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

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Abstract

Background To investigate the outcomes, prognostic factors, patterns of failure, and adverse events in patients with salivary gland cancer (SGC) treated with surgery and postoperative intensity-modulated radiotherapy (IMRT).

Methods We identified 60 patients with major SGC treated with surgery followed by postoperative 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 calculated with the Kaplan–Meier method. Multivariable analysis (MVA) was used to identify prognostic factors for OS, PFS, LRRFS and DMFS.

Results Adenoid cystic carcinoma (ACC) was the most common histology (n =21; 35%). With a median follow-up of 55.5 months, OS and PFS were 90.7%, 85.1%, and 85.1%; and 80.1%, 72.7%, and 63.1%, at 3, 5, and 10 years, respectively. LRRFS and DMFS at 3, 5, and 10 years were 87.4%, 82.1%, and 82.1%; and 85.3%, 78.4%, and 66.1%, respectively. Five-year OS, PFS, LRRFS, and DMFS for ACC was 100%, 67.7%, 76.2%, and 90.2%, respectively. In MVA, N stage was an independent predictor of PFS (p =0.047). Positive margin was a significant prognostic factor for PFS, LRRFS, and DMFS (p =0.036, 0.026, and 0.011, respectively). Major nerve involvement was significantly correlated with PFS and DMFS (p =0.034 and 0.008, respectively). Interval from surgery to radiotherapy (RT) predicted PFS and DMFS (p =0.036 and 0.012, 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.

Conclusion Postoperative IMRT leads to improved survival for SGC patients with acceptable toxicities.

Introduction

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

However, it is difficult to compare studies owing to differences in the number of patients enrolled in each study, pathological types, and treatment strategies. 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 that 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 rate and quality of life and has been widely adopted for the treatment of head and neck

cancer in recent decades. Because of the differences in biological behavior between major and minor SGC, prognosis varies considerably. Here, 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.

Materials And Methods

Patients

We retrospectively reviewed 60 patients with histologically confirmed primary SGC treated at the First Affiliated Hospital of Zhejiang University from January 2009 to December 2016. All the patients had newly diagnosed diseases and received upfront surgery followed by external beam RT using IMRT. Patients with recurrent or metastatic disease or those who failed to finish the scheduled RT were excluded.

Evaluation

All patients were initially evaluated by a multimodality treatment team consisting of an otolaryngologist, a medical oncologist, and a RT oncologist. All patients 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 patients had also undergone either magnetic resonance imaging (MRI) or positron emission tomography (PET). Histological diagnosis was confirmed according to the WHO histologic subtype criteria for SGC [5]. All patients were restaged based on the 2018 American Joint Committee on Cancer 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) therapeutically (if clinically positive lymph node; cN+) or electively in high-risk cN0 (clinically negative lymph node) patients. For 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. Simulation CT scan was performed with 3-mm slice thickness and transported to the treatment planning system. Clinical target volume (CTV) was defined as postoperative tumor bed and the elective nodal area (Figure 1). Elective nodal irradiation target volume comprised the positive lymph nodal areas plus at least one level beyond. Organ-at-risk volumes (spinal cord, optic apparatus, 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 high pathological 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-FU (1000 mg/m^2 continuous infusion over 120 h), or cisplatin (80 mg/m^2 intravenously, day 1) and capecitabine (1250 mg/m^2 orally twice a day, day 1 to day 14) repeated every 3 weeks followed by PORT.

Follow-up

After treatment completion, patients were evaluated every 3 months for the first 1 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 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

Survival was analyzed using the Kaplan–Meier method and compared using the log-rank test. A Cox proportional hazards regression model was used for MVA. $p<0.05$ was considered significant. Statistical tests were two-sided. All data were analyzed using SPSS 20.0.

Results

Clinicopathological characteristics

Patient characteristics are summarized in Table 1. The median follow-up was 55.5 months (range 1–114 months). Median age at initial diagnosis was 52 years (range 15–76 years). Among the patients, 35 (58.3%) were male and 25 (41.7%) female. Median tumor size was 2.5 cm (range 1–15 cm). Most patients presented with a palpable mass at initial presentation. Twenty-three (38.3%) experienced pain and 5 (8.3%) showed facial nerve paralysis. In some patients, painless masses had remained stable for several years and then began to grow rapidly. Histologic types included ACC in 21 patients (35%), lymphoepithelial carcinoma (LELC) in 12 (20%), mucoepidermoid carcinoma (MEC) in 8 (13.3%), salivary duct carcinoma (SDC) in 5 (8.3%), squamous cell carcinoma (SCC) in 4 (6.7%), basal cell adenocarcinoma (BCAC) in 3 (5%), myoepithelial carcinoma in 2 (3.3%), acinic cell carcinoma (AcCC) in 1 (1.7%), and others in 4 (6.7%). The primary sites were the parotid gland in 34 patients (56.7%), submandibular gland in 17 (28.3%), and sublingual gland in 9 (15%). The T stage distribution was 14 (23.3%) T1–T2 and 46 (76.7%) T3–T4b. The N stage distribution was 41 (68.3%) N0, 8 (13.3%) N1, 8 (13.3%) N2b, and 3 (5%) N2c. Eleven (18.3%) presented with stage Ⅱ–Ⅱ disease and 49 (81.7%) with stage Ⅱ–Ⅱb. Skin involvement was observed in 5 patients (8.3%), positive margin in 7 (11.7%), extra-

parenchymal extension in 34 (56.7%), perineural invasion in 19 (31.7%), and major nerve involvement in 28 (46.7%).

Treatment characteristics

All patients received primary tumor resection with curative intention; 42 (70%) received concurrent ND, 19 of which (31.7%) had pathologic evidence of N+. The median interval from surgery to RT was 30 days. The median dose to the tumor bed was 63 Gy (range 60–68 Gy). Four patients (6.7%) received tumor bed irradiation only. Forty-nine (81.7%) were treated with tumor bed and unilateral neck nodal irradiation, while the rest received tumor bed and bilateral neck nodal irradiation. Four patients received concurrent three-weekly cisplatin chemotherapy. Two received adjuvant chemotherapy after PORT, one with cisplatin and 5-FU and the other with cisplatin and capecitabine. Of the 4 patients who received chemotherapy, 2 exhibited advanced nodal stage (N2b) and 2 major nerve involvement; all presented with stage T3–T4 disease.

Survival

Kaplan–Meier curves for OS, PFS, LRRFS, and DMFS are shown in Figure 2. The 3-, 5-, and 10-year OS was 90.7%, 85.1%, and 85.1%, while that for PFS was 80.1%,72.7%, and 63.1%, respectively. The 3-, 5-, and 10-year LRRFS was 87.4%, 82.1%, and 82.1%, while that for DMFS was 85.3%, 78.4%, and 66.1%, respectively.

Prognostic factors for OS

Risk factors for survival are summarized in Table 2&Additional file 1. Univariable analysis (UVA) suggested that a higher N stage was associated with decreased survival, with patients having stage N0 disease surviving significantly longer than those with stages N1, N2b, and N2c (p=0.025). 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). However, no significant association was found between OS and N stage or 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, 0.092). MVA indicated that major nerve involvement (hazard ratio [HR]=2.394, 95% confidence interval [CI]=0.664–8.89, 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 3).

Prognostic factors for LRRFS

In UVA, the 5-year LRRFS for patients with positive margin was 57.1%, compared with 85.9% for those with negative margin (p=0.029). In MVA, positive margin was an independent predictor for LRRFS (HR=5.064, 95% CI=1.211–21.187, p=0.026) (Figure 4).

Prognostic factors for DMFS

Major nerve involvement, N stage, and clinical stage were prognostic factors for poor DMFS in UVA (p=0.024, 0.014, and 0.049, respectively). 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 4).

In ACC subgroup analysis, 5-year OS, PFS, LRRFS, and DMFS were 100%, 67.7%, 76.2%, and 90.2%, respectively. In UVA, perineural invasion was significantly associated with PFS and DMFS (p=0.021 and 0.026, respectively); major nerve involvement was was strongly associated with PFS (p=0.014); parotid gland and N stage were associated with poor LRRFS (p=0.041 and 0.023, respectively); and positive margin was an important prognostic factor for PFS, LRRFS, and DMFS (p=0.021, 0.002, and 0.021, respectively). 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 □/□ mucositis (n=44, 73.3%) and grade□/□ 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 patients (Figure 5). Locoregional recurrence occurred in 9 (15%), local failure in 8 (13.3%), and regional failure in 3 (5%). Distant metastasis occurred in 14 patients (23.3%). In the 7 patients with distance-related failure, metastasis was accompanied by locoregional recurrence. The median time to distant metastasis was 49.5 months. Distant metastasis 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 that 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, for SDC, adenocarcinoma and undifferentiated carcinoma have worse prognosis [8, 9], we performed an ACC subgroup analysis. Our clinical 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. Probable reason was 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 were previously 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 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.

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, positive margin, local advanced stage, lymph node metastasis, soft tissue or bone infiltration, and perivascular and perineural invasion [14–17]. Terhaard et al. 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) ($p = 0.0005$) [18].

A comparison of our outcomes with those of other institutions is difficult because of different case mix and wide variety of histological subtypes involved. Overall, the outcomes in our study are better than those reported for historical data of other institutions using PORT use for SGC treatment (5-year OS: 85.1% vs 61–74%; 10-year OS: 85.1% vs 48–71%) [15, 16, 19–21]. 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 patients 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. This offers improved locoregional control in SGC patients, which corresponds to better OS [22, 23]. Furthermore, because a greater amount of normal tissue is spared, IMRT is less toxic, resulting in a smaller impact on quality of life [24]. Our patients exhibited a reduced incidence of xerostomia (30%) compared with those from historical studies (83%) [25].

In agreement with the published literature [26, 27], 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 [28].

Recent studies have also indicated that postoperative chemoradiotherapy (POCRT) promotes higher survival and locoregional control than PORT treatment alone [29–32]. 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 [31, 33]. 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 permit an evaluation of outcome 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 extent of sampling. Nevertheless, our observations have potential for use in the design of prospective SGC clinical trials.

Conclusion

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

Abbreviations

SGC: salivary gland cancer; IMRT: intensity-modulated radiotherapy; OS: overall survival; PFS: progression-free survival; LRRFS: locoregional relapse-free survival; DMFS: distant metastasis-free survival; ACC: adenoid cystic carcinoma; MVA: multivariable analysis; RT: radiotherapy; PORT: postoperative radiotherapy; UVA: Univariable analysis; POCRT: postoperative chemoradiotherapy; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; ND: neck dissection; CTV: Clinical target volume; PTV: planning target volume; LELC: lymphoepithelial carcinoma; MEC: mucoepidermoid carcinoma; SDC: salivary duct carcinoma; SCC: squamous cell carcinoma; BCAC: basal cell adenocarcinoma; AcCC: acinic cell carcinoma; POCRT: postoperative chemoradiotherapy

Declarations

Ethics approval and consent to participate

For this type of study ethics approval is not required. Written informed consent was obtained ‘front door’ from all patients allowing collection of their clinical data.

Consent for publication

Not applicable. The MRI images displayed in the paper have been anonymized, and cannot be used to identify patients.

Availability of data and materials

The datasets generated and/ or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

Conflicts of interest

There are no conflicts to declare.

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Authors' contributions

Danfang Yan and Senxiang Yan designed this study; Senxiang Yan also revised the main manuscript content; Shoumei Zang and Huijie Huang carried out analysis and wrote the manuscript; Xinli Zhu and Meiqin Chen were responsible for data collection.

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Not applicable.

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Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Figures

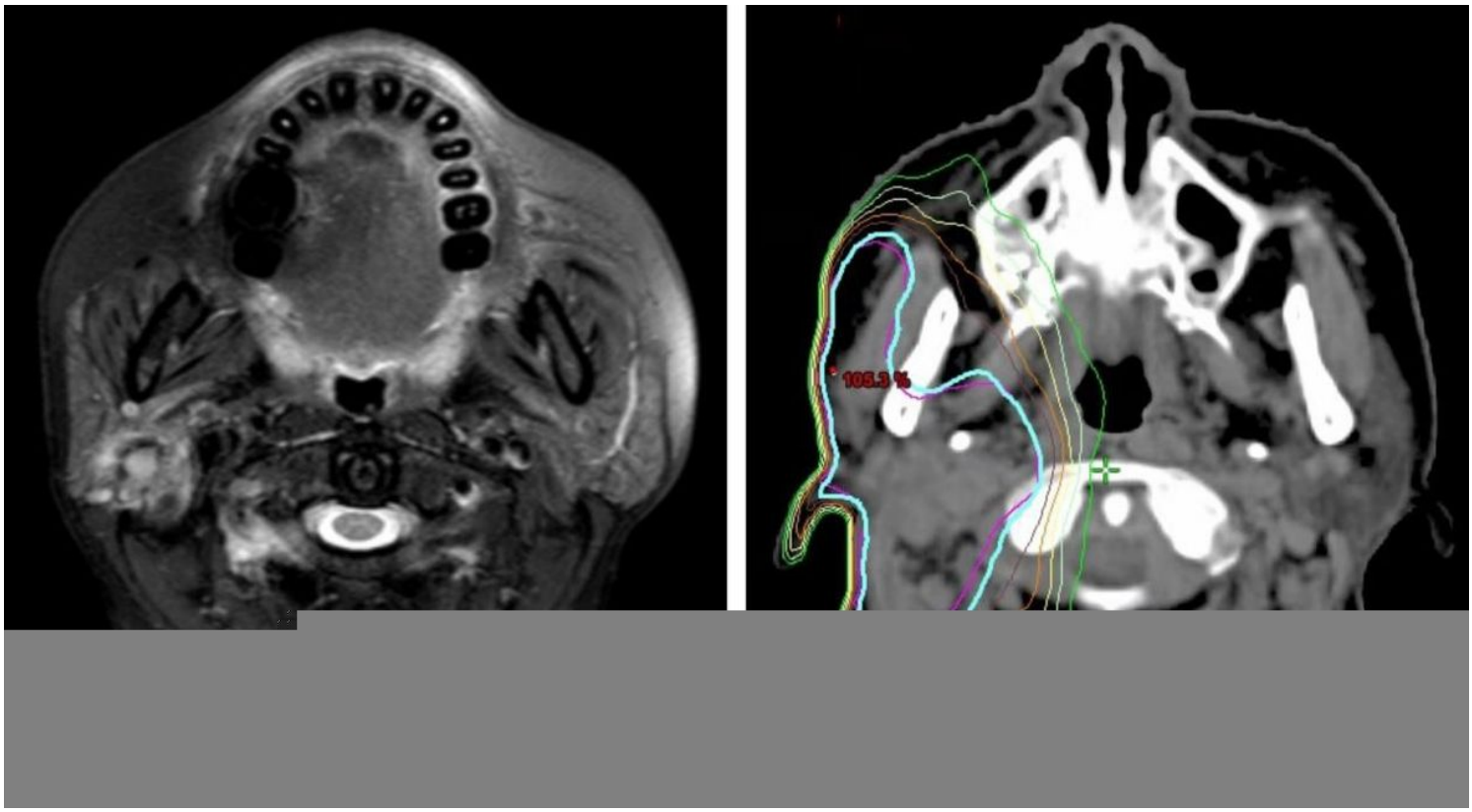

Figure 1

A typical case of right parotid gland tumor (a) Axial T2-weighted magnetic resonance imaging (MRI) (b) Isodose line of treatment plans of intensity modulated radiotherapy (IMRT)

Figure 2

Kaplan-Meier curves of overall survival (OS), progression-free survival (PFS), locoregional relapse-free survival (LRRFS), distant metastasis-free survival (DMFS)

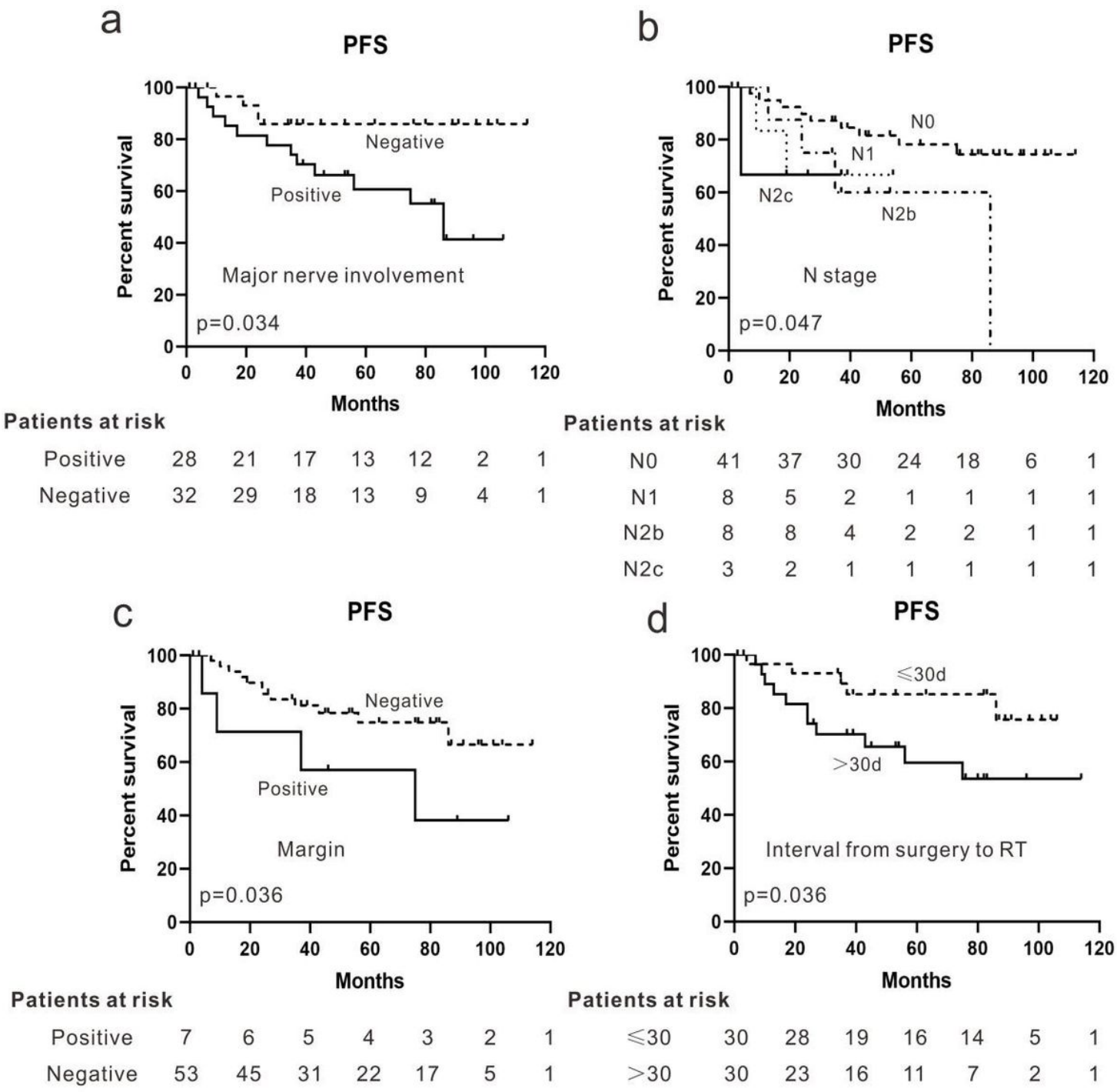

Figure 3

Comparison of survival according to clinicopathologic factors. (a) N stage (p=0.047); (b) margin (p=0.036); (c) major nerve involvement (p=0.034), (d) interval from surgery to RT (p=0.036)

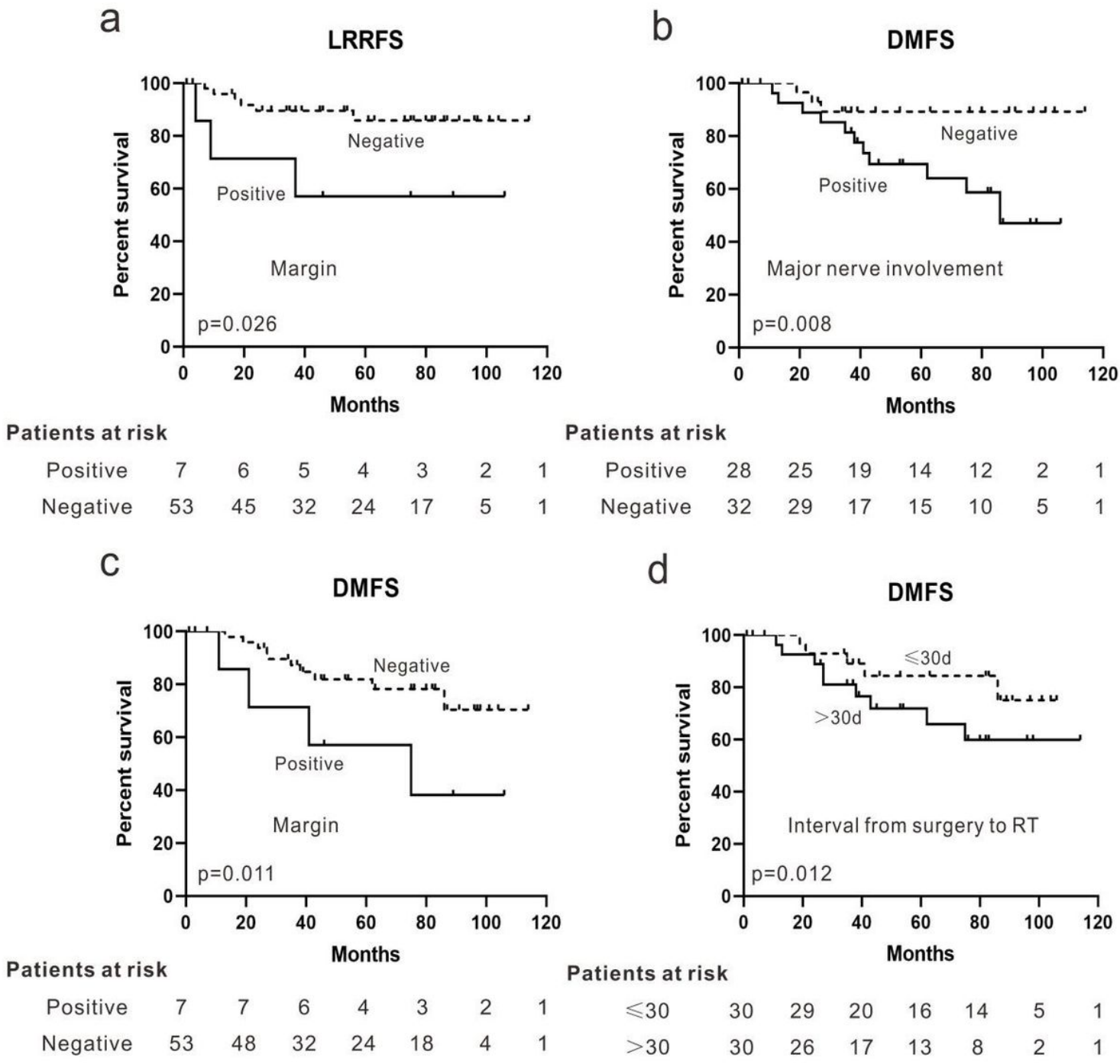

Figure 4

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)

Figure 5

Venn diagram of patterns of failure (16/60 patients)

Supplementary Files

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