available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

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

Elham Jouzdani [a], *Jacques Yachouh* [b], *Valérie Costes* [c], *Jean Luc Faillie* [d], *César Cartier* [a], *Flora Poizat* [c], *Guillemette Pierre* [a], *Vincent Burcia* [a], *Marc Makeieff* [a], *Louis Crampette* [a], *Bernard Guerrier* [a], *Renaud Garrel* [a,*]

[a] *Head and Neck Surgery Department, Gui de Chauliac Hospital, Montpellier University Hospital Center, France*
[b] *Maxillo Facial Surgery, Lapeyronie Hospital, Montpellier University Hospital Center, France*
[c] *Pathology Department, Gui de Chauliac Hospital, Montpellier University Hospital Center, France*
[d] *Medical Statistics Department, Arnaud de Villeneuve Hospital, Montpellier University Hospital Center, France*

ARTICLE INFO

Article history:
Received 9 September 2009
Accepted 9 October 2009

Keywords:
Parotid cancer
TNM classification
Tumour grading
Prognostic factor
Surgery

ABSTRACT

Background: The tumour grading of primary parotid cancers (PPCs) remains controversial.
Methods: A 20-year standardised single centre treatment has been assessed retrospectively. The histological review of 155 consecutively treated parotid malignancies identified 96 suitable cases for univariate and multivariate survival analyses.
Results: Treatment involved total parotidectomy, neck dissection and post-operative radiotherapy in, respectively, 91.7%, 83.3% and 70.4% of cases. The 5-year overall survival, disease-specific and recurrence-free survival rates were 79.4%, 83.5% and 70.8%, respectively. Univariate analysis confirmed the classical prognostic factors, i.e. age > 60 years, male gender, facial palsy, hardness of the tumour, clinical stage, tumour grade, facial nerve invasion and lymph node metastases. Multivariate analysis identified a three-grade classification just after the clinical stage as the most important prognostic factor.
Conclusion: This study identifies the prognostic significance of intermediate grade tumours.

1. Introduction

Parotid cancers are usually considered as rare tumours representing 6% of the reported head and neck malignancies[1] with an incidence ranging from 0.4 to 2.6/100,000 inhabitants per year in North America[2] and in Europe.[3] However, head and neck surgeons are frequently confronted with the management of such tumours in their daily practice with a rate of malignancy confirmed during parotidectomy ranging between 12% and 20%.[4,5] Hence, clear guidelines need to be kept in mind for their adequate management. As outlined by many authors, the role of initial surgery is of primary importance in their diagnosis, treatment and prognosis.[5] Although complete tumour removal followed by radiation therapy for high risk patients is the mainstay of their treatment,[6] the extent of parotid gland surgery and the role of neck dissection remain

* *Corresponding author:* Address: Head and Neck Surgery Department, Gui de Chauliac Hospital, Pole of Head and Neck Neurosciences, Montpellier University Hospital Center, France. Tel.: +33 4 67 33 68 03; fax: +33 4 67 33 67 28.
E-mail address: r-garrel@chu-montpellier.fr (R. Garrel).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.10.012

controversial.[7] Furthermore, though prognostic factors have been intensely studied, the clinical relevance of intermediate grade tumours, ignored in the classical two-grade classification remains unclear.

Taking advantage of 20 years of experience in a single institution with a constant strategy of treatment of primary parotid cancers, i.e. systematic total parotidectomy with tailored neck dissection, a retrospective study with histological review has been conducted firstly to evaluate the outcome of such treatment and secondly to identify the main prognostic factors in resectable tumours.

2. Materials and method

Among the 1466 parotidectomies performed in the Montpellier University Hospital tertiary care centre between 1986 and 2006, the files of 155 consecutive patients treated for parotid gland cancer were reviewed. A flow diagram of the patients is provided in Fig. 1.

The histopathology was retrospectively scrutinised and reclassified where necessary by the authors (VC and FP) using the 2005 WHO histological classification of salivary gland tumours.[8] Patients with intra-parotideal metastasis ($n = 36$), undifferentiated nasopharyngeal type carcinoma ($n = 4$), benignant pleomorphic adenoma ($n = 6$) and lymphoma ($n = 11$) were excluded from the study, leaving 98 patients with primary epithelial carcinoma of the parotid gland for the analyses. Tumours were staged in accordance with the 2002 UICC TNM classification[9] based on clinical findings and preoperative imaging. The histopathological review allowed an establishment of the pTNM staging and facilitated the retrieval of tumoural features such as intra-parotideal lymph node invasion (pNPar), extraparotid extension, perineural and vascular invasion. Tumours were initially classified as either of low or of high grades.[8] Subsequently in order to evaluate any prognostic significance of intermediate grade tumours, a three-group classification derived from that proposed by Therkildsen et al.[7,10] was studied (Table 1).

The institutional strategy of treatment was as follows. Parotid surgery consisted of a total parotidectomy once malignancy was established by frozen section. The facial nerve was systematically conserved unless it was macroscopically invaded. A nerve graft was performed if either a major branch or the trunk was concerned. A selective neck dissection involving at least levels II and III with frozen section was performed. A modified radical neck dissection was considered in case of positive neck nodes. In cases of proven high grade tumour, facial nerve invasion, extraparotid spread, tumour size more than 4 cm, a post-operative radiotherapy was advocated.

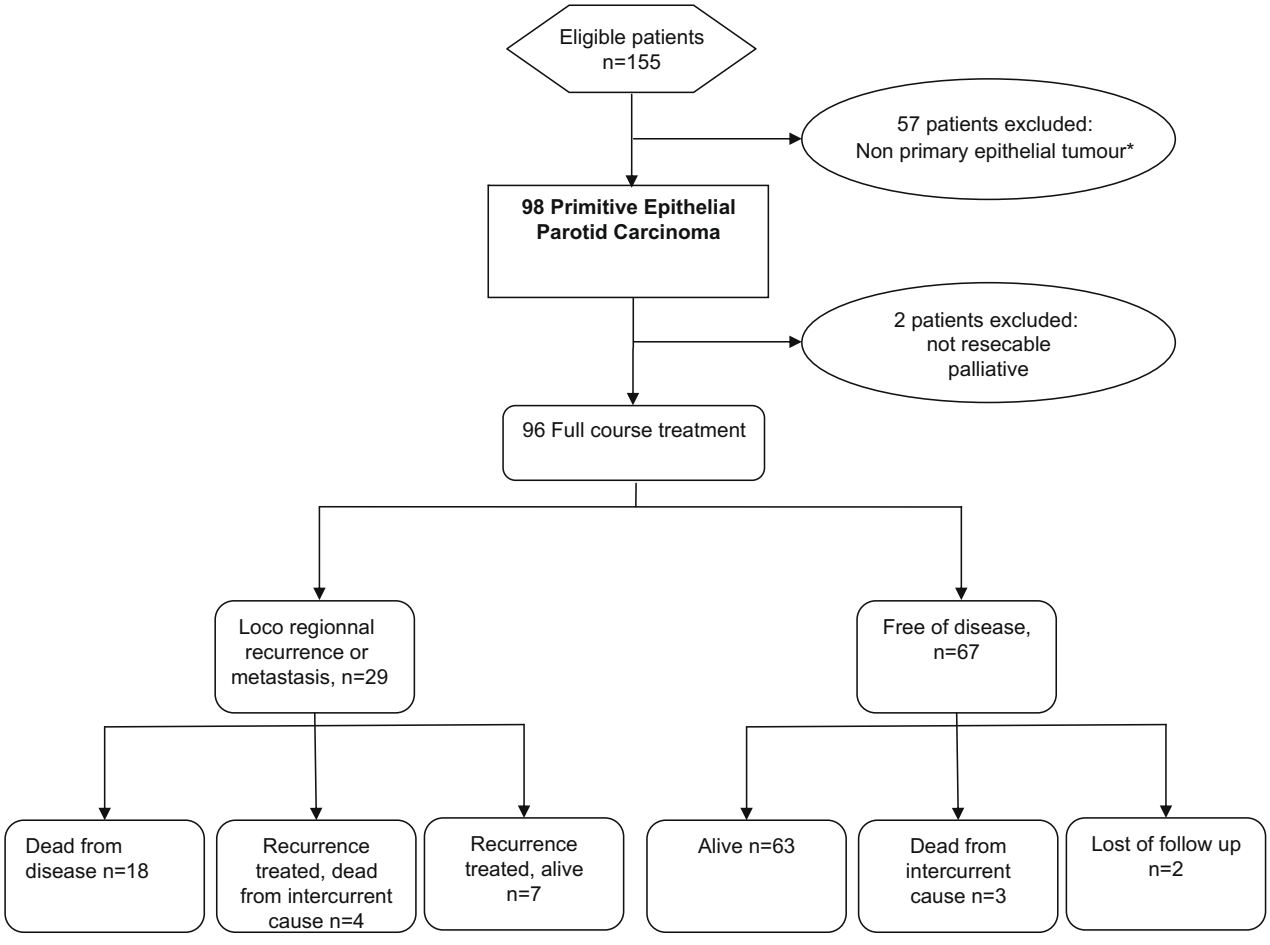

Fig. 1 – Flow diagram of the patients. *: Intraparotid metastases, lymphoma, benignant pleomorphic adenoma, undifferentiated nasopharyngeal type carcinoma.

Table 1 – Tumour types and grade repartition using two groups according to the 2005 WHO classification[9] and three groups according to Therkildsen et al.[12]. NOS: Not Otherwise Specified.

Histology	No.	Percent (%)	2 Grades	3 Grades
High grade adenocarcinoma	14	14.3	High = 61 (62.2)	High = 28 (28.6)
High grade mucoepidermoid carcinoma	11	11.2		
Adenocarcinoma NOS	3	3.1		
Cystic adenoid carcinoma	13	13.3		Intermediate = 39 (39.8)
Malignant mixed tumor	12	12.2		
Intermediate grade adenocarcinoma	8	8.2		
Intermediate grade mucoepidermoid carcinoma	6	6.2	Low = 37 (37.8)	
Low grade mucoepidermoid carcinoma	12	12.2		Low = 31 (31.6)
Acinic cell carcinoma	11	11.2		
Low grade adenocarcinoma	6	6.1		
Cystadenocarcinoma	2	2.0		
Total	98	100.0		

pN stage was established with routine analysis of lymph nodes collected during neck dissection. pNPar stage was established from the routine analysis of intraparotid lymph nodes harvested with the total parotidectomy, as proposed by Klussman et al.[11]

The main patient characteristics and follow-up data were collected from the institutional files. Patients or their family and their physicians were called by phone to gather the latest available information. Data were collected in an Excel file (Microsoft® Corporation) and then anonymised. Data were summarised by frequency and percentage for categorical variables. For continuous variables the means, the median and the range were computed. To investigate the association between categorical variables, univariate statistical analysis was performed using Pearson's χ^2 test and the Cochran–Armitage trend test. All survival times were calculated from the date of surgery. The 5-year rates for overall survival (OS, the event being death from all causes), disease-specific survival (DSS, the event being death from disease) and recurrence-free survival (RFS, the event being the first to happen: metastasis, recurrence, death related to parotid cancer) were estimated by the Kaplan–Meier method with standard deviation (SD) calculation. A comparison of two or more groups of a prognostic factor was performed with the logrank test. Independent prognostic values of factors were analysed with the Cox proportional hazard model using a stepwise selection process. Discrete variables were introduced in the model as continuous after verification of linearity assumption. The results of the Cox model analysis were reported with the relative risks (RRs) and their 95% confidence limits. In all statistical analyses, a $p < 0.05$ was considered significant. Statistical analyses were performed using SAS software V.9 (SAS Institute, Cary, NC, USA). The study was approved by the institutional board of clinical research.

3. Results

3.1. Population data

The studied group was composed of 39 men and 59 women (sex-ratio = 0.66). The mean patient age at the time of surgery was 55.7 years (range 9–86 years). At the initial examination, patients presented with a growing tumour of the parotid, reported as "hard" in 42 cases (42.9%), and "painful" in 15 cases (15.3%). There were 20 cases (20.4%) of skin invasion or inflammation. A partial or a complete facial palsy was observed in 21 cases (21.4%). Thirty-eight of 98 patients (38.8%) were classified as T1, 39 (39.8%) as T2, 10 (10.2%) as T3, 1 (1.0%) as T4a, 5 as (5.1%) T4b tumours and 5 patients were termed Tx for whom data were missing. Eleven of 98 patients (11.2%) had palpable lymph nodes that were visible on the imaging or at the initial examination (9 N1 and 2 N2b). Tumours from 82 patients (83.7%) were classified as cN0, whilst data were missing for 5 patients (Nx). The tumours from 95 of 98 patients (96.9%) were classified as M0, 2 (2.0%) as M1 and one as Mx.

Thirty-six of 98 patients (36.7%) were stage I, 34 (34.7%) were stage II, 14 (14.3%) were stage III, 4 (4.1%) were stage IVa, 3 (3.1%) were stage IVb, 2 (2.0%) were stage IVc and 5 (5.1%) were not staged because of the missing data.

3.2. Parotid surgery and histology

Among the 98 cases, two patients did not undergo a full course of treatment because they had an unresectable tumour and so only had excisional biopsy and palliative treatment. This left 96 patients for survival analyses. Only one cM1 patient with adenoid cystic carcinoma has been completely treated because of the young age of the patient (43-years-old), and the usual long survival rate of such tumour types.[12]

Eighty-eight patients were treated with a total parotidectomy (91.7%), extended in 43 cases to the skin, the temporal bone or to the muscles. A partial resection of the facial nerve was performed in 16 cases (16.7%) and a total resection in 13 cases (13.5%).

Eight patients underwent a lateral parotidectomy for a superficial lobe tumour (4 elderly or weak patients, 1 false negative frozen section, 3 for unreported reasons).

The intraoperative histology diagnosed the malignancy in 90.4% (75/83) of the cases. In 13 cases frozen section was not performed (oldest cases). The grading in two groups was concordant between FS and definitive histopathology in 84.0% (63/75) of the cases. Twelve patients were diagnosed with an adenocarcinoma without any grading at frozen section and then classified as an intermediate grade mucoepidermoid carcinoma ($n = 6$), intermediate grade adenocarcinoma ($n = 4$)

and high grade adenocarcinoma ($n = 2$) by the definitive analysis.

Tumour staging showed pT1 = 26 (27.1%), pT2 = 28 (29.2%), pT3 = 9 (9.4%), pT4a = 25 (26.0%) and pT4b = 5 (5.2%). Three patients were classified as pTx because of missing data.

A facial nerve invasion was found in 28 patients (29.2%). Such an invasion was statistically positively correlated with the grade of the tumour in two groups ($p = 0.007$, χ^2 test) and in three groups ($p < 10^{-3}$, Cochran–Armitage trend test). Perineural invasion was found in 13 cases alone and associated with facial nerve invasion in 25 cases.

3.3. *Neck surgery and nodal status*

Eighty of 96 operated patients had a neck dissection (83.3%). Eleven (13.8%) patients were initially classified with tumours as cN1 or cN2. Routine histological analyses performed on tumours from these 80 patients showed 66 (82.5%) classified as pN0, 5 (6.3%) as pN1, and 9 (11.3%) as pN2b. The total with positive neck involvement was 17.5%. The levels of involvement were II in 67.2%, III in 34.5%, IV in 18.1% and I in 4.6%. Among the 69 cN0 patients, 14 actually had cervical lymph node metastasis (pN+) or intraparotideal positive lymph nodes (pNPar+) according to the definitive histology. Therefore, there were 20.3% occult lymph node metastases.

Three patients (4.3%) had intraparotideal and cervical lymph node metastases (pNPar+/pN+). Intraparotideal metastases alone (pNPar+/pN0) were detected in 9 patients (9.4%). Cervical lymph node metastases alone (pNPar0/pN+) were detected in 2 patients (2.9%).

Lymph nodes with a capsular invasion were seen in 11 of 80 patients (13.8%). Among these, 4 were initially classified as cN0 (5.0%).

pN status was positively correlated with the grade of tumour when analysed in either two ($p = 0.01$, χ^2-test) or three groups ($p = 0.005$, Cochran–Armitage trend test).

3.4. *Pathological stage*

Tumours from 95 out of 96 patients were initially classified as pM0. One patient's tumour was classified as pM1. According to UICC staging, 19 patients (19.8%) were found to have pathological stage I disease, 21 (20.9%) p stage II, 11 (11.5%) p stage III, 24 (25%) p stage IVa, 5 (5.2%) p stage IVb and 1 (1.0%) p stage IVc. Tumours from 16 patients (16.7%) were not staged because of the missing data.

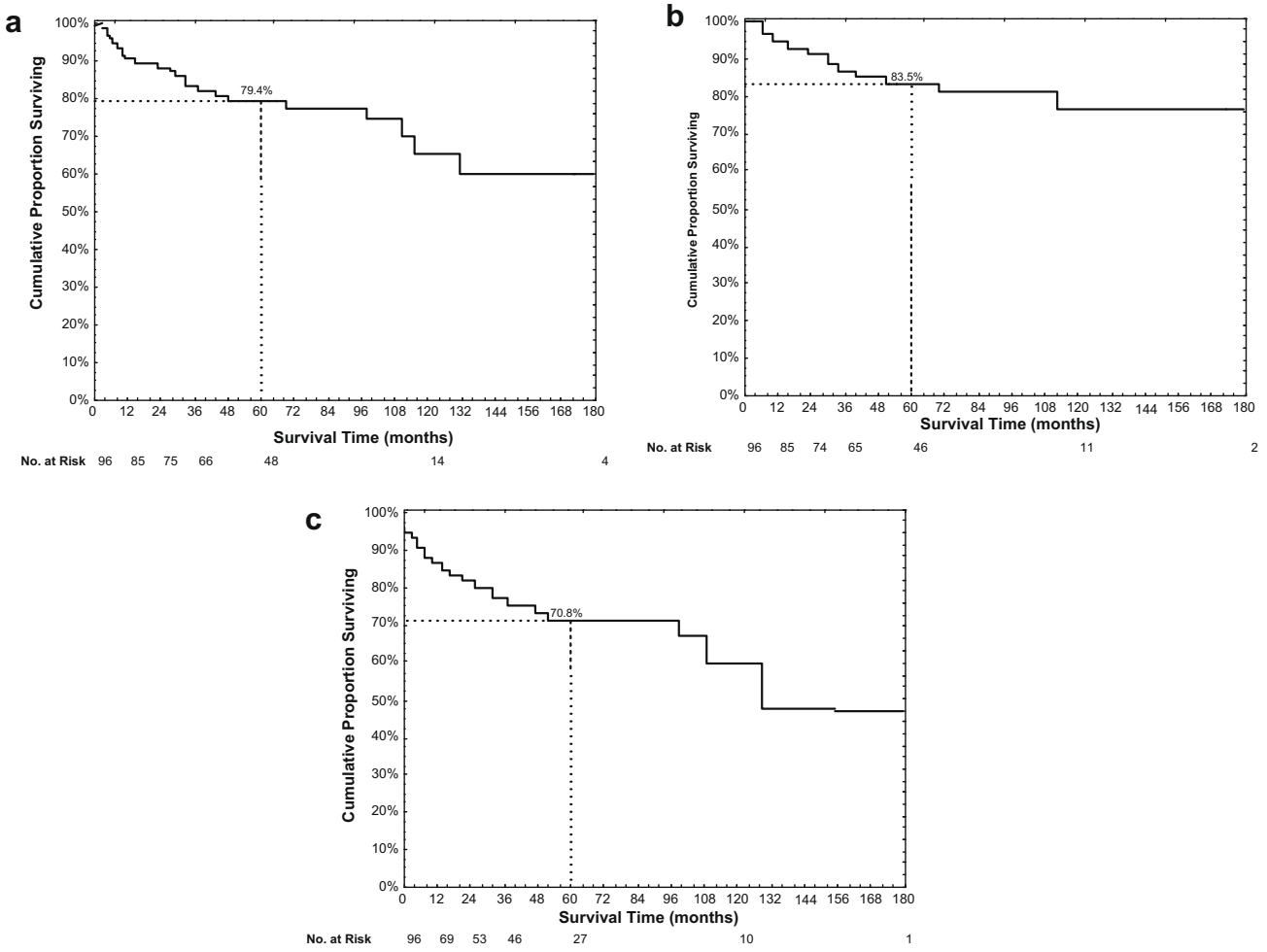

Fig. 2 – Kaplan–Meier plots for 96 patients with a primary carcinoma of the parotid gland, (a) overall survival (OS), (b) disease-specific survival (DSS) and (c) recurrence-free survival (RFS). The dotted lines and percentages display the 5-year survival.

Table 2 – Univariate survival analyses. Asterisks indicate significant *p* values. PN or V: perinervous or vascular; Not P.: not present.

Patient groups	At risk	Five-year RFS (%)	*p* value	Five-year DSS (%)	*p* value
Age			0.1335		0.0020*
>60 years	45	60.6		67.9	
<60 years	51	79.2		97.4	
Gender			0.0442*		0.0160*
Men	38	61.6		70.8	
women	58	77.2		92.5	
Pain			0.4531		0.6319
Present	15	62.9		78.0	
Not P.	81	72.9		84.4	
Hard mass			0.1347		0.0072*
Present	41	61.5		70.3	
Not P.	55	80.3		94.0	
Facial palsy[a]			0.0011*		0.0147*
Present	21	46.1		63.8	
Not P.	75	77.1		88.7	
T stage			0.0003*		0.0061*
T3–T4	15	41.5		60.0	
T1–T2	76	76.4		87.0	
N stage			0.0067*		0.0004*
N1–N2	10	22.9		50.0	
N0	81	76.2		86.8	
Clinical stage			0.0002*		0.0035*
I–II	70	80.3		87.3	
III–IV	21	36.8		66.7	
Two grades			0.0007*		0.0055*
High	59	56.7		75.0	
Low	37	95.5		96.8	
Three grades			0.0055*		<.0001*
High	27	50.6		56.8	
Intermediate	38	66.6		88.1	
Low	31	94.7		100.0	
VII invasion			0.04*		0.0002*
Present	28	53.6		62.9	
Not P.	68	78.0		0.9227	
PN or V invasion			0.0587		0.0137*
Present	38	59.0		72.4	
Not P.	58	78.4		91.2	
Pathological stage			0.0161*		0.1233
I–II	40	83.3		86.6	
III–IV	41	53.1		73.9	
pT stage			0.0075*		0.0132*
pT1–pT2	54	80.1		90.4	
pT3–pT4	38	53.7		71.3	
pN stage			0.0464*		0.0060*
pN0	67	75.2		87.1	
pN1–pN2	13	32.1		53.5	
pN stage + pNPar			0.0604		0.0239*
pN0	59	77.9		86.1	
pN+	22	44.0		66.1	
Capsular invasion			0.017*		0.0276*
Present	12	21.4		54.6	
Not P.	67	75.5		84.7	

a Pre-operative facial palsy.

3.5. Adjuvant treatment

External post-operative radiotherapy was delivered in 69 cases (71.4%); 44 of these patients (44.5%) were also irradiated in the ipsilateral cervical area. The delivered dose ranged between 60 and 65 Gy on the tumour and between 40 and 60 Gy on the neck.

Chemotherapy alone was indicated in five palliative cases.

3.6. Outcome

The median follow-up was 57.7 months. Oncologic events were 6.2% of recurrences ($n = 6$), 4.1% of persisting tumour progression, e.g. evolution within the 6 first months ($n = 4$), 18.4% of metastases ($n = 18$) and a total of 16.7% of death related to cancer ($n = 16$) for the 96 patients (Fig. 1).

The 5-year rates for overall survival, the disease-specific survival and recurrence-free survival were, respectively, 79.4% (SD = 4.4), 83.5% (SD = 4.1) and 70.8% (SD = 5.6) (Fig. 2).

Univariate analysis of CS, DSS and RFS showed that significant prognostic factors were: age > 60, male gender, hardness of the tumour, facial palsy, cT, cN, clinical stage, histological grade (in two and three groups), facial nerve invasion, perinervous or vascular embolism, pT, pN and capsular invasion of invaded lymph nodes. The main prognostic factors for the 5-year DSS and RFS are presented in Table 2.

Multivariate analysis using the Cox models found that the clinical stage IV and the histopathological grade, especially using three groups were the most pertinent predictive factors in the three survival analyses. Using the DSS Cox model (Model B in Table 3), the relative risk (hazard ratio) for high grade was 7.80 [95% CI: 2.39–25]. Pathological grade, when analysing only the two groups showed statistical significance in the multivariate analyses in relation to RFS (Table 2). Plots of actuarial DSS concerning relating to the four more interesting prognostic factors are reported in Fig. 3.

4. Discussion

It is generally agreed that combined therapy with a complete surgical tumour removal followed by radiotherapy in high risk patients is the best approach to avoid recurrences and to improve survival.[6] However, the completeness of the parotidectomy and the management of cervical lymph nodes remain matters of discussion especially in low grade tumours and in cN0 patients.[13,14] Tumour grading into two groups may also be refined with the identification of intermediate risk tumours showing a particular pattern of evolution, as previously reported.[7,8]

The present study reports the results of a homogeneous treatment strategy in a single institution based on a total parotidectomy and a neck dissection for primary parotid carcinoma, followed by radiotherapy if required. With this treatment, the outcome showed 5-year rates of OS = 79.4%, of DSS = 83.5% and of RFS = 70.8% that are ranked among the highest previously reported survival rates, despite a large proportion of high grade tumours. One of the key of the good oncologic results was the systematic review of the histological cases excluding non-primary epithelial cell tumours especially intraparotideal metastasis of skin and aerodigestive

Table 3 – Multivariate analyses assessing several Cox models. Models A and B involved the grading of the tumours into either two groups (2 grades) or three groups (3 grades).

Survival type	Cox models tested	Variable	Parameter estimate	Standard error	*p* value	Hazard ratio	95% Hazard ratio confidence limits
Overall survival	Model A	2 Grades	1.07	0.64	0.0956	2.92	[0.82–10.30]
		Clinical stage	0.78	0.56	0.1646	2.19	[0.72–6.64]
		Facial palsy[a]	0.94	0.44	**0.0357**	2.56	[1.06–6.18]
		Age > 60	1.42	0.50	**0.0051**	4.15	[1.53–11.27]
	Model B	3 Grades[c]	0.98	0.35	**0.0062**	2.67	[1.32–5.39]
		Clinical stage[b]	1.33	0.52	**0.0110**	3.80	[1.35–10.66]
		Age > 60	1.02	0.51	**0.0479**	2.78	[1.01–7.70]
Disease-specific survival	Model A	2 Grades	1.72	1.05	0.1033	5.61	[0.70–44.72]
		Clinical stage[b]	1.48	0.55	**0.0075**	4.43	[1.48–13.20]
		Age > 60	1.41	0.67	**0.0377**	4.09	[1.08–15.50]
		Tumour hardness	1.09	0.60	0.0693	2.99	[0.91–9.74]
	Model B	3 Grades[d]	2.05	0.60	**0.0007**	7.80	[2.39–25.42]
		Clinical stage[b]	2.49	0.63	**<.0001**	12.09	[3.51–41.58]
		Tumour hardness	1.23	0.60	**0.0405**	3.44	[1.05–11.22]
Recurrence-free survival	Model A	2 Grades	1.88	0.74	**0.0119**	6.57	[1.51–28.56]
		Clinical stage[b]	1.59	0.46	**0.0006**	4.90	[1.98–12.13]
	Model B	3 Grades[c]	0.85	0.30	**0.0045**	2.36	[1.30–4.27]
		Clinical stage[b]	1.94	0.46	**<.0001**	6.97	[2.80–17.37]

a Pre-operative facial palsy.
b The clinical stage compares stage IV versus other stages (I, II and III). Bold values indicate the significant cofactors.
c Graded into three groups, introduced in the Cox model as a continuous variable after verification of linearity assumption.
d In the DSS model, graded into three groups did not verify assumption of linearity; therefore it was taken as dichotomous: high grade versus intermediate and low grades.

tract squamous cell carcinoma (36/155 eligible patients) related to poor prognosis.[15] A careful review of the clinical history and the histology usually permit the exclusion of more than 80% of SSC, leaving approximately 2% of "true" primary SCC in parotid malignancy cohorts.[16] Series reporting more than 2% of primary SCC are therefore questionable with regard to the accuracy of histological diagnosis. The other differential diagnosis is high grade mucoepidermoid carcinoma recognisable by mucin (mucicarmine stains) in conjunction with appropriate morphology.[8] Adopting these diagnostic criteria, the present series included no primary SCC and 11.2% of high grade mucoepidermoid carcinoma. The other key to increase of the survival rates may be the extent of the surgical treatment. The parotid surgery consisted first, in a monobloc tumour removal surrounded by healthy parotid gland tissue. The intra-operative diagnosis confirmed the malignancy in a large majority of the cases (91.7%). Although the grading was concordant between FS and definitive histopathology in 84.0%, in true positive cases, prognostic factors, i.e. the precise tumour type, the perineural and/or vascular invasion are frequently unknown at the time of surgery.[17] Yet, these prognostic factors are related to lymph nodes metastases whose first basin of drainage is the intraparotideal lymph nodes.[11] Hence, in our institution totalisation of the parotidectomy was the basis of the parotid surgery and this was performed in 91.7% of the cases irrespective of the tumour location, so as to avoid any misdiagnosis of intraparotid metastases and local recurrences. In the same way, neck dissection was also systematically advocated so as to establish the pN stage and to remove any tumoural lymph node extension present (17.5% of proven invaded cervical lymph nodes). Among cN0 tumours, 20.3% were pN+ with capsular invasion in 5%. Therefore, as previously reported, we definitely recommend a total parotidectomy as initial time surgery[11] with a systematic neck dissection,[18] i.e. modified radical neck dissection in cN+ patients and, at least in cN0 patients with levels II and III, as a staging and therapeutic procedure. Based on the prognostic factors established with these surgical procedures, adjuvant radiotherapy targeting the tumoural area and the neck with a high dose into the invaded neck level was advocated. Sixty-nine patients (71.4%) underwent radiotherapy; these were patients with clinical stage IV and high grade tumours.

Regarding the value of prognostic factors, the univariate analysis confirmed the previously described clinical and histological criteria relating to a poor prognosis such as

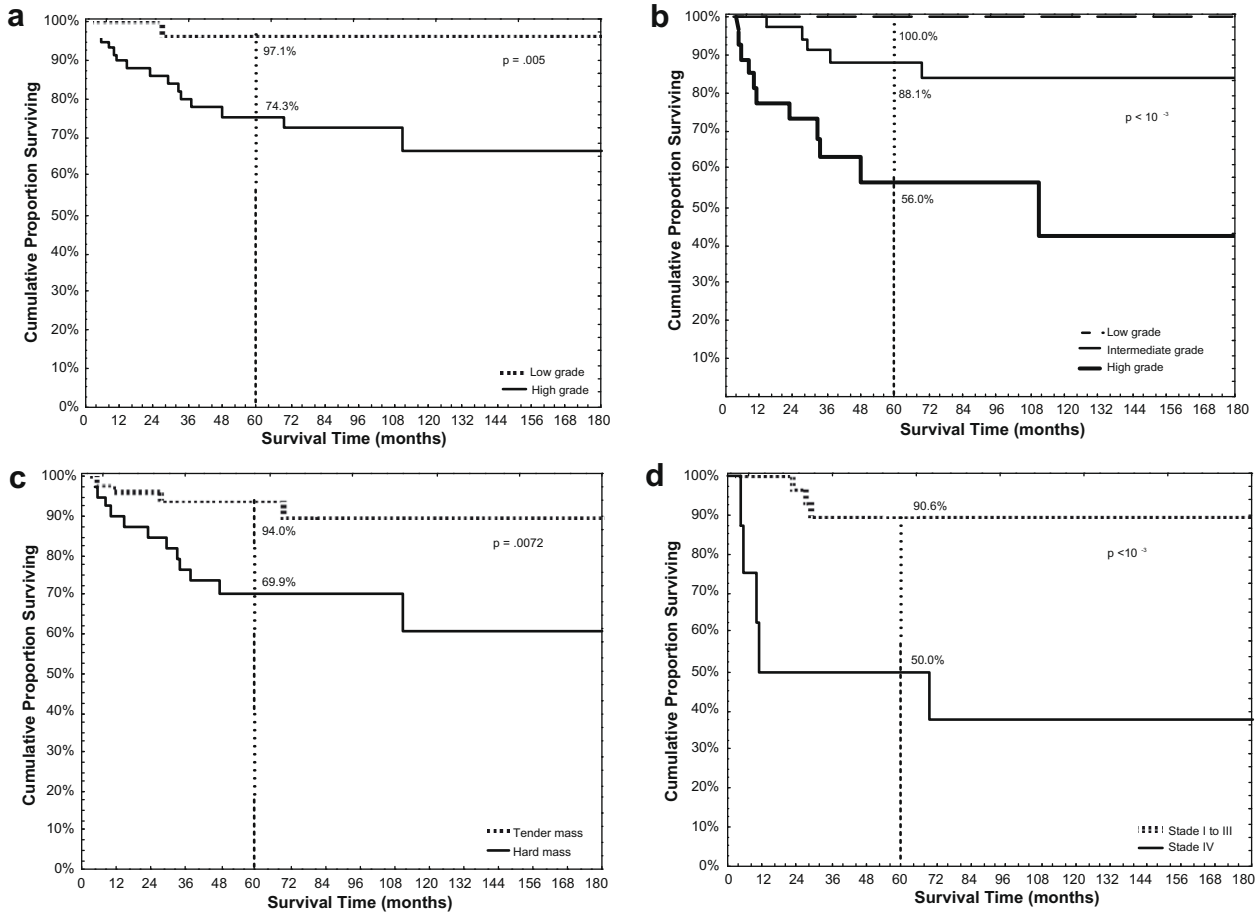

Fig. 3 – Actuarial analysis of disease-specific survival (DSS) according to tumour grade (a: graded into two-grade classification; b: three-grade classification), clinical hardness of the tumour (c) and clinical stage comparing stage IV versus other stages (I, II and III) (d).

age > 60, male gender, facial palsy, hardness of the tumour, clinical stage, tumour grade, facial nerve invasion and lymph node metastases. However, many of these criteria are interrelated and can appear as confounding factors. For example, facial nerve invasion, found in 30% of patients was statistically positively correlated with the grade of the tumour when analysed in two groups ($p = 0.007$) or in three ($p < 10^{-3}$). pN status was positively correlated with the tumour grade when classified in either two ($p = 0.01$) or three groups ($p = 0.005$). These data emphasise the need for multivariate analyses to identify independent prognostic factors and to classify such criteria as a function of the hazard ratio. In this analysis, the clinical stage IV and the clinical hardness of the tumour were significant prognostic factors. Therefore, the clinical examination was of great importance first to evaluate malignancy but also to find clinically relevant prognostic factors. If identified as present, then an aggressive therapeutic approach can be advocated. Histopathological grade of the tumours was also a relevant prognostic factor. The WHO 2005 classification into two groups, i.e. high and low grades, was pertinent for the recurrence-free survival analysis. However, special attention has to be paid to the tumour grading when classifying into three groups, which appeared to be, after the clinical stage, the most significant prognostic factor through the multivariate overall and disease-specific survival analyses. In the Cox models studied, considering the grade shift in low, intermediate and high risk, an elevation of one level multiplied by 2.6 the risk of non-specific death and by 2.3, the risk of disease recurrence. As far as the DSS was concerned, patients with tumours judged as high grade compared with intermediate and low grades showed a relative risk of dying of parotid cancer of 7.8. As a consequence, intermediate grade tumours may have their own pattern of evolution, and thus be of prognostic value. However, the separation of these tumour types into the three grades is not yet widely accepted and tends to vary between authors.[19] For instance, in the present study, cystic adenoid carcinoma were classified as intermediate risk, although, at least two subgroups actually exist, cribriform and/or tubular and solid cystic adenoid carcinomas with probably a better prognosis for the first subgroup.[20] In the same way, acinic cell carcinomas were classified as low grade tumours, although, some aggressive tumour subtypes have been described.[21] Hence, the main limitation of the study was the small sample sizes precluding further refinements in tumour grading analysis.

Vander Poorten et al., have adopted an alternative prognostic approach in their analyses of pre- and post-treatment prognostic index and obtained a validated prognostic system for patients,[22] underlining the lack of prognostic value of a two-grade classification.

In conclusion, although larger prospective studies are required, the present work based on a homogeneous strategy of treatment and histopathological review has highlighted the prognostic significance of a three-grade histological classification in PPC.

Conflict of interest statement

None declared.

REFERENCES

1. Ries L, Harkins D, Krapcho M, et al., editors. SEER cancer statistics review, 1975–2003, National Cancer Institute. Bethesda, MD. <http://seer.cancer.gov/csr/1975_2003/>, based on November 2005 SEER data submission, posted to the SEER web site; 2006 [In: Cancer S, editor.; 2006].
2. Pinkston JA, Cole P. Incidence rates of salivary gland tumors: results from a population-based study. *Otolaryngol Head Neck Surg* 1999;**120**:834–40.
3. Ostman J, Anneroth G, Gustafsson H, Tavelin B. Malignant salivary gland tumours in Sweden 1960–1989—an epidemiological study. *Oral Oncol* 1997;**33**:169–76.
4. Nagler RM, Laufer D. Tumors of the major and minor salivary glands: review of 25 years of experience. *Anticancer Res* 1997;**17**:701–7.
5. Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. *Head Neck Surg* 1986;**8**:177–84.
6. Bensadoun RJ, Blanc-Vincent MP, Chauvel P, et al. Malignant tumours of the salivary glands. *Br J Cancer* 2001;**84**(Suppl.):42–8.
7. Godballe C, Schultz JH, Krogdahl A, Moller-Grontved A, Johansen J. Parotid carcinoma: impact of clinical factors on prognosis in a histologically revised series. *Laryngoscope* 2003;**113**:1411–7.
8. Barnes L, Evenson J, Reichart P, Sidransky D. Pathology and genetics head and neck tumours. In: *World Health Organisation classification of tumours*. 3rd ed. IARC; 2005. p. 212–81.
9. Sobin LH, Wittekind C. *TNM classification of malignant tumours*. 6th ed. New York: Wiley-Liss; 2002.
10. Therkildsen MH, Christensen M, Andersen LJ, Schiodt T, Hansen HS. Salivary gland carcinomas–prognostic factors. *Acta Oncol* 1998;**37**:701–13.
11. Klussmann JP, Ponert T, Mueller RP, Dienes HP, Guntinas-Lichius O. Patterns of lymph node spread and its influence on outcome in resectable parotid cancer. *Eur J Surg Oncol* 2008;**34**:932–7.
12. van der Wal JE, Becking AG, Snow GB, van der Waal I. Distant metastases of adenoid cystic carcinoma of the salivary glands and the value of diagnostic examinations during follow-up. *Head Neck* 2002;**24**:779–83.
13. 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.
14. Kane WJ, McCaffrey TV, Olsen KD, Lewis JE. Primary parotid malignancies. A clinical and pathologic review. *Arch Otolaryngol Head Neck Surg* 1991;**117**:307–15.
15. Moore BA, Weber RS, Prieto V, et al. Lymph node metastases from cutaneous squamous cell carcinoma of the head and neck. *Laryngoscope* 2005;**115**:1561–7.
16. Flynn MB, Maguire S, Martinez S, Tesmer T. Primary squamous cell carcinoma of the parotid gland: the importance of correct histological diagnosis. *Ann Surg Oncol* 1999;**6**:768–70.
17. Zbaren P, Nuyens M, Loosli H, Stauffer E. Diagnostic accuracy of fine-needle aspiration cytology and frozen section in primary parotid carcinoma. *Cancer* 2004;**100**:1876–83.
18. Zbaren P, Tschumi I, Nuyens M, Stauffer E. Recurrent pleomorphic adenoma of the parotid gland. *Am J Surg* 2005;**189**:203–7.
19. Brandwein MS, Ivanov K, Wallace DI, et al. Mucoepidermoid carcinoma: a clinicopathologic study of 80 patients with special reference to histological grading. *Am J Surg Pathol* 2001;**25**:835–45.
20. Norberg-Spaak L, Dardick I, Ledin T. Adenoid cystic carcinoma: use of cell proliferation, BCL-2 expression,

histologic grade, and clinical stage as predictors of clinical outcome. *Head Neck* 2000;**22**:489–97.
21. Gomez DR, Katabi N, Zhung J, et al. Clinical and pathologic prognostic features in acinic cell carcinoma of the parotid gland. *Cancer* 2009;**115**:2128–37.
22. Vander Poorten VL, Hart A, Vauterin T, et al. Prognostic index for patients with parotid carcinoma: international external validation in a Belgian–German database. *Cancer* 2009;**115**:540–50.