in vivo *33*: 843-853 (2019)
doi:10.21873/invivo.11549

Carboplatin and Docetaxel in Patients With Salivary Gland Carcinoma: A Retrospective Study

TAKURO OKADA[1,2*], TAKASHI SAOTOME[3*], TOSHITAKA NAGAO[4], TATSUO MASUBUCHI[1], CHIHIRO FUSHIMI[1], TAKASHI MATSUKI[1], HIDEAKI TAKAHASHI[1], KOUKI MIURA[1], KIYOAKI TSUKAHARA[2] and YUICHIRO TADA[1*]

[1]*Department of Head and Neck Oncology and Surgery, International University of Health and Welfare Mita Hospital, Tokyo, Japan;*
[2]*Department of Otolaryngology Head and Neck Surgery, Tokyo Medical University, Tokyo, Japan;*
[3]*Division of Medical Oncology, Matsudo City Hospital, Chiba, Japan;*
[4]*Department of Anatomic Pathology, Tokyo Medical University School of Medicine, Tokyo, Japan*

Abstract. *Background/Aim: The aim of this study was to evaluate the efficacy and safety of carboplatin/docetaxel combination therapy in patients with locally advanced and/or recurrent/metastatic (LA/RM) salivary gland carcinoma (SGC). Materials and Methods: This was a retrospective analysis of 24 patients that included six patients with AR-positive salivary duct carcinoma (SDC) after progressive disease treated with combined androgen blockade (CAB). Carboplatin (AUC5) and docetaxel (70 mg/m^2) were administered for six courses every three weeks. Results: The overall response rate was 42%, the median progression-free survival was 8.4 months, and the median overall survival was 26.4 months. Among the six patients with CAB-resistant SDC, two achieved a partial response and two long-term stable disease. Grade 3/4 neutropenia and anemia were observed in 20-30% of the patients; all adverse events were manageable. Conclusion: Carboplatin/docetaxel combination therapy may be a chemotherapeutic option for patients with LA/RM SGC, and a valuable second-line chemotherapy for CAB-resistant, AR-positive SDC.*

*These Authors contributed equally to this study.

Correspondence to: Yuichiro Tada, Department of Head and Neck Oncology and Surgery, International University of Health and Welfare Mita Hospital, 1-4-3 Mita, Minato-ku, Tokyo 108-8329, Japan. Tel: +81 334518121, Fax: +81 334540067, e-mail: ytada@iuhw.ac.jp

Key Words: Salivary gland carcinoma, salivary duct carcinoma, carboplatin, docetaxel, androgen receptor, human epithelial growth factor receptor 2.

Salivary gland carcinoma (SGC) is a rare cancer that affects 1.04 per 100,000 individuals annually and accounts for 0.2% of all and approximately 8% of the head and neck cancers (1). The classification published by the World Health Organization (WHO) in 2017 includes 20 different histological types of SGC with varying biological features (2). The treatment of salivary gland tumors commonly consists of surgical resection, regardless of whether they are benign or malignant. For high-grade malignancies, postoperative radiotherapy is usually administered (3). Systemic therapy has been attempted in patients with recurrent and/or metastatic (RM) tumors, but because SGC is rare, randomized controlled studies are difficult to carry out, and no regimen capable of prolonging survival has yet been established (3, 4).

Cytotoxic chemotherapy, molecular targeted therapy, and immune checkpoint inhibitors have been used in the treatment of adenoid cystic carcinoma of the salivary glands, but all reports showed a low response rate (3-5). Recently, molecular targeted therapies, including those targeting the androgen receptor (AR) and human epithelial growth factor receptor 2 (HER2) have shown efficacy for the treatment of salivary duct carcinoma (SDC) (3, 4, 6, 7). Moreover, molecular targeted therapies tailored to genetic mutations, including the *ETV6-NTRK3* gene fusion (8, 9), *BRAF* V600E mutation (10), *BRAF* kinase domain duplications (11), and *RET* gene mutation (12) have been reported, raising expectations regarding "precision medicine"-based medical care. However, the frequency of genomic driver alterations that can be exploited in targeted therapy is limited, and targeted therapy is not effective in all patients (13). Thus, although future progress with molecular targeted therapies is highly likely, many patients will likely need treatment with cytotoxic anticancer agents.

Several studies using cytotoxic anticancer agents, administered cisplatin, either as a single agent (14) or as a

combination of cyclophosphamide/doxorubicin/cisplatin (15), gemcitabine/cisplatin (16), or vinorelbine/cisplatin (17). Combination therapy of platinum and taxanes is widely used for head and neck squamous cell carcinomas, but its efficacy and safety for SGC remains unclear. A recent retrospective study of combination therapy with carboplatin/paclitaxel reported that the response rate was comparable to that of cisplatin regimens (18); thus, this combination may be useful as palliative chemotherapy (19). Docetaxel is less toxic regarding peripheral sensory neuropathy than paclitaxel (20). Moreover, it can be re-administered after recurrence, especially in patients with paclitaxel-resistant cancers (21-25). Therefore, in this study, the efficacy and safety of carboplatin/docetaxel in the treatment of locally advanced (LA) and/or RM SGC was retrospectively examined.

Materials and Methods

Patients. This study was a retrospective analysis including two institutions (International University of Health and Welfare Mita Hospital and Matsudo City Hospital). The clinical records of patients with LA/RM SGC who were treated with combination chemotherapy using carboplatin/docetaxel between January 2011 and February 2018 were reviewed.

All tumors were histologically confirmed by an expert pathologist (TN) and reviewed according to the criteria of the 2017 WHO classification of head and neck tumors (2). All tumors were also assessed for HER2 and AR status, as described elsewhere (26, 27). Briefly, HER2-positivity was defined as either immunohistochemically 3+ or the presence of a *HER2* gene amplification, according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines for breast cancer (28). For the AR, a case was considered to be positive when ≥20% of the tumor cell nuclei showed strong staining. Carcinoma ex pleomorphic adenoma was classified based on the histological type of each malignant component, and independent categories were considered unclassified (2, 26, 27).

Written informed consent for the publication of this work was obtained from all patients. This study was approved by the institutional review board of the International University of Health and Welfare Mita Hospital (No. 5-18-12).

Treatment. Treatment consisting of six courses of chemotherapy with carboplatin (AUC 5) and docetaxel (70 mg/m^2) was administered every three weeks. The doses were reduced and granulocyte colony-stimulating factor was administered according to the patient's condition [including age, comorbidity, and adverse events (AE)].

Statistical analyses. The following parameters were examined: overall response rate [ORR: complete response (CR) + partial response (PR)]; clinical benefit rate [CBR: CR, PR, and stable disease (SD) for at least 24 weeks], median progression-free survival (PFS), median overall survival (OS), and safety. PFS was defined as the period from the day of the initiation of treatment to the day of progressive disease (PD) or death; OS was defined as the period from the day of the initiation of treatment until the day of death, regardless of the cause. The determination of the treatment effects was based on the Response Evaluation Criteria in Solid Tumors

Table I. *Patient characteristics*.

Characteristic	All patients (n=24) n (%)	SDC (n=12) n (%)	Non-SDC† (n=12) n (%)
Age (years)			
Median	58	57	63
Range	35-77	35-68	40-77
Gender			
Male	16 (67)	8 (67)	8 (67)
Female	8 (33)	4 (33)	4 (33)
Primary site			
Parotid gland	18 (75)	10 (83)	8 (67)
Submandibular gland	3 (13)	1 (8)	2 (17)
Minor salivary gland	2 (8)	0 (0)	2 (17)
Accessory parotid gland	1 (4)	1 (8)	0 (0)
Histopathology			
SDC	12 (50)	12 (100)	
Adenocarcinoma NOS	4 (17)	0 (0)	4 (33)
Myoepithelial carcinoma	3 (13)	0 (0)	3 (25)
Acinic cell carcinoma	1 (4)	0 (0)	1 (8)
Adenoid cystic carcinoma	1 (4)	0 (0)	1 (8)
Basal cell adenocarcinoma	1 (4)	0 (0)	1 (8)
Mucoepidermoid carcinoma	1 (4)	0 (0)	1 (8)
Poorly differentiated carcinoma	1 (4)	0 (0)	1 (8)
Immunohistochemistry			
HER2-positive‡	0 (0)	0 (0)	0 (0)
AR-positive§	7 (29)	7 (58)	0 (0)
Prior treatment			
None	8 (33)	2 (17)	6 (50)
Surgery	13 (54)	9 (75)	4 (33)
Radiotherapy	13 (54)	6 (50)	5 (42)
Systemic therapy	11 (46)	9 (75)	2 (17)
CAB	6 (25)	6 (50)	0 (0)
S-1	3 (13)	1 (8)	2 (17)
Cisplatin + docetaxel	1 (4)	0 (0)	1 (8)
Abiraterone	1 (4)	1 (8)	0 (0)
Cisplatin (+ radiotherapy)	2 (8)	2 (17)	0 (0)
Docetaxel (+ radiotherapy)	2 (8)	1 (8)	1 (8)
TPF (+ radiotherapy)	1 (4)	1 (8)	0 (0)
Target lesion			
Locoregional	7 (29)	3 (25)	5 (42)
Metastatic	13 (54)	7 (58)	4 (33)
Locoregional + metastatic	4 (17)	1 (8)	3 (25)
Site of metastasis			
Lung	9 (38)	5 (42)	4 (33)
Lymph nodes	9 (38)	5 (42)	4 (33)
Bone	6 (25)	2 (17)	4 (33)
Skull base	2 (8)	2 (17)	0 (0)
Soft tissue (skin, muscle)	2 (8)	1 (8)	1 (8)
Liver	1 (4)	0 (0)	1 (8)

AR: Androgen receptor; CAB: combined androgen blockade; HER2: human epidermal growth factor receptor 2; SDC: salivary duct carcinoma; TPF: docetaxel/cisplatin/5-fluorouracil. †Included adenocarcinoma NOS, myoepithelial carcinoma, acinic cell carcinoma, adenoid cystic carcinoma, basal cell adenocarcinoma, mucoepidermoid carcinoma, and poorly differentiated carcinoma. ‡HER2 status was defined according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines for breast cancer (28). §A case was considered to be AR-positive when ≥20% of the tumor cell nuclei showed strong staining (26).

Table II. *Treatment efficacy.*

Efficacy	All patients (n=24)	SDC (n=12)			Non-SDC[§] (n=12)
		All SDC (n=12)	AR-negative SDC[†] (n=5)	CAB-resistant SDC[‡] (n=6)	
Complete response, n (%)	2 (8)	2 (17)	2 (40)	0 (0)	0 (0)
Partial response, n (%)	8 (33)	4 (33)	1 (20)	2 (33)	4 (33)
Stable disease, n (%)	9 (38)	3 (25)	1 (20)	2 (33)	6 (50)
Progressive disease, n (%)	5 (21)	3 (25)	1 (20)	2 (33)	2 (17)
Objective response[¶], n (%, 95%CI)	10 (42, 22-63)	6 (50, 21-79)	3 (60, 15-95)	2 (33, 4-78)	4 (33, 10-65)
Stable disease ≥24 weeks, n (%)	9 (38)	3 (25)	1 (20)	1 (14)	6 (50)
Clinical benefit[‖], n (%, 95%CI)	19 (79, 58-93)	9 (75, 43-95)	4 (80, 28-96)	3 (50, 12-88)	10 (83, 52-98)
Median progression-free survival, months (95%CI)	8.4 (6.2-13.5)	8.0 (1.4-12.7)	9.6 (1.3-NR)	6.9 (1.4-NR)	10.6 (1.8-27.2)
Median overall survival, months (95%CI)	26.4 (11.6-38.2)	32.6 (5.8-55.8)	33.5 (10.9-NR)	11.6 (2.9-NR)	21.8 (6.7-NR)

AR: Androgen receptor; CAB: combined androgen blockade; CI: confidence interval; NR: not reached; SDC: salivary duct carcinoma. [†]A case was considered to be AR-negative when <20% of the tumor cell nuclei showed staining (26); [‡]Patients who developed progressive disease after combined androgen blockade; [§]Included adenocarcinoma NOS, myoepithelial carcinoma, acinic cell carcinoma, adenoid cystic carcinoma, basal cell adenocarcinoma, mucoepidermoid carcinoma, and poorly differentiated carcinoma; [¶]Confirmed complete and partial response; [‖]Complete response, partial response, and stable disease ≥24 weeks.

(RECIST), version 1.1. The evaluation of the AEs was based on the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The Kaplan–Meier method was used to analyze PFS and OS. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Patient characteristics. Twenty-four patients were enrolled in the study (Table I). The median follow-up was 19.7 months (range=2.2-64.3 months). SDC was the most frequent histological type (12 patients, 50%). None of the patients were HER2-positive. AR immunoreactivity was detected in nine of 24 patients (38%), and seven (29%) were considered to be AR-positive. A total of 11 patients (46%) had received previous systemic chemotherapy; in five of these patients, postoperative chemo-radiotherapy had been administered, including cisplatin or docetaxel in two patients each and cisplatin/docetaxel/fluorouracil in one patient. A total of eight patients (33%) had undergone systemic therapy for RM lesions; one patient had been treated with docetaxel three years before the study, and six had received combined androgen blockade therapy (CAB: bicalutamide and leuprorelin). These six cases were all castration-resistant. None of the patients had a history of carboplatin treatment.

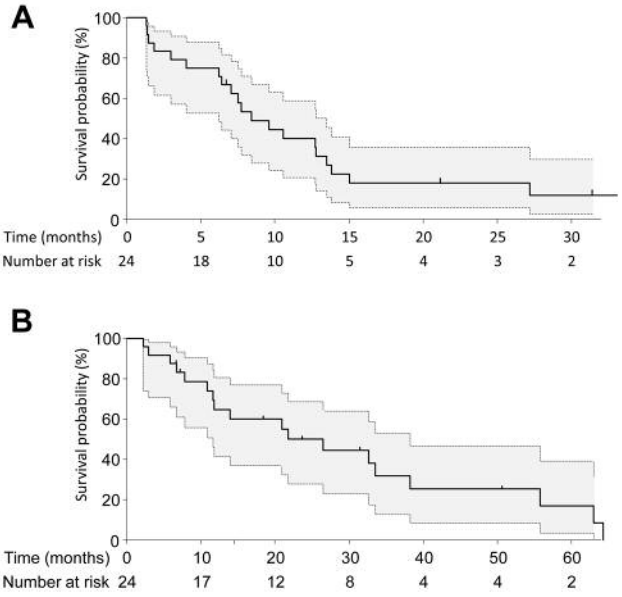

Figure 1. *Kaplan–Meier curves of (A) progression-free survival and (B) overall survival. The shaded bands represent the 95% confidence intervals.*

Treatment outcomes. Table II shows the treatment outcomes, and Figure 1 depicts the Kaplan–Meier survival curves for PFS and OS. A CR, PR, and long-term SD was observed in two, eight, and nine patients, respectively. The ORR was 42% (10 of 24 patients), the CBR was 79% (19 of 24 patients), the median PFS was 8.4 months, and the median OS was 26.4 months. The details of the five patients who responded to treatment are shown in Figures 2-6.

Among patients with SDC, the ORR was 50% (six of 12 patients), the CBR was 75% (nine of 12 patients), the median

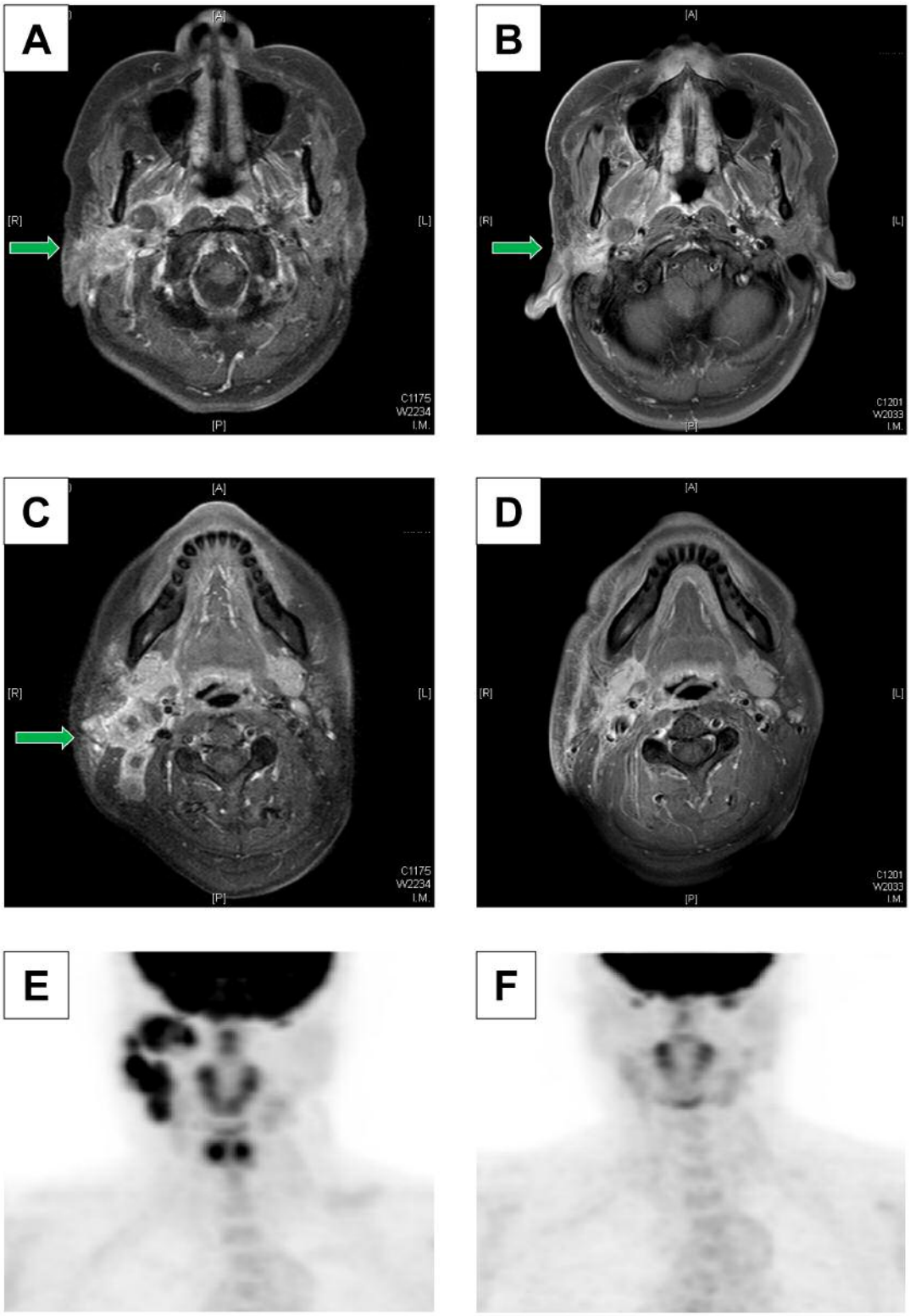

Figure 2. *Representative images before (A, C, E) and after (B, D, F) carboplatin/docetaxel treatment in a patient with locally advanced, androgen receptor-negative salivary duct carcinoma. Post-treatment magnetic resonance imaging scans revealed a partial response of the right salivary gland tumors and the right cervical lymph node metastases. A fluorodeoxyglucose (FDG)-positron emission tomography scan after three cycles of therapy revealed disease resolution. The green arrows indicate the primary lesion (A, B) and multiple cervical lymph node metastases (C).*

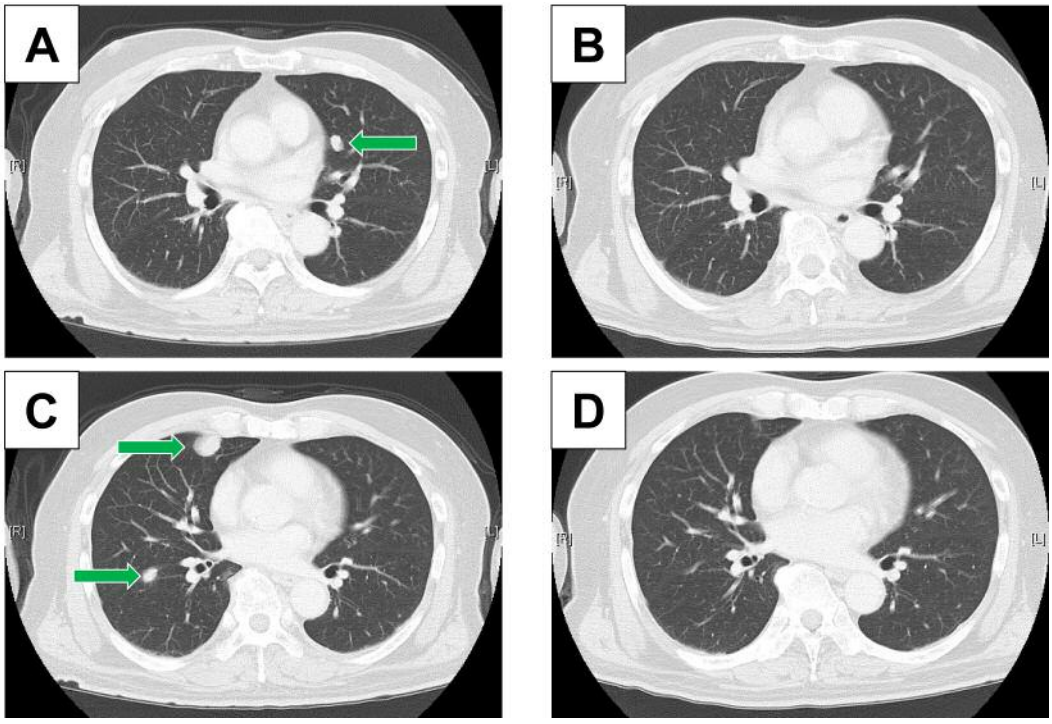

Figure 3. *Representative images before (A, C) and after (B, D) carboplatin/docetaxel treatment in a patient with recurrent/metastatic, castration-resistant salivary duct carcinoma. Post-treatment computed tomography scans revealed a complete response of all pulmonary metastatic lesions (green arrows).*

PFS was 8.0 months, and the median OS was 32.6 months. Of the five patients with AR-negative SDC, two achieved a CR, one achieved a PR, one showed long-term SD, and one developed PD. Of the six patients who developed PD after CAB, two achieved a PR, two showed long-term SD, and two developed PD. Among the four patients with adenocarcinoma NOS, two achieved a PR and two long-term SD. Last, of the three patients with myoepithelial carcinoma, one achieved a PR and two showed long-term SD.

Adverse events. All patients experienced AEs (Table III). The most common AEs were anemia (19 patients, 83%), hypoalbuminemia (17 patients, 71%), leukopenia (14 patients, 58%), and nausea (13 patients, 54%). Grade 3/4 AEs were observed in 10 patients (42%). The most common Grade 3/4 AEs were leukopenia (nine patients, 38%) and neutropenia (eight patients, 33%). Febrile neutropenia was seen in two patients (8%). Grade 1/2 peripheral sensory neuropathy was found in nine patients (38%). No treatment-related deaths were reported.

Safety. The administration of six courses of chemotherapy was completed in 18 patients (75%). In one patient, chemotherapy was given every three weeks, up to a total of nine courses; in another patient, six additional courses were administered after two years. A median of six courses were administered to the patients (range=1-12 courses). A total of six patients could not complete all six courses of treatment; the reasons included PD in four patients, edema in one patient, and a change of treatment to radiation therapy due to achieving a CR in one patient. In one patient with Grade 2 edema, treatment was terminated after five courses, following the patient's request. During the administration of the six courses, dose reduction was required in six patients for the following reasons: Grade 3 thrombocytopenia in two patients, old age in two patients, Grade 3 anemia in one patient, and febrile neutropenia in one patient.

Discussion

In this retrospective study of combination chemotherapy with carboplatin/docetaxel in patients with LA/RM SGC, an ORR of 42% was found; the rate of completion of all six courses of chemotherapy was 75%. The analysis of the treatment outcomes among the 12 cases of SDC showed an ORR of 50%, a CBR of 75%, median PFS of 8.0 months, and median OS of 32.6 months. Tumor shrinkage by more than 30% was observed in cases of adenocarcinoma NOS, myoepithelial carcinoma, and poorly differentiated carcinoma.

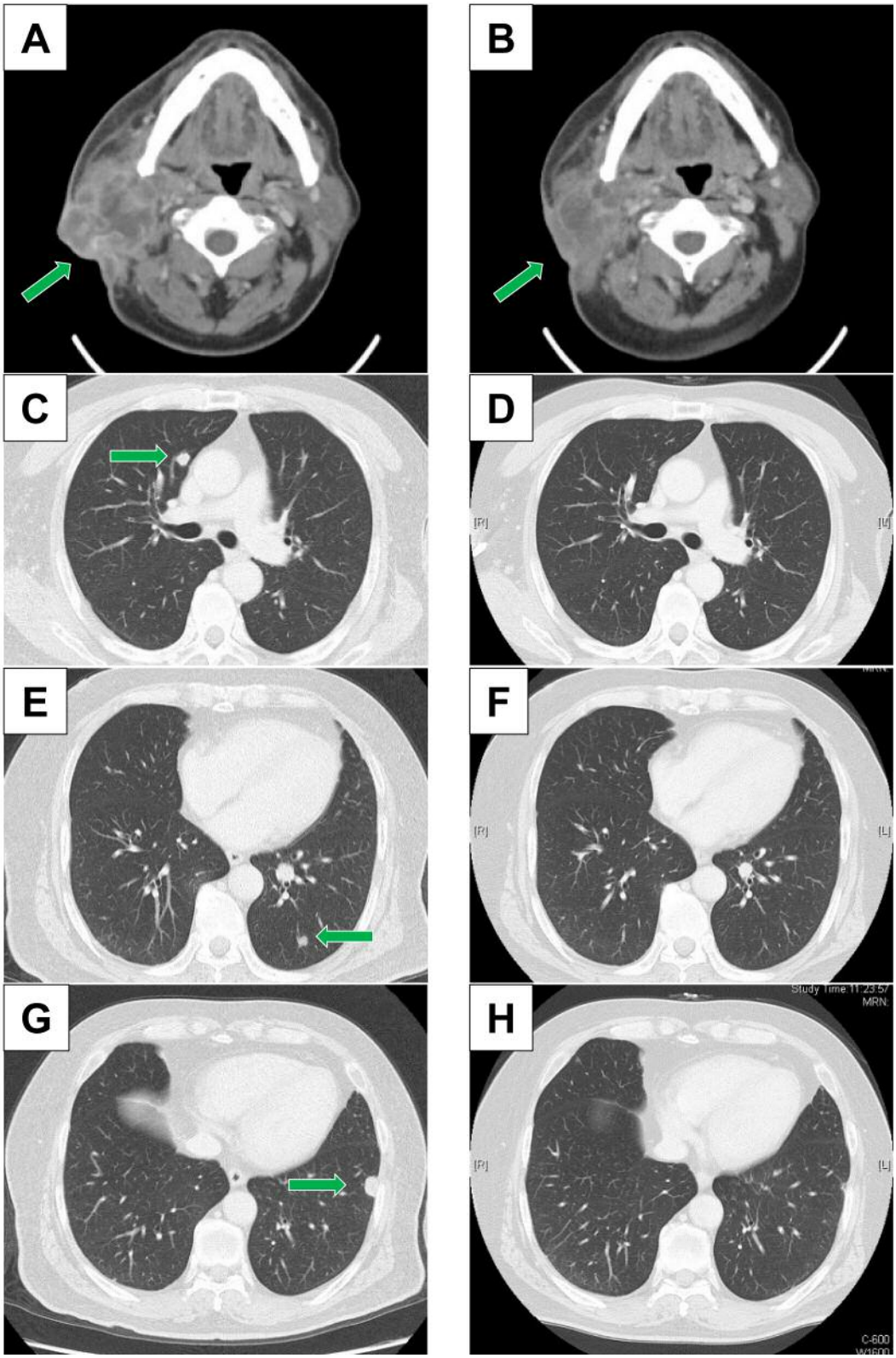

Figure 4. *Representative images before (A, C, E, G) and after (B, D, F, H) carboplatin/docetaxel treatment in a patient with myoepithelial carcinoma. Post-treatment computed tomography scans revealed a partial response of the primary lesion and a complete response of all pulmonary metastatic lesions. The green arrows indicate the primary lesion (A, B) and lung metastases (C, E, G).*

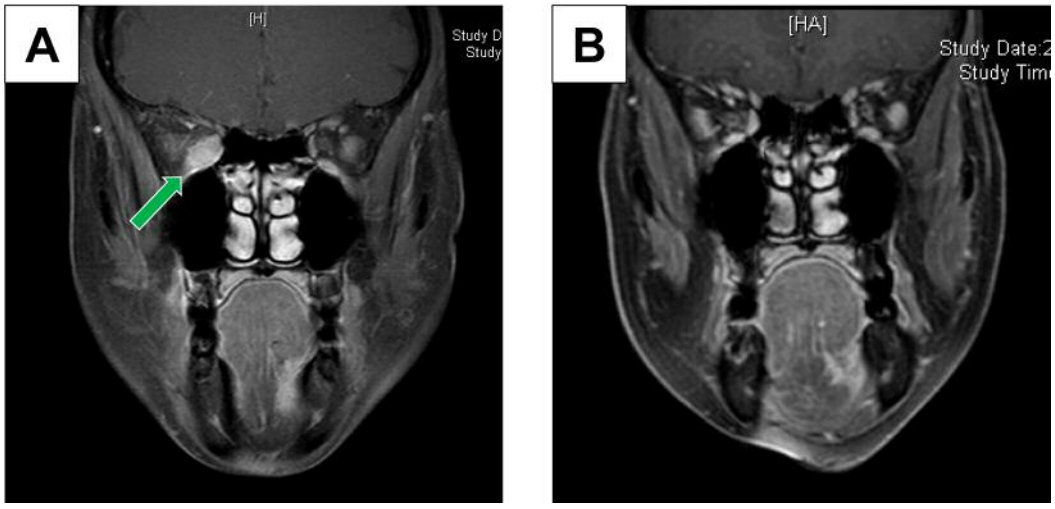

Figure 5. *Representative images before (A) and after (B) carboplatin/docetaxel treatment in a patient with recurrent/metastatic androgen receptor-negative salivary duct carcinoma. A post-treatment magnetic resonance imaging scan revealed a complete response of the right orbital metastasis (green arrow).*

Numerous studies have reported data on cytotoxic chemotherapies in patients with RM SGC (Table IV) (14-18, 29, 30). Studies using cisplatin (14-17) enrolled between 22 and 60 patients and showed ORRs of 5-31%, median PFS of 4-7 months, and median OS of 10-26.5 months. A study of carboplatin/paclitaxel conducted in 38 patients demonstrated an ORR of 39% (18); our study of carboplatin/docetaxel showed an ORR of 42%, indicating that a response rate similar to cisplatin treatment was achieved (14-17). Regarding AEs, a study on carboplatin/paclitaxel and our study on carboplatin/docetaxel found Grade 3 or higher neutropenia in 53% (18) and 33% of patients, respectively; otherwise, the incidence of severe AEs was low. Carboplatin is preferred to cisplatin because of a better quality of life (QOL), no need for hospitalization, a lower burden of intravenous hydration, and lower toxicity regarding emesis and neuropathy (19, 20). Carboplatin/paclitaxel has also been used as palliative chemotherapy. While Grade 1/2 peripheral sensory neuropathy was observed in 89% of patients treated with carboplatin/paclitaxel (18), the rate of peripheral sensory neuropathy in our study was lower, at 38%. Carboplatin/docetaxel is less likely to cause neuropathy than carboplatin/paclitaxel and should be considered a useful treatment option based on an increased QOL (20). Meanwhile, docetaxel and paclitaxel are not completely cross-resistant in many other cancers (21-25); docetaxel can be re-administered after recurrence and is a promising second-line treatment after the administration of paclitaxel. Therefore, both paclitaxel and docetaxel regimens should be studied for the treatment of patients with SGC.

Table III. *Adverse events.*

Event	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Max Grade	24 (100)	4 (17)	6 (25)
Hematological			
Max Grade	20 (83)	4 (17)	6 (25)
Anemia	19 (79)	5 (21)	0
Decreased white blood cell count	14 (58)	8 (33)	1 (4)
Decreased neutrophil count	12 (50)	2 (8)	6 (25)
Decreased platelet count	6 (25)	2 (8)	0
Febrile neutropenia	2 (8)	2 (8)	0
Non-hematological			
Max Grade	23 (96)	2 (8)	0
Hypoalbuminemia	17 (71)	0	0
Nausea	13 (54)	0	0
Anorexia	12 (50)	2 (8)	0
Alopecia	11 (46)	0	0
Peripheral sensory neuropathy	9 (38)	0	0
Dysgeusia	7 (29)	0	0
Edema, limbs	6 (25)	0	0
Constipation	5 (21)	0	0
Dehydration	3 (13)	1 (4)	0
Diarrhea	3 (13)	0	0
Mucositis, oral	3 (13)	0	0
Hyponatremia	2 (8)	1 (4)	0
Weight loss	2 (8)	0	0
Hypocalcemia	2 (8)	0	0
Vomiting	2 (8)	0	0
Hypokalemia	2 (8)	0	0
Hyperkalemia	2 (8)	0	0
Watering eyes	1 (4)	0	0
Fever	1 (4)	0	0
Cough	1 (4)	0	0

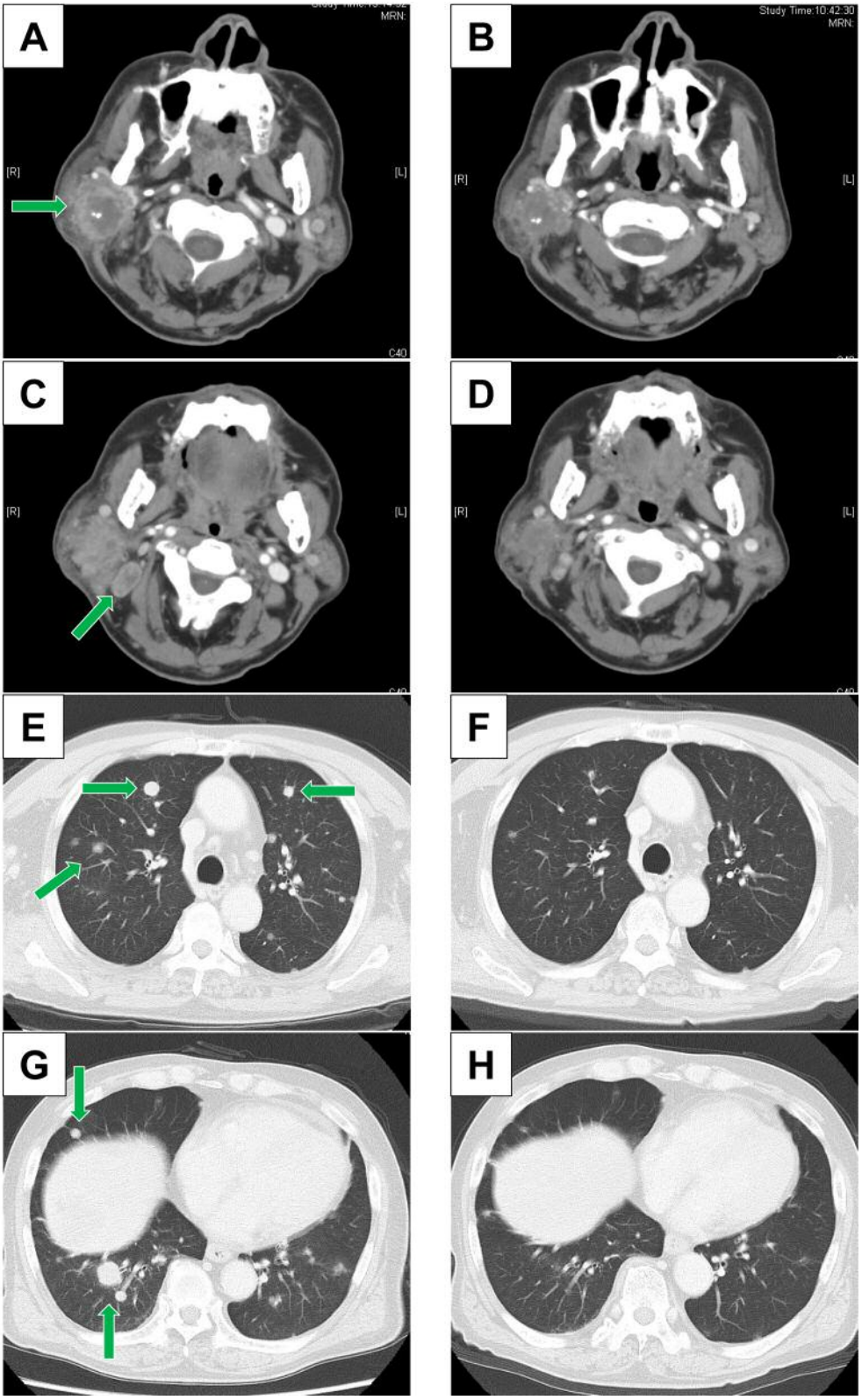

Figure 6. *Representative images before (A, C, E, G) and after (B, D, F, H) carboplatin/docetaxel treatment in a patient with poorly differentiated carcinoma. Post-treatment computed tomography scans revealed a partial response of the right salivary gland tumor as well as the cervical lymph node and pulmonary metastatic lesions. The green arrows indicate the primary lesion (A), cervical lymph node metastasis (B), and multiple lung metastases (E, G).*

Table IV. *Summary of literature reports on chemotherapy for salivary gland carcinoma.*

Authors	Year of publication	Regimen	All histopathology				SDC or "Adenocarcinoma"			
			n	RR, %	Median PFS, months	Median OS, months	n	RR, %	Median PFS, months	Median OS, months
Licitra *et al*. (14)	1991	Cisplatin	25	18	7	14	5†	0	NA	NA
Licitra *et al*. (15)	1996	Cisplatin/DXA/CPA	22	27	7	21	4†	25	NA	NA
Gilbert *et al*. (29)	2006	Paclitaxel	45	18	4	12.5	17†	29	NA	NA
Laurie *et al*. (16)	2010	Cisplatin/gemcitabine	33	24	6.7	13.8	9†	44	NA	NA
Airoldi *et al*. (17)	2014	Cisplatin/vinorelbine (first-line)	60	23	6	10	15†	53	NA	13.6
Nakano *et al*. (18)	2016	Carboplatin/paclitaxel	38	39	6.5	26.5	18‡	39	6.5	34.7
Rodriguez *et al*. (30)	2018	Eribulin	29	10	3.5	16	7†	14	NA	NA
This study	2019	Carboplatin/docetaxel	24	42	8.4	26.4	12‡	50	8.0	32.6

CPA: Cyclophosphamide; DXA: doxorubicin; OS: overall survival; PFS: median progression-free survival; NA: not available; RR: response rate; SDC: salivary duct carcinoma. †Included the histologic diagnoses of adenocarcinoma, salivary duct carcinoma, adenocarcinoma NOS, and carcinoma ex pleomorphic adenoma; ‡Included the histologic diagnosis of salivary duct carcinoma.

To the best of our knowledge, this is the first report of cases in which a cytotoxic chemotherapy was effective in patients with AR-negative or CAB-resistant SDC. Recently, AR- and HER2-targeted therapies have been used as systemic chemotherapy for LA/RM SDC. We have previously reported an SDC classification system for the selection of an appropriate and personalized systemic therapy with anti-HER2, anti-AR, and/or cytotoxic drugs (26). We have also recently reported two prospective studies of anti-AR and anti-HER2 therapy that were based on this classification system (6, 7). In a phase II study of CAB in 36 patients with AR-positive SGC, including 34 cases of SDC, an ORR of 42% was observed (6). No Grade 4 AEs were found, and Grade 3 AEs were found in 7 of 36 patients (19%). Grade 3/4 AEs were more frequent with carboplatin/docetaxel in this study when compared to the CAB study; however, no marked superiority or inferiority in efficacy was noted. Furthermore, in some cases, beneficial effects were found when either carboplatin/docetaxel or CAB was administered and followed by the other after PD. In addition, we have also reported on the treatment with trastuzumab/ docetaxel in 57 patients with HER2-positive SDC and observed an ORR of 70% (7). All patients with SDC included in the current study were HER2-negative; thus, the two studies cannot be compared due to the different molecular backgrounds. However, carboplatin/docetaxel appears to have an inferior response rate in HER2-negative cases, and this combination of cytotoxic agents may pose a higher risk of AEs. Therefore, treatment with trastuzumab/docetaxel might be preferable in HER2-positive patients. In studies conducted on SDC, (26, 27, 31, 32) HER2-negative cases accounted for about 60-80%, and HER2- and AR-negative cases accounted for about 15%. Therefore, carboplatin/docetaxel combination therapy may be a promising treatment option for AR- and HER2-negative SDC or may be beneficial as second-line chemotherapy for CAB-resistant, AR-positive SDC.

Adenocarcinoma NOS, myoepithelial carcinoma, and poorly differentiated carcinoma also showed a response to carboplatin/docetaxel. Previous studies that assessed treatment of patients with "adenocarcinoma" with gemcitabine/cisplatin (16) and cisplatin/vinorelbine (17), 3 of 8 (38%) and 7 of 15 (47%) cases, respectively, responded to treatment. The "adenocarcinoma" group likely included patients diagnosed as adenocarcinoma NOS or poorly differentiated carcinoma, based on the 2017 WHO classification (2). Since rapid progression is often seen in patients with these histopathologies, carboplatin/docetaxel is considered a promising option in conjunction with cisplatin-containing regimens.

Only one case of adenoid cystic carcinoma, muco-epidermoid carcinoma, acinic cell carcinoma, and basal cell adenocarcinoma were included in this study. Although no tumor shrinkage occurred, the durations of SD in the adenoid cystic carcinoma and acinic cell carcinoma cases were 15 and 61 months, respectively. Treatment was started with a radiological finding of progression within the previous six months in both cases, and a certain therapeutic effect was likely obtained by maintaining SD for a long period. In adenoid cystic carcinoma, mucoepidermoid carcinoma, and acinic cell carcinoma, the indication of systemic therapy should be carefully considered based on the tumor growth rate before the start of treatment as previous studies have indicated that both cytotoxic chemotherapy and targeted therapy showed a low response rate; many cases show slow tumor growth, and long treatment periods increase the rate or occurrence of AEs (3, 4).

Because of the retrospective nature of this study, the superiority or inferiority of the carboplatin/docetaxel combination therapy in comparison to other regimens cannot

be concluded. Moreover, a comparative analysis of the treatment effects by histopathology was not possible because only few cases were included. Although it is desirable to solve these problems with a large-scale randomized controlled trial, this is a difficult task for SGC and a common problem for other rare cancers. Currently, a comparison trial of bicalutamide/triptorelin *vs*. cisplatin/doxorubicin *vs*. carboplatin/paclitaxel, using a Bayesian theory analysis, is in progress in Europe (ClinicalTrials.gov Identifier: NCT 0 196 9578).

In conclusion, patients with LA/RM SGC treated with combination therapy of carboplatin/docetaxel showed an ORR of 42% and had manageable AEs. Thus, carboplatin/ docetaxel may be an option for chemotherapy in patients with LA/RM SGC, in particular AR- and HER2-negative SDC, and a valuable second-line chemotherapy for CAB-resistant, AR-positive SDC.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

YT and TS designed the study. TO and YT contributed to the collection and interpretation of the data. TO, TS, TM, CF, TM, HT, KM, KT, and YT contributed to data collection and patient management. TN contributed to diagnostic pathology. YT was a major contributor in writing the manuscript. All Authors read and approved the final manuscript.

Acknowledgements

This work was supported by JSPS Grants-in-Aid for Scientific Research (C) to Dr. Yuichiro Tada (No. 18K09386) and Dr. Toshitaka Nagao (No. 17K08705). The authors thank Editage (www.editage.jp) for English language editing.

References

1 Tamaki T, Dong Y, Ohno Y, Sobue T, Nishimoto H and Shibata A: The burden of rare cancer in Japan: application of the RARECARE definition. Cancer Epidemiol *38(5)*: 490-495, 2014. PMID: 25155209. DOI: 10.1016/j.canep.2014.07.014

2 World Health Organization: CHAPTER 7 Tumours of salivary glands. In: WHO Classification of Head and Neck Tumours. 4th ed. El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ (eds.). Lyon, IARC., pp. 159-202, 2017.

3 Lewis AG, Tong T and Maghami E: Diagnosis and management of malignant salivary gland tumors of the parotid gland. Otolaryngol Clin North Am *49*: 343-380, 2016. PMID: 27040585. DOI: 10.1016/j.otc.2015.11.001

4 Alfieri S, Granata R, Bergamini C, Resteghini C, Bossi P, Licitra LF and Locati LD: Systemic therapy in metastatic salivary gland carcinomas: A pathology-driven paradigm? Oral Oncol *66*: 58-63, 2017. PMID: 28249649. DOI: 10.1016/j.oraloncology. 2016.12.016

5 Cohen RB, Delord JP, Doi T, Piha-Paul SA, Liu SV, Gilbert J, Algazi AP, Damian S, Hong RL, Le Tourneau C, Day D, Varga A, Elez E, Wallmark J, Saraf S, Thanigaimani P, Cheng J and Keam B: Pembrolizumab for the treatment of advanced salivary gland carcinoma: findings of the phase 1b KEYNOTE-028 study. Am J Clin Oncol *41*: 1083-1088, 2018. PMID: 29462123. DOI: 10.1097/COC.0000000000000429

6 Fushimi C, Tada Y, Takahashi H, Nagao T, Ojiri H, Masubuchi T, Matsuki T, Miura K, Kawakita D, Hirai H, Hoshino E, Kamata S and Saotome T: A prospective phase II study of combined androgen blockade in patients with androgen receptor-positive metastatic or locally advanced unresectable salivary gland carcinoma. Ann Oncol *29*: 979-984, 2018. PMID: 29211833. DOI: 10.1093/annonc/mdx771

7 Takahashi H, Tada Y, Saotome T, Akazawa K, Ojiri H, Fushimi C, Masubuchi T, Matsuki T, Tani K, Osamura RY, Hirai H, Yamada S, Kawakita D, Miura K, Kamata SE and Nagao T: Phase II trial of trastuzumab and docetaxel in patients with human epidermal growth factor receptor 2-positive salivary duct carcinoma. J Clin Oncol *37*: 125-134, 2019. PMID: 30452336. DOI: 10.1200/JCO.18.00545

8 Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, Nathenson M, Doebele RC, Farago AF, Pappo AS, Turpin B, Dowlati A, Brose MS, Mascarenhas L, Federman N, Berlin J, El-Deiry WS, Baik C, Deeken J, Boni V, Nagasubramanian R, Taylor M, Rudzinski ER, Meric-Bernstam F, Sohal DPS, Ma PC, Raez LE, Hechtman JF, Benayed R, Ladanyi M, Tuch BB, Ebata K, Cruickshank S, Ku NC, Cox MC, Hawkins DS, Hong DS and Hyman DM: Efficacy of larotrectinib in *TRK* fusion-positive cancers in adults and children. N Engl J Med *378*: 731-739, 2018. PMID: 29466156. DOI: 10.1056/NEJMoa1714448

9 Drilon A, Li G, Dogan S, Gounder M, Shen R, Arcila M, Wang L, Hyman DM, Hechtman J, Wei G, Cam NR, Christiansen J, Luo D, Maneval EC, Bauer T, Patel M, Liu SV, Ou SH, Farago A, Shaw A, Shoemaker RF, Lim J, Hornby Z, Multani P, Ladanyi M, Berger M, Katabi N, Ghossein R and Ho AL: What hides behind the MASC: clinical response and acquired resistance to entrectinib after ETV6-NTRK3 identification in a mammary analogue secretory carcinoma (MASC). Ann Oncol *27*: 920-926, 2016. PMID: 26884591. DOI: 10.1093/annonc/ mdw042

10 Hyman DM, Puzanov I, Subbiah V, Faris JE, Chau I, Blay JY, Wolf J, Raje NS, Diamond EL, Hollebecque A, Gervais R, Elez-Fernandez ME, Italiano A, Hofheinz RD, Hidalgo M, Chan E, Schuler M, Lasserre SF, Makrutzki M, Sirzen F, Veronese ML, Tabernero J and Baselga J: Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med *373*: 726-736, 2015. PMID: 26287849. DOI: 10.1056/ NEJMoa1502309

11 Klempner SJ, Bordoni R, Gowen K, Kaplan H, Stephens PJ, Ou SH, Ali SM: Identification of BRAF kinase domain duplications across multiple tumor types and response to raf inhibitor therapy. JAMA Oncol *2*: 272-274, 2016. PMID: 26562024. DOI: 10.1001/jamaoncol.2015.4437

12 Wang K, Russell JS, McDermott JD, Elvin JA, Khaira D, Johnson A, Jennings TA, Ali SM, Murray M, Marshall C, Oldham DS, Washburn D, Wong SJ, Chmielecki J, Yelensky R, Lipson D, Miller VA, Stephens PJ, Serracino HS, Ross JS and Bowles DW: Profiling of 149 salivary duct carcinomas, carcinoma ex pleomorphic adenomas, and adenocarcinomas, not otherwise specified reveals actionable genomic alterations. Clin Cancer Res *22*: 6061-6068, 2016. PMID: 27334835. DOI: 10.1158/1078-0432.CCR-15-2568

13 Ross JS, Gay LM, Wang K, Vergilio JA, Suh J, Ramkissoon S, Somerset H, Johnson JM, Russell J, Ali S, Schrock AB, Fabrizio D, Frampton G, Miller V, Stephens PJ, Elvin JA and Bowles

DW: Comprehensive genomic profiles of metastatic and relapsed salivary gland carcinomas are associated with tumor type and reveal new routes to targeted therapies. Ann Oncol *28*: 2539-2546, 2017. PMID: 28961851. DOI: 10.1093/annonc/mdx399

14 Licitra L, Marchini S, Spinazzè S, Rossi A, Rocca A, Grandi C and Molinari R: Cisplatin in advanced salivary gland carcinoma. A phase II study of 25 patients. Cancer *68*: 1874-1877, 1991. PMID: 1913539

15 Licitra L, Cavina R, Grandi C, Palma SD, Guzzo M, Demichell R and Molinari R: Cisplatin, doxorubicin and cyclophosphamide in advanced salivary gland carcinoma. A phase II trial of 22 patients. Ann Oncol *7*: 640-642, 1996. PMID: 8879381.

16 Laurie SA, Siu LL, Winquist E, Maksymiuk A, Harnett EL, Walsh W, Tu D and Parulekar WR: A phase 2 study of platinum and gemcitabine in patients with advanced salivary gland cancer: a trial of the NCIC Clinical Trials Group. Cancer *116*: 362-368, 2010. PMID: 19924794. DOI: 10.1002/cncr.24745

17 Airoldi M, Garzaro M, Pedani F, Ostellino O, Succo G, Riva G, Sensini M, Naqe N, Bellini E, Raimondo L and Pecorari G: Cisplatin+vinorelbine treatment of recurrent or metastatic salivary gland malignancies (RMSGM): a final report on 60 cases. Am J Clin Oncol *40*: 86-90, 2017. PMID: 25089531. DOI: 10.1097/COC.0000000000000112

18 Nakano K, Sato Y, Sasaki T, Shimbashi W, Fukushima H, Yonekawa H, Mitani H, Kawabata K and Takahashi S: Combination chemotherapy of carboplatin and paclitaxel for advanced/metastatic salivary gland carcinoma patients: differences in responses by different pathological diagnoses. Acta Otolaryngol *136*: 948-951, 2016. PMID: 27094013. DOI: 10.3109/00016489.2016.1170876

19 Matsuda A, Yamaoka K and Tango T: Quality of life in advanced non-small cell lung cancer patients receiving palliative chemotherapy: A meta-analysis of randomized controlled trials. Exp Ther Med *3*: 134-140, 2012. PMID: 22969858. DOI: 10.3892/etm.2011.368

20 Argyriou AA, Kyritsis AP, Makatsoris T and Kalofonos HP: Chemotherapy-induced peripheral neuropathy in adults: a comprehensive update of the literature. Cancer Manag Res *6*: 135-147, 2014. PMID: 24672257. DOI: 10.2147/CMAR.S44261

21 Valero V, Jones SE, Von Hoff DD, Booser DJ, Mennel RG, Ravdin PM, Holmes FA, Rahman Z, Schottstaedt MW, Erban JK, Esparza-Guerra L, Earhart RH, Hortobagyi GN and Burris HA 3rd: A phase II study of docetaxel in patients with paclitaxel-resistant metastatic breast cancer. J Clin Oncol *16*: 3362-3368, 1998. PMID: 9779713. DOI: 10.1200/JCO.1998.16.10.3362

22 Rose PG, Blessing JA, Ball HG, Hoffman J, Warshal D, DeGeest K and Moore DH: A phase II study of docetaxel in paclitaxel-resistant ovarian and peritoneal carcinoma: A Gynecologic Oncology Group study. Gynecol Oncol *88*: 130-135, 2003. PMID: 12586591.

23 Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, Kalman L, Miller V, Lee JS, Moore M, Gandara D, Karp D, Vokes E, Kris M, Kim Y, Gamza F and Hammershaimb L: Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol *18*: 2354-2362, 2000. PMID: 10856094. DOI: 10.1200/JCO.2000.18.12.2354

24 Sonpavde G, Pond GR, Mullane S, Qu AQ, Di Lorenzo G, Federico P, Necchi A, Rosenberg JE, Bellmunt J and Choueiri TK: Incomplete cross-resistance between taxanes for advanced urothelial carcinoma: implications for clinical practice and trial design. Clin Genitourin Cancer *13*: 250-256, 2015. PMID: 25481485. DOI: 10.1016/j.clgc.2014.10.005

25 Ando T, Hosokawa A, Kajiura S, Itaya Y, Ueda A, Fujinami H, Nishikawa J, Kobayashi T, Horikawa N, Tsukioka Y, Yabushita K, Note M, Ogawa K and Sugiyama T: Efficacy of weekly paclitaxel in patients with advanced gastric cancer refractory to docetaxel-based chemotherapy. Gastric Cancer *15*: 427-432, 2012. PMID: 22252156. DOI: 10.1007/s10120-011-0135-0

26 Takase S, Kano S, Tada Y, Kawakita D, Shimura T, Hirai H, Tsukahara K, Shimizu A, Imanishi Y, Ozawa H, Okami K, Sato Y, Sato Y, Fushimi C, Okada T, Sato H, Otsuka K, Watanabe Y, Sakai A, Ebisumoto K, Togashi T, Ueki Y, Ota H, Hanazawa T, Chazono H, Osamura RY and Nagao T: Biomarker immunoprofile in salivary duct carcinomas: clinicopathological and prognostic implications with evaluation of the revised classification. Oncotarget *8*: 59023-59035, 2017. PMID: 28938615. DOI: 10.18632/oncotarget.19812

27 Shimura T, Tada Y, Hirai H, Kawakita D, Kano S, Tsukahara K, Shimizu A, Takase S, Imanishi Y, Ozawa H, Okami K, Sato Y, Sato Y, Fushimi C, Takahashi H, Okada T, Sato H, Otsuka K, Watanabe Y, Sakai A, Ebisumoto K, Togashi T, Ueki Y, Ota H, Ando M, Kohsaka S, Hanazawa T, Chazono H, Kadokura Y, Kobayashi H and Nagao T: Prognostic and histogenetic roles of gene alteration and the expression of key potentially actionable targets in salivary duct carcinomas. Oncotarget *9*: 1852-1867, 2017. PMID: 29416736. DOI: 10.18632/oncotarget.22927

28 Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, Allred DC, Bartlett JM, Bilous M, Fitzgibbons P, Hanna W, Jenkins RB, Mangu PB, Paik S, Perez EA, Press MF, Spears PA, Vance GH, Viale G and Hayes DF; American Society of Clinical Oncology; College of American Pathologists: Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol *31*: 3997-4013, 2013. PMID: 24101045. DOI: 10.1200/JCO.2013.50.9984

29 Gilbert J, Li Y, Pinto HA, Jennings T, Kies MS, Silverman P and Forastiere AA: Phase II trial of taxol in salivary gland malignancies (E1394): a trial of the Eastern Cooperative Oncology Group. Head Neck *28*: 197-204, 2006. PMID: 16470745. DOI: 10.1002/hed.20327

30 Rodriguez CP, Martins RG, Baik C, Chow LQ, Santana-Davila R, Goulart BH, Lee S and Eaton KD: Phase II trial of eribulin mesylate in recurrent or metastatic salivary gland malignancies. Head Neck *40*: 584-589, 2018. PMID: 29283469. DOI: 10.1002/hed.25020

31 Masubuchi T, Tada Y, Maruya S, Osamura Y, Kamata SE, Miura K, Fushimi C, Takahashi H, Kawakita D, Kishimoto S and Nagao T: Clinicopathological significance of androgen receptor, HER2, Ki-67 and EGFR expressions in salivary duct carcinoma. Int J Clin Oncol *20*: 35-44, 2015. PMID: 24553861. DOI: 10.1007/s10147-014-0674-6

32 Di Palma S, Simpson RH, Marchiò C, Skálová A, Ungari M, Sandison A, Whitaker S, Parry S and Reis-Filho JS: Salivary duct carcinomas can be classified into luminal androgen receptor-positive, HER2 and basal-like phenotypes. Histopathology *61(4)*: 629-643, 2012. PMID: 22882517. DOI: 10.1111/j.1365-2559.2012.04252.x

Received February 5, 2019
Revised February 28, 2019
Accepted March 1, 2019