

# Clinicopathological study of distant metastases of salivary adenoid cystic carcinoma

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**Abstract.** Most studies of the clinicopathological characteristics and prognosis of patients with distant metastasis of salivary adenoid cystic carcinoma (SACC) have used small patient samples. To further explore this issue, a descriptive and prognostic study of 467 patients with SACC who were treated from 1963 to 2009 was conducted at a single institution. One hundred and forty-five patients (31.0%) had distant metastases. At least 20% of patients who presented with the early-stage disease and no recurrence developed distant metastasis. The overall 5-, 10-, and 20-year survival rates were 85.6%, 67.4%, and 50.4%, respectively, for patients without distant metastasis, and 69.1%, 45.7%, and 14.3%, respectively, for patients with distant metastasis. The median survival time after distant metastasis was 36 months (range 1–112 months). The prognosis was similar between patients who received treatment for metastasis and those who did not. Patients who were diagnosed with early-stage disease and without local recurrence of the primary tumours could also develop distant metastases. The biological characteristics of adenoid cystic carcinoma were different from those of squamous cell carcinoma. At present, the effectiveness of treatment for distant metastases is not ideal and further research is needed.

**Keywords:** salivary adenoid cystic carcinoma; distant metastasis; prognosis; risk factor; squamous cell carcinoma.

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Adenoid cystic carcinoma (ACC) is one of the most common malignant salivary gland tumours. It is characterized by invasive local growth and a high incidence of distant metastasis.<sup>1–8</sup> Whereas ACC primarily metastasizes to the lung, it can also metastasize to bone, liver, the cerebrum, and to multiple organs.<sup>1–3,6,9–</sup>

<sup>11</sup> Most previous studies on distant metastasis of ACC have been clinicopathological analyses of small patient samples, and more comprehensive research on the clinical and pathological

characteristics of distant metastasis of salivary adenoid cystic carcinoma (SACC) is needed. The aim of this study was to investigate the clinical and pathological characteristics of distant metastases of SACC by reviewing clinicopathological data from a large patient series at a single institution.

## Materials and methods

From 1963 to December 2009, 613 patients with SACC were admitted to

the study institution. Among them, 467 patients (76.2%) were given follow-up. The follow-up period, defined as the period from the time of diagnosis of SACC to the time of last data collection or of the patient's death, ranged from 6 months to 32 years (median 12 years). The diagnosis of distant metastasis was confirmed by the histopathological examination of samples obtained by metastasectomy or by detection of metastasis by computerized tomography (CT), chest X-ray film, B ultrasound, or bone scans. The distant

metastasis interval was defined as the period from the time of diagnosis of SACC to the time of diagnosis of distant metastasis.

The 2010 criteria of the International Union against Cancer (UICC) were used for the clinical staging of the major salivary gland tumours, whereas the criteria for squamous cell carcinoma (SCC) were used for the clinical staging of the minor salivary gland tumours.<sup>12</sup> All histopathological specimens were reviewed by two experienced pathologists who independently allocated each tumour to one of three groups: tubular, cribriform, or solid.<sup>5,13,14</sup> Each pathologist's assessment was blinded to the other's. Both pathologists agreed to classify a specimen as the solid subtype if the solid area comprised more than 30% of the tumour.

Of the 467 patients with SACC, 430 received surgery for the primary tumour. One hundred and seventy-one of the 430 patients received preoperative or post-operative radiotherapy (average radiation dose 60 Gy, range 40–76 Gy). The other 37 patients underwent radiotherapy or chemotherapy to treat the primary tumour without surgery because of their general physical condition.

The statistical analysis was performed using the SPSS software package (version 13.0; SPSS Inc., Chicago, IL, USA).

Kaplan–Meier survival curves were constructed to plot the percent survival as a function of time. The log-rank test was applied to assess the statistical significance of clinicopathological differences among the SACC groups and of differences in survival rates.

## Results

### General clinical data

Of the 467 patients with SACC who had available clinicopathological and follow-up information, 210 (45.0%) were male and 257 (55.0%) were female. Their ages ranged from 16 to 80 years, with a median age of 47 years. Two hundred and thirty-two patients (49.7%) had SACC of the minor salivary glands and 235 patients (50.3%) had SACC of the major salivary glands.

### Distant metastasis rate and sites

One hundred and forty-five patients (31.0%) had distant metastasis among the 467 SACC patients with follow-up. The lung was the predominant organ of distant metastasis (108 patients; 74.5%), followed by bone (10 patients; 6.9%), liver (five patients; 3.4%), cerebrum (three patients; 2.1%), and multiple sites (19 patients; 13.1%).

### Distant metastasis period

The distant metastasis interval ranged from 0 to 252 months. Seventeen patients had distant metastasis at the time they were diagnosed with SACC, and 128 patients developed distant metastasis during follow-up. The median distant metastasis interval was 48 months. Eighty percent of the patients in our series developed distant metastasis within 8 years after the diagnosis of SACC. However, 20% of patients developed distant metastasis from 8 to 20 years after the diagnosis of SACC.

### Relationship between the primary tumour and distant metastases

Table 1 shows distant metastasis rates by primary cancer site, T stage, and histological subtype. SACC that originated from the submandibular gland, tongue, or maxillary sinus had a higher distant metastasis rate than SACC that originated from other sites. Larger tumours had higher distant metastasis rates than smaller tumours. Of note, the distant metastasis rate was 23.9% among patients who were diagnosed with T1, early-stage SACC, compared with 38.6% among patients who were diagnosed with the most advanced disease. The distant metastasis rates were 27.3%, 29.9%, and 47.7% for the tubular, cribriform, and solid subtypes, respectively.

Table 1. Clinicopathological characteristics of 467 patients with salivary adenoid cystic carcinoma (SACC) and the rate of distant metastasis.

	Patients with SACC, <i>n</i>	Median follow-up, months (95% CI)	Patients with distant metastases, <i>n</i>	Distant metastasis rate (%)	<i>P</i> -value*
Primary site					0.575
Parotid gland	87	64 (49–79)	25	28.7	
Submandibular gland	72	48 (36–60)	27	37.5	
Sublingual gland	72	48 (37–59)	22	30.6	
Palate	125	60 (51–69)	32	25.6	
Tongue	41	48 (31–63)	15	36.6	
Buccal	24	69 (44–94)	7	29.2	
Postmolar triangle	22	69 (49–89)	6	27.3	
Maxillary sinus	18	60 (26–94)	8	44.4	
Lip	6	108 (61–155)	3	50.0	
Tumour stage classification <sup>12</sup>					0.042
T1	117	60 (49–71)	28	23.9	
T2	174	72 (63–81)	49	28.2	
T3	49	49 (33–65)	19	38.8	
T4	127	36 (29–43)	49	38.6	
Histological subtypes <sup>5,13,14</sup>					0.038
Tubular	99	86 (73–99)	27	27.3	
Cribriform	324	54 (48–60)	97	29.9	
Solid	44	36 (20–52)	21	47.7	
Primary site recurrence					0.030
Recurrence	242	72 (64–79)	86	35.5	
No recurrence	225	48 (41–55)	59	26.2	
Total	467	144 (110–177)	145	31.0	

CI, confidence interval.

\* Chi-square test, two-sided.

There was a statistically significant difference among the three groups. Patients with the solid subtype of SACC were most likely to develop distant metastasis.

During the follow-up period, 242 of the 467 (51.8%) SACC patients presented with recurrence. Table 1 also shows the relationship between primary tumour recurrence and distant metastasis: 35.5% of patients with recurrent tumours developed distant metastasis, whereas 26.3% of patients without recurrent tumours developed distant metastasis. The difference between these two groups was statistically significant.

#### Survival rates in patients with and without distant metastasis

The 5-, 10-, 15-, and 20-year cumulative survival rates were 79.5%, 58.3%, 43.8%, and 32.1%, respectively, for the 467 patients with SACC. The 5-, 10-, 15-, and 20-year cumulative survival rates were 69.1%, 45.7%, 26.5%, and 14.3%, respectively, for the 145 patients with distant metastasis, compared with 85.6%, 67.4%, 57.6%, and 50.4%, respectively, for the patients without distant metastasis, as illustrated in Fig. 1. Thus, the survival rate was much lower for patients with distant metastasis ( $P < 0.001$ ).

#### Post-distant metastasis survival times according to the distant metastasis sites

Among the 145 patients with distant metastasis, there were 108 patients (74.5%) with pulmonary metastasis alone, who were referred to as the 'pulmonary metastasis group'. Thirty-seven patients (25.5%) had metastases to bone, liver, cerebrum, or multiple sites, and this group was referred to as the 'other distant metastasis group'. The median survival time after distant metastasis was 36 months (range 1–112 months). The survival rates of the pulmonary metastasis group and the other distant metastasis group are illustrated in Fig. 2. Patients in the other distant metastasis group had significantly lower survival rates than those in the pulmonary metastasis group ( $P = 0.005$ ).

For the 145 patients with distant metastasis, the 1-, 3-, and 5-year survival rates after distant metastasis were 75.3%, 47.1%, and 26.5%, respectively. The median survival time was 36 months. The post-distant metastasis survival analysis according to the different sites of distant metastasis is shown in Table 2. The median survival time after distant metastasis in patients with isolated lung metastasis was 44 months and the 1-, 3-, and 5-year

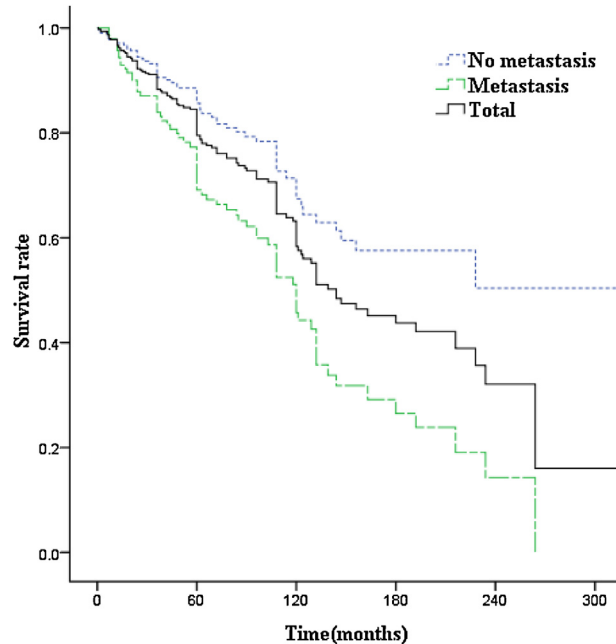


Fig. 1. Cumulative survival rates in a cohort of 467 patients with salivary adenoid cystic carcinoma (SACC).

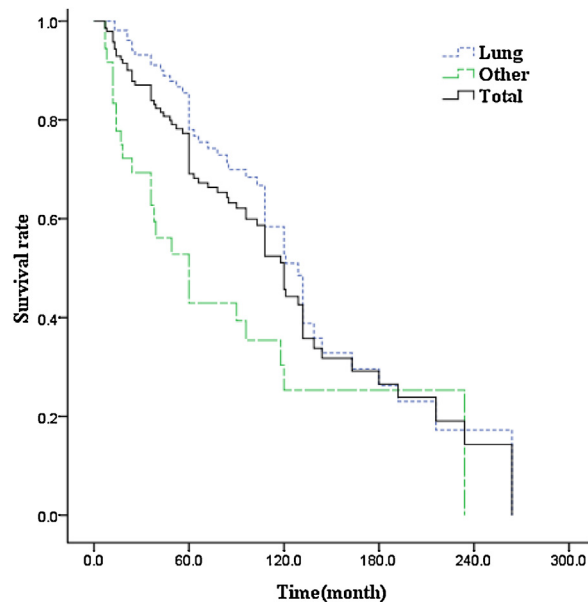


Fig. 2. Survival rates among 145 patients with salivary adenoid cystic carcinoma (SACC) and distant metastasis by site of distant metastasis.

survival rates were 90.0%, 55.1%, and 28.2%, respectively. In contrast, the median survival time after distant metastasis to bone, liver, and cerebrum was 8 months and the 1-, 3-, and 5-year survival rates in this group were 36.7%, 28.5%, and 28.5%, respectively. The post-distant metastasis survival rates were significantly different between the pulmonary metastasis group and the other distant metastasis group ( $P = 0.005$ ).

#### Survival rates of different treatment groups

In our study, only 25 (17.2%) patients with distant metastasis of SACC underwent treatment. Two patients underwent a pulmonary lobectomy. Ten patients received radiotherapy with iodine-125 implant brachytherapy and external-beam radiotherapy. Ten patients received chemotherapy. The combination of radiotherapy and

Table 2. Survival rates after the diagnosis of distant metastasis in patients with salivary adenoid cystic carcinoma (SACC).

	Patients, <i>n</i>	Survival rate (%)			Median survival time, months (95% CI)	<i>P</i> -value*
		1-year (95% CI)	3-year (95% CI)	5-year (95% CI)		
Distant metastasis sites						<0.005
Lung	108	90.0 (83.7–96.3)	55.1 (42.7–67.4)	28.2 (15.3–41.1)	44 (33–55)	
Other organs	37	36.7 (20.4–52.9)	28.5 (12.4–44.6)	28.5 (12.4–44.6)	8 (3–13)	
Distant metastasis treatment						0.478
No	120	72.9 (64.3–81.5)	45.6 (34.0–57.2)	29.9 (17.8–42.0)	36 (27–45)	
Yes	25	82.0 (67.9–96.1)	54.7 (32.2–77.2)	13.7 (0–35.6)	44 (28–59)	
Total	145	75.3 (67.7–82.9)	47.1 (36.7–57.5)	26.5 (15.7–37.3)	36 (29–43)	

CI, confidence interval.

\*Log-rank test, two-sided.

chemotherapy was adopted for three patients. The survival rates of the patients who received treatment for distant metastasis were not significantly different from those of the patients who did not receive treatment for distant metastasis, as shown in Table 2 ( $P = 0.478$ ).

## Discussion

SACC is characterized by the persistent and indolent growth of the primary tumours and a high incidence of haematogenous metastasis, which ranges from 8.5% to 58.8%.<sup>1–8</sup> The lung is the predominant anatomical site of distant metastasis. However, SACC can also metastasize to bone, liver, the cerebrum, and to multiple organs.<sup>1,3,6,9–11</sup> van der Wal et al. reported that 28 of 51 patients with SACC developed distant metastasis, an incidence of 54.9%. Among those 28 patients, there were 12 (42.8%) who developed pulmonary metastasis alone, five other patients (17.8%) who had metastasis to bone, cerebrum, thyroid, or spleen, and 11 patients (39.3%) who had metastases to the lung and other organs.<sup>1</sup> In the present study, among 467 SACC patients with available clinicopathological and follow-up information, 145 (31.0%) had distant metastases, in accordance with the literature. The lung, again, was the predominant organ of distant metastasis (108 patients; 74.5%), followed by bone (10 patients), liver (five patients), cerebrum (three patients), and multiple organs (19 patients). Not all the distant metastases were confirmed histopathologically, although the circumstantial evidence for the diagnosis was strong. The lungs should be routinely checked upon physical examination of patients with SACC to determine whether distant metastasis disease has developed during the follow-up period. At the same time, more attention should be paid to looking for distant metastasis in bone, liver, cerebrum, and

multiple organs. When necessary, bone scanning, CT, or positron emission tomography (PET)-CT should be considered to detect distant metastasis as early as possible.

The median distant metastasis interval was 48 months in the present study. Eighty percent of the patients in our study developed distant metastasis within 8 years after the diagnosis of SACC. However, 20% of patients developed distant metastasis from 8 to 20 years after the diagnosis of SACC. Sung et al.<sup>9</sup> reported that in 46 patients with SACC, the median distant metastasis interval was also 48 months after the initial treatment of SACC. Matsuba et al.<sup>15</sup> reported that distant metastasis can occur more than 10 years after the initial treatment. The above studies show that the predominant characteristics of SACC are different from SCC of the head and neck region. Eighty-four percent of patients with SCC developed distant metastasis within 2 years of the initial diagnosis.<sup>16</sup> Because patients with SACC can develop distant metastases more than 8 years after their initial treatment, patients should be followed for a long time and further research should be done to evaluate easily administered chemotherapy drugs with few side effects as therapies to prevent distant metastases.

There is an association between distant metastasis of SACC and the location of primary tumours.<sup>3,4,9,13</sup> In the present study, when the primary tumours were located in the submandibular gland or at the base of the tongue, maxillary sinus, or lip, there was a higher rate of distant metastasis, as also reported in the literature.<sup>3,13,17–19</sup> In the maxillary sinus, ACC was occult and usually appeared as advanced disease with infiltration of the bone and surrounding tissue; this feature made radical resection difficult, which might be an important reason for the high distant metastasis rate.<sup>20</sup> Patients with lip SACC had a higher distant metastasis rate.

These patients had a long follow-up, with a median period of 105 months. On the other hand, a tumour of the lip is easy to find and resect radically. Therefore the patient with lip SACC could survive for a long time. This is possibly the reason why the patients with lip SACC had a high incidence of distant metastasis.

Distant metastasis of SACC occurs irrespective of complete control of the tumour at the primary site.<sup>9,21</sup> Many patients who did not experience recurrent tumour growth at the primary site did develop distant metastasis. In the study of Sung et al.,<sup>9</sup> half of the 46 patients with distant metastasis of SACC had no recurrent tumours at the primary site. However, in other studies, the distant metastasis rate was found to be related to the recurrence of SACC at the primary site.<sup>3,15</sup> The distant metastasis rates reported by Spiro<sup>3</sup> were 50% for patients with recurrent tumours and 33% for patients without recurrent tumours. Similarly, in the study of Matsuba et al.,<sup>15</sup> the distant metastasis rates were 74% for patients with and 33% for patients without recurrent tumours. In our study, the distant metastasis rates were 35.5% and 26.3% for patients with and without recurrent tumours, respectively. It seems that radical surgery to resect the primary tumour might be more effective, because the patients with local recurrent SACC were more prone to develop distant metastasis, and when surgical margins are positive, postoperative radiotherapy to control local recurrence is advisable.

The incidence of distant metastasis in SACC is also related to the clinical stage of the primary tumour. The larger the tumour was, the higher the distant metastasis rate was. A higher risk of distant metastasis is associated with advanced-stage SACC.<sup>3,9,15,22</sup> In the present study, the distant metastasis rates were 23.9%, 28.2%, 38.8%, and 38.6%, respectively, for patients with T1–T4 stage tumours. The biological characteristics of ACC

are different from those of SCC. For head and neck SCC, in the large sample analyses of Garavello et al.<sup>23</sup> and Leon et al.,<sup>24</sup> the distant metastasis rate was low (9.2–9.5%) and distant metastasis usually occurred in the advanced-stage patients. However, for SACC, the distant metastasis rate was high, and more than 20% of patients with early-stage tumours developed distant metastasis in our series. Bhayani et al.<sup>11</sup> also reported that of 60 patients who received treatment for clinical stages I and II ACC of the major salivary glands, 20% developed distant metastasis over the course of their follow-up. Therefore, even for patients who have early-stage SACC, it is advisable to routinely examine the whole body during follow-up for evidence of distant metastases.

There is a close correlation between histological type and the occurrence of distant metastasis for patients with SACC.<sup>6,10,11,15,17</sup> Our analysis showed that the distant metastasis rates were 47.7%, 29.9%, and 27.3% for patients whose tumours were of the solid subtype, cribriform type, and tubular type, respectively. Because patients with solid SACC were especially likely to have distant metastases, they are the most important candidates for further surveillance and preventative treatment.

Different researchers have reported different survival rates for patients with SACC. The noticeable characteristics of SACC were that the short-term survival rate was high and that the long-term survival rate continued to decline with the prolongation of the follow-up.<sup>17,25–27</sup> In Spiro's<sup>26</sup> study involving 275 SACC patients, the 5-, 10-, 15-, and 20-year survival rates were 70%, 50%, 40%, and 35%, respectively. Our analysis showed the 5-, 10-, 15-, and 20-year cumulative survival rates to be 79.5%, 58.3%, 43.8%, and 32.1%, respectively. The characteristics were markedly different from those of oral SCC.<sup>16,23,24</sup>

Distant metastasis is an important prognostic factor for survival with SACC. The overall survival rate of patients with distant metastasis has been reported to be significantly lower than that of patients without distant metastasis.<sup>3,9,11</sup> Spiro<sup>3</sup> reported 5- and 10-year overall survival rates of 88% and 72%, respectively, for patients without distant metastasis, and 76% and 48%, respectively, for patients with distant metastasis. In the present study, the patients with distant metastasis had significantly lower survival rates than patients without distant metastasis, both in the short-term and long-term. The 5-, 10-, 15-, and

20-year survival rates were 69.1%, 45.7%, 26.5%, and 14.3%, respectively, for patients with distant metastasis, compared with 85.6%, 67.4%, 57.6%, and 50.4%, respectively, for patients without distant metastasis. More than half of the patients with distant metastasis died within 10 years after the diagnosis of SACC. More than half of the patients without distant metastasis survived more than 20 years after the diagnosis of SACC. Therefore, it is crucial for prevention and treatment of distant metastasis to improve the survival of SACC patients.

According to the research of Sung et al.,<sup>9</sup> survival times ranged from 1 month to 149 months (median 38 months) after the diagnosis of distant metastasis for SACC patients, and the 2- and 5-year survival rates were 69% and 35%, respectively, after the diagnosis of distant metastasis. In the study of Matsuba et al.,<sup>15</sup> the median survival time of SACC patients after the diagnosis of distant metastasis was 4 years. In the present study, the median survival time after the diagnosis of distant metastasis was 36 months. The 1-, 3-, and 5-year cumulative survival rates after the diagnosis of distant metastasis were 75.3%, 47.1%, and 26.5%, respectively. By contrast, nearly 90% of patients with head and neck SCC died within 1 year after diagnosis of distant metastasis, and almost none of them survived longer than 2 years.<sup>16</sup> All the above studies have indicated that patients with distant metastasis of SACC can survive for a longer time than patients with distant metastasis of head and neck SCC. The distant metastasis of SACC grew slowly in some patients. If the primary tumour can be radically cured, the attitude to treatment of the disease should be positive, even though pulmonary metastasis may occur.

Depending on the site at which distant metastasis occurred, patients had a different prognosis. For example, the patients with a single pulmonary metastasis had a better prognosis.<sup>3,9</sup> According to our study, the median survival time after distant metastasis in patients with isolated lung metastasis was 44 months and the 1-, 3-, and 5-year survival rates were 90.0%, 55.1%, and 28.2%, respectively. However, the median survival time after distant metastasis to bone, liver, and cerebrum was 8 months and the 1-, 3-, and 5-year survival rates in this group were 36.7%, 28.5%, and 28.5%, respectively. These findings indicate that the survival rate for SACC patients with a single lung metastasis is greater than for SACC patients with metastases to other

organs. More attention should be paid to patients with bone, liver, and cerebral metastases.

There is currently no effective treatment for distant metastasis of SACC.<sup>9,10</sup> In our study, only 25 patients with distant metastasis of SACC underwent treatment. Surgery, iodine-125 brachytherapy, external-beam radiation, chemotherapy, and chemoradiotherapy were used. There was no statistically significant difference in survival between patients with and without treatment of distant metastases. The development of more effective treatments for distant metastasis of SACC should be explored to further improve patient survival and prognosis.

Both a review of the literature and our own clinical experience with a large patient sample lead us to conclude that distant metastasis may develop more than 8 years after treatment of patients for SACC. Even patients who presented with early-stage SACC and who had no recurrence of the primary tumour sometimes developed distant metastasis. Some patients with pulmonary metastasis survive for longer than 5 years. The biological characteristics of adenoid cystic carcinoma were different from those of squamous cell carcinoma. At present, the effectiveness of treatment for distant metastases is not ideal and further research is needed.

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### Competing interests

None.

### Ethical approval

Not required.

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