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ORIGINAL ARTICLE

Major and minor salivary gland cancers: A multicenter retrospective study

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Abstract

Background: Most of the studies on salivary gland cancers are limited for various reasons such as being single-center, small number of patients, including only major or minor SGCs, or only including epidemiological data.

Methods: A total of 37 medical oncology clinics from different regions of Turkey participated in this retrospective-multicenter study. The analyzed data included clinical and demographical features, primary treatment, metastasis localizations, and treatments and includes certain pathologic features.

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Results: The study included data from a total of 443 SGCs. 56.7% was in major salivary glands and 43.3% was in minor salivary glands. Distant metastasis in the major SGCs was statistically significantly more common than in the minor SGCs, locoregional recurrence was statistically significantly more common in the minor SGCs than in the major SGCs ($p = 0.003$).

Conclusions: Epidemiological information, metastasis and recurrence patterns, treatment modalities, and survival analysis of the patients over 20 years of follow-up are presented.

KEYWORDS

histopathology, incidence, major salivary gland, minor salivary gland, salivary gland cancers

1 | INTRODUCTION

Squamous cell histology constitutes 90%–95% of head and neck cancers, and this histologic type of head and neck cancer is the 7th most common tumor worldwide. Its annual incidence is 625 173 new cases, and the estimated deaths are 323 160 in 2018.[1] Although sarcomas, malignant melanoma, basal cell carcinoma, and squamous cell skin cancers can be seen in the head and neck region, rare histological types can be seen especially located in the salivary glands. Although they are usually located in the salivary glands, they can be located in any head and neck region.[2] These rare malignant tumors can be seen in many different histological types. In the 5th edition of the World Health Organization (WHO) classification of the salivary gland tumors update, more than 20 malign histological types were specified and two more new malignant entities are added; microsecretory adenocarcinoma and sclerosing microcystic adenocarcinoma.[3] These many different histologic types and their rarity make prospective randomized studies in these tumors very difficult. Previous retrospective studies have generally included major or minor salivary glands in small patient groups. In some studies, only the more common histological types were included, and no information was given about the rarer histological types.

In this study we aimed to investigate the incidence, clinicopathological features, treatment modalities as well as recurrence and metastasis patterns, and outcomes of both major and minor salivary gland malignancies treated in a large Turkish patient population.

2 | METHODS

2.1 | Study design

A total of 37 medical oncology clinics from different regions of Turkey participated in this retrospective-multicenter study. Medical records of patients with head and neck cancer, who were admitted to oncology outpatient clinics from the years 2000 through 2021, were analyzed. Squamous cell carcinomas, sarcomas, neuroendocrine tumors, small cell carcinomas, malign melanoma, basal cell carcinomas, and thyroid carcinomas were excluded. The diagnosis of salivary gland cancers was based on the histopathological findings. The clinical and demographical features; age, gender, The Eastern Cooperative Oncology Group Performance Status (ECOG PS), histologic type and pathologic features (grade, ki-67, androgen receptor, human epidermal growth factor receptor −2 (HER-2), programmed death ligand −1 (PD-L1) status), primary tumor localization, clinic and pathologic stage, primary treatment (e.g., surgery, radiotherapy, chemoradiotherapy), metastasis localizations, treatments at first, second and third lines were recorded. The files of a total of 533 patients with the specified characteristics were reviewed, 90 patients with missing data were not included in the study. Finally, 443 patients with salivary gland cancer with complete data were included in the analysis.

2.2 | Ethics approval

This study was conducted after obtaining ethical approval from the Local Research Ethics Committee, with decision number 09/05. All procedures and stages in this multicenter retrospective study were carried out in line with the World Medical Association Declaration of Helsinki, "Ethical Principles for Medical Research Involving Human Subjects," modified in October 2013.

2.3 | Statistical analysis

Statistical analyses were performed using SPSS software, version 22 (Chicago, IL). Data were presented as mean

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± SD (standard deviation) or median and interquartile ranges, as appropriate. Categorical variables were reported as frequencies and group percentages. The relationship between nonparametric variables was studied by the chi-square test. Parametric variables were compared with the independent-sample *t* test. Survival estimates were calculated by using the Kaplan–Meier method. The log-rank test was used to compare survival estimates. A *p*-value of <0.05 was accepted as statistically significant.

3 | RESULTS

The study included data from a total of 443 salivary gland cancer (SGC) patients. The median age at diagnosis was 56 (interquartile range 46–65). Two-hundred and fifty (56.4%) of 443 patients were male. Demographic and clinical characteristics of the patients are summarized in Table 1.

Of the operated patients, 146 (41.4%) received adjuvant radiotherapy, and 129 (36.5%) received adjuvant chemoradiotherapy. Three (0.5%) of the operated patients received neoadjuvant chemotherapy with docetaxel-5-fluorouracil-platinum combination and partial response was obtained in all three of them. Seven of the patients (22.6%) who underwent curative chemoradiotherapy received induction chemotherapy, four of them had a partial response, and three had a radiological complete response.

In the metastatic first-line treatment a total of 153 patients received chemotherapy. Chemotherapy regimens were taxane-platinum combination in 42 patients, docetaxel-5-fluorouracil-platinum combination in 32 patients, platinum-5-fluorouracil combination in 32 patients, platinum-doxorubicin-cyclophosphamide combination in 26 patients, platinum-doxorubicin combination in 14 patients, taxane-vinorelbine combination in 7 patients.

Patological features; grade, Ki-67, androgen receptor, human epidermal growth factor receptor −2, programmed death ligand −1 status, are presented in Table 2.

Next-generation sequencing (NGS) was performed in 27 patients. In one AdCC case c-kit mutation, in one MEC case NTRK rearrangement, and in one SDC case PI3K mutation was detected. Androgen receptor expression examined in 106 of 177 AdCCs, in 18 of 37 SDCs, a in 12 of 63 MECs. It was positive in 13 (72.2%) of SDCs, in 3 (25%) of MECs, and positive in 8 (7%) of AdCCs. Also, in 1 sebase carcinoma, 1 secretuar carcinoma, and 1 adenocarcinoma androgen receptor expression was positive.

When patients examined for HER-2 were analyzed according to their histology, 7 of 121 AdCC, 5 of 15 SDCs, 3 of 15 MECs, and 1 of 15 adenocarcinomas were HER-2 positive.

TABLE 1 Demographic and clinical characteristics of the patients

Characteristics	
Age, year, median (interquartile range)	56 (46–65)
Gender, *n* (%)	
Male	250 (56.4)
Female	193 (43.6)
ECOG performance score, *n* (%)	
0–1	420 (94.8)
≥2	23 (5.2)
Primary site, *n* (%)	
Major salivary gland	251 (56.7)
Minor salivary gland	192 (43.3)
Oral cavity	53 (26.7)
Maxillary sinus	36 (18.8)
Nasal cavity	28 (14.6)
Orophayrnx	24 (12.5)
Nasophayrnx	12 (6.3)
Hypophayrnx	10 (5.2)
Paranasal sinus	10 (5.2)
Sphenoid sinus	8 (4.2)
Larynx	8 (4.2)
Lip	3 (1.6)
Histopathology, *n* (%)	
Adenoid cystic carcinoma	177 (40.0)
Adenocarcinoma	66 (14.9)
Mucoepidermoid carcinoma	63 (14.2)
Salivary ductal carcinoma	37 (8.4)
Undifferentiated carcinoma	35 (7.9)
Myoepithelial carcinoma	15 (3.4)
Acinic cell carcinoma	13 (2.9)
Lymphoepithelial carcinoma	8 (1.8)
Carcinoma ex pleomorphic carcinoma	6 (1.4)
Intestinal type	4 (0.9)
Clear cell carcinoma	3 (0.7)
Oncocytic carcinoma	3 (0.7)
Other[a]	13 (2.9)
Nonmetastatic stage at initial diagnosis, *n* (%)	
Operated[b]	353 (79.7)
Curative chemoradiotherapy	31 (6.9)
Metastatic stage at initial diagnosis, *n* (%)	70 (15.8)
Visceral	44 (9.9)
Liver	6 (1.3)
Lung	38 (8.5)
Bone	12 (2.7)
Missing	12 (2.7)

[a]Other: secretory, whartin, trichilemmal carcinoma, sebase carcinoma, pleomorphic, inflamatuary myofibroblastic carcinoma, large cell carcinoma, ameloblastom.

[b]Primary surgery and metastasectomy were performed in 11 of the metastatic patients.

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TABLE 2 Pathological features of the patients

Pathological features	
Ki-67, *n* (%)	
1–9	68 (15.3)
10–19	43 (9.7)
20–29	46 (10.3)
30–39	51 (11.5)
40–49	47 (10.6)
≥50	29 (6.5)
Unknown	159 (36.1)
Grade, *n* (%)	
Grade 1	60 (13.5)
Grade 2	81 (18.3)
Grade 3	70 (15.8)
Unknown	232 (52.4)
HER-2 alteration evaluated patients, *n* (%)	171 (38.3)
IHC, negative	139 (81.7)
IHC, 1+	9 (5.2)
IHC, 2+	10 (5.8)
IHC, 3+	11 (6.4)
ISH, positive	7 (4)
Unknown	272 (61.7)
Androgen receptor expression evaluated patients, *n* (%)	151 (34)
Positive	27 (17.8)
Negative	124 (82.2)
Unknown	292 (66)
PD-L1 expression level evaluated patients, *n* (%)	125 (28.2)
Positive	105 (84)
≥1%	105 (100)
≥10%	61 (58)
≥50%	16 (15.2)
Negative	20 (16)
Unknown	318 (71.8)
NGS performed patients, *n* (%)	27 (6)
NGS detected alteration, *n* (%)	10 (2.3)
CDK	2 (20)
c-kit	3 (30)
EGFR amplification	1 (1)
EGFR exon 18 (pT725T)	1 (1)
NTRK fusion	2 (2)
PI3K	1 (1)
Unknown	433 (94)

Abbreviations: CDK, cyclin dependent kinase; EGFR, epidermal growth factor receptor; HER-2, human epidermal growth factor receptor −2; IHC, immunehistochemical; ISH, in situ hybridization; NTRK, neurotrophic tropomyosin receptor kinase; PI3K, phosphatidylinositol-3-kinase; PD-L1, programmed death ligand −1.

3.1 | Localization and histopathologic type

The histologic types seen in the major salivary glands are shown in Figure 1 according to their frequency. The histologic types seen in the minor salivary glands are shown in Figure 2 according to their frequency.

Minor salivary gland tumors were localized mostly in oral cavity 56 (29.2%). AdCC 95 (53.7%), MEC 46 (73%), SDC 31 (83.8%) and adenocarcinoma 29 (43.9%) were most common in the major salivary glands. Although AciCC and lymphoepithelial carcinoma were less in number, 12 (92.3%) of 13 AciCCs and 7 (87.5%) of 8 lymphoepithelial carcinomas were in the major salivary glands. In Table S1, Supporting Information, the frequencies of salivary gland cancers by localization and the frequency of histological types according to localizations are summarized.

3.2 | Patients with recurrence and metastasis

Thirty-seven (14.7%) of 251 patients with major salivary glands and 33 (17.2%) of 192 patients with minor salivary glands were in the metastatic stage at the time of diagnosis. There was no statistically significant difference between major and minor salivary gland tumors according to their distant metastatic stage at the time of diagnosis.

The most common metastatic histologic type at diagnosis was undifferentiated carcinoma (20%), followed by adenocarcinoma (19.7%), SDC (18.9%), CxPA (16.7%), AdCC (16.4%), AciCC (15.4%), MEC (12.7%), and myoepithelial carcinoma (6.7%). None of the patients with lymphoepithelial carcinoma, clear cell carcinoma, intestinal type carcinoma, and oncocytic carcinoma had metastasis at the time of diagnosis.

At the time of diagnosis, 50% of all metastatic patients had lung metastasis. Lung metastases were present in 62.1% of AdCC cases, 53.8% of adenocarcinoma cases, and 50% of MEK cases that were in the metastatic stage at the time of diagnosis. Although the number of patients was small, one patient with SDC had brain metastasis at the time of diagnosis. Primary surgery was performed in 204 (95.3%) of 214 nonmetastatic patients with major salivary glands and 123 (77.4%) of 159 patients with minor salivary glands. There was a statistically significant difference in terms of performing primary tumor surgery in major and minor salivary gland tumors ($p < 0.0001$).

Curative chemoradiotherapy was performed in 5 (2.3%) of 214 nonmetastatic major SGCs and 25 (25.7%) of 159 minor SGCs. There was a statistically significant

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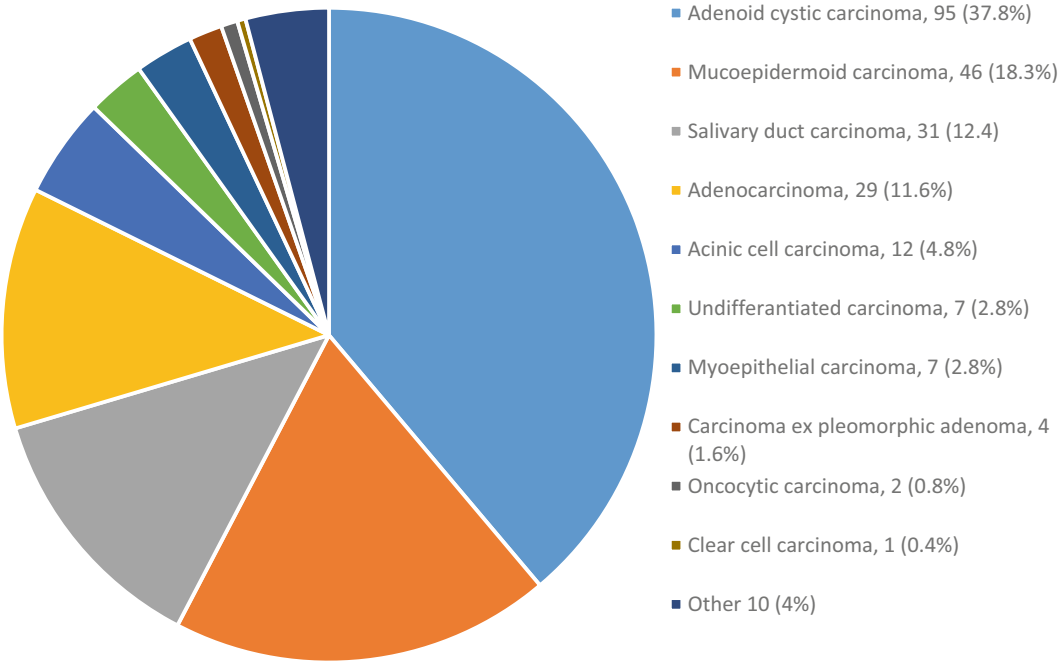


FIGURE 1 Histologic types in the major salivary glands, *n* (%) [Color figure can be viewed at wileyonlinelibrary.com]

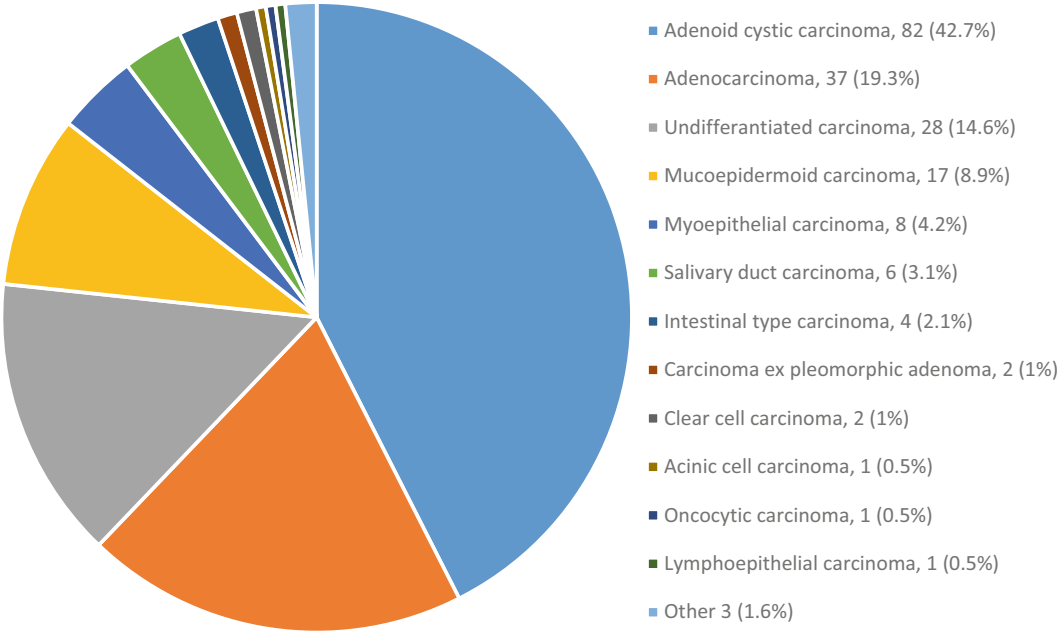


FIGURE 2 Histologic types in the minor salivary glands, *n* (%) [Color figure can be viewed at wileyonlinelibrary.com]

difference in terms of curative chemoradiotherapy in major and minor SGCs ($p < 0.0001$).

Locoregional recurrence and/or distant metastasis (R/M) developed in 197 (53%) of 372 patients who were not metastatic at the time of diagnosis. Local recurrence was seen in 73 (37.1%) of these patients, distant metastases in 124 (33.3%), and both local recurrence and distant metastasis in 26 (13.6%). Of those who developed metastases during follow-up, 50 (26.2%) were to the lung and 22 (11.5%) to the bone.

According to histologic types, 87 (58.8%) of AdCCs, 28 (52.8%) of adenocancers, 28 (50.9%) of MECs, 15 (50%) of SDCs, 10 (35.7%) of undifferentiated cancers, 10 (71.4%) of myoepithelial carcinomas, 5 (45.5%) of acinic cell cancers, 3 (42.9%) of lymphoepithelial carcinomas, 2 (40%) of CxPAs, 2 (50%) of intestinal type

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carcinomas, 2 (66.7%) of oncocytic carcinomas, 1 (33.3%) of clear cell carcinomas, R/M was developed at follow-up.

Distant metastasis in the major SGCs is statistically significantly more common than in the minor SGCs. Locoregional recurrence is statistically significantly more common in the minor SGCs than in the major SGCs ($p = 0.003$).

Lymph node metastases were most common in undifferentiated carcinoma 25 (73.9%), SDC 25 (69.4%), and MEC 38 (61.3%). Myoepithelial carcinoma 2 (14.3%), AdCC 30 (19.5%), AciCC 2 (33.3%), and CxPA 2 (33.3%) are the rarest histological types with lymph node metastasis.

There was a trend towards a lower rate of R/M in AdCCs receiving adjuvant therapy but did not reach statistical significance ($p = 0.06$). There was no association between adjuvant therapy and R/M in the other histologic types.

Recurrence and/or metastasis rates after curative treatment according to the histology was most common in myoepithelial carcinoma (71.4%). In the other histologies it was 66.7% in oncosytic carcinoma, 56.8% in AdCC, 52.8% in adenocarcinoma, 50% in SDC, 47.3 in MEC, 45.5% in AciCC, 42.9% in lymphoepithelial carcinoma, 40% in CxPA, 50% in intestinal type carcinoma, 33.3% in clear cell carcinoma, and 32.1% in undifferentiated carcinoma, respectively.

The median relapse-free survival (RFS) in the group of patients who developed R/M after curative treatment was 21.4 (17.1–25.7) months. In the four most common histological types; AdCC, adenocarcinoma, SDC, and MEC; median RFS was 25.7 (19.6–31.8), 20.2 (1.29–39.1), 15.1 (11.4–18.7), 13.2 (6.8–19.6) months; respectively (Figure 3).

Log-rank analysis of histological types showed that AdCC was significantly longer in terms of RFS compared to MEC ($p = 0.01$) and SDC ($p = 0.001$). In log-rank analysis, there was no difference in terms of RFS between adenocarcinoma and other histological types, and between MEC and SDC.

The median progression-free survival (PFS) was 10.2 (7.1–13.4) months in the de-novo metastatic patients' group. In the four most common histological types, AdCC, adenocarcinoma, MEC, SDC; median PFS was 10.4 (2.2–18.6), 10.4 (4.5–16.3), 7.6 (1.2–15.9), 5.1 (0.33–9.8) months, respectively (Figure 4). No significant difference was found in terms of PFS in log-rank analysis in histological types.

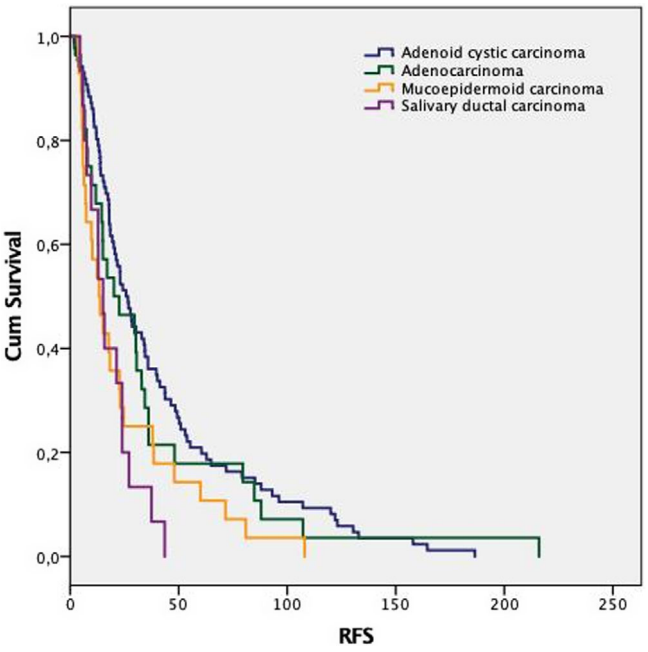


FIGURE 3 Relapse-free survival of four most common histologic types [Color figure can be viewed at wileyonlinelibrary.com]

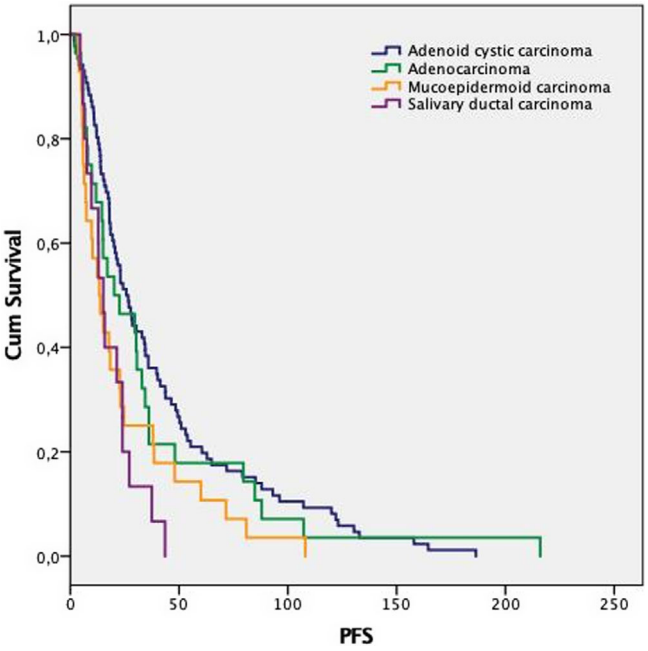


FIGURE 4 Progression free survival of four most common histologic types [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

Salivary gland neoplasms are a rare and heterogeneous group of tumors with significant heterogeneity in histological types and exhibit very different clinical behavior. In this study experience of 443 SGC patients treated between 2000 and 2021 at 36 medical oncology clinics from different regions of Turkey is presented. All pathologic types and subsites of salivary glands in the head and neck are included in this study.

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In our study, the median age at diagnosis was 56, and consistent with the literature. Two-hundred and fifty (56.4%) of 443 patients were male. Although the ratio of women to men is higher in favor of women in some studies, there are also studies with similar results to ours.[4–7]

Malignant tumors in the major salivary glands are extremely rare. In different studies, there were different results for most histologic types seen in major SGCs.

In the study of Benchetrit et al. and in another German population-based state cancer registry the most common histological type is MEC (29.8% and 20.8%, respectively).[8,9] In another study the most frequently diagnosed histological type is adenocarcinoma not otherwise specified (18.5%).[5] In our study, the most common histologic types in the major salivary glands were AdCC 95 (37.8%), followed by MEC 46 (18.3%).

This difference in the frequency of histological types in major SGCs may be due to the fact that the studies were conducted in different regions. In the multicenter study of Alsanie et al., when the differences according to regions were examined, the frequency of histological types differed compared to the total population.[9] One of the missing data in our study was the lack of information on which major salivary gland the tumor was located.

In the literature, there are differences in the frequency of histological types in minor SGCs as well as in major SGCs. In the experience of Memorial Sloan Kettering and in a far east study the most common histological type is MEC (40% and 27.6%, respectively).[2,4] In another study, the most histologic types were AdCC 71 (29.8%).[10] In our study, the most common histologic type in minor salivary glands was AdCC, with similar rates, in all localizations except the nasal cavity.[9,11,12] The most common histological type was undifferentiated carcinoma 9 (32.1%), followed by AdCC 7 (25%) in tumors located to the nasal cavity.

Minor salivary gland tumors can occur in a wide variety of sites, and the most common site is the oral cavity.[7] Similar results were obtained in many studies, and these results were consistent with the findings of our study (29.2%).[13–16]

Considering the frequencies of patients in the metastatic stage at the time of diagnosis, there are different results in studies. In a study of 5776 patients with major salivary gland carcinoma, 333 (5.8%) patients were in the metastatic stage at the time of diagnosis.[8] In another study, 454 SGCs were included, 95 (20.9%) of these were presented with distant metastases; 7 (7.4%) of these 95 patients were at the initial diagnoses, while 88 (92.6%) were detected during the follow-up period. AdCC and SDC tumors were the most common metastatic histologic types.[17] In the study of Ali et al., the two histological types most likely to develop distant metastases were SDC (9 of 17 patients, 53%) and adenocarcinoma (14 of 33 patients, 42%).[18] In our study, compared to other studies in the literature, there were more patients in the metastatic stage at the time of diagnosis (15.8%, $n = 70$). Its reason may be the late presentation of the patients to the medical oncology clinics after surgery and the incomplete staging of the patients before surgery. In our study, the most frequently metastatic histologic types at the time of diagnosis were undifferentiated carcinoma (20%), adenocarcinoma (19.7%), and SDC (18.9%), and these results were consistent with the literature. SDC, adenocarcinoma, and undifferentiated carcinoma are higher-grade cancers, so this may be the cause of more frequent metastases in these histologies. In accordance with the literature, the most common metastatic site was lung (50% of all metastatic patients) in our study. Furthermore, lung metastasis was the most common site of metastasis for all histologies.[17,19,20]

In the management of all salivary gland malignancies, surgical excision with negative margins is indispensable. The type, grade, and stage of malignancy are determining factors in the extent of surgery and the necessity of neck dissection.[21]

In our study, the rate of primary surgery in major SGCs (95.3%) was statistically significantly higher than the rate of primary surgery in minor SGCs (77.4%) ($p < 0.0001$). No difference has been reported in the literature in terms of the rate of primary surgery in major and minor SGCs. However, in minor SGCs, the most common histologic type is AdCC in many series, and AdCCs tend to spread along nerves and subperiosteal/perichondral planes. In addition, minor salivary glands can be found in different localizations, and surgery with negative margins may not be possible because localizations such as sinonasal and nasopharynx contain critical anatomical structures.[22] This may explain the lower rate of primary surgery for minor SGCs compared to major SGCs in our study.

Due to the lower rate of primary surgery in nonmetastatic minor SGCs, the rate of curative chemoradiotherapy was statistically significantly higher than in major SGCs; 25.7% vs. 2.3%, respectively ($p < 0.0001$). Concurrent chemoradiotherapy (CRT) is controversial for locally advanced SGCs. The benefit of CRT is not supported by randomized clinical trials. In addition, some prospective clinical studies have shown that systemic chemotherapy is effective in SGCs. Especially with cisplatin monotherapy, 18% objective response was achieved in patients with recurrent or locally advanced salivary gland malignancies. By deduction from these, CRT is used in locally advanced and high-risk adjuvant SGCs.[23,24]

As in metastatic disease at the time of diagnosis, the most common site of metastasis was the lung in patients

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who developed metastasis during follow-up. This was followed by bone metastasis with 11.5%. Park et al. showed that local recurrence was 38.7%, regional recurrence 16.1%, and distant metastasis was 67.7% in their study.[25] Different studies had similar results to each other and to ours.[17,19]

Myoepithelial carcinoma had the highest rate of recurrence (71.4%) and AdCC, MEC, adenocarcinoma, SDC had similar rates of recurrence in our study. In recent studies metastasis rate of AdCC was stated 29%–38% and 45%–50% for SDCs. SGC and AdCC were the most common histologies for metastasis development. SDC is one of the aggressive histologies and R/M is common. Survival outcomes are poor. R/M are also common in AdCC, but it has a persistent disease and better survival outcomes. Since myoepithelial carcinoma is a rare histological type, its clinicopathological and prognostic features are still unclear. Like AdCC, R/M can be seen frequently, and survival is longer due to its slower course.[17,19,26–29]

In our study distant metastasis in the major SGCs is statistically significantly more common than in the minor SGCs ($p = 0.003$). In a recent study distant metastasis was more common in major SGCs (56% vs. 44%).[19] Most studies have shown that the risk of developing metastases is associated with high-grade histology rather than localization.[17,25,30] In this study high-grade histologic tumors like as SDC were more common in the major salivary glands. This may explain the higher incidence of distant metastases in major SGCs.

In this study locoregional recurrence is significantly more common in the minor SGCs than in the major SGCs ($p = 0.003$). In the literature a direct relationship between locoregional recurrence and localization has not been specified. Local and regional recurrence seems to be more related to tumor grade, histological type, T and N stage at diagnosis, and R0 resection rate.[31,32] In our study primary surgery was significantly lower in minor SGCs and CRT rate was higher than major SGCs. This may explain the higher rate of locoregional recurrence in minor SGCs than in major SGCs.

In our study, we showed that relapse-free survival is associated with histologic types. RFS was found to be shorter in SDC and adenocarcinoma, which are more aggressive histologic types. As expected, RFS was significantly longer in AdCC than in other histologic types. In a recent study, RFS was found to be 20.3 months and shorter for SDC and adenocarcinoma histologic types, similar to the results in our study.[19,33] In many studies, information on DFS was reported as 5-year and 10-year rates, and aggressive histologic types were shown among the factors affecting DFS, as in our study.[31,34]

In a previous study including adenocarcinoma and SDC cases, the most frequently used treatments were platinum-based doublet chemotherapies, with a PFS of 5.7 months, similar to our study.[6] In a phase 2 study, cisplatin plus docetaxel was tried in a population with 63% AdCC, the median PFS was found to be 9.4 months, similar to our study.[35] In many studies, treatment responses and PFS were specified separately for AdCC and for other histologies. In our study, the median PFS for the entire population was 10.2 months, 10.4 months for AdCC, and 5.1 months for SDC. Most of the patients received platinum-based chemotherapies (57.5%), and 37.9% of the patients received platinum-based triplet chemotherapy. There was a limited number of patients received targeted therapy with or without chemotherapy in first line treatment. This may be due to the fact that some of the patients included in the study were before evidence of targeted therapies emerged. The PFS results of our study were compatible with the literature.

The significance of PD-L1 expression in SGC remains controversial. There are current studies about PD-L1 expression that is associated with poor prognosis.[36] Also recent studies revealed that PD-L1 positivity is not associated with poor survival rates but PD-L1 positive tumors are in higher stages.[37] Also in studies with a low number of patients, high level of microsatellite instability expression was not identified in SGCs.[38] There are some targetable molecular alterations identified in SGCs including HER2 upregulation, androgen receptor overexpression, Notch receptor activation, NTRK gene fusions, and RET alterations and there are several clinical trials with multikinase inhibitors, NTRK inhibitors, anti-HER-2 therapies, immune check point inhibitors, or different combinations of these drugs. While some of these treatments have been shown to significantly improve treatment outcomes, many trials are ongoing.[39] In the light of these results, it is important to perform molecular profiling in terms of targetable mutations in metastatic SGCs and PD-L1, MSI and tumor mutation burden evaluations in terms of immune check point inhibitors. In our study, some data are lacking because the data were obtained from different oncology centers and the patients were included for a very wide time interval, and there was insufficient evidence of treatment at the time of diagnosis for those with PD-L1 positive, MSI high, and targetable mutations, and this is one of the limitations of our study.

Despite all this, our study is valuable in that it includes both major and minor SGCs; although this made the group more heterogeneous, the statistical analysis was therefore more reliable as it allowed more patients to be compared. The fact that it includes treatment and survival results as well as descriptive analysis makes this study more valuable.

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5 | CONCLUSION

In this multicenter study, curative surgery was applied more frequently in major SGCs, curative chemoradiotherapy was applied more frequently in minor SGCs. Major SGCs had a higher risk of distant metastasis, while minor SGCs had a higher risk of local and/or regional recurrence. Tumors with high R/M rates, such as SDC and adenocarcinoma, should be followed more closely. While early R/M may be seen, it should be kept in mind that there may be late recurrence and/or metastases, and patients should be followed up for a long time. In addition, markers such as PD-L1 level, HER-2 mutations, androgen receptors, and NGS should be evaluated in order to evaluate new treatment methods.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

Data are available for review upon request.

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SUPPORTING INFORMATION

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