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The implicated clinical factors for outcomes in 304 patients with salivary duct carcinoma: A multi-institutional retrospective analysis in Japan

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| Complete List of Authors: | Kusafuka, Kimihide; Shizuoka General Hospital, Department of Pathology  
Sato, Yoko; Shizuoka General Hospital, Division of Clinical Biostatistics, Research Support Center  
Nakatani, Eiji; Shizuoka General Hospital, Division of Clinical Biostatistics, Research Support Center  
Baba, Satoshi; Hamamatsu University School of Medicine Hospital, Department of Diagnostic Pathology,  
Maeda, Matsuyoshi; Toyohashi Municipal Hospital, Department of Clinical Pathology,  
Yamahagi, Koji; Hyogo Medical College, Department of Pathology  
Ueda, Kaori; Nagoya City University, Department of Pathology and Molecular Diagnostics  
Inagaki, Hiroshi; Nagoya City University; Nagoya City University, Department of Pathology and Molecular Diagnostics  
Otsuki, Yoshiro; Seirei Hamamatsu General Hospital, Department of Pathology,  
Kuroda, Naoto; Kobe Kyoudou Hospital, Department of Diagnostic Pathology  
Suzuki, Kensuke; Kansai Medical University Hirakata Hospital, Otolaryngology-Head and Neck surgery  
Iwai, Hiroshi ; Kansai Medical University, Department of Otorhinolaryngology-Head and Neck Surgery  
Imamura, Yoshiaki; University of Fukui Hospital, Division of Diagnostic Pathology/Surgical Pathology,  
Itakura, Junya; Kurashiki Central Hospital, Department of Anatomic Pathology  
Yamanaka, Shoji; Yokohama City University, Department of Diagnostic Pathology  
Takahashi, Hideaki; Yokohama City University, School of Medicine, Otorhinolaryngology, Head and Neck Surgery  
Ito, Ichiro; Nagano Red Cross Hospital, Department of Diagnostic Pathology  
Akashi, Takumi; Tokyo Medical and Dental University, Division of Surgical Pathology  
Daa, Tsutomu; Oita University School of Medicine Graduate School of Medicine, Department of Diagnostic Pathology,  
Hamada, Mei; Saitama Medical University International Medical Center, Department of Diagnostic Pathology, |
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Clinical factors affecting outcomes of 304 patients with salivary duct carcinoma: A multi-institutional retrospective analysis in Japan

Kimihide Kusafuka, D.D.S., Ph.D.\(^1\) (k-kusafuka@i.shizuoka-pho.jp); Yoko Sato, D.D.S., Ph.D.\(^2\) (sato.yoko.shiz@gmail.com); Eiji Nakatani, Ph.D.\(^2\) (nakatani.eiji.int@gmail.com); Satoshi Baba, M.D., Ph.D.\(^3\) (baba@hama-med.ac.jp);

Matsuyoshi Maeda, M.D., Ph.D.\(^4\) (maeda-matsuyoshi@toyohashi-mh.jp); Koji Yamanegi, D.D.S, Ph.D.\(^5\) (yamanegi@hyo-med.ac.jp); Kaori Ueda, D.M.D, Ph.D.\(^6\) (kaori.u.0201@gmail.com); Hiroshi Inagaki, M.D., Ph.D.\(^6\) (hinagaki@med.nagoya-cu.ac.jp); Yoshihiro Otsuki, M.D., Ph.D.\(^7\) (otsuki@sis.seirei.or.jp); Naoto Kuroda, M.D., Ph.D.\(^8\) (kurochankochi@yahoo.co.jp); Kensuke Suzuki, M.D.\(^9\) (suzukken@hirakata.kmu.ac.jp); Hiroshi Iwai, M.D., Ph.D.\(^9\) (iwai@hirakata.kmu.ac.jp);

Yoshiaki Imamura, M.D., Ph.D.\(^10\) (suki@u-fukui.ac.jp); Junya Itakura, M.D., Ph.D.\(^11\) (ji14830@kchnet.or.jp); Shoji Yamanaka, M.D., Ph.D.\(^12\) (kowanyamanaka@gmail.com); Hideaki Takahashi, M.D.\(^13\) (htk98@yokohama-cu.ac.jp); Ichiro Ito, M.D., Ph.D.\(^14\) (ichirito@nifty.com); Takumi Akashi, M.D., Ph.D.\(^15\) (akashi.path@tdm.ac.jp); Tsutomu Daa, M.D., Ph.D.\(^16\) (daatom@med.oita-u.ac.jp); Mei Hamada, D.D.S., Ph.D.\(^17\) (de421042@s.okayama-u.ac.jp), Masanori Yasuda, M.D., Ph.D.\(^18\)
Ph.D.¹⁷ (m_yasuda@saitama-med.ac.jp); Ryo Kawata, M.D., Ph.D.¹⁸ (oto034@osaka-med.ac.jp); Hidetaka Yamamoto, M.D., Ph.D.¹⁹ (hidetaka@surgpath.med.kyushu-u.ac.jp); Yuri Tachibana, D.M.D., Ph.D.²⁰ (y.tachibana19890221@gmail.com); Junya Fukuoka, M.D., Ph.D.²⁰ (fukuokaj@nagasaki-u.ac.jp); Aya Muramatsu, M.D., Ph.D.¹ (aya-muramatsu@i.shizuoka-pho.jp); Kazumori Arai, M.D., Ph.D.¹ (m-arai@ny.tokai.or.jp); Makoto Suzuki, M.D., Ph.D.¹ (makoto-suzuki@i.shizuoka-pho.jp)

¹Department of Pathology and ²Division of Clinical Biostatistics, Research Support Center, Shizuoka General Hospital, Shizuoka, Japan, ³Department of Diagnostic Pathology, Hamamatsu University School of Medicine Hospital, Shizuoka, Japan, ⁴Department of Clinical Pathology, Toyohashi Municipal Hospital, Aichi, Japan, ⁵Department of Pathology Hyogo Medical College, Hyogo, Japan, ⁶Department of Pathology and Molecular Diagnostics, Nagoya City University, Nagoya, Japan, ⁷Department of Pathology, Seirei Hamamatsu General Hospital, Shizuoka, Japan, ⁸Department of Diagnostic Pathology, Kobe Koudou Hospital Center, Hyogo, Japan, ⁹Department of Otorhinolaryngology-Head and Neck Surgery, Kansai Medical University, Osaka, Japan, ¹⁰Division of Diagnostic Pathology/Surgical Pathology, University of Fukui Hospital, Fukui, Japan, ¹¹Department of Anatomic Pathology,
Kurashiki Central Hospital, Okayama, Japan, \textsuperscript{12}Department of Diagnostic Pathology,

\textsuperscript{13}Department of Otorhinolaryngology-Head and Neck Surgery, Yokohama City University Graduate School of Medicine, Kanagawa, Japan, \textsuperscript{14}Department of Diagnostic Pathology, Nagano Red Cross Hospital, Nagano, Japan, \textsuperscript{15}Division of Surgical Pathology, Tokyo Medical and Dental University Hospital, Tokyo, Japan; \textsuperscript{16}Department of Diagnostic Pathology, Oita University, Oita, Japan, \textsuperscript{17}Department of Diagnostic Pathology, Saitama Medical University International Medical Center, Saitama, Japan,

\textsuperscript{18}Department of Otorhinolaryngology-Head and Neck Surgery, Osaka Medical College, Osaka, Japan, \textsuperscript{19}Department of Anatomic Pathology, Kyushu University, Fukuoka, Japan and \textsuperscript{20}Department of Pathology, Nagasaki University, Nagasaki, Japan

\textbf{Correspondence to:} Dr. Kimihide Kusafuka, D.D.S., Ph.D.

Department of Pathology, Shizuoka General Hospital

4-27-1 Kita-ando, Aoi-ku, Shizuoka city, Shizuoka 420-8527, Japan

TEL.: +81-54-247-6111

E-mail: k-kusafuka@i.shizuoka-pho.jp

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Author contributions
KK designed and drafted the manuscript, and KK, AM, KA, and MS made the histopathological diagnosis for the central pathological review. KK, SB, MM, KY, KU, HIn, YO, NK, KS, HIw, YI, JI, SY, HT, II, TA, TD, MH, YY, RK, and HY selected cases and provided samples with pathological and clinical data. KK, YS, and
EN performed statistical analyses of all data. MS supervised this manuscript. All of the authors have read and approved the final manuscript.

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**Competing interests**

The authors declare that they have no competing interests related to this study.

**Ethical approval and consent to participate**

The present study was approved by the Institutional Review Board of Shizuoka General Hospital (SGHIRB#2019007). All subjects signed informed consent forms before participating.

**Availability of data and materials**

The datasets used and analyzed during the present study are available from the corresponding author upon reasonable request.
Abstract:

Background. Salivary duct carcinoma (SDC) is a high-grade salivary malignancy that frequently occurs as the carcinomatous component of carcinoma ex pleomorphic adenoma. We herein examined the clinical factors affecting outcomes in a large cohort of SDC.

Methods. We selected 304 SDC cases and investigated clinical characteristics and the factors affecting outcomes.

Results. The median age of the cases examined was 68 years, the most common primary site was the parotid gland (238 cases), and there was a male predominance (M/F=5:1). Outcomes were significantly worse when the primary tumor site was the minor salivary glands (SG) than when it was the major SG. Outcomes were also significantly worse in pN(+) cases (161 cases) than in pN0 cases, particularly those with a metastatic lymph node number ≥11. The cumulative incidence of relapse and distant metastases was significantly higher in stage IV cases than in stage 0-III cases.

Conclusions. The absolute number of lymph node metastases, higher stages, and the minor SG as the primary tumor site were identified as factors affecting the outcome of SDC.
Introduction

Salivary duct carcinoma (SDC) is a high-grade malignant tumor of the salivary glands (SG) [1]. However, it frequently occurs as the carcinomatous component of carcinoma ex pleomorphic adenoma (CXPA) [2]. Although SDC shares histological similarities with invasive ductal carcinoma of the breast, it typically shows an apocrine phenotype, which differs from the immunophenotypes (estrogen receptor [ER]+ and/or progesterone receptor [PgR]+) of breast cancer; the majority of SDC cases were immunohistochemically negative for ER and/or PgR, but variably positive for the androgen receptor (AR) and gross cystic disease fluid protein-15 [1,3]. Boon et al. previously reported that the absolute number of positive lymph nodes (LN) was associated with a poor overall survival (OS) and distant metastasis-free survival (DMFS) in a multivariable analysis of patients presenting without distant metastases in the Netherlands [4]. In contrast, Otsuka et al. showed that an advanced N stage independently affected both OS and disease-free survival (DFS) [5]. Therefore, the present study investigated the clinical features of SDC and attempted to identify the clinical factors affecting outcomes in the largest cohort of SDC patients in Japan.

Materials and methods
Case selection

We initially collected data on 392 cases of “SDC”, “CXPA”, and “adenocarcinoma” from the pathology files of 18 institutions and a set of consultation files (from K.K.) between 1992 and 2020. Among them, SDC cases, including CXPA cases, were extracted from the central diagnostic system by four expert pathologists (K.K., A.M., K.A., and M.S.; Supplemental Figure 1). The following clinical data were collected from the medical records of each institution: age, sex, site, treatments, TNM classification, pathological stage, outcome, and follow-up data. Tumors were staged according to the eighth edition of the TNM Classification of Malignant Tumours [6]. Hashimoto’s classification for T factors and pathological stages was used to stage CXPA [7]: intracapsular (IC), minimally invasive (MinI), and widely invasive (WI), based on the invasive distance from the fibrous capsule, with MinI being ≤2 mm from the fibrous capsule of a co-existing pleomorphic adenoma (PA) and WI >2 mm from the capsule.

Statistical analysis

OS was measured from the date of diagnosis until death by any cause. Patients alive at the last known follow-up date were censored. The cumulative incidence of relapse
(CIR) was defined as the number of cases in which local or regional recurrence or
distant metastasis occurred after the primary surgery, regardless of which occurred first.
Patients that were alive without disease at the last known follow-up examination were
censored for the purposes of the DFS analysis. The cumulative incidence of distant
metastasis relapse (CIDMR) was defined as the number of cases in which distant
metastasis occurred after the primary surgery. Frequencies and percentages were used
for categorical variables. Survival curves were estimated by the Kaplan-Meier method
and cumulative incidence curves using a competing-risk model analysis with Grey's test
when the competing-risk event was death [8,9]. A univariate Cox proportional hazards
regression model or Fine-Grey proportional hazard regression model was used for
comparisons of patient and tumor characteristics and survival. A multivariate Cox
proportional hazards regression model or Fine-Grey proportion hazard regression model
was then performed by adjusting variables with P-values <0.05 in the univariate
analysis. Hazard ratios, 95% confidence intervals (CI), and corresponding P-values
were calculated based on the Wald test. The variables used in regression models for the
cumulative accumulation of the overall incidence, relapse incidence, late cervical LN
metastasis (CLNM), and distant metastasis incidence included sex, age (categorical), the
T-, N-, and M-status, pathological stage, number of positive LN (categorical), CXPA,
and the primary tumor site. We also investigated the pattern of treatment failure, including locoregional recurrence and distant metastasis. Patients with metastatic disease at diagnosis and those with missing values for one or more of the variables were excluded from the multivariable analysis. Data were analyzed using R version 3.6.2 software (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient and tumor characteristics

A central pathological review and preserved data led to the inclusion of 304 eligible SDC cases from 392 cases in the initial collection (Figure 1). Patient characteristics are shown in Table 1. Median age was 68 years (range: 27-91) and there was a male predominance (83%). Although the univariate analysis of OS showed poorer outcomes for males than for females, a significant difference was not observed in the multivariate analysis. The most common primary tumor site was the parotid gland in 238 out of 304 cases (78%), followed by the submandibular gland in 55 (18%), and then the sublingual gland (1 case), palate (5 cases), parapharynx (2 cases), buccal gland (1 case), nasal cavity (1 case), and intraoral minor SG (1 case). Sixty-nine cases (23%) had Tis and T1 as early cancer, whereas 71 (23%), 79 (26%), and 80 (26%) had T2, T3, and T4,
respectively, as advanced cancer. CLNM was detected in 161 cases (53%) in the primary surgery. Distant metastases were detected in 19 cases (6.3%). Based on the histological origin, the 304 SDC cases selected for the present study comprised 122 (40%) of de novo SDC and 182 (60%) of SDC arising from PA (CXPA cases), including 47 of the IC subtype, 23 of the MinI subtype, and 112 of the WI subtype. Pathological stages were as follows: stages 0-I in 59 cases (20%), stages II and III in 78 (26%), and stage IV in 156 (51%).

The most frequent target organs for late distant metastases (n=93) were the lungs (61 cases: 66%), followed by bone (32 cases: 34%), the central nervous system (19 cases: 20%), including the brain, meninges, and spine, distant LN (13 cases: 14%), including the mediastinal, axillary, and/or abdominal LN, the liver (11 cases: 12%), skin (8 cases: 8.6%), and other organs (4 cases), including the thyroid gland, breast, tongue, and kidney.

**Therapy**

A total of 107 patients underwent surgery only, while 197 received post-operative radiotherapy [RT] (102 patients: 52%), adjuvant chemotherapy [Ch] (13 patients: 6.6%), adjuvant chemoradiotherapy [CRT] (70 patients: 36%), and additional surgery (5
patients: 2.5%) after the primary surgery (Supplemental Table 1). After the primary surgery, 25, 30, and 93 patients showed local recurrence, late CLNM (regional relapse), and distant metastasis, respectively. Among 110 patients with recurrence, five underwent additional surgery, while 102, 11, and 70 received additional RT, Ch, and CRT, respectively. Only 3 out of 61 patients with lung metastases recovered from the status of being alive with disease to the status of being alive without disease with additional surgery and RT for metastatic lesion(s).

Clinical outcomes and survival analysis

The median follow-up period was 2.93 years (minimum-maximum: 0.01-21.70 years). At the time of the analysis, 149 patients were alive without disease, 66 died of disease, 38 were alive with disease, and 19 died of other causes. Kaplan-Meier curves for OS, DFS, and DMFS are shown in Figure 2. The cumulative incidence rates of 1- and 5-year relapse were 26.2% (95% confidence interval [CI], 20.7-32.1%) and 49.0% (95% CI 41.9-55.7%), respectively. The cumulative incidence rates of 1- and 5-year local relapse (CILR), CLNM (CICLNM), and CIDMR were 7.0% (95%CI, 4.2-10.8%) and 12.0% (95% CI, 8-16.9%), and 7.0% (95% CI, 4.2-10.8), and 12.0% (95% CI, 8-
16.9%), 20.3% (95% CI, 15.4-25.7%), and 41.6% (95% CI, 34.7-48.4%), respectively
(Supplemental Figures 1 and 2).

Cumulative incidence curves stratifying prognostic factors identified by univariate
and multivariate regression models are shown in Figures 3 and 4 and Supplemental
Figures 2 and 3, whereas those analyzed by the Fine-Grey proportional hazards model
are shown in Tables 2 and 3. OS was significantly worse in patients with a higher
pathological stage and larger number of LN metastases (p<0.001: 0 vs 1-10 vs ≥11
cancer-positive nodes). On the other hand, no significant differences were observed in
CIR, CILR, CICLNM, and CIDMR between de novo (CXPA[-]) and CXPA-WI cases,
whereas OS, CIR, CILR, CICLNR, and CIDMR were better in CXPA-IC/MinI cases
than in de novo and CXPA-WI cases. The multivariate analysis identified stage IV
(p<0.001 vs. stages 0, I, II, and III, respectively) and ≥11 positive LN (p=0.028; vs. no
LN metastasis) as independent prognostic factors for OS. In addition to stage IV, ≥11
positive LN (p<0.001; vs. no LN metastasis) and minor SG as the primary tumor site
(p<0.001 and p=0.003; vs the parotid gland and submandibular gland, respectively)
were identified as strongly independent factors for CIR. Similarly, minor SG as the
primary tumor site (p<0.001 and p=0.012; vs. the parotid gland and submandibular
gland, respectively), stage IVA/B (p=0.005; vs. stages 0, I, II, and III), and ≥11 positive
LN (p<0.001; vs. no LN metastasis) were also independent prognostic factors for
CIDMR.

Patterns of treatment failure

As shown in Figure 5A, treatment failure occurred in 110 cases (36%), including 25
(8.2%) local, 30 (9.9%) regional, and 93 (31%) distant failures, of which 65 (59%) were
without locoregional failure. As shown in Figure 5B, the most common sites of distant
metastasis were the lungs (n=61 cases), followed by bone (n=32 cases), the central
nervous system (n=19 cases), distant LN (n=13 cases), the liver (n=11 cases), and skin
(n=8 cases). Pre-operative distant metastases were detected in 19 patients (cM1: lungs,
10 cases; liver, 3 cases; bone, 4 cases; axillary LN, 1 case; pleurae 1 case). Among cM1
cases, 11 died of disease and 5 were alive with disease.

Discussion

The present study examined 304 SDC cases, which represents the largest cohort of
SDC reported to date, and provides extensive insights into the clinical outcomes,
treatment, and prognostic factors of SDC. The results obtained support an aggressive
clinical course in spite of the lower rate of distant metastases (31%) than in Boon’s
retrospective study [4] and a median OS of 11.61 years. In the study by Boon, the
number of positive LN was the only factor independently associated with poor OS and
DMFS [4]. Previous studies reported that 5-year OS rates in patients with SDC ranged
between 12 and 55%: the weighted average of five-year DFS and OS rates were 46 and
35%, respectively [9-17]. The majority of studies on the clinical outcome of SDC
presented data from a single institution. However, Jayaprakash et al. [18] conducted an
analysis of 228 patients using the Surveillance, Epidemiology, and End Results
database. The findings obtained showed that the 10-year OS rate was 42% and median
OS was 79 months, with the majority of deaths occurring within the first five years of
the diagnosis of SDC [18]. Even in patients with early T stage SDC, the overall
prognosis was poor (five-year DFS and OS rates of 49%) [16]. Otsuka et al. [5] reported
3-year OS and DFS rates of 70.5 and 38.2%, respectively, in 141 SDC cases from
multiple institutions, showed that an advanced N stage independently affected both OS
and DFS, and identified the most common treatment failure as distant metastasis. In the
present study, the most common treatment failure in SDC patients was also distant
metastasis. Although another analysis of a larger cohort (n=56) subsequently showed
similar outcomes, with 3- and 5-year OS rates of 42.7 and 26.9%, respectively, recent
studies with similar cohort sizes reported a better 5-year OS rate of 55.1%, suggesting
the benefits of the intensification of both surgery and adjuvant RT for treatment outcomes [12,19,20]. However, marked differences were observed between OS and DFS; the 5-year DFS was 29% in one study [19], whereas Otsuka et al. [5] indicated 3-year OS and DFS rates of 70.5% and 38.2%, respectively. This discrepancy reflects the markedly high ratio of treatment failure for SDC. In the present study, 3-, 5- and 10-year CIR were 46.3, 49.0, and 57.4%, respectively (3-, 5-, and 10-year DFS rates were 48.5, 41.7, and 32.6%, respectively; data not shown). In our cohort, Three-year DFS was slightly better in the present study than previously reported [5,12,18,19], which may be attributed to advances in post-operative therapies.

In the present study, a higher pathological stage, which was associated with advanced T and N factors, and large numbers of cancer-positive LN were identified as independent prognostic factors. Boon et al. [4] and Otsuka et al. [5] indicated that advanced N factors and/or the number of positive LN correlated with OS and DFS or DMFS. In the present study, an advanced N factor (N0 vs N2/N3) and ≥11 cancer-positive LN correlated with poor 5-year OS, 5-year CIR, and 5-year CIDMR. These were consistent with previous studies [4,5]. SDC had higher incidences of LN and distant metastases than those reported by Osborn (46.5%) and Jayaprakash et al. (49%), respectively [18,21]. In the present study, outcomes were worse in cases with minor SG
than in those with the parotid gland and submandibular gland as the primary tumor site.

Since standard therapeutic strategies have not yet been established for SDC cases in which minor SG is the primary tumor site, and, thus, adequate therapies were not performed for these cases, their outcomes were worse. Furthermore, a negative surgical margin may not have been achieved in these cases, resulting in incomplete resection. Therefore, clinicians need to consider these factors in cases of SDC arising from minor SG.

In the statistical analyses, we mainly used competing-risk analysis, in which death was employed as a competing risk, to analyze the cumulative incidence of relapse, local relapse, LN metastasis, and distant metastasis in order to produce more precise statistical results. Kaplan-Meier curve analysis frequently leads to the cumulative risk that patients are exposed to being overestimated, and when a competing risk is present the cumulative risk of patients with certain diseases is not as high as the cumulative risk indicated by the Kaplan-Meier method [9,22,23].

Otsuka et al. [5] (n=141) and Jayaprakash et al. [18] (n=228) identified age and the N factor as independent prognostic factors for OS and DFS/disease-specific survival, in addition to the tumor size and grade in a multivariate analysis. However, a correlation was not observed between age and outcomes in the 304 SDC cases examined in the
present study. However, LN metastasis (N[+]) was associated with worse OS, CIR, CICLNM, and CIDMR than N0 cases, and was one of the independent factors predicting a poor outcome.

In our cohort, the most common form of treatment failure was late distant metastases (n=93 in our series), which is consistent with the findings from smaller cohorts [11,20,24] and a larger cohort [5]. Previous studies identified the lungs and bone as the most common sites of distant metastasis in SDC [5,12,21,25], which is in accordance with the present results. A high ratio of distant metastases is presumed to be the leading cause of high CIR and CIDMR or low DFS and DMFS. Although extended resection with wider margins combined with intensified adjuvant RT appear to have contributed to better treatment outcomes in SDC patients by improving locoregional control, these strategies alone cannot prevent the development of delayed distant metastasis. Therefore, effective systemic therapy after curative surgery is imperative for improving CIR and CIDMR in SDC patients. Immunohistochemical studies revealed the expression of AR in 69-100% of SDC cases [25-27], whereas that of HER2 was only observed in 26-77%, both of which were confirmed in other reports, suggesting a potential role for agents targeting these receptors in molecular-targeted therapy for SDC [5,28,29]. Despite the focal or heterogenous expression of AR, androgen deprivation
therapy (ADT) was found to be clinically beneficial for patients with AR-positive SDC, with 18% achieving a partial response and 50% stable disease in addition to longer DSF [30–32]. However, some cases acquire resistance to ADT due to the aberrant expression of SRD5A1 and loss of FOXA1 expression [33,34]. The administration of trastuzumab and docetaxel to patients with HER2-positive SDC achieved a good overall response (70.2%: 95%CI, 56.6-81.6%), including partial and complete responses, and was clinically beneficial (84.2%; 95%CI, 72.1-92.5%), with increases in OS and progression-free survival [35]. Since the status of patients with early or late distant metastasis is systemic, novel chemotherapy regimens are needed, such as ADT for AR-positive SDC and/or trastuzumab therapy for HER2-positive SDC [36]. Similar to our cohort, only a few patients have been treated with ADT or trastuzumab and, thus, the therapeutic effects of these agents remain unclear. AR, HER2, and EGFR profiles in SDC patients in our series are currently being investigated.

In the present study, the outcomes of SDC ex-PA-WI and de novo SDC were both poor, whereas that of SDC ex-PA-IC/MinI was better. Hashimoto’s classification was used in the present study to stage CXPA [7] because the TNM classification focused on the extent of invasion of carcinoma and not the tumor size; since CXPA-IC cases may exhibit large tumors, and CXPA-WI cases small tumors. Since the extent of invasion of
MinI CXPA markedly varies between 1.5 and 8 mm in the 4th WHO classification, we established MinI ≤2 mm from the fibrous capsule of a co-existing PA for a more practical and easily measurable value. Few studies have investigated differences between CXPA(-) and CXPA(+) cases [4,10]. Griffith et al. showed that OS was significantly worse in extracapsular invasive-type SDC ex-PA than in IC-type SDC ex-PA [37]. IC-type SDC ex-PA is an indolent tumor, whereas invasive-type SDC ex-PA is an aggressive tumor, similar to de novo SDC; therefore, WI-type SDC ex-PA need to be added to the analytical cohort. In our series, nine out of the 47 cases of IC-type SDC ex-PA died mainly due to other diseases except for one case. Therefore, IC-type SDC ex-PA has a better outcome than invasive SDC.

In conclusion, SDC frequently occurs in major SG, mostly in the parotid gland; however, outcomes are worse in minor SG cases than in major SG cases. A high N factor, particularly large numbers (11≥) of cancer-positive LN, or high pathological stage were identified as factors contributing to a worse prognosis, and the main reason for treatment failure was delayed distant metastases.

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Figure legends

Figure 1. Consort diagram of the inclusion of SDC cases. All data were collected from 18 institutions and consultation cases (K.K.) and 304 eligible cases of SDC were ultimately selected.

Figure 2 (A) Overall survival (OS), (B) disease-free survival curve (DFS), and (C) distant metastasis-free survival (DMFS) in 304 patients with SDC. The non-dotted line represents survival probability and dotted lines show the 95% confidence interval. Three- and five-year OS, DFS, and DMFS rates were 77.9 and 64.6%, 48.5 and 41.7%, and 53.5 and 45.8%, respectively.

Figure 3. Cumulative incidence of relapse (CIR) curves according to each prognostic factor identified in the univariate analysis and multivariate Fine-Grey proportional hazard regression model. CIR according to the site (A) (p<0.001), pStage (B) (p<0.001) and number of LN metastasis (C) (p<0.001).
Figure 4. Cumulative incidence of distant metastasis relapse (CIDMR) curves according to each prognostic factor identified in the univariate analysis and multivariate Fine-Grey proportional hazard regression model. CIDMR according to the site (A) (p=0.0476), pStage (B) (p<0.001), and number of LN metastasis (C) (p<0.001).

Figure 5. Patterns of disease recurrence. (A) Local and regional recurrence and distant metastases in 110 patients with recurrence. The numbers in the circles represent the absolute number of patients with local and regional recurrence and the presence of distant metastases. Patients with primarily metastatic disease were not included in this figure. (B) Localization of distant metastases sorted by absolute numbers in 93 patients with distant metastases. Patients with primarily metastastic diseases were not included in this figure.

Supplemental figures

Supplemental Figure 1. (A) Typical histology of a de novo (CXPA[-]) case showing Roman bridge structures of large atypical cells with an eosinophilic cytoplasm, and
comedonecrosis (hematoxylin & eosin stain). (B) Typical histology of a CXPA(+) case showing the co-existence of a pleomorphic adenoma (PA) circumscribed with a fibrous capsule (yellow dotted line). The intracapsular component (IC) showed the growth of atypical glandular cells within the PA component, whereas the invasive component (Inv) showed the extracapsular growth of SDC cells (hematoxylin & eosin stain).

Supplemental Figure 2. Cumulative incidence of relapse (CIR) (A), cumulative incidence of local relapse (CILR) (B), cumulative incidence of cervical lymph node relapse (CICLNR) (C), and cumulative incidence of distant metastasis relapse (CIDMR) (D). The non-dotted line represents each incidence and dotted lines show the 95% confidence interval.
Figure 1. Consort diagram of inclusion of SDC patients. All data were collected from 18 institutions and consult cases (K.K.) and according to this diagram, eligible 304 cases of SDC were finally selected.  

190x254mm (96 x 96 DPI)
Figure 2

(A) Overall survival (OS), (B) disease free survival curve (DFS) and (C) distant metastasis free survival (DMFS) of all 304 patients with SDC. The non-dotted line represents the survival probability and the dotted lines represents the 95% confidence interval. The 3-year and 5-year OS, DFS and DMFS rates were 77.9% and 64.6%, 48.5% and 41.7 %, and 53.5% and 45.8%, respectively.

190x254mm (96 x 96 DPI)
Figure 3. The cumulative incidence of relapse (CIR) curves according each of the prognostic factors that were found to be significant on both univariate analysis and multivariate Fine-Grey proportional hazard regression model are shown as follows: CIR according to the site (A) \( p < 0.001 \), Stage (B) \( p < 0.001 \) and numbers of LN metastasis (C) \( p < 0.001 \), respectively.
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Figure 5. Patterns of disease recurrence. (A) Breakdown of local and regional recurrences and distant metastases in 110 patients with a recurrence. The numbers in the circles represent the absolute number of patients with local and regional recurrences and the presence of distant metastases. Patients with primarily metastatic disease are not included in this figure. (B) Localization of distant metastases sorted by absolute numbers of presence in 93 patients with distant metastases. Patients with primarily metastatic diseases are not included in this figure.
Table 1. Characteristics of 304 patients with salivary duct carcinoma

| Age(y); median=68 (27-91) | No. of patients | percentage (%) |
|----------------------------|-----------------|----------------|
| ≤49                        | 34              | 11             |
| 50-59                      | 53              | 17             |
| 60-69                      | 99              | 33             |
| 70-79                      | 81              | 27             |
| ≥80                        | 37              | 12             |

| Gender                | No. of patients | percentage (%) |
|-----------------------|-----------------|----------------|
| male                  | 253             | 83             |
| female                | 51              | 17             |

| Site                    | No. of patients | percentage (%) |
|-------------------------|-----------------|----------------|
| parotid gland           | 238             | 78             |
| SMG                     | 55              | 18             |
| others                  | 11              | 3.6            |

| CXPA                  | No. of patients | percentage (%) |
|-----------------------|-----------------|----------------|
| CXPA(-)/de novo cancer| 121             | 40             |
| CXPA(+): IC           | 47              | 15             |
| CXPA(+): MinI         | 23              | 7.6            |
| CXPA(+): WI           | 112             | 37             |
| unknown               | 1               | 0.3            |

| Stage                  | No. of patients | percentage (%) |
|------------------------|-----------------|----------------|
| T factor               |                 |                |
| Stage 0—Tis            | 28              | 0.72-6         |
| Stage I—T1             | 5864            | 1920           |
| Stage II—T2            | 3374            | 1123           |
| Stage III—T3           | 4579            | 1526           |
| Stage IVA—T4           | 11880           | 3926           |
| Stage IVB—Tx           | 192             | 60.7           |

| Stage                  | No. of patients | percentage (%) |
|------------------------|-----------------|----------------|
| IVCN factor            |                 |                |
| unknown—N0             | 10434           | 3.343          |
| unknown—Nx             | 1942            | 64             |

| No. of LN metastasis   | No. of patients | percentage (%) |
|------------------------|-----------------|----------------|
| N0                     | 126408          | 4136           |
| N2                     | 10215           | 345            |
| N3                     | 572             | 190.7          |
| N(+)                   | 1942            | 64             |
| Nx                     |                 |                |
SMG, submandibular gland; CXPA, carcinoma ex pleomorphic adenoma;

IC, intracapsular; MinI, minimally invasive; WI, widely invasive;

No., number; LN, lymph node; S, surgery; POT, post-operative therapy.

*N does not include the late cervical LN metastases.

**M does not include the late distant metastases.
Table 1. Characteristics of 304 patients with salivary duct carcinoma

|                  | No. of patients | percentage (%) |
|------------------|-----------------|----------------|
| **Age (y); median=68 (27-91)**                      |                 |                |
| ≤49              | 34              | 11             |
| 50-59            | 53              | 17             |
| 60-69            | 99              | 33             |
| 70-79            | 81              | 27             |
| ≥80              | 37              | 12             |
| **Gender**       |                 |                |
| Male             | 253             | 83             |
| Female           | 51              | 17             |
| **Site**         |                 |                |
| Parotid gland    | 238             | 78             |
| SMG              | 55              | 18             |
| Others           | 11              | 3.6            |
| **CXPA**         |                 |                |
| CXPA(-)/de novo cancer | 121     | 40             |
| CXPA(+): IC      | 47              | 15             |
| CXPA(+): MinI    | 23              | 7.6            |
| CXPA(+): WI      | 112             | 37             |
| Unknown          | 1               | 0.3            |
| **Stage**        |                 |                |
| Stage 0          | 2               | 0.7            |
| Stage I          | 58              | 19             |
| Stage II         | 33              | 11             |
| Stage III        | 45              | 15             |
| Stage IVA        | 118             | 39             |
| Stage I VB       | 19              | 6              |
| Stage I VC       | 19              | 6              |
| Unknown          | 10              | 3.3            |
| **No. of LN metastasis** |             |                |
| 0                | 126             | 41             |
| 1-10             | 102             | 34             |
| ≥11              | 57              | 19             |
| Unknown          | 19              | 6              |
| Therapy | 107 | 35 |
|---------|-----|----|
| S+POT   | 197 | 65 |

SMG, submandibular gland; CXPA, carcinoma ex pleomorphic adenoma;

IC, intracapsular; MinI, minimally invasive; WI, widely invasive;

No., number; LN, lymph node; S, surgery; POT, post-operative therapy.

*N does not include the late cervical LN metastases.

**M does not include the late distant metastases.
Table 2. Univariate analyses for overall survival, cumulative incidence of recurrence and cumulative incidence of distant metastasis

|          | OS                        | CIR                        | CIDMR                       |
|----------|---------------------------|----------------------------|-----------------------------|
|          | N  | HR           |  p-  | (95%) CI | HR           | p-  | (95%) CI | HR           | p-  | (95%) CI |
| Age      |    |              |      |          |              |      |          |              |      |          |
| <65y/o   | 131| 0.83         | 0.380| (0.55-1.26)| 0.79         | 0.200| (0.54-1.14)| 0.83         | 0.27 |
|          |    |              |      |          |              |      |          |              |      |          |
| ≥65y/o   | 173| Ref.         | Ref. | Ref.     | Ref.         | Ref. | Ref.     | Ref.         |      |          |
| Gender   |    |              |      |          |              |      |          |              |      |          |
| female   | 51 | Ref.         | Ref. | Ref.     | Ref.         |      |          |              |      |          |
| male     | 252| 2.05         | 0.041| 1.68     | 0.081        | 1.88 | 0.058    |              |      |          |
|          |    |              |      |          |              |      |          |              |      |          |
| Site     |    |              |      |          |              |      |          |              |      |          |
| parotid  | 238| 2.33         | 0.402| 0.21     | <0.00        | 0.33 | 0.050    |              |      |          |
|          |    |              |      |          |              |      |          |              |      |          |
|          |    |              |      |          |              |      |          |              |      |          |
| SMG      | 55 | 1.68         | 0.617| 0.14     | <0.00        | 0.24 | 0.023    |              |      |          |
|          |    |              |      |          |              |      |          |              |      |          |
|          |    |              |      |          |              |      |          |              |      |          |
|                 |          | Ref. | Ref. | Ref. |
|----------------|----------|------|------|------|
| **CXPA**       | (-) de novo | 121  | Ref. | Ref. | Ref. |
| (+) IC/MinI   | 70       | 0.6  | 0.098| 0.63 | 0.190| 0.64(0.3 | 0.220 |
|               |          |      |      |      |      | 1.10 |      |
|               |          |      |      |      |      | (0.32- | 2-1.31)|
|               |          |      |      |      |      | 1.25) |      |
| (+) WI        | 112      | 1.12 | 0.615| 0.91 | 0.630| 0.77  | 0.220 |
|               |          |      |      |      |      | (0.72- | (0.5- |
|               |          |      |      |      |      | 1.75) | 1.34) |
|               |          |      |      |      |      | 1.17) |      |
| **T**         | Tis/pT1  | 69   | Ref. | Ref. | Ref. |      |      |
| T2/3          | 150      | 2.15 | 1.11 | 0.023| 2.41 | 0.026 | 3.44  |
|               |          |      |      |      |      | (1.11- | (1.27- |
|               |          |      |      |      |      | 5.24) | 9.27) |
| T4            | 80       | 3.39 | <0.00| 4.84 | <0.00| 6.29  | <0.00 |
|               |          |      |      |      |      | (1.69- | 1     |
|               |          |      |      |      |      | 4-10.45) | 1   |
|               |          |      |      |      |      | (2.23- | 1    |
|               |          |      |      |      |      | 6.82) | 17.06 |
| **N**         | N0       | 131  | reference | reference | reference |
| N1            | 36       | 0.98 | 0.958 | 2.21 | 0.018 | 3.05  | 0.003 |
| N2/N3/N(+) | 123 | 2.9 (1.82-<0.00) | 4.07 (2.5-<0.00) | 5.23 | <0.00 |
|------------|-----|------------------|------------------|------|-------|
|            |     | 4.63             | 1                | 2-6.59 | 1    | (2.98-1) | 9.18 |

| M          | M0  | 281 | Ref. | Ref. | Ref. |
|------------|-----|-----|------|------|------|
| M1         | 19  | 2.578 (1.5<0.00) | 1.32 | 0.460 | 1.43 | 0.330 |
|            |     | 1-5.12 | 1 | (0.64-2.74) | (0.69-2.95) | 0.330 |
|            |     |          | 2.74 | 2.95 |

| Stage      | Stage | 138 | Ref. | Ref. | Ref. |
|------------|-------|-----|------|------|------|
| 0/I/II/III |       |     |      |      |      |

| Stage IVA/B | 137 | 3.38 | <0.00 | 4.86 | <0.00 | 4.25 | <0.00 |
|            |     |      | (2.05-5.6) | 1 | (2.9-1) | (2.47-1) | 8.14 | 7.32 |

| Stage IVC  | 19  | 5.61 | <0.00 | 3.56(1.5 | 0.004 | 3.6 | 0.004 |
|            |     |      | (2.77-1) | -8.14 | (1.52-1) | 11.35 | 8.53 |

| No. of     | 0   | 126 | Ref. | Ref. | Ref. | 0.001 |
|------------|-----|-----|------|------|------|-------|

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| LN | metastasis | 1-10 | 102 | 1.87 (1.1- 0.020) | 2.94 | <0.00 | 4.02 | <0.00 |
|  |  |  |  |  |  |  |  |  |
|  |  |  |  | 3.15) | (1.78- | 1 | (2.23- | 1 |
|  |  |  |  |  | 4.88) | 7.27) |  |
|  |  |  |  |  |  |  |  |  |
| ≥11 |  | 57 | 4.14 | <0.00 | 5.39 | <0.00 | 7.32 | <0.00 |
|  |  |  |  |  | (2.41- | 1 | (3.09- | 1 |
|  |  |  |  |  | 7.11) | 9.39) | 13.81) |  |
| Therapy | S | 107 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
|  | S+POT | 197 | 1.1(0.7- 0.669) | 1.63 | 0.055 | 2.27 | 0.006 |
|  |  |  |  | 1.74) | (0.99- | (1.27- | |
|  |  |  |  |  | 2.69) | 4.05) |  |

Bold shows p<0.05.

HR, hazard ratio; 95%CI, 95% confidence interval; OS, overall survival; CIR, cumulative incidence of recurrence; CIDMR, cumulative incidence of distant metastasis relapse; No, number; Ref., reference; CXPA, carcinoma ex pleomorphic
adenoma; IC, intracapsular type; MinI, minimally invasive type; WI, widely invasive type; SMG, submandibular gland; LN, lymph node; S, surgery; POT, post-operative therapy.
Table 3. Multivariate analysis for overall survival, cumulative incidence of recurrence and cumulative incidence of distant metastasis

|           | OS          | CIR         | CIDMR        |
|-----------|-------------|-------------|--------------|
|           | HR          | p-value     | HR           | p-value     | HR           | p-value     |
|           | (95% CI)    |             | (95% CI)     |             | (95% CI)     |             |
| Gender    |             |             |              |             |              |             |
| male      | 1.54 (0.76- | 0.230       | ND           | ND          | ND           | ND          |
|           | 3.09)       |             |              |             |              |             |
| female    | Ref.        | ND          | ND           | ND          | ND           | ND          |
| Site      |             |             |              |             |              |             |
| parotid   | ND          | ND          | 0.28 (0.16-  | <0.001      | 0.28 (0.14-  | <0.001      |
| gland     |             |             | 0.52)        |             | 0.59)        |             |
| SMG       | ND          | ND          | 0.27 (0.12-  | 0.003       | 0.3 (0.12-   | 0.012       |
|           |             |             | 0.63)        |             | 0.77)        |             |
| others    | ND          | ND          | Ref.         | Ref.        |              |             |
| Stage     |             |             |              |             |              |             |
| Stage     | Ref.        | Ref.        | Ref.         |             |              |             |
| 0/I/II/III|             |             |              |             |              |             |
| Stage | IVA/B |  | IVC |  |
|-------|-------|---|-----|---|
|       | 2.65 (1.44- **0.002**) | 3.35 (1.83- **<0.001**) | 2.42 (1.3- **0.005**) | 4.88) |
|       | 6.14) | 4.49) | 8.41) | 5.85) | 4.91) |

| No. of LN metastasis |
|-----------------------|
| 0                     | Ref.          | Ref.          | Ref.          |
| 1-10                  | 1.09 (0.59- 0.777) | 1.75 (1.03- **0.040**) | 2.73 (1.45- **0.002**) |
|                       | 2.02)         | 2.99)         | 5.14)         |
| ≥11                   | 2.07 (1.08- **0.028**) | 2.86 (1.57- **<0.001**) | 4.63 (2.33- **<0.001**) |
|                       | 3.94)         | 5.2)          | 9.22)         |

Bold shows p<0.05.

HR, hazard ratio; 95% CI, 95% confidence interval; OS, overall survival; CIR, cumulative incidence of recurrence; CIDMR, cumulative incidence of distant metastasis relapse; Ref., reference; SMG, submandibular gland; LN, lymph node; No, number; ND, not done.

*p-value of Wald’s test relating to “recurrence coefficient=0”*
Supplemental figure 1

190x254mm (96 x 96 DPI)
Supplemental figure 2

A

B

C

D

190x254mm (96 x 96 DPI)
Supplemental figure 3

A

B

C

D

190x254mm (96 x 96 DPI)
Supplemental table 1. The summary of post-operative therapy (POT).

|                  | No. of patients (n=197) | percentage |
|------------------|-------------------------|------------|
| S→RT             | 102                     | 52%        |
| S→Ch*/**         | 13                      | 6.6%       |
| S→CRT**          | 70                      | 36%        |
| S→S#             | 5                       | 2.5%       |
| S→unknown        | 7                       | 3.6%       |

S, surgery; RT, radiotherapy; Ch, chemotherapy; CRT, chemoradiotherapy.

*Including TS-1 administration (2 cases) and S-1 administration (1 case)

**Including Trastuzumab administration (6 cases), Nivolumab administration (3 case), and androgen deprivation therapy (5 cases).

#Including additional resection for local recurrence (2 cases), neck dissection (1 case), resection for distant metastasis (3 cases) and addition resection for recurrence (unknown location) (2 case).
Supplemental table 2. Univariate and multivariate analyses for cumulative incidence of local relapse (CILR) and cumulative incidence of cervical lymph node metastasis (CICLN)

|                | Univariate analysis |          | Multivariate analysis |          |
|----------------|---------------------|----------|-----------------------|----------|
|                | CILR                | CICLN    | CILR                  | CICLN    |
|                | M                   |          |                       |          |
| No             | HR                  | p-       | HR                    | p-       |
|                | (95% value)         |          | (95% value)           |          |
|                | e                   | CI       | e                     | CI       |
|                | CI                  |          | CI                    |          |

**Age**

| Age | No | HR  | p- | HR  | p- | HR  | p- | HR  | p- |
|-----|----|-----|----|-----|----|-----|----|-----|----|
|     | 13 | 0.87| 0.72| 0.68| 0.280| ND  | ND |
| <65y|    |     |     |     |     |     |     |     |     |
|     | 1  | (0.41| 0   | (0.34-| 1.37)| 1.87) |     |
| ≥65y| 17 | Ref.| Ref.| ND  | ND  |     |     |
|     |    |     |     |     |     |     |     |     |     |

**Gender**
|        |    |    |    |    |    |    |    |
|--------|----|----|----|----|----|----|----|
| male   | 25 | 1.08 | 0.89 | 1.04 | 0.940 | ND | ND |
|        | 3  | (0.37 | 0 | (0.4- | - | 2.67) | 3.13) |
| female | 51 | Ref. | Ref. | ND | ND |

**Site**

|        |    |    |    |    |    |    |    |
|--------|----|----|----|----|----|----|----|
| parotid | 23 | 0.25 | 0.04 | 0.16 | 0.003 | 0.34 | 0.12 | 0.26 | 0.02 |
|        | 8  | (0.06 | 7 | (0.05- | (0.08 | 0 | (0.09- | 0 |
|        | -  | 0.55) | - | 0.81) | 0.98) | 1.34) |
| SMG    | 55 | 0.04 | 0.01 | 0.11 | 0.006 | 0.08 | 0.03 | 0.2 | 0.05 |
|        | 0- | 0 | (0.02- | (0.01 | 0 | (0.04- | 3 |
|        | 0.47) | 0.53) | - | 1.02) | 0.78) |
| others | 11 | Ref. | 0.02 | Ref. | 0.009 | Ref. | 0.08 | Ref. | 0.05 |
|        | 7  | 4 | 7 |

**CXPA**

|        |    |    |    |    |    |    |
|--------|----|----|----|----|----|----|
| (-)/de | 12 | Ref. | 0.64 | Ref. | 0.335 | ND | ND |
|       | 1  | 6  |
|-------|----|----|
| **cancer** |    |    |
| (+)IC/  | 70 | 1.29 | 1.99 | **0.003** | ND | ND |
| MinI    | (0.59) | (0.72-2.83) | 5.51 | 2.83 |    |    |
| (+)WI   | 11 | 1.26 | 1.63 | 0.230 | ND | ND |
|         | 2  | (0.76) | (0.74-2.11) | 3.6 | 2.11 |    |
| **T**   |    |    |    |    |    |    |
| Tis /1  | 69 | Ref. 0.09 | Ref. 0.262 | ND | ND |
|         | 5  |    |    |    |    |    |
| T2/3    | 15 | 3.27 | 1.14 | 0.840 | ND | ND |
|         | 0  | (0.45) | (0.32-4.02) | 4.02 | 24.0 |    |
|         |    |    |    |    | 4) |    |
|   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
| T4 | 80 | 6.14 | 2.02 | 0.280 | ND | ND |
|    | (0.84 | (0.56- | 0.56- | 7.31) | 7.31) | 7.31) |
|    | - | 7.31) | 7.31) | 45.0 | 45.0 | 45.0 |
|    | 8) | 8) | 8) | | | |
| N  |   |   |   |   |   |   |
| N0 | 13 | Ref. | 0.09 | Ref. | 0.003 | ND | ND |
|    | 1 | 9 | 9 | | | |
| N1 | 36 | 1.35 | 0.67 | 2.91 | 0.190 | ND | ND |
|    | (0.34 | 0 | 0 | (0.59- | (0.59- | (0.59- |
|    | -5.3) | 14.33) | 14.33) | | | |
| N2/3 | 12 | 2.62 | 0.04 | 7.2 | 0.001 | ND | ND |
|    | 3 | 3 | 3 | (2.15- | (2.15- | (2.15- |
|    | - | 24.18) | 24.18) | | | |
|    | 6.65) | 6.65) | 6.65) | | | |
| M  |   |   |   |   |   |   |
| M0 | 28 | 1.16 | 0.84 | 0.95 | 0.940 | ND | ND |
|    | 1 | 0 | 0 | (0.22- | (0.22- | (0.22- |
|     |     |     |     |     |
|-----|-----|-----|-----|-----|
| M1  | 19  | Ref. | Ref. | ND  | ND  |
| Stage |     |     |     |     |     |
| 0/I/II | 13  | Ref. | Ref. | 0.009 | 0.05 | Ref. | 0.26 |
| / III  | 8   | 2   | 8   |     |     |     |     |
| IVA /B | 13  | 4.33 | 0.00 | 5.28 | 0.002 | 3.56 | 0.01 | 3.42 | 0.13 |
|        | 7   | (1.5-7) | (1.82-7) | (1.28-5) | (0.71-0) |     |     |     |     |
|        | 12.4 | 15.35 | - | 6) | 9.93) |     |     |     |     |
| IVC  | 19  | 3.11 | 0.19 | 3.11 | 0.200 | 2.53 | 0.28 | 2.06 | 0.49 |
|       | (0.57-0) | (0.54-0) | (0.48-0) | (0.27-0) |     |     |     |     |     |
|       | - | 17.31 | - |     | 15.85) |     |     |     |     |
|       | 16.9 |     |     |     | 13.5) |     |     |     |     |
|      |     |     |     |     |     |     |     |     |     |

No. of LN

meta.
|   | 12 | Ref. | 0.27 | Ref. | **0.001** | ND. | Ref. | 0.09 |
|---|----|------|------|------|-----------|-----|------|------|
| 6 | 9  |      |      |      |           |     |      |      |
|   |    |      |      |      |           |     |      |      |
|   | 10 | 2.19 | 0.11 | 3.9  | **0.035** | 2.24| 0.30 |
| 2 |    | (0.83| 0    | (1.1- |           | (0.49-| 0    |
|   |    |     |      |   5.78) |         |      |      |
|   |    |      |      |      |           |     |      |      |
| ≥11| 57 | 1.84 | 0.29 | 9.21 | **<0.0**  | 4.65| 0.06 |
|    |    | (0.59| 0    | (2.67-| **01**    | (0.92-| 2    |
| 7 |    | -5.7 | 31.72 |      | 23.4)     |      |      |

**Therapy**

|   | 10 | Ref. |      | Ref. | ND     | ND  |
|---|----|------|------|------|-------|-----|
| 7 |    |      |      |      |       |     |

|   | 19 | 0.56 | 0.27 | 0.93 | 0.850 | ND  | ND  |
|---|----|------|------|------|-------|-----|-----|
|   |    | (0.26| 3    | (0.43)|       |     |     |
|   |    |      |      |      | 1.24  | 2.03|

Bold shows p<0.05.

HR, hazard ratio; 95%CI, 95% confidence interval; CILR, cumulative incidence of
local relapse; CICLNM, cumulative incidence of cervical lymph node metastasis; Ref., reference; No, number; CXPA, carcinoma ex pleomorphic adenoma; IC, intracapsular type; MinI, minimally invasive type; WI, widely invasive type; SMG, submandibular gland; LN, lymph node; S, surgery; POT, post-operative therapy; ND, not done.