Early Stage Minor Salivary Gland Adenoid Cystic Carcinoma has Favourable Prognosis

Hanna Hämetoja DDS[1,2], Karoliina Hirvonen MD[3*], Jaana Hagström DDS, PhD[1,4], Ilmo Leivo MD, PhD[5], Kauko Saarilahti MD, PhD[6], Satu Apajalahti DDS, PhD[7], Caj Haglund MD, PhD[4,8], Antti Mäkitie MD, PhD[3,9#], Leif Bäck MD, PhD[3#]

1 Department of Pathology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

2 Department of Oral Pathology, University of Turku, Turku, Finland

3 Department of Otorhinolaryngology - Head and Neck Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

4 Research Programs Unit, Translational Cancer Biology Program, University of Helsinki, Helsinki, Finland

5 Department of Pathology, University of Turku and Turku University Hospital, Turku, Finland

6 Department of Oncology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

7 Department of Radiology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

8 Department of Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

9 Division of Ear, Nose and Throat Diseases, Department of Clinical Sciences, Intervention and Technology, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

*Shared first authorship

#Equal contribution

Corresponding author: Hanna Hämetoja, hanna.hametoja@helsinki.fi, Department of Oral Pathology, University of Turku – Lemminkäisenkatu 2 – 20520 Turku, Finland

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ABSTRACT (Word count 241)

To evaluate long-term outcome of minor salivary and mucous gland (MiSG) adenoid cystic carcinoma (ACC) of the head and neck and to compare the results with earlier reports including our recently published series on major salivary gland (MaSG) ACC.

The study comprised 68 MiSG ACCs operated during 1974-2012 at the Helsinki University Hospital, Helsinki, Finland. Medical records and histological samples were reviewed. Our previously published cohort comprising 54 MaSG ACCs during the years from 1974 to 2009 was used for comparison.

The most common locations were oral cavity and sinonasal cavities. Most patients presented stage IV (33.8 %) and I (23.5 %) disease. Primary treatment with curative intent, mainly surgery, was offered for 64 patients. Thirty-three (51.6 %) of these patients developed a disease recurrence and twenty-two (66.7 %) patients in less than five years. The difference in the length of recurrence-free time (<5 yrs. vs. >5 yrs.) had an impact on OS and DSS ($p<0.001$) showing worse prognosis for the earlier recurring group. T classes 2-4 ($p=0.005$, $p<0.001$, and $p=0.001$, respectively) and stages II-IV ($p=0.019$, $p<0.001$, and 0.002, respectively) were associated with worse OS, DSS, and DFS. MiSG ACC had a similar long-term survival compared to MaSG ACC.

Patients with stage I MiSG ACC seem to carry a favourable prognosis compared with those with stage II, III and IV tumours. It is thus noteworthy, that stage II tumours represent a truly advanced disease entity warranting a more aggressive treatment approach.

INTRODUCTION

Adenoid cystic carcinoma (ACC) is a salivary and mucous gland malignancy with poor long-term prognosis. It has a slow but persistent clinical course and diagnosis is often made at the advanced stage with occurrence of perineural invasion. ACC has a distinctive tendency to develop local and distant metastases at a late stage, even after one or two decades. According to our previous study on major salivary gland (MaSG) ACC, most distant metastases appear within a 10-year period [1].

The 2017 World Health Organization (WHO) classification of salivary gland tumours comprises 19 malignant entities. ACC is denoted as the second most common malignancy [2]. Some nationwide studies from Finland, Denmark and Pakistan, however, have reported that the most common salivary gland cancer in those countries is ACC [3-5].

The primary treatment for ACC is radical surgery with possible post-operative radiotherapy [6]. Chemotherapy is used in advanced, recurrent or metastatic ACC. However, effective chemotherapeutic agents are lacking [6]. In the future, cumulative knowledge on genomic alterations of ACC may lead to novel chemotherapeutic treatments [7].

About 70 % of all ACC cases originate in salivary glands. Minor glands (MiSG) are more often involved than MaSGs [8, 9]. ACC of MiSGs represents 2-4 % of all head and neck malignancies [10, 11]. These typically appear in areas with salivary or mucous glands (i.e., in the oral cavity, oropharynx, sinonasal area and upper respiratory tract) [12].

Most previous studies have included all cases of salivary gland ACCs, and only a few reports focus especially on MiSGs [9, 11, 13-17]. Therefore, the aim of this study was to investigate the clinical presentation, treatment and outcome in the group of rarely investigated MiSG ACCs at a tertiary-care academic referral centre during a 38-year period, and to compare the outcome to that of MaSG ACC. Moreover, our goal was to generate whole-population information based on regional data covering one-third of the Finnish population.

MATERIALS AND METHODS

We evaluated 68 patients with MiSG ACC who were treated between 1974 and 2012 at the Department of Otolaryngology, Head and Neck Surgery, Helsinki University Hospital, Helsinki, Finland. The previously reported 54 patients with MaSG ACCs were operated on during 1974-2009 at the same institution [1]. This single tertiary-care academic centre represents 1.6 million inhabitants, covering approximately one-third of the Finnish population.

We collected data on patient characteristics, histological parameters and clinical features of the tumour, treatment modalities and survival outcome. Tumour size measurement was based on histological samples or identified from medical records. In three cases where there was inadequate tumour size information, the head and neck radiologist identified sizes from MRI images. An experienced head and neck pathologist (J.H.) confirmed the histopathological diagnoses using the histopathological diagnostic criteria validated and updated according to the WHO classification (2005) [18].

The Institutional Research Ethics Board approved the study concept (Dnro 31/13/03/02/2010, 01 February 2010). Statistics Finland provided the dates and causes of death. Overall survival (OS) was determined from the interval between the end of primary treatment and the last day of follow up or the date of death. Disease-specific survival (DSS) was defined as the interval between the last day of treatment and death due to disease. Disease-free survival (DFS) was determined as the interval between the last day of treatment and any sign of disease recurrence. All patients had a minimum follow up of at least three years or until death.

Statistical analyses were performed using SPSS software (version 23.0, Chicago, IL, USA). We report values as medians with range for descriptive purposes. Calculations for survival rate were performed using the Kaplan-Meier method and survival functions by the log-rank test. Univariate associations of risk factors with OS, DSS and DFS were analysed using Cox regression analysis. Risk factors associated ($p<0.05$ in univariate analysis) with OS, DSS or DFS were included in multivariable Cox regression model. Stage was not included in the same multivariable model with T

class and neck metastases at presentation to avoid multicollinearity problems. Results are expressed using hazard ratios (HR) with 95% confidence intervals (CI). We considered *p*-values <0.05 statistically significant.

RESULTS

Patient characteristics

Table 1 shows patient and tumour characteristics of 68 patients with ACC. The current TNM classification did not cover the six (8.8 %) tracheal tumours. The TNM class could not be defined in four (5.9 %) cases. Table 2 presents the relationship between tumour location and stage. Almost half of the tumours in the oral cavity (n=41) were located in the palate (n=20), with the hard palate being the most frequent site (n=15).

Primary symptoms varied depending on tumour location. The most common clinical presentations were a lump (27.9 %) and pain (17.6 %). Symptom duration varied from one to 240 months with a median of six months. Three (4.4 %) patients had a second malignancy at the time of diagnosis (prostate carcinoma, chromophobic renal cell carcinoma or thyroid papillary microcarcinoma).

Preoperative investigations

The imaging methods used before treatment for most patients included computed tomography (CT) (57.8 %) and magnetic resonance imaging (MRI) (45.6 %) of the head and neck. Other examinations included chest CT scan (30.9 %), ultrasound (16.2 %), fine needle aspiration (11.8 %) and positron emission tomography CT (5.9 %).

Tumour characteristics

The median tumour size was 21 mm (range, 3-100 mm). For 19 (27.9 %) tumours, size determination was not possible from clinical data, histopathological report, re-evaluation of the histological specimen or MRI and CT images. The most common histopathologic growth pattern

was cribriform (33.8 %) followed by tubular (22.1 %) and solid (8.8 %) patterns. Most of the tumours showed a combination of growth patterns including tubular and cribriform (19.0 %), solid and cribriform (7.4 %) and solid and tubular (1.5 %). Information on the growth pattern was not available in five (7.4 %) cases. Tumours were classified under one growth pattern if more than 80 % of the histologic sample was composed of that particular pattern. However, in cases with a combination of growth patterns, a pattern with more than 30 % solid growth was classified in the solid group. Neural invasion (perineural, intraneural or both) was present in 39 (57.4 %) tumours. Information on neural invasion was not available for eight (11.8 %) tumours.

Treatment

Most of the patients were treated with curative intent (n=64, 94.1 %). Approximately half of these patients (n=35, 54.7 %) received surgery only as their primary treatment. A neck dissection was performed in 17 (26.6 %) cases; in 14 (82.4 %) patients the dissection was elective and in three (17.6 %) patients the dissection was therapeutic.

Twenty-four (37.5 %) patients received postoperative radiotherapy to their primary tumour area. One (1.6 %) patient received radiotherapy only with curative intent. The median radiation dose was 60 Gy (range, 32-70 Gy). Five (7.8 %) patients received chemotherapy as part of the oncological treatment. One patient was lost to follow up.

Four (5.9 %) patients received palliative treatment only.

Outcome

Figure 1 shows a flowchart of the presentation of patients with metastatic disease across various sites at diagnosis and during follow up. In 22 (66.7 %) patients, the first appearance of their metastatic disease occurred within five years after treatment; nine (27.3 %) patients later than five years after treatment. Patients with early metastatic disease had poorer OS and DSS than patients with no metastases during follow up (Table 3) (Figure 3). Among the patients treated with curative intent, the appearance of distant metastases was seen in 22 (66.7 %) patients during follow up. The most common location of distant metastasis was lungs (64.0 %), followed by bone (12.0 %)

and liver (12.0 %). Information on the exact locations of metastases was not available in three (12.0 %) patients. The mean interval for the detection of distant metastases was 43 months (range, 1-156 months). For the group treated with curative intent, the 5-year Kaplan-Meier estimates for OS and DSS were 69.7 % and 78.9 %, respectively, and 10-year OS and DSS rates were 42.0 % and 51.6 %, respectively.

T classes 2-4 and disease stage II-IV were associated with poorer survival. No patients with T class 1 and stage I disease died of cancer (Figure 2). In contrast, half of T class 2-4 and stage II-IV patients died of cancer. Four patients had neck metastasis at presentation and this was associated with poorer OS and DSS, but not with DFS. Female gender and age <65 were associated with better OS but not with DSS or DFS. Neural invasion was associated with poorer DFS (Table 3). However, neural invasion was not associated with the rate of local or locoregional recurrent disease. Appearance of distant metastases during follow up was associated with poorer OS and DSS. Appearance of locoregional lymph node metastases was associated with poorer DSS but not poorer OS (Table 3). The solid growth pattern did not affect survival.

In multivariable Cox regression analysis, male gender, age >65 years, T class 2-4, stage II-IV and neck metastases at presentation (N+) were associated with poorer OS. T class 2-4 and stage II-IV were independently associated with poorer DFS, but neural invasion did not remain significant in multivariable analysis (Table 4).

Patients with stage I disease had a significantly better prognosis and survival than those with stage II, III and IV disease. Even with disease failures, none of the stage I patients died of ACC. It is noteworthy that survival of stage II patients was significantly poorer than that of stage I patients, even though the treatment did not differ significantly.

Patients with stage I tumours

Sixteen patients had stage I disease. Three (18.8 %) of these patients experienced disease failure; two local and one distant. Both patients with local failure had their primary tumour in the ear canal. The distant failure and one of the local failures appeared within five years. During follow up, only

one patient with local disease failure died; this was however due to causes other than ACC. Altogether, ten patients were alive with no evidence of disease and two with disease at the end of the follow up (range, 36-204 months). Four patients died due to causes other than ACC.

Patients with stage II tumours

Twelve patients had stage II disease; eight (66.7 %) of these patients had disease failure. All cases in this group had their primary tumour located in the oral cavity. Five (62.5 %) patients had disease failure within five years and three (37.5 %) after five years. At the end of follow up, four patients were alive with no evidence of disease, two patients were alive with disease, five had died due to disease and one died due to other causes.

Patients with stage III and IV tumours

Seven patients had stage III disease; four (57.0 %) of these patients experienced disease failure. Three (75.0 %) patients developed metastatic disease within five years and one (25.0 %) after five years. All patients with disease failure died due to the disease (range, 4-58 months) and the remainder were alive with no evidence of disease.

Twenty patients had stage IV disease; 14 (70.0 %) of these patients experienced disease failure. Twelve (85.7 %) disease failures appeared within five years and two (14.3 %) after five years. Twelve patients died due to the disease (range, 13-143 months), and one patient was lost to follow up.

DISCUSSION

To characterize the behaviour and prognosis of MiSG ACC, we reviewed retrospective cases of 68 MiSG ACC patients treated between 1974 and 2012 in the Helsinki University Hospital region. According to our study, patients with stage I disease had good prognosis during follow up and

none died of ACC. On the contrary, advanced T class and advanced stage correlated negatively with OS, DSS and DFS.

Our group recently reported a similar investigation on ACC behavioural pattern in MaSGs [1]. Accordingly, we were able to compare these results between MiSGs and MaSGs. Only a few studies have reported separately the outcome of ACC in MiSGs and MaSGs [9, 11, 13-17, 19, 20] or compared ACCs in these different locations [21, 22].

In the present study on ACCs in MiSGs, the most common tumour location was the oral cavity (60 %), with palate (49 %) as the most frequent site as reported before [9, 13, 15, 16]. Among palatal tumours, the stage distribution was constant with slightly more advanced tumours (Table 2). In other intraoral sites, however, the tumours tended to be less advanced. On the contrary, in the series by Shum et al., palatal ACCs were predominantly of advanced T3-T4 classes (90 %) [17]. Detection of palatal tumours may be clinically difficult compared to other intraoral sites, which might lead to diagnostic delay and allow extensive neoplasm infiltration consequently resulting in more advanced stages at presentation. It is noteworthy in our series that ACCs of the nasopharynx and paranasal sinuses were all of advanced stage, although the number of these cases was limited. Furthermore, according to previous studies, ACCs of the paranasal sinuses are usually diagnosed late and the tumours are more advanced (T3-T4) [23-25]. It is possible that the nasopharynx and paranasal sinuses harbour tumour growth without early symptoms.

In previous studies, ACC has shown female predominance [9, 11, 13], which was also seen in our study (female to male ratio of 1.35). However, our previous study on MaSGs showed male predominance [1]. In the current study, female gender was associated with better OS, which may also reflect the higher life expectancy of women in general. On the other hand, a large series of head and neck ACC by Ellington et al. comprising 1754 MaSGs, 1117 oral cavity MiSGs and 138 neck and pharynx ACCs showed a better prognosis for females [21].

Contrary to our study, earlier reports have not emphasized a good prognosis for stage I tumours in general, although similar findings for MiSG ACCs have also been reported. Mücke et al. did not

find significant differences between stage I and II tumours, and other studies have also considered the behaviour of stage II tumours to be less aggressive [9, 15, 16]. DeAngelis et al. showed that T class was the only factor affecting survival, whereas Mücke et al. and Bianchi et al. both reported that T and N classes and stage affected survival [9, 15, 16]. In our study, T classes 2-4 and stages II-IV correlated negatively with OS, DSS and DFS. The present results highlight the favourable survival of patients with stage I disease. For instance, none of the patients with a stage I tumour died due to the disease. The only treatment failures in this patient group occurred in patients with a tumour in the ear or in the oropharynx. Patients with an oral cavity ACC were free of disease failures. Disease-free surgical margins are probably easier to achieve for smaller tumours in the oral cavity than in the oropharynx or in the ear, which have a more complex anatomy. Both of the present stage I patients with ACC in the ear showed local disease failures, which highlights the complexity of surgical anatomy. On the other hand, two other patients with advanced-stage ACC in the ear did not suffer from disease failures but were also treated more aggressively with surgery combined with radiotherapy. It might be feasible to consider more aggressive treatment also for stage I patients with ACC in this challenging location. According to our results, stage II disease in the oral cavity presents with poor outcome and with a high percentage of disease failures (67 %). Considering these observations, patients with stage II ACC might benefit from more intensive treatment modalities. Similarly to MiSGs, advanced T class, N class and advanced stage in MaSGs also had a negative effect on survival [1].

A well-known feature of ACC is neurotropism, which remains controversial considering that ACC metastasizes primarily haematogenously [26]. Neural invasion did not affect survival of MaSG ACC patients [1], but for the MiSG ACC patients in the present study neural invasion had a negative effect on DFS. In addition, neural invasion was not associated with the rate of either local, regional or locoregional recurrences. Contrary to our findings, some studies have reported that perineural invasion affects treatment outcome of both MiSG and MaSG ACC [14, 24, 27].

Growth pattern did not have an effect on survival. A solid pattern is related to poorer survival. According to the WHO, tumours with more than 30 % of solid pattern have more aggressive

behaviour [2, 18]. With MaSG, there was a slightly negative trend on survival but no statistically significant correlation was observed [1].

In both MiSG and MaSG, disease failures appearing within five years of the primary diagnosis significantly influenced OS and DSS. Primary and locoregional metastases negatively affected DSS in MiSGs but not in MaSGs. Distant metastases affected OS and DSS in both MiSGs and MaSGs. Most of the distant metastases appeared within 10 years in MiSGs and MaSGs. [1]. Ellington et al. compared MiSGs ACC to MaSGs and found decreased survival in MiSGs [21]. In the present study, long-term survival of MiSG ACC patients was similar to that of the MaSG ACC patients in our previous study [1].

The limitations of this study include its retrospective nature, which led to a shortage of necessary data on some single cases. Unfortunately, data concerning surgical margins were not sufficient enough to produce a reliable statistical assessment. The diagnostic assessment and treatment approach has also varied slightly during the course of the study. However, we were able to retrieve follow-up data covering a lengthy time period for all patients except one. Although our sample size was limited to only one tertiary-care academic centre, the number of the cases was large when compared to previous studies on MiSG ACC.

CONCLUSIONS

Patients with stage I ACC seem to have a good prognosis differing from that of patients with stage II tumours. Therefore, stage II tumours should be considered as truly advanced disease, which warrants a more aggressive treatment approach. As most disease failures tend to appear within approximately 10 years, we recommend an extended follow-up time of 10 years for MiSG ACC patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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Figure Legends

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