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# Combination Chemohormonal Therapy in Metastatic Salivary Duct Carcinoma

## Authors' Contribution:

Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

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**Patient:** Male, 68-year-old  
**Final Diagnosis:** Salivary duct carcinoma  
**Symptoms:** Bone pain • dyspnea  
**Medication:** —  
**Clinical Procedure:** Chemotherapy  
**Specialty:** Oncology

**Objective:** Rare disease**Background:** Salivary duct carcinoma (SDC) is a rare, aggressive head and neck cancer with frequent metastases. Current treatment options for recurrent or metastatic SDC include targeted anti-androgen therapy, HER2-targeted therapy, or systemic chemotherapy. We report the first use of a combination chemohormonal strategy.**Case Report:** A 68-year-old male who had never smoked with a past medical history of two-vessel coronary artery disease and systolic heart failure presented with a parotid mass and underwent surgical resection. Biopsy of the mass revealed high-grade, androgen receptor-positive and Erb-B2 receptor tyrosine kinase-2 (ERBB2)-amplified positive SDC. He subsequently received adjuvant radiation therapy. Four months after completion of adjuvant radiation therapy, recurrence with symptomatic pleural effusion and nodes, hepatic metastases, and bony metastases occurred. Due to significant symptomatic tumor, a rapid treatment response was desired. Combination chemohormonal therapy (CHT) was initiated with carboplatin area under the curve 4 and paclitaxel, 200 mg/m<sup>2</sup> in 21-day cycles along with combined androgen blockade using leuprolide, 45 mg subcutaneously every 6 months and bicalutamide, 50 mg daily. The treatment was well tolerated with fatigue as the main adverse event. Positron emission tomography-computed tomography at 3 and 6 months after treatment initiation showed good partial response. The patient experienced uveal progression after 8 months and alternate treatment was started.  
**Conclusions:** Combination CHT with carboplatin, paclitaxel, and combined androgen deprivation may be a good treatment option in androgen receptor-positive recurrent or metastatic SDC if rapid treatment response is desired. Combination chemotherapy with androgen deprivation for validation through clinical trials.**MeSH Keywords:** **Androgens • Antineoplastic Combined Chemotherapy Protocols • Carboplatin • Leuprolide • Paclitaxel • Salivary Ducts****Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/925181>

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## Background

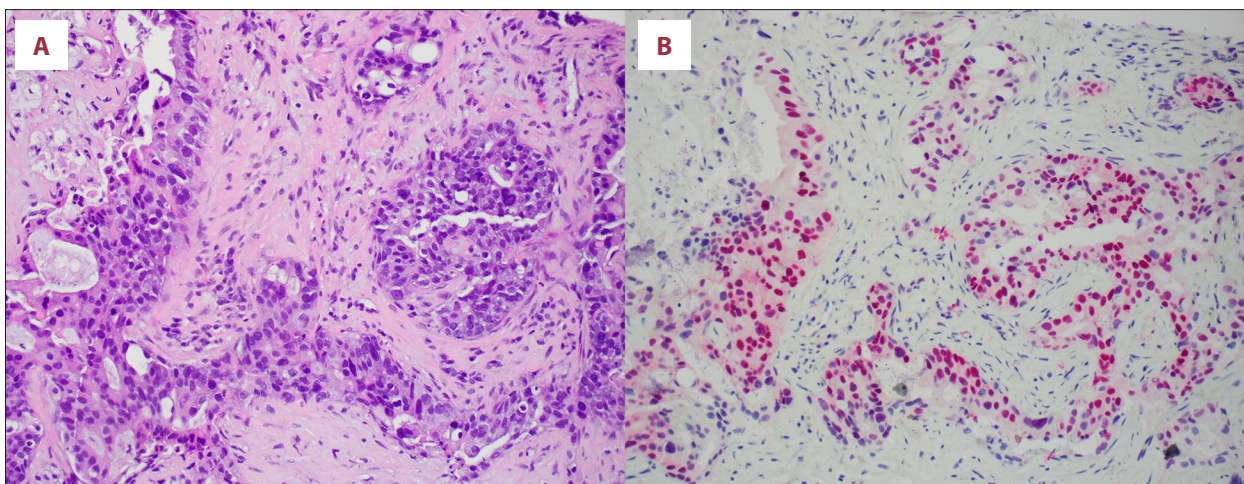
Salivary duct carcinoma (SDC) is a rare, aggressive histologic subtype of salivary gland carcinoma (SGC) with a predilection to present as locally advanced disease and to undergo early metastasis [1]. Prognosis of metastatic disease is poor with median overall survival of only 15 months [1]. It has histologic resemblance to invasive ductal carcinoma of the breast and commonly expresses androgen receptor (AR) in up to 79% of cases and human epidermal growth factor receptor 2 (HER2) overexpression or ErbB receptor tyrosine kinase-2 (ErbB-2) amplification in 25% of tumors [2]. Although there is no standard treatment for SDC, current treatment options for recurrent or metastatic SDC utilize chemotherapy, anti-HER2-targeted therapy, or antiandrogen therapy. Common systemic therapy options have included anthracycline or platinum-based combination or single-agent chemotherapy with response rates between 20% and 60% [3,4]. Similarly, antiandrogen hormonal therapies have been used for AR-positive tumors with response rates between 20% and 65% [5]. Herein, we present the first reported case of metastatic SDC treated with combination chemohormonal therapy (CHT).

## Case Report

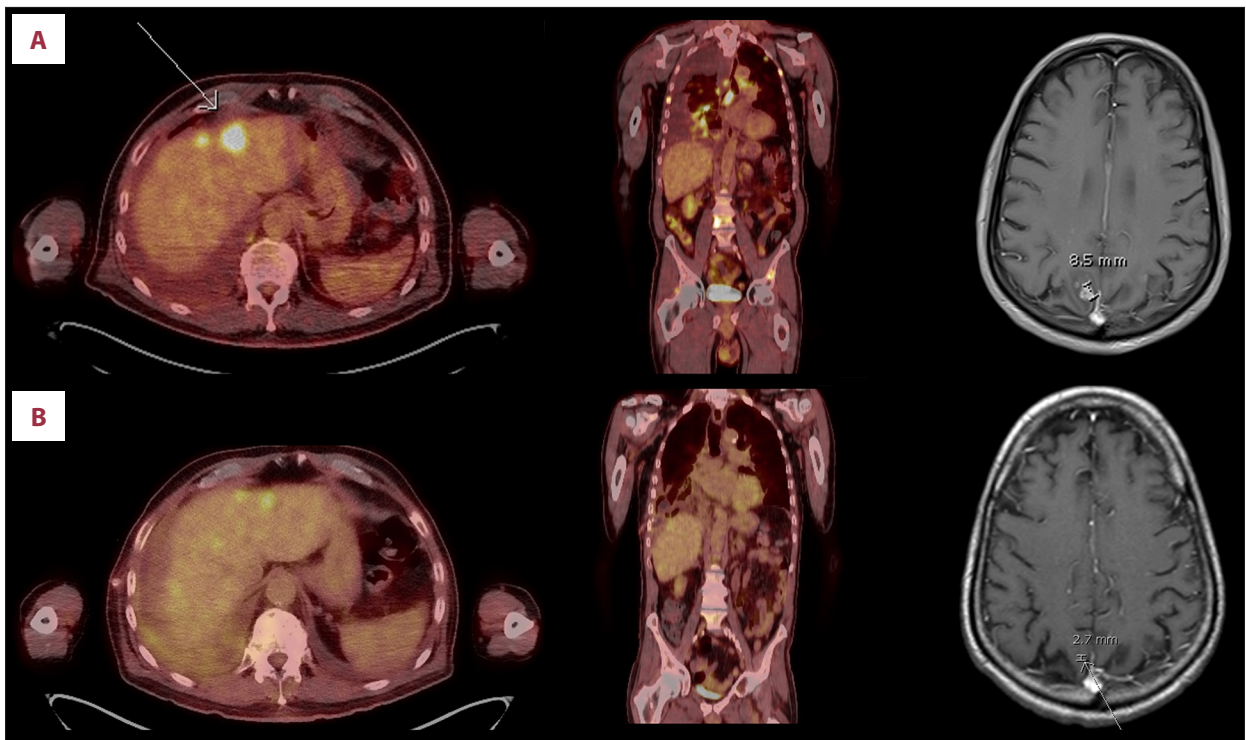
A 68-year-old male who had never smoked with normal performance status and a history of two-vessel coronary artery disease and systolic heart failure presented with a left parotid mass. Surgical resection with cervical lymph node dissection showed 3.5-cm high-grade SDC with multiple positive margins and 12/29 nodes positive for metastasis with extracapsular extension to the stratified muscle (pT4aN3b). The patient subsequently underwent 66 Gray of adjuvant radiation over

33 fractions. Four months after completing adjuvant therapy, a surveillance computed tomography (CT) scan revealed multiple lung nodules, large pleural effusion, cervical adenopathy, and diffuse bony metastases of the axial and appendicular skeleton. Biopsy of a cervical node and pleural fluid revealed recurrent metastatic AR-positive SDC (Figure 1). Next-generation sequencing revealed ErbB-2 amplification. A thoracic drainage catheter was placed for symptomatic control.

Given the symptomatic large burden of disease and desire for rapid response, combination therapy was initiated with carboplatin AUC 4 and paclitaxel, 200 mg/m<sup>2</sup> in 21-day cycles along with leuprolide, 45 mg subcutaneous every 6 months and bicalutamide, 50 mg daily. During Cycle 1 of therapy, the patient developed diplopia and headache. Brain magnetic resonance imaging (MRI) revealed multiple cerebral and cerebellar metastases. He underwent 30 Gray of whole brain radiation over 10 fractions. After three cycles of therapy, a positron emission tomography (PET)/CT scan of the chest revealed partial response with decreased fluorodeoxyglucose activity of bony metastases and reduced thoracic catheter drainage. During Cycle 5, the patient was hospitalized for acute heart failure and non-ST-elevation myocardial infarction thought to be secondary to his pre-existing cardiovascular disease (CVD). He was subsequently maintained on androgen deprivation therapy (ADT) alone with continued partial response. Six months after beginning CHT, PET-CT showed further improvement of tumor burden in axial and appendicular skeletons and lungs (Figure 2). However, blurred vision after 8 months of therapy showed new uveal metastases on orbital MRI and the patient began alternate treatment for disease progression.



**Figure 1.** (A) Hematoxylin and eosin staining (20×) of salivary duct carcinoma showing ducts with cribriform pattern in a background of fibrosis. The tumor cells are markedly pleomorphic with ample eosinophilic cytoplasm. (B) Androgen receptor immunohistochemical staining with red chromogen (20×) of salivary duct carcinoma showing immunoreactivity.



**Figure 2.** (A) Pretreatment PET/CT and brain MRI showing pleural effusion, mediastinal adenopathy, and bony, liver, and cerebellar metastases. (B) PET/CT after 6 months of treatment showing good partial response to treatment with near resolution of pleural effusion, chest adenopathy, and bony metastases with shrinking of cerebellar metastasis.

## Discussion

Our patient experienced a rapid partial and sustained response to combination CHT with amelioration of his symptomatic pleural effusion, liver metastases, and bony metastasis. We developed this treatment regimen due to his tumor characteristics and desire for quick response.

Standard single-agent or combination chemotherapy regimens have low response rates with significant hematologic, cardiac, and neurologic toxicities. For those eligible, the response rates of nearly 40% have been seen with combination regimens including cyclophosphamide, doxorubicin, and cisplatin (CAP); carboplatin and paclitaxel; and carboplatin and docetaxel [5–8]. In contrast, single-agent cytotoxic chemotherapy has limited activity with response rates varying between 10% and 40% with cisplatin, doxorubicin, mitoxantrone, or vinorelbine [3,5]. Recently, targeted therapies have come to the forefront of salivary gland carcinomas for those with AR-positive, HER2-expressing, or *NTRK* gene fusion-positive tumors.

Anti-HER2 therapy has become the preferred therapy for those with HER2 overexpression or amplification of the *ErB-B2* gene [9]. The combination of anti-HER2 trastuzumab with docetaxel was found to be promising in a single-center phase II study of 57 patients that achieved an overall response rate of

70.2% with an overall survival of 39.7 months [10]. The treatment was noted to have manageable toxicity with hematologic adverse events as the most common Grade 3–4 reactions (anemia, neutropenia, and febrile neutropenia). Moreover, the MYPATHWAY Phase IIa basket trial to assess the efficacy of dual anti-HER2 therapy with trastuzumab and pertuzumab on *ErB-B2*-amplified tumors included five patients with advanced or metastatic SGC. Four of 5 patients with SGC achieved a partial response on therapy [11]. The antibody-drug conjugate ado-trastuzumab emtansine (TDM-1), has been used in the NCI-MATCH basket trial in three patients with SGC as well as a case series of seven patients with SGC by Swed et al. in which response was seen in all 10 patients between cohorts [12,13]. Unfortunately, heart failure is a potential side effect of all anti-HER2 therapies, which are contraindicated in patients with significant preexisting heart failure and could not be used for our patient due to preexisting ischemic cardiomyopathy [14].

A recent single-arm, single-institution, prospective phase II trial using combined ADT for recurrent or metastatic AR-positive SDC showed less toxicity and an overall response rate of 41.7%, similar to historical response rates with conventional chemotherapy without dose-limiting toxicity [15]. The largest retrospective cohort study of 58 recurrent or metastatic AR-positive patients found median overall survival to be 25 months in both the first-line androgen therapy and first-line chemotherapy

groups while the overall response rate favored first-line ADT in 45% versus 12% [16]. Because response to androgen blockade was reported to take months, we were concerned about whether treatment could produce improvement quickly enough, given significant respiratory decline.

While combination CHT has not been employed in SDC, it is standard of care for advanced and metastatic hormone-sensitive prostate cancer. Two large phase III randomized controlled trials, CHARTED and STAMPEDE, in advanced or metastatic prostate cancer trial showed superior safety and efficacy of combination docetaxel with androgen deprivation compared to standard-of-care androgen deprivation alone [17,18]. Androgen blockade with chemotherapy was well tolerated in prostate cancer with predominant AEs including hematologic and peripheral neuropathy. This provided evidence of safety for combining androgen blockade with cytotoxic chemotherapy.

This treatment regimen was well tolerated by our patient. His primary complaint was Grade II fatigue that he experienced after four cycles of chemotherapy. Furthermore, he was hospitalized for heart failure exacerbation during the course of treatment.

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## Conclusions

Combination CHT may be an efficacious treatment option in AR-positive recurrent or metastatic SDC requiring rapid treatment response or when anti-HER2 therapy is contraindicated. This combination strategy should be considered for validation in prospective trials.