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Original

Immunohistochemical Analysis of Various Salivary Gland Carcinomas Focusing on the Possibility of Molecular-targeted and Hormonal Therapy

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Abstract: This study aimed to determine the expression of c-kit, human epidermal growth factor receptor type 2 (HER2), insulin-like growth factor receptor (IGFR), estrogen receptor (ER), progesterone receptor (PgR), vascular endothelial growth factor (VEGF), c-MET, and survivin in adenoid cystic carcinomas (ACC), carcinomas ex pleomorphic adenomas (CXPA), and mucoepidermoid carcinomas (MEC) of the salivary glands. These expression levels and locations were compared to estimate the availability of molecular and hormonal targets for therapy in salivary gland carcinomas. Forty patients with a salivary gland carcinoma, diagnosed and treated at our hospital, were studied. On the basis of histopathology, 13, 12, and 15 patients were diagnosed with ACC, CXPA, and MEC, respectively. Associations between histological types were evaluated by Fisher's exact test, with a significance level of $P < 0.05$. Compared with the other two histological types, ACC samples demonstrated significantly higher c-kit (85%), IGFR (77%), and ER (38%) expression, while CXPA demonstrated significant HER2 (75%) staining, and MEC demonstrated significant IGFR (77%) staining. The differences in expression of the tested markers among the histological types in our study suggested that c-kit- and IGFR-targeted therapy and anti-estrogen treatment could be effective in ACC, HER2-targeted therapy could be effective in CXPA, and that IGFR-target therapy could be effective in MEC of the salivary glands.

Key words: salivary gland carcinomas, molecular-targeted therapy, hormonal therapy, immunohistology

Introduction

Salivary gland tumors constitute approximately 5% of all head and neck neoplasms[1)]. Of these tumors, 70% arise from the parotid gland, 10% arise from the submandibular glands, 20% arise from the minor salivary glands, and less than 1% arise from the sublingual glands[2)].

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Approximately 25% of tumors in the parotid gland and 50% of tumors in the other salivary glands are malignant[1]. Adenoid cystic carcinomas (ACC), carcinomas ex pleomorphic adenomas (CXPA), and mucoepidermoid carcinomas (MEC) are the main histological types, with each accounting for approximately 10% of salivary gland tumors[1].

The principal treatment for salivary gland carcinoma in the absence of distant hematogenous metastases is surgical resection. The use of adjuvant postoperative radiotherapy is indicated in patients who have close or positive margins, lymph node metastases, locally advanced disease, bone or nerve involvement, recurrent disease, or a combination of other adverse features such as high nuclear grade, perineural invasion, or lymphovascular invasion[2]. Moreover, the use of systemic chemotherapy has, in general, been confined to those patients. The most active single agents include cisplatin, cyclophosphamide, doxorubicin, and 5-fluorouracil, with a typical treatment-response rate of 10～46%, although with a short effect duration and unknown long-term effectiveness[1]. Therefore, there is a definite need for additional therapeutic strategies to improve the survival and quality of life for these patients.

Molecular-targeted therapy and hormonal therapy are impacting positively on the daily practice of clinical oncology and are potential treatment strategies for patients with salivary gland carcinoma. Tumor biomarker overexpression also has therapeutic implications, and several studies have demonstrated the *in vitro* and *in vivo* efficacy of some antibodies on human carcinomas including c-kit in chronic myelogenous leukemia and advanced c-kit–positive gastrointestinal stromal tumor (GIST)[3], human epidermal growth factor receptor type 2 (HER2) in breast carcinoma[4], insulin-like growth factor receptor (IGFR) in non-small cell lung carcinoma[5], estrogen receptor (ER) and progesterone receptor (PgR) in breast carcinoma[6], vascular endothelial growth factor (VEGF) in colon carcinoma and non-small cell lung carcinoma[7,8], c-MET in squamous cell carcinoma[9], and survivin in non-small cell lung carcinoma[10]. Accordingly, the present study sought to determine the expression of c-kit, HER2, IGFR, ER, PgR, VEGF, c-MET, and survivin in ACC, CXPA, and MEC of the salivary glands, to investigate their different levels and locations of expression and to estimate the efficacy of molecular-targeted and hormonal therapy in salivary gland carcinomas.

Materials and Methods

Patients and samples

This study included 40 patients diagnosed and treated for a primary malignant salivary gland tumor at our hospital from 1990 to 2011. All patients underwent surgical resection of the tumor. On the basis of histopathology, 13, 12, and 15 patients were identified with ACC, CXPA, and MEC, respectively.

Immunohistochemical staining

Details of the antibodies used in this study are provided in Table 1. Prior to the antibody incubations, 3-μm tumors sections were subjected to antigen retrieval by heat treatment, followed by the inhibition of endogenous peroxidase activity using hydrogen peroxide solution.

Table 1. Antibody details

Antibody	Clone	Company	Dilution	Antigen retrieval	Incubation (min)
c-kit	polyclonal	DAKO, Glostrup, Denmark	1 : 50	heat-treated with EDTA for 60 min	32
HER2/neu	4B5	Ventana Medical Systems, Inc, Tucson, AZ, USA	Prediluted	heat-treated with EDTA for 60 min	32
IGF1R	G11	Ventana Medical Systems, Inc, Tucson, AZ, USA	Prediluted	heat-treated with EDTA for 60 min	32
ER	SP1	Ventana Medical Systems, Inc, Tucson, AZ, USA	Prediluted	heat-treated with EDTA for 60 min	16
PgR	1E2	Ventana Medical Systems, Inc, Tucson, AZ, USA	Prediluted	heat-treated with EDTA for 60 min	16
VEGF	polyclonal	Biotechnology, Santa Cruz, California, USA	1 : 500	heat-treated with EDTA for 90 min	32
c-MET	SP44	Ventana Medical Systems, Inc, Tucson, AZ, USA	Prediluted	heat-treated with EDTA for 60 min	16
survivin	polyclonal	Abcam, Cambridge Science Park, UK	1 : 250	heat-treated with EDTA for 30 min	32

Primary antibody binding was detected using a secondary antibody raised against biotinylated immunoglobulin (Ventana Medical Systems, Inc, Tucson, Arizona, USA) for 8 minutes and conjugated with avidin-horseradish peroxidase (HRP). Each staining was visualized using a Ventana I-View DAB universal kit (Roche, Tokyo, Japan). The antibody-antigen reaction was enhanced using copper sulfate, after nuclear staining with Mayer's hematoxylin.

Scoring

The intensity of the immunoreactions (negative, positive) was assessed for each marker and tissue combination. Expression was considered positive only if distinct immunoreactivity was present. To determine percentage labelling indices, all carcinoma cells in each section were analyzed. The cellular location of immunoreactivity and the cutoff value for a positive reaction of each marker are presented in Table 2, as described in previous reports[11-17].

All slides were evaluated independently by at least two investigators.

Analysis

The associations between histological types were evaluated using Fisher's exact test. Differences were considered statistically significant at $P < 0.05$.

Table 2. Interpretation of immunohistochemical staining patterns

Marker	Cellular location	Cut-off value
c-kit	Membrane	5%
HER2/neu	Membrane	10%
IGF1R	Membrane	10%
ER	Nucleus	3～8※
PgR	Nucleus	3～8※
VEGF	Cytoplasm	20%
c-MET	Membrane	60%
survivin	Cytoplasm	5%

※Allred score

Table 3. Expressions of c-kit, HER2, IGFR, ER, PgR, VEGF, c-MET, and survivin determined by immunohistochemical analysis and differences in marker expressions among ACC, CXPA, and MEC.

Marker	Adenoid cystic carcinomas % (n/13)	Carcinoma ex pleomorphic adenomas % (n/12)	Mucoepidermoid carcinomas% (n/15)	*P*-value
c-kit	85% (11)	25% (3)	7% (1)	0.00004
HER2/neu	0% (0)	75% (9)	7% (1)	0.00001
IGFR	77% (10)	0% (0)	40% (6)	0.00021
ER	38% (5)	25% (3)	0% (0)	0.01807
PgR	0% (0)	17% (2)	0% (0)	0.08462
VEGF	8% (1)	17% (2)	0% (0)	0.18411
c-MET	0% (0)	0% (0)	0% (0)	1
survivin	8% (1)	17% (2)	13% (2)	0.85064

Results (Table 3, Figs. 1-3)

C-kit-positive expression was observed in 85% of ACC, 25% of CXPA, and 7% of MEC. HER2-positive expression was observed in 0% of ACC, 75% of CXPA, and 7% of MEC. IGFR-positive expression was observed in 77% of ACC, 0% of CXPA, and 40% of MEC. ER-positive expression was observed in 38% of ACC, 25% of CXPA, and 0% of MEC. PgR-positive expression was observed in 0% of ACC, 17% of CXPA, and 0% of MEC. VEGF-positive expression was observed in 8% of ACC, 17% of CXPA, and 0% of MEC. No c-MET expression was detected in any of the tumor types. Survivin-positive expression was observed in 8% of ACC, 17% of CXPA, and 13% of MEC.

There were significant differences ($P < 0.05$) in marker expressions among the tumor types

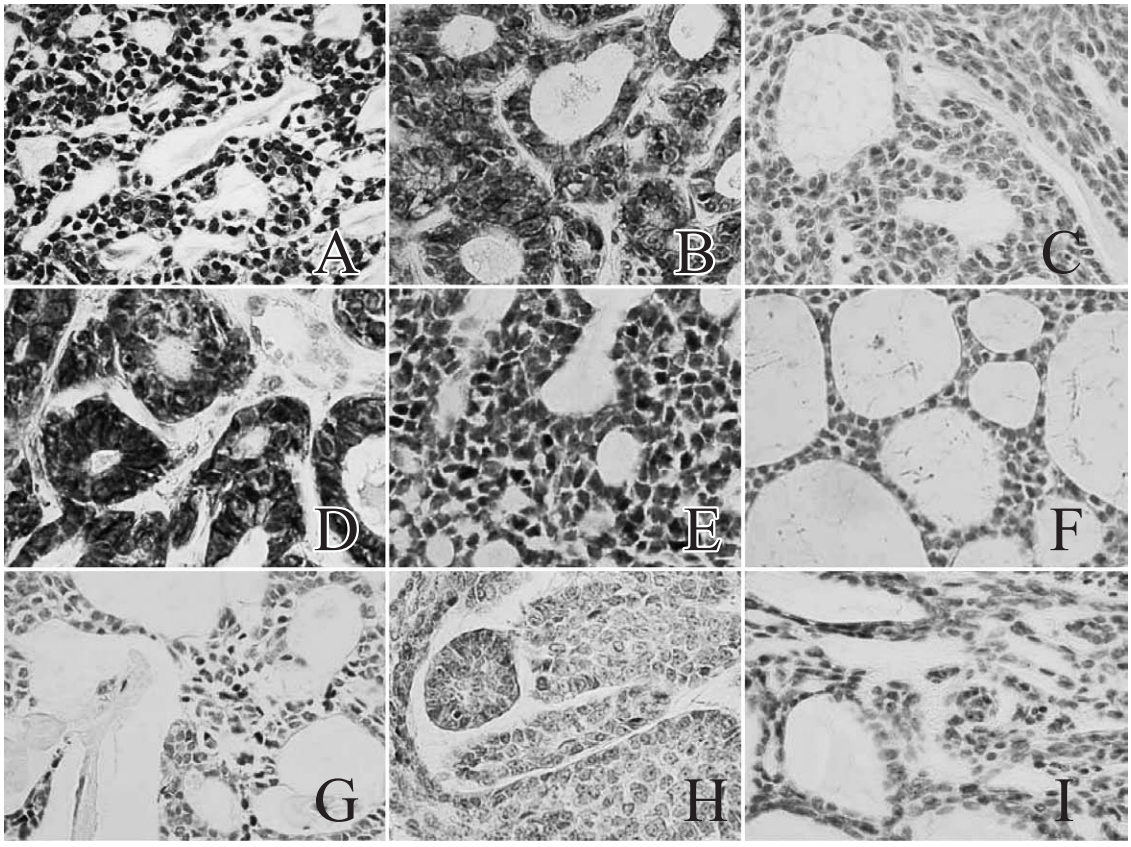

Fig. 1. Immunohistochemical expression in ACC (A, H & E staining)
High expressions were observed for c-kit (B), IGFR (D), and ER (E), while low expressions were observed for HER2 (C), PgR (F), VEGF (G), c-MET (H), and survivin (I).

as follows: c-kit expression between ACC and CXPA, and between ACC and MEC (Fig. 4); HER2 and IGFR expression between ACC and CXPA, and between CXPA and MEC (Fig. 4); ER expression between ACC and MEC (Fig. 4). Moreover, across the three histological types, there were significant differences in c-kit, HER2, IGFR, and ER expressions, while there were no significant differences in PgR, VEGF, c-MET, or survivin expression (Table 3, Fig. 4).

With respect to HER2, ER, and PgR, no cases of ACC or CXPA showed were identified as immunopositive for more than two these markers, with 62% of ACC and 87% of MEC scored as triple negative. However, in the CXPA samples, all ER-positive cases also showed HER2 overexpression and all PgR-positive cases showed both HER2 and ER overexpression, with only 17% scored as triple negative.

Discussion

The identification of molecular targets in salivary gland carcinomas is crucial for improving treatment outcomes. In several other carcinomas, molecular-targeted therapy with antibodies or antagonists and hormonal therapy are promising therapeutic strategies, with some reports that the appearance rates of these markers are reflected in the therapeutic gain *in vitro* and *in vivo*[3-10].

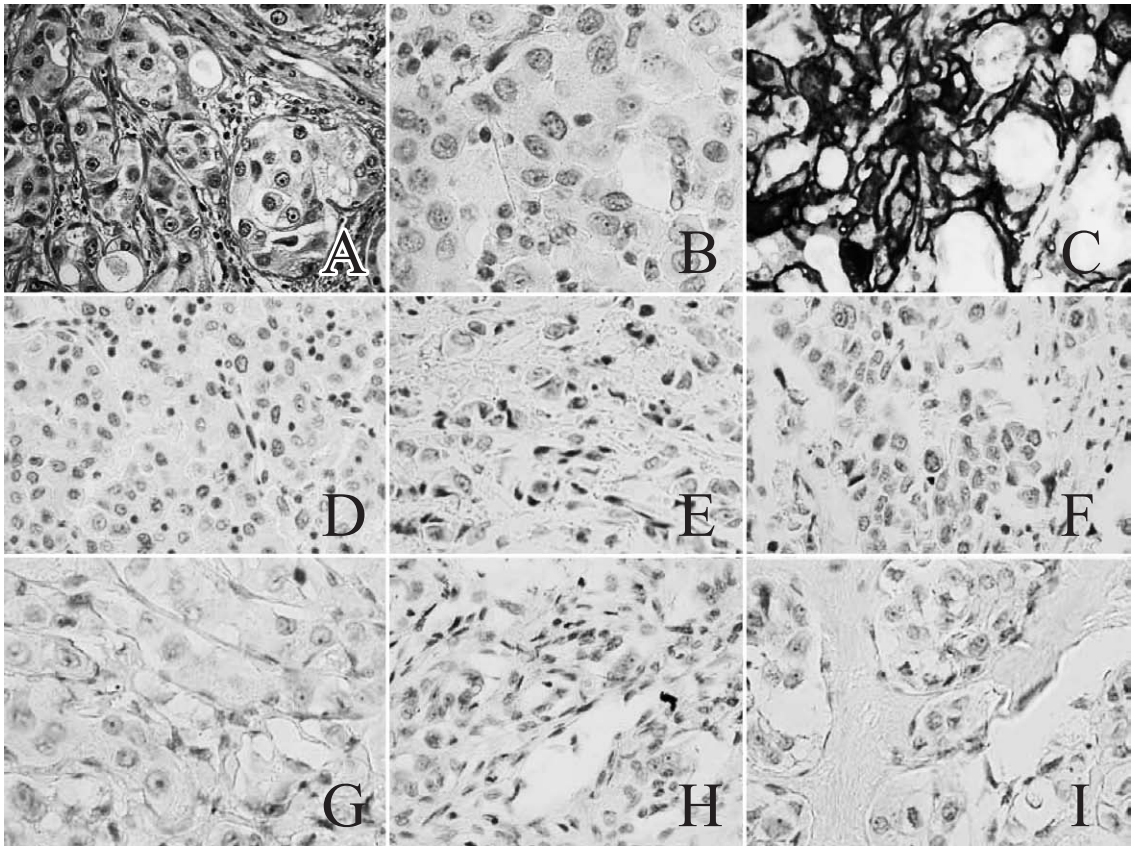

Fig. 2. Immunohistochemical expression in CXPA (A, H&E staining)
High expression was observed for HER2 (C), while low expressions were observed for c-kit (B), IGFR (D), ER (E), PgR (F), VEGF (G), c-MET (H), and survivin (I).

The c-kit proto-oncogene encodes a transmembrane receptor-type tyrosine kinase, which belongs to a family of receptors that includes those for colony-stimulating factor-1 and platelet-derived growth factors. C-kit overexpression is found in GIST, testicular seminoma, mast cell disease, melanoma, and acute myeloid leukemia[3]. The tyrosine kinase inhibitor against c-kit (imatinib mesylate) has demonstrated significant treatment response to chronic myelogenous leukemia and advanced c-kit–positive GIST[3], and several studies demonstrated c-kit expression in the majority of ACC[18]. However, there are few previous studies of c-kit expression in MEC or CXPA. In our study, similar to these previous reports, expression of c-kit in ACC was higher than in the other two histological subtypes, suggesting that the c-kit receptor could be specifically targeted in the treatment of patients with ACC. Ghosal *et al*[18] suggested that imatinib combined with cisplatin could reduce distant metastasis or local progression in ACC of the salivary gland. Mutations in the KIT gene could also affect the efficacy of such targeted therapies, although this remains a controversial issue for ACC and needs to be clarified in future studies. Thus, c-kit in ACC is a potentially useful biomarker for targeted therapies and advanced clinical trials testing this are ongoing. Whether c-kit could similarly be a biomarker for targeted therapies in CXPA and MEC remains unclarified.

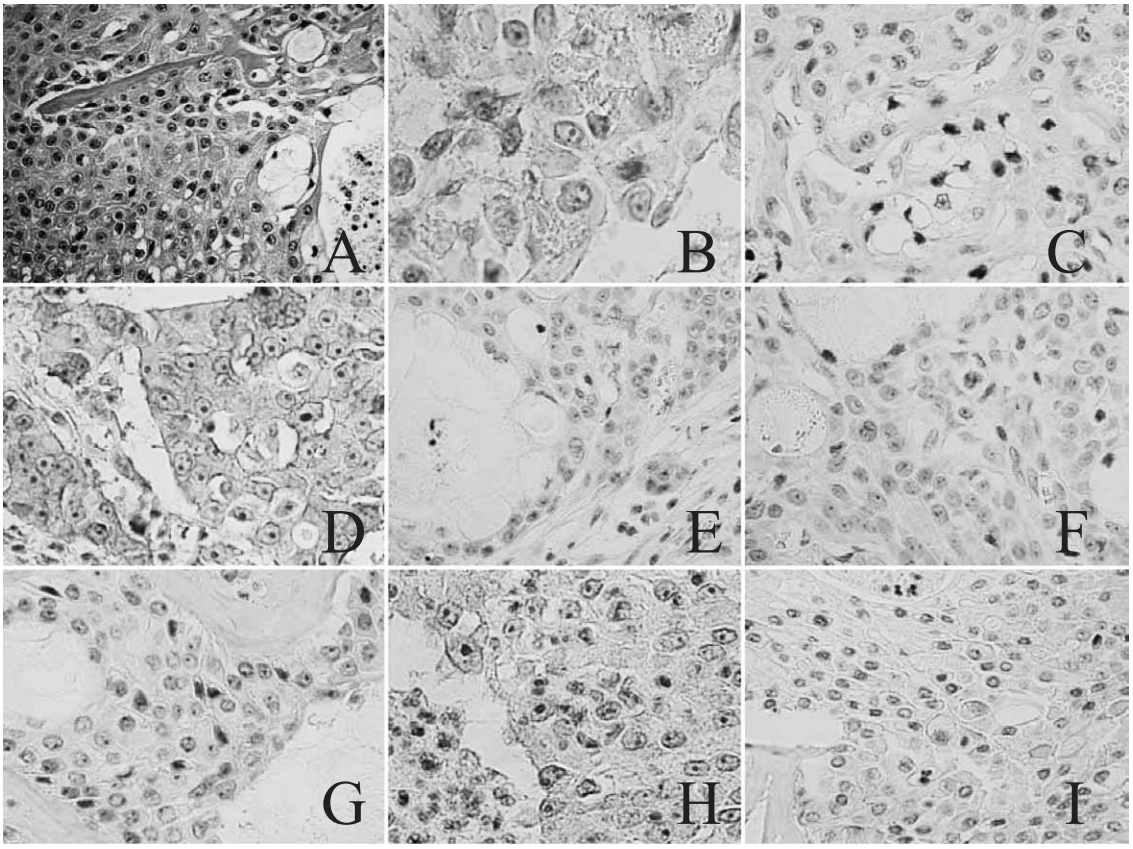

Fig. 3. Immunohistochemical expression in MEC (A, H&E staining)
High expression was observed for IGFR (D), while low expressions were observed for c-kit (B), HER2 (C), ER (E), PgR (F), VEGF (G), c-MET (H), and survivin (I).

HER2-overexpressing breast carcinomas and gastric carcinomas are responsive to trastuzumab (herceptin), and the antitumor effect of trastuzumab on other HER2-overexpressing carcinomas is being examined[19]. There are few previous studies about HER2 overexpression in salivary gland carcinomas, especially in CXPA and MEC. Of these, Glisson *et al*[12] reported HER2 expression in 4% of ACC, 25% of CXPA, and 21% of MEC, while Mori *et al*[20] reported HER2 expression in 10% of ACC, 84% of CXPA, and 18% of MEC. Other reports include a case of HER2-positive metastatic submandibular salivary ductal carcinoma with a complete and durable clinical response to treatment with trastuzumab in combination with chemotherapy, and a 58-year old man with metastatic CXPA who achieved a sustained long-term response to combination therapy with trastuzumab and capecitabine[21, 22]. In our study, HER2 expression in CXPA was significantly higher than in other histological types, suggesting that the HER2 receptor should be specifically targeted in the treatment of patients with CXPA.

IGFR is a tyrosine kinase transmembrane receptor implicated in the regulation of cell metabolism, growth, and survival. According to Ouban *et al*[23] IGFR overexpression is commonly found in breast, ovarian, endometrial, gastrointestinal, pulmonary, bladder, and prostatic carcinomas. Karp *et al*[5] reported that figitumumab (a monoclonal antibody targeting

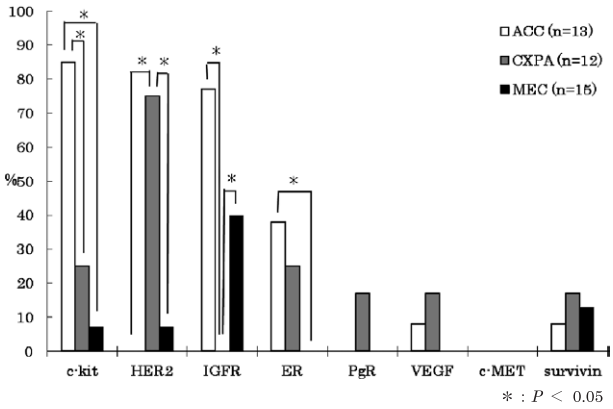

Fig. 4. C-kit, HER2, IGFR, and ER showed significant differences in expression among the histological types ($P<0.05$). Significant differences between ACC and CXPA and between ACC and MEC were observed in c-kit, significant differences between ACC and CXPA and between CXPA and MEC were observed in HER2 and IGFR, and a significant difference between ACC and MEC was observed in ER. In PgR, VEGF, c-MET, and survivin, no significant differences among the histological types were observed.

IGFR-1) in combination with carboplatin and paclitaxel was safe and effective in previously untreated, locally advanced, or metastatic non-small-cell lung carcinomas. There are few previous studies about IGFR overexpression in salivary gland carcinoma, and one study found no IGFR overexpression was in CXPA and ACC types of salivary gland carcinomas (0/8)[23]. However, the present study demonstrated significant higher IGFR expression in ACC and MEC than in CXPA. Thus, although there has been no report concerning anti-IGFR therapies in salivary gland carcinomas, our findings suggest the possibility of specifically targeting this receptor in the treatment of patients with ACC or MEC.

ER and PgR are valid markers for anti-hormone therapies of many hormone-dependent tumors, such as breast and prostate cancers. Barnes *et al*[6] reported that ER- and PgR-positive breast carcinomas are highly responsive to the ER antagonist tamoxifen, while there are several studies about ER and PgR overexpression in salivary gland carcinomas. Ito *et al*[24] reported no ER or PgR immunopositivity in ACC or MEC patients, while Jeannon *et al*[25] reported that 50% of ACC and 30% of MEC were positive for ER, but that none were positive for PgR. In our study, expression of ER in ACC was higher than in the other histological types and expression of PgR was low in all histological types. There are few reports on anti-hormone therapies in salivary gland carcinomas, although Elkin and Jacobs.[26] reported long-term therapeutic effect in two ACC patients treated with tamoxifen/toremifene. Thus, ER is another possibility for specific targeting in the treatment of patients with ACC.

Regarding HER2, ER and PgR, a positive combination of these three affects therapeutic

effect and prognosis, and triple-negative carcinomas (TNT) have a poor prognosis in breast carcinomas[6]. In ACC and MEC of our study, no cases showed two or three positive expressions between them and 62% of ACC and 87% of MEC were TNT. In CXPA of our study, all ER-positive cases had HER2 overexpression and all PgR-positve cases had HER2 and ER overexpression. TNT made up only 17% of CXPA, which may be related to the fact that CXPA generally have a good prognosis[1]. There are no studies on the relationship of expressions between them in CXPA. More research may contribute to the treatment and prognosis in the future.

VEGF, a chemical signal produced by cells, stimulates the growth of new blood vessels. It is part of the system that restores the oxygen supply to tissues when blood circulation is inadequate. VEGF overexpression is found in many carcinomas, such as gastrointestinal and lung[7,8]. Clinically, bevacizumab (a monoclonal antibody against VEGF) shows high response rates against colon carcinomas and non-small cell lung carcinomas[7,8]. There are several previous studies on VEGF overexpression in salivary gland carcinomas. VEGF is frequently expressed in ACC, CXPA and MEC[15,27]. Chau *et al* reported that sunitinib (a multi-targeted small molecule inhibitor of the receptor tyrosine kinases including VEGF) prolonged stable disease beyond 6 months although no objective responses were identified[27]. In our study, expression of VEGF was rare in ACC, CXPA and MEC. Whether VEGF in salivary gland carcinomas can be a biomarker for the targeted therapies remains controversial.

C-Met is a proto-oncogene that encodes a protein known as hepatocyte growth factor receptor. It is reported that c-MET takes part in cancer invasions and metastases including pancreatic, mammary, pulmonary, and renal cell carcinomas[28]. Seiwert *et al*[9] also reported that single-agent foretinib (an inhibitor of the kinase enzymes c-Met and VEGF-2) showed prolonged disease stabilization and a tolerable side-effect profile in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. Suzuki *et al*[29] reported c-Met expression in 67% of ACC; however, our study found no c-Met expression in any of the salivary gland carcinomas tested. Whether c-Met in salivary gland carcinomas can be a biomarker for targeted therapies remains unclarified.

Survivin is a protein that functions to inhibit apoptosis, promote proliferation, and enhance invasion. Survivin overexpression has been reported in breast carcinomas, non-small cell lung carcinomas, ovarian carcinomas, pancreatic carcinomas, and esophageal carcinomas[30]. Giaccone *et al*[10] reported that YM155 (small-molecule suppressor of survivin) exhibited modest single-agent activity in patients with refractory, advanced NSCLC. There are few studies on survivin overexpression in salivary gland carcinomas; Stenner *et al*[16] reported high cytoplasmic expression of survivin in 18.5% of ACC, 12.5% of CXPA, and 31.8% of MEC. In our study, similar to the previous report, there are few cases with high expression of survivin in salivary gland carcinomas. Whether survivin in salivary gland carcinomas can be a biomarker for targeted therapies remains controversial.

In summary, we investigated the expression of c-kit, HER2, IGFR, ER, PgR, VEGF, c-MET, and survivin in salivary gland carcinomas. There are almost no studies comparing the

expressions of these markers in ACC, CXPA, and MEC. This study emphasized the importance of discriminating the histological type in salivary carcinomas and showed the potential beneficial effect of markers according to each histological type, bringing new insight especially in MEC. Differences in the expression of markers among the various histological types indicate the efficacy of targeted therapy for salivary gland carcinomas.

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