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Feasibility of Lower Neck Sparing in Postoperative Radiotherapy for Parotid Gland Cancer

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Abstract

Background/Aim: To analyze failure patterns and evaluate the clinical necessity of lower neck irradiation (LNI) during elective neck irradiation (ENI) in patients with parotid gland cancers (PGCs).

Patients and Methods: Forty patients with PGCs who received postoperative radiotherapy (PORT) following parotidectomy between 2006 and 2024 were included. LNI was defined as the elective inclusion of neck levels III and IV in the irradiated field. The primary endpoint was progression-free survival (PFS), while secondary endpoints included local-regional failure-free survival (LRFFS), distant metastasis-free survival (DMFS), and overall survival (OS).

Results: The median follow-up time was 68.7 months. Among the 40 patients, 19 (47.5%) received LNI as part of their PORT. Five-year rates of LRFFS, DMFS, OS, and PFS were 91.2%, 80.2%, 88.7%, and 76.3%, respectively. While LNI showed no significant association with survival outcomes, multivariate analysis confirmed that perineural invasion

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(PNI) was a significant prognostic factor for PFS [hazard ratio (HR)=5.17, *p*=0.028], OS (HR=7.97, *p*=0.017), and DMFS (HR=9.67, *p*=0.009). The major failure pattern was distant metastasis (N=8). Regional failures were infrequent (5%), involving level II (N=1) and levels Ib, II, and IV (N=1).
Conclusion: Regional failures in PGC are rare and predominantly confined to the upper neck. Omitting LNI did not compromise regional control. Treatment strategies for PGCs with PNI should focus on the intensification of systemic therapy and close monitoring for distant metastasis.

Keywords: Parotid gland cancer, postoperative radiotherapy, elective neck irradiation, lower neck node irradiation, pattern of failure.

Introduction

Salivary gland malignancies represent a heterogeneous group of rare tumors, accounting for less than 6% of all head and neck cancers and encompassing over 20 distinct histological subtypes (1). Among these malignancies, the parotid gland is the most frequent site of origin (2). For patients with parotid gland cancers (PGCs), surgical resection is the primary treatment modality, which is tailored as either total or superficial parotidectomy based on tumor location and size. Postoperative radiotherapy (PORT) is indicated in the presence of adverse clinicopathological risk factors following parotidectomy, such as advanced T and N stages, high tumor grade, positive resection margins, lymphovascular invasion (LVI), and perineural invasion (PNI) (3).

In accordance with general management principles for head and neck cancers, irradiating the adjacent nodal echelons with an elective dose is typically recommended for regional control in patients with pathologically positive nodes following neck dissection. In patients without neck nodal involvement, elective neck irradiation (ENI) may be suggested for those with high-risk features (3). However, the optimal extent of ENI remains a subject of ongoing clinical debate. Current guidelines lack a clear consensus, suggesting that ipsilateral levels Ib, II, III, and IV may be included within low-risk treatment volumes (4).

Anatomically, the lower pole of the parotid gland frequently extends to the level of the hyoid bone, which corresponds to the lower border of level II neck nodes. Consequently, the clinical necessity of lower neck irradiation (LNI) targeting level III and IV neck nodes warrants careful re-evaluation, particularly in patients with negative neck nodes or those with limited involvement of periparotid nodes. This study aimed to analyze failure patterns and evaluate the clinical necessity of LNI in patients with PGCs who received PORT following parotidectomy.

Patients and Methods

This multi-institutional study utilized data from four academic tertiary centers, and the study protocol was approved by the Institutional Review Board of each participating institution. We retrospectively reviewed the medical records of patients with PGCs who were treated with curative-intent parotidectomy followed by PORT between March 2006 and March 2024. Patients presenting with distant metastasis at initial diagnosis, those with a history of prior malignancies, or those receiving incomplete courses of PORT were excluded. A total of 40 patients were included in the present analysis.

We collected clinical and pathological data, including perioperative imaging, surgical type, pathologic findings, and details of PORT. Specifically, the irradiated fields were examined to confirm the inclusion of neck nodal levels, and the delivered radiation doses were reviewed. LNI was defined as the elective inclusion of neck nodal levels III and IV within the clinical target volume. Regarding failure patterns, the sites and dates of the first recurrence were recorded for both locoregional and distant failures.

The primary endpoint of this study was progression-free survival (PFS), defined as the time from surgery to any disease recurrence or death from any cause. Secondary endpoints included local-regional failure-free survival (LRFFS), distant metastasis-free survival (DMFS), and overall survival (OS). Survival intervals were calculated from the date of surgical resection to the date of the first event or the last follow-up. Survival curves were estimated using the Kaplan-Meier method.

For univariate analysis, survival outcomes were compared between groups using the log-rank test. Multivariate analysis was conducted using the Cox proportional hazards model to identify independent prognostic factors. Associations between categorical variables were assessed using either Pearson's chi-square test or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using R software version 4.4.3 (R Development Core Team, Vienna, Austria).

Results

Patient characteristics. Among the 40 patients, the median age was 55 years (range=24-80 years). The primary surgical procedure consisted of either superficial parotidectomy (N=22, 55.0%) or total parotidectomy (N=18, 45.0%), depending on the location and extent of the primary tumor. Ipsilateral neck dissection was performed in 13 patients (32.5%) based on clinical or radiological suspicion of nodal involvement. Most patients had pT1-2 (N=32, 80.0%) and pN0 (N=32, 80.0%) disease. Following surgery, 21 patients (52.5%) had close or positive resection margins. In postoperative imaging, eight patients (20.0%) were found to have residual tumors. Regarding adverse features, LVI and PNI were noted in 10 (25.0%) and eight (20.0%) patients, respectively. Detailed patient characteristics are summarized in Table I.

Table I. *Patient characteristics.*

Variables		N	(%)
Sex	Male	22	(55.0)
	Female	18	(45.0)
Deep lobe invasion	Yes	13	(32.5)
	No	27	(67.5)
Parotidectomy type	Total	18	(45.0)
	Superficial	22	(55.0)
Neck dissection	Yes	13	(32.5)
	No	27	(67.5)
Histology	Adenocarcinoma	4	(10.0)
	Adenoid cystic carcinoma	6	(15.0)
	Carcinoma ex pleomorphic adenoma	8	(20.0)
	Epithelial-myoepithelial carcinoma	2	(5.0)
	Mucoepidermoid carcinoma	9	(22.5)
	Salivary duct carcinoma	5	(12.5)
	Others*	6	(15.0)
T stage	T1	9	(22.5)
	T2	23	(57.5)
	T3	5	(12.5)
N stage	N0	32	(80.0)
	N1	2	(5.0)
	N2	5	(12.5)
	N3	1	(2.5)
Grade**	Low	3	(7.5)
	Intermediate	5	(12.5)
	High	8	(20.0)
LVI**	Yes	10	(25.0)
	No	25	(62.5)
PNI**	Yes	8	(20.0)
	No	26	(65.0)
Resection margin**	Negative	14	(35.0)
	Close	2	(5.0)
	Positive	19	(47.5)
Residual mass	Yes	8	(20.0)
	No	32	(80.0)
Radiotherapy	IMRT	30	(75.0)
	3D-CRT	10	(25.0)

LVI: Lymphovascular invasion; PNI: perineural invasion; IMRT: intensity-modulated radiotherapy; 3D-CRT: three-dimensional conformal radiotherapy. *Others include acinic cell carcinoma, basal cell adenocarcinoma, carcinoma with sebaceous differentiation, myoepithelial carcinoma, secretory carcinoma, and undifferentiated carcinoma. **Non-reported data exist.

Radiotherapy protocol. All patients received PORT at a median interval of 4.6 weeks (range=1.9-14.3 weeks) after surgery. Intensity-modulated radiotherapy and three-dimensional conformal radiotherapy were performed in 30 (75.0%) and 10 (25.0%) patients, respectively. Regarding the treatment volume, ENI was performed in 29 patients (72.5%), and LNI was performed in 19 patients (47.5%). The rate of ENI was not

Table II. *Univariate analysis.*

Variables		N	5Y LRFFS	*p*-Value	5Y DMFS	*p*-Value	5Y OS	*p*-Value	5Y PFS	*p*-Value
Sex	Female	18	93.8	0.752	86.6	0.458	94.1	0.626	85.6	0.341
	Male	22	89.6		76.1		84.8		70.1	
Age	≤65 years	29	88.4	0.311	85.1	0.069	92.6	0.058	80.2	0.126
	>65 years	11	100.0		61.4		75.8		61.4	
Histology	Aggressive types*	23	84.8	0.128	71.8	0.205	81.0	0.601	65.0	0.118
	Others	17	100.0		91.7		100.0		91.7	
pT	1-2	32	93.3	0.561	87.1	0.122	89.7	0.224	87.4	0.013
	3-4	8	83.3		48.6		85.7		25.0	
pN	0	32	88.9	0.369	85.8	0.266	96.7	0.056	85.2	0.109
	1-3	8	100.0		60.0		62.5		50.0	
Resection margin	Negative	14	92.9	0.941	85.1	0.404	90.0	0.446	85.7	0.294
	Others	26	90.6		78.1		87.8		72.0	
Residual tumor	Yes	8	68.6	0.033	27.3	0.002	72.9	0.055	18.2	0.000
	No	32	96.7		90.4		93.0		90.2	
LVI	Yes	10	88.9	0.731	58.3	0.042	57.1	0.000	46.7	0.012
	Others	30	91.8		87.8		100.0		87.3	
PNI	Yes	8	85.7	0.603	37.5	0.000	75.0	0.004	37.5	0.000
	Others	32	93.3		93.3		92.6		88.7	
Radiotherapy	3D-CRT	10	88.9	0.809	67.5	0.106	90.0	0.539	67.5	0.197
	IMRT	30	92.9		84.6		88.7		79.8	
ENI	Yes	29	92.6	0.905	84.0	0.118	88.2	0.483	78.9	0.230
	No	11	90.0		70.7		90.9		70.7	
LNI	Yes	19	94.4	0.631	80.5	0.617	81.4	0.507	73.8	0.854
	No	21	88.8		79.3		94.7		78.4	

LRFFS: Local-regional failure-free survival; DMFS: distant metastasis-free survival; OS: overall survival; PFS: progression-free survival; LVI: lymphovascular invasion; PNI: perineural invasion; IMRT: intensity-modulated radiotherapy; 3D-CRT: three-dimensional conformal radiotherapy; ENI: elective neck irradiation; LNI: lower neck irradiation. *Aggressive types include adenoid cystic carcinoma, carcinoma ex pleomorphic adenoma, grade 3 mucoepidermoid carcinoma, and salivary duct carcinoma.

significantly different by pN stage: 22 patients (68.8%) with pN0 and seven patients (87.5%) with pN+ (p=0.405). In contrast, patients with pN+ disease were more likely to undergo LNI (N=7, 87.5%) compared to those with pN0 disease (N=12, 37.5%; p=0.017).

The median radiation dose delivered to the tumor bed was 66 Gy (range=58.8-67.5 Gy) in 2 Gy daily fractions. The median doses delivered to the neck nodes were 59.4 Gy (range=54-67.5 Gy) for level I (N=18), 59.4 Gy (range=50-67.5 Gy) for level II (N=29), 56 Gy (range=50-67.5 Gy) for level III (N=19), and 54.12 Gy (range=50-60 Gy) for level IV (N=16).

Treatment outcomes. The median follow-up duration was 68.7 months (range=7.9-179.1 months). Five-year survival rates were 91.2% for LRFFS, 80.2% for DMFS, 88.7% for OS, and 76.3% for PFS. In univariate analysis (Table II), pT stage, residual tumor, LVI, and PNI were associated with PFS (Figure 1). Notably, LNI showed no significant association with any survival outcomes. Multivariate analysis (Table III) confirmed that PNI was an independent prognostic factor for PFS [hazard ratio (HR)=5.17, 95% confidence interval (CI)=1.20-22.4; p=0.028], OS (HR=7.97, 95%CI=1.46-43.6; p=0.017), and DMFS (HR=9.67, 95%CI=1.78-52.6; p=0.009). Residual tumor was another significant prognostic factor for PFS (HR=5.04, 95% CI=1.10-23.1; p=0.037).

As detailed in Table IV, distant metastasis was the predominant pattern of failure. The most frequent site of metastasis was the lung (N=5), followed by bone (N=2) and brain (N=1). Local and regional failures occurred in three and two patients, respectively. Both patients with

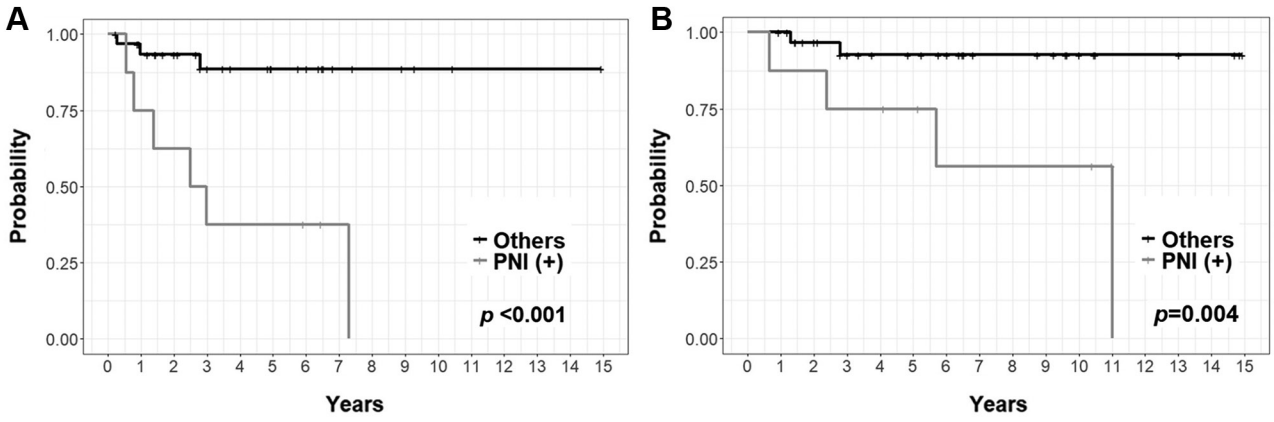

Figure 1. *Survival curves according to the presence of perineural invasion (PNI). (A) Progression-free survival and (B) overall survival.*

Table III. *Multivariate analysis.*

	LRFFS		DMFS		OS		PFS	
Variable	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
pT3-4	-		-		-		-	
Residual tumor	8.68 (0.787-95.8)	0.078	3.20 (0.651-15.8)	0.152	-		5.04 (1.10-23.1)	0.037
LVI	-		-				3.68 (0.932-14.6)	0.063
PNI	-		9.67 (1.78-52.6)	0.009	7.97 (1.46-43.6)	0.017	5.17 (1.20-22.4)	0.028

LRFFS: Local-regional failure-free survival; DMFS: distant metastasis-free survival; OS: overall survival; PFS: progression-free survival; HR: hazard ratio; CI: confidence interval; LVI: lymphovascular invasion; PNI: perineural invasion.

regional failure had pN0 disease. One patient with pT4N0 adenoid cystic carcinoma did not receive ENI and failed at level II. The other patient with pT2N0 carcinoma ex pleomorphic adenoma received ENI only to level II and subsequently experienced regional failure involving levels Ib, II, and IV.

Table IV. *Pattern of failure.*

Failures	N
Local + distant	1
Local + regional + distant	2
Distant	5

Adverse effects. Three patients (7.5%) experienced significant adverse events, all of whom had received LNI. One patient with pT1N0 secretory carcinoma developed Grade 2 chronic otitis media with effusion at 5.5 months after superficial parotidectomy and 2.8 months after PORT. Another patient with pT4N2 salivary duct carcinoma experienced a Grade 3 mandible fracture at 32.8 months after superficial parotidectomy and 29.7 months after PORT. The third patient with pT4N3 adenoid cystic carcinoma presented with a Grade 3 wound complication at 4.5 months after total parotidectomy and 1.7 weeks after PORT.

Discussion

The clinical rationale for elective neck treatment is based on the risk of occult nodal metastasis. For upfront surgery in head and neck cancers, elective neck dissection is generally indicated when the risk of occult metastasis exceeds 15% to 20% in patients without clinical nodal involvement (5). In PGCs, the rate of occult nodal metastasis has been reported to reach up to 30% in the presence of high-risk features (6, 7). Although current guidelines suggest ENI in such cases, the appropriate extent of elective coverage remains poorly defined (3, 4). To the best of our knowledge, this is the first study to investigate the clinical necessity of LNI during ENI specifically for patients with PGCs.

Anatomically, the caudal extension of the parotid tail often necessitates the inclusion of level II within the parotid bed volume. In contrast, elective coverage of levels III and IV is an empirical practice that requires robust evidence-based justification. However, our data showed no statistically significant difference in locoregional control between patients who received LNI and those who did not (5-year rates: 94.4% *vs*. 88.8%, respectively; p=0.631). This suggests that the routine addition of LNI may not provide additional benefit in locoregional control over upper-neck-only irradiation.

In this study, we observed only two cases of regional failure (5%). One case occurred in level II in a patient who did not receive ENI, while the other was a multi-level recurrence (levels Ib, II, and IV) in a patient whose ENI was confined to level II. Notably, no isolated failures in level III or IV were observed. Given that 80% of our cohort had pN0 disease and regional failure was also noted in pN0 patients, these patterns suggest that the primary echelon at risk is level II. Furthermore, isolated skip metastasis to the lower neck nodes appears to be exceedingly rare in PGC. Our results are consistent with previous reports identifying level II as the predominant site of occult metastasis in parotid malignancies (8, 9).

Beyond locoregional control, the clinical significance of PNI as a poor prognosis should be emphasized. In our multivariate analysis, PNI was the most potent prognostic factor for DMFS (HR=9.67, p=0.009), OS (HR=7.97, p=0.017), and PFS (HR=5.17, p=0.028), which aligns with recent evidence. A comprehensive meta-analysis reported that PGC patients with PNI have a significantly higher risk of mortality (HR=3.64) and distant metastasis (HR=3.84) compared to those without PNI. Furthermore, the prognostic value of PNI remained significant even after adjusting for potential moderators such as T stage, resection margin, histology, tumor grade, and LVI (10). In addition to skull base failures, a well-known consequence of PNI (11), lung metastasis is the most common type of distant failure (12, 13). As our findings also confirm the dominance of lung metastasis, close monitoring of the lung should be emphasized for patients with PNI.

Our failure patterns reinforce the concept that regional failures are infrequent and localized to the upper neck. Consequently, sparing the lower neck nodes can be an oncologically safe approach that preserves the quality of life for patients with PGCs. Since PGCs often present with a relatively favorable prognosis compared to other head and neck cancers, preserving the quality of life is a critical component of the treatment strategy.

Dysphagia, one of the most significant adverse effects of radiotherapy for head and neck cancers, can lead to chronic malnutrition, depression, and social isolation (14, 15). Although radiotherapy planning optimized to reduce doses to dysphagia-related structures can improve swallowing function (16), the process is multifactorial, involving the pharyngeal constrictors and the larynx (17). Therefore, target delineation of these structures needs a high degree of sophistication and is prone to significant inter-observer variability.

Hypothyroidism is another frequent adverse event following LNI. While the radiation dose to the thyroid gland is associated with hypothyroidism, there is no clear threshold dose (18). Furthermore, a recent study suggests that even low doses can lead to hypothyroidism, such as the thyroid volume receiving at least 10 Gy (19).

Omitting LNI is the most straightforward approach to reducing radiation-induced toxicities, as the inferior

pharyngeal constrictor muscles, the larynx, and the thyroid gland are all located beneath the hyoid bone.

Study limitations. First, the relatively small sample size and heterogeneous histologic subtypes may limit the statistical power to detect subtle differences in regional failure rates. Despite the retrospective nature, demanded by the rarity of PGCs, the long median follow-up of 68.7 months strengthens the clinical relevance of our findings. Second, the potential benefits of omitting LNI were not directly measured in terms of toxicity reduction, such as dysphagia or hypothyroidism. Future prospective trials incorporating patient-reported outcomes are necessary to further validate the advantages of omitting LNI.

Conclusion

Regional failure is infrequent in PGCs treated with PORT, occurring in only 5% of patients. These failures are predominantly confined to the upper neck, and omitting LNI does not appear to compromise regional control. Our study highlights that distant spread is the primary failure pattern and that PNI is an independent prognostic factor. Therefore, treatment strategies for PGCs with PNI should focus on the intensification of systemic therapy and close monitoring for metastasis.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

TK conceptualized and designed this study. HKK and TK collected and analyzed data. MYL, KHC, YP, HJP, KJK, SP, TH, SKK, BH, JWY, MYK, and HB participated in the interpretation of results. HKK and TK drafted the article, and TK revised the article. All Authors read and approved the article.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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