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Retrospective Study of Cisplatin/Carboplatin, 5-Fluorouracil Plus Cetuximab (EXTREME) for Advanced-stage Salivary Gland Cancer

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Abstract. *Background/Aim: Surgery remains the standard treatment for salivary gland carcinoma (SGC). Our study investigated the association between epidermal growth factor receptor (EGFR) status in recurrent/metastatic SGC and the effectiveness of treatment with cisplatin/carboplatin and 5-fluorouracil plus cetuximab (EXTREME). Patients and Methods: We retrospectively collected 19 SGCs from patients treated with the EXTREME regimen. After analyzing EGFR expression and gene copy number gain, we evaluated the correlation between EGFR status and clinicopathological factors and prognosis. Results: EGFR overexpression was detected in 77.8% cases, but not statistically associated with clinicopathological factors or prognosis. EGFR gene copy number gain was detected in 16.7% cases, and statistically positively correlated with lymph node metastasis (p=0.0291). The best overall response was partial response in two cases, stable disease in 15, and progressive disease in one case. The EXTREME regimen was discontinued in all cases. Conclusion: Our results suggest that SGCs are positive for EGFR protein expression but the response rate to the EXTREME regimen was unremarkable.*

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Recurrent, locally advanced or distant metastatic salivary gland cancer (SGC) has no established systemic therapy. Surgical resection followed by radiation therapy is sometimes performed for SGC of advanced stage or with poor prognostic factors (1). SGC has different kinds of histopathological subtypes and three grading systems (2, 3), so it is frequently difficult to choose an optimum treatment.

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that has an important role in tumor growth and progression in various kinds of cancer and serves as a therapeutic target of molecular targeted therapy (*e.g.*, cetuximab) (4, 5). In fact, the EXTREME regimen (cisplatin/carboplatin, 5-fluorouracil plus cetuximab) is

reported to be effective for head-and-neck squamous cell carcinoma irrespective of EGFR protein expression (4). EGFR protein overexpression has also been reported in at least 40% of SGC cases (6, 7). However, EGFR protein overexpression is not a prognostic factor, and there is no association between EGFR protein overexpression and the effectiveness of EGFR-targeted therapy in patients with SGC (8). Additionally, the effectiveness of the EXTREME regimen for SGC is not well understood (9).

In this study, we evaluated EGFR protein expression and *EGFR* gene copy number gain in SGC, then investigated the association between EGFR abnormalities and the effectiveness of the EXTREME regimen in SGC.

Patients and Methods

Case selection. This study was approved by the Institutional Review Board at Kyushu University (approval number: 2021-222). After retrospectively identifying 19 SGC cases for inclusion who were treated with the EXTREME regimen, we collected biopsies or surgically resected formalin-fixed paraffin-embedded tissues from Kyushu University Hospital, Kyushu National Cancer Center, Fukuoka University Hospital, Saga University Hospital, Kyushu Medical Center, Kitakyushu Municipal Medical Center, Hamanomachi Hospital, and Sasebo Kyosai Hospital, all taken prior to the initiation of therapy and treatment with the EXTREME regimen. Histopathologically, all 19 cases were diagnosed as SGC based on the pathological findings of the initial biopsy/surgically resected tissues and were subsequently treated with the EXTREME: namely, cisplatin/carboplatin and 5-fluorouracil and cetuximab. We classified the best overall response as complete response, partial response, stable disease, and progressive disease according to the Response Evaluation Criteria in Solid Tumors version 1.1 (10).

Immunohistochemical staining (IHC) and fluorescence in situ hybridization (FISH) for EGFR. EGFR IHC and FISH were performed using formalin-fixed paraffin-embedded tissue sections and a primary antibody for EGFR [IHC: 31G7; dilution 1:50 (Abcam, Cambridge, UK); FISH: Vysis LSI EGFR SpectrumOrange/CEP 7 SpectrumGreen Probe Kit (Abbott Molecular, Des Plaines, IL, USA)]. EGFR IHC and FISH were evaluated as described elsewhere (6). In this study, we defined ≥10% of tumor cells with membranous staining of EGFR as EGFR IHC-positive, and *EGFR* gene amplification or high polysomy as *EGFR* FISH-positive.

Statistical analyses. All analyses were carried out using JMP Statistical Discovery software (ver. 16.0; SAS, Cary, NC). We used Fisher's exact test to evaluate results between variables. A p-value under 0.05 was considered statistically significant. Overall and progression-free survival were calculated with the Kaplan-Meier method, and the differences were compared using the log-rank test.

Results

Clinicopathological findings. The clinicopathological findings of 19 SGC cases are summarized in Table I. The median age was 65 years (range=34-77 years). More than half of the cases were male (n=10, 52.6%). Twelve tumors were located in a major salivary gland: the parotid gland (n=8, 42.1%), submandibular gland (n=3, 14.3%), or sublingual gland (n=1, 5.3%). The other seven tumors were located in a minor salivary gland: the hard palate (n=2, 10.5%), paranasal cavity (n=2, 10.5%), oral floor (n=1, 5.3%), nasal cavity (n=1, 5.3%), or oropharynx (n=1, 5.3%). According to the fourth edition of the World Health Organization classification (3), the most frequent histopathological tumor was adenoid cystic carcinoma (n=8, 42.1%), followed by carcinoma ex pleomorphic adenoma (n=4, 21.1%), salivary duct carcinoma (n=3, 15.8%), mucoepidermoid carcinoma (n=3, 15.8%), and lymphoepithelial carcinoma (n=1, 5.3%). According to the eighth edition of the Union for International Cancer Control TNM classification (11), before starting the initial therapy, the tumors included six (31.6%) cases with a low T-stage (T1/T2) and 13 (68.4%) cases with a high-T stage (T3/T4), nine (47.4%) cases of clinically positive lymph node metastasis, and four (21.1%) cases of distant metastasis. At that time, four (21.1%) cases were clinically low-stage (I/II), and 15 (78.9%) cases were clinically high-stage (III/IV). Before starting the EXTREME regimen, the tumors included 11 (57.9%) cases of low T-stage (T0/T1/T2) and eight (42.1%) cases of high T-stage (T3/T4), five (26.3%) cases of clinically positive lymph node metastasis, and 16 (84.2%) cases of distant metastasis. Ultimately, all cases became clinically high stage (III/IV).

As for the best overall response of the EXTREME regimen among the 18 cases analyzed, a partial response was seen in two out of 18 (10.5%) cases: one of mucoepidermoid carcinoma and one of lymphoepithelial carcinoma. Stable disease was found in 15 (83.3%) patients, and progressive disease in one (5.6%) with adenoid cystic carcinoma. One case could not be evaluated for overall response due to refusal of treatment.

All patients discontinued the EXTREME regimen, either due to progressive disease (n=10, 52.6%), adverse events (n=8, 42.1%), or refusal of treatment (n=1, 5.3%). Nine (47.4%) of 19 cases remain alive with tumor; the other 10 (52.6%) cases died of their tumors.

EGFR protein expression and EGFR copy-number gain. EGFR protein overexpression (Figure 1A) was positive for 14 (77.8%) out of 18 cases (Table I). FISH for *EGFR* was positive for three (16.7%) cases out of 18 (Table I and Figure 1B). One case was unreadable and did not show any EGFR expression or *EGFR* signals because of the poor sample condition. All FISH-positive cases were positive by IHC, but this association was not statistically significant (Table I).

EGFR expression by IHC was not statistically associated with any of the clinicopathological variables (Table I). Histopathologically, EGFR was positive by IHC for four out

Table I. *Clinicopathological findings and epidermal growth factor receptor (EGFR) status of 19 salivary gland cancer cases treated with the EXTREME regimen.*

			IHC				EGFR-FISH			
			Positive	Negative	Not informative	*p*-Value	Positive	Negative	No signal	*p*-Value
Variable	Subgroup	N=19	14 (77.8%)	4 (22.2%)	1		3 (16.7%)	15 (83.3%)	1	
Age, years	Median (range)	66 (34-77)								
	<65 Years, n	8	6	2		0.7998	2	6		0.3958
	>66 Years, n	11	8	2	1		1	9	1	
Gender, n	Male	10	7	2	1	>0.999	1	8	1	0.5237
	Female	9	7	2			2	7		
Primary site, n	Major salivary gland	12	10	2		0.4319	3	9		0.0988
	Minor salivary gland	7	4	2	1		0	6	1	
Histopathological classification, n	ACC	8	4	3	1	0.0939	0	7	1	0.0681
	Non-ACC	11	10	1			3	8		
	CPA	4	3	1			0	4		
	SDC	3	3	0			2	1		
	MC	3	3	0			1	2		
	LC	1	1	0			0	1		
T-Stage, n*	T1/2	6	6	0		0.0515	1	5		>0.999
	T3/4	13	8	4	1		2	10	1	
N-Stage, n*	N0	10	7	2	1	>0.999	0	9	1	**0.0291**
	N1-3	9	7	2			3	6		
M-Stage, n*	M0	15	11	3	1	0.8807	3	11	1	0.1960
	M1	4	3	1			0	4		
Stage, n	I/II	4	4	0		0.1279	4	0		0.1960
	III/IV	15	10	4	1		3	11	1	
T-Stage, n**	T0/1/2	11	9	2		0.6084	2	9		0.8275
	T3/4	8	5	2	1		1	6	1	
N-Stage, n**	N0	14	10	3	1	0.8873	2	11	1	0.8166
	N1-3	5	4	1			1	4		
M-Stage, n**	M0	3	1	1	1	0.3553	0	2	1	0.3778
	M1	16	13	3			3	13		
Stage, n**	I/II	0	0	0		-	0	0		-
	III/IV	19	14	4	1		3	15	1	
	Partial	2	2	0		0.1352	0	2		0.5232
Best overall response, n	Stable disease	15	11	3	1		3	11	1	
	Progressive disease	1	0	1			0	1		
	Not given	1	1	0			0	1		
Reason for discontinuation, n	Progressive disease	10	7	3		0.3641	1	9		0.3958
	Adverse event	8	7	1			2	6		
	Refusal of treatment	1	0	0	1		0	0	1	
Last known status, n	Alive with tumor	9	6	3		0.2482	1	8		0.5237
	Died of tumor	10	8	1	1		2	7	1	
EGFR-FISH, n	Positive	3	3	0		0.1960				
	Negative	15	11	4						
	No signal	1	0	0	1					

ACC: Adenoid cystic carcinoma; CPA: carcinoma ex pleomorphic adenoma; FISH: fluorescent *in situ* hybridization; IHC: immunohistochemistry; LC: lymphoepithelial carcinoma; MC: mucoepidermoid carcinoma; SDC: salivary duct carcinoma. *Before initial therapy; **before EXTREME regimen. Statistically significant *p*-values are shown in bold.

of seven (57.1%) adenoid cystic carcinoma cases, and 10 out of 11 (90.9%) non-adenoid cystic carcinoma cases: three of four carcinoma ex pleomorphic adenoma cases, three of three salivary duct carcinoma cases, three of three mucoepidermoid carcinoma cases, and in the one lymphoepithelial carcinoma case. Among the nine surviving patients, six (66.7%) were positive for EGFR-IHC expression. Among the 10 non-surviving patients, eight

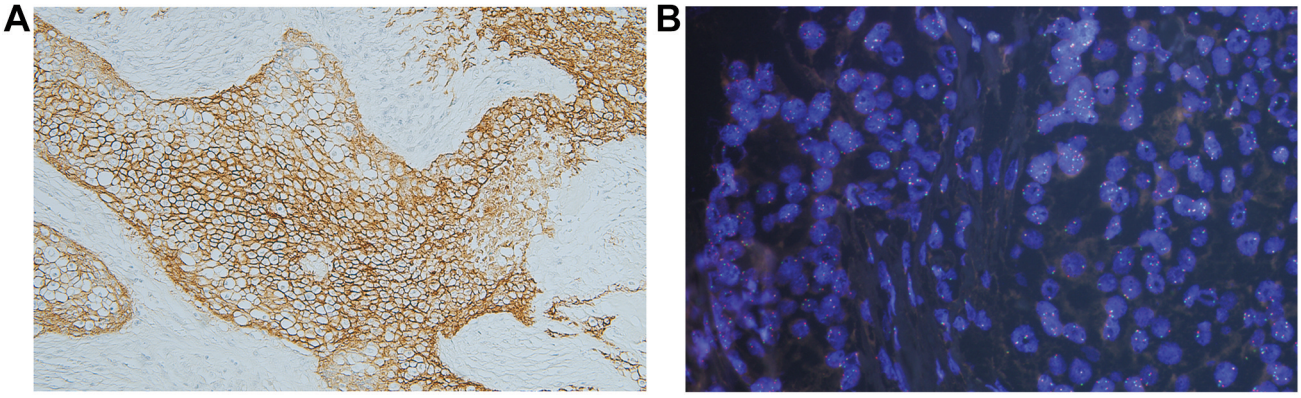

Figure 1. *A: Strong membranous expression of epidermal growth factor receptor (EGFR) (×200). B: Multiple signals for EGFR (red) and chromosome 7 (green) were detected in the tumor nucleus, indicating high EGFR-type polysomy (×400).*

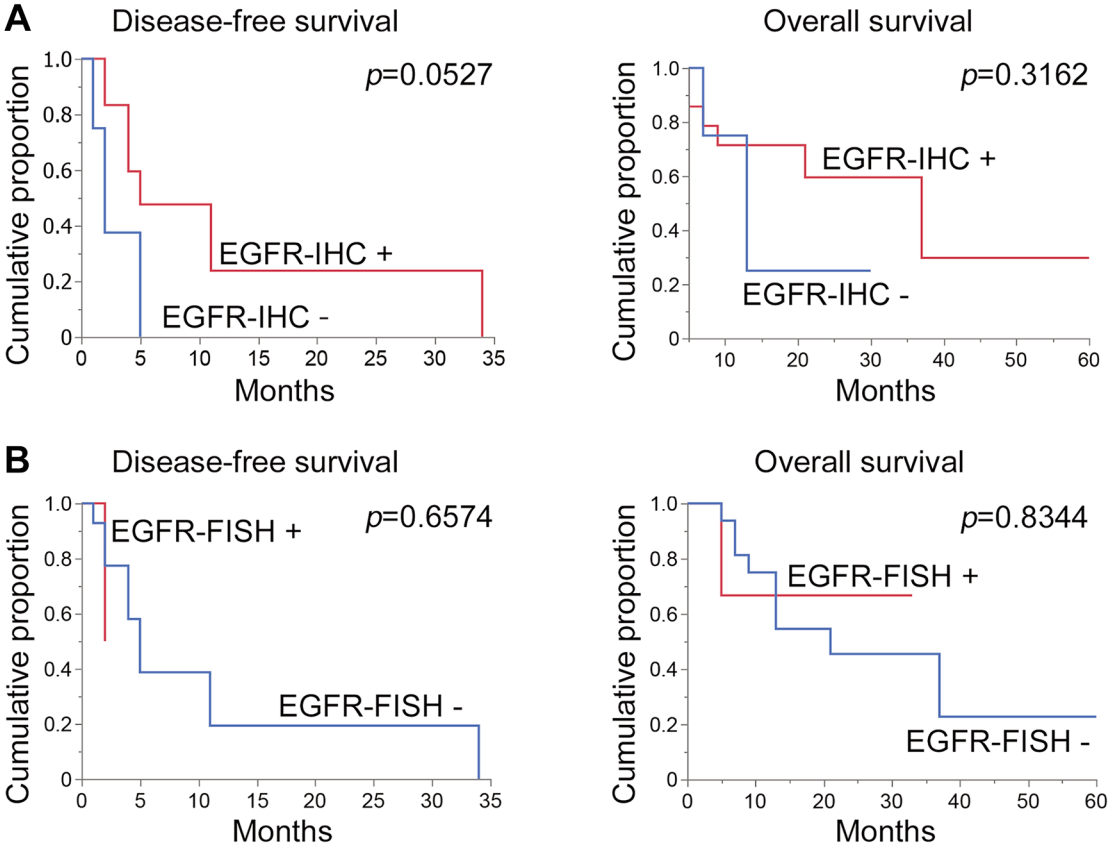

Figure 2. *Kaplan-Meier analysis for progression-free and overall survival according to epidermal growth factor receptor (EGFR) expression status by immunohistochemistry (IHC) (A) and EGFR gene copy number gain by fluorescent in situ hybridization (B). Neither EGFR expression by IHC nor EGFR gene copy number gain were statistically correlated with progression-free or overall survival.*

(80.0%) were positive for EGFR-expression by IHC. EGFR expression by IHC showed a tendency towards better progression-free and overall survival but this was not statistically significant (Figure 2A).

EGFR positivity by FISH was associated with lymph node metastasis (p=0.0291) but was not correlated with the other clinicopathological variables (Table I) or prognosis (Figure 2B). Histopathologically, high *EGFR*-type (chromosome 7)

polysomy was detected for three out of 11 (27.3%) non-adenoid cystic carcinoma cases, including two of the three salivary duct carcinoma cases and one of the three (33.3%) mucoepidermoid carcinoma cases.

Discussion

The major challenge for treatment of locally advanced, recurrent, or metastatic SGC is its resistance to systemic chemotherapy therapy (12). Unfortunately, the effectiveness of EGFR-targeted therapy (*e.g.,* cetuximab) for SGC has not been sufficiently proven (9, 13-15). The EXTREME regimen (cisplatin/carboplatin, 5-fluorouracil plus cetuximab) has been reported to have the potential to prolong the survival of patients with head-and-neck squamous cell carcinoma (4). However, there is no evidence that the EXTREME regimen is effective in advanced-stage SGC, and there are only a few case reports (9). In our study, the best response to the EXTREME regimen was partial response, which occurred in only two cases, one of mucoepidermoid carcinoma and one of lymphoepithelial carcinoma. During the period of treatment with the EXTREME regimen, no cases with adenoid cystic carcinoma, carcinoma ex pleomorphic adenoma or salivary duct carcinoma showed an objective response (complete or partial response). Moreover, all cases discontinued the EXTREME regimen because of progressive disease and adverse events. Our results suggests that the EXTREME regimen might not be suitable for the treatment of SGC. Immune-checkpoint inhibitors (*e.g.,* nivolumab and pembrolizumab) have become well established in the treatment of recurrent or metastatic head-and-neck squamous cell carcinoma in recent years but there is not enough data regarding their effect on SGC, especially in adenoid cystic carcinoma (13). Therefore, we need to consider a new treatment strategy for advanced-stage SGC.

Near-infrared photoimmunotherapy (NIR-PIT) was recently developed as a treatment for head-and-neck carcinoma (16). NIR-PIT is as follows: RM-1929, which consists of cetuximab and IR700, is intravenously injected, and 1 day later the tumor is exposed to light; the disruption of cell membranes leads to an antitumor effect. This new treatment is used in the clinical setting for squamous cell carcinoma. We also consider NIR-PIT to be another possibility for the treatment of SGC, and focused on the use of NIR-PIT in the treatment of SGC. In this regard, the most important finding of the present study is that most of the SGC cases expressed EGFR protein; in other words, most SGC cases might benefit from NIR-PIT. Adenoid cystic carcinoma, which has no cure other than surgical resection, frequently exhibits EGFR protein overexpression and perineural extension; it also frequently develops superficial local recurrence. Therefore, NIR-PIT might be suitable for adenoid cystic carcinoma; since light illumination activates IR700, the target lesion must be shallow. Thus, even in the case of adenoid cystic carcinoma, SGC may respond well to NIR-PIT.

In this study, we also evaluated *EGFR* gene copy-number gain by FISH analysis. Among 19 SGC cases, FISH for *EGFR* was positive in 16.7% cases and was associated with N-stage but did not correlate with the other variables, including EGFR protein expression (Table I) or prognosis (Figure 2B). Depending on the histopathological subtype of SGC, *EGFR* copy-number gain might be a prognostic factor (6). However, there was no correlation between EGFR protein expression and gene copy-number gain in this study, as we and other researchers previously reported (6, 14). Thus, assessing *EGFR* copy-number gain may not be required when initiating NIR-PIT treatment for SGC.

In summary, we evaluated EGFR status by IHC and FISH analysis using formalin-fixed paraffin-embedded samples taken before treatment with the EXTREME regimen. We revealed that most SGCs, including adenoid cystic carcinomas, were positive for EGFR expression by IHC but that EGFR-targeting by the EXTREME regimen showed little efficacy. However, further clinical study of SGC treatment is needed.

Conflicts of Interest

The Authors declare that there are no conflicts of interest to disclose.

Authors' Contributions

Conception and design: T. Nakano and R. Yasumatsu. Acquisition of data: T. Nakano, R. Yasumatsu, H. Yamamoto, R. Jiromaru, T. Manako, M. Masuda, M. Yamauchi, Y. Kuratomi, H. Uryu, T. Nakashima, A. Tamae, R. Tanaka, M. Taura and T. Takeuchi. Analysis and interpretation of data: T. Nakano, R. Yasumatsu, K. Hashimoto, M. Matsuo, T. Wakasaki, S. Toh and M. Masuda. Writing of the article: T. Nakano and R. Yasumatsu. Administrative, technical, or material support: T. Nakano, R. Yasumatsu, K. Hashimoto, R. Kuga, T. Hongo, H. Yamamoto, M. Matsuo, T. Wakasaki, R. Jiromaru, T. Manako, S. Toh, M. Masuda, M. Yamauchi, Y. Kuratomi, H. Uryu, T. Nakashima, A. Tamae, R. Tanaka, M. Taura, T. Takeuchi and T. Yoshida. Study supervision: T. Nakano, R. Yasumatsu and T. Nakagawa.

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