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Salivary duct carcinoma: A prospective multicenter study of 61 cases of the Réseau d'Expertise Français des Cancers ORL Rares

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Abstract

Background: The purposes of this study were to describe the characteristics of a prospective multicenter series of patients with salivary duct carcinoma and to investigate prognostic factors.

Methods: Patients included for salivary duct carcinoma between 2009 and 2016 in the Réseau d'Expertise Français des Cancers ORL Rares (REFCOR) database were selected. Immunohistochemical analyses were performed.

Results: Sixty-one patients were included in this study. The primary site was the parotid gland in 90% of the cases. Fifty-seven percent of the tumors were stage IV, 65% of patients had lymph node involvement, and 10% had metastases. Tumors showed androgen receptor (89%) and human epidermal growth factor receptor 2 (HER2)/neu (36%). Ninety-four percent of patients underwent surgery and 86%

had postoperative radiotherapy. Six patients were treated with targeted therapies. The 3-year overall survival (OS) was 74% and the 3-year disease-free survival (DFS) was 44%. Tumor stages III to IV reduced DFS (hazard ratio [HR] 4.3; P = .04). The N2/3 class reduced distant metastasis-free survival (HR 7.3; P = .007).

Conclusion: Salivary duct carcinoma prognosis is poor and is correlated with tumor stage and lymph node classification. Androgen receptor and HER2/neu should be tested as they offer the possibility of targeted therapies.

KEYWORDS

androgen receptors, human epidermal growth factor receptor 2 (HER2)/neu, prognostic factors, salivary duct carcinoma, targeted therapies

1 | INTRODUCTION

The Réseau d'Expertise Français des Cancers ORL Rares (REFCOR) is a national network, initiated in 2008, with funding from the French National Institute of Cancer. Access to care is organized through regional reference centers for malignant tumors of salivary gland, sinusonasal tract, ear, as well as for nonsquamous cell carcinoma tumors of the upper aerodigestive tract. Epidemiological data is prospectively collected in a national database. Tumor samples are collected in regional tumor banks. Expert pathologists review the difficult cases. Clinical trials are centralized and inclusion can be offered during bimonthly national multidisciplinary clinics.

Therefore, the REFCOR has a database on salivary duct carcinoma, a rare salivary gland malignancy, which resembles high-grade breast ductal carcinoma. This entity represents 3%-5% of the salivary gland malignancies.[1,2] Its structure is that of a high-grade ductal carcinoma with an invasive component and an intraductal component.[3] Salivary duct carcinoma expresses human epidermal growth factor receptor 2 (HER2)/neu in 15%-40% of the cases[4] and androgen receptors in most cases.[5–7] This neoplasm occurs typically in men during the sixth decade of life[5–11] and its main location is the parotid gland.[5–13]

Salivary duct carcinoma is an aggressive neoplasm. Regional lymph node metastases are frequent at the time of diagnosis, in 54%-82% of the cases according to the previous studies.[5,8,10,11,13–27] Locoregional and distant recurrence rates are high: local recurrence arises in 11%-48% of the cases, regional recurrence arises in 16%-26% of the cases, and distant recurrence arises in 18%-63% of the cases in the literature.[8,10,11,13,16–20,22–27]

The prognosis of this disease is poor. Five-year overall survival (OS) is estimated between 41% and 55% in the literature.[11,24–27] In the study of Jaehne et al,[8] about 50 cases of salivary duct carcinoma, mean 5-year survival rate, was 56.2 months. Disease-specific mortality rate ranges between 33% and 58% according to the previous studies.[16,21–23] In the study of Luk et al,[5] of 23 cases of salivary duct carcinoma, the 5-year disease-free survival (DFS) rate was 36%, and the 5-year disease-specific survival was 43%. The assessment of prognostic factors is, therefore, essential.

The standard treatment of salivary duct carcinoma is currently the same as for any high-grade salivary gland carcinoma: a surgery with cervical lymph node dissection and adjuvant radiotherapy. In case of recurrence and/or metastasis, there is currently no specific systemic treatment. The expression of androgen receptors and HER2/neu, or the discovery of alterations in other molecular pathways may provide therapeutic options. However, to validate targeted therapies for salivary duct carcinoma is a challenge because of its rarity.

The purposes of this study were to describe the clinical, histological, and therapeutic characteristics of a prospective multicenter series of 61 patients with salivary duct carcinoma, and to investigate prognostic factors for OS, DFS, and metastasis-free survival.

2 | MATERIALS AND METHODS

The study design was a prospective multicenter cohort study with inclusion of incident cases. Patients included between 2009 and 2016 were selected for salivary duct carcinoma in the REFCOR database. Time of diagnosis ranged from 2002 to 2016. Ten patients had been diagnosed for their primary salivary duct carcinoma before 2009. Data harvesting, with systematic anonymity, was performed in each hospital, either by the patient's physician or by a clinical research technician. Patients were informed and signed a consent form, according to the French Law. The TNM staging on the American Joint Committee on Cancer classification was based on clinical examination, imaging data, and histological analysis of the surgical specimen, the stage being that of the primary site. The REFCOR pathologist group advised a second histological examination and reviewed all tumor samples.

2.1 | Immunohistochemistry and in situ hybridization

The paraffin-embedded tumor samples were examined immunohistochemically for androgen receptors and HER2/neu in each center. For immunohistochemical studies, 4-μm thick sections were cut from paraffin blocks and deparaffinized.

For HER2/neu immunohistochemistry (IHC), sections were reacted with CC1 buffer (short). Then, sections were subjected to antigen retrieval (HER2/neu; Ventana Medical Systems, Tucson, AZ) for 16 minutes. Finally, slides were counterstained with hematoxylin (Ventana Medical Systems) and Bluing Reagent (Ventana Medical Systems). The intensity of HER2/neu staining was graded using a widely accepted 4-point system, as defined in the literature for breast ductal carcinoma[28]: the tumor cells were scored as 0, 1+, 2+, or 3+ for HER2/neu protein expression: 0 (negative), no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within ≤10% of tumor cells; 1+ (negative), incomplete membrane staining that is faint/barely perceptible and within >10% of tumor cells; 2+(equivocal), circumferential membrane staining that is incomplete and/or weak/moderate and within >10% of tumor cells or complete and circumferential membrane staining that is intense and within ≤10% of tumor cells; and 3+ (positive), circumferential membrane staining that is complete, intense, and within >10% of tumor cells.

The screening of HER2/neu gene amplification was performed with in situ hybridization (ISH) techniques in 7 centers.

Per the 2014 American Society of Clinical Oncology/College of American Pathologists guideline edition, HER2-positive status was diagnosed when there was evidence of protein overexpression (IHC with 3+) or gene amplification with ISH. If results were equivocal, reflex testing was performed using an alternative assay (IHC or ISH).[28]

For androgen receptor IHC, sections were reacted with CC1 buffers (short, standard, and long). Then, sections were subjected to antigen retrieval (Prep Kit 99; Ventana Medical Systems) for 44 minutes at 37°C. Finally, slides were counterstained with hematoxylin (Ventana Medical Systems) and Bluing Reagent (Ventana Medical Systems). The test was positive in case of a nuclear staining.

2.2 | Statistical analyses

Statistical analyses on OS, DFS, locoregional recurrence-free survival, distant metastasis-free survival (DMFS) were performed using R software.[29] Graphs were drawn up using the Kaplan-Meier method with the log-rank test. The P values < .05 were considered statistically significant. The date of diagnosis was the date of histological diagnosis of salivary duct carcinoma. The last follow-up date was the date of the last consultation.

3 | RESULTS

3.1 | Study population

Between 2009 and 2016, 61 patients with histologic diagnosis of salivary duct carcinoma were included in the REFCOR database. They came from 18 hospital centers.

Centers were asked for updating and providing missing data. The response rate was poor on 3 main points: immunohistologic data were collected for only 60% of the cases (37/61), precise treatment data were collected for only 84% of the cases (51/61), and follow-up data were collected for only 72% of the cases (44/61).

The median age of the cohort was 66 years (range 40-92 years) and 74% were men. Median body mass index was 25.1 (range 17.0-35.5). Thirty-eight percent of the patients were regular smokers (19/50). Alcohol abuse (>10 g per day) was infrequent (18%). General health status was good in most cases, patients having a mean Karnofsky index of 90% at diagnosis.

The primary site was the parotid gland in 51 cases (90%), the submandibular gland in 3 cases (5%), and a minor salivary gland in 3 cases (5%). Sixty-five percent of the patients had cervical lymph node involvement and 10% of the patients had metastases at diagnosis (located in the lungs, the mediastinum, or the bones). The tumor was stage IV in 57% of the cases at diagnosis. Patient characteristics are summarized in Table 1.

Histologically, the tumors resembled high-grade invasive and in situ ductal carcinoma of the breast. Data on androgen receptors expression were available for 60% of the cases (n = 37), and among these cases 89% were positive (n = 33; see Figure 1).

Data on HER2/neu expression were available for 59% of the cases (n = 36), and among these cases 36% were positive (n = 13). Immunohistochemistry for HER2/neu was positive (3+) in 12 cases, equivocal (2+) in 6 cases, and negative (1 + and 0) in 18 cases (see Figure 2). The ISH was performed in 11 positive or equivocal cases.

The screening of other makers (epithelial markers, such as cytokeratins, for example) was performed only in a few centers.

Type of treatment was known for 51 patients (84%). Sequences and techniques are shown in Table 2. Forty-eight of 51 patients (94%) underwent surgery. Resection margin quality was known for 35 of the 48 patients (73%). Among these, only 18 had negative margins on definitive histology. Only 42 of the patients with primary site resection had neck dissection. For 44 patients (86%), primary treatment included radiotherapy.

Three patients had no surgery: 2 of them underwent radiotherapy (they had initial tumoral classifications T3N2M0 and T4N1M0, respectively) and 1 of them underwent radiochemotherapy (initial classification unknown).

TABLE 1 Characteristics of 61 patients with salivary duct carcinoma

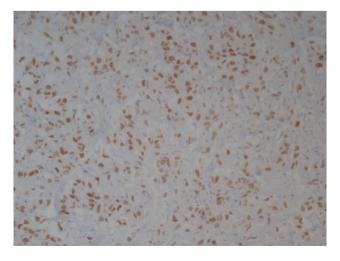| Characteristics	No. of patients	Percentage
Age, years, median (range)	66 (40-92)	
Sex		
Male	45	74
Female	16	26
Tumor site[a]		
Parotid	51	90
Submandibular gland	3	5
Minor salivary gland	3	5
TNM classification at diagnosis		
T1/T2/T3/T4[b]	6/21/14/10	12/41/27/20
N0/N1/N2/N3[c]	17/10/21/1	35/20/43/2
M0/M1[c]	44/5	90/10
Overall I/II/III/IV[d]	3/7/10/27	6/15/21/58

[a] Data available for 57 patients.
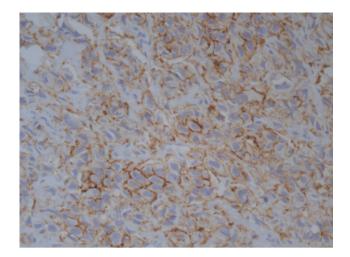[b] Data available for 51 patients.
[c] Data available for 49 patients.
[d] Data available for 47 patients.

Five patients had metastasis at diagnosis. Among them, the treatment was unknown for 2 patients. Three patients had surgery with lymph node dissection followed by conventional radiotherapy and chemotherapy (the first line was respectively cisplatin and gemcitabine, carboplatin and paclitaxel, paclitaxel and trastuzumab). These 3 patients had a progression and, therefore, benefited from other treatments.

Six patients, whose tumors expressed HER2/neu and/or androgen receptors, had targeted therapies. One patient with metastases at diagnosis was administrated trastuzumab (a humanized anti-HER2 monoclonal antibody) in first intention, in combination with paclitaxel. One patient with a relapse was administrated trastuzumab and pertuzumab in association with paclitaxel. One patient was treated with pazopanib (a vascular endothelial growth factor tyrosine kinase inhibitor) as part of the PACSA phase II

FIGURE 1 Salivary duct carcinoma with a positive expression of androgen receptors in immunochemistry. A nuclear staining is observed (brown staining; original magnification ×40) [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 2 Salivary duct carcinoma with a positive expression of human epidermal growth factor receptor 2 (3+) in immunochemistry. A strong, membranous immunostaining is observed (brown staining; original magnification ×40) [Color figure can be viewed at wileyonlinelibrary.com]

clinical trial. This patient had cancer progression and was, therefore, excluded from the trial and a treatment with trastuzumab, bicalutamide, and goserelin was administered. Three relapsing patients had androgen deprivation therapy with bicalutamide and goserelin. Partial responses or prolonged stability were observed only with androgen deprivation in tumors with androgen receptor expressions.

Follow-up data were available for only 44 patients (72%). Mean follow-up was 35.3 months; the median was 28.5 months (range 2-164 months). During follow-up, 9 patients (20%) died, 21 (48%) developed metastases, and 21 (48%) showed recurrence or local progression. The 2-year OS was 91% (95% confidence interval [CI] 0.81-1.00) and the 3-year OS was 74% (95% CI 0.59-0.93; see Figure 3). The 2-year DFS was 56% (95% CI 0.43-0.75) and the 3-year DFS was 44% (95% CI 0.30-0.66; see Figure 4). The 2-year DMFS was 67.5% (95% CI 0.55-0.83) and the 3-year DMFS was 60% (95% CI 0.43-0.80; see Figure 5).

Tumoral stages III to IV were associated with reduced DFS and DMFS (respectively, hazard ratio [HR] 4.3; P = .038 and HR 4.4; P = .036) but it was not associated with reduced OS.

There was a significant difference between the lymph node classification N0/1 and N2/3 on DMFS (HR 7.3; P = .0068) but not on OS nor on DFS (respectively, HR 0.53; P = .47 and HR 3.0; P = .085).

There was a trend for an association between positivity of HER2/neu and reduced DFS (HR 3.46; P = .06). The positivity of HER2/neu was not associated with reduced OS nor reduced metastasis-free survival.

4 | DISCUSSION

Our cohort of salivary duct carcinomas is one of the most important in recent literature. The clinicoepidemiological

TABLE 2 Treatment strategy

	No. of patients	Percentage
Treatment sequence (data available for n = 51)		
Surgery → adjuvant radiotherapy	35	68
Surgery → concomitant radiochemotherapy	6	12
Excusive radiotherapy	2	4
Exclusive surgery	7	14
Exclusive concomitant radiochemotherapy	1	2
Exclusive chemotherapy	0	0
Not known (n = 10)	…	…
Lymph node dissection (data available for n = 42)		
Positive (data available for n = 35)	23	66
Capsular rupture (data available for n = 20)	16	80
Clinical N0 patients (n = 17) with positive lymph node dissection	7	41
No lymph node dissection (n = 9)	…	…
Not known (n = 10)	…	…
Radiotherapy protocol (n = 44)		
Conventional	20	46
IMRT	13	30
Hyperfractionated	1	2
Accelerated	1	2
Tomotherapy	1	2
Others	8	18
No radiotherapy (n = 7)	…	…
Not known (n = 10)	…	…
Targeted therapies (androgen deprivation therapy and/or anti-HER2/neu) (n = 6)		
First intention in metastatic patients	1	17
Second intention (locoregional relapse and/or distant metastasis)	5	83

Abbreviations: HER2, human epidermal growth factor receptor 2; IMRT, intensity-modulated radiotherapy.

data were consistent with the former studies on salivary duct carcinoma: the median age of the cohort was in the sixth decade of life and there was 74% male predominance. The primary site was the parotid gland in most cases (90%).

The screening of androgen receptors and HER2/neu was inconsistent in our study, as these data were collected for only 60% of the cases (37/61). However, these immunohistological data are essential on several levels. They guide a difficult histological diagnosis on salivary gland carcinoma, as the positivity of androgen receptors is a main argument for salivary duct carcinoma. These data are also important regarding prognosis and treatment.

We studied prognostic factors for OS, DFS, and DMFS. Tumoral stages III to IV were statistically associated with reduced DFS and metastasis-free survival.

In our study, there was an association between lymph node classification N/1 versus N2/3 at diagnosis and reduced
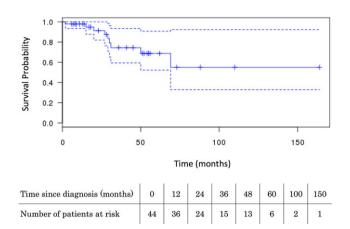

FIGURE 3 Overall survival curve in our cohort of patients with salivary duct carcinoma. The non-dotted line represents the survival probability and the dotted lines represent the 95% confidence interval [Color figure can be viewed at wileyonlinelibrary.com]

DMFS (HR 7.3; $P = .0068$). An association between survival and lymph node metastasis in salivary duct carcinomas was described in previous studies: lymph node involvement was significantly associated with reduced OS,[7,11,27,30] reduced DFS,[31,32] reduced disease-specific survival,[27,33] reduced progression-free survival (PFS),[27] and reduced DMFS.[27,31] We probably lacked statistical power to highlight the same result.

We described a trend for an association between positivity of HER2/neu and reduced DFS (HR 3.46; $P = .06$). Jaehne et al[8] concluded, in their study on 50 salivary duct carcinomas, that expression of HER-2/neu was statistically linked to early local disease recurrence, distant disease metastasis, and survival rates. In 3 other studies (about 32, 28, and 75 patients, respectively), no statistical association was found between the positivity of HER2/neu and survival.[9,30,31] Therefore, further studies with a greater number of patients, to prevent a lack of statistical power, are required to confirm whether the positivity of HER2/neu is a prognostic factor or not.
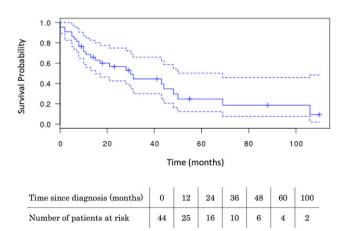

FIGURE 4 Disease-free survival curve in our cohort of patients with salivary duct carcinoma. The non-dotted line represents the survival probability and the dotted lines represent the 95% confidence interval [Color figure can be viewed at wileyonlinelibrary.com]

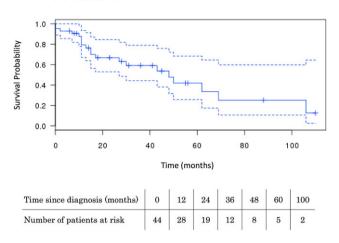| Time since diagnosis (months)	0	12	24	36	48	60	100
Number of patients at risk	44	28	19	12	8	5	2

FIGURE 5 Distant metastasis-free survival curve in our cohort of patients with salivary duct carcinoma. The non-dotted line represents the survival probability and the dotted lines represent the 95% confidence interval [Color figure can be viewed at wileyonlinelibrary.com]

In most cases from our cohort, the primary treatment was a surgical tumor resection with lymph node dissection and adjuvant radiotherapy. However, only 42 of the 48 patients with primary site resections had neck dissections. The 6 remaining patients had an initial classification of cN0 (n = 5) or cNx (n = 1). Four of them had adjuvant radiotherapy and 2 others had no adjuvant treatment. Follow-up data were available for only 5 patients. One of them, having had no adjuvant treatment, had locoregional recurrence after 15 months. On the other hand, cervical lymph node dissection was performed in 17 patients with no clinical and radiological lymph node metastasis. The ratio of positive regional metastasis in the patients with cT1-4cN0 disease was 41% (7/17 patients). This ratio was even greater for the patients with cT1cN0 and cT2cN0 disease: 50% of them (4/8) had positive regional metastasis. Our data support the fact that homolateral lymph node dissection should be systematic in case of salivary duct carcinoma.

Adjuvant radiotherapy is also a main part of the treatment. Kim et al[24] studied clinical outcomes and prognostic factors of 35 patients with salivary duct carcinoma treated postoperatively with radiation. Despite a high nodal involvement rate of 74% at diagnosis, the locoregional recurrence rate was 25.7%, lower than the rate of 45%-66% reported previously.[8,10,13,17,18,20–22] Moreover, all nodal recurrence was at the level of the undissected neck or the contralateral neck. The authors suggested that aggressive treatment through neck dissection and adjuvant locoregional radiotherapy may lead to successful locoregional control, as well as a lower distant metastasis rate (37.8%). Several other studies suggested that radiotherapy delays the time of recurrence in salivary duct carcinoma.[27,34,35] However, the benefit of adjuvant radiotherapy on survival in these tumors is still discussed[33–35] and needs to be further explored.

No prospective randomized trial currently compares adjuvant radiotherapy versus adjuvant radiochemotherapy in salivary duct carcinoma. Mifsud et al,[36] in a retrospective study on 17 cases of salivary duct carcinoma, concluded that intensification with adjuvant concurrent chemotherapy did not improve outcomes on univariate survival analysis. Gilbert et al,[30] in a 20-year retrospective review of 75 cases of salivary duct carcinoma, observed no difference in OS or DFS between patients receiving radiotherapy versus radiotherapy plus chemotherapy, although regimens were not standardized. The SANTAL trial of the REFCOR/Groupe Oncologie Radiothérapie Tête Et Cou (GORTEC) started in November 2016 and is designed to compare adjuvant radiotherapy versus adjuvant radiochemotherapy in salivary gland carcinomas. This study may be able to better ascertain if the addition of chemotherapy actually affects OS or DFS in patients with salivary duct carcinoma.

In case of recurrence and/or metastasis and in case of expression of hormonal receptors, targeted therapies with androgen deprivation and/or trastuzumab were administered to 6 patients in our cohort. Partial responses or prolonged stability were observed only with androgen deprivation in tumors with androgen receptor expressions. Targeted therapies did not provide spectacular responses in our cohort of patients, suggesting that other associations of treatments may be investigated.

In the literature about androgen deprivation in recurrent and/or metastatic salivary duct carcinoma, bicalutamide ± luteinizing hormone-releasing hormone agonists resulted in partial responses and a prolongation of the PFS. However, these studies had 1 to 10 patients.[37–40] The European Organisation for Research and Treatment of Cancer 1206 trial, a phase II randomized study, is intended to evaluate the efficiency and tolerance of chemotherapy versus androgenic deprivation (with triptorelin and bicalutamide) of patients with recurrent and/or metastatic salivary gland carcinoma positive for androgen receptors. This trial started in the spring of 2016.

By analogy to the treatment of metastatic breast cancer HER-2/neu +, anti-HER-2 (trastuzumab: Herceptin or Herceptine) were tested in patients with recurrent and/or metastatic salivary duct carcinoma HER2/neu + in a few studies. Trastuzumab was administered alone or associated with paclitaxel and carboplatin or with bevacizumab and lapatinib. The results seemed to be encouraging but the series of patients were limited to between 1 and 13 patients.[41–49] Further studies are required to confirm the benefit of these treatments in patients with salivary duct carcinoma.

As genomic alterations of the PI3K/AKT/mTOR pathway occur in 19%-54% of the patients with salivary duct carcinoma,[41,50,51] anti-PI3K-targeted therapies were tested on patients with recurrent and/or metastatic salivary duct carcinoma with an alteration of this pathway. The results were also encouraging (respectively 2 and 5 patients tested).[50,52]

Pazopanib, an oral small molecule inhibitor of vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and KIT, was tested in the phase II trial

PACSA.[53] This treatment seemed promising, with a 6-month PFS rate >40%. Nevertheless, among the 63 progressive recurrent or metastatic salivary gland carcinomas of this study, only 2 were salivary duct carcinomas. Cabozantinib, a receptor tyrosine kinase inhibitor with activity against RET, was studied in 2 recurrent and/or metastatic salivary duct carcinomas by Wang et al,[41] with observed responses. Therefore, targeted therapies may still be tested in the treatment of recurrent and/or metastatic salivary duct carcinoma.

The efficacy of immunotherapy (anti-CTLA-4, anti-PD-1, and anti PDL-1) has been demonstrated for several malignancies, including head and neck squamous cell carcinoma. Ferris et al[54] studied nivolumab (an anti-PD-1 monoclonal antibody) in patients with platinum-refractory, recurrent squamous cell carcinoma of the head and neck. It resulted in longer OS than treatment with standard, single-agent therapy. Furthermore, Daste et al[55] invited the consideration of immunotherapy in a strategy for tumor treatment, not only because of its efficiency, but also because it can induce sensitivity to systemic treatment, as in their reported case of head and neck squamous cell carcinoma. To our knowledge, there is no study on immune checkpoint blockade in salivary duct carcinoma. The Dual Anti-CTLA-4 and Anti-PD1 Blockade in Rare Tumors (DART) trial started in June 2017 and includes major salivary gland carcinomas. Patients must have histologically confirmed rare cancer and/or cancer of unknown primary, and be ineligible for molecularly guided therapy.

5 | CONCLUSION

The screening of androgen receptor and HER2/neu should be systematic in case of salivary duct carcinoma. Indeed, IHC data guide a difficult histological diagnosis of salivary gland carcinoma, and they have a prognostic and therapeutic impact.

The prognostic factors for survival in our series of salivary duct carcinoma were tumor stage and lymph node classification. There was a trend for an association between positivity of HER2/neu and reduced DFS.

Regarding the treatment, in addition to the tumor resection, homolateral lymph node dissection should be systematic because of the lymphophilic character of salivary duct carcinoma. Adjuvant radiotherapy delays the time of recurrence in these aggressive tumors; its effects on survival, however, needs further explorations. Moreover, the benefits of adjuvant radiochemotherapy should be tested in prospective randomized studies.

In case of recurrence and/or metastasis with an expression of hormonal receptors, the results of targeted therapies with androgen deprivation and/or trastuzumab seem encouraging in the literature. In our study, partial responses or prolonged stability were observed only with androgen deprivation in tumors with androgen receptor expressions.

The other targeted therapies tested in our cohort did not provide spectacular responses, suggesting that other associations of treatments need to be investigated.

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