Original Article

Oncological outcomes of patients with salivary gland cancer treated with surgery and postoperative intensity-modulated radiotherapy: a retrospective cohort study

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Background: Salivary gland cancer (SGC) is relatively rare and constitutes a variety of histological subtypes. Previously published studies of SGC patients suggest that postoperative radiation using conventional radiotherapy (RT) or 3-dimensional (3D) conformal radiotherapy may have led to suboptimal oncological outcomes.

Methods: We identified 60 patients with major SGC treated with surgery followed by postoperative intensity-modulated radiotherapy (IMRT). Data for overall survival (OS), progression-free survival (PFS), locoregional relapse-free survival (LRRFS), distant metastasis-free survival (DMFS), prognostic factors, and treatment-related toxicities were analyzed. Survival was analyzed using the Kaplan-Meier method and compared using the log-rank test.

Results: With a median follow-up of 55.5 months, based on Kaplan-Meier analyses, the OS and PFS rates for SGC patients at 3, 5, and 10 years were 90.7%, 85.1%, and 85.1% and 80.1%, 72.7%, and 63.1%, respectively. The LRRFS and DMFS rates at 3, 5, and 10 years were 87.4%, 82.1%, and 82.1% and 85.3%, 78.4%, and 66.1%, respectively. In multivariable analysis (MVA), the node stage (N stage) was an independent predictor of PFS [P=0.047; hazard ratio (HR) =0.089]. A positive margin was a significant prognostic factor for PFS (P=0.036; HR =4.086), LRRFS (P=0.026; HR =5.064), and DMFS (P=0.011; HR =6.367). Major nerve involvement was significantly correlated with PFS (P=0.034; HR =2.394) and DMFS (P=0.008; HR =2.115). The interval from surgery to radiotherapy predicted PFS (P=0.036; HR =3.934) and DMFS (P=0.012; HR =6.231). Adenoid cystic carcinoma (ACC) was the most common histology (n=21; 35%). For ACC, the 5-year OS, PFS, LRRFS, and DMFS were 100%, 67.7%, 76.2%, and 90.2%, respectively. The most common acute toxicities were mucositis and dermatitis, and xerostomia was the most common late adverse event. Lung metastasis was the most common pattern of distant failure.

Conclusions: N stage, positive margin, major nerve involvement, and interval from surgery to radiotherapy were important factors associated with PFS, LRRFS, and DMFS. Postoperative IMRT leads to improved survival for SGC patients, with acceptable toxicities.

Keywords: Salivary gland cancer (SGC); intensity-modulated radiotherapy (IMRT); survival

Submitted Aug 22, 2021. Accepted for publication Jan 14, 2022.
doi: 10.21037/qims-21-836
View this article at: https://dx.doi.org/10.21037/qims-21-836

Introduction

Salivary gland cancer (SGC) constitutes a heterogeneous group of diseases, accounting for only 3–6% of all cases of head and neck cancer (1). Although its etiology remains unclear, the prognosis of SGC has improved thanks to combined treatments of surgery, postoperative radiotherapy (PORT), and chemotherapy. Retrospective reviews have shown that the prognosis of SGC depends on the histology, grade, and stage (2-4) of SGC. Other characteristics affecting prognosis include positive margin, extracapsular extension, and bone and perineural invasions (1).

Owing to differences in the number of patients enrolled in each study, pathological types, and treatment strategies, it is difficult to compare studies. Intensity-modulated radiotherapy (IMRT) has led to increased treatment accuracy and the possibility of delivering higher doses to the tumor region. This suggests that previous studies which have included patients who were irradiated using conventional radiotherapy (RT) or 3-dimensional conformal radiotherapy (3-DCRT) may have yielded lower locoregional control rates. We focused on postoperative IMRT, which was developed to improve local tumor control rates and quality of life and has been widely adopted for the treatment of head and neck cancer in recent decades. Due to the differences in the biological behavior between major and minor SGC, prognoses vary considerably. Herein, we collected and analyzed comprehensive treatment outcomes for major SGC patients treated with surgery and postoperative IMRT, and explored survival, related adverse prognostic factors, treatment failure patterns, and adverse events.

We present the following article in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-21-836/rc).

Methods

Patients

We reviewed 75 patients with histologically confirmed primary SGC treated at the First Affiliated Hospital of Zhejiang University from January 2009 to December 2016. Of these, 15 patients were excluded from our retrospective study: 7 had minor SGC, 5 had recurrent or metastatic disease, 2 failed to complete the scheduled RT, and 1 was lost to follow-up. Thus, 60 patients were available for analysis. All patients had newly diagnosed disease and received upfront surgery followed by external beam RT using IMRT. The median follow-up was 55.5 months (*Figure 1*). Patients with missing data or lost to follow-up were deleted.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the First Affiliated Hospital, Zhejiang University, and individual consent for this retrospective analysis was waived.

Evaluation

All cases were initially evaluated by a multimodality treatment team consisting of an otolaryngologist, a medical oncologist, and an RT oncologist. All cases underwent a detailed physical examination. Histological confirmation of SGC was required before treatment. Axial imaging with computed tomography (CT) was a routine part of patient evaluation, and most cases had also undergone either magnetic resonance imaging (MRI) or positron emission tomography (PET). Histological diagnosis was confirmed according to the World Health Organization (WHO) histologic subtype criteria for SGC (5). All cases were restaged based on the 2018 American Joint Committee on Cancer (AJCC) classification. Acute adverse events were graded according to electronic records. Late toxicity was assessed based on follow-up visits.

Treatment

All patients underwent initial primary resection, with neck dissection (ND) conducted therapeutically in clinically positive lymph node (cN+) patients or electively in high-risk clinically negative lymph node (cN0) patients. For

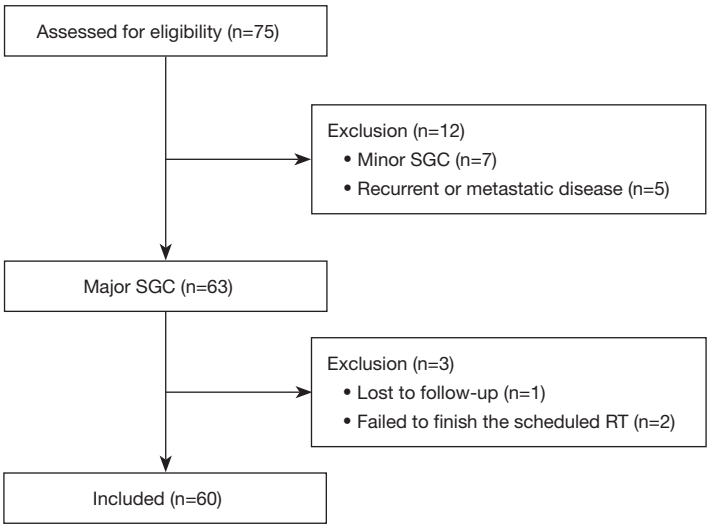

Figure 1 Flowchart of all included patients. SGC, salivary gland cancer; RT, radiotherapy.

IMRT, patients were immobilized in the supine position with a thermoplastic head-neck or head-neck-shoulder mask to ensure the daily reproducibility of treatments. A simulation CT scan was performed with 3 mm slice thickness and transported to the treatment planning system. The clinical target volume (CTV) was defined as the postoperative tumor bed and the elective nodal area (*Figure 2*). The elective nodal irradiation target volume comprised the positive lymph nodal areas plus at least 1 level beyond. Organ-at-risk volumes (spinal cord, optic apparatus, and mandible) were delineated on each slice. The maximal dose constraints were below 45 Gy for the spinal cord, 55 Gy for the optic apparatus, and 70 Gy for the mandible. For the planning target volume (PTV), a 0.3 cm margin was applied to the CTV, considering daily setup error. The prescribed dose was 60–68 Gy, administered at a daily 2 Gy/fraction, 5 days/week over 6–6.8 weeks (30–34 fractions).

Chemotherapy was administered to patients with advanced disease or in the presence of pathological high-risk factors. Cisplatin (80 mg/m^2 intravenously every 3 weeks) was the most commonly used concomitant chemotherapy schedule. Several patients received adjuvant chemotherapy of cisplatin (80 mg/m^2 intravenously, day 1) and 5-fluorouracil (5-FU; 1,000 mg/m^2 continuous infusion over 120 h), or cisplatin (80 mg/m^2 intravenously, day 1) and capecitabine (1,250 mg/m^2 orally twice a day, day 1 to day 14) repeated every 3 weeks, followed by PORT.

Follow-up

After treatment completion, cases were evaluated every 3 months for the first year, every 3–6 months over the following 4 years, and yearly thereafter. At each follow-up visit, a physical examination and imaging were performed, including fiberoptic endoscopy if indicated. A PET scan was performed if recurrence or metastasis was suspected. Overall survival (OS) was defined as the time from surgery to the date of death, progression-free survival (PFS) as the time from surgery to the date of local or regional recurrence, distant metastases, or death from any cause, locoregional relapse-free survival (LRRFS) as the absence of disease recurrence in the local site or regional lymph node, and distant metastasis-free survival (DMFS) as the time to distant metastasis.

Statistical analysis

The cumulative incidences of OS, PFS, LRRFS, and DMFS were evaluated using the Kaplan-Meier method. Survival was analyzed using the Kaplan-Meier method, and all subgroups were compared using the log-rank test. Multivariable analysis (MVA) was conducted if there were statistically significant factors in the univariable analysis (UVA). Univariable/multivariable Cox regression analysis was used to assess the association of prognostic factors with survival. The proportional hazards assumption of the Cox model was verified through "logarithm of negative

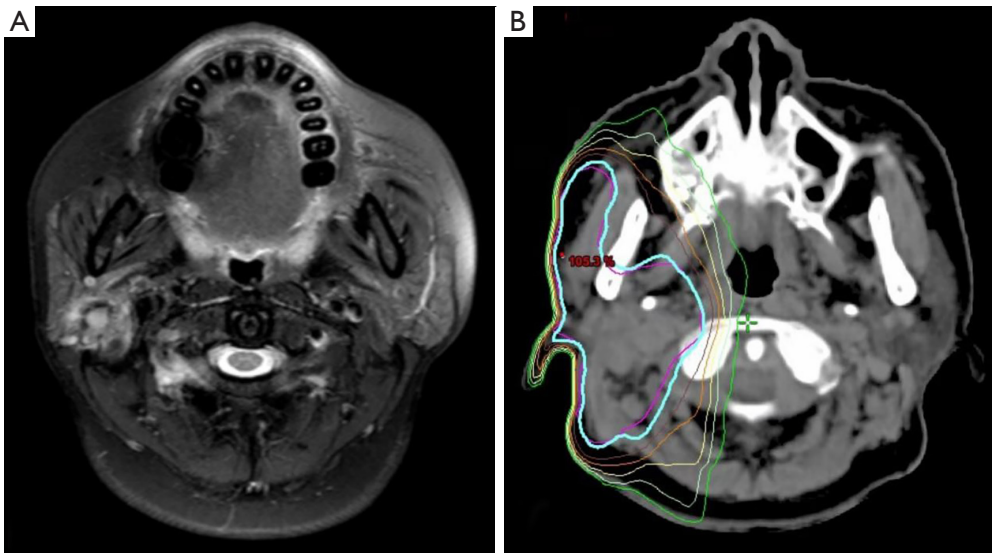

Figure 2 A typical case of right parotid gland tumor (A) axial T2-weighted MRI (B) isodose line of treatment plans of IMRT. MRI, magnetic resonance imaging; IMRT, intensity modulated radiotherapy.

logarithm" to show whether the curves of different groups were parallel and disjointed. A P value of <0.05 was considered significant. Statistical tests were 2-sided. All data were analyzed using the SPSS v. 20.0 (SPSS Inc., Chicago, IL, USA) statistical software package.

Results

Clinicopathological characteristics

Patient characteristics are summarized in *Table 1*. The median follow-up was 55.5 months (range, 1–114 months). The median age at initial diagnosis was 52 years (range, 15–76 years). Patients were divided based on age ≤52 or >52 years. Among the cases, 35 (58.3%) were male and 25 (41.7%) were female. The median tumor size was 2.5 cm (range, 1–15 cm). Most cases presented with a palpable mass at initial presentation. A total of 23 (38.3%) cases experienced pain and 5 (8.3%) showed facial nerve paralysis. Histologic types included adenoid cystic carcinoma (ACC) in 21 (35%) cases, lymphoepithelial carcinoma (LELC) in 12 (20%) cases, and mucoepidermoid carcinoma (MEC) in 8 (13.3%) cases. The primary sites were the parotid gland in 34 (56.7%) cases, the submandibular gland in 17 (28.3%) cases, and the sublingual gland in 9 (15%) cases. The tumor stage (T stage) distribution included 14 (23.3%) T1–T2 and 46 (76.7%) T3–T4b patients. The node stage (N stage) distribution was included 41 (68.3%) N0, 8 (13.3%) N1, 8 (13.3%) N2b, and 3 (5%) N2c patients. A total of 11 (18.3%) cases presented with stage I–II disease and 49 (81.7%) cases with stage III–IVb disease. Skin involvement was observed in 5 (8.3%) cases, a positive margin in 7 (11.7%) cases, extra-parenchymal extension in 34 (56.7%) cases, perineural invasion in 19 (31.7%) cases, and major nerve involvement in 28 (46.7%) cases. Only 16 (26.6%) cases had pathology results that indicated the grade of cancer, of which 6 were MEC and 4 SDC. Of the 6 MEC patients, 4 had a low/intermediate grade of differentiation.

Treatment characteristics

All cases received primary tumor resection with curative intention; 42 (70%) received concurrent ND, of whom 19 (31.7%) had pathologic evidence of N+. The median interval from surgery to RT was 30 days. The interval from surgery to RT (days) was divided based on ≤30 or >30 days. The median dose to the tumor bed was 63 Gy (range, 60–68 Gy). A total of 4 patients (6.7%) received tumor bed irradiation only and 49 (81.7%) cases received tumor bed and unilateral neck nodal irradiation, while the rest received tumor bed and bilateral neck nodal irradiation. There were 4 patients who received concurrent 3-weekly cisplatin chemotherapy and 2 patients received adjuvant chemotherapy after PORT, 1 with cisplatin and 5-FU and the other with cisplatin and capecitabine. Of the 4 patients who received chemotherapy, 2 exhibited advanced

Table 1 Characteristics of the 60 SGC patients

Characteristics	n (%)
Median age (years)	52
Gender	
Male	35 (58.3)
Female	25 (41.7)
Primary site	
Parotid gland	34 (56.7)
Submandibular gland	17 (28.3)
Sublingual gland	9 (15.0)
Median size of tumor (cm)	2.5
Pain	
Yes	23 (38.3)
No	37 (61.7)
Facial nerve paralysis	
Yes	5 (8.3)
No	55 (91.7)
Histologic types	
ACC	21 (35.0)
LELC	12 (20.0)
MEC	8 (13.3)
SDC	5 (8.3)
SCC	4 (6.7)
BCAC	3 (5.0)
Myoepithelial carcinoma	2 (3.3)
AcCC	1 (1.7)
Others	4 (6.7)
Clinical stage	
I–II	11 (18.3)
III–IVb	49 (81.7)
Skin involvement	
Yes	5 (8.3)
No	55 (91.7)
Margin	
Positive	7 (11.7)
Negative	53 (88.3)
Extra-parenchymal extension	
Yes	34 (56.7)
No	26 (43.3)
Perineural invasion	
Yes	19 (31.7)
No	41 (68.3)
Major nerve involvement	
Positive	28 (46.7)
Negative	32 (53.3)
Surgery	
Primary tumor resection	18 (30.0)
Primary tumor resection + ND	42 (70.0)
Interval from surgery to RT (days)	
≤30	30 (50.0)
>30	30 (50.0)
RT	
T stage	
T1–T2	14 (23.3)
T3–T4b	46 (76.7)
N stage	
N0	41 (68.3)
N1	8 (13.3)
N2b	8 (13.3)
N2c	3 (5.0)
Tumor bed	4 (6.7)
Tumor bed + unilateral neck	49 (81.7)
Tumor bed + bilateral neck	7 (11.6)
Median dose (Gy)	63
Chemoradiotherapy	
Yes	4 (6.7)
No	56 (93.3)

SGC, salivary gland cancer; ACC, adenoid cystic carcinoma; LELC, lymphoepithelioid carcinoma; MEC, mucoepidermoid carcinoma; SDC, salivary duct carcinoma; SCC, squamous cell carcinoma; BCAC, basal cell adenocarcinoma; AcCC, acinic cell carcinoma; ND, neck dissection; RT, radiotherapy.

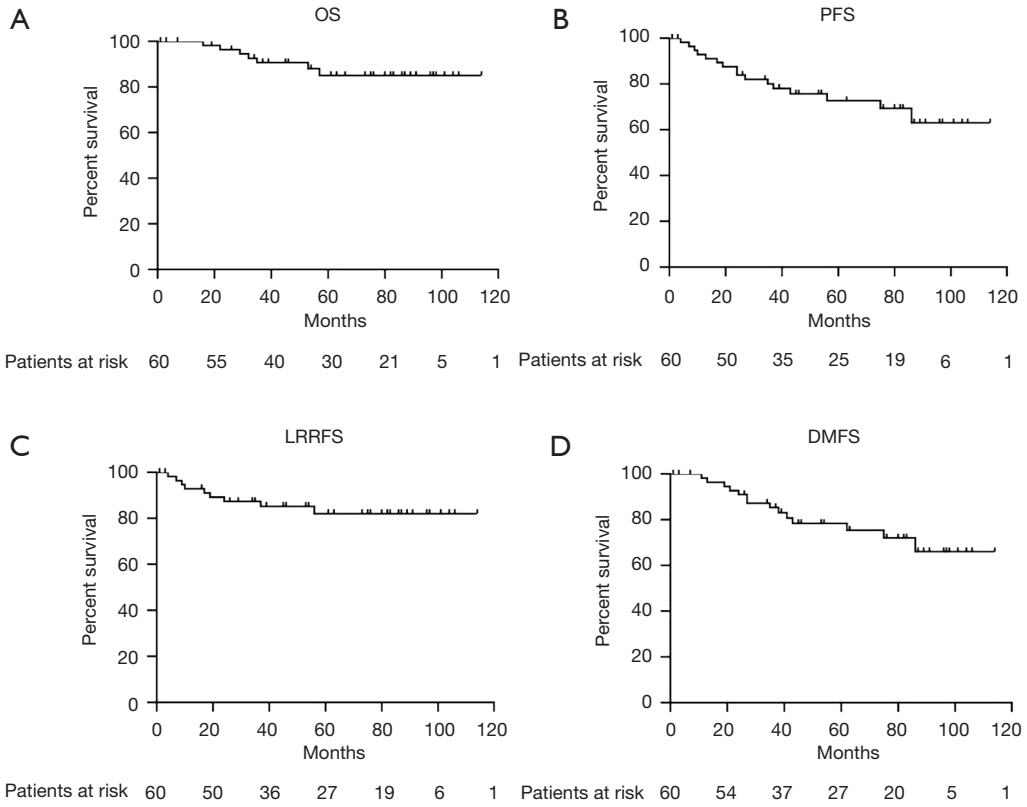

Figure 3 Kaplan-Meier curves of OS, PFS, LRRFS, and DMFS. OS, overall survival; PFS, progression-free survival; LRRFS, locoregional relapse-free survival; DMFS, distant metastasis-free survival.

nodal stage (N2b) disease and 2 exhibited major nerve involvement; all presented with stage T3–T4 disease.

Survival analysis

Kaplan-Meier curves for OS, PFS, LRRFS, and DMFS are shown in *Figure 3*. The 3-, 5-, and 10-year OS rates were 90.7%, 85.1%, and 85.1%, while the PFS rates were 80.1%, 72.7%, and 63.1%, respectively. The 3-, 5-, and 10-year LRRFS rates were 87.4%, 82.1%, and 82.1%, respectively, while the DMFS rates were 85.3%, 78.4%, and 66.1%, respectively.

Prognostic factors for OS

Risk factors for survival are summarized in *Table 2* and Table S1. The UVA suggested that a higher N stage was associated with decreased survival, with stage N0 disease patients surviving significantly longer than those with stages N1, N2b, and N2c (P=0.025). The primary site was a prognostic factor for OS, with 5-year OS rates of 90%, 67.6%, and 100% for parotid, submandibular, and sublingual gland tumors (P=0.039), respectively. However, no significant association was found between OS and N stage or the primary site in MVA.

Prognostic factors for PFS

Based on our log-rank test, gender was strongly associated with PFS (P=0.018), although it did not reach significance as a predictor in MVA. For patients with and without major nerve involvement, the 5-year PFS was 85% and 59.5% (P=0.019), respectively. Notably, when interval from surgery to RT was analyzed as a categorical variable using the median interval of 30 days as a cutpoint, a significant difference in PFS was observed (P=0.044). No significant difference in PFS was observed among patients with N stage and positive margin in UVA (P=0.164 and 0.092, respectively). The MVA indicated that major nerve involvement [hazard ratio (HR) =2.394; 95% confidence

Table 2 UVA and MVA for OS and PFS

Variables	Number	OS						PFS					
		At 5 years (%)	UVA	MVA				At 5 years (%)	UVA	MVA			
			P value	HR	AR	95% CI	P value		P value	HR	AR	95% CI	P value
Gender			0.989			–			0.018	–	–	–	–
Male	35	84.9						62.1					
Female	25	85.2						87.1					
Age (years)			0.228			–			0.172	–	–	–	–
≤52	31	90.8						77.4					
>52	29	80.2						66.7					
Perineural invasion			0.373			–			0.951	–	–	–	–
No	41	84.1						71.8					
Yes	19	94.1						77					
Major never involvement			0.665			–			0.019	2.394	25.5	0.664–8.896	0.034
Negative	32	82.8						85					
Positive	28	86.9						59.5					
Extra-parenchymal extension			0.268			–			0.581	–	–	–	–
No	26	95						71.2					
Yes	34	82.5						74.9					
Primary site			0.039			–			0.641	–	–	–	–
Parotid gland	34	90						70					
Submandibular gland	17	67.6						64.7					
Sublingual gland	9	100						88.9					
T stage			0.154			–			0.244	–	–	–	–
T1–T2	14	100						79.1					
T3–T4b	46	81.1						71					
N stage			0.025			–			0.164	0.089	18.2	0.008–0.964	0.047
N0	41	91.5						78.2					
N1	8	–						–					
N2b	8	43.8						60					
N2c	3	–						–					
Clinical stage			0.188			–			0.141	–	–	–	–
I–II	11	100						85.7					
III–IVb	49	81.6						70.5					
Margin			0.206			–			0.092	4.086	17.8	1.097–15.219	0.036
Positive	53	88.4						74.9					

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Number	OS						PFS					
		At 5 years (%)	UVA	MVA				At 5 years (%)	UVA	MVA			
			P value	HR	AR	95% CI	P value		P value	HR	AR	95% CI	P value
Negative	7	64.3						57.1					
Skin involvement			0.55			–			0.458	–	–	–	–
No	55	85.7						75.3					
Yes	5	80						40					
Interval from surgery to RT (days)			0.635			–			0.044	3.934	25.6	1.097–14.105	0.036
≤30	30	84.7						85.2					
>30	30	84.4						59.6					

P was calculated using log-rank test. UVA, univariable analysis; MVA, multivariable analysis; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; AR, absolute risk; CI, confidence interval; RT, radiotherapy.

interval (CI): 0.664–8.896; P=0.034], N stage (HR =0.089; 95% CI: 0.008–0.964; P=0.047), positive margin (HR =4.086; 95% CI: 1.097–15.219; P=0.036), and interval from surgery to RT (HR =3.934; 95% CI: 1.097–14.105; P=0.036) were significant independent predictors of PFS (*Figure 4*).

Prognostic factors for LRRFS

In UVA, the 5-year LRRFS rate for patients with a positive margin was 57.1%, compared with 85.9% for those with a negative margin (P=0.029). In MVA, the positive margin was an independent predictor for LRRFS (HR =5.064; 95% CI: 1.211–21.187; P=0.026) (*Figure 5*).

Prognostic factors for DMFS

Major nerve involvement (P=0.024), N stage (P=0.014), and clinical stage (P=0.049) were prognostic factors for poor DMFS in UVA. When a Cox proportional hazards regression model was used to predict distant metastases, major nerve involvement (HR =2.115; 95% CI: 0.521–8.583; P=0.008), positive margin (HR =6.367; 95% CI: 1.524–26.603; P=0.011), and interval from surgery to RT (HR =6.231; 95% CI: 1.503–25.829; P=0.012) were identified as independent predictors of distant metastases (*Figure 5*).

In ACC subgroup analysis, 5-year OS, PFS, LRRFS, and DMFS rates were 100%, 85.7%, 76.2%, and 90.2%, respectively. In UVA, perineural invasion was significantly associated with PFS (P=0.021) and DMFS (P=0.026), major nerve involvement was strongly associated with PFS (P=0.014), the parotid gland (P=0.041), and N stage (P=0.023) were associated with poor LRRFS; and positive margin was an important prognostic factor for PFS (P=0.021), LRRFS (P=0.002), and DMFS (P=0.021). However, there were too few ACCs to allow for MVA. For detailed information, see *Table 3*.

Adverse events

The most acute adverse events were grade II/III mucositis (n=44; 73.3%) and grade I/II dermatitis (n=46; 76.7%). Xerostomia was the most common late adverse event (n=18; 30%), followed by hearing impairment (n=17; 28.4%), taste abnormalities (n=15; 25%), paresthesia (n=14; 23.3%), fibrosis of the skin (n=11; 18.3%), trismus (n=6; 10%), and osteoradionecrosis (n=2; 3.3%). No grade 4 acute or late adverse events were observed.

Patterns of failure

Treatment failure occurred in 16 (26.7%) of the 60 cases (*Figure 6*). Locoregional recurrence occurred in 9 (15%), local failure in 8 (13.3%), and regional failure in 3 (5%) cases. Distant metastasis occurred in 14 cases (23.3%). In the 7 cases with distance-related failure, metastasis was accompanied by locoregional recurrence. The median time to distant metastasis was 49.5 months. Distant metastasis

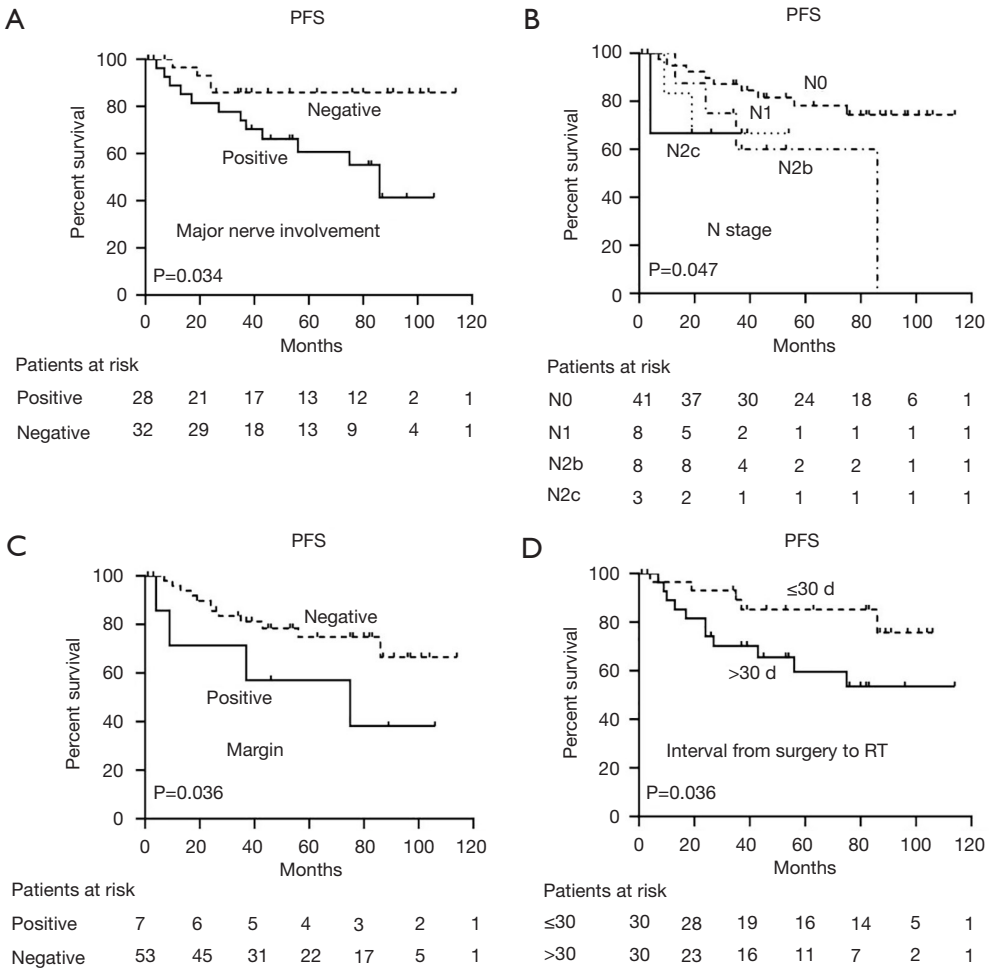

Figure 4 Comparison of survival according to clinicopathologic factors. (A) Major nerve involvement (P=0.034); (B) N stage (P=0.047); (C) margin (P=0.036); (D) interval from surgery to RT (P=0.036). PFS, progression-free survival; RT, radiotherapy.

occurred in the lung (n=10; 16.7%), bones (n=3; 5%), brain (n=1; 1.7%), elsewhere (n=1; 1.7%), and at multiple sites (n=2; 3.3%).

Discussion

This retrospective study focused on the clinical outcomes, prognostic factors, failure patterns, and adverse events in patients with major SGC treated with surgery and postoperative IMRT. Similar to already reported in the literature (3,6,7), our study showed that ACC was the most common histology, followed by LELC. As histology is an important prognostic factor in SDC patients and adenocarcinoma and undifferentiated carcinoma have worse prognoses (8,9), we performed an ACC subgroup analysis. Our cohort exhibited excellent clinical outcomes that compared very favorably with those reported in the literature (10).

Our MVA showed that N stage, positive margin, major nerve involvement, and interval from surgery to RT were unfavorable prognostic factors. With regard to the relationship between clinicopathologic parameters and OS, there was no negative prognostic factor for survival in MVA. A probable reason was the excellent survival of our patients. Although positive margin and N stage were not prognostic factors for PFS in the UVA, and neither was N stage for LRRFS, we nevertheless included them in the Cox proportional hazards regression model, as positive margin and positive lymph nodes had previously been shown to be important predictive factors for SGC (3,11-13). After adjusting for factors that might affect prognosis, N stage and positive margin were found to be independent prognostic

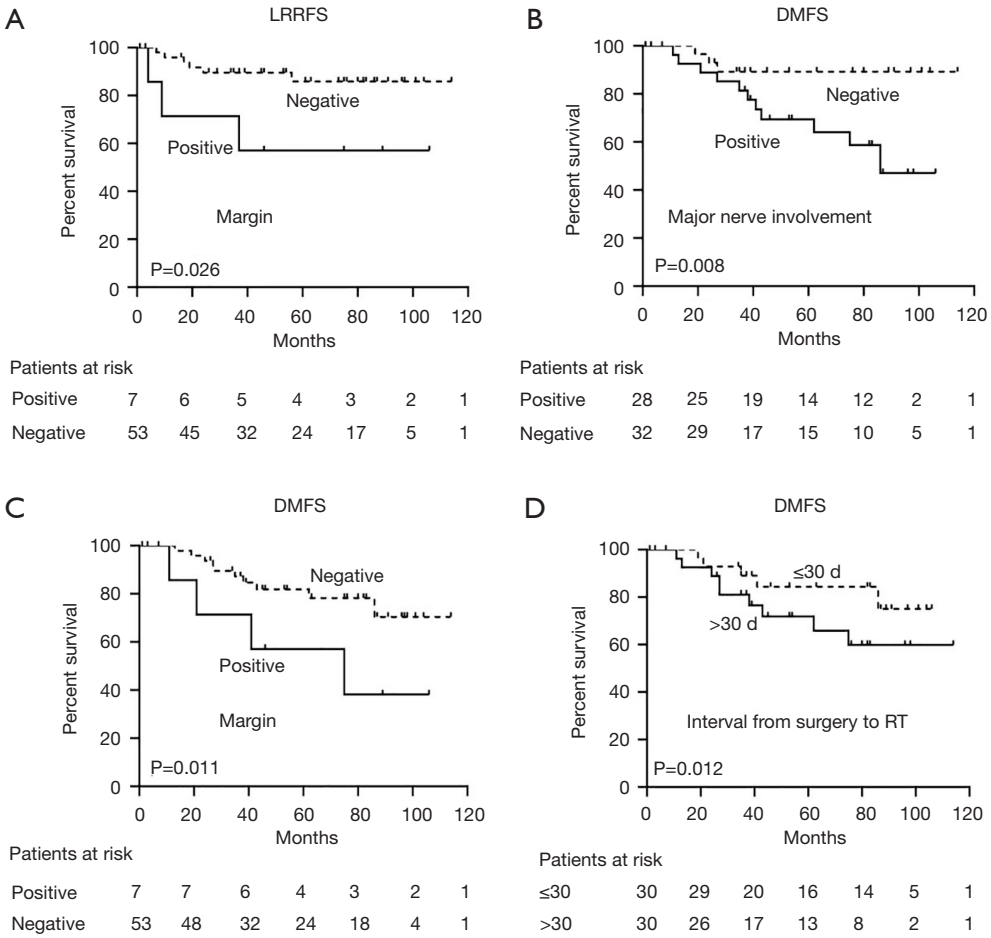

Figure 5 Comparison of survival according to clinicopathologic factors. (A) Margin (P=0.026); (B) major nerve involvement (P=0.008); (C) margin (P=0.011); (D) interval from surgery to RT (P=0.012). LRRFS, locoregional relapse-free survival; DMFS, distant metastasis-free survival; RT, radiotherapy.

factors for PFS, although N stage was not a predictive factor for LRRFS. Positive margin was also an independent prognostic factor for LRRFS and DMFS, suggesting that margin status information should be included in clinical pathology reports. Major nerve involvement was an independent prognostic factor for poor PFS and DMFS, while a time from surgery to RT >30 days resulted in worse PFS and DMFS. A previous study showed clear tendencies for worsening effects of poor differentiation in SCC and high grade in MEC (14). Other research has shown that high-grade tumor histology is a highly significant predictor of shorter survival in SGC, irrespective of histological subtype (15). The subgroups of patients with MEC and SCC were too small to allow adequate statistical analysis.

Combination treatment modalities are usually required for SGC. Surgical resection followed by PORT is practical and effective at increasing survival and locoregional control rates in patients with a tumor size ≥4 cm, deep lobe settlement, high grade tumor, positive margin, local advanced stage, lymph node metastasis, soft tissue or bone infiltration, and perivascular and perineural invasion (16-19). Terhaard *et al.* (20) revealed that the 5- and 10-year actuarial local control rates were significantly higher for PORT *vs.* surgery alone (94% *vs.* 84% and 91% *vs.* 76%, respectively; P=0.0005). Scherl *et al.* (21) showed that postoperative chemoradiotherapy (POCRT) in high-risk and high-grade SDC patients featured with perineural invasion, positive margins, advanced T status, or lymph node involvement which reduced the rate of locoregional recurrences.

A comparison of our outcomes with those of other

Table 3 UVA of prognostic factors for ACC

Variables	Number	PFS		LRRFS		DMFS	
		At 5 years (%)	UVA P value	At 5 years (%)	UVA P value	At 5 years (%)	UVA P value
Perineural invasion			0.021				0.026
No	15	75		–		100	
Yes	6	–		–		–	
Major nerve involvement			0.014				
Negative	13	–		–		–	
Positive	8	100		–		–	
Margin					0.002		0.021
Negative	19	–	0.021	80		94.4	
Positive	2	94.7		–		–	
Primary site					0.041		
Parotid gland	14	–		66.7		–	
Submandibular gland	4	–		100		–	
Sublingual gland	3	–		–		–	
N stage					0.023		
N0	12	–		80		–	
N1	4	–		–		–	
N2b	3	–		–		–	
N2c	2	–		–		–	

P was calculated using log-rank test. UVA, univariable analysis; ACC, adenoid cystic carcinoma; PFS, progression-free survival; LRRFS, locoregional relapse-free survival; DMFS, distant metastasis-free survival.

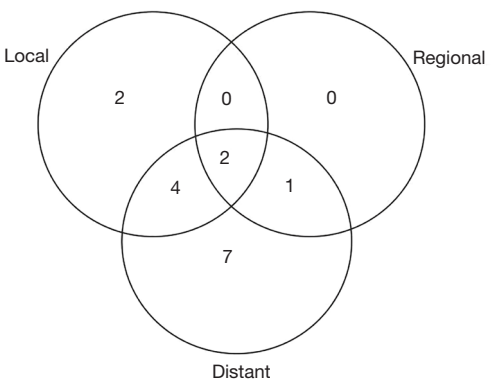

Figure 6 Venn diagram of patterns of failure (16/60 patients).

institutions would be difficult due to the different case mix and wide variety of histological subtypes involved. Overall, the outcomes in our study are better than the reported historical data of other institutions using PORT for SGC treatment (5-year OS: 85.1% *vs.* 61–74%; 10-year OS: 85.1% *vs.* 48–71%) (17,18,22-24). The better survival rates in this series could be explained by a "cohort effect" resulting from improved diagnostic capabilities and treatment modalities. Previous studies have involved conventional RT or 3-DCRT treatment; however, all the cases in this study received IMRT. Compared with conventional RT or 3-DCRT, IMRT permits a greater precision and modulation of the RT beam to keep high doses away from vital structures. It offers improved locoregional control in SGC patients, which corresponds to better OS (25,26). Furthermore, because a more generous amount of normal tissue is spared, IMRT is less toxic, resulting in a smaller impact on quality of life (27). Our patients exhibited a reduced incidence of xerostomia (30%) compared with those from historical studies (83%) (28,29).

In agreement with the published literature (30,31),

distant metastasis was the predominant mode of failure, highlighting the need for effective systemic therapies. Chemotherapy is generally reserved for the palliative treatment of symptomatic locally recurrent or metastatic disease, and has a limited effect (32). Recent studies have also indicated that POCRT promotes higher survival and locoregional control than PORT treatment alone (33-36). However, no significant differences in DMFS, disease-free survival, and OS were observed when adding concurrent chemotherapy to PORT, while POCRT has been associated with increased mortality and toxicity (35,37). We could not evaluate the effect of POCRT on outcomes owing to the small number of patients who received chemotherapy.

Our study had several significant limitations. The small sample size did not permit an evaluation of outcomes stratified by various histological subtypes. Additionally, our median follow-up was approximately 55.5 months, and median OS, PFS, LRRFS, and DMFS were not reached. Lastly, the pathological detection of SGC margin status and perineural invasion may vary greatly depending on the sampling extent. Nevertheless, our observations have the potential for use in the design of prospective SGC clinical trials.

Conclusions

Our series of 60 SGC patients showed that postoperative IMRT led to the improved OS for SGC with acceptable toxicities. The N stage, positive margin, major nerve involvement, and interval from surgery to RT were important factors associated with oncological outcomes.

Acknowledgments

Funding: This study was an independent research funded by the Department of Health of Zhejiang Province (No. 2018265493 and No. 2017197137).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-21-836/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-21-836/coif). All authors report that this study was an independent research funded by the Department of Health of Zhejiang Province (grant No. 2018265493 and No. 2017197137). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of the First Affiliated Hospital, Zhejiang University, and individual consent for this retrospective analysis was waived.

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Cite this article as: Zang S, Chen M, Huang H, Zhu X, Li X, Yan D, Yan S. Oncological outcomes of patients with salivary gland cancer treated with surgery and postoperative intensity-modulated radiotherapy: a retrospective cohort study. Quant Imaging Med Surg 2022;12(5):2841-2854. doi: 10.21037/qims-21-836

Supplementary

Table S1 UVA and MVA for LRRFS and DMFS

Variables	Number	LRRFS						DMFS					
		At 5 years (%)	UVA	MVA				At 5 years (%)	UVA	MVA			
			P value	HR	AR	95% CI	P value		P value	HR	AR	95% CI	P value
Gender			0.159						0.06				
Male	35	74.8						71.8					
Female	25	91.5						87.1					
Age (years)			0.222						0.485				
≤52	31	88.4						75.7					
>52	29	74.8						80.5					
Perineural invasion			0.601						0.676				
No	41	80.9						81					
Yes	19	88.9						76.7					
Major never involvement			0.215						0.024	2.115	21.1	0.521–8.583	0.008
Negative	32	89.5						89.3					
Positive	28	74.5						68.2					
Extra-parenchymal extension			0.84						0.476				
No	26	82.4						83.8					
Yes	34	84.2						77.3					
Primary site			0.591						0.762				
Parotid gland	34	82.5						79.4					
Submandibular gland	17	75.3						68.8					
Sublingual gland	9	88.9						74.1					
T stage			0.337						0.13				
T1–T2	14	85.7						92.3					
T3–T4b	46	80.9						74.7					
N stage			0.173						0.014				
N0	41	83.7						86.1					
N1	8	–						–					
N2b	8	–						60					
N2c	3	–						–					
Clinical stage			0.495						0.049				
I–II	11	85.7						100					
III–IVb	49	82						73.8					
Margin			0.029	5.064	28.8	1.211–21.187	0.026		0.055	6.367	24.8	1.524–26.603	0.011
Positive	53	85.9						81.9					
Negative	7	57.1						57.1					
Skin involvement			0.136						0.932				
No	55	85.8						78.3					
Yes	5	40						80					
Interval from surgery to RT (days)			0.239						0.157	6.231	12.5	1.503–25.829	0.012
≤30	30	88.9						84.4					
>30	30	75						71.9					

P was calculated using log-rank test. UVA, univariable analysis; MVA, multivariable analysis; LRRFS, locoregional relapse-free survival; DMFS, distant metastasis-free survival; HR, hazard ratio; AR, absolute risk; CI, confidence interval.

https://dx.doi.org/10.21037/qims-21-836