid malignancies (HR 21.36 [95% CI: 2.40–189.90], p = 0.006). Furthermore, age was a statistically significant prognostic factor in terms of cancer-specific survival among patients with primary parotid malignancies (HR 8.01 [95% CI:1.45–44.21] per one-year increase; p = 0.017).

## 4. Discussion

The aim of this study was to compare the overall and cancer-specific survival of patients with primary parotid malignancies and those with metastatic cSCC of the parotid gland. Furthermore, associations between locoregional lymph node metastasis, adjuvant therapy and age with cancer-specific survival were examined in both groups. To the best of our knowledge, this study is the first to describe both the cancer-specific survival and overall survival of the abovementioned malignancies.

Similar to prior reports, most patients with parotid gland malignancy in the present study were male (72.3%) and of advanced age (73.7 ± 13.8 years) (Meyer et al., 2021b; O'Brien et al., 2002). Moreover, patients with metastatic cSCC were significantly older and more frequently male than those with a primary parotid malignancy, which is concordant with other studies (Mayer et al., 2021; Meyer et al., 2021b). Interestingly, there was no statistically significant difference in terms of neck involvement when comparing both groups (47.1% metastatic cSCC vs. 25.6%; p = 0.054), which contrasts with a previous study that found nodal involvement in 100% of patients with metastatic cSCC, and in only

27.3% of those with primary parotid malignancies (Meyer et al., 2021b). This difference may be attributed to the fact that nodal involvement was defined as additional cervical lymph node involvement in the present study. The finding that a higher percentage of patients with cSCC (76.5%) than of those with a primary parotid malignancy (48.8%; $p = 0.01$) had received adjuvant therapy in the present study is most likely due to the fact that metastatic disease is generally treated more aggressively than a primary malignancy, and that metastatic cSCC of the parotid gland is associated with a rather poor prognosis as shown in the previous literature (Meyer et al., 2021b; Bron et al., 2003; O'Brien et al., 2001).

Five-year cancer-specific survival was significantly better for primary parotid malignancies than for metastatic cSCC of the parotid gland (87.3% vs. 54.5%, $p = 0.006$). This is in line with a study by Bron et al. which showed a 5-year disease-specific survival of 77% for primary parotid malignancies and 65% for metastatic cSCC of the parotid gland (Bron et al., 2003). Five-year cancer-specific survival among patients with metastatic cSCC was worse in the present study compared to the one reported by Bron et al., even though neck dissection (ND) had been performed in all patients with metastatic cSCC, whereas ND had only been performed in 75% of patients with metastatic SCC in the study by Bron et al., (2003). This finding once again emphasizes the unclear benefit of ND in cases of metastatic cSCC of the parotid gland without clinical signs of cervical lymph node involvement. The worse 5-year outcome of patients with metastatic cSCC in the present study compared to the abovementioned study (54.5% vs. 65%) may be explained by a higher percentage of additional cervical nodal involvement in the present series (47.1% vs. 36.7%) and the fact that additional cervical lymph node involvement had been shown to be associated with a worse outcome in patients with metastatic cSCC of the parotid gland (Bron et al., 2003; O'Brien et al., 2001).

In the present study the five-year overall survival was 70.2% for patients with primary parotid malignancies and 27.4% for patients with metastatic cSCC of the parotid gland ($p < 0.001$), similar to previously published data showing five-year overall survival rates of 77.2% and 32.6% (Meyer et al., 2021b).

As metastatic cSCC of the parotid gland is associated with a poor prognosis (Xiao et al., 2021) it is of utmost importance to perform an ultrasound of the parotid gland and the cervical lymph nodes in all patients with cSCC of the head and neck, both at the time of the initial diagnosis and at follow-up. Ultrasound is a non-invasive and widely established modality used in the diagnosis of parotid lesions (Heine et al. 2018; Koischwitz and Gritzmann 2000) and is a pivotal tool for the staging process. Ultrasound is a cost-effective method and quick to perform, especially during routine tumor follow-up by the otolaryngologist. Regular follow-up with ultrasound can lead to earlier detection of intraparotideal metastasis and may improve patient outcome. Nevertheless, CT or MRI of the neck (including the parotid gland) are necessary in case of a parotid lesion suspected to be malignant to assess the deep lobe preoperatively.

In concordance with previously published studies, this study shows that cervical lymph node metastasis significantly worsened the cancer-specific survival (O'Brien et al., 2002; Bron et al., 2003). This was mainly due to the excellent outcome of patients with primary parotid malignancies N- who had a 5-year cancer-specific survival of 100.0%. In contrast, the other three groups, i.e., primary parotid malignancies N+, metastatic cSCC P + N- and metastatic cSCC P+N+ had similar 5-year cancer-specific survival of 53.0%, 50.2%, and 61.2% respectively. Our findings suggest that the additional involvement of cervical lymph nodes in cases of metastatic cSCC of the parotid gland may not worsen the patient's survival, which is congruent with the results of Meyer et al., but in contrast to other previously published studies (Bron et al., 2003; O'Brien et al., 2001; Girardi et al., 2021). These conflicting results with regards to the prognostic role of cervical lymph node metastases in patients with metastatic cSCC of the parotid gland underline that further research in this field is warranted. However, it has already been shown that the number of nodal metastases, regardless of the location in the parotid gland or the neck, plays a prognostic role with more than 2 nodal metastases being an independent risk factor for a worse outcome (Grammatica et al., 2021). The N-status as an important prognostic factor among patients with primary parotid malignancy ($p = 0.006$) is confirmed in the present study and is consistent with previous literature (Bron et al., 2003; Meyer et al., 2021b).

Adjuvant therapy is currently indicated in patients with positive postoperative tumor margins, adenoid cystic histology, lymph node involvement or intermediate/high grade cancers (O'Brien et al., 2001; Toonkel et al., 1994; Lewis et al. 2016). Multiple studies have demonstrated the importance of adjuvant radiotherapy in advanced parotid gland primary malignancies and high-grade cancer in improving overall survival. High-grade cancers are more likely to recur locally and lead to relapse with distant metastasis (Jeannon et al., 2009). Scherl et al. reported in their retrospective study a disease-specific five-year survival of 69.8% in high-grade salivary carcinoma after adjuvant radio (chemo)therapy (Scherl et al., 2019). Koul et *al.* showed in their study that the histologic subgroup of the parotid tumor is a risk factor for a worse disease-specific survival (Koul et al., 2007). In this study adjuvant therapy was performed more frequently in metastatic cSCC than in primary malignancies of the parotid gland. Neither in metastatic cSCC of the parotid gland, nor in primary parotid malignancies was adjuvant therapy associated with a higher cancer-specific survival, which contrasts with previous studies (Sood et al. 2016; Scherl et al., 2019; Terhaard et al., 2005). A potential explanation is the low number of patients at risk among the adjuvant/non-adjuvant groups for metastatic cSCC and primary parotid malignancy.

Strengths of this study are the investigation of the cancer-specific survival as well as overall survival and the high number of parotid malignancies treated in a relatively short period of time resulting in up-to-date survival data in the context of a homogenous treatment approach within a period of five years. The typical limitations of retrospective studies must be considered when interpreting the results of this study. A further limitation is the varying follow-up. Though, a median follow-up of 50 months was achieved.

## 5. Conclusion

Earlier diagnosis of parotid metastases of cSCC of the head and neck may potentially improve the survival rate of these patients. Ultrasound of the parotid gland and the neck in first diagnosis and regular follow-up of cSCC of the head and neck may have the potential to lead to earlier diagnosis. Further research is warranted in this field to improve patients' prognosis.

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## Declaration of competing interest

No competing interests have to be declared.

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