Oncological outcomes of preoperatively unexpected malignant tumors of the parotid gland

Hanaro Park[1] · Sungjun Han[2] · Sung Joon Park[3] · Young Ho Jung[4] · Soon-Hyun Ahn[4,5] · Woo-Jin Jeong[4]

Abstract

Purpose Unexpected parotid cancers are often encountered due to inaccuracies in the preoperative evaluation. This study aimed to examine the clinical characteristics and oncological outcomes of these cancers and to propose the appropriate management strategy.

Methods This is a multicenter case series study in which a total of 302 patients were diagnosed postoperatively with parotid cancers between 2003 and 2017. Of these, 85 cases without evidence of malignancy prior to surgery but identified as malignant on postoperative pathology were included.

Results Of 85 patients, 76 and 9 underwent superficial and total parotidectomy, respectively. A positive resection margin was present in 24.7% of the cases. Postoperative radiotherapy was administered to 43.6% of patients; 4.2% had a local recurrence, and no patients died of the disease. The 5-year overall and relapse-free survival rates were 100.0% and 95.2%, respectively. Patients who underwent piecemeal resection had significantly poorer oncologic outcomes. Age, sex, histologic grade, T stage, extracapsular extension, resection margin status, and postoperative radiotherapy did not affect recurrence and survival.

Conclusion Preoperatively unexpected parotid cancers had excellent local control and overall survival despite positive or close resection margin, with or without postoperative radiotherapy. Therefore, patients with unexpected parotid malignancies may benefit from less aggressive postoperative management option.

Keywords Parotid cancers · Preoperative biopsy · Adjuvant radiotherapy · Outcome · Recurrence

✉ Woo-Jin Jeong
  safar@snubh.org

1 Department of Otorhinolaryngology-Head and Neck Surgery, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, South Korea

2 Department of Otorhinolaryngology-Head and Neck Surgery, College of Medicine, The Catholic University of Korea, Seoul, South Korea

3 Department of Otorhinolaryngology-Head and Neck Surgery, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea

4 Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea

5 Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Hospital, Seoul National University, College of Medicine, Seoul, South Korea

Introduction

Malignant tumors of the parotid gland represent 1–3% of all head and neck tumors [1]. When treated with appropriate surgery, patients have a good chance of recovery and retaining normal facial nerve function. Surgical planning and decisions on whether to perform superficial parotidectomy or total parotidectomy, are based on a firm diagnosis of malignancy obtained preoperatively. However, in the parotid gland, it is often difficult to establish a diagnosis of malignancy prior to surgery, especially in histologically low grade or early-stage cases. Physical examination, imaging studies [computed tomography (CT) and/or magnetic resonance imaging (MRI)], and pathological assessment based on fine-needle aspiration cytology (FNA) or core needle biopsy (CNB) often fail to identify malignancy. The parotid gland is well known to have a relatively low yield for preoperative FNA/CNB [2].

Hence, it is not infrequent to encounter an unexpected parotid malignancy which was not anticipated preoperatively.

In such cases, the pathological diagnosis of cancer becomes obvious only after the surgery, or at the earliest, during the surgery based on an intraoperative frozen section. Because multiple factors including the extent of surgery, safety margin of resection, incorporation of neck node excision, and preservation of important structures such as the facial nerve depend on the preoperative diagnosis of cancer, it is often challenging for the surgeon and the patient to devise a proper post hoc management plan in such circumstances.

We designed this study with aims to identify patients with unexpected malignant tumors of the parotid gland, in whom malignancy was not anticipated preoperatively but apparent only after or during the surgery. We sought to examine the characteristics of these patients, the long-term oncological follow-up results, and factors affecting the outcomes. In doing so, we intended to suggest an acceptable postoperative management approach for these selected patients.

Material and methods

Patients and eligibility criteria

This consecutive case series included patients with parotid malignancies who underwent parotidectomy between 2003 and 2017 in Seoul National University Bundang Hospital, Seoul National University Hospital, and Seoul National University Boramae Medical Center. A flow chart describing the process, of selecting the study, participants of research, is shown in Fig. 1. A total of 302 cases were diagnosed as parotid cancer after surgery. Prior to surgery, ultrasonography-guided FNA or CNB and imaging workups (CT and/or MRI) were performed in all patients. The criteria for eligibility were: no previous parotid surgery; postoperative histologically confirmed malignancy, but no malignant feature in the preoperative evaluation (CT/MRI, and FNA/CNB); and follow-up duration of at least six months. Ultrasonography guided FNA/CNB was performed by a radiologist, and the interpretation of FNA/CNB was made by faculty pathologists. Patients with cancer or suspicion for cancer based on the results of FNA/CNB were excluded from the study. The interpretation of CT/MRI was made by faculty radiologists. A group of patients with suspected cancer or nodal metastasis detected by imaging, raising the possibility of malignancy prior to surgery, was excluded.

After the initial exclusion of patients with inadequate data or follow-up periods of less than six months, 267 patients remained. Following further selection during the study period, 85 patients (34.9%) met the inclusion criteria. Medical records (including demographic data, surgical records, and pathology reports) were retrospectively analyzed. We investigated patient characteristics including age, sex, operation type, tumor pathology [histology, grade, extracapsular
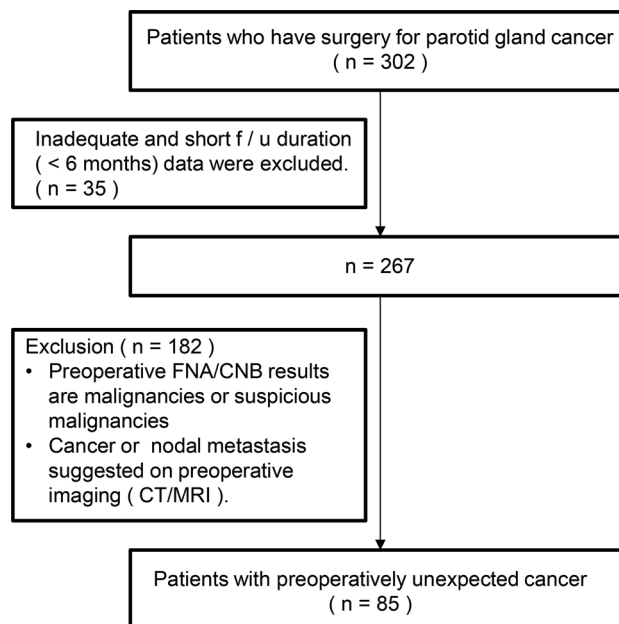

Fig. 1 Flow chart showing the selection of the eligible cases

extension (ECE), perineural invasion (PNI), resection margin status], pathologic tumor-node-metastasis (TNM) stage, postoperative complications, and postoperative radiation therapy (PORT). The histologic grade of each cancer was classified as low/intermediate, or high in accordance with the WHO classification [3]. The pathological stages were classified using the American Joint Committee on Cancer TNM staging system, 8th edition [4].

Statistical analysis

Statistical analysis was carried out using SPSS version 23.0 statistical package software (IBM Corp., Armonk, NY, USA). Kaplan–Meier survival curves were used to show overall survival (OS) and relapse-free survival (RFS), and the relationships between characteristics and outcomes data were compared using the log-rank test with a p value of < 0.05 as statistically significant. RFS was defined as the duration from the date of surgery to the date on which the recurrence was detected and OS was defined as the duration from the date of surgery to the date when the patient died or was last known to be alive. This retrospective study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB Number: B-1802-450-107) which granted a waiver of informed consent to the retrospective design of the study.

Results

Clinical and histopathologic characteristics are summarized in Table 1. According to the histological classification, cases with mucoepidermoid carcinoma (MEC; 30 patients, 35.3%) were most common; and among patients with MEC, 27 had low-grade MEC, two were with intermediate grade, and one patient had high-grade MEC. Furthermore, there was one patient with a low-grade adenocarcinoma, one patient with an intermediate grade, and a patient with a high grade.

A frozen biopsy was obtained in 36 cases. The decision to perform for frozen biopsy was determined individually by the surgeon based on preoperative FNA/CNB results (benign tumors with either no specified histology or with a histology that known to have relatively low accuracy in FNA/CNB, e.g., pleomorphic adenoma) and intraoperative findings of suspected malignancy, such as the invasion to the surrounding tissue or the facial nerve. Fourteen tumors (38.9%) were found to be malignant; 10 of them were low-grade cancer, whereas in four cases, it was impossible to determine the histologic grade in the frozen biopsy sample for an accurate histological diagnosis.

None of the patients in this cohort underwent elective neck dissection because patients with preoperatively suspected malignancy or lymph node metastasis were excluded. In two cases, the mass was not resected en bloc resulting in undetermined margins, whereas all other patients underwent en bloc resections. Thirty patients (35.3%) had a clear resection margin, 32 patients (37.6%) had a clear but close margin, and 21 patients (24.7%) had a positive margin. A close margin was defined as the distance from the tumor to the margin of less than 5 mm.

Forty-five (52.9%) patients were treated with surgery only and 40 (47.1%) patients underwent surgery and postoperative radiation therapy (PORT). Of the PORT-treated patients, 23 patients presented histopathological low/intermediate grade tumors and 17 patients had high-grade tumors. According to the evaluation of the resection margins in PORT-treated patients, 25 patients had a clear margin, whereas 14 patients had a positive margin. In one patient, the status of margin could not be assessed, due to the piecemeal resection of the tumor. Among the study participants who underwent PORT were 12 patients with low/intermediate grade tumors and clear margins.

Postoperative complications occurred in 17 patients, including 10 patients with facial nerve palsy, all of which were temporary except for one patient whose marginal mandibular branch of nerve was sacrificed. Additional temporary complications occurred in six patients with Frey syndrome, one patient with first bite syndrome.

During the follow-up, one patient was lost to follow-up, but all other participants survived. Four patients had

Table 1 Clinical and histopathologic characteristics of the parotid tumors ($N=85$)

Variables	
Mean age (range), years	51.4 (19–80)
Sex (%)	
Male	35 (41.2)
Female	50 (58.8)
Mean size (SD), mm	22.6 (± 11.4)
Histopathology (%)	
Low/intermediate grade	65 (76.5)
Mucoepidermoid carcinoma, low/intermediate grade	29 (34.1)
Acinic cell carcinoma	11 (12.9)
Carcinoma ex pleomorphic adenoma, low grade	8 (9.4)
Basal cell adenocarcinoma	4 (4.7)
Epithelial-myoepithelial carcinoma	3 (3.5)
Myoepithelial carcinoma	3 (3.5)
Adenocarcinoma, low/intermediate grade	2 (2.4)
Others[a]	5 (6.0)
High grade	20 (23.5)
Mucoepidermoid carcinoma, high grade	1 (1.2)
Adenoid cystic carcinoma	14 (16.5)
Carcinoma ex pleomorphic adenoma, high grade	1 (1.2)
Adenocarcinoma, high grade	1 (1.2)
Others[b]	3 (3.5)
pT stage[c] (%)	
T1	42 (49.4)
T2	26 (30.6)
T3	17 (20.0)
Surgery extent (%)	
Superficial parotidectomy	76 (89.4)
Total parotidectomy	9 (10.6)
Results of frozen biopsy, $n=36$ (%)	
Malignant	14 (38.9)
Benign	13 (36.1)
Indeterminate	9 (25.0)
Extracapsular extension (%)	
+	21 (24.7)
−	51 (60.0)
Perineural invasion (%)	
+	3 (3.5)
−	50 (58.8)
Resection margin (%)	
Positive	21 (24.7)
Clear	30 (35.3)
Clear but close	32 (37.6)
Uncheckable	2 (2.4)
Postoperative complication (%)	17 (20.0)
Facial nerve paralysis	10 (11.8)
Others	7 (8.2)
Adjuvant therapy (Postoperative radiation therapy)	
Yes	40 (47.1)

Table 1 (continued)

Variables	
No	45 (52.9)
Radiation toxicity (%)	10 (25.0)
Xerostomia	7 (17.5)
Dermatitis	5 (12.5)
Mean follow-up (range), months	55.5 (7–162)

[a]Includes polymorphous low grade adenocarcinoma 2, low grade cribriform cystadenocarcinoma 2, mammary analog secretory carcinoma 1

[b]Includes squamous cell carcinoma, carcinosarcoma, sebaceous lymphadenocarcinoma

[c]AJCC, 8th edition, there was no nodal metastasis or distant metastasis

a tumor recurrence and all recurrences were local. Two patients with recurrence underwent surgery only and the others had surgery and PORT (Table 2).

The 5-and 10-year OS rates were 100% and 100%, and the 5- and 10-year RFS rates were 95.2% and 78.2%, respectively (Fig. 2). Excluding the group with malignancy determined in frozen biopsy samples, the 5-and 10-year OS rates were 100% and 100%, and the 5- and 10-year RFS rates were 93.8% and 73.8%, respectively. We performed a univariate analysis with age, sex, histologic grade, pathologic T stage, pathologic findings (resection margin status, ECE, PNI), resection fashion, and PORT as risk factors (Table 3). The 1-year RFS rate of patients who underwent an operation with piecemeal resection was significantly poorer (50.0% vs. 96.3%, $p = 0.004$; Fig. 3), and was still significantly reduced (50.0% vs. 95.0%, $p = 0.015$) after exclusion of the cases with malignancy confirmed intraoperatively using frozen biopsies. All other examined risk factors did not show a significant difference.

Discussion

Achieving the clinical diagnosis of parotid cancer preoperatively is challenging. In our study, about one-third of the patients were diagnosed with parotid cancer postoperatively; this finding reflects the difficulty of diagnosing parotid cancer and the low diagnostic sensitivity of preoperative examination including CT, MRI, FNA, and CNB for tumors of the parotid gland. Indeed, Ryu et al. [5] reported that 33.3% of salivary cancers were misdiagnosed as benign before surgery. Moreover, Kim et al. [6] reported that the sensitivity of FNA for salivary gland tumors was 64.2% which was similar to our findings. In addition, FNA has low sensitivity in differentiating malignant parotid tumors from benign ones [7]. For these reasons, surgeons often encounter patients with

Table 2 Clinical-pathological data and follow-up of patients with local recurrence

	Age	Sex	Histology	pT	Margin status	Size (mm)	PORT	Treatment after recurrence	RFS (months)	OS (months)	Final status
1	35	M	AciCC	3	Clear	30	–	Revision parotidectomy + adjuvant RT	73	105	NED
2	31	F	AciCC	2	Exposed	28	+	Revision parotidectomy	119	142	NED
3	46	F	AdCC	1	Clear but close	18	+	Follow-up loss	67	70	FUL
4	63	M	AciCC	2	Uncheckable	39	–	Revision parotidectomy + adjuvant RT	8	24	NED

AciCC acinic cell carcinoma, *AdCC* adenoid cystic carcinoma, *PORT* postoperative radiotherapy, *RFS* relapse free survival, *OS* overall survival, *NED* no evidence of disease, *FUL* follow-up loss
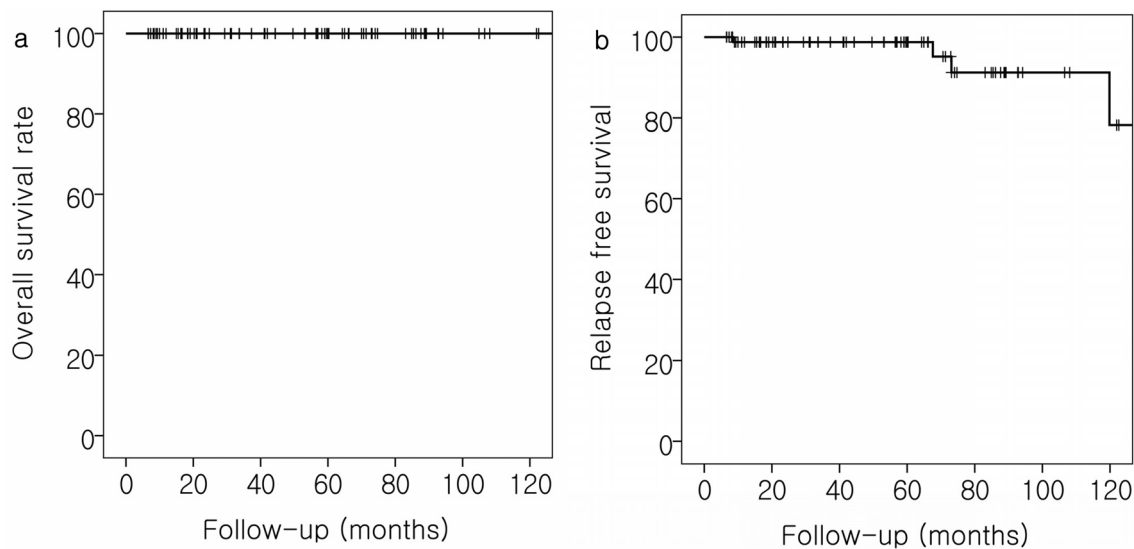
Fig. 2 Kaplan–Meier curves of (**a**) overall survival and (**b**) relapse-free survival. *p* values were calculated by the log-rank test

malignant tumors that were not identified preoperatively, and the literature regarding this set of patients is sparse.

When malignancy is suspected intraoperatively, the examination of a frozen section should be considered. According to a meta-analysis of frozen section studies, this method has an acceptable accuracy (90% sensitivity, 99% specificity) [8]. However, another study reported that the sensitivity of the frozen section for the diagnosis of malignancy was only 74.0% and that it was relatively low for parotid cancer compared with that for head and neck squamous cell carcinoma because the histology and grade of parotid tumors vary widely [9]. In the present study, 36.1% of the frozen section results were misdiagnosed. Therefore, our results are consistent with those of previous studies suggesting that is relatively difficult to diagnose malignancy using frozen sections. In the present study, there were 14 cases with malignancy diagnosed using frozen sections, and the frozen biopsy results either revealed low-grade tumors or it was impossible to classify the histologic risk grade. These cases were patients in whom the surgeon was not prepared to conduct an ablative surgery which would be oncologically sufficient—i.e., sacrifice the facial nerve, perform a total parotidectomy, or incorporate node dissection. Having said that, even if the surgeon knew from the analysis of the frozen sections that the tumor is indeed malignant, there would not have been many options to perform an even more aggressive dissection in these patients. Ryu et al. [5] excluded patients with malignancies diagnosed in frozen biopsy samples when determining misdiagnosed patients. Although minor changes might have occurred in the low number of patients in our study undergoing frozen biopsy examinations during surgery,

we think that the oncological outcome as a whole was not affected; therefore, we considered it inappropriate to remove cases with malignancy determined in frozen biopsies. In addition, we performed a subgroup analysis and found out that our assumption was indeed true—the results were not significantly different from the overall cohort for the group with malignancy confirmed in frozen biopsy samples. However, these results must be interpreted with caution because the criteria for frozen biopsy were determined by each surgeon based on intraoperative findings and preoperative FNA/CNB results.

When parotid cancer is not predicted preoperatively, clinicians must perform a challenging review of their treatment strategies. Subsequently, they consider revision operation, adjuvant radiation therapy (RT), or a wait-and-watch approach as postoperative treatment. In this study, the 5-year OS and RFS rates were 100.0% and 93.9%, respectively. Another study revealed 5-year OS and disease-free survival rates of 80.6% and 74.4%, respectively [10], and a study in patients with preoperatively misdiagnosed salivary gland cancer revealed 5-year estimated loco-regional control rates of 81.5% [5]. The prognosis of patients in the present study was similar or better than those reported in previous studies [5, 10], which might have been due to the exclusion of patients with suspected malignancy or nodal metastasis on imaging during the patient selection process. On the other hand, this also provides a basis to avoid aggressive adjuvant therapy for unexpected cancer. Since our study is a multi-center study that analyzed a relatively large number of cases compared to other studies, it will be difficult to infer whether the oncological outcomes of our study are overestimated in comparison to other studies [5].

Table 3 Results of univariate analysis in relapse-free survival rate

Variable	n	5-year RFSR (%)	p value
Age			
> 45	60	93.5	0.340
≤ 45	25	85.7	
Sex			
Male	35	80.7	0.368
Female	50	95.2	
Histopathologic grade			
Low/intermediate	65	93.2	0.857
High	20	87.5	
Pathologic T stage			
T1	42	91.7	0.532
T2/3	43	90.6	
ECE			
+	21	85.7	0.875
−	51	92.3	
PNI		NA	NA
Resection margin			
Positive	21	75.0	0.833
Clear/clear but close	62	94.7	
En bloc vs. piecemeal[a]			
En bloc resection	83	96.3	0.004*
Piecemeal resection	2	50.0	
PORT			
Yes	40	93.3	0.861
No	45	97.7	

The log rank test was used for analysis

RFSR relapse free survival rates, *ECE* extracapsular extension, *PNI* perineural invasion, *NA* not available, *PORT* postoperative radiation therapy

[a]one-year relapse free survival rates

*$p < 0.05$

T stage, nodal metastasis status, facial nerve dysfunction, pathologic grade, and surgical margin status are known to be representative prognostic factors for parotid cancer [11–13]. However, in this study, patients with nodal positivity or preoperative facial nerve paralysis were excluded from the analysis because of preoperative suspicion of malignancy. Moreover, the univariate analysis revealed that the resection margin and T stage were not associated with RFS. In the present study, the positive PNI rate was 3.5% which is lower than the rates determined by other studies. Huyett et al. [14] reported that the percentage of positive PNI in parotid gland cancer was 46.2%. Because we focused on tumors where malignancy was not anticipated in the first place, patients with any sign of malignancy, including but not confined to facial paralysis or infiltrative features in the radiological image, were not included in this study, which may explain the low rate of adverse events in our study population. Ryu
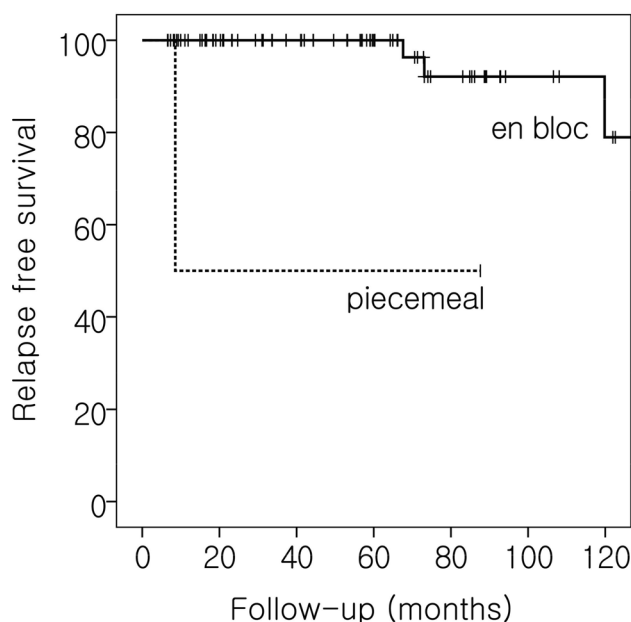

Fig. 3 Kaplan–Meier curves of relapse-free survival according to operation fashion. *p* values were calculated by the log-rank test

et al. [5] conducted their study in a setting similar to ours; their proportion of PNI-positive patients was also lower than those in other literatures and similar to that in our study. In addition, our percentage of high-grade carcinoma ex pleomorphic adenoma was lower than that in the other literature [15], and this is also due to our selection criteria for the study population. Yet, patients who underwent piecemeal resection that did not meet the 2020 National Comprehensive Cancer Network (NCCN) guidelines [16], were found to have a significantly poorer RFS. According to the principles described in the surgery section of NCCN guideline [16], en bloc resection should always be attempted when feasible—we could confirm the importance of this principle once again in our study. Although our data do not directly support PORT for piecemeal resections, it may be prudent to consider PORT if sufficient en bloc removal of the tumor has not been achieved.

PORT is well known to provide satisfactory local control in patients with parotid gland cancer and is associated with increased survival [17–19]. Despite a positive or close margin of resection, patients with small-sized, histologically low-risk parotid cancer who received PORT had excellent local control and low treatment-related morbidity [20]. However, some studies have found that patients with low-risk histology and low TNM stage had a good prognosis without RT [21, 22] and that a watch-and-wait strategy with intensive follow-up should be considered in cases of close margin after excision [23]. In the present study, 40 patients (47.1%) underwent PORT, which did not have a significant effect on the RFS rate. According to the retrospective analysis of

the medical records, the administration of PORT was determined by each surgeon and tended to be applied when the histologic grade was high or when there was a resection margin involvement. However, in our study, 12 patients with clear margins and histologic low-/intermediate-grade tumors underwent PORT. This may be considered overtreatment. It may be assumed that the surgeons were intraoperatively not convinced they had a generous resection margin because they did not anticipate the tumor. Nonetheless, there was no significant difference in the oncological outcomes of PORT in our study. Therefore, our study provides, albeit retrospectively, evidence to consider the careful application of adjuvant therapy in these patients.

This study has some limitations. The study is retrospective in nature and the sample size is relatively small; therefore, multivariate analysis was not possible because of the low number of events. However, despite the small number of patients and the statistical analysis method used, it may be more meaningful that significant results have been obtained under such conditions. Another limitation of this study is that it included patients treated at three different institutions over a period of about 15 years. However, we regard this long-term, multicenter study meaningful because the long-term oncological outcomes were assessed in as many patient populations as possible that meet the study inclusion criteria. Besides, the three participating institutions of this study are branch hospitals that belong to the same university health system, and the surgeons were trained in the same department, thus sharing remarkably similar policies, and surgical skills. This homogeneity may serve as an advantage. On the other hand, despite this homogeneity, the decision to administer frozen biopsy examination and PORT were different for each patient, due to the heterogeneity of the subjects; based on various histopathology and intraoperative findings, and absence of clear guidelines for the PORT for "unexpected" parotid cancers, and it is also a limitation of this study. Furthermore, the histological diagnoses have not been reviewed in the present study; however, it may be considered that the necessity to review histological diagnoses is not high, because the purpose of our study is not focused on an accurate preoperative diagnosis, but on the oncological outcomes of unexpected parotid cancer. Because we only selected patients who had no clinically suspected cancer, selection bias may have influenced the oncological outcome. Moreover, long-term follow-up was not possible in all patients, so our findings may not be sufficient to describe long-term outcomes. We planned to apply propensity score matching prior to comparisons but this was not possible for RFS comparisons of PORT-treated patients because the number of cases in the control group was insufficient. We believe that studies with a larger sample size are warranted to enable a better understanding of this condition and related survival outcomes.

Conclusions

We showed that malignancies of the parotid gland that were not anticipated preoperatively and diagnosed postoperatively as unexpected cancer had excellent local control and overall survival rates. Patients who underwent piecemeal resection had significantly poorer oncologic outcome but there was no significant difference in the outcome regardless of the margin status, pathologic grade, and PORT administration. Therefore, our study suggests that in patients with unexpected parotid cancer, close observation can be a feasible option in carefully selected patients as well as the administration of PORT as adjuvant therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (Institutional Review Board) of Seoul National University Bundang Hospital approved this study.

Consent to participate This study was granted waiver of informed consent to participate from the Human Investigation Committee (Institutional Review Board) of Seoul National University Bungdang Hospital. This permission is based on the following reasons:

1. Obtaining informed consent is not practical in the course of research or has a significant impact on the validity of the research.
2. There is no reason to presume the subject's refusal to consent, and even if the consent is waived, the risk to the subject is extremely low.

Consent for publication This study was granted waiver of informed consent from the Human Investigation Committee (Institutional Review Board) of Seoul National University Bundang Hospital. This permission is based on the following reasons:

1. Obtaining informed consent is not practical in the course of research or has a significant impact on the validity of the research.
2. There is no reason to presume the subject's refusal to consent, and even if the consent is waived, the risk to the subject is extremely low.

References

1. Kane WJ, McCaffrey TV, Olsen KD, Lewis JE (1991) Primary parotid malignancies. A clinical and pathologic review. Arch Otolaryngol Head Neck Surg 117:307–315. https://doi.org/10.1001/archotol.1991.01870150075010

2. Jeong WJ, Park SJ, Cha W, Sung MW, Kim KH, Ahn SH (2013) Fine needle aspiration of parotid tumors: diagnostic utility from a clinical perspective. J Oral Maxillofac Surg 71:1278–1282. https://doi.org/10.1016/j.joms.2013.01.017

3. El-Naggar AK, Chan JK, Grandis JR, Takata T, Slootweg PJ (eds) (2017) WHO classification of head and neck tumours, 4th edn. International Agency for Research on Cancer, Lyon

4. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR (eds) (2017) AJCC cancer staging manual, 8th edn. Springer, New York

5. Ryu IS, Roh JL, Cho KJ, Lee SW, Choi SH, Nam SY, Kim SY (2013) Clinical outcomes of patients with salivary gland carcinomas preoperatively misdiagnosed as benign lesions. Head Neck 35:1764–1770. https://doi.org/10.1002/hed.23228

6. Kim BY, Hyeon J, Ryu G, Choi N, Baek CH, Ko YH, Jeong HS (2013) Diagnostic accuracy of fine needle aspiration cytology for high-grade salivary gland tumors. Ann Surg Oncol 20:2380–2387. https://doi.org/10.1245/s10434-013-2903-z

7. Gavín-Clavero MA, Usón-Bouthelier T, Jariod-Ferrer UM, Fernández-Larrañaga A, Pantilie B, Lobera-Molina F, Simón-Sanz MV, Nadal Cristóbal B (2018) Accuracy of FNAC and CT in the differentiation of benign and malignant parotid tumours in a case series. Acta Otorrinolaringol Esp 69:25–29. https://doi.org/10.1016/j.otorri.2017.05.003

8. Schmidt RL, Hunt JP, Hall BJ, Wilson AR, Layfield LJ (2011) A systematic review and meta-analysis of the diagnostic accuracy of frozen section for parotid gland lesions. Am J Clin Pathol 136:729–738. https://doi.org/10.1309/AJCP2SD8RFQEUZJW

9. Badoual C, Rousseau A, Heudes D, Carnot F, Danel C, Meatchi T, Hans S, Bruneval P, Brasnu D, Laccourreye O (2006) Evaluation of frozen section diagnosis in 721 parotid gland lesions. Histopathology 49:538–540. https://doi.org/10.1111/j.1365-2559.2006.02527.x

10. Erovic BM, Shah MD, Bruch G, Johnston M, Kim J, O'Sullivan B, Perez-Ordonez B, Weinreb I, Atenafu EG, de Almeida JR, Gullane PJ, Brown D, Gilbert RW, Irish JC, Goldstein DP (2015) Outcome analysis of 215 patients with parotid gland tumors: a retrospective cohort analysis. J Otolaryngol Head Neck Surg 44:43. https://doi.org/10.1186/s40463-015-0097-z

11. Mercante G, Marchese C, Giannarelli D, Pellini R, Cristalli G, Manciocco V, Ruscito P, Pichi B, Marchesi P, Spriano G (2014) Oncological outcome and prognostic factors in malignant parotid tumours. J Craniomaxillofac Surg 42:59–65. https://doi.org/10.1016/j.jcms.2013.02.003

12. Kandaz M, Soydemir G, Bahat Z, Canyilmaz E, Yoney A (2016) Prognostic factors and clinical outcome in parotid gland tumors: a single institution experience from the Eastern Black Sea region of Turkey. Asian Pac J Cancer Prev 17:1169–1174. https://doi.org/10.7314/apjcp.2016.17.3.1169

13. Lima RA, Tavares MR, Dias FL, Kligerman J, Nascimento MF, Barbosa MM, Cernea CR, Soares JR, Santos IC, Salviano S (2005) Clinical prognostic factors in malignant parotid gland tumors. Otolaryngol Head Neck Surg 133:702–708. https://doi.org/10.1016/j.otohns.2005.08.001

14. Huyett P, Duvvuri U, Ferris RL, Johnson JT, Schaitkin BM, Kim S (2018) Perineural invasion in parotid gland malignancies. Otolaryngol Head Neck Surg 158:1035–1041. https://doi.org/10.1177/0194599817751888

15. Hu YH, Zhang CY, Xia RH, Tian Z, Wang LZ, Li J (2016) Prognostic factors of carcinoma ex pleomorphic adenoma of the salivary glands, with emphasis on the widely invasive carcinoma: a clinicopathologic analysis of 361 cases in a Chinese population. Oral Surg Oral Med Oral Pathol Oral Radiol 122:598–608. https://doi.org/10.1016/j.oooo.2016.06.005

16. Network NCC (2020) Head and neck cancers (Version 1.2020). https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed 5 March 2020

17. Chen AM, Garcia J, Bucci MK, Quivey JM, Eisele DW (2007) The role of postoperative radiation therapy in carcinoma ex pleomorphic adenoma of the parotid gland. Int J Radiat Oncol Biol Phys 67:138–143. https://doi.org/10.1016/j.ijrobp.2006.07.1380

18. Matsuda S, Iguchi H, Tada T, Hosono M, Osawa M, Kuwae Y, Morimoto H, Okazaki E, Amano K, Miki Y, Tsutsumi S, Shimatani Y, Miki Y (2015) Results of surgery plus postoperative radiotherapy for patients with malignant parotid tumor. Jpn J Radiol 33:533–537. https://doi.org/10.1007/s11604-015-0450-1

19. Garden AS, el-Naggar AK, Morrison WH, Callender DL, Ang KK, Peters LJ (1997) Postoperative radiotherapy for malignant tumors of the parotid gland. Int J Radiat Oncol Biol Phys 37:79–85. https://doi.org/10.1016/s0360-3016(96)00464-6

20. Richter SM, Friedmann P, Mourad WF, Hu KS, Persky MS, Harrison LB (2012) Postoperative radiation therapy for small, low-/intermediate-grade parotid tumors with close and/or positive surgical margins. Head Neck 34:953–955. https://doi.org/10.1002/hed.21843

21. Seethala RR (2009) An update on grading of salivary gland carcinomas. Head Neck Pathol 3:69–77. https://doi.org/10.1007/s12105-009-0102-9

22. Cho JK, Lim BW, Kim EH, Ko YH, Oh D, Noh JM, Ahn YC, Baek KH, Jeong HS (2016) Low-grade salivary gland cancers: treatment outcomes, extent of surgery and indications for postoperative adjuvant radiation therapy. Ann Surg Oncol 23:4368–4375. https://doi.org/10.1245/s10434-016-5353-6

23. Stodulski D, Mikaszewski B, Majewska H, Wiśniewski P, Stankiewicz C (2017) Close surgical margin after conservative parotidectomy in early stage low-/intermediate-grade parotid carcinoma: outcome of watch and wait policy. Oral Oncol 68:1–4. https://doi.org/10.1016/j.oraloncology.2017.03.001