ONCOLOGY

# Clinical approach and treatment of benign and malignant parotid masses, personal experience

## *Approccio clinico e terapeutico alle neoplasie della parotide. Esperienza personale*

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SUMMARY

Parotid gland tumours account for 80% of all salivary gland neoplasms, 20% of these are malignant, but in daily clinical practice most parotid masses are operated on before obtaining the final histological diagnosis. This clinical setting further complicates the critical point of parotid surgery, which is the management of the facial nerve. In the present study, data were evaluated referring to 540 patients who underwent parotidectomy for a mass which was discovered to be a benign (470 cases) or a malignant (70 cases) neoplasm, between November 1994 and December 2007, at our Institution. The most significant single parameter in this series of malignancies regarding disease specific survival was the clinical involvement of the facial nerve at diagnosis (p = 0.006). Also for this reason, as there is no evidence that liberal VIIth nerve sacrifice improves prognosis, when it is not clinically involved, every attempt is made to dissect and preserve it. At present, the most complicated situation concerning nerve preservation may be, on the other hand, recurrence of a benign tumour, in particular pleomorphic adenoma, which, in our series, has a higher incidence (8.3%) of permanent facial dysfunction, than surgery with nerve preservation for malignancy (3.7%).

KEY WORDS: Parotid tumours • Prognostic factors • Facial nerve

RIASSUNTO

*L'80% dei tumori delle ghiandole salivari originano a livello della parotide, il 20% dei tumori parotidei sono maligni. Nella pratica clinica solitamente non è tuttavia possibile stabilire con certezza la diagnosi di natura di una neoformazione parotidea prima della sua asportazione ed esame istologico definitivo. Tale incertezza della diagnosi rende ancora più complicato l'aspetto chiave della chirurgia parotidea, ovvero la gestione del nervo facciale. Abbiamo valutato retrospettivamente 540 pazienti consecutivi sottoposti a parotidectomia presso il nostro reparto di Clinica Otorinolaringoiatrica del Policlinico Gemelli di Roma per una massa della ghiandola, risultata benigna in 470 e maligna in 70 casi, tra il novembre 1994 ed il dicembre 2007. Il singolo parametro clinico più significativo ai fini della prognosi è risultato essere il danno funzionale del nervo facciale alla diagnosi (p = 0,006). Anche per questa ragione, e dal momento che non ci sono prove che il sacrificio sistematico del nervo migliori la prognosi, quando questo non è clinicamente coinvolto, ogni sforzo è effettuato al fine di liberarlo e preservarlo. Particolarmente insidiose da questo punto di vista si sono rivelate le recidive, soprattutto se multifocali, dei tumori benigni, soprattutto degli adenomi pleomorfi. Queste ultime hanno un'incidenza di paresi del facciale permanente post-chirurgica più elevata (8,3%) persino rispetto ai tumori maligni operati con preservazione del nervo (3,7%). In questi casi è fondamentale il consenso del paziente che deve essere adeguatamente informato circa la possibilità di una disfunzione post-chirurgica anche permanente del VII nervo cranico.*

PAROLE CHIAVE: *Tumori della parotide • Fattori prognostici • Nervo facciale*

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## Introduction

Salivary cancers account for approximately 3% of all head and neck malignancies diagnosed in the United States each year; most of these are located in the parotid glands [1]. Approximately 80% of salivary gland tumours occur in the parotid gland. Of these, approximately 75-80% are benign. There is no consistent correlation between the rate of tumour growth and whether a tumour is benign or malignant. The majority of benign tumours of the parotid gland are epithelial tumours.

Most benign parotid tumours present as slow growing, painless masses often in the tail of the parotid gland. In the presence of a parotid mass, physical examination is the first diagnostic tool, since, in most cases it guides the clinician in the right direction (benign versus malignant). Ultrasonography (US) is a low-cost modality with high sensitivity in detecting masses in the superficial lobe of the parotid gland. Its inability to show part of the deeper parotid lobe is overcome by computerized tomography (CT) and/or magnetic resonance imaging (MRI) which can be particularly useful, as complementary studies, for correct surgical planning. Fine-needle aspiration biopsy (FNAB) is also indicated by some Authors [2-4]. Nevertheless, none of these tools provide definitive information re-

garding the nature and the precise histology of a parotid mass and, furthermore open biopsy of a parotid mass is not recommended due to the risk of seeding in the case of solid malignancy. Therefore, what usually occurs in clinical practice is that most parotid masses are operated upon in order to obtain the final histological diagnosis. Obviously, lumpectomy must be avoided whenever possible and an oncologically safe surgical approach, involving at least the superficial lobe of the parotid should always be performed also in cases of a clinically benign lesion.

Surgery of the parotid gland is challenging because the VII cranial nerve, which emerges at the stylomastoid foramen, enters the gland and branches out inside the parotid, defining the superficial and the deep lobe, and must always be identified and dissected when performing parotidectomy. Even in the presence of normal anatomy and normal surrounding parotid tissue, dissection of the branches of the facial nerve requires patience and special attention both to detail and to landmarks [5]. We always seek and dissect the facial nerve under magnification. When the course of a nerve is distorted and attenuated by a tumour, preservation of facial nerve fibres can be very difficult. Experience shows that most of the primary salivary tumours of the parotid are found directly adjacent to at least one branch of the facial nerve, and rarely, if ever, will the surgeon feel that dissection of the nerve has been useless; also for these reasons, we believe that the most conservative operation should be superficial parotidectomy, also in the case of a clearly benign mass. Furthermore, in the event of recurrence, the risk to the facial nerve increases exponentially, particularly in the relatively frequent event of a multi-nodular relapse of apleomorphic adenoma [6].

Enucleation alone is, therefore, inadequate for tumours of the parotid gland, on account both of the increased risk of facial nerve lesions and the increased risk of recurrence. Some Authors believe that the only exception to this rule could be Warthin tumours especially when presenting posterior to the facial nerve [7].

In the present report, data are described emerging from a retrospective review of personal experience in this setting, evaluating the pathological, prognostic and surgical parameters (including complications) of a consecutive series of patients who underwent parotidectomy in our Institution, and were found to be affected by a benign or by a malignant neoplasm.

## Materials and methods

The data evaluated refer to approximately 540 consecutive patients who underwent parotidectomy for benign and malignant neoplasms between November 1994 and December 2007, at the Institute of Otorhinolaryngology of Università Cattolica del Sacro Cuore, Policlinico Agostino Gemelli, Rome, Italy.

For every patient, personal data were recorded including habits (in particular smoking and alcohol consumption), family history, with particular regard to tumours (salivary and not), clinical presentation of the parotid neoplasm. Data were collected regarding surgery, complications, complementary and rehabilitative treatments, as well as respective follow-up, by means of revision of charts, direct clinical re-examination and imaging of surviving patients, as well as phone calls to relatives of patients who had died. Before surgery, in all patients, stage had been defined by clinical examination and contrast enhanced CT scans of the head and neck, in the presence of a suspicion for malignancy this work-up was completed with imaging of the lungs, contrast enhanced MRI of the head and neck, salivary US, FNAB. In cases of malignancy, also collected were data regarding TNM UICC/AJCC staging (VI edition - 2002).

As far as concerns clinical presentation of parotid tumours, especially malignant, we evaluated the involvement of the facial nerve, staging it according to the the House-Brackmann scale, and of other cranial nerves, as well as the involvement of other structures outside the parotid such as masseter, sternocleidomastoid muscle, mastoid, skin, ear canal, mandible, skull base.

The masses operated upon were classified, based upon the site of origin, as deep or superficial, and, when they were demonstrated to be malignant, namely primitive (when the parotid was the site of origin of the neoplasm) or metastatic (when parotid localization was a metastasis); based upon the clinical history, as primary or recurrent.

As far as concerns surgery, the parotidectomies were classified as superficial with facial preservation or total with nerve sacrifice (of the main trunk or of branches) and when extension of the resection to other structures was necessary this was recorded.

In cases presenting malignancy, follow-up data were collected from the records of the visits performed in the multidisciplinary outpatient unit with the involvement of Otolaryngologists (the surgeons), Radiation Oncologists, Radiologists. In the first year, we recommend a CT scan of the parotid and neck every 4 months, and, in the second year every 6 months; we also suggest a chest CT, every year, during follow-up since lung metastases are not infrequent [8-10].

A statistical analysis was performed using the JMP in software, release 5.1 by the SAS institute. Survival curves were calculated from the day of surgery using the Kaplan-Meier method. Considered as endpoints for the Kaplan-Meier overall, disease-specific, disease-free, metastasis (regional and distant) free survival. For comparison of survival curves, both the log-rank and Wilcoxon tests were used. The $\alpha$ level was fixed at 0.05 for all the statistical tests we performed.

## Results

The overall study population comprised 293 males and 247 females. None of the patients was affected by Sjögren's syndrome or by other inflammatory disease of the parotid. Overall 470 (87%) masses were found to be benign, and 70 malignant. In the "benign" group the median age at diagnosis was 49 years (range 4-94 years); age followed a bimodal Gaussian distribution with a peak in the first half of the seventh decade and another in the second half of the fifth decade (Fig. 1A). In the group of malignancies, the median age at diagnosis was 60 years (range 19-94 years). Age followed a unimodal Gaussian distribution with a peak in the seventh decade (Fig. 1B). In the case of benign disease, the clinical presentation was usually a swelling of the gland, slowly growing or apparently stable in dimensions. In cases of malignant disease, clinical presentation was an asymptomatic parotid mass in 57 patients (81%), 13 patients came to our observation with a facial deficit, associated, in 3 cases, with pain, of Grade II (2 cases), III (3 cases), IV (6 cases) and V (2 cases).

Among the benign lesions, the most frequent, by far, were pleomorphic adenomas (almost 50%) and Warthin's tumours (almost 40%) (Fig. 2); only 44 cases (less than 10%), all pleomorphic adenomas, were localized in the deep lobe. This proportion significantly changes when considering malignancies, 25 of which (36%) arose in the deep lobe. Among benign lesions, 48 pleomorphic adenomas were recurrences (mostly after enucleation), 13 of these had undergone their first surgical operation in our institution (10 of them before 1994, with enucleation).

When considering malignancies, primary masses (including parotid nodal and extra-nodal lymphomas) were about 74.2% (52 patients) of the treated parotid tumours, 11.5% (8) were recurrences of parotid malignancies incompletely resected at other Institutions and still requiring revision parotidectomy, 14.3% (10) were relapses of a previously resected tumour outside the parotid. In the latter group, 1 case was local recurrence of a submandibular SCC, the others were intra-parotid nodal metastases

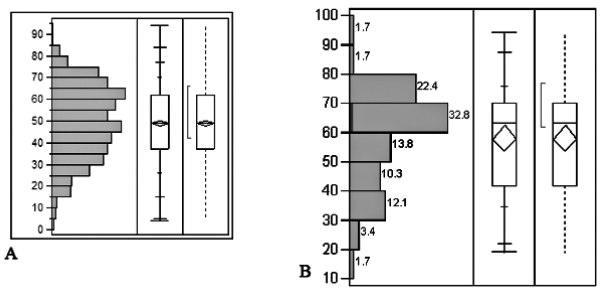


**Fig. 1.** In the "benign" group age follows a bimodal Gaussian distribution with a peak in the first half of the seventh decade and another in the second half of the fifth decade (Fig. 1A). In the group of malignancies, age follows an unimodal Gaussian distribution with the peak in the seventh decade (Fig. 1B).

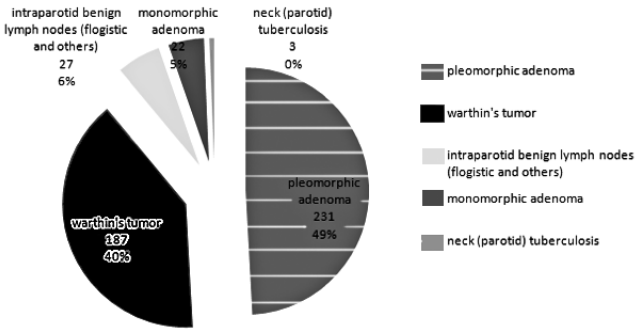


**Fig. 2.** Distribution of histotypes in the 470 benign parotid neoplasms.

from skin SCC (7 cases) and melanomas (2 cases). Three nodal metastases were thought to be primitive parotid neoplasms before resection, because the patients had not reported the resection, considered irrelevant, of small skin SCCs, several months before. In 6% (4) of cases, revision was performed within two weeks after a first operation for a "histological surprise", we considered these masses as primary: in all but one of these cases, no histological residual disease was found. Among those tumours arising primarily from the parotid (60 cases), the most frequent histological finding was adenocarcinoma (15 cases, 21%), followed by SCC (11, 16%) and lymphoma (10, 14%) (4 nodal, 6 extra-nodal), adenoid cystic carcinoma (7, 10%), mucoepidermoid carcinoma (6, 9%), epithelial-mioepithelial carcinoma (5, 7%), malignant mixed tumour (4, 6%), synovial sarcoma (1 case), acinic cell carcinoma (1 case). In the 10 operated lymphomas, cytology had not led to the suspicion of the final histological diagnosis.

Our clinical staging of the 60 primary parotid malignancies, with the aid of diagnostic imaging, had been quite accurate and did not usually change after the operation: one case, which had been considered to be a cT4N0 before surgery, was found to be a pT4N2b, and 2 cases considered cN1, which became pN0 after the neck dissection. Stage distribution as stated after resection (pTNM) was as follows: Stage I 25% (15 patients), Stage II 33% (20), Stage III 17% (10) and Stage IV 25% (15). All Stage I, II and III were N0. Among Stage IV cases, there were 6 pT4N2b, 1 pT4N1, 1 pT3N2b, 7 pT4N0. None of the patients was M1 at diagnosis. Overall 8 out of 70 (11%) of the patients had the diagnosis of a second metachronous malignant tumour previously or following the parotid malignancy: we recorded 3 adenocarcinomas of the prostate, 2 breast cancers, 2 kidney adenocarcinomas, 1 Hodgkin lymphoma. These metachronous malignancies were never the cause of death in the present series. None of the patients presenting malignancy reported a case of salivary malignant neoplasm among relatives. 23/60 patients with primary salivary malignant neoplasms reported one or more malignancies among first-degree relatives: the sites of such tumours were lung (4 cases), colon or rectum (4 cases), breast (4 cases), bladder (1 case), haematopoietic

and lymphatic system (3 cases), larynx (1 case), oral cavity (1 case), stomach (6 cases), kidney (1 case), liver (1 case), ovary (1 case). Overall, 5 out of the 6 gastric cancers occurred in relatives of patients with a primary parotid cancer arising from the glandular epithelium (2 mucoepidermoid carcinomas, 2 adenocarcinomas, 1 malignant mixed tumour).

As far as concerns surgery, in benign lesions, superficial parotidectomy was performed in 396 cases, enucleation in 10 cases of Warthin's tumour (all before 2003), total parotidectomy with facial preservation in 64 cases (mostly recurrences and primaries of the deep lobe). A trans-mandibular approach was never needed (not even in malignancies), the deep lobe tumours always being resectable using a standard parotidectomy approach [11], by modifying the neck incision when needed.

In malignancies, a superficial parotidectomy was performed in 40% of cases (28 patients), total parotidectomy with VIIth nerve preservation in 36% (25 patients), total parotidectomy with VIIth nerve sacrifice in 24% (17 patients). In the latter group, only in 4 patients was the facial nerve functioning normally at the time of surgery, in one of these cases, however, it was possible to preserve the superior (orbitofrontal) branch, in one case we reconstructed the nerve with a sural graft. Due to the suspected or clinically evident involvement, resection was extended to other structures in 15 cases (external auditory canal: 4 cases, auricle: 1, overlying skin: 9, mastoid: 2, sternocleidomastoid muscle: 7, digastric muscle: 7, masseter: 3, submandibular gland: 1). In 3 cases, in which a wide area of skin had to be resected, we reconstructed the defect with a free flap (1 DIEP and 1 ALT) or a regional pedicled flap (*pectoralis major*). In 82% (58) of cases, the resection margins were adequate, in 4% (3) no residual disease was found (see above), in 14% (9) the margins were close (6) or positive (3). Homolateral comprehensive neck dissection in metastases of skin neoplasms in 7 cases was performed (2 melanomas and 5 SCCs), and 9 comprehensive (8 modified radical type III, 1 modified radical type I) in cN+ primaries of the parotid. None of the skin SCCs were found to have positive nodes in the neck, both the melanomas had also micro-metastases in the neck; among the parotid primaries 2 were found to be pN0. Furthermore, 13 homo-lateral prophylactic neck dissections (selective of levels I, II, III), were performed in locally advanced primary tumours, with only 1 pN+ (N2b).

Adjuvant treatment was recommended and performed in all the metastatic masses: radio-chemotherapy in SCCs (7 cases) (60 Gy and three cycles of concurrent CDDP 100 mg/m on days 1, 22, and 43), IFN alpha in melanomas (2 cases). Primitive neoplasms of epithelial origin underwent adjuvant radiotherapy (50-60 Gy) on the surgical bed and on the neck nodes when indicated by principal international guidelines [8], i.e., in the event of intermediate or high grade or adenoid cystic tumours, close or positive margins, neural/perineural invasion, lymph node metastases, lymphatic/vascular invasion, Stage IV disease, deep lobe salivary malignancies. When 2 or more of the above adverse characteristics we found to be associated, concurrent CDDP 100 mg/m was added on days 1, 22, and 43. Overall 23% (16) of patients with a parotid primary tumour underwent adjuvant radiochemotherapy, 20% (14) radiotherapy alone. Lymphomas were referred to haematologists and underwent chemotherapy.

Early complications of surgery are the same both in the case of benign and malignant lesions: post-operative bleeding, within 36 hours after the parotidectomy, always controlled in the Operatory Room without further late sequelae, in 26 cases, and sialocele, which is by far the most frequent complication of surgery in our series, occurring in 103 patients (19%), but was always a self-limiting problem within 2 weeks of local medications, aspiration and compressive dressing. As fas as concerns facial nerve, in the cases with anatomical nerve preservation, 50 cases of post-operative facial weakness occurred (always more evident on the marginal branch), but only 6 presented a permanent dysfunction (2 malignancies and 4 recurrences of pleomorphic adenoma). Two out of these 4 recurrences of pleomorphic adenoma with the permanent dysfunction, actually had a macroscopic lesion of the facial nerve during an extremely difficult dissection from multi-nodular lesions: in these cases, the facial nerve was reconstructed with a sural graft.

The most frequent long-term sequela, in our series, is the sensory deficit, probably present in every patient after parotidectomy (due to section of the great auricular nerve). Overall, 15% of patients, in our series, complained of a residual sensory deficit 4 months after surgery, this rate increased to about 60% in the event of post-operative radiotherapy. Overall 9 neuromas of the stump of the transected great auricular nerves were recorded, both diagnosed within 2 years after the parotidectomy and excised with no further problems. Clinical Frey syndrome (we do not usually perform objective tests for detecting subclinical Frey syndrome) is not as frequent as in other series (17%), irradiation prevents it as it inhibits both glandular secretion and nerve regeneration (none of the irradiated patients had Frey syndrome).

Of course, it is useless to evaluate oncological outcome in the case of a benign lesion. Albeit, an attempt was made to trace the follow-up charts of every patient operated upon for a benign lesion, and if no record, more recent than 6 months before, was found among the clinical reports of our Department then an attempt was made to contact the patients by phone. In this way, the clinical follow-up of 383 out of the 470 patients with benign lesions were recovered. Among these, there were no cases of malignant transformation of a previously benign lesion. Only 3 recurrences submitted to revision surgery were recorded, all pleomorphic adenomas which underwent superficial

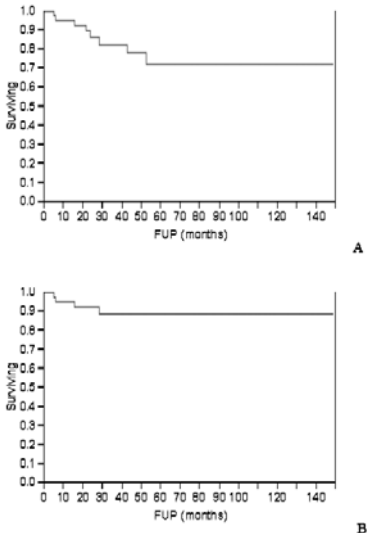


**Fig. 3.** In the salivary histotypes, overall survival in the present series was 85% at 2 years and 72% at 5 years (A); disease specific survival was 93% at 2 years and 89% at 5 years (B).

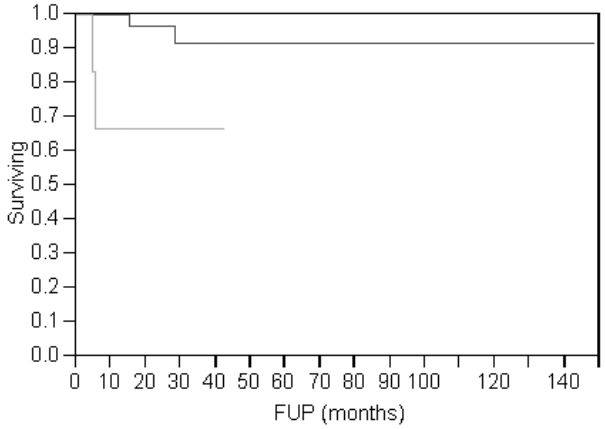


**Fig. 4.** The most significant clinical parameter in the present series was involvement of the facial nerve at diagnosis (p = 0.006 at Log-Rank), associated with a 66% 5-year disease specific survival, *versus* a 91% 5-year disease specific survival for patients with normal nerve function at diagnosis.

parotidectomy, in the first operation, and the recurrence was located in the deep lobe. The overall recurrence rate among primary pleomorphic adenomas with an adequate follow-up is, therefore, 3/134, i.e., 2.2%.

When comparing survival between the different histological findings by log-rank and Wilcoxon tests, no statistically significant differences were found (p = 0.4 and 0.53, respectively), recording the worst 5-year disease specific survival in the cases of metastatic melanomas (both dead), skin SCC (74%), primitive parotid SCC (68%), consistently with a previous report referring to a larger series [12].

Oncological outcome was then analyzed excluding tumours occurring primarily in other sites, the synovial sarcoma and lymphomas, in order to obtain a group of 49 malignancies of salivary origin. In this group, overall survival was 85% at 2 years and 72% at 5 (Fig. 3A); disease specific survival was 93% at 2 years and 89% at 5 (Fig. 3B).In this same group, no significant differences in survival were observed between lesions arising in the deep (5-year survival: 89%) and in the superficial lobe (5-year survival: 92%), between resections with/without VIIth nerve preservation (92% and 79% 5-year survival, respectively), among the IV stages according to TNM classification (even if stage IV, not surprisingly, was less successful than the others with a 5-year disease-specific survival of 82%). The most significant single parameters in the salivary histotypes, as for disease specific survival, were the presence of positive/close margins (p = 0.01 at Log-Rank) and, most of all, the involvement of the facial nerve at diagnosis (p = 0.006 at Log-Rank) (Fig. 4).

Distant metastases to the lung occurred in 5 patients with salivary neoplasms (distant dissemination occurred in the patients with melanoma). At present, 3 of these patients are still alive with the disease, while 2 of them died due to the metastases. Therefore, distant metastases, together with local recurrence, are the main cause of cancer-related death (50% each) in our series; no patient died on account of regional relapse.

## Discussion

The causes of salivary gland cancer have not been determined. Several factors have been aetiologically suggested, including ionizing radiation with all salivary cancers [13] and a familial predisposition to parotid cancer [14]. Proof of cause and effect remains to be established, however in these postulated associations, and the aetiology of most salivary gland cancers cannot be determined. We observed an increased incidence of malignant second primary tumours arising from glandular epithelia in patients with a primary salivary tumour. It is worthwhile pointing out that our patients did not develop second primaries in the lungs, which is a typical occurrence in mucosal head and neck malignancies [15-18]. In 5/50 (10%) of our patients with a primitive parotid malignancy (excluding lymphomas), a family history positive for gastric cancer was recorded, which usually accounts for 1.5% of all malignancies in the general population of Western countries [19]. This would appear to be a quite striking observation which requires further studies in order to be confirmed, and may indicate common predisposing factors for salivary and gastric cancer. In our series, salivary malignancies might not have occurred among relatives of the patients, because salivary cancer is altogether much rarer than cancer of the stomach even in susceptible subjects; on the other hand, a familial predisposition for gastric cancer has, long since, been postulated [20 21].

The histology of primary salivary gland tumours varies considerably. If, on the one hand, the benign histotypes are not as numerous and the histopathological issues are less urgent, on the other, the histological diagnosis of malignant lesions is a critical point. Primary malignant salivary gland histotypes have been classically subdivided into

high grade and low grade, based mainly upon the criterion of clinical aggressiveness. Some histotypes (such as mucoepidermoid carcinomas) can be either high grade or low grade, while for others the grade is always the same (adenoid cystic carcinoma is always considered high grade). In the series described by the Sloan Kettering Cancer Center (MSKCC) [9 10 22-24], 6 relatively frequent histotypes accounted for more than 95% of malignant salivary tumours. The remaining 5% of primary salivary malignancies can be considered referable to at least another 10 epithelial, and to several mesenchymal, rare histotypes. Considering the overall low incidence of salivary gland cancers, each of these histotypes is very rare and can be very difficult to diagnose for the histopathologist, whose experience in this specific field is often limited. The distribution of the various histotypes encountered in the present series shows marked differences in incidence when compared with the large MSKCC series, as well as with data reported in the literature. These differences may be of epidemiological origin but may also be related to the readings of the various histopathologists; several aspects, such as the above-mentioned difficulties in diagnosis and the unexpected prognosis of SCCs in our series, which was worse than that of adenoid cystic carcinomas, have led us to hypothesize that the subjectivity of the Histopathological examinations played a fundamental role. For this reason, following the foundation of the "Multidisciplinary Head and Neck Tumor Board", in our Institution, in 2005, we began to submit all our samples (of salivary glands, as well as of the other sites in the head and neck) to the same histopathologist, who is interested in the pathological condition under study, and moreover, being involved in our group, is rapidly gaining experience. A correct histopathological diagnosis is fundamental, and is often the limiting factor in clinical practice, both as far as concerns the best management and for the evaluation of the results of treatment.

The parotid is the only salivary gland with intra-parenchymal lymph nodes (5 to 7) that can collect metastatic cells; these nodes within the substance of the gland are not easily palpated and become visible only when they are enlarged. Distinguishing them from primary parotid gland tumours by means of palpation or by imaging can be difficult. Masses with an aggressive growth can, therefore, be secondary, most frequently due to nodal metastases from cutaneous squamous cell carcinomas (SCC) and melanomas [25], or related to haematologic malignancies and, in particular, to lymphomas. Lymphomas of the parotid, arising from diffuse lymphatic tissue within the gland (extra-nodal lymphomas), have also been described, especially in Sjögren disease [26]. All these non-salivary malignancies often undergo surgical primary treatment as if they were primarily salivary, since it may be impossible to define a diagnosis before the histological report on the surgical sample when the clinical history is not clear. An adequate anamnesis is, therefore, fundamental in at least suspecting that a parotid mass is secondary. Albeit, before surgery, it is mandatory for the surgeon to assess the risk of malignancy, because it affects prognosis and, most of all the attitude towards the facial nerve, the sacrifice of which may be necessary in solid malignant neoplasms. A suspicion of malignancy, therefore, changes the informed consent, avoiding the legal controversies related to the so-called histological surprises. In our opinion, histological surprises should be extremely rare: malignancy can almost always be at least suspected, we experienced only 4 (about 6%) histological surprises, with no suspicion of malignancy before the operation, in 2 of these cases the surprise was intra-operative, with difficulties arising in dissecting the nerve (which was anyways preserved). Avoiding surprises is achieved by adequate anamnesis, physical examination, imaging and FNAB. With the exception of surgical exploration, physical examination remains the most important tool for the experienced diagnostician: a hard mass with fixation is likely to be malignant; NCCN guidelines for the management of head and neck cancer suggest some suspicion criteria such as a mass > 4 cm, or arising from the deep lobe [8]. The origin in the deep lobe is probably actually a suspicion criterion for malignancy, the frequency of deep lobe masses, in the series presented herewith, is definitely higher in malignant (35%) lesions than in benign masses (about 10%), as confirmed also by another recent study [21]. At the first clinical observation of a parotid mass, symptoms and signs such as compromise in nerve function (10-20% of malignant parotid tumours) and/or facial pain (10-15%) greatly increase concern regarding malignancy [22 27]. In our series, facial deficit was practically as frequent as data reported in the literature (19%), while facial pain is definitely more unusual (4%). Imaging helps in defining the dimensions, the site of origin, the involvement in adjacent structures which can be difficult to evaluate by means of physical examination (such as the parapharyngeal space). The role of cytological analysis achieved through FNAB, in cases with suspected malignancy, is still debated and has already been investigated by our group [3;4]. Some Authors objected that it never modifies the clinical attitude because of its low sensitivity (relatively high rate of false negatives). This is not completely true, and, in our opinion, FNAB can often be helpful:

- when it is positive, it almost confirms the suspicion of malignancy (high specificity) and allows us not only to plan the surgical procedure and possibly a reconstructive procedure on the facial nerve, but, most of all, to obtain an adequately informed consent regarding management of the facial nerve;
- when surgery is not indicated due to the characteristics not only of the patient (poor general conditions), but also of the tumour (disseminated disease), making a diagnosis by FNAB of the parotid lesion can be important;
- if the FNAB report reveals or suggests lymphoma, the diagnostic and therapeutic path changes radically and parotidectomy may be avoided.

However, the present series, which includes only patients who underwent surgery, is not an adequate model for the evaluation of the effectiveness of FNAB, the most useful role of which is to offer the possibility to avoid surgery.
As far as concerns malignancies, as for regional lymphatic metastasis, in a large series reported from the Memorial Sloan-Kettering Cancer Center, 14% of patients presented with palpable nodal metastases. Furthermore, 24% of the patients with high-grade tumours demonstrated this finding, compared to only 2% of patients with low-grade lesions. Moreover, in the group of patients who had clinically negative neck but underwent elective neck dissections, 49% of the high-grade and 7% of the low-grade tumours were found to have histologically positive neck [22 28]. Based upon our data, the problem of neck metastasis would appear to be less crucial: in our series, we performed a prophylactic neck dissection in 13 cN0 cases with only a pN+ (7.7%) and we had no treatment failures due to regional relapse. Neck irradiation in high risk cases (as defined above and by NCCN guidelines) appears to be adequate for regional control in most salivary cancers and in non-dissected patients, when we irradiated the surgical bed, we performed prophylactic irradiation also on the neck.
Findings from various studies confirm that loco-regional control and survival tend to be better in Stage III/IV and high-grade lesions submitted to surgery and adjuvant radiotherapy than with surgery alone [29 30] and this is confirmed also by international guidelines [8]. This observation seems appopriate in particular for malignancies of the parotid deep lobe, because these are frequently surrounded by little or no glandular parenchyma; thus, even the best of surgical techniques consists primarily of tumour enucleation with a high probability of leaving *in situ* histological residual tumour tissue. Therefore, we performed radiotherapy + chemotherapy in those cases of intermediate, high grade or adenoid cystic tumours, with close or positive margins, neural/perineural invasion, lymph node metastases, lymphatic/vascular invasion, Stage IV disease, deep lobe salivary malignancies.
Disease-specific survival decreases for many years, especially in patients with adenoid cystic carcinoma and malignant mixed tumour, because of distant metastases, which have been reported in approximately 20% of parotid malignancies, mainly high grade, and are predictive of poor prognosis [22]. In particular, 40% of patients with adenoid cystic carcinoma and 26-32% with malignant mixed tumours demonstrated this feature [9 10]. In all these lesions, the site of distant metastases is most often the lung(s). In our series, lung metastases occurred in 10% of patients with malignancies arising from salivary tissue, and distant metastases is a cause of failure as frequent as local recurrence. Nevertheless, distant metastases may not always represent a terminal event and, therefore, do not necessarily preclude the treatment of primary disease, especially in adenoid cystic carcinoma. In our series, 3 patients are still alive with their metastases *in situ,* one of them, with adenoid cystic carcinoma, is alive 2 years after the diagnosis of pulmonary relapse. It is worthwhile pointing out that in the present series none of the patients had a diagnosed distant metastases when parotidectomy was performed.
Overall, the prognosis for parotid gland cancer is better than that for the submandibular gland lesions: 50-81% 5-year survival is reported for the former and 30-50% for the latter [22]. In the present series, 5-year overall survival and 5-year disease-specific survival were, respectively, 72% and 89% in patients with primary salivary cancers of the parotid. Several previous investigations showed that advanced stage, higher histological grade, and sub-mandibular location were prognostic for poorer outcome and, moreover, differences in histological features were reported to affect the natural history [9 14 23 31-34]. In our series, grading was not always assessed by histopathologists and histotype was not demonstrated to significantly affect prognosis, probably also on account of all the above-mentioned difficulties of histopathological diagnosis and the lack, in the years under examination, of a dedicated histopathologist in our Institution. VIIth nerve involvement and positive/close margins in the histological sample are the only clinical parameters, at diagnosis, associated with significant differences in survival in our series. In particular, VIIth nerve clinical involvement, at diagnosis, is the most significant prognostic marker (Fig. 4, $p = 0.006$ at Log-Rank) in agreement with most of the data in the literature [35 36].
The significance of positive/close margins might suggest extending the indications for nerve sacrifice, because the attempt to preserve the nerve sometimes leads the surgeon to leave microscopic (or even macroscopic) disease behind. Nevertheless, such a "destructive" attitude with liberal resection of the facial nerve (and of other important structures) no longer dominates surgical philosophy. Instead, the surgeon's reliance upon post-operative radiation therapy to manage histological disease and the likelihood of distant metastases make many surgeons reluctant to sacrifice a functioning facial nerve also in the event of a clear malignancy which is difficult to dissect. If we analyze our results more in-depth, we come to share this form of surgical minimalism which has been gaining consent over the last few years. In fact, facial nerve sacrifice, in our series, is associated with a less favourable survival, even if not of statistical significance, because the most significant prognostic parameter in our series, the clinical involvement on VIIth nerve, always required resection of this structure, which clearly did not help in improving prognosis.
At present, the worst problems in dissecting the nerve, especially in consideration of the benign histology, are encountered in multi-nodular recurrences of pleomorphic adenomas, in the present series, as in others in the literature [6 37 38]. In fact, the incidence of permanent facial dysfunction is markedly higher in in cases of recurrence

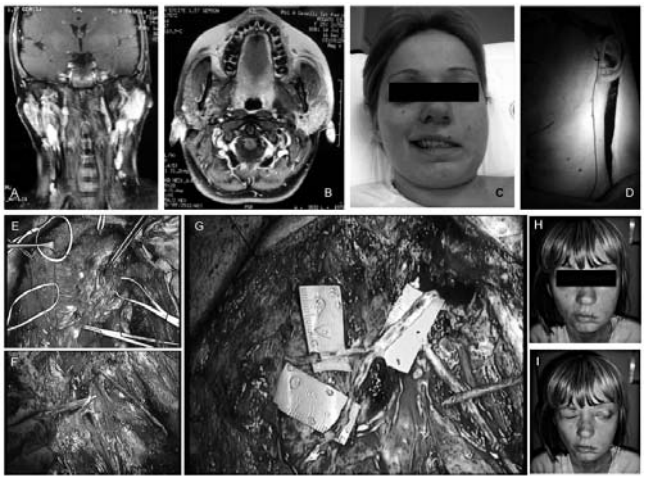

**Fig. 5.** A relatively small volume (A, B) malignancy (SCC) of the parotid gland in a 25-year-old female, with a marked static and dynamic facial nerve dysfunction (C) (Grade V according to the House-Brackmann classification). Total parotidectomy, was performed together with modified radical neck dissection (pT4, N2b) and reconstruction with a sural nerve interposition between the proximal and distal (buccal and ocular) stumps (D, E, F, G). The patient then underwent adjuvant radiotherapy. Functional recovery was not successful, as the residual deficit was Grade IV-V as well (H, I).

of pleomorphic adenomas (8.3%) than in cases of surgery with nerve preservation for malignancy (3.7%). In our opinion, in these cases, the best defense for the surgeon is adequate informed consent of the patients, who must be informed regarding the concrete possibility of facial palsy following an operation for a benign disease. This event is the main argument in favour of extensive surgery (at least a superficial parotidectomy) in pleomorphic adenomas. On the other hand, we do not believe in the usefulness of irradiation in these cases, as it can make subsequent surgery even more complicated, without significant data regarding the clinical effectiveness [37 39].

Most of our patients operated upon for a malignancy with positive margins had undergone total parotidectomy with nerve sacrifice, which is, therefore, not a solution for the issues of margins. In fact, when available on the histopathological report, the positive margins were found to be usually outside the parotid, due to the involvement of other structures, so probably a more aggressive attitude is warranted on extra-glandular structures, possibly resorting more often to reconstructive techniques.

In our opinion, clinical nerve dysfunction and extra-parotid extension, often not associated with bulky tumours, in our experience (Fig. 5), are, in themselves, expression of intrinsically more aggressive tumours and can be interpreted as independent prognostic factors.

## Conclusions

Results emerging from the present study confirm many of the well-known prognostic parameters for parotid malignant neoplasms and data related to the clinical history, which is often affected by distant metastases.

Clinical involvement of the VIIth nerve and positive margins after resection are the most significant of these parameters, as they are probably the expression of an intrinsic "biological" potential for malignancy.

On the other hand, there is no evidence showing that liberal VIIth nerve sacrifice improves prognosis, thus our attitude remains to resect the nerve when it is clinically involved and when it is totally embedded in a clearly malignant neoplasm, but to, at least, attempt to dissect and preserve it in all other cases. This guidance is strengthened by the consideration that ultimate diagnosis of malignancy, and definition of histotype, always rely on final histological findings on the surgical sample (often with the help of immunohistochemistry) and that, at present, neither clinical and surgical feeling, nor frozen section, or FNAB can provide reliable and legally acceptable indications for VIIth nerve sacrifice.

At present, the worst problems concerning the nerve may be encountered in the eventual resection of recurrences of pleomorphic adenomas [6 37 38]; in these cases, adequate informed consent of the patients is mandatory.

## References


1 Spiro R, Spiro J. *Cancer of the salivary glands*. In: Meyers E, Suen J, eds. *Cancer of the head and neck.* New York: Churchill Livingstone; 1984, p. 645.

2 Zbaren P, Schar C, Hotz MA, et al. *Value of fine-needle aspiration cytology of parotid gland masses.* Laryngoscope 2001;111:1989-92.

3 Sergi B, Contucci AM, Corina L, et al. *Value of fine-needle aspiration cytology of parotid gland masses.* Laryngoscope 2004;114:789.

4 Contucci AM, Corina L, Sergi B, et al. *Correlation between fine needle aspiration biopsy and histologic findings in parotid masses. Personal experience.* Acta Otorhinolaryngol Ital 2003;23:314-8.

5 Rea PM, McGarry G, Shaw-Dunn J. *The precision of four commonly used surgical landmarks for locating the facial nerve in anterograde parotidectomy in humans.* Ann Anat 2010;192:27-32.

6 Redaelli de Zinis LO, Piccioni M, Antonelli AR, et al. *Management and prognostic factors of recurrent pleomorphic adenoma of the parotid gland: personal experience and review of the literature.* Eur Arch Otorhinolaryngol 2008;265:447-52.

7 Heller KS, Attie JN. *Treatment of Warthin's tumor by enucleation*. Am J Surg 1988;156:294-6.

8 Forastiere AA, Ang KK, Brizel D, et al., National Comprehensive Cancer Network (NCCN). *Clinical Practice Guidelines in Oncology. Head and Neck Cancers.* Version 1.2009. 2009. Ref Type: Serial (Book, Monograph).

9 Spiro RH, Huvos AG, Strong EW. *Adenoid cystic carcinoma of salivary origin. A clinicopathologic study of 242 cases*. Am J Surg 1974;128:512-20.

10 Spiro RH, Huvos AG, Strong EW. *Malignant mixed tumor of salivary origin: a clinicopathologic study of 146 cases.* Cancer 1977;39:388-96.

[11] Shah JP, Patel KJ. *Head and Neck Surgery and Oncology*. 3rd Edition. St. Louis: Mosby Ltd.; 2003.

[12] Spiro RH. *Salivary neoplasms: overview of a 35-year experience with 2,807 patients*. Head Neck Surg 1986;8:177-84.

[13] Katz AD, Preston-Martin S. *Salivary gland tumors and previous radiotherapy to the head or neck. Report of a clinical series.* Am J Surg 1984;147:345-8.

[14] Hollander L, Cunningham MP. *Management of cancer of the parotid gland.* Surg Clin North Am 1973;53:113-9.

[15] Spector JG, Sessions DG, Haughey BH, et al. *Delayed regional metastases, distant metastases, and second primary malignancies in squamous cell carcinomas of the larynx and hypopharynx.* Laryngoscope 2001;111:1079-87.

[16] Narayana A, Vaughan AT, Fisher SG, et al. *Second primary tumors in laryngeal cancer: results of long-term follow-up.* Int J Radiat Oncol Biol Phys 1998;42:557-62.

[17] Franchin G, Minatel E, Gobitti C, et al. *Radiotherapy for patients with early-stage glottic carcinoma: univariate and multivariate analyses in a group of consecutive, unselected patients.* Cancer 2003;98:765-72.

[18] Almadori G, Bussu F, Cadoni G, et al. *Multistep laryngeal carcinogenesis helps our understanding of the field cancerisation phenomenon: a review.* Eur J Cancer 2004;40:2383-8.

[19] Jemal A, Siegel R, Ward E, et al. *Cancer statistics, 2007.* CA Cancer J Clin 2007;57:43-66.

[20] Aird I, Bentall HH, Roberts JA. *A relationship between cancer of stomach and the ABO blood groups.* Br Med J 1953;1:799-801.

[21] Lin CC, Tsai MH, Huang CC, et al. *Parotid tumors: a 10-year experience.* Am J Otolaryngol 2008;29:94-100.

[22] Spiro RH, Huvos AG, Strong EW. *Cancer of the parotid gland. A clinicopathologic study of 288 primary cases*. Am J Surg 1975;130:452-9.

[23] Spiro RH, Huvos AG, Berk R, et al. *Mucoepidermoid carcinoma of salivary gland origin. A clinicopathologic study of 367 cases*. Am J Surg 1978;136:461-8.

[24] Spiro RH, Huvos AG, Strong EW. *Acinic cell carcinoma of salivary origin. A clinicopathologic study of 67 cases.* Cancer 1978;41:924-35.

[25] Cassisi NJ, Dickerson DR, Million RR. *Squamous cell carcinoma of the skin metastatic to parotid nodes.* Arch Otolaryngol 1978;104:336-9.

[26] Hyjek E, Smith WJ, Isaacson PG. *Primary B-cell lymphoma of salivary glands and its relationship to myoepithelial sialadenitis*. Hum Pathol 1988;19:766-76.

[27] Frankenthaler RA, Luna MA, Lee SS, et al. *Prognostic variables in parotid gland cancer.* Arch Otolaryngol Head Neck Surg 1991;117:1251-6.

[28] Armstrong JG, Harrison LB, Thaler HT, et al. *The indications for elective treatment of the neck in cancer of the major salivary glands*. Cancer 1992;69:615-9.

[29] Armstrong JG, Harrison LB, Spiro RH, et al. *Malignant tumors of major salivary gland origin. A matched-pair analysis of the role of combined surgery and postoperative radiotherapy.* Arch Otolaryngol Head Neck Surg 1990;116:290-3.

[30] Malata CM, Camilleri IG, McLean NR, et al. *Malignant tumours of the parotid gland: a 12-year review.* Br J Plast Surg 1997;50:600-8.

[31] Spiro RH, Huvos AG, Strong EW. *Adenocarcinoma of salivary origin. Clinicopathologic study of 204 patients.* Am J Surg 1982;144:423-31.

[32] Borthne A, Kjellevold K, Kaalhus O, et al. *Salivary gland malignant neoplasms: treatment and prognosis.* Int J Radiat Oncol Biol Phys 1986;12:747-54.

[33] Matsuba HM, Simpson JR, Mauney M, et al. *Adenoid cystic salivary gland carcinoma: a clinicopathologic correlation*. Head Neck Surg 1986;8:200-4.

[34] Lima RA, Tavares MR, Dias FL, et al. *Clinical prognostic factors in malignant parotid gland tumors.* Otolaryngol Head Neck Surg 2005;133:702-8.

[35] Jouzdani E, Yachouh J, Costes V, et al. *Prognostic value of a three-grade classification in primary epithelial parotid carcinoma: result of a histological review from a 20-year experience of total parotidectomy with neck dissection in a single institution.* Eur J Cancer 2010;46:323-31.

[36] Cederblad L, Johansson S, Enblad G, et al. *Cancer of the parotid gland; long-term follow-up. A single centre experience on recurrence and survival.* Acta Oncol 2009;48:549-55.

[37] Yugueros P, Goellner JR, Petty PM, et al. *Treating recurrence of parotid benign pleomorphic adenomas*. Ann Plast Surg 1998;40:573-6.

[38] Valentini V, Fabiani F, Perugini M, et al. *Surgical techniques in the treatment of pleomorphic adenoma of the parotid gland: our experience and review of literature*. J Craniofac Surg 2001;12:565-8.

[39] Barton J, Slevin NJ, Gleave EN. *Radiotherapy for pleomorphic adenoma of the parotid gland.* Int J Radiat Oncol Biol Phys 1992;22:925-8.


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