Parotid carcinoma: Current diagnostic workup and treatment

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Received: 10 December 2009
Accepted: 30 April 2010
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Oncology 2010

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Abstract

In this review we present recent progress in diagnostic workup, prognostic evaluation, treatment options and resulting outcomes. Whenever possible, complete resection remains the mainstay of treatment. Sacrifice of facial nerve branches is reserved for the clinically or electromyographically dysfunctioning facial nerve. Clinical or radiological neck disease demands combined surgery and radiotherapy. Treatment of the N0 neck is indicated for advanced stage-high grade tumors but the question remains unanswered whether this should be surgical or radiotherapeutic elective treatment. Surgery alone will cure low stage, low grade tumors, that show no additional negative prognostic factors following adequate resection. In all other tumors postoperative radiotherapy will improve locoregional control. This approach results in good locoregional control, in a way that distant metastasis remains the typical presentation of treatment failure. In this setting, the results of systemic treatment today remain limited, but a huge effort in the molecular biology field has been done to introduce targeted therapy into this domain of head and neck cancer. Disease control remains variable within the patient population. This variation can increasingly be predicted by systems that incorporate the combined information of multivariately identified and quantified prognostic factors into an individualized prognosis for the parotid carcinoma patient.

Keywords Salivary gland neoplasms · parotid-carcinoma · review · management

Introduction

Incidence rates of ‘salivary gland carcinoma’ range from 4 to 65 new patients per 10⁶ per year, with very high rates in Greenland¹ and the Canadian Arctic (135 per 10⁶).² Within salivary gland carcinoma, about 64–70% of carcinomas arise in the parotid.^{3–6} The World Standard Popu-

lation age-adjusted incidence of parotid carcinoma per 10⁶ person-years in Belgium in the period 2004–2005 was 6 for men and 4 for women, accounting for 3.9% of head and neck cancers in Belgium.⁷ In the international literature typically 1 to 3% of all head and neck carcinomas are reported to be parotid carcinomas.⁸ Chances of cure following treatment vary remarkably by prognostic indicators including patient characteristics, tumor characteris-

tics (a range of 24 malignant histotypes, specific growth characteristics, tumor stage at diagnosis), and treatment characteristics.^{9,10}

Diagnostic workup

The clinical presentation of a parotid tumor is typically an asymptomatic preauricular swelling. Proportional to the amount of parotid tissue below the facial nerve, 10 to 20 percent of tumors originate in the deep lobe. A small subgroup of these patients presents with an asymptomatic swelling of the lateral oropharyngeal wall or soft palate^{11,12} and about 1% of tumors arise in the accessory parotid tissue on the masseter muscle.^{13,14} Any parotid tumor is malignant in less than 25% but the likelihood of malignancy increases when there is pain or clinical examination indicates suspect lymph nodes in the neck, fixation to the skin or the deep structures, facial nerve dysfunction, or rapid tumor growth.^{15,16} The chance of malignancy is maximal if these signs and symptoms are jointly present.¹⁷ Pain in parotid carcinoma occurs in up to 44% of patients.¹⁸ Facial palsy, too, is alarming and, independent of the T classification of the disease, is present in 12 to 25% of patients with a malignant parotid lump.^{16,19–24} Also in a patient with ‘Bell’s palsy’, even if initial MRI (magnetic resonance imaging) is normal, the chance of parotid carcinoma still remains 6% and should remain in the differential diagnosis if the paresis is progressive or no recovery is seen in a period up to 8 months.^{25,26}

The further work-up focuses on estimating location of the tumor, extent, and chance of malignancy. These factors determine the risk to the facial nerve in view of the operative removal of the lesion, which is the first and most important step in the further management, if technically feasible and if there are no medical contraindications. An important tool is fine needle aspiration cytology (FNAC). This examination is safe (no tumor seeding) and reasonably accurate in discriminating malignant from benign lesions (accuracy 79%) in the hands of experienced cytologists. Accurate tumor typing is not to be expected, but knowing that a tumor is likely to be malignant often helps in planning the timing and extent of the surgical intervention and in counseling the patient.^{27–33} That is why we routinely use FNAC in the work-up of parotid neoplasms, preferably under ultrasound guidance, allowing in the same setting for ultrasound staging of the neck.^{34,35} If at all possible, an immediate on-site procurement and evaluation gives the highest accuracy.³⁶ A huge series of 1355 FNAC’s in malignant parotid lesions at the Institut Curie in Paris showed an 80.5% correct identification of malignancy (true positive), 4.6% suspicious lesions, 11.9% false negatives and 3% of uninterpretable samples. If FNAC points at benign dis-

ease, surgical removal of the tumor for further histopathological purposes remains mandatory.^{27,37} Incisional biopsy is only advised for large tumors infiltrating the skin.

Additional imaging is not required for mobile circumscribed tumors.^{16,38–40} Further imaging is advised when mobility is impaired. In this situation MRI is superior to CT regarding the retromandibular parotid and the area of the stylomastoid foramen, where facial nerve invasion and perineural extension should be evaluated.^{26,35,38,39} Conventional MRI is not more accurate than FNAC in determining the benign or malignant nature of a parotid swelling but diffusion weighted MRI (DW-MRI) is investigated and seems to improve the preoperative identification of malignant tumors in tumors with a specific washout pattern.^{41,42} Positron emission tomography (PET) with or without CT is mainly useful in estimating the presence of distant disease in clinically and radiologically strongly suspected or FNAC proven malignancy.^{43–48} For differentiation between benign and malignant disease, the false positive rate of PET is too high, with also Warthin’s tumors and pleomorphic adenomas showing increased uptake.^{49,50}

The combined information of clinical investigation and imaging then helps to summarize local extent, regional and distant metastasis, using the TNM-classification.^{51,52} This anatomical extent is an important determinant of treatment planning, together with other clinical and histopathological patient and tumor features. In this setting the TNM-classification has a diagnostic role in facilitating comparison of treatment results among patients with the same anatomical tumor extent. A difficulty here is that over the years the definition of T classification levels has changed, complicating comparison of older with newer studies. The older analyses used the 1987 UICC/1988 AJCC classification that remained unchanged in the 1992 edition, where T classification consists of tumor size (T1–T4) and an *a–b* suffix indicating local extension.⁵³ This suffix system proved difficult to work with and disappeared in the 1997 revision.⁵⁴ In the latter local extension and facial nerve palsy upstage the T classification, regardless of size, based on information from multivariate analyses one wanted to incorporate. The current classification dates from 2002 and here the definition changed to include an unresectable category T4a, conform to the other head and neck sites. A new TNM classification is expected in 2010.

Anatomical extent as summarized in the TNM components also proved to have an independent prognostic role in multivariate analyses.^{8,22,55–59} For this purpose TNM-constellations with a comparable prognosis are grouped together in a stage group. The stage grouping guidelines are empirical and need validation like any other prognostic system.⁶⁰ Following a validation attempt the Japanese Joint Committee on Cancer questioned the adequacy of

the 1997 stage grouping system upon observing that in 1074 parotid carcinoma patients only 9 were assigned to the stage III subgroup.⁶¹ With one subgroup virtually empty this system is evidently poorly balanced.³⁷

Treatment of the primary

Type and extent of primary parotid surgery are determined by the size of the lesion, the position in relation to the facial nerve and the surrounding structures involved. Most superficial lobe tumors with normal preoperative facial nerve function will be adequately removed by a standard superficial parotidectomy. More extended surgery is needed in tumors with deep lobe or facial nerve involvement. Some authors advocate a total conservative parotidectomy in every case of malignancy, because of the finding of occult metastatic disease in the lymph nodes in the deep parotid lobe in a significant number of patients.^{62,63} Until this is prospectively evaluated in a randomized way, clinical experience to date shows very little local recurrence in tumors that are well localized in the superficial lobe and that are adequately removed remaining superficial to the nerve, so probably postoperative radiotherapy – as indicated by parameters resulting from definitive histology – will also adequately control eventual microscopic disease in the deep lobe lymph nodes.

Facial nerve branches or the main trunk are only sacrificed when preoperatively paralyzed or peroperatively adherent to or surrounded by tumor. A more sensitive tool than clinical examination is electromyography (EMG) and in suspected malignant tumors this tool should be considered to help in counseling the patient.⁶⁴ Most preoperatively intact nerves can be dissected macroscopically free from the tumor. The risk of leaving microscopical disease behind is accounted for by postoperative radiotherapy.^{24,37,57,65,66} Nerve sacrifice in these instances induces a disproportionate morbidity at the expense of very little gain in tumor control.²⁰ This point of view is underscored by the observation by Charabi et al that radical parotidectomy fails to improve survival compared to conservative nerve management in patients with residual microscopic disease.⁶⁷ When nerve resection is needed the margins should be checked with frozen section and skip metastasis should be suspected. Immediate nerve repair provides the best cosmetic and functional results. The greater auricular is an ideal donor nerve, combining easy access, good diameter and adequate arborization.^{68,69} For longer defects the greater auricular can be backtraced and part of the cervical sensory plexus can be included. The sural nerve can also be used.⁶⁴ A reachable objective seems the House Brackman grade II and III (light to obvious paresis with synkinesis but possible eye closure).^{70,71} Although EMG signs of reinnervation

start to appear after 4.5 months and first objective movements can be observed from 6 months on, a two year-period is needed to reach this final result.^{64,68,69} Negative prognostic factors in this respect are presence and duration of preoperative facial nerve dysfunction and advanced age (> 60 year).⁷¹ Radiotherapy does not impair facial nerve recovery following cable grafting. Brown et al. illustrate this in a cohort of 52 patients and show a House-Brackmann grade III or IV in 69% of irradiated patients versus in 78% of non-irradiated patients, a non-significant difference ($P = 0.54$), nicely replicating previous experimental findings of 80% axon recovery in both irradiated and non-irradiated facial nerves.^{69,72}

Treatment of the neck

Clinical or radiological detection of locoregional metastasis at presentation occurs in 15–29% of patients.^{18,55,73} When present, mainly levels II, III and IV are involved.⁷⁴ In these patients the consensus is that a (modified) radical neck dissection, removing levels I to V, is indicated, with radicality towards the accessory nerve, jugular vein or sternocleidomastoid muscle dictated by proximity and/or involvement with the lymph node metastasis.⁷⁵ For pN+ patients, postoperative radiotherapy of the parotid area and the ipsilateral neck increases locoregional control by a factor 2, and also improves survival.^{59,75–79}

The majority of patients present with a cN0 neck. In these patients elective neck surgery is considered in the presence of risk factors for occult neck disease, but elective radiotherapy seems a good alternative.⁷⁸ We routinely inspect and perform frozen section of the subdiaphragmatic lymph nodes and perform a comprehensive neck dissection in case of regional metastasis in the frozen section material.^{55,80,81} The risk factors for occult neck disease are large primary tumor size (> 4 cm) and histology with clinical high grade behavior and these imply a 20% and 49% risk for occult nodal metastasis respectively,^{74,78,82} and so do advanced age (> 54 year), perilymphatic spread and extraparotid extension. The combination of these three factors corresponds to a 95% risk.⁸² These high risk patients are candidates for elective neck treatment, be it elective neck dissection or elective radiotherapy to the neck.

Kelley and Spiro advocate elective neck dissection (including level III and IV, as level II can be skipped in patients with disease in III and IV), especially if removal of the primary is facilitated by surgical management of the neck.⁷⁸ Some European authors advocate a routine elective neck dissection for patients with parotid carcinoma. Zbären et al. find a 22% occult rate using this strategy and finds a better locoregional control when comparing to patients that are merely observed.^{83,84} Stenert et al. report even a 45% occult rate in their series

where all the patients underwent neck dissection.⁶³ Using Armstrong's⁷⁴ criteria to perform elective neck dissection, Magnano et al. found a 22% occult disease rate in N0 patients undergoing elective neck dissection.⁸⁵ Brazilian researchers found a 37% risk of occult metastasis to be predicted by histology (adenocarcinoma, undifferentiated carcinoma, high-grade mucoepidermoid carcinoma (MEC), salivary duct carcinoma (SDC) and squamous cell carcinoma, together presenting 68% occult rate), T classification and severe desmoplasia.⁸⁶ In our experience, the surgical approach to the N0 neck can be optimized using preoperative USgFNAC of the neck and peroperative frozen section.³⁷

Frankenthaler et al promote elective radiotherapy to the N0 neck in these high risk patients.⁸² This approach, relying on definitive histopathology of the resected primary, is generally well accepted. This is understandable because the indications for elective neck treatment largely concur with the indications for postoperative radiotherapy to the primary, and also because pre- and peroperative adequate typing of salivary tumour is very difficult (accuracy 51–62%⁸⁷), so not all information needed to preoperatively classify a tumor as high risk is available at the moment the decision has to be made.^{38,75,87–89} Furthermore, radiotherapy still will have to be added if a cN0 neck turns out to be pN+, and radiotherapy is effective in controlling microscopic disease.⁷⁹ The definitive answer whether an elective neck dissection (followed by radiotherapy if indicated) provides a better treatment result than elective radiation to the cN0 neck in high risk parotid cancer patients can only be given by a prospective randomized trial which so far has not been performed.⁸⁶

Histopathological typing and grading

Resection of the primary allows for accurate typing, grading, and description of negative prognostic features such as perineural growth, vascular and perilymphatic growth, and involved margins. Furthermore, molecular biological studies are increasingly performed. The mainstay for typing is the 2005 WHO classification (Table 1), featuring 24 different phenotypes.⁹

In the clinic it often proves difficult to locate these different types on the scale of biological aggressiveness, as nicely commented by Leivo.¹⁰ In population based studies, the majority of tumors are acinic cell carcinoma (AcCC) 15–17%, adenoid cystic carcinoma (AdCC) 16–27%, and mucoepidermoid carcinoma (MEC) 14.5–19.2%.^{73,90}

Practically, the different histotypes are attributed to a clinically low grade group, a clinically high grade group, and a group with an intermediate grade of malignancy. Typically the low grade group consists of AcCC, polymorphous low grade adenocarcinoma (PLGA), and low-

grade MEC, the high grade group of high-grade MEC, salivary duct carcinoma (SDC), carcinoma ex pleomorphic adenoma, adenocarcinoma NOS and undifferentiated carcinoma, and the intermediate group containing AdCC and epithelial myoepithelial carcinoma. The latter two are often attributed to the high grade group when one chooses to work with only two groups; AdCC because it is a very hard to cure disease with often a protracted clinical course, and epithelial myoepithelial carcinoma is linked to a recurrence rate of 40% and a disease specific survival of only 60%.^{91–94}

The link of 'grade' to clinical behavior is sometimes not so clear: some allegedly low grade histotypes show aggressive subgroups. A high-grade subgroup of AcCC definitely has a poorer prognosis.^{95,96} Conversely, in the highly aggressive SDC a low-grade variant of microscopically typical SDC is suggested.^{97,98}

Histopathological light microscopical grading is an effort to explain variable biologic behavior within one histotype. This grading suffers from lack of uniformity and insufficient independent prognostic power. Different grading criteria are used in different centers, and even when experienced pathologists use the same set of grading criteria significant disparity remains.^{20,99,100} In multivariate analysis, multiple collinearities (stage-grade^{101,102}/age-grade/irradiation-grade/perineural growth-grade^{55,103}) often make grading a less essential piece of information in clinical decision making than its coinciding factors that are more reliably reproducible. A grading effort is done

Table 1. The WHO 2005 histologic classification of malignant salivary gland tumors⁹

1. Acinic cell carcinoma
2. Mucoepidermoid carcinoma
3. Adenoid cystic carcinoma
4. Polymorphous low-grade adenocarcinoma
5. Epithelial myoepithelial carcinoma
6. Clear cell carcinoma, Not Otherwise Specified (NOS)
7. Basal cell adenocarcinoma
8. Sebaceous carcinoma
9. Sebaceous lymphadenocarcinoma
10. Cystadenocarcinoma
11. Low grade cribriform cystadenocarcinoma
12. Mucinous adenocarcinoma
13. Oncocytic carcinoma
14. Salivary duct carcinoma
15. Adenocarcinoma NOS
16. Myoepithelial carcinoma
17. Carcinoma in pleomorphic adenoma
18. Carcinosarcoma
19. Metastasizing pleomorphic adenoma
21. Small cell carcinoma
22. Large cell carcinoma
23. Lymphoepithelial carcinoma
24. Sialoblastoma

in the three most frequent types: MEC^{99–101,104–108}, AcCC^{109,110} and AdCC.^{102,111–113}

In our center treatment implications only follow grading of MEC into low grade versus intermediate and high grade types, low grade low stage and completely resected MEC requiring no additional radiotherapy.³⁸ The aggressive ‘high grade’ subset of AcCC (16.5% of 438 graded tumors out of a total of 1353 AcCC) patients should receive postoperative radiotherapy.^{95,110,114}

Molecular biology advances

Identifying molecular biological markers of clinically aggressive or high grade behavior might prove more reliable than light microscopical grading. A lot of work has been done on identification and quantification of proliferation markers, markers of the endpoint of the cascade of cumulative genetic and epigenetic alterations leading to deranged growth. Independent of the exact cascade that has occurred, these markers reflect the number of cells going through the cell cycle towards division and thus constitute a cell cycle based proliferation index. Typical markers that have entered clinical pathological analysis are Ki-67 (MIB-1 antibody against this nuclear antigen found in proliferating cells),^{101,115,116} Proliferating cell nuclear antigen (PCNA – an essential co-factor of DNA polymerase delta – present during S-phase),^{99,117,118} hTERT (subunit of telomerase),¹¹⁹ TUNEL (identification of DNA breaks in apoptotic cells),¹²⁰ and AgNOR (argyrophilic proteins specific for cell cycle). The role of these markers has been described in AdCC, AcCC, MEC and SDC.^{10,121} In several studies these proliferation markers correlate with optical grading and outcome and remain independently important in multivariate models including classical clinical and pathological factors, proving their added value.^{99,101,115–118,122} The advantage of these endpoint markers or overall proliferation indices is that they are not too expensive, widely applicable and correlate well with prognosis.

Many groups also studied the different elements of the cascade that finally leads to deranged growth, at every step describing ‘Yet Another Prognostic Indicator’ – the so-called YAPI phenomenon. The first class of markers are growth factor receptor proteins and their ligands. This category contains KIT (targeted by imatinib and axinitib),^{123–128} angiogenesis related growth factor receptors (VEGF, VEGF-R, PDGF and bFGF – targeted by axinitib),^{129–131} human epidermal growth factor receptors (EGFR aka HER-1 or ErbB-1 and its ligands Amphiregulin and TGF- α – targeted by antibodies such as cetuximab and lowmolecular weight tyrosine kinase inhibitors such as gefinitib),¹³² HER-2 or ErbB-2 – targeted by antibodies such as trastuzumab and lowmolecular weight tyrosine kinase inhibitors such as lapatinib,^{122,132–136} HER-3 or ErbB-3; HER-4 or ErbB-

4)^{137–141} and Insulin-like growth factor IGF-1R.^{142–144} The second class of markers are cell cycle oncogenes that are activated by the above mentioned growth factor- growth factor receptor interaction. These are SOX-4, NF κ B, K-ras, PI3K/Akt, Src, STAT3, mTOR, c-myc, and are less well studied in salivary gland cancer.^{121,145} A specific oncogene studied in salivary gland tumorigenesis is activated by a translocation resulting in β catenin promoter swapping and is called Pleomorphic Adenoma Gene 1–PLAG1.^{146–151} Another fusion oncogene is the mucoepidermoid carcinoma translocated 1 gene with exons 2–5 of the Mastermind-like gene MECT1–MAML2 (translocation t(11;19) (q21;p13)), the fusion protein typically indicating low-grade mucoepidermoid carcinoma.^{10,152–157} The third class of markers are proteins involved in DNA damage repair and well studied are p53 and ERCC1 (excision repair crosscomplementation group 1).¹⁵⁸ A fourth group are proteins involved in apoptosis, the Bcl-2 group containing pro-apoptotic proteins such as Bax, Bad and Bak and anti-apoptotic proteins such as Bcl-2, BclxL and Survivin. A fifth group of proteins are those involved in cell-cell adhesion (hemidesmosome proteins B180 and B230, E-cadherin, α -catenin),^{159–161} migration (matrix metalloprotease, heparanase)^{10,162} and epithelial-mesenchymal transition (NBS-1 and snail).¹²¹ The last group of markers consists of estrogen, progesterone and androgen receptors.^{121,141}

Finally, a cDNA microarray can help us give a quick, tumor specific overview of all these overexpressed oncogenes and underexpressed tumor suppressor genes, and as such can be used as a prognostic blueprint of a tumor.¹⁶³ This is established and helps in deciding treatment for other tumors such as breast cancer, but to date still remains to be fully elaborated for salivary gland cancers. For all these individual markers, but also for the high throughput blueprints, the general truth holds that prognostic value can only be attributed to those standing firm in multivariate analysis that includes the classical clinical and pathological factors.

Postoperative radiotherapy

Postoperative radiotherapy to the primary classically consisted of conformal wedged-pair beams to a dose of 60 Gy^{38,59,79} but – like in other head and neck sites – increasingly 3-dimensional (3D) conformal radiotherapy and lately intensity modulated radiotherapy (IMRT) is becoming the standard.^{164,165} The need for radiotherapy following surgery is determined by stage and adverse prognostic factors (close or positive margins, perineural and vascular invasion) in the histopathologic report. Current policy recommends this treatment in most high grade and stage III and IV lesions. Lacking randomized trials, we rely on retrospective reports demonstrating improved locoregional control, in spite of negative bias in selecting patients for combined therapy.^{56,79,165–169} In a large dataset

of the Dutch Head and Neck Oncology Cooperative Group, relative risk (RR) for local recurrence in surgery only patients was 9.7 times the risk of patients receiving combined surgery and radiotherapy, the RR for regional recurrence was 2.3 higher in surgery only patients. An older but methodologically very good study is the matched pair analysis of parotid and submandibular carcinomas by Armstrong et al. They found a significant difference in DSS and local control in patients with AJCC stage III and IV and in patients with nodal disease.⁷⁶ For low stage lesions postoperative radiotherapy can only be omitted in AcCC and low grade MEC if resection is complete and no other adverse pathological factors are present (close surgical margins, perineural or perilymphatic invasion, or recurrent disease).^{37,55} Similarly to the observations in high-risk head and neck squamous cell carcinoma, for high-risk salivary gland carcinomas a first report indicating the usefulness of using a platinum-based concomitant chemoradiation scheme has been recently published, and indicates a likely evolution in the management.¹⁷⁰

Radiotherapy and chemotherapy in unresectable disease

In unresectable salivary gland cancer or resectable cancer in medically unfit patients, conventional photon radiotherapy achieves local control in 17–57% at 10 years follow-up, the higher percentages found in series dealing with mainly early stage disease.^{171,172} A reduced oxygen enhancement factor, decreased repair of sublethal cell damage, and less variability of sensitivity through the cell cycle implies that neutron radiotherapy improves 5 year local control to up to 75% in unresectable disease, especially for unresectable AdCC.^{171,173–176} There is, however, no clear survival benefit due to unaffected distant metastasis (incidence in 40% of these patients after a median follow-up of 51 months) and there are more severe late side effects, including cervical myelopathy, sensorineural hearing loss, and necrosis of the soft tissues, the mandibular and temporal bone and the temporal brain lobe.

In this setting, the benefit of chemotherapy remains palliative. A temporary complete remission in one in five patients seems the best achievable at the moment.^{177–181} In metastatic adenocarcinoma NOS, high response rates are observed with cisplatin, doxorubicin and cyclophosphamide. However, these responses are generally short-lived (Debaere et al., submitted for publication). Of explored targeted therapies so far, none has been shown to improve the result in this patient group, but a lot of effort continues to go in this direction.^{121,123–130,137–145}

Outcomes and prognosis

Treatment results in major treatment centers are displayed in Table 2. These numbers have to be appreciated

in their specific context of stage, percentage high grade, treatment period and corresponding treatment regimens, patient inclusion criteria, and adequacy of follow-up. As an example, the decision to exclude palliative intent patients in the 1999 Manchester series⁶⁶, results in a group with relatively low stage at presentation (only 1 in 5 patients in stage III–IV) and DSS in the high range of the results displayed in Table 2, as opposed to the 1999 Amsterdam series where palliative patients were included, increasing the proportion of advanced stage disease (1 in 4 is stage IV disease in this series), and explaining a lower overall DSS.

Many univariate^{8,21,23,167,169,182–185} and multivariate statistical analyses^{8,22,55–57,66,185–188} have focused on prognostic factors in salivary gland carcinoma, to help locate the individual patient's expected result above or below the overall results as displayed in Table 2. Histological type^{58,58,189} and grade,¹⁹⁰ stage,^{8,22,55,57,58,86} age,^{8,57,57,58,82,190} gender,^{8,56} pain,^{8,21,55,184} skin^{55,56} and facial nerve involvement (perineural growth),^{22,55,56,58,59,184} treatment (resection margins)^{55,188,190,191} and comorbidity¹⁹² emerged as important prognostic factors for this disease.

In this research different prognostic factors are studied for their relation with different outcomes: survival, disease specific survival, recurrence (any recurrence,^{18,55,73} local recurrence,⁵⁹ neck recurrence^{59,86} and distant metastasis).^{58,59} Most frequently the relevant prognostic factors are cited separately, accompanied by a 'P-value' mirroring to so-called 'importance' of that factor. The clinician is then expected to make an intuitive amalgam of different prognostic factors present in a given patient to get an estimate of prognosis. One way to deal with the increasing prognostic information is seen in the evolution from

Table 2. Disease specific survival (DSS) following treatment of patients with parotid carcinoma.

Authors	Year of publication	DSS 5 y (%)	DSS 10 y (%)
Frankenthaler et al. ²²	1991	75	70
Kane et al. ⁸	1991	69	68
Pedersen et al. ²³	1992		52
Poulsen et al. ¹⁸⁸	1992	71	65
Renahan ⁶⁶	1999	78	65
Spiro ⁶	1986	55	47
Spiro and Wang ²²²	1993	77	65
Spiro et al. ⁵⁷	1989	63	47
Therkildsen et al. ¹⁸⁶	1998	76	72
Leverstein et al. ²⁴	1998	75	67
Vander Poorten et al. ⁵⁵	1999	59	54
Vander Poorten et al. ⁷³	2003	62	
Mendenhall et al. ²²³	2005		57
Harbo et al. ¹⁸⁵	2002	57	51
Godballe et al. ¹⁸⁴	2003	52	
Lima et al. ²²⁴	2005	72	69
Vander Poorten et al. ¹⁸	2009	69	58

Table 3. Prognostic indices PS1 (pretreatment variables) and PS2 (post-treatment variables)

PS1 = 0.024 A + 0.62 P + 0.44 T + 0.45 N + 0.63 S + 0.91 F		PS2 = 0.018 A + 0.39 T + 0.34 N + 0.70 S + 0.56 F + 0.78 PG + 0.65 PM	
Variable	Number to enter in the formula	Variable	Number to enter in the formula
A = age at diagnosis	Number in years	A = age at diagnosis	Number in years
P = Pain on presentation	1 = no pain 2 = pain or numbness	T = clinical T Classification*	<2 cm = 0, 2–4 cm = 1, 4–6 cm = 2, >6 cm = 3
T = clinical T Classification*	<2 cm = 0, 2–4 cm = 1, 4–6 cm = 2, > 6 cm = 3	N = clinical N Classification*	N0 = 0, N1 = 1, N2a = 2, N2b = 3, N2c = 4, N3 = 5
N = clinical N classification*	N0 = 0, N1 = 1, N2a = 2, N2b = 3, N2c = 4, N3 = 5	S = skin invasion	1 = no invasion, 2 = invasion
S = skin invasion	1 = no invasion, 2 = invasion	F = facial nerve dysfunction	1 = intact function, 2 = paresis-paralysis
F = facial nerve dysfunction	1 = intact function, 2 = paresis-paralysis	PG = perineural growth in the resection specimen	1 = no, 2 = yes
		PM = positive surgical Margins	1 = no, 2 = yes

*1992 TNM classification of the International Union against Cancer⁵¹

the 1992,^{53,193} to the 1997 staging¹⁹⁴ system where facial nerve involvement and evidence of local extension imply a higher T classification. We believe a better alternative is to create a prognostic index combining the multivariately important patient and tumor specific prognostic factors, each with their proper mathematical weight, into a single number that corresponds to an estimate of tumor recurrence.^{55,190} Our research group constructed such an index for the situation before (PS1) and after (PS2) primary treatment (Table 3).⁵⁵ Following completion of the formula, the resulting score places the patient in one of four prognostic groups (Figs 1a and b). This prognostic index was validated in a nationwide database and subsequently in an international database, indicating its usefulness in parotid carcinoma patients in general.^{18,73} A recent validation effort in a Brazilian population did not show the same performance of the index,¹⁹⁵ but a critical analysis of the studied population and the methods used identified several arguments reducing the strength of this observation.¹⁹⁶ Since the introduction of aspects of molecular biology in salivary gland research, the question exists what the contribution of this new information to our prognostic possibilities will be. It was nicely stated already 15 years ago by Batsakis that critical multivariate assessment together with clinical and pathological factors, as well as proper validation, are needed before acceptance of new putative prognostic factors.⁹⁹

Complications

Typical surgical complications are temporary or permanent facial palsy (in experienced hands, normal function

can be achieved in 96% of patients after superficial parotidectomy),¹⁹⁷ hemorrhage, infection, skin necrosis, Frey's syndrome and salivary fistula.¹⁹⁸ Frey's syndrome is relatively rarely encountered in parotid cancer patients, as most of them receive radiotherapy, inhibiting its development.^{199,200} Although effective, treatment of this condition with topical anticholinergics, is marked by non-compliance.^{199,201} The current treatment of choice is chemodenervation using botulinum toxin type A.^{201,202} The median effectiveness is 8–11 months and the treatment can be repeated.^{201,203–206} Interposition grafts have been proposed as preventive strategies. The sternocleidomastoid muscle flap has opponents²⁰⁷ but is considered an effective preventive means in surgery by most clinicians.^{208–210} In malignant pathology there is a drawback to its use as it complicates reintervention.²⁰⁷ The same remark holds for the SMAS (superficial musculoaponeurotic system) flap, reported to be quite effective in Frey prevention.^{211,212} Foreign material as interposition results in an unacceptable rate of complications (hematoma, seroma and salivary fistula).²¹³ Another problem is paresthesia in the greater auricular nerve (GAN) area. In the study of Patel this occurs in 57% of patients after sectioning the GAN, in 90% of patients this is not cumbersome and a rapid decrease in time is noticed, so that no impact on quality of life is reported.²¹⁴ However, recent evidence suggests that the posterior branch of the GAN can be saved in 2/3 of patients undergoing parotidectomy, at the expense of little extra surgical time, resulting in sensibility returning to normal in 80–100% of patients.^{215,216} And as stated above, the preserved GAN can be a good interposition graft in surgery for malignant disease.⁶⁸

Fig. 1a, b Kaplan–Meier recurrence free interval curves by prognostic score PS1, based on pretreatment factors (**Fig. 1a**) and by prognostic score PS2, based on post-treatment factors (**Fig. 1b**)

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Radiotherapy complications include mucositis, skin ulceration, hair loss, mandibular and temporal bone osteoradionecrosis, fibrosis, cerebral radionecrosis, hearing loss (sensorineural and conductive due to refractory external otitis) and xerostomia. These are minimized nowadays since the implementation of 3D conformal RT and IMRT.^{164,165,217–220}

Conclusions

Preoperative evaluation increasingly informs doctor and patient about the extent and the nature of resectable disease and helps tailoring the corresponding surgery,

immediately dealing with expected complications. Whenever possible, an adequate resection of obvious disease using a conservative approach to the facial nerve remains the key. The resulting histopathological information determines the need for additional radiotherapy to the primary site and the involved neck, and the need for elective neck treatment in the N0 neck. Recent literature provides doctor and patient with more precise information as to what to expect following parotid carcinoma management. Treatment failure is most frequently at distance. To tackle this, a lot of effort goes in unraveling the molecular biological mechanism of tumorigenesis, and several targeted therapies have resulted from this. To date, however, no clinical bene-

fit has arisen here. To make further progress in this difficult area, the only way to go is creating adequate, all encompassing, detailed multi-institutional databases (national head and neck task forces, European Salivary Gland Soci-

ety www.esgs.ch, Eurocare²²¹) to provide the necessary material for assessment and validation of diagnostic and prognostic approaches, and to set up multicenter treatment trials if new promising new agents appear.

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