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Treatment of Locally Advanced and Metastatic Salivary Gland Cancer: A 10-year Experience of an Oncology Center in Portugal

Tratamento de Neoplasias das Glândulas Salivares Metastizadas ou Localmente Avançadas: Experiência de 10 Anos de um Centro Oncológico em Portugal

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ABSTRACT

Introduction: Scientific evidence regarding salivary gland cancer systemic treatment is limited and the therapeutic approach to locally advanced or metastatic disease is mainly based on consensus. This study aimed to evaluate treatment patterns and outcomes in patients with advanced salivary gland cancer.

Methods: We conducted a retrospective cohort study in a comprehensive cancer center in Portugal, including adult patients diagnosed with primary malignant salivary gland tumors between 2012 and 2021. Data on demographics, tumor characteristics, treatments, and outcomes were collected from institutional cancer registries and electronic medical records. The study was approved by the institutional Ethics Committee.

Results: A total of 116 patients with salivary gland cancer were identified and, of these, 45 had locally advanced or metastatic disease: 24 received systemic anti-neoplastic treatment and 21 received best supportive care. One-year overall survival in systemic anti-neoplastic treatment group was 70% (*versus* 14% in best supportive care group, $p < 0.001$) and progression-free survival was 37%. The most commonly used systemic treatment was chemotherapy (n = 29, 59%). Seven patients (14%) received androgen deprivation therapy, and two patients (4%) received other targeted therapy (olaparib and erdafitinib).

Conclusion: Systemic treatment was associated with significantly improved survival in patients with advanced salivary gland cancer. Despite the heterogeneity of therapeutic approaches, including emerging biomarker-driven therapies, clinical decision-making remains largely consensus-based. These findings underscore the need for further research to support personalized treatment strategies and guide evidence-based care.

Keywords: Molecular Targeted Therapy; Salivary Gland Neoplasms/drug therapy

RESUMO

Introdução: A evidência científica relativa ao tratamento sistémico das neoplasias das glândulas salivares é limitada e a abordagem terapêutica da doença localmente avançada ou metastática baseia-se principalmente em consensos. O objetivo deste estudo foi avaliar os padrões de tratamento e os desfechos em doentes com carcinoma das glândulas salivares avançado.

Métodos: Realizámos um estudo de coorte retrospetivo num centro oncológico em Portugal, incluindo doentes adultos diagnosticados com tumores malignos primários das glândulas salivares entre 2012 e 2021. Os dados demográficos, as caraterísticas do tumor, os tratamentos e os resultados foram recolhidos a partir dos registos oncológicos institucionais e dos registos médicos eletrónicos. O estudo foi aprovado pela Comissão de Ética institucional.

Resultados: Foi identificado um total de 116 pacientes com neoplasias das glândulas salivares e, desses, 45 tinham doença localmente avançada ou metastática: 24 receberam tratamento antineoplásico sistémico e 21 receberam os melhores cuidados de suporte. A sobrevivência global a um ano no grupo que recebeu tratamento antineoplásico sistémico foi 70% (*versus* 14% no grupo que recebeu os melhores cuidados de suporte, $p < 0,001$) e a sobrevivência livre de progressão foi 37%. O tratamento sistémico mais frequentemente utilizado foi a quimioterapia (n = 29, 59%). Sete doentes (14%) receberam terapia de privação de androgénios e dois doentes (4%) receberam outra terapêutica dirigida (olaparib e erdafitinib).

Conclusão: O tratamento sistémico foi associado a uma melhoria significativa da sobrevivência em doentes com cancro avançado das glândulas salivares. Apesar da heterogeneidade das abordagens terapêuticas, incluindo as terapias baseadas em biomarcadores, a tomada de decisões clínicas continua a ser largamente baseada em consensos. Estes resultados sublinham a necessidade de mais investigação para apoiar estratégias de tratamento personalizadas e orientar os cuidados baseados na evidência.

Palavras-chave: Neoplasias das Glândulas Salivares/tratamento farmacológico; Terapia-Alvo

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KEY MESSAGES

- Significant overall survival benefit with systemic treatment: Patients with locally advanced or metastatic salivary gland cancer (SGC) who received systemic anti-neoplastic treatment had a one-year overall survival rate of 70%, compared to only 14% in those receiving best supportive care ($p < 0.001$).
- Diversity of systemic therapies employed: The study confirmed the variety of systemic treatments used, with chemotherapy being the most common (59%), followed by androgen deprivation therapy (14%) and emerging targeted therapies such as olaparib and erdafitinib.
- Emerging role of agnostic targeted therapies: The use of agnostic targeted therapies, although limited, demonstrates the potential of biomarker-driven approaches to improve outcomes in selected patient subgroups.
- Scarce evidence guiding clinical practice: The therapeutic approach to advanced SGC remains largely consensus-based, highlighting the need for further research.
- Foundation for future investigations: This study provides important data to explore personalized therapeutic strategies, including biomarker-driven treatments, and to develop more comprehensive clinical guidelines for this rare and heterogeneous cancer population.

INTRODUCTION

Primary salivary gland tumors are a very heterogeneous entity, making their classification challenging.[1,2] The fifth edition of the World Health Organization (WHO) classification, introduced in 2022, identifies 39 salivary gland conditions grouped into four categories: non-neoplastic epithelial lesions, malignant and benign epithelial tumors and mesenchymal tumors specific to the salivary glands.[2,3] Approximately 20% of all salivary glands lesions are malignant and include 21 histologically subtypes.[1-3] This diversity results in distinct biological behaviors, influencing different treatment decisions and prognosis.[4]

Salivary gland cancers (SGC) are rare malignancies and account for 5% of all head and neck cancers.[4] They typically occur in the sixth and seventh decade of life.[5] Risk factors include history of prior head and neck cancer and cervicofacial radiotherapy (RT), industrial activity and smoking.[5] Nevertheless, only ionizing radiation is a well-established risk factor.[5] Globally, the estimated age-standardized incidence rate was 0.56 cases per 100 000, with 55 083 new cases in 2022.[6] Most SGCs are located in major salivary glands (parotid gland around 70%, submandibular gland 10% and sublingual gland < 1%).[1]

Surgery is the preferred treatment for localized SGC, with post-operative RT recommended in advanced stages.[5,7] Patients with locally advanced or metastatic (LAM) disease may receive systemic treatment, although evidence remains limited due to the rarity and heterogeneity of SGC.[5,7] Molecular profiling - using immunohistochemistry (IHC) and next-generation sequencing (NGS) - has helped identify LAM SGC patients who might benefit from targeted therapies.[8-10] Metastatic SGC is associated with a poor prognosis, with a median overall survival (OS) of 15 months and a 1-year OS of 54.5% across all subtypes.[5] For all these reasons, a multidisciplinary approach is recommended.[7]

The aim of this study was to review clinicopathologic characteristics, treatment and outcomes of a cohort of patients with major SGCs and LAM disease, treated at our comprehensive cancer center over 10 years.

METHODS

Setting and population

IPO-Porto is a highly differentiated institute, belonging to the Portuguese National Health Service and which provides specialized cancer care. It is a comprehensive cancer center, admitting around ten thousand new patients annually and providing healthcare to 50 thousand patients covering the entire cancer continuum, from diagnosis to treatment and follow-up.[11]

Study design and data collection

We identified a retrospective cohort of adult patients (age ≥ 18 years) diagnosed between 2012 and 2021 with primary malignant of major salivary gland tumors (topography codes C07-C08, according to the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems ICD-10) and any histology code from the International Classification of Diseases for Oncology ICD-O-3, except sarcomas).[12,13] Patients who participated in clinical trials were excluded from the study.

Information on demographics (sex and age), cancer (ICD-10 code, site, histological type and stage) and treatment (type, duration and response) characteristics was retrieved from the IPO-Porto Cancer Registry database and enhanced by reviewing electronic medical records (EMRs), specifically for information about the treatment response and disease progression from early stages. Vital status and date of death were assessed through the National Health Service database until 30 June 2024, allowing for a

minimum follow-up of 30 months since cancer diagnosis.

Statistical analyses

Sociodemographic, clinical and treatment characteristics are presented as counts and proportions and compared using the Chi-square test or Fisher exact test (whichever was appropriate), for categorical variables, or as median and percentiles 25 and 75 (P25 - P75) and compared using Mann-Whitney test, for continuous variables.

Overall survival (OS) was defined as the time between the date of diagnosis of LAM disease and the date of death due to any cause or to the date of censoring at the last time the subject was known to be alive. Progression-free survival (PFS) was defined as the time between the systemic treatment initiation with palliative-intent and the date of disease progression or death, whichever occurred first, and was censored at the last contact date for patients who neither have progression nor died. Survival curves were plotted using the Kaplan-Meier estimator and were compared using the log-rank test.

All analyses were performed using R version 4.1.2® (R Core Team, Vienna, Austria). Results were considered statistically significant for *p*-values less than 0.05.

Ethics

This study was approved by the local Ethics Committee of the IPO-Porto (code 101/2044). The need for patient informed consent was waived as the data comprised no unique personal identifiers and were extracted from the IPO-Porto Cancer Registry database and EMRs, and due to the retrospective nature of the study.

RESULTS

Patients and tumor characteristics

We identified 116 patients with major SGC treated in our center. Table 1 summarizes the main demographic, clinical, and treatment characteristics. The median age at diagnosis was 66 years, with seven patients (6%) under 40 years. The most common histologies were salivary duct carcinoma (n = 20, 17%), mucoepidermoid carcinoma (n = 18, 16%) and adenoid cystic carcinoma (n = 17, 15%). The parotid gland was the most frequent primary site (n = 95, 82%). Most patients (n = 93, 80%) received at least one curative-intent treatment, primarily surgery (n = 90, 78%), followed by adjuvant RT in 58 cases (50%) and adjuvant chemoradiotherapy (CRT) in six cases (5%). Adjuvant CRT was delivered in patients with advanced disease (pathological stage III-IVB). Among these, four (3%) presented perineural invasion, three (3%) presented lymphovascular invasion and two (2%) had positive surgical margins.

Disease recurrence occurred in 30 patients (26%): 12 (10%) had local recurrence, 22 (19%) had distant recurrence, and four (3%) experienced both.

Treatment group and outcomes

Among the 116 patients, 45 (39%) had LAM SGC, including 21 identified after disease recurrence [Appendix

Table 1 – Demographic and clinical characteristics of the overall population

	Overall (n = 116)
Age at diagnosis (years), **median** (P25 - P75)	66 (54 - 74)
Sex, n (%)	
Male	63 (54)
Female	53 (46)
Stage at diagnosis*, n (%)	
I	21 (18)
II	27 (23)
III	26 (22)
IVA	22 (19)
IVB	6 (5)
IVC	14 (12)
Primary tumor site, n (%)	
Parotid gland	95 (82)
Submandibular gland	20 (17)
Sublingual gland	1 (1)
Tumor histology, n (%)	
Salivary duct carcinoma	20 (17)
Mucoepidermoid carcinoma	18 (16)
Adenoid cystic carcinoma	17 (15)
Carcinoma, NOS	13 (11)
Squamous cell neoplasm	13 (11)
Acinar cell carcinoma	10 (9)
Adenocarcinoma, NOS	6 (5)
Epithelial-myoepithelial carcinoma	5 (4)
Small cell neuroendocrine carcinoma	4 (3)
Basal cell adenocarcinoma	3 (3)
Oncocytic carcinoma	3 (3)
Others	4 (3)
Curative-intent therapy, n (%)	
Yes	93 (80)
No	23 (20)
Recurrence (local and/or distant), n (%)	
Yes	30 (26)
No	86 (74)

NOS: not otherwise specified; P25: percentile 25; P75: percentile 75.
*: According to AJCC 8th Edition

1, Fig. 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22800/15734)]. Of these, 21 (47%) received only best supportive care (BSC group) and 24 (53%) received systemic treatment (ST group). Table 2 summarizes the main demographic, clinical, and treatment characteristics of both groups.

Significant differences were observed between the groups in terms of age, prior curative-intent treatment, and recurrence. Patients in the ST group patients were younger, more likely to have received prior treatment with curative intent and had a higher recurrence rate compared to those in the BSC group (p = 0.001, p = 0.024 and p = 0.011, respectively).

In the BSC group, the most common histologies were carcinoma not otherwise specified (NOS) and adenocarcinoma NOS (both n = 5, 24%). In the ST group, salivary duct carcinoma was the most frequent (n = 9, 38%). In both groups, the parotid gland was the most common primary site – 16 patients (76%) in the BSC group and 21 (88%) in the ST group.

By the end of follow-up, 20 deaths (83%) were recorded in the ST group and all 21 patients (100%) in the BSC

Table 2 – Comparison of demographic and clinical characteristics of patients with locally advanced or metastatic disease and receiving systemic therapy or best supportive care

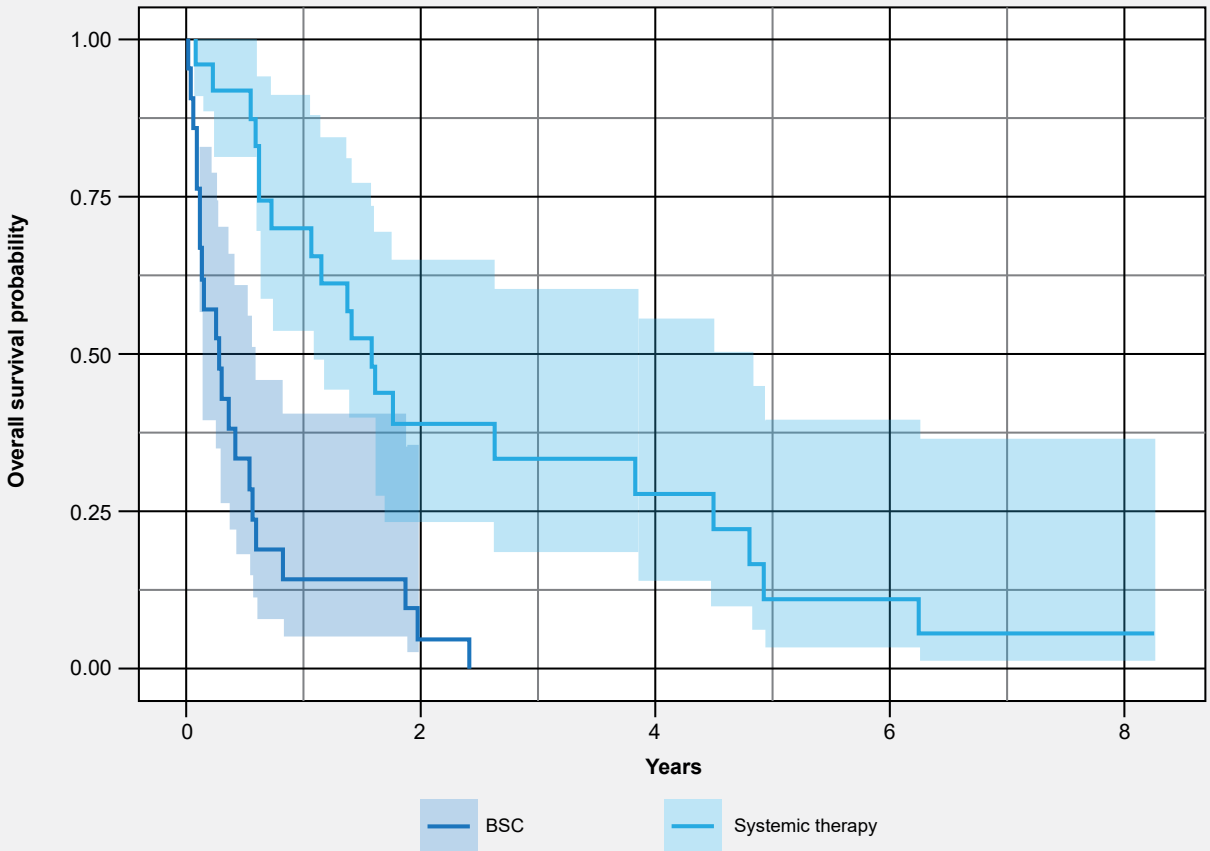
	Best supportive care (n = 21)	Systemic therapy (n = 24)	*p*-value
Age at diagnosis (years), **median** (IQR)	79 (66 - 87)	66 (56 - 71)	< 0.001
Sex, n (%)			
Male	11 (52)	17 (71)	0.334
Female	10 (48)	7 (29)	
Cancer stage at diagnosis*, n (%)			
II	1 (5)	1 (4)	0.725
III	4 (19)	5 (21)	
IVA	5 (24)	10 (42)	
IVB	3 (14)	2 (8)	
IVC	8 (38)	6 (25)	
Primary tumor site, n (%)			
Parotid gland	16 (76)	21 (88)	0.250
Submandibular gland	5 (24)	2 (8)	
Sublingual gland	0 (0)	1 (4)	
Tumor histology, n (%)			
Carcinoma, NOS	5 (24)	5 (21)	0.274
Adenocarcinoma, NOS	5 (24)	1 (4)	
Salivary duct carcinoma	4 (19)	9 (38)	
Squamous cell neoplasm	3 (14)	2 (8)	
Small cell neuroendocrine carcinoma	2 (10)	2 (8)	
Mucoepidermoid carcinoma	1 (5)	1 (4)	
Adenoid cystic carcinoma	0 (0)	3 (12)	
Acinar cell carcinoma	0 (0)	1 (4)	
Others	1 (5)	0 (0)	
Prior curative-intent treatment, n (%)			
Yes	7 (33)	18 (75)	0.012
No	14 (67)	6 (25)	
Recurrence, n (%)			
Yes	6 (29)	17 (71)	0.011
No	15 (71)	7 (29)	

NOS: not otherwise specified; P25: percentile 25; P75: percentile 75.
*: According to AJCC 8th Edition

group had died. Figure 1 shows a higher one-year overall survival (OS) in the ST group than in the BSC group [70%, 95% confidence interval (95% CI): 53% - 91% *vs* 14% (5% - 41%), $p < 0.001$]. The corresponding age- and stage-adjusted HR (95% CI) for the BSC group was 6.10 (2.54 - 14.67) [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22800/15734)]. Male patients and patients diagnosed with cancer of parotid gland showed a significantly higher mortality [age-and stage-adjusted HR = 5.62 (2.00 - 15.78) and age-and stage-adjusted HR = 5.92 (2.31 - 15.17), respectively]. Absence of prior curative-intent treatment was associated with significantly higher mortality [HR = 9.98 (1.71 - 58.18)], as well as absence of disease recurrence [age-and stage-adjusted HR = 8.12 (1.79 - 36.89)]. Even though some differences in mortality were observed in other subgroups, the estimates did not remain statistically significant following adjustment for age and stage (Table 2).

Systemic treatment and outcomes

In ST group, 22 patients (92%) had metastatic disease and two patients had local recurrence. The most common sites of metastases were the lungs (n = 12, 50%), followed by non-locoregional lymph nodes (n = 10, 42%) and bone (n = 9, 38%) [Appendix 1, Table 2 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22800/15734)]. Five patients (21%) had metastases in three or more locations [Appendix 1, Table 2 (Appendix 1:



	BSC				
At risk	21	1	0	0	0
Events	0	20	21	21	21
	Systemic therapy				
At risk	24	7	5	2	1
Events	0	14	16	19	20

Figure 1 – Overall survival probability in best supportive care and systemic treatment groups
BSC, best supportive care

https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22800/15734)].

Immunohistochemistry analyses of androgen receptor (AR) and HER2 were performed in 12 (50%) and 11 (46%) patients, respectively [Appendix 1, Table 3 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22800/15734)]. Next-generation sequencing analysis was conducted in 11 patients (46%), identifying targetable mutations in eight patients (33%) [Appendix 1, Table 3 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22800/15734)]. Two patients (8%) had a splice site alteration in AR-V7 in the AR gene.

A total of 49 systemic treatments were administered across up to seven lines. The median number of treatment lines was two (interquartile range 1 - 3) and six patients (25%) received at least three lines. Chemotherapy was the most frequently used treatment (n = 39, 80%), with platinum-based regimens preferred (n = 29, 59%) (Table 3). Monotherapy chemotherapy was used in 10 patients (20%). Androgen deprivation therapy (ADT) was chosen in seven patients (14%). Two patients received other targeted therapy: one received olaparib (2%) and another erdafitinib (2%).

Regarding best overall response, four (8%) achieved partial response (PR) and 28 (57%) had stable disease (SD) (Table 3). Eight patients (16%) had disease progression (DP) in the first disease response evaluation.

The one-year progression free survival (PFS) in ST group was 37% (Fig. 2).

DISCUSSION

In this study, we reviewed our 10-year experience in managing SGC. Most patients received upfront curative-intent treatment with surgery, followed or not by RT, in line with current guidelines.[6,7] However, some patients in our cohort received adjuvant concurrent CRT, which is not routinely recommended.[6,7,9] Retrospective data suggest that adjuvant concurrent CRT may improve locoregional control, although its impact on OS remains unclear.[14-17] Clinical trials in this setting are ongoing.[18]

Our recurrence rate (26%) was lower than most reports in the literature, which typically describes rates around 50%.[4,19] However, it aligns with findings from another Portuguese retrospective study, likely due to similarities in patient population and histological subtypes.[20]

In the LAM SGC subgroup, patients in the BSC group were significantly older than those in the ST group, had received prior curative-intent therapy and experienced fewer recurrences. This may reflect a later diagnosis in the BSC group. In addition, older patients usually present greater clinical frailty and more comorbidities, which may limit the initiation of systemic antineoplastic treatment.

Absence of prior curative treatment and absence of recurrence were associated with higher mortality, possibly reflecting more aggressive biological behavior and more advanced disease at diagnosis. Male sex and parotid gland location were also associated with higher mortality, which is consistent with the literature. Male patients are more frequently diagnosed with high-grade tumors and advanced disease, which may partly explain their worse outcomes.[21]

Table 3 – Systemic treatment and response evaluation

	1st LoT	2nd LoT	3rd LoT	≥ 4th LoT	Total
Type of treatment, n (%)					
Carboplatin + paclitaxel	17 (35)	3 (6)	0 (0)	0 (0)	20 (41)
Other platinum-based schemes	6 (12)	2 (4)	0 (0)	1 (2)	9 (18)
ADT	1 (2)	2 (4)	3 (6)	1 (2)	7 (14)
Monotherapy chemotherapy	0 (0)	6 (12)	2 (4)	2 (4)	10 (20)
Olaparib	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)
CAPTEM	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)
Erdafitinib	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)
Total	24 (49)	14 (29)	6 (12)	5 (10)	49 (100)
Best overall response, n (%)					
PR	3 (6)	0 (0)	0 (0)	1 (2)	4 (8)
SD	15 (31)	8 (16)	3 (6)	2 (4)	28 (57)
DP	2 (4)	4 (8)	0 (0)	2 (4)	8 (16)
DCR	18 (37)	8 (16)	3 (6)	3 (6)	32 (65)
N/E	4 (8)	2 (4)	3 (6)	0	9 (18)
Total	24 (49)	14 (29)	6 (12)	5 (10)	49 (100)

ADT: androgen deprivation therapy; CAPTEM: capecitabine and temozolomide; DP: disease progression; DCR: disease control rate (partial response + stable disease); LoT: line of treatment; N/E: not evaluated; PR: partial response; SD: stable disease.

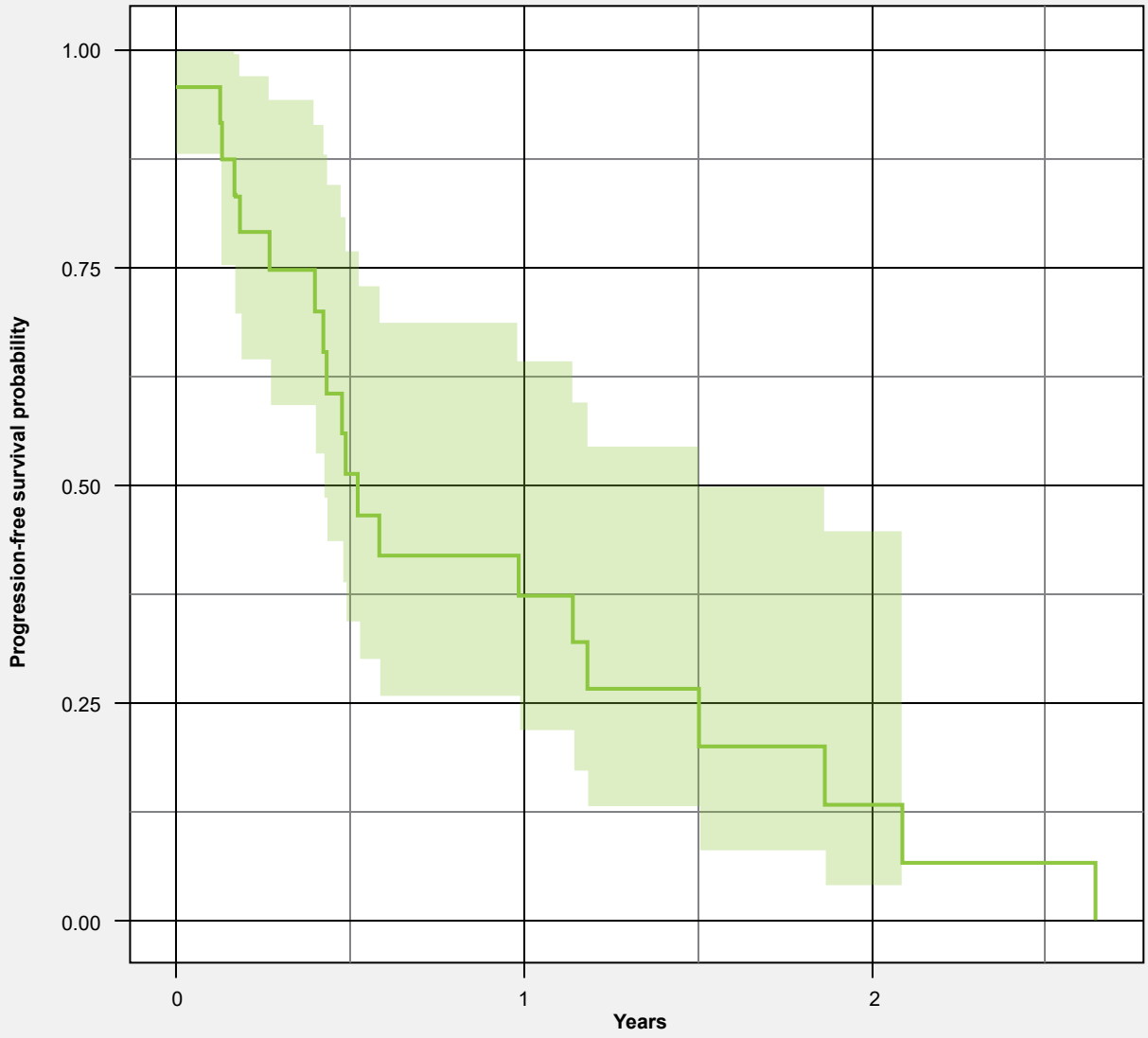


Figure 2 – Progression-free survival probability in systemic treatment group

Additionally, although many parotid tumors are benign, this site can harbor aggressive malignant subtypes such as high-grade mucoepidermoid carcinoma or carcinoma ex pleomorphic adenoma.[22] Nevertheless, the wide confidence intervals observed suggest variability or uncertainty in the estimates, likely due to factors such as small sample size or variability in the data.

Systemic treatment for advanced SGC remains challenging due to the heterogeneity of tumor subtypes and diverse biological behavior.[5] In our cohort, chemotherapy was the most frequent treatment, consistent with expert recommendations and findings from other cohort studies.[5,19] Platinum-based chemotherapy is widely used in this context, with reported objective response rate (ORR) between 27% and 50%.[18,23,24] Common regimens include platinum combined with taxane (docetaxel or paclitaxel), CAP (cyclophosphamide/ doxorubicin/ cisplatin) or platinum combined with vinorelbine, gemcitabine or fluorouracil.[5,18,23,24] Another treatment option is single-agent chemotherapy, as paclitaxel monotherapy, with lower objective response rates (0%

- 20%).[5,18,24] We reported four cases of neuroendocrine carcinoma (NEC), two patients in BSC group and two patients in ST group, both of whom received carboplatin/etoposide. Neuroendocrine carcinoma of the SGC (small or large cell carcinoma) is a rare subtype (1% - 3%) and is associated with aggressive clinical behavior.[25,26] The parotid gland is the most common location, as observed in our cohort, although NEC of the sublingual gland has also been reported.[27]

Evaluation of AR and HER2 status is recommended in advanced SGC, as both represent potential therapeutic targets.[23] Androgen receptor status should be assessed by IHC and HER2 expression by IHC and/or in situ hybridization (ISH).[23] Of note, this information was unavailable for some patients in the ST group, likely due to referral from other centers or insufficient tumor material for analysis. Furthermore, in certain cases, such as neuroendocrine carcinoma, this assessment is not clinically relevant.

For AR-positive tumors, ADT – either with combined androgen blockade (CAB) or antiandrogen monotherapy – is a treatment option in the first-line setting or beyond.[5,18] A phase two study of first-line CAB (bicalutamide and leuprorelin acetate) reported an ORR 42% and a clinical benefit rate of 75%.[28] Following ADT resistance, another phase two study showed benefit in the use of abiraterone/prednisone plus luteinizing hormone releasing hormone (LHRH) analog, with an ORR of 21% and a disease control rate of 63%.[29] To our knowledge, there are no prospective studies comparing ADT versus chemotherapy in first-line setting. However, a retrospective study including 58 patients reported similar overall-survival (OS) with both treatments but higher response rates for ADT.[30]

In HER2-positive SGC, HER2-target therapies are used both in first- or subsequent-line treatment.[18] In the first-line setting, the preferred regimen is trastuzumab combined with a taxane, with an ORR 70% reported for trastuzumab-docetaxel in salivary duct carcinoma.[5,31] Evidence supporting the addition of pertuzumab to this combination remains limited.[23] More recent data suggest that the antibody-drug conjugate T-DM1 may be more effective in this setting, with an ORR of 90%.[5,23] In our cohort, no HER2-positive cases were identified, possibly due to the exclusion of patients enrolled in clinical trials.

In addition to AR and HER2 status, tumor genomic profiling may contribute to a more precise diagnosis and a personalized treatment in LAM SGC.[8,32,33] Up to 50% of patients may present actionable mutations or fusion genes.[5] In our cohort, erdafitinib and olaparib were used as off-label treatment.[34,35] Erdafitinib was used in a case of acinic cell carcinoma harboring FGFR3-TACC3 fusion, who presented disease progression in the first imaging assessment. A 217 patient-phase two study demonstrated the clinical benefit of Erdafitinib in previously treated and advanced solid tumors with FGFR alterations (ORR 30%), which included rare cancers such as SGC (n = 5, 2%).[36] Olaparib was prescribed to a patient with a salivary duct carcinoma and an ATM mutation, who maintained stable disease for nine months. Evidence on the efficacy of PARP inhibitors in ATM-mutated tumors is conflicting. The PROfound clinical trial showed benefit of Olaparib in men with metastatic castration-resistant prostate cancer previously treated and who had alterations in the ATM gene.[37] In the other hand, a tumor-agnostic phase two study demonstrated no efficacy in the ATM cohort but it did not include any patient with SGC.[38]

Our study has some limitations. First, it was conducted at a single comprehensive cancer center in Northern Portugal, which may limit the generalizability of the findings. Additionally, the small number of patients receiving targeted therapies, combined with the heterogeneity of histological subtypes and treatment approaches, restricts the ability to draw definitive conclusions about treatment efficacy. Lastly, molecular testing was not consistently performed across the cohort, potentially underestimating the use of biomarker-driven therapies. Nevertheless, our center is the largest in the country, treating patients from diverse regions and varied sociodemographic backgrounds. Consequently, the findings likely reflect a wider real-world scenario despite these limitations. We suggest prospective studies to validate our results and further explore the efficacy of agnostic therapies in biomarker-selected subgroups.

CONCLUSION

In our cohort, patients who received exclusively BSC were older and less likely to have undergone prior curative-intent therapy. We also confirmed the heterogeneity of systemic treatments for SGC and illustrated the use of agnostic therapeutics in this setting. We believe earlier implementation of NGS in advanced SGC could improve patient outcomes by enabling access to targeted therapies and achieving better clinical responses. Based on our experience, we propose a practical therapeutic algorithm (Fig. 3) to assist clinicians in the initial management of advanced SGC. We recommend the initial evaluation of disease behavior. In cases of stable or indolent disease, surveillance is recommended until progression. For progressive disease, AR and HER2 status should be assessed. Androgen receptor-positive tumors may be treated with androgen deprivation strategies such as aLHRH combined with bicalutamide or abiraterone/prednisolone. HER2-positive tumors are managed with chemotherapy plus trastuzumab or T-DM1. For tumors AR- and HER2-negative, comprehensive tumor genetic profiling should be performed and treatment should be guided accordingly. In the absence of targetable mutations, chemotherapy remains the standard treatment option.

Given the rarity and heterogeneity of these tumors, collaborative national or multicenter registries are essential to generate robust, generalizable data. Furthermore, multidisciplinary tumor boards play a critical role in interpreting molecular results and guiding personalized treatment strategies.

Prospective studies are needed to validate our findings and further explore the efficacy of agnostic therapies in biomarker-selected subgroups.

AUTHOR CONTRIBUTIONS

ART: Study design, writing and critical review of the manuscript.

CA, CD, RS, MP, JD, CV: Study design and critical

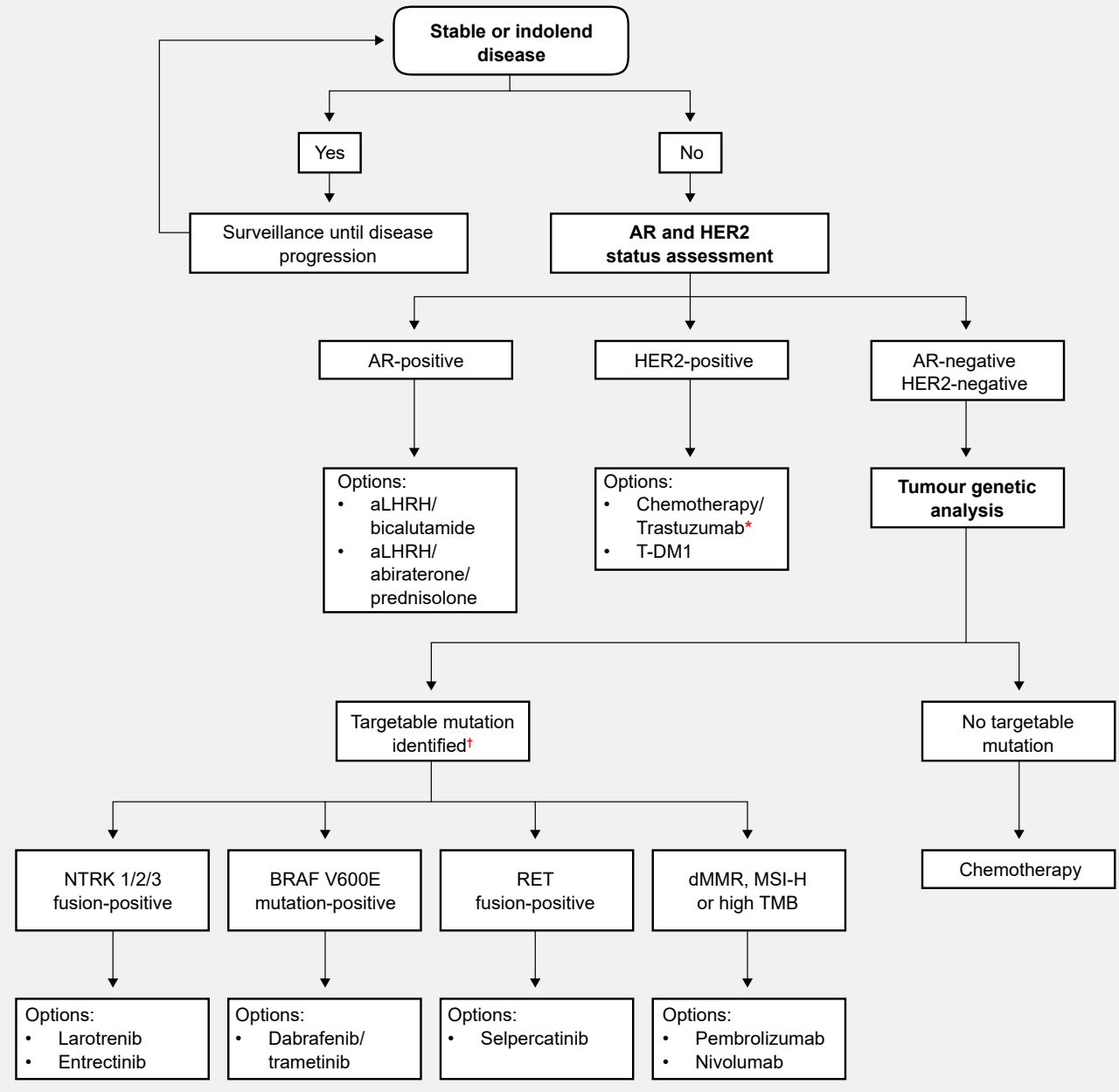


Figure 3 – Suggested systemic therapy algorithm of locally advanced or metastatic salivary gland cancers, based on our experience
AR: androgen receptor; dMMR: mismatch repair deficient; HER2: human epidermal growth factor receptor 2; MSI-H: microsatellite instability high; NTRK: neurotrophic tyrosine receptor kinase; RET: rearranged during transfection; TMB: tumor mutational burden.
* Upon disease progression, consider other anti-HER2 drugs;
† Mentioned only examples of actionable genetic alterations and other target therapies could be used (we recommend discussing these cases by a molecular tumor board).

review of the manuscript.

LLC: Statistical analysis and critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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