Clinicopathologic factors and their association with outcomes of salivary ductal carcinoma: a multi-center experience

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Abstract

Introduction: This series reports long-term clinical outcomes of patients with salivary duct carcinoma (SDC), which is associated with a poor prognosis.

Materials/Methods: Eighty-nine patients with SDC were treated with curative intent from February 5, 1971 - September 15, 2018. Kaplan Meier and competing risk analyses were used to estimate

locoregional control (LRC), distant metastasis-free survival (DMFS), progression-free survival (PFS), and overall survival (OS). Cox regression analyses of disease and treatment characteristics were performed to discover predictors of LRC, DMFS, and OS.

Results: Median follow-up was 44.1 months (0.23 – 356.67 months). The median age at diagnosis was 66 years (IQR 57-75). Curative surgery followed by adjuvant radiotherapy (RT) was performed in 73 (82%) patients. Chemotherapy was delivered in 26 (29.2%) patients. The 5-year local recurrence and distant metastasis rates were 27% and 44%, with death as a competing risk. Distant metastasis was associated with lymph node(LN)-positive disease (HR 3.16 (95% CI: 1.38, 7.23), p = 0.006], stage 4 disease [95% CI: HR 4.78 (1.14, 20.11), p = 0.033), perineural invasion (PNI) [HR 4.56 (1.74, 11.97), p = 0.002], and positive margins [HR 9.06 (95% CI: 3.88, 21.14), p<0.001]. Median OS was 4.84 years (95% CI: 3.54 – 7.02). The 5-year OS was 42%. Reduced OS was associated with lymphovascular space invasion (LVSI) [HR 3.49 (95% CI: 1.2, 10.1), p = 0.022], PNI [HR 2.05 (95% CI: 1.06, 3.97), p = 0.033], positive margins [HR 2.7 (95% CI: 1.3, 5.6), p = 0.011], N2 disease [HR 1.88 (95% CI:1.03, 3.43), p = 0.04], and N3 disease [HR 11.76 (95% CI:3.19, 43.3), p<0.001].

Conclusion: In this single institution, multi-center retrospective study, the 5-year survival was 42% in SDC patients. LVSI, LN involvement, and higher staging at the diagnosis were associated with lower DMFS and OS.

Introduction

Salivary gland cancers are rare, with incidence rates of 0.1-2.7 per 100,000 individuals globally.[1] They have a predilection for older men, with 8.2 cases per 100,000 American men older than 65 compared to only 3.6 for their female counterparts in 2018.[2] The average age of diagnosis is 64, with

a 5-year survival rate of 72%.[3] Salivary duct carcinomas (SDC) make up a tiny fraction (< 2%) of these tumors and are considered to be very aggressive, with a reported 5-year survival rate of 35%. [4-7]

Salivary ductal carcinomas are aggressive primary salivary malignancies that are microscopically similar to breast ductal carcinomas, including large ducts with comedo necrosis, papillary-cribriform growth patterns, and many mitotic figures. [8, 9] SDCs arise either *de novo* or as carcinoma ex pleomorphic adenomas.[9] These tumors typically present in major salivary glands, with the parotid gland representing 80% of the cases.[10] Salivary duct carcinoma is a rapidly growing cancer with a high proliferation index and propensity to spread.[11, 12]. Following curative treatment, up to 50% of recurrences occur as distant metastases, often occurring in bone, lung, liver, and brain. [7, 10, 13, 14] SEER and NCDB analyses have shown that age, male sex, late-stage, and node-positive (N+) disease are negative prognostic survival factors.[4, 10] Additionally, adverse pathological features such as perineural invasion and nerve resection have been demonstrated to be associated with worse survival, though the studies have been inconsistent.[7]

SDCs have distinct molecular markers that could impact prognosis and treatment response. SDCs often exhibit copy number gain of ERBB2 (Receptor tyrosine-protein kinase erbB-2, also known as HER-2/neu) and overexpression of EGFR, although the prognostic value remains unclear.[15-17] Additionally, androgen receptor (AR) expression is a common feature of SDC and can be helpful in diagnosis and determining potential therapies.[7, 18] Given the limited role of systemic therapies in treating SDC, these genetic alterations may drive treatment decisions and prognosis.

Current NCCN guidelines recommend complete surgical resection of the tumor, with neck dissection in T3-4 or any N+ tumors, followed by adjuvant radiotherapy if there is evidence of adverse features, namely high grade, T3-4, positive margins, perineural invasion, lymphovascular space invasion, and lymph node metastasis. [19] SDC carries a high risk of occult lymphatic spread, prompting prophylactic neck dissections, radiotherapy, and systemic therapy in many cases.[20, 21]

Although there are improved diagnostics and WHO reclassifications, the low incidence of SDC continues to be a challenge for employing extensive, prospective studies to optimize treatment and

prognostication.[6] This study reports the clinical features and outcomes of a single-institution multi-center series of salivary ductal carcinoma.

Methods

This study was reviewed and approved by the Institutional Review Board. Retrospectively acquired data were de-identified according to the Health Insurance Portability and Accountability Act guidelines. Eligibility criteria included patients with SDC ≥18 years of age who had a Karnofsky performance of ≥50. Out of 114 patients with histological confirmation of SDC, 89 patients treated between February 5, 1971 - September 15, 2018, were included. Patients were excluded if treatment was palliative intent (N=14) and if staging (N=4) or locoregional control (LRC) status (N=7) was not recorded. Parotidectomy, in which the superficial and deep lobes of the parotid gland are removed, was performed in 75 patients. The median time between surgery and the start of radiotherapy was 40 days (IQR: 35-47 days). Single-agent chemotherapy consisted of cisplatin. Multiagent chemotherapy consisted of cisplatin plus an additional agent.

Radiation Treatment Planning and Delivery

Patients were treated with 2D radiotherapy, 3D conformal radiotherapy, intensity-modulated radiotherapy, or proton beam therapy (PBT). Patients were simulated with computed tomography (CT) in the treatment position. In the 1970s and early 1980s, neck rests, tape, and sandbags were used for immobilization. Since the last 1980s, customized head and neck rests, and oral bite blocks have been used. For patients treated with 2D radiotherapy, the primary tumor and draining lymphatics were treated with 6 MV photons and parallel opposed lateral fields. Opposed lateral fields included the zygoma superiorly, posterior to the mastoid tip, inferior to the thyroid notch, and anterior to the anterior edge of the masseter muscle. The dose was prescribed to the central axis (SAD) but also calculated every 1-2 cm throughout the volume with wedges used to compensate for missing tissue (heels posterior). Two centimeters were added to the preop or intact tumor volume to the lead block edge. It was matched, using various techniques, to an anterior-posterior field with the superior border at the thyroid notch, and the inferior border at the caudal aspect of the heads of the clavicles, and it flashed the neck laterally. The dose

was prescribed to a depth of 3 cm (SSD set up). There was a midline larynx block to protect the larynx and to prevent overlap on the spinal cord by the opposed lateral beams and the anterior beam. The isocenter of the anterior beam was placed at the inferior border of the opposed lateral beams.

More recently, patients were simulated with a thermoplastic mask for immobilization appropriate for each patient's anatomy. Intravenous contrast was used unless contraindicated. In the modern era, the definition of target volume and organ at risk (OAR) and treatment planning was performed in Eclipse (Varian Medical Systems). In patients undergoing adjuvant radiotherapy for parotid SDC, a clinical target volume was delineated, including the postoperative bed of the parotid gland, parapharyngeal space, and fossa infratemporalis. Ipsilateral neck nodes level Ib-V were included in the case of pathologically proven positive nodes. In patients receiving definitive radiotherapy, a gross tumor volume (GTV) was delineated based on CT simulation with image fusion with magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging when available. The GTV was expanded by 1-2 cm to create a CTV constrained by natural anatomic barriers. The CTV was expanded by 3-5 mm to create a planning treatment volume (PTV) to account for interfraction, intrafraction movement, and set-up errors. The same principles were applicable to patients with submandibular gland SDC.

Patients were evaluated for treatment response with clinical exams and imaging such as positron emission tomography-computed tomography (PET-CT) or CT head and neck three months after completion of therapy and every 3-6 months after that. LRC and DMFS cumulative incidence rates and Kaplan-Meier survival curves for OS and PFS were calculated using JMP® Pro, R, and RStudio. LRC was defined as the time from treatment completion to local or regional recurrence. DMFS was defined as the time from final intervention to the development of distant metastatic disease. PFS was defined as the time from final intervention to disease progression or death from any cause. OS was defined as the time from final intervention to time of death from any cause. One patient did not have dates recorded for their intervention, and we used the date of diagnosis as a surrogate. Cox proportional hazards models were used to perform univariate survival analysis with the time of treatment, sex, age, AJCC stage, T classification, N classification, perineural invasion, extranodal extension, lymphovascular space invasion,

and ERBB2 amplification as variables. A competing risk analysis was completed for LRC and DMFS, with death as the competing risk. P values were derived from two-tailed tests. P values less than 0.05 were considered statistically significant.

Results

Eighty-nine patients were treated for salivary duct carcinoma at multiple centers of a single institution between February 5, 1971, and June 7, 2018. The median follow-up was 44.1 months (range 0.23 – 356.67 months). Table 1 and Table 2, respectively, present patient characteristics and disease characteristics. Patients were predominantly male (72% [n = 64]) and had a median age of 66 years (range: 32-89). Females presented slightly younger than males (62.8 vs. 65.1 years, p = 0.373). Most patients had a history of tobacco (61.2% [n = 49]) or alcohol (56.2% [n = 45]) use, with 42.5% [n = 34] having a history of both. Tumor origin was parotid, submandibular, or not classified in 77 (86.5%), 9 (10.1%), and 3 (3.4%) patients, respectively. Lymph node involvement was present in 60 (67.4%) patients. Clinical node classification follows: 29 (32.6%) N0, 9 (10.1%) N1, 48 (53.9%) N2, and 3 (3.4%) N3.

AJCC 8th edition staging was as follows: 12 (13.5%) I, 5 (5.6%) II, 11(12.4%) III, 55 (61.7%) IVa, and 6 (6.8%) IVb. Following surgical resection (Table 2), most patients had evidence of extranodal extension (60.9% [n =28]), lymphovascular space invasion (LVSI, 72.7% [n = 32]), extra parenchymal involvement (EI, 54.2% [n =45]), and perineural invasion (PNI, 63.4% [n = 45]). HER2/neu staining was performed in 41 patients, with 25 (52.1%), 4 (8.3%), and 3 (6.2%) with evidence of amplification, aneusomy, and monosomy, respectively. Androgen receptor (AR) staining was completed in 56 (62.9%) patients; AR positivity was present in 49 (87.5%) and negative in 7 (12.5%). Thirty (33.7%) patients were identified as having HER2/neu amplification/aneusomy/monosomy and AR positivity. Thirty (33.7%) patients were classified as carcinoma ex pleomorphic adenoma, indicating previous pleomorphic adenoma.

Seventy-three (82%) patients were treated with combined modality therapy consisting of surgical resection followed by adjuvant radiotherapy (Table 2). Surgery was performed on 85 patients. A total of

75 (89.3%) patients underwent parotid surgery: 65 (86.7%) total parotidectomy and 10 (13.3%) superficial parotidectomy. Nine (11.7%) patients underwent submandibular gland resection. The median tumor size at resection was 2.5 cm. Margins were positive in 10 patients (11%). Unilateral neck dissection was performed in 65 patients (76.4%). The median number of positive nodes was 8.0 (range 1 -113). Twenty-six (29%) patients received concurrent chemotherapy; single-agent cisplatin was given to 19 patients (73%). Due to unresectable status, 4 (5%) patients underwent definitive radiotherapy; two (2%) received concurrent chemotherapy. Surgical resection alone was performed in 12 (14%) patients. The median radiotherapy dose was 61.2 Gy (range 49.8-76). 2D radiotherapy, 3D conformal radiotherapy, intensity modulated radiation therapy, and proton beam therapy was delivered in 1 (1.3%), 32 (41.6%), 42 (54.5%), and 2 (2.6%) patients, respectively.

Univariate modeling for overall survival, progression-free survival, local recurrence, and distant metastasis is detailed in Table 3. At the last follow-up, death occurred in 60 (67.4%) patients. The median overall survival was 4.84 years. The 5-year overall survival was 42%, and the 5-year progression-free survival was 36.8% (Figures 1A and 1B). Overall survival was associated with surgery alone [HR 2.41 (95% CI: 1.15, 5.06), p = 0.02], LVSI [HR 3.59 (95% CI: 1.2, 10.4), p = 0.019], PNI [HR 1.97 (95% CI: 1.0, 3.7), p<0.038], positive margins [HR 2.7 (1.3, 5.6), p<0.011], N2 disease [HR 1.88 (95% CI:1.03, 3.43), p = 0.04], and N3 disease [HR 11.76 (95% CI:3.19, 43.3), p<0.001]. Androgen receptor status [HR 1.7 (95% CI: 0.6, 4.7), p =0.331] was not associated with OS. Patients receiving chemotherapy had worse 5-year OS (59% vs. 25%, p = 0.012, Figure 2A) and worse 5-year PFS (46.0% vs. 12.5%, p = 0.0014), Figure 2B)

Two patients developed local recurrence during radiotherapy and were excluded from the local-regional control analysis. The 5-year local-regional recurrence and distant metastasis rates were 27% and 44%, with death as a competing risk (Figure 1C and 1D). Five (5.6%) patients developed both a local recurrence and distant metastatic disease. With death as a competing risk, the 1-year local recurrence and distant metastasis rate was 25% and 50%, respectively, in patients who received concurrent chemotherapy (Figure 2C and Figure 2D). The most common locations for distant metastatic disease include bone

(18/39, 46%), lung (18/39, 46%), and liver (7/39, 17.9%). Local recurrence was associated with surgery alone [HR 4.73 (95% CI: 2.14, 10.47), p < 0.001] and tumor size [HR 1.36 (1.03, 1.8), p = 0.03]. Higher rates of distant metastasis occurred in patients receiving concurrent chemotherapy [HR 4.77 (95% CI: 2.42, 9.40), p<0.001]. Distant metastasis was also associated with unilateral neck dissection [HR 2.87 (95% CI: 1.24, 6.64), p = 0.01], N2 disease [HR 3.34 (95% CI: 1.43, 7.8), p = 0.01], N3 disease [HR 5.35 (95% CI: 1.1, 25.98), p = 0.04], stage 4 disease [HR 4.78 (95% CI: 1.14, 20.11), p = 0.033), PNI [HR 4.56 (1.74, 11.97), p = 0.002], and positive margins [HR 9.06 (95% CI: 3.88, 21.14), p<0.001].

Discussion

Salivary duct carcinoma (SDC) is an aggressive malignancy associated with a poor prognosis, given its high recurrence rates and propensity to metastasize to regional lymph nodes and distant sites. The current treatment regimen, consisting of multi-modality therapy with surgical excision, adjuvant radiotherapy, and platinum-based chemotherapy, achieves variable local and distant disease control with high disease-related mortality rates. Herein, we demonstrate a multi-center single, institution experience of salivary duct carcinoma with 89 patients. Like other series, we demonstrate a predominance of male patients, smoking history, and parotid predilection. Similarly, we demonstrated that advanced staging, LN involvement, PNI, and LVSI are associated with lower overall and progression-free survival in univariate analysis.

With the paucity of data in the literature, we present one of the largest cohorts of SDC patients. Reports of outcomes for patients with salivary duct carcinoma are limited, primarily from retrospective reviews. A SEER database review from 1973 to 2008 by Jayaprakash et al. evaluated 228 patients with SDC.[4] The median overall survival (OS) for patients with SDC was 79 months, and the 5-year disease-specific survival (DSS) rate was 64%. However, most patients in this study had Stage I – III disease, with the majority having stage I disease (34.7%). Our institutional experience is one of the few retrospective series with a large cohort of patients. There are approximately four other series with greater than 50 patients.[11, 22-24]. In their 20-year experience, Gilbert and colleagues reported a median OS of 3.1 years and a median disease-free survival of 2.7 years.[22] In their series, Johnston et al. reported a 5-year

OS, locoregional control, and distant control rate of 43%, 70%, and 48% in 54 patients.[24] Our institutional experience compares favorably, with a median survival of 4.84 years and a 5-year OS of 42%. However, this is in the setting of most patients having locally advanced disease at the time of presentation (68.5%).

Several adverse prognostic factors demonstrated in the literature may signify a poor prognosis for patients with salivary duct carcinoma. Jayaprakash et al. demonstrated that negative prognostic indicators include age $\geq$ 50, tumor size, lymph node involvement, and no survival advantage with radiotherapy.[4] On univariate analysis, Gilbert and colleagues demonstrated that facial nerve sacrifice and extracapsular extension were associated with worse OS.[22] On multivariate analysis, OS was significantly worse in patients with N2 and N3 disease.[22] In a study of 56 patients by Roh et al., advanced stage such as T3/T4 tumors, node-positive disease, and PNI were associated with worse OS, DSS, and PFS.[23] Johnston and colleagues demonstrated similar findings, with univariate analysis confirming ECE, LVSI, and N2b/c classification as negative prognostic factors for OS.[24] On multivariate analysis, OS was negatively impacted by N2b or N2c classification. Our series confirmed previously demonstrated findings, in which N2/N3 disease, PNI, LVSI, as well as positive margins and surgery alone, are associated with worse OS.

Salivary duct carcinomas have the propensity for distant metastatic disease. In our series, most patients presented with locally advanced disease at diagnosis (68.5% Stage IVA and Stage IVB) and were treated with surgical resection followed by adjuvant radiotherapy and chemotherapy. Despite multi-modality therapy, there was a roughly 67-69% risk of local recurrence and distant metastasis over five years. Distant metastasis occurred most frequently in bone (46%) and lung (46%), which is consistent with other series.[25] In the SEER database review of 228 patients, 36.9%, 43.6%, and 19.5% presented with localized primary disease, regional lymph node metastasis, and distant metastasis, respectively.[4] In our study, patients with Stage IVA or IVB disease were found to have worse DMFS (HR 4.78 (1.14 – 20.11) p =0.03).

Several challenges, including low incidence, lack of prospective data, and poor prognosis, make it challenging to identify new therapies for SDC. In our study, there was no benefit in OS or PFS with the addition of cisplatin. Patients with adverse features typically receive chemotherapy; therefore, these patients have worse oncologic outcomes. Similar findings have been reported in a large cohort of salivary gland cancers.[26] Given the lack of prospective data, the 2021 ASCO guidelines recommend against chemotherapy in treating salivary gland malignancies unless given within a clinical trial. [27] Currently, three randomized prospective studies (NCT01220583, NCT02776163, and NCT02998385) seek to evaluate the role of chemotherapy.

Molecular markers are potential targets for new systemic therapies in the treatment of SDCs. Salivary duct carcinoma is associated with high recurrence rates and distant metastases with no clear systemic therapy options. Given its aggressive nature, potential targets need to be identified for therapies for salivary duct carcinoma. Copy number gain of ErbB2, also known as HER-2/neu, is the most widely studied genomic alteration in SDC.[7] The percentage of SDC tumors with HER2 positivity ranges between 25–30% of SDC.[28] Androgen receptors are also targets for which targeted agents can potentially lead to a better prognosis. The prevalence of AR+ salivary duct carcinomas is high, from 75-95%.[28] In a multi-institutional collaboration, 66 patients with SDC were evaluated for molecular patterns using a commercially available targeted gene panel.[28] Although AR was not a significant predictor for DFS in univariate analysis, after adjusting for the impact of gender, age, and lymph node involvement, AR positivity was associated with higher DFS ((HR 0.16, 95% CI 0.05–0.53, p = 0.003).[28] Multiple case series and reports have also demonstrated that androgen receptor inhibitors such as bicalutamide or enzalutamide may lead to complete or prolonged responses in patients with recurrent/metastatic SDC.[7, 29, 30] A retrospective study of 35 patients with recurrent/ metastatic SDC or adenocarcinoma NOS (not otherwise specified) compared first-line chemotherapy vs. first-line androgen deprivation therapy.[30] The median overall survival was comparable at 2.1 years.[30] However, the response rate was higher for ADT (45%, 9/20 patients) vs. chemotherapy (14%, 2/14 patients).[30] Current ASCO guidelines support offering treatments with androgen blockade in the setting

of recurrent or metastatic disease.[27] In our study, we observed 52.1% and 87.5% of patients to be positive for ERBB2 and AR, respectively. However, we did not observe an association between AR and ERBB2 status and OS. Given the change in understanding of SDC over time, molecular testing and immunostaining were not done for all patients. As targeted therapies are used more for these molecular markers, including these agents in the upfront setting could become possible.

This study has several limitations. Our conclusions must be interpreted cautiously as a retrospective study due to potential selection bias. This retrospective analysis included patients over 47 years, with multiple advances in surgical techniques and radiotherapy planning. Given the retrospective nature of such an extended period, there is heterogeneity in identifying pertinent pathologic information, including the extent of extranodal extension, lymphovascular space invasion, ERBB2 amplification, and androgen staining. Additionally, many of the patients in this study presented with locally advanced disease at the time of diagnosis. Due to this, directly comparing this multi-center experience to other series of SDC series is more challenging.

Conclusion

In conclusion, salivary duct carcinoma is highly aggressive and has a poor prognosis. We demonstrated a 5-year overall survival of 42%, comparable to other institutions. An aggressive multi-modality treatment approach, including appropriate surgical resection, elective neck dissection, and postoperative radiotherapy, can improve local control and overall survival. Multinodal involvement and perineural and lymphovascular space invasion are associated with poor disease control and prognosis. Systemic therapies targeting molecular alterations must be further investigated in the first-line setting.

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Legend

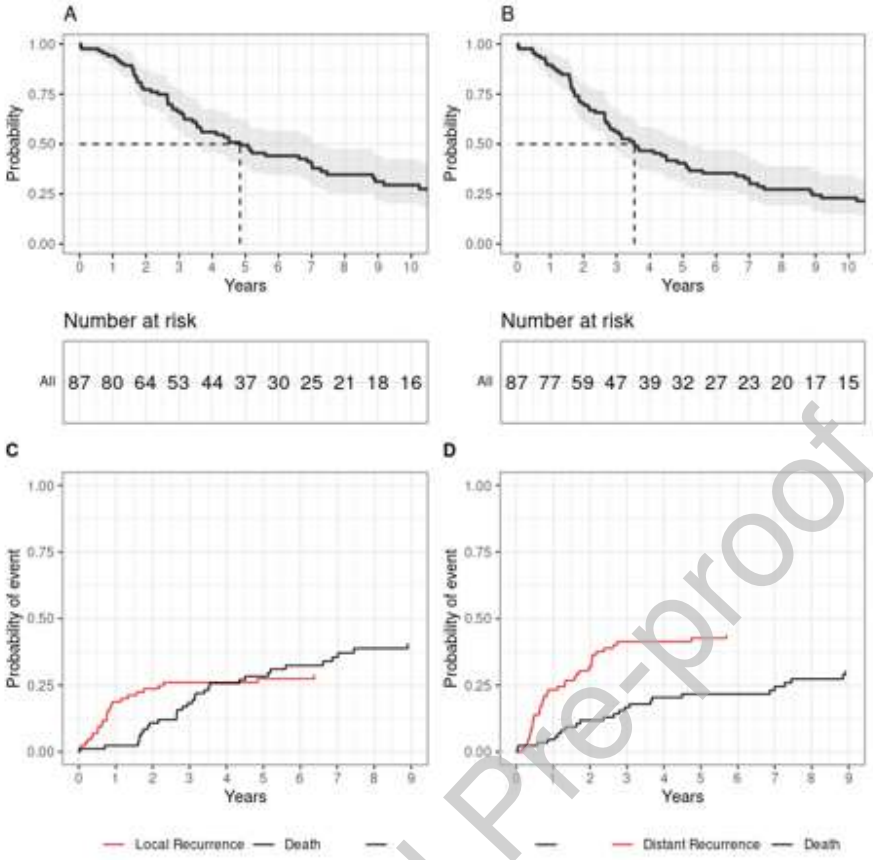

Figure 1. Kaplan Meier curves for overall survival (a) and progression-free survival (b) and cumulative incidence of local recurrence (c) and distant recurrence (d) in patients with salivary duct carcinoma.

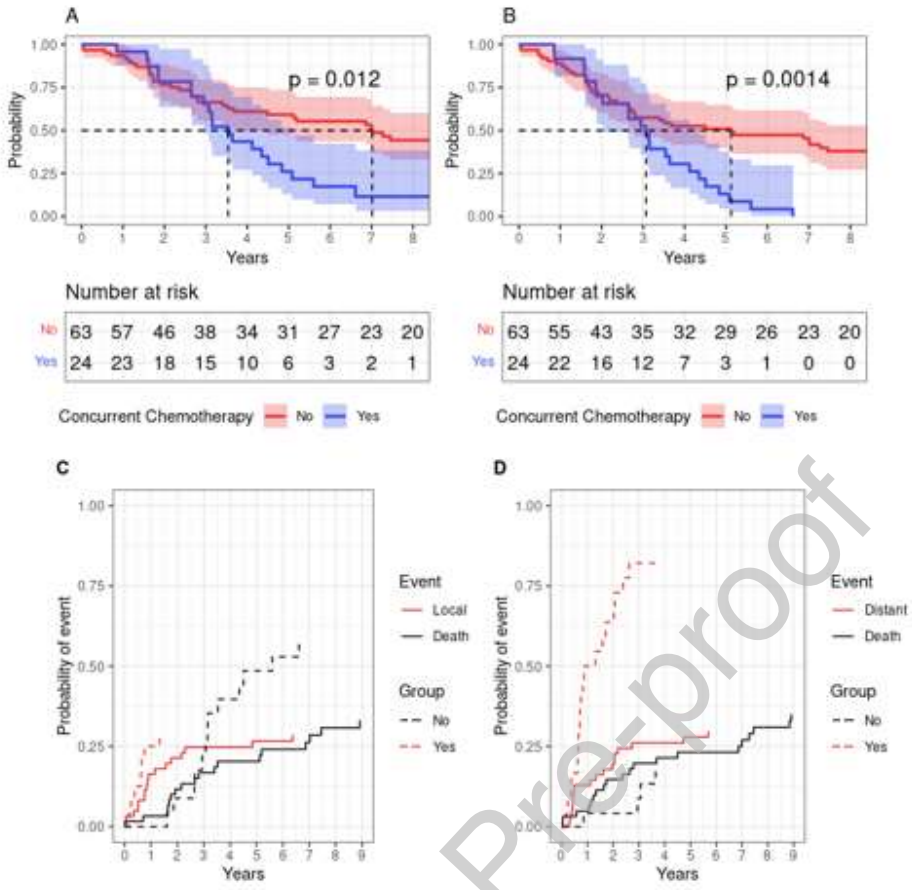

Figure 2. Kaplan Meier curves overall survival (a) and progression-free survival (b) and cumulative incidence of local recurrence (c) and distant recurrence (d) by concurrent chemotherapy.

Table 1. Patient characteristics of patients with salivary duct carcinoma

	Overall (N=89)
Gender	
Female	25 (28.1%)
Male	64 (71.9%)
Age at Diagnosis (yr)	
Mean (SD)	64.416 (13.353)
Median	66.000
Q1, Q3	57.000, 75.000
Range	32.000 - 89.000
Age Categorical	
Less_60	27 (30.3%)
60-70	29 (32.6%)
More_70	33 (37.1%)
Diagnosis Site	
Parotid	77 (86.5%)
Salivary Gland NOS	3 (3.4%)
Submandibular	9 (10.1%)
Smoking Status	
No	31 (38.8%)
Yes	49 (61.2%)
N-Miss	9
Alcohol	
No	35 (43.8%)
Yes	45 (56.2%)
N-Miss	9
Smoking & Alcohol Status	
Both	34 (42.5%)
Neither	20 (25.0%)
Only one	26 (32.5%)
N-Miss	9
T Stage	
T1	18 (20.5%)
T2	12 (13.6%)
T3	26 (29.5%)
T4	32 (36.4%)
N-Miss	1
N Stage	

	Overall (N=89)
N0	29 (32.6%)
N1	9 (10.1%)
N2	48 (53.9%)
N3	3 (3.4%)
AJCC Overall Stage	
1	12 (13.5%)
2	5 (5.6%)
3	11 (12.4%)
4	61 (68.5%)

Table 2. Disease and treatment characteristics of patients with salivary duct carcinoma

	Overall (N=89)
Extracapsular Spread	
No	18 (39.1%)
Yes	28 (60.9%)
N-Miss	43
Vascular Invasion	
No	12 (27.3%)
Yes	32 (72.7%)
N-Miss	45
CNVII Sacrifice	
No	53 (63.1%)
Yes	31 (36.9%)
N-Miss	5
Perineural Invasion	
No	26 (36.6%)
Yes	45 (63.4%)
N-Miss	18
Extraparenchymal Involvement	
No	38 (45.8%)
Yes	45 (54.2%)
N-Miss	6
HER2 Amplified	
No	16 (39.0%)
Yes	25 (61.0%)
N-Miss	48
Androgen Staining	
Negative	7 (12.5%)

	Overall (N=89)
Positive	49 (87.5%)
N-Miss	33
Carcinoma ex pleomorphic adenoma	
No	59 (66.3%)
Yes	30 (33.7%)
Primary Treatment	
SURG/RAD	73 (82.0%)
SURG	12 (13.5%)
RAD	4 (4.5%)
Concomitant Chemotherapy	
No	63 (70.8%)
Yes	26 (29.2%)
Total Radiation Dose (n=77) cGy	
N-Miss	34
Mean (SD)	63.271 (4.805)
Median	61.200
Q1, Q3	60.000, 66.000
Range	49.800 - 76.000
Chemotherapy Type	
N-Miss	69
Single Agent	25 (96.1%)
Multi-Agent	0 (0.0%)
Chem NOS	1 (3.9%)

Table 3: Time to Event Univariate Modeling for Overall Survival, Progression Free Survival, Local Recurrence, and Distant Recurrence

Variable	Level	Death HR (95CI)	Death P-value	PFS HR (95CI)	PFS-P-value	LR HR(95%CI)	Local P-value	Distant HR (95%CI)	DR P-value
Concomitant Chemotherapy	Yes	2.05 (1.16, 3.64)	0.01	2.38 (1.37, 4.12)	0	1.19 (0.49, 2.88)	0.7	4.77 (2.42, 9.4)	0
Gender	Male	1.3 (0.71, 2.36)	0.39	1.43 (0.82, 2.5)	0.21	1.6 (0.6, 4.3)	0.35	1.89 (0.83, 4.3)	0.13
Age at Diagnosis (yr)	numeric	1.02 (1, 1.05)	0.06	1.02 (1, 1.04)	0.05	1.03 (0.99, 1.06)	0.15	0.99 (0.96, 1.01)	0.27
Diagnosis Site	Salivary Gland NOS	0 (0, Inf)	1	0.68 (0.09, 4.96)	0.71	NA	NA	0.95 (0.13, 6.93)	0.96
Diagnosis Site	Submandibular	1.08 (0.49, 2.4)	0.84	1.16 (0.55, 2.43)	0.7	0.67 (0.16, 2.86)	0.59	0.64 (0.2, 2.09)	0.46
T Stage	T2	1.46 (0.54, 3.98)	0.46	1.49 (0.58, 3.81)	0.41	0.63 (0.07, 6.05)	0.69	2.88 (0.64, 12.85)	0.17
N Stage	N1	0.93 (0.34, 2.54)	0.89	1.36 (0.57, 3.22)	0.48	1.8 (0.43, 7.53)	0.42	2.1 (0.61, 7.17)	0.24
N Stage	N2	1.88 (1.03, 3.43)	0.04	1.58 (0.91, 2.74)	0.1	2.16 (0.78, 5.96)	0.14	3.34 (1.43, 7.8)	0.01
N Stage	N3	11.76 (3.19, 43.32)	0	7.3 (2.07, 25.8)	0	3.59 (0.41, 31.14)	0.25	5.35 (1.1, 25.98)	0.04
AJCC Overall Stage	2	2.21 (0.58, 8.43)	0.24	2.94 (0.88, 9.84)	0.08	NA	NA	4.36 (0.61, 30.96)	0.14
AJCC Overall Stage	3	0.93 (0.3, 2.86)	0.9	1.56 (0.56, 4.33)	0.39	3.49 (0.36, 33.54)	0.28	2.83 (0.52, 15.46)	0.23
AJCC Overall Stage	4	2.06 (0.95, 4.44)	0.07	2.4 (1.12, 5.14)	0.02	5.07 (0.68, 37.91)	0.11	4.78 (1.14, 20.11)	0.03
Smoking Status	Yes	1.32 (0.74, 2.35)	0.35	0.89 (0.53, 1.51)	0.67	1.65 (0.63, 4.31)	0.3	0.94 (0.47, 1.91)	0.87
Alcohol	Yes	1.03 (0.58, 1.81)	0.92	0.95 (0.56, 1.61)	0.86	0.51 (0.21, 1.24)	0.14	1.88 (0.89, 3.98)	0.1
Smoking & Alcohol Status	Neither	0.86 (0.43, 1.74)	0.67	1.21 (0.63, 2.31)	0.57	1.23 (0.42, 3.53)	0.71	0.71 (0.29, 1.72)	0.45
Extracapsular Spread	Yes	1.9 (0.86, 4.2)	0.11	2.09 (0.99, 4.41)	0.05	1.98 (0.52, 7.53)	0.31	1.61 (0.7, 3.75)	0.26
CNVII Sacrifice	Yes	1.13 (0.65, 1.98)	0.66	1.19 (0.71, 1.98)	0.51	1.28 (0.52, 3.2)	0.59	1.41 (0.73, 2.71)	0.31
Perineural Invasion	Yes	2.05 (1.06, 3.97)	0.03	2.47 (1.32, 4.6)	0	0.58 (0.24, 1.4)	0.22	4.56 (1.74, 11.97)	0
HER2 Amplified	Yes	0.72 (0.33, 1.57)	0.41	0.66 (0.33, 1.36)	0.26	0.44 (0.13, 1.43)	0.17	0.74 (0.31, 1.76)	0.49
Lymphovascular Invasion	Yes	3.49 (1.2, 10.4)	0.02	1.99 (0.86, 4.62)	0.11	NA	NA	2.04 (0.75, 5.52)	0.16
Androgen Staining	Positive	2.2 (0.67, 7.2)	0.19	3 (0.92, 9.72)	0.07	0.91 (0.21, 3.98)	0.9	0.99 (0.3, 3.32)	0.99
Pathologic Report	SDC	0.85 (0.5, 1.46)	0.56	1.02 (0.61, 1.69)	0.95	0.54 (0.24, 1.2)	0.13	1.45 (0.7, 3)	0.31
Primary Treatment	SURG	2.41 (1.15, 5.06)	0.02	1.85 (0.89, 3.85)	0.1	4.73 (2.14, 10.47)	0	0.67 (0.16, 2.73)	0.58
Primary Treatment	RAD	1.92 (0.93, 3.95)	0.08	1.99 (0.97, 4.09)	0.06	1.58 (0.63, 4)	0.33	3.69 (0.61, 22.25)	0.15
Tumor Size (cm)	numeric	0.91 (0.74, 1.12)	0.37	1.09 (0.89, 1.33)	0.4	1.36 (1.03, 1.8)	0.03	1.01 (0.79, 1.3)	0.94
Margin Status	Positive	2.65 (1.25, 5.61)	0.01	2.61 (1.3, 5.28)	0.01	1 (0.23, 4.38)	1	9.06 (3.88, 21.14)	0