Positive lymph nodes predict distant metastasis of salivary duct carcinoma after postoperative radiotherapy

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Article

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Abstract

Purpose: Salivary duct carcinoma (SDC) is a high-grade subtype of salivary gland malignancy. Distant metastasis was the common pattern of failure for patients receiving surgery and adjuvant radiotherapy. We are aimed to analyze the prognostic value of positive lymph nodes for distant metastasis in the SDC following postoperative radiotherapy.

Patients and Methods: We reviewed the data of patients with SDC receiving surgical resection and radiotherapy. The univariate analysis was conducted using Log-rank method for the clinicopathological features with distant-metastasis-free survival (DMFS). The multivariable analysis was performed by Cox regression hazards method. A risk stratification model was established by the score calculated with the variables qualified by multivariate P<0.05.

Results: 91 patients were enrolled, and the median age at diagnosis was 58.5 years. 53.8%(n=49) of the patients appeared with the involvement of neck lymph nodes after surgery. The advanced T stage (95% CI 1.325-5.38; P=0.006), number of positive lymph nodes (PLN≥8) (95% CI 1.241-6.58; P =0.013), and peripheral invasion (PNI) (95% CI 1.059-4.65; P=0.034) were significantly associated with DMFS for the SDC in the multivariate analysis. Patients were divided into two subgroups based on the risk factors, while significant differences of DMFS and OS were observed between the risk cohorts (5-year DMFS:35% vs.64.4%, P=0.0001; 5-year OS:53.6% vs.70.4%; P=0.048).

Conclusion: Higher number of positive lymph nodes was associated with worse DMFS in SDC following PORT. The patients at high risk appeared with significantly poor DMFS and survival, and clinical trials on adjuvant therapy are warranted for this subgroup.

1 Introduction

Salivary duct carcinoma (SDC) is a rare malignancy accounting for 1–3% of salivary gland carcinomas(SGCs)(1). It was typically originated from major salivary glands and more likely to occur in elderly male patients. The histology of the SDC resembles high-grade ductal breast carcinoma which presented with high aggression. Consequently, high rates of locoregional and distant failure were reported in the patients with SDC(2). As the majority of the patients were initially diagnosed with distant metastasis, the 5-year overall survival (OS) for SDC ranged from 20–50%(3). In addition, the 3-year disease-free survival (DFS) was reported as 35.5%-38.2% in those cases without distant metastasis(4, 5).

Because of the low incidence, no large or prospective studies have explored the treatment strategy for the SDC. The primary therapeutic approach for the SDC was referred to the management of high-grade SGCs which included surgical resection and postoperative radiotherapy (PORT)(6). Adjuvant radiotherapy was significantly associated with better locoregional control rate(P = 0.004) in the patients with SDC(7). However, distant metastasis remained the main failure pattern in the SDC after PORT. Studies with a number of cases have showed that nodal involvement, HER-2 overexpression, and perineural invasion

(PNI) were associated with poor overall survival (OS) in the SDC(8, 9). However, little was known about the distant metastatic risk after PORT.

The absolute number of tumor-associated lymph nodes was an independent prognostic risk factor for head and neck cancer(10). In addition, the involvement of regional lymph nodes was significantly correlated with poor disease-free survival (DFS) in ductal breast cancer(11). A positive correlation was observed between the presence of cervical lymph nodes in salivary gland malignancies and high pathological aggression or advanced stages. As a high-grade histological type, cervical lymph metastasis occurred in more than 50% of the patients with SDC(12). Yet, the prognostic value of positive lymph nodes (PLN) in SDC was inconclusive because of the very low incidence.

In this study, we reviewed the cohort with SDC following PORT in our institution, and evaluated the association of PLN and other features with DMFS. Moreover, we conducted a risk stratification model with the risk variables to identify the patients with poor long-term outcome.

2 Methods

2.1 Patients and study design

This study was conducted retrospectively on a primary cohort of patients histologically proven to be primary salivary malignancy in Fudan Cancer Shanghai Cancer Center (Shanghai, China) from January 2008 to December 2020. All patients were reviewed by the pathologists in this institution for the diagnosis of salivary duct carcinoma. The patients who underwent complete resection of the primary tumor and adjuvant radiotherapy were included. Exclusion criteria were as follows: distant metastasis at initial diagnosis; no treatment of surgery or radiotherapy was delivered; medical data and follow-up information unavailable. All the data of participants were collected retrospectively through medical records, ethical approval was obtained through the ethics committee if needed. We confirm that all experiments were performed in accordance with relevant guidelines and regulations

2.2 Endpoints and statistical analysis

The treatment decisions for the patients were made with the consistency of the multidisciplinary head and neck oncology board. Radiotherapy was delivered covering tumor bed and elective nodes after primary tumor removal. The positive lymph nodes were confirmed by pathological examination after surgical resection. The primary endpoint for this study was distant-metastasis-free survival (DMFS), which was defined as the time from the date of initial surgery to the date of the first-time distant metastasis, death of any cause, or the last contact time. The second endpoint was overall survival (OS) which was calculated from the date of initial surgery to the latest follow-up visit or death of any cause.

The characteristics of continuous variables were descriptively displayed using mean values and standard deviations. Categorical variables were listed based on the clinical findings. Kaplan-Meier method was adopted for drawing survival curves. The log-rank test was used for statistical comparison of the DMFS

and OS in univariate analysis. The multivariable survival analysis was performed using the Cox proportional hazards model. The relationship between the number of positive lymph nodes (PLN) and DMFS was defined by the restricted cubic spline functions method. The optimal cutoff value of the number was determined by maximally selected rank statistics. P 0.05 was considered statistically significant. All of the statistical analyses were performed using R software (4.15 vision) and SPSS 24.0.

3 Results

3.1 Clinicopathologic characteristics of the participants

After reviewing the medical records, 91 patients with histologically confirmed as de novo SDC and SDC ex pleomorphic adenoma (CaExPA) met the inclusion criteria and entered into this analysis (Table 1). In which, 5.5%(n = 5) of the patients were reported with the pathological SDC arising from pleomorphic adenoma. The median age at diagnosis was 58.5 years (Range 39–79 years), and 93.4%(n = 85) of the patients were male. Tumors originated from the parotid in 61(67%) cases and the submandibular in 30(33%) cases. About half of the patients appeared with advanced T (T3-4) stage (n = 48, 52.8%) by surgical confirmation. The involvement of lymph nodes occurred in 53.9%(n = 49) of the patients. The median cumulative dose for Plan Tumor Volume (PTV) was 58.5Gy (Range 56-70.4Gy). Furthermore, chemotherapy was administrated using platinum-based regimen in 18.7%(n = 17) of the patients after surgery.

Table 1
Characteristics and Treatment of the patients 2008–2020

Characteristics	N = 91, %	Characteristics	N = 91, %
Gender:		Primary tumor site	
Male	85 (93.4)	Parotid	61 (67.0)
female	6 (6.59)	Submandibular	30 (33.0)
Age	58.5 (39–79)	Pathology	
Pathological T stage		De novo	86 (94.5)
T1	16 (17.6)	CaExPA	5 (5.5)
T2	27 (29.7)	AR	
T3	38 (41.8)	Positive	48 (53.9)
T4	10 (11.0)	Negative	2 (2.2)
Pathological N stage		Unknown	41 (45.1)
N0	42 (46.2)	Her-2	
N1	15 (16.5)	Positive	39 (45.3)
N2	30 (33.0)	Negative	5 (5.5)
N3	4 (4.40)	Unknown	47 (51.6)
Stage		PNI	
I	8 (8.8)	Negative	47 (51.6)
II	18 (19.8)	Positive	44 (48.4)
III	27 (29.8)	LVI	
IVa	34 (37.4)	Negative	63 (69.2)
IVb	4 (4.4)	Positive	28 (30.8)
Chemotherapy		Surgical margin	
Yes	17 (18.7)	Negative	87 (95.6)
No	74 (81.3)	Positive	4 (4.40)
PLN	4.2 (0–44)	RT dose (Gy)	58.5 (56-70.4)
*Notes: LVI: lymph vascular invasion, PLN: positive lymph number, PNI: peripheral invasion			

3.2 follow-up and outcomes

The median follow-up time for the cohort was 56.23 months (range 4.5–160 months). We observed 37.4%(n = 34) of the patients presenting with distant metastasis after PORT. Lung failure (n = 20, 58.8%) was the most reported, followed by bone and liver metastasis. The estimated 3, and 5-year DMFS were 57% and 47.2%, respectively. In addition, 28 (30.8%) of the cases died during the follow-up because of the failure of distant metastasis (28/28, 100%). The estimated 3, and 5-year OS were 82.1% and 60.5%, respectively. The median survival time was not reached and median distant-metastasis free time was 52.1 months (95% CI 28.89–75.31).

3.3 Positive lymph number (PLN) and prognostic factors

The mean number of 4.2 (range 0–44) positive lymph nodes was detected after surgery. A linear correlation was observed between the risk of distant metastasis and the PLN(Figure.1A). Therefore, we determined the best cutoff number for PLN with the maximally selected rank statistics(Fig. 1B), which showed that the cutoff value was PLN = 8. Significantly worse DMFS was observed for the patients with high PLN(≥ 8) compared with those with low PLN (< 8)(Fig. 1.C).

In the univariate analysis for DMFS, pathological T stage (P = 0.001), pathological N (P = 0.003), peripheral invasion (PNI) (P = 0.001), lymph vascular invasion (LVI) (P = 0.027), PLN ≥ 8 (P = 0.003) and chemotherapy(P = 0.038) were associated with decreasing DMFS for the SDC after PORT. Following the multivariable Cox regression analysis, advanced T stage (T3-4) (95% CI 1.325–5.38; P = 0.006), PLN ≥ 8 (95% CI 1.241–6.58; P = 0.013) and PNI (95% CI 1.059–4.65; P = 0.034) were significantly correlated with poor DMFS(Table 2).

Table 2
Univariate and multivariable analysis of factors for DMFS (n = 91)

	Univariate analysis		Multivariable analysis	
	HR (95%CI)	P-value	HR (95%CI)	P-value
Gender:				
Male	1.36 (0.49–3.83)	0.556		
Female	Ref.			
Age	1 (0.97–1.03)	0.994		
Primary site				
Parotid	Ref.			
Submandibular	1.2 (0.63–2.28)	0.579		.
Pathological T				0.006
T1-2	Ref.		Ref.	
T3-4	3.26 (1.66–6.39)	0.001	2.669 (1.325–5.38)	
Pathological N				
N0	Ref.			
N+	2.69 (1.4–5.2)	0.003		
PLN				0.013
<8	Ref.		Ref.	
≥8	2.81 (1.36–5.81)	0.005	2.858 (1.241–6.58)	
PNI				0.034
Negative	Ref.			
Positive	2.83 (1.5–5.35)	0.001	2.218 (1.059–4.65)	
LVI				0.619
Negative	Ref.		Ref.	
Positive	2.01 (1.08–3.74)	0.027	0.822 (0.379–1.78)	
Pathological margin:				
Negative	Ref.			

*Note: PLN: positive lymph number, LVI: Lymph vascular invasion, PNI: peripheral invasion

	Univariate analysis		Multivariable analysis	
Positive	2.11 (0.5–8.92)	0.308		
Chemotherapy:				0.094
No	Ref.		Ref.	
Yes	2.16 (1.04–4.48)	0.038	1.96 (0.891-4.30)	
*Note: PLN: positive lymph number, LVI: Lymph vascular invasion, PNI: peripheral invasion				

3.3 Risk stratification for distant metastasis

To build the risk stratification for DMFS of the patients with SDC following PORT, we calculated the risk-score based on the weighting(β-coefficient) of significant factors of the multivariate analysis. In that cases, the pathological T stage, PLN, and PNI were included for the establishment of the final model, and patients were divided into two risk subgroups based on the cutoff value representative of the 50th percentile risk-score (Table 3). The 5-year DMFS and OS for the high and low-risk groups were 35%, 64.4%, 53.6%, and 70.4%, respectively. Significant differences in DMFS (P = 0.00018) and OS (P = 0.049) were observed between the high-risk and low-risk subgroup of the patients after PORT(Figure.2).

Table 3
Risk stratification of DMFS in patients with SDC (n = 91)

Covariate	β-coefficient	Risk-score
Pathological T		
T1-2	Ref.	1*β (T1-2 = 1)
T3-4	0.9818	2*β (T3-4 = 2)
PLN		
PLN < 8	Ref.	1*β (PLN < 8 = 1)
PLN ≥ 8	1.0500	2*β (PLN ≥ 8 = 2)
PNI		
Negative	Ref.	1*β (Negative = 1)
Positive	0.7967	2*β (Positive = 2)
Group		
High-risk		≥ 3.6252 (n = 54)
Low-risk		< 3.6252 (n = 37)
*PLN: positive lymph number; PNI: Peripheral invasion		

Discussion

Salivary duct carcinoma (SDC) was a highly aggressive subtype of salivary gland malignancy according to the WHO classification(13). Previous studies(14, 15) have shown that this subtype of patients presented with a high rate of distant metastasis in the clinic. In this study, we retrospectively collected the data of patients with SDC who underwent PORT and analyzed the prognostic value of the number of positive lymph nodes (PLN) and other risk factors for the DMFS. Moreover, we constructed the risk stratification which may be useful to identify the patients at high risk of poor survival.

Primary tumor resection was essential for the treatment of the head and neck cancer according to the National Comprehensive Cancer Network (NCCN) guidelines(6), while it could provide accurate diagnosis and treatment for the major salivary gland carcinomas. Regardless of the stage of SDC, postoperative radiotherapy (PORT) was strongly recommended because that adjuvant radiotherapy could significantly improve the local-regional control rate for the SDC (P =0.004)(7, 14). However, distant metastasis remained the major cause affecting the survival of the patients after PORT. But, few studies have investigated the prognostic predictors for distant failure with more than 50 cases due to its rarity. The largest study including the patients from the SEER database with 228 cases(16) showed that older age,

large tumor size, and lymph node involvement were significantly associated with poor prognosis for the SDC. Nevertheless, factors involving distant metastasis were not reported in that study.

Regional lymph nodes played a significant role as a predictor of disease metastasis in most solid tumors. In breast cancer, the sentinel lymph node was the initial region for the tumor spreading to other organs. The tumor-positive nodes were a significant prognostic predictor for local regional and distant recurrence in breast cancer(17). The SDC shared a similar histological type with breast cancer, and nodal metastasis could predict the disease metastasis in the early time. Two retrospective studies have shown that advanced N stages (N2-3) were correlated with decreasing disease-free survival (DFS) and DMFS for the SDC(15, 18). In addition, the positive lymph ratio has also been reported as an indicator for poorer DMFS in the major salivary gland carcinoma(19, 20). And, T. J. Roberts(21) has illustrated the superior predicting value of positive lymph number (PLN) than lymph node ratio in head and neck cancer. In the major SGCs, the number of positive lymph nodes was associated with worse OS ($P < 0.001$) (22). However, different subgroups of the SGCs appeared with heterogeneous histological types and clinical phenotypes. Of note, the SDC was a highly aggressive subtype of malignancy compared with other SGCs, and the highest proportion of nodal involvement was observed among the major histological types in SGCs (54% vs. 24%, SDC vs. others)(23). In another study from the Netherlands, increasing PLN was associated with worse OS and DMFS in a non-linear way(24). For cases with 0 nodes being the reference, significantly worse DMFS was observed for those patients with 3-15 lymph nodes ($P=0.007$). Nevertheless, the study also included those patients with initial metastasis (stage M1) and those without radiotherapy. In our opinion, PORT was the standard approach for the SDC without distant metastasis. Thus, we analyzed the cohort after radical PORT and found that the risk of distant metastasis increased linearly by the PLN (Figure1.A). Moreover, we believe that several other pathological features (such as PNI, LVI) could predict the DMFS of the SDC, which were also not reported in that paper(24).

In our findings, the advanced T stage was an independent predictor for poor OS and DMFS in the multivariate analysis, which was consistent with the results from several other studies of salivary gland carcinomas following PORT(25, 26). Despite the factors of the TNM stage, PNI was correlated with decreasing DMFS in the univariate and multivariable analysis of the SDC($P=0.003$). The PNI represented the metastatic ability through peripheral nerves and could predict the high risk of distant metastasis for patients with SGCs(27). The probability of PNI was higher in the SDC than that of other SGCs(28). However, few reports have included PNI into the analysis because of the very low incidence. Another study with 35 cases has illustrated the significant prognostic value of PNI for OS in the SDC($P=0.005$)(8). While 48.4% of the patients were confirmed as PNI by pathological examination in our study, which indicated that the SDC appeared with high pathological aggressiveness. Furthermore, the patients with positive PNI were reported with significantly higher risk of distant recurrence($P<0.05$).

For effective utility in the clinic, we combine the independent predictors to figure the risk score for every individual. Furthermore, the cohort was divided into two risk groups, whereas significant worse OS and DMFS were observed in the high-risk group and the administration of consolidation therapy may be beneficial. Several studies have investigated the efficacy of therapeutic approaches targeting AR and

HER-2(29, 30), and the evaluation of AR and HER-2 was strongly recommended in NCCN guidelines for the SDC(6). However, nearly half of the patients in our study were reported with unknown status with AR and HER-2 due to the long timeline. In addition, identification of the patients at high risk could provide a reference for the trials of immune checkpoint inhibitor therapy in the SDC(13).

However, there were several limitations of this study. Firstly, the retrospective nature of the study may lead to the selection bias of the cohort. Secondly, the data of the patients were collected over a 15-year period, which could explain the lack of pathological information in AR and HER-2 (50% patients with unknown status). Lastly, the sample size was still small as the data was based on a single institution, and external validation is needed for the risk stratification model. Nevertheless, given the rarity of incidence in SDC, our study demonstrated the clinicopathologic factors that could predict the risk of distant metastasis in a moderate number of cases. In addition, some other prognostic information such as AR, HER-2, and other potential biomarkers were to be further explored.

Conclusion

Salivary duct carcinoma (SDC) was a high-grade subtype of salivary gland malignancy with a poor prognosis and high risk of distant metastasis. Positive lymph nodes (PLN), advanced T stage, and peripheral invasion (PNI) were significant risk factors for the SDC following PORT. Moreover, we reported a distant metastasis risk stratification system for the SDC with primary resection and adjuvant radiotherapy. Further work for validating the model in various institutions was needed. More potential biomarkers in SDC are expected to be investigated for predicting the prognosis of the tumor.

Declarations

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request

Author contribution

Wenbin Yan, Xiaomin Ou, Chunying Shen, and Chaosu Hu were responsible for the conceptualization, methods, analysis, writing, and editing. Wenbin Yan, and Xiaomin Ou were responsible for statistical analysis and writing; Chunying Shen, and Chaosu Hu were responsible for supervision, and final editing. All authors have read and approved the final manuscript.

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Ethics declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the Fudan University shanghai cancer center. And informed consent was obtained from all subjects and/or their legal guardian(s).

Consent for publication

Not applicable

Competing interests

None of the authors have any conflicts of interest to declare.

References

1. D'Heygere E, Meulemans J, Vander Poorten V. Salivary duct carcinoma. Curr Opin Otolaryngol Head Neck Surg. 2018;26(2):142–51.
2. Johnston ML, Huang SH, Waldron JN, Atenafu EG, Chan K, Cummings BJ, et al. Salivary duct carcinoma: Treatment, outcomes, and patterns of failure. Head & neck. 2016;38 Suppl 1:E820-E6.
3. Guzzo M, Di Palma S, Grandi C, Molinari R. Salivary duct carcinoma: clinical characteristics and treatment strategies. Head & neck. 1997;19(2):126–33.
4. Mifsud M, Sharma S, Leon M, Padhya T, Otto K, Caudell J. Salivary Duct Carcinoma of the Parotid: Outcomes with a Contemporary Multidisciplinary Treatment Approach. Otolaryngology–head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2016;154(6):1041–6.
5. Otsuka K, Imanishi Y, Tada Y, Kawakita D, Kano S, Tsukahara K, et al. Clinical Outcomes and Prognostic Factors for Salivary Duct Carcinoma: A Multi-Institutional Analysis of 141 Patients. Annals of surgical oncology. 2016;23(6):2038–45.
6. Pfister DG, Spencer S, Adelstein D, Adkins D, Anzai Y, Brizel DM, et al. Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network: JNCCN. 2020;18(7):873–98.
7. Haderlein M, Scherl C, Semrau S, Lettmaier S, Hecht M, Erber R, et al. Impact of postoperative radiotherapy and HER2/new overexpression in salivary duct carcinoma: A monocentric clinicopathologic analysis. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al]. 2017;193(11):961–70.
8. Kim JY, Lee S, Cho KJ, Kim SY, Nam SY, Choi SH, et al. Treatment results of post-operative radiotherapy in patients with salivary duct carcinoma of the major salivary glands. The British

journal of radiology. 2012;85(1018):e947-e52.

9. Roh J-L, Lee J-I, Choi S-H, Nam SY, Kim S-O, Cho K-J, et al. Prognostic factors and oncologic outcomes of 56 salivary duct carcinoma patients in a single institution: high rate of systemic failure warrants targeted therapy. Oral oncology. 2014;50(11):e64-e6.
10. Zumsteg ZS, Luu M, Kim S, Tighiouart M, Mita A, Scher KS, et al. Quantitative lymph node burden as a 'very-high-risk' factor identifying head and neck cancer patients benefiting from postoperative chemoradiation. Annals of oncology: official journal of the European Society for Medical Oncology. 2019;30(1):76–84.
11. Querzoli P, Pedriali M, Rinaldi R, Lombardi AR, Biganzoli E, Boracchi P, et al. Axillary lymph node nanometastases are prognostic factors for disease-free survival and metastatic relapse in breast cancer patients. Clinical cancer research: an official journal of the American Association for Cancer Research. 2006;12(22):6696–701.
12. Bradley PJ. Frequency and Histopathology by Site, Major Pathologies, Symptoms and Signs of Salivary Gland Neoplasms. Adv Otorhinolaryngol. 2016;78.
13. Nakaguro M, Tada Y, Faquin WC, Sadow PM, Wirth LJ, Nagao T. Salivary duct carcinoma: Updates in histology, cytology, molecular biology, and treatment. Cancer Cytopathol. 2020;128(10):693–703.
14. Breinholt H, Elhakim MT, Godballe C, Andersen LJ, Primdahl H, Kristensen CA, et al. Salivary duct carcinoma: a Danish national study. J Oral Pathol Med. 2016;45(9):664–71.
15. Gilbert MR, Sharma A, Schmitt NC, Johnson JT, Ferris RL, Duvvuri U, et al. A 20-Year Review of 75 Cases of Salivary Duct Carcinoma. JAMA Otolaryngol Head Neck Surg. 2016;142(5):489–95.
16. Jayaprakash V, Merzianu M, Warren GW, Arshad H, Hicks WL, Rigual NR, et al. Survival rates and prognostic factors for infiltrating salivary duct carcinoma: Analysis of 228 cases from the Surveillance, Epidemiology, and End Results database. Head & neck. 2014;36(5):694–701.
17. Truong PT, Berthelet E, Lee J, Kader HA, Olivotto IA. The prognostic significance of the percentage of positive/dissected axillary lymph nodes in breast cancer recurrence and survival in patients with one to three positive axillary lymph nodes. Cancer. 2005;103(10):2006–14.
18. Villepelet A, Lefèvre M, Verillaud B, Janot F, Garrel R, Vergez S, et al. Salivary duct carcinoma: Prospective multicenter study of 61 cases of the Réseau d'Expertise Français des Cancers ORL Rares. Head & neck. 2019;41(3):584–91.
19. Suzuki H, Hanai N, Hirakawa H, Nishikawa D, Hasegawa Y. Lymph node density is a prognostic factor in patients with major salivary gland carcinoma. Oncology letters. 2015;10(6):3523–8.
20. Liu Z, Fang Z, Dai T, Zhang C, Sun J, He Y. Higher positive lymph node ratio indicates poorer distant metastasis-free survival in adenoid cystic carcinoma patients with nodal involvement. J Craniomaxillofac Surg. 2015;43(6):751–7.
21. Roberts TJ, Colevas AD, Hara W, Holsinger FC, Oakley-Girvan I, Divi V. Number of positive nodes is superior to the lymph node ratio and American Joint Committee on Cancer N staging for the prognosis of surgically treated head and neck squamous cell carcinomas. Cancer. 2016;122(9):1388–97.

22. Aro K, Ho AS, Luu M, Kim S, Tighiouart M, Clair JM-S, et al. Development of a novel salivary gland cancer lymph node staging system. Cancer. 2018;124(15):3171–80.
23. Xiao CC, Zhan KY, White-Gilbertson SJ, Day TA. Predictors of Nodal Metastasis in Parotid Malignancies: A National Cancer Data Base Study of 22,653 Patients. Otolaryngology–head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2016;154(1):121–30.
24. Boon E, Bel M, van Boxtel W, van der Graaf WTA, van Es RJJ, Eerenstein SEJ, et al. A clinicopathological study and prognostic factor analysis of 177 salivary duct carcinoma patients from The Netherlands. International journal of cancer. 2018;143(4):758–66.
25. Jegadeesh N, Liu Y, Prabhu RS, Magliocca KR, Marcus DM, Higgins KA, et al. Outcomes and prognostic factors in modern era management of major salivary gland cancer. Oral oncology. 2015;51(8):770–7.
26. Al-Mamgani A, van Rooij P, Verduijn GM, Meeuwis CA, Levendag PC. Long-term outcomes and quality of life of 186 patients with primary parotid carcinoma treated with surgery and radiotherapy at the Daniel den Hoed Cancer Center. International journal of radiation oncology, biology, physics. 2012;84(1):189–95.
27. Terhaard CHJ, Lubsen H, Van der Tweel I, Hilgers FJM, Eijkenboom WMH, Marres HAM, et al. Salivary gland carcinoma: independent prognostic factors for locoregional control, distant metastases, and overall survival: results of the Dutch head and neck oncology cooperative group. Head & neck. 2004;26(8).
28. Hosal AS, Fan C, Barnes L, Myers EN. Salivary duct carcinoma. Otolaryngology–head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2003;129(6):720–5.
29. Fushimi C, Tada Y, Takahashi H, Nagao T, Ojiri H, Masubuchi T, et al. A prospective phase II study of combined androgen blockade in patients with androgen receptor-positive metastatic or locally advanced unresectable salivary gland carcinoma. Annals of oncology: official journal of the European Society for Medical Oncology. 2018;29(4):979–84.
30. van Boxtel W, Locati LD, van Engen-van Grunsven ACH, Bergamini C, Jonker MA, Fiets E, et al. Adjuvant androgen deprivation therapy for poor-risk, androgen receptor-positive salivary duct carcinoma. European journal of cancer (Oxford, England: 1990). 2019;110:62–70.

Figures

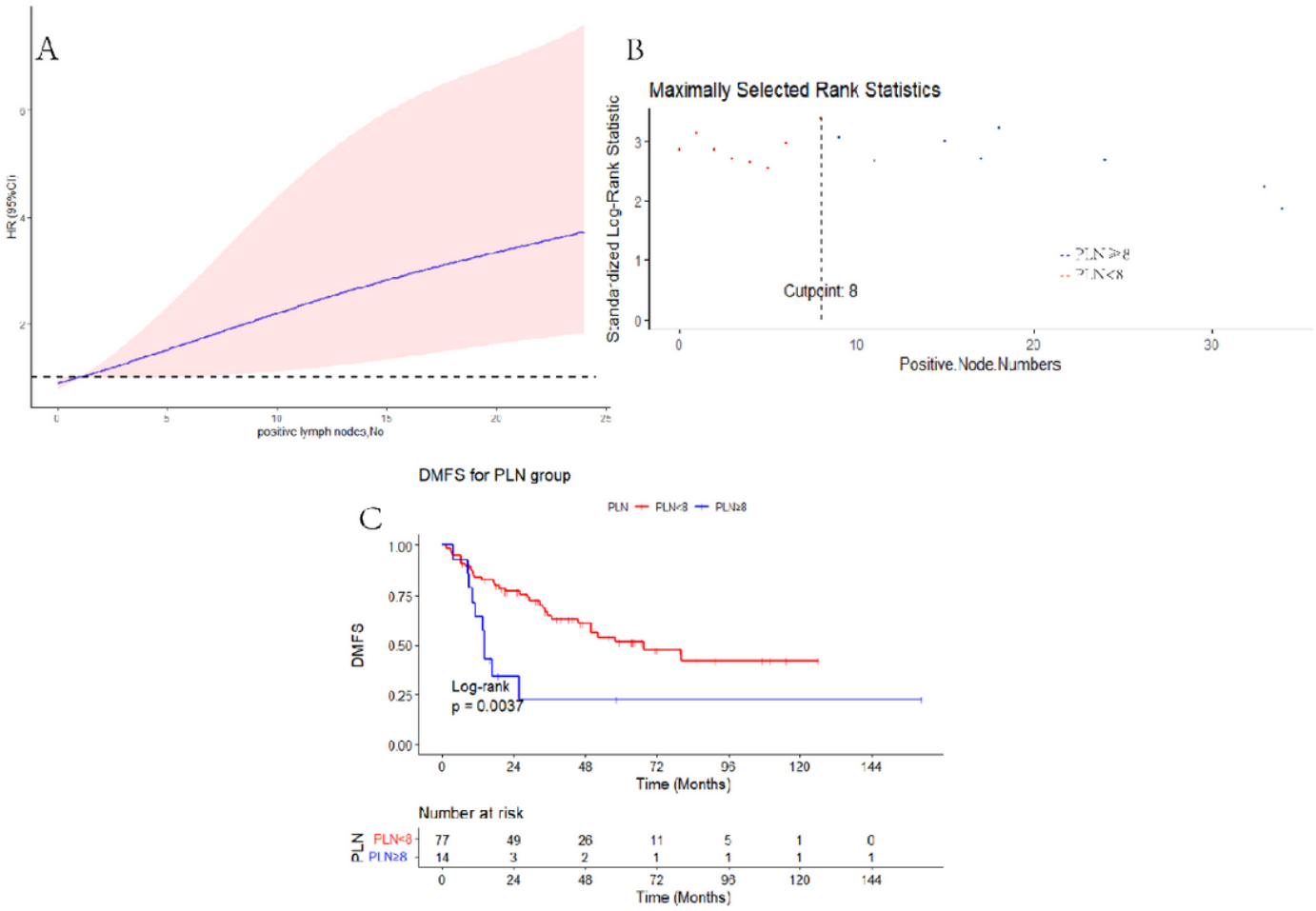

Figure 1

(A). a linear relationship between PLN and hazard risk of distant metastasis; (B). The best cutoff value for PLN was 8;(C). DMFS for the group (PLN≥8, blue line) and group (PLN<8, red line) compared using Log-Rank

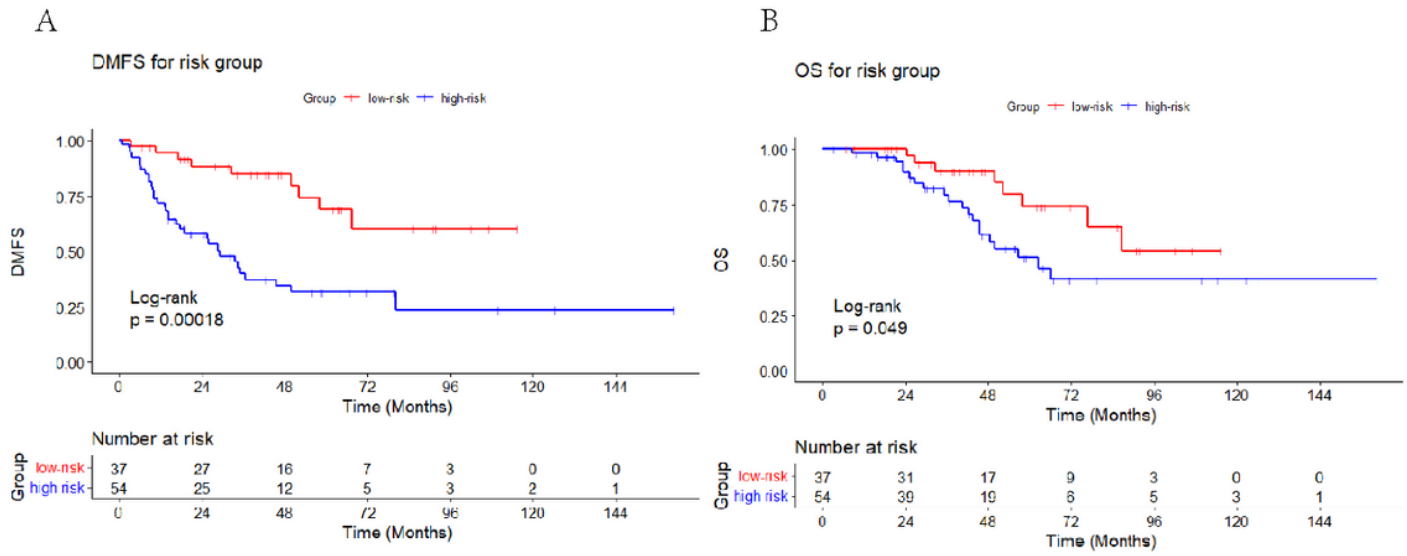

Figure 2

(A). DMFS for the risk groups of SDC (high-risk: blue line; low-risk: red line) by Log-Rank test(P<0.001);
(B). OS for the two risk groups (high-risk: blue line; low-risk: red line) compared using Log-rank (P=0.049)