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ORIGINAL ARTICLE

# Diagnosis and Management of Parotid Gland Cancer with Focus on the Role of Preoperative Fine-Needle Aspiration Cytology: A 10-Year-Long Retrospective Study with 5-Year Follow-Up

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**Abstract**

*Introduction* Salivary gland cancers represent a rare heterogeneous group of neoplasms with complex clinicopathological characteristics and distinct biological behaviour. The appropriate diagnosis and management of parotid gland cancer are challenging and should be based on the clinical, imaging, cytological, and histological features. The present study analysed the use of preoperative fine-needle aspiration cytology (FNAC) and intraoperative frozen section (FS) to guide the appropriate surgical and postoperative treatment of parotid gland cancers.

*Materials and Methods* We selected 48 patients with primary malignancy of the parotid gland surgically treated between 1 January 2008 and 30 June 2017 at the Maxillo-Facial Surgery Division, University Hospital of Parma, Italy. The patients had postoperative histological diagnosis of malignant parotid cancer and were followed up for longer than 5 years.

*Results* The 48 patients included in this study had a mean age of 56.7 years. The most frequent type of parotid gland cancer was carcinoma ex pleomorphic adenoma (22.9%), followed by mucoepidermoid carcinoma (16.7%) and acinic cell carcinoma (14.6%). All 48 patients underwent preoperative FNAC: 29 (60.4%) and 19 (39.6%) were suggestive of malignant and benign lesions, respectively. In 31 patients, intraoperative FS was performed.

*Discussion* Compared to previous studies, the present study showed significantly lower diagnostic sensitivity of FNAC for parotid gland cancers. The preoperative diagnostic accuracy for suspected malignant cases may be improved by repeat analysis of the cytological specimen by experts, preoperative core needle biopsy, and/or intraoperative FS analysis of the suspected mass.

**Keywords** Parotid gland cancer · Fine-needle aspiration cytology (FNAC) · Intraoperative frozen section (FS)

## Introduction

Salivary gland cancers are rare tumours that account for less than 1% of all head and neck cancers [1, 2]. The prevalence of malignant lesions can vary depending on the salivary gland involved: approximately 20%, 50%, 70%, and 50% of parotid, submandibular, sublingual, and minor salivary glands tumours are malignant, respectively [3, 4]. However, due to the extremely higher absolute incidence of parotid neoplasms compared to the other salivary glands, most salivary cancers occur in the parotid gland [5, 6].

Tumours of the salivary glands represent a heterogeneous group of neoplasms with complex clinicopathological characteristics and distinct biological behaviour [4]. In 2017, the World Health Organization (WHO) published the fourth edition of its classification of head and neck tumours, which described new entities and variants of salivary gland tumours [4, 7].

Therefore, the appropriate diagnosis and management of parotid cancer are challenging [2, 5, 8]. Parotid gland cancer is diagnosed based on clinical, imaging (ultrasound and/or magnetic resonance imaging), cytological, and histological features [9, 10].

Cytological and histological analyses aid in the selection of the appropriate surgery type and extent [10]. Fine-needle

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aspiration cytology (FNAC) of salivary gland lesions has a diagnostic accuracy of 87–96%, which is particularly high when performed under ultrasound guidance. However, its diagnostic usefulness is controversial and depends on the cytologist analysing the specimen [11].

Surgery is the mainstay of treatment for parotid cancers, and it should be performed when negative surgical margins can be achieved. Partial, total, or extended parotidectomy is performed according to tumour size, position, and/or involvement of surrounding structures (such as facial nerve, maxillary or mandibular bone, and masticatory muscles) [5, 12, 13]. The facial nerve must be preserved if possible, and its sacrifice can be justified only in case of clinically documented neoplastic neural invasion (i.e. preoperative facial nerve deficiency and/or intraoperative neoplastic gross invasion/adherence of the nerve) [12, 14]. Although therapeutic neck dissection (and associated adjuvant radiotherapy) is strongly recommended for patients with clinically and/or radiologically positive nodes, elective neck dissection of clinical and radiological N0 patients is controversial [15, 16]. More than one-third (38%) of patients have occult lymph node metastases; this rate increases in patients with high-grade carcinomas, tumour diameter ≥ 4 cm, extra-parotid tissue invasion, and/or facial nerve deficiency (independent of the histological features). Because most of these features cannot be detected preoperatively, the need to perform neck dissection during parotidectomy is difficult to assess [17].

For small or low-grade cancers, surgical resection with negative margins is considered adequate without any adjuvant treatment [18]. Postoperative radiotherapy improves loco-regional control in cancers with high-risk features (such as close or positive surgical margins, nodal metastases, extracapsular spread, perineural invasion, lymphovascular invasion, advanced tumour stage, and high-grade histopathology) [5, 19]. Systemic chemotherapy for parotid gland cancers is reserved for patients with advanced disease, recurrence, and/or distant metastases [3, 18].

In the present study, we analysed the use of preoperative FNAC and intraoperative frozen section (FS) for the appropriate surgical and postoperative treatment.

## Patients and Methods

This observational study retrospectively selected patients with primary malignant cancer of the parotid gland surgically treated between 1 January 2008 and 30 June 2017 at the Maxillo-Facial Surgery Division, University Hospital of Parma, Italy. The study protocol was approved by the Institutional Review Board and Ethics Committee. The study was performed in accordance with the Declaration of Helsinki.

Patients with postoperative histological diagnosis of malignant parotid cancer and follow-up duration of longer than 5 years were included. Patients with benign salivary gland lesions, malignancies of the submandibular, sublingual, or minor salivary glands, parotid metastasis from other tumours, and previous surgery for parotid malignancy performed at other healthcare centres were excluded.

We recorded the sex, age at surgery, site of parotid gland lesion, histological diagnosis and grading, infiltrated margins, stage, parotidectomy type, associated neck dissection, adjuvant radiotherapy and/or chemotherapy, preoperative FNAC results, intraoperative FS results (if performed), survival, recurrence, and/or occurrence of metastasis during the follow-up. The histological diagnoses were recorded according to the latest 2017 WHO classification of head and neck tumours [7].

Each patient underwent a clinical examination and an ultrasound-guided FNAC as a preoperative staging protocol. If the FNAC reported a malignant tumour, a MRI with and without contrast of the face and neck was requested. In case of highly biologically aggressive lesions (cT3–cT4, lymph node involvement, high grade on FNAC), a CT scan of the thorax–abdomen with and without contrast was requested to evaluate possible distant metastases.

Because none of the patients underwent cancer enucleation or extracapsular dissection, the analysed surgical procedures were categorized into five groups: partial parotidectomy, total parotidectomy, total parotidectomy with facial nerve resection, extended parotidectomy, and extended parotidectomy with facial nerve sparing. The facial nerve was sacrificed only in cases of gross neoplastic invasion and/or preoperative facial nerve deficiency. In this case, an intraoperative FS of the resected nerve stumps was always performed to assess and eradicate possible perineural spread of the neoplasia.[13, 20].

We also analysed the neck dissection procedures and separately assessed whether neck dissection was performed during the first surgery or a secondary intervention.

The preoperative FNAC and intraoperative FS (if performed) data were categorized into benign and malignant lesions. FNAC suggestive of salivary gland neoplasms of uncertain malignant potential or suspicious for malignancy (according to the Milan system) were considered malignant lesions [21]. Similarly, intraoperative FS findings suspicious for malignancy were considered malignant lesions.

## Results

In total, 48 patients were included in the study (22 males and 26 females; mean age: 56.7 years; age range 10–90 years). The histological diagnoses are summarized in Table 1. The most common type of parotid gland malignancy was carcinoma ex pleomorphic adenoma (22.9%), followed by

**Table 1** Demographic, clinical, pathological findings, surgical, and adjuvant treatment

| *N* | 48 |
|---|---|
| Age | 56.7 (10–90) years |
| Follow-up | 84 (60–130) months |
| *Sex* | |
| Male | 22 (46%) |
| Female | 26 (54%) |
| *Site* | |
| Right parotid gland | 22 (46%) |
| Left parotid gland | 26 (54%) |
| *Histological diagnosis* | |
| Carcinoma ex pleomorphic adenoma | 11 (22.9%) |
| Mucoepidermoid carcinoma | 8 (16.7%) |
| Acinic cell carcinoma | 7 (14.6%) |
| Salivary duct carcinoma | 6 (12.5%) |
| Adenoid cystic carcinoma | 4 (8.3%) |
| Epithelial-myoepithelial carcinoma | 3 (6.3%) |
| Adenocarcinoma, not otherwise specified (NOS) | 2 (4.2%) |
| Oncocytic carcinoma | 2 (4.2%) |
| Squamous cell carcinoma | 2 (4.2%) |
| Myoepithelial carcinoma | 1 (2.1%) |
| Polymorphous adenocarcinoma | 1 (2.1%) |
| Poorly differentiated carcinoma | 1 (2.1%) |
| *Surgery—parotidectomy* | |
| Partial parotidectomy | 20 (41.6%) |
| Total parotidectomy | 8 (16.7%) |
| Total parotidectomy + facial nerve resection | 5 (10.4%) |
| Extended parotidectomy + facial nerve sparing | 7 (14.6%) |
| Extended parotidectomy | 8 (16.7%) |
| *Surgery—neck dissection* | |
| No | 29 (60.4%) |
| Yes | 19 (39.6%) |
| *During first surgery* | *17 (35.4%)* |
| *Secondary surgery* | *2 (4.2%)* |
| *Radiotherapy* | |
| No | 23 (47.9%) |
| Yes | 25 (52.1%) |
| *IMRT* | *22 (45.8%)* |
| *Proton therapy* | *3 (6.3%)* |
| *Chemotherapy* | |
| No | 44 (91.7%) |
| Yes | 4 (8.3%) |

Italic values indicate titles

mucoepidermoid carcinoma (16.7%) and acinic cell carcinoma (14.6%).

The surgical procedures performed in the study are summarized in Table 1. Most patients underwent partial parotidectomy (20 cases). Total parotidectomy was performed in 8 cases preserving the facial nerve and in 5 cases resecting it. Extended parotidectomy was performed in 15 cases: 7 with facial nerve sparing and 8 with facial nerve sacrifice.

In 29 cases, neck dissection was not performed. Of the 19 cases of neck dissection, 17 were performed during the first surgery, whereas 2 were performed during a secondary intervention within 1 month after the histological diagnosis. In particular, one patient underwent neck dissection after extended parotidectomy, while another underwent total parotidectomy and neck dissection after a previous partial parotidectomy (with positive histological margins). In 11 cases, preoperative MRI showed nodal involvement and therapeutic neck dissection was performed to resect level I–V nodes. In 8 patients who were clinically and radiologically N0, stadiative/elective neck dissection was performed to resect level I–III nodes. In 4 patients, intraoperative FS of the suspected nodes was performed to determine the need for neck dissection, and all 4 demonstrated no nodal involvement so neck dissection was not performed.

The preoperative FNAC results were available for all 48 patients (Table 2), of whom 29 (60.4%) and 19 (39.6%) were suggestive of malignant and benign parotid lesions, respectively. In these 19 false-negative FNAC, the wrong cytological diagnosis was: pleomorphic adenoma in 17 cases (89.5%), Warthin tumour in 1 (5.25%), oncocytoma in 1 case (5.25%).

In 31 cases, FS was performed during the surgical intervention (Table 2), which were suggestive of malignant and benign lesions in 26 and 5 cases, respectively.

Of the 31 cases in which intraoperative FS was performed (Table 3), 22 with malignant preoperative FNAC result and 5 with benign preoperative FNAC result were

**Table 2** Preoperative FNAC and intraoperative FS results

| *N* | 48 |
|---|---|
| *Preoperative FNAC* | |
| Malignant | 29 (60.4%) |
| Benign | 19 (39.6%) |
| *Intraoperative FS* | |
| Not executed | 17 (35.4%) |
| Malignant | 26 (54.2%) |
| Benign | 5 (10.4%) |

**Table 3** FNAC and intraoperative FS results concordance

| Preoperative FNAC | Intraoperative FS | *N* = 31 |
|---|---|---|
| Malignant | Malignant | 22 (71%) |
| Benign | Malignant | 4 (12.9%) |
| Benign | Benign | 5 (16.1%) |
| Malignant | Benign | 0 |

confirmed intraoperatively. In addition, 4 with preoperative FNAC result suggestive of a benign lesion was contradicted by a malignant intraoperative FS result, whereas no case with preoperative FNAC suggestive of a malignant lesion was followed by an intraoperative FS suggestive of a benign lesion. Surgical treatment in patient with preoperative FNAC suggestive of malignant lesion is summarized in Table 4, while Table 5 summarizes if it was suggestive of bening lesion.

Adjuvant radiotherapy was administered to 25 patients after surgery. In particular, 22 patients underwent intensity-modulated radiation therapy (IMRT) and 3 underwent proton therapy (Table 1). Chemotherapy was administered to 4 patients, and all 4 also received radiotherapy. Two patients received chemotherapy due to symptomatic pulmonary metastases. No patient underwent isolated postoperative chemotherapy.

The minimum and maximum follow-up durations were 60 months (based on the study inclusion criteria) and 130 months, respectively, with a mean of 84 months.

The overall 1-, 3-, and 5-year postoperative survival rates were 93.75%, 85.42%, and 85.42%, respectively (Fig. 1).

In total, 7 patients (14.6%) died, 3 due to the disease within the first year, while the remaining 4 died during the second and third years due to other conditions. The disease-specific survival was 93.7% at 1 year and remained stable at 3 and 5 years after surgery. The disease-free survival was 91.7% 1 year after surgery, which decreased to 89.6% at 3 years and remained stable at 5 years of follow-up.

## Discussion

The adequate preoperative assessment, diagnosis, treatment, and follow-up of parotid gland cancers have been studied extensively in the literature [12, 22]. Due to the rarity and heterogeneity of parotid gland cancers, most previous studies have included a small sample and several different histological subtypes [23–25].

The recent 2017 updates to the WHO classification and TNM system of head and neck tumours make it difficult to compare data present in the literature because the reported data have not necessarily been recorded in accordance with the latest modifications [7, 26]. Several previous studies were retrospective and included prolonged study periods

**Table 4** Surgical treatment in patient with preoperative FNAC suggestive of a malignant lesion

| *N* | 29 | Radical resection |
|---|---|---|
| *Surgery—parotidectomy* | | |
| Partial parotidectomy | 6 (20.7%) | 5 (17.2%) |
| Total parotidectomy (with or without facial nerve resection) | 10 (34.5%) | 7 (24.1%) |
| Extended parotidectomy (with or without facial nerve sparing) | 13 (44.8%) | 9 (31.1%) |
| **Overall radical resection after surgery** | | **21 (72.4%)** |
| *Surgery—neck dissection* | | |
| No | 13 (44.8%) | |
| Yes | 16 (55.2%) | |
| *During first surgery* | *15 (51.8%)* | |
| *Secondary surgery* | *1 (3.4%)* | |

Bold value indicates final result and Italic values indicate titles

**Table 5** Surgical treatment in patient with preoperative FNAC suggestive of a benign lesion

| *N* | 19 | Radical resection |
|---|---|---|
| *Surgery—Parotidectomy* | | |
| Partial parotidectomy | 14 (73.7%) | 12 (63.2%) |
| Total parotidectomy (with or without facial nerve resection) | 3 (15.8%) | 2 (10.5%) |
| Extended parotidectomy (with or without facial nerve sparing) | 2 (10.5%) | 1 (5.2%) |
| **Overall radical resection after surgery** | | **15 (78.9%)** |
| *Surgery—Neck dissection* | | |
| No | 16 (84.2%) | |
| Yes | 3 (15.8%) | |
| *During first surgery* | *2 (10.5%)* | |
| *Secondary surgery* | *1 (5.3%)* | |

Bold value indicates final result and Italic values indicate titles

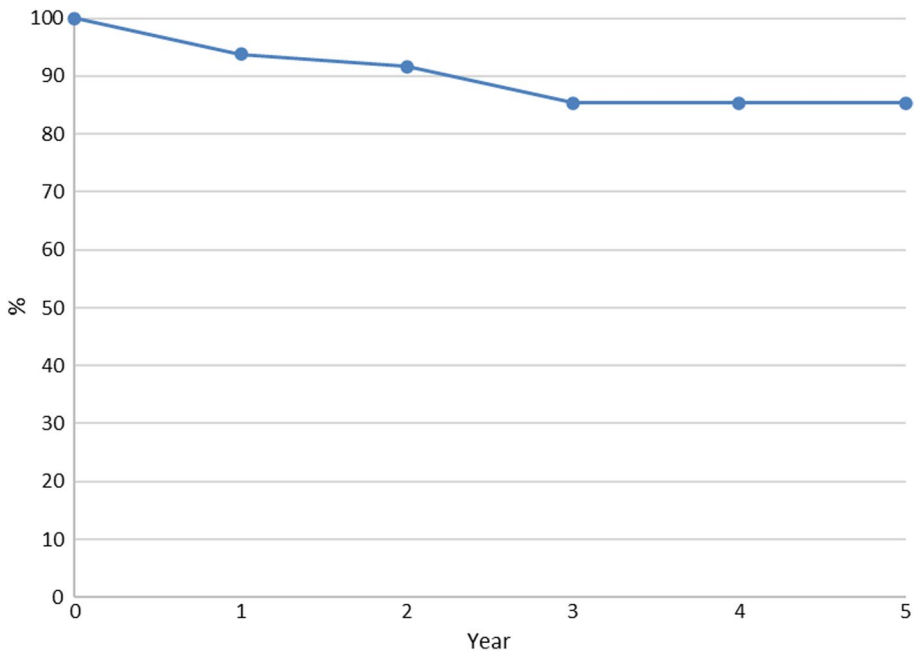


**Fig. 1** Overall survival

(10–40 years), without the consideration of the aforementioned biases.

In the present study, we evaluated the management of parotid gland cancers, with an emphasis on multidisciplinary diagnostic and therapeutic modalities, as well as the outcomes of patients over 10 years (2008–2017). We highlighted the importance of pathologists' expertise in guiding the selection of appropriate surgical and postoperative treatment of parotid cancers. To improve further studies and meta-analysis, we updated the collected data according to the latest version of the WHO classification and TNM system of head and neck tumours.

The mean age of patients was similar between our study (56.7 years) and previous studies (55–65 years). The most frequent histological diagnoses were carcinoma ex pleomorphic adenoma (22.9%), followed by mucoepidermoid carcinoma (16.7%) and acinic cell carcinoma (14.6%). In comparison, in previous studies, the most common malignant tumour of the parotid gland was mucoepidermoid carcinoma, followed by adenoid cystic carcinoma and adenocarcinoma not otherwise specified [4, 8, 27].

These differences may have several explanations. First, carcinoma ex pleomorphic adenoma is usually an anamnestic, rather than a histological, diagnosis; therefore, most patients have a history of pleomorphic adenoma. Second, the present study was conducted at a tertiary referral centre for salivary gland neoplasms, and thus many patients with recurrence of pleomorphic adenoma were referred to us after previous surgical treatment performed at primary or secondary centres.

Our data show a significantly lower diagnostic accuracy of preoperative FNAC (60.4%) compared to previous studies (73–86.6%) [28–30], which may be because, in our study, FNACs of several patients were analysed by external laboratories (72.7% of the false-negative results). Therefore, the differences may be due to the operator dependence of FNAC analysis. As already reported in the literature, also in this study, the most common false-negative FNAC diagnosis was pleomorphic adenoma (89.5%).

FNAC of the salivary glands should be analysed by experienced cytologists to reach an acceptable level of accuracy. In addition, preoperative repeat FNAC analysis by an experienced cytologist is highly recommended, particularly if there are discrepancies among clinical, radiological, and cytological findings.

Intraoperative FS showed a higher diagnostic sensitivity compared to FNAC, with 83.9% of true-positive results among a total of 31 cases. These results are similar to previously reported data, which may be because FS was analysed by experienced pathologists. When there is suspicion of malignancy in a patient with a preoperative FNAC suggestive of a benign lesion, intraoperative FS can be performed to decide the need for extended resection (total or extended parotidectomy) or neck dissection. However, intraoperative evaluation by an experienced surgeon remains invaluable in early differentiating between clearly benign and suspicious lesions (even in front of a preoperative FNAC suggestive of a benign lesion).

In the present study, four patients had intraoperative FS suggestive of malignancy and a previous FNAC compatible with benign lesions: total parotidectomy without neck dissection was performed in two of these cases, and extended parotidectomy with neck dissection was performed in one case. In the remaining case, partial parotidectomy

was performed, which was followed by total parotidectomy and neck dissection after the postoperative histological diagnosis.

Although postoperative histopathological diagnosis is mandatory for comprehensive cancer characterization, intraoperative FS may allow the appropriate management without the need for secondary intervention in suspected malignancies. In particular, if intraoperative FS demonstrates features of a high-grade carcinoma, the surgeon may perform radical intervention (total or extended parotidectomy with or without neck dissection). In cases of intraoperative FS compatible with low-grade carcinoma or only suspicious findings, radical procedures should be considered after postoperative histopathological characterization. For this purpose, a high-volume pathological laboratory with experience in salivary gland lesion analysis is required.

The patient should be informed preoperatively regarding the various therapeutic options (nerve sacrifice, partial/total/extended parotidectomy, and neck dissection) and the potential need to perform any option on the basis of the FS results and the intraoperative surgical evaluation.

To improve the accuracy of diagnosis between malignant and benign salivary gland tumours, radiologic features are also important. In particular, predictive signs of malignancy on MRI can be considered: irregular margins, infiltration of neighbouring tissues (subcutis, parapharyngeal space or nerves), and hyposignal in T2 sequences. In fact, benign or low-grade lesions more frequently present serous or mucinous secretions or a good amount of stroma, so they will have a high T2 signal; lesions with a high degree of malignancy, having a significant cellularity, manifest an intermediate-low signal in T2. Contrast-enhanced and T1 fat-suppressed MRI is useful in the evaluation of perineural invasion.

Diffusion imaging (DWI) improves both specificity, sensitivity and accuracy for the diagnosis of malignant tumours on MRI; most benign lesions have high ADC (with the exception of Warthin's tumour and oncocytoma). In contrast, at present, perfusion imaging (DCE) does not seem to provide much advantage [31].

Although previous studies have evaluated the usefulness of histopathological grading and preoperative core needle biopsy (CNB), we could not analyse the prognostic value of these factors [32, 33]. In fact, the main limitations of our study are that less than half of our patients had a histopathological grading score available (23 cases; 47.9%) and none of our patients underwent preoperative CNB.

## Surgical Treatment

Our data support the role of partial parotidectomy in cases with benign or malignant findings in preoperative FNAC, even in the case of a false-negative result. In cases of aggressive biological features, large lesions (> 4 cm), or neoplastic invasion of the surrounding tissues (T3–T4a), total or extended parotidectomy should be considered.

Radical neck dissection (levels I–V) should be performed in preoperative N + patients. In the present study, postoperative histopathological analysis of the nodes confirmed the presence of neoplastic cells in all cases, confirming the need for surgical procedures and the usefulness of the standard guidelines [17, 34].

Interestingly, among the eight N0 patients who underwent stadiative/elective neck dissection (levels I–III), no patient had neoplastic invasion of nodes in the postoperative pathological analysis. These data are significantly different from the rate of occult metastases reported in previous studies [34, 35].

Some researchers have suggested that intraoperative nodal FS should be performed to evaluate lymphatic infiltration and determine the need for neck dissection during surgery. In the present study, four patients underwent intraoperative FS for nodes and neoplastic cells were not detected in any of the cases. Therefore, neck dissection was not performed. None of the 29 patients who did not undergo neck dissection showed nodal metastasis during follow-up [34, 36]. Surgical treatment of patients with malignant and benign features in preoperative FNAC is presented in Tables 4, 5, respectively.

## Adjuvant Therapy

In the present study, adjuvant radiotherapy was performed in cases of positive/close margins after surgery, high-grade tumours, high T classification, perineural invasion, and/or presence of cervical node metastases. Radiotherapy is effective for loco-regional disease control [37, 38]. IMRT was administered to most cases (28 patients), while proton therapy was administered to 3 cases. The role of proton therapy is controversial because of a lack of significant advantages, as well as several important side effects, compared to IMRT.

Small malignant lesions (pT1–pT2) and cancers with favourable histological features were treated with surgery alone; none of these patients died or experienced recurrence and/or secondary lesions during follow-up, suggesting the long-term efficacy of this protocol.

Previous studies have shown that radiotherapy is useful for cases of adenoid cystic carcinoma and salivary duct carcinoma, irrespective of T dimensions and positive/close margins, because of their loco-regional and perineural spread [39, 40]. In the present study, only one patient with pT1 lesions and the aforementioned histological features did not receive adjuvant radiotherapy.

Chemotherapy still plays a limited role in the treatment of salivary gland cancers and is generally reserved for the palliative treatment of symptomatic locally recurrent and/or metastatic disease with no indication for surgery or

radiation therapy [15]. This explains the limited application of chemotherapy in our patients, of whom only 4 received chemotherapy (2 received chemotherapy after developing metastatic pulmonary lesions). All 4 patients received combination chemotherapy with cyclophosphamide, adriamycin and platinum (CAP).

### Overall Survival

The overall survival was higher in the present study (91.7% at 3 and 5 years after surgery) than in previous studies (69% at 3 years and 65% at 5 years after surgery), with no histological differences, but we must view this result with caution due to the heterogeneity and small size of our sample [25, 41, 42]. In our study, the 3 patients who died because of parotid cancer died within 1 year after surgery: 1 developed local–regional disease recurrence (within 6 months after intervention) and the remaining 2 developed pulmonary metastases.

## Conclusion

FNAC showed a significantly lower diagnostic sensitivity for parotid gland lesions compared to previous studies, which may be because FNAC analysis was not performed at a centre with experience in cytological analysis of salivary gland lesions. In suspected malignant cases, preoperative diagnostic accuracy can be improved by repeat analysis of the FNAC specimen by other laboratories, preoperative CNB, and/or intraoperative FS analysis of the suspected mass (which has a higher diagnostic accuracy). Further studies with a larger sample are required to better understand the role of different diagnostic tools (such as FNAC, CNB, and intraoperative FS) in the management of salivary gland tumours.

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**Declarations**

**Conflict of interest** There are no financial or other relations that could lead to a conflict of interest.

**Ethics Approval** The study protocol was approved by the Institutional Review Board and Ethics Committee of the University Hospital of Parma. The study was performed in accordance with the Declaration of Helsinki.

**Consent to Participate** Informed consent was obtained from all individual participants included in the study.

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