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HEAD AND NECK

Recurrent parotid gland carcinoma: how effective is salvage surgery?

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Abstract

Objective Recurrent parotid gland carcinomas (PGCs) are poorly characterized and studies focusing on this topic are rare due to their low incidence. The goal of this study is to analyze the therapeutic strategies, prognostic factors, and oncological outcomes of a series of patients with recurrent PGCs.

Patients and Methods Retrospective chart review (1997–2012) of patients with recurrent PGCs was initially treated with curative intent.

Results We identified 20 patients with recurrent PGCs. Eleven patients presented isolated local, regional, or distant metastases, while the rest had recurrences in multiple sites. Recurrent tumors tended to present more advanced T-stage ($p=0.01$) and overall stage ($p<0.001$), but not N-stage ($p=0.74$) when compared to the initial tumors. Half the patients (50%) had distant metastases at the moment of recurrence diagnosis, and another three developed them after attempted salvage surgery. Only 8/20 patients with isolated local or regional recurrences were surgically salvaged with extended revision parotidectomy and neck dissection, respectively. The remaining 12 patients were managed on palliative basis. Overall survival (31.70 months vs. 20.73 months) and progression-free survival (28.70 months vs. 13.61 months) were not significantly different in patients managed surgically vs. palliatively.

Conclusion Recurrent PGCs are aggressive neoplasms with a high rate of distant metastases. Surgical salvage can be considered in patients with limited local and/or regional recurrences. The alternative to surgical salvage is palliative management with different chemotherapeutic regimens. Survival does not differ between the two strategies in the present series.

Keywords Parotid cancer · Recurrence · Salvage surgery · Palliative therapy · Outcomes

Introduction

Parotid gland carcinomas (PGCs) are histologically heterogeneous malignancies that represent less than 5% of all head and neck cancers [1]. PGCs are primarily managed with surgery (parotidectomy +/- neck dissection). In certain cases, additional radiotherapy and/or chemotherapy is administered [2, 3]. Primary radiotherapy remains an option for patients not suitable for the initial surgical resection [4].

Several risk factors for decreased survival and disease control have been established in a number of studies, including histological grade, presence of neck lymph node metastases, disease stage, resection margins, infiltration of the facial nerve, presence of intraglandular lymph node metastases, and adjuvant therapy [5–12].

In contrast, the number of publications specifically addressing the topic of recurrent PGCs is restricted, probably because of the relatively low incidence of PGCs [13–15]. Recurrence rates of PGCs (including loco-regional or distant failure) are substantially variable and range between 15 and 50% [16].

The goal of this study is to retrospectively analyze the therapeutic strategies, prognostic factors, and oncological outcome of patients with recurrent PGCs.

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Patients and methods

Study population and inclusion criteria

We obtained approval from our Institutional Review Board and Ethic Committee for this retrospective study. All paper- and computer-based records of patients with PGCs treated in our institution between January 1997 and June 2012 were reviewed. For the study, we considered patients with histologically proven recurrent PGCs, initially managed with curative intent without treatment interruption, and with sufficient follow-up data (at least 2 years since the diagnosis of recurrence or until the moment of event). If the minimally required features for retrieval were not clear or not available (see "Data collection" below), patients were equally excluded.

We excluded patients with parotid malignancies other than epithelial, patients initially diagnosed with distant metastases, or in case of concomitant cancer (except for basal cell carcinomas arising in anatomic regions other than the head and neck, and carcinoma in situ of the cervix). Metastases to the parotid were equally excluded.

Data collection

We recorded the following features in a standard spreadsheet: clinical presentation, imaging modalities, and initial and recurrent disease stage, histopathological diagnosis, management strategy, and outcome. All recorded data underwent an unmasked double check (LN, UB, and RG).

Statistical analysis

Summary statistics were calculated, and subsequently, several subgroup comparisons were performed with the Chi-squared test for proportions and Student's *t* test for averages. Survival curves were plotted according to the Kaplan–Meier method and comparisons were performed with the log-rank test. Disease progression was monitored clinically and radiologically according to a standard institutional protocol. Progression-free survival was defined as the period after recurrence diagnosis without clinical or radiological signs of detectable tumor growth or appearance of new lesions. All *p* values were two-sided and significance was set at alpha < 0.05.

Results

Study population and general features

Our search identified a total of 20 patients with recurrent PGCs. All patients were initially managed surgically and all of them received postoperative radiotherapy with or without chemotherapy. Recurrences were diagnosed within a mean time of 18.41 ± 11.87 months (range 3.0–41.3). Patients' average age at recurrence was 66.79 ± 10.17 years (range 54.74–87.94). Four patients were female (20%) and sixteen were male (80%).

More than half the recurrences were diagnosed following patients' complains, but importantly, four patients (20%) were completely asymptomatic (Table 1). A mass was palpated in ten patients and five patients complained of pain at the site of recurrence. One recurrence was diagnosed due to pain related to a bone metastasis (Table 1).

The general characteristics and initial treatment of patients with recurrent PGCs are summarized in Table 2 according to the treatment administered (i.e., surgical vs. non-surgical). Globally, the predominant histological subtypes were salivary duct carcinoma, mucoepidermoid carcinoma, and primary squamous cell carcinoma of the parotid gland. As the initial surgical approach, the majority of patients underwent total parotidectomy and neck dissection ($n = 16$). Only one patient received partial parotidectomy (for T1 N0 adenoid cystic carcinoma that failed distantly after 17.94 months). Initially, all 20 patients received adjuvant radiotherapy, with concomitant chemotherapy in three cases (15%).

Patterns of recurrence

Local and/or regional recurrences without concomitant distant metastases were diagnosed in ten patients. Eight

Table 1 Detection and presentation of recurrent PGCs

Features		Nr. (%)
Mode of detection	Following patients' complains	11 (55%)
	By physician (routine follow-up)	5 (25%)
	Scheduled imaging follow-up	4 (20%)
Presentation	Mass (parotid gland or neck)	10 (50%)
	Pain at site of recurrent tumor	5 (25%)
	No symptoms/no signs (radiological dg.)	4 (20%)
	New-onset facial paralysis	1 (5%)
	Symptoms related to distant metastases	1 (5%)

PGCs parotid gland carcinomas, *dg*. diagnosis

Table 2 Characteristics of patients with recurrent PGCs managed surgically and non-surgically

Characteristic	Surgical salvage (n = 8)	Non-surgical management (n = 12)
Age (average ± SD; range [yrs])	70.19 ± 13.11 (55.64–87.94)	64.52 ± 7.43 (54.74–78.96)
Gender (female:male)	1:7	3:9
Histology (Nr., [%])	SDC (3, [37.5%]) MEC (3, [37.5%]) ACC (1, [12.5%]) AC NOS (1, [12.5%])	SDC (3, [25%]) AC NOS (2, [16.67%]) SCC (2, [16.67%]) MEC (1, [8.33%]) ACC (1, [8.33%]) EMC (1, [8.33%]) Large cell carcinoma (1, [8.33%]) CEPA (1, [8.33%])
Initial surgery primary (Nr., [%])	TP (7, [87.5%]) TP + VII (1, [12.5%])	TP (9, [75%]) TP + VII (2, [16.67%]) PP (1, [8.33%])
Initial neck dissection (Nr., [%])	6 [75%]	10 [83.33%]
Initial adjuvant therapy (Nr., [%])	RT (8 [100%])	RT (9 [75%]) CRT (3 [25%])
rT-stage	No recurrence (4, [50%]) T4 (4, [50%])	No recurrence (7,[58.33]) T4 (5, [41.67%])
rN-stage	No recurrence (4, [50%]) N+ (4, [50%])	No recurrence (7, [58.33%]) N+ (5, [41.67%])
rM-stage	No metastases (8, [100%]) M1 (0, [0%])[a]	No metastases (2, [16.67%]) M1 (10, [83.33%])
Time to recurrence (average ± SD; range [months])	16.44 ± 10.80 (3.02–34.27)	21.36 ± 13.51 (6.31–41.3)
Status at last follow-up	AwoD (3, [37.5%]) AwD (1, [12.5%]) DwoD (0, [0%]) DwD (4, [50%])	AwoD (0, [0%]) AwD (5, [41.67%]) DwoD (0, [0%]) DwD (7, [58.33%])

AC NOS adenocarcinoma not otherwise specified, *ACC* adenoid cystic carcinoma, *AwD* alive with disease, *AwoD* alive without disease, *CEPA* carcinoma ex pleomorphic adenoma, *CRT* chemoradiation therapy, *DwD* dead with disease, *DwoD* dead without disease, *EMC* epithelial-myoepithelial carcinoma, *MEC* mucoepidermoid carcinoma, *PGCs* parotid gland carcinomas, *PP* partial parotidectomy, *RT* radiation therapy, *SCC* squamous cell carcinoma, *SDC* salivary duct carcinoma, *TP* total parotidectomy, *TP + VII* total parotidectomy with facial nerve resection

[a]In these groups, three patients developed distant metastases after salvage surgery

patients presented local and/or regional recurrences with distant metastases. Distant metastases alone were found in two patients at the moment of diagnosis (Table 2), and three more patients developed distant metastases after attempted surgical salvage.

All locally recurrent tumors were classified as rcT4: 3/9 (33.33%) were rcT4a and 6/9 (66.67%) were rcT4b. In contrast, only four of these tumors were initially classified as cT4a, thus resulting in a significantly more advanced stage in recurrent tumors ($p = 0.01$). All rcT4a tumors were isolated local recurrences, while rcT4b tumors presented with concomitant distant metastases in 4 cases, two of which had additional regional recurrences, and 1 case presented with concomitant regional recurrence without distant metastases. The N-stage of recurrences did not significantly differ from the initial tumors ($p = 0.74$). All patients with regional recurrences except one underwent a neck dissection, and only two did not receive elective neck irradiation as the initial management.

Of the 13 patients with distant metastases (10 at the moment of recurrence diagnosis and 3 after salvage surgery), 6 patients had one single and 7 multiple distant sites involved (lung, mediastinum, bone, brain, and gastrointestinal tract).

With respect to overall UICC stage, all recurrences were classified stage IV, while only 13/20 (65%) initial tumors were classified stage III or IV ($p < 0.001$).

Management strategies and patient selection criteria

In this cohort, eight patients (40%) underwent attempted salvage surgery, and 12 (60%) were managed on a palliative basis (Table 2). Reasons for palliative management

were unresectable local or regional recurrences, and/or presence of distant metastasis. Patients that underwent salvage surgery had isolated local ($n=4$) or regional recurrences ($n=4$). Table 3 shows the details of all management strategies applied and the eventual reasons for failure in patients managed with salvage surgery (Fig. 1 illustrates an example of extended salvage parotidectomy). Of all four patients with local recurrence, only one presented a preoperative facial nerve palsy. Nevertheless, extended salvage parotidectomy systematically encompassed sacrifice of the facial nerve in the current series. Static facial reanimation was performed in a single patient at the time of salvage surgery.

Most patients non-surgically managed underwent palliative chemotherapy or best supportive care. All these patients had concomitant loco-regional and/or distant metastases. One patient who had a loco-regional recurrence without distant metastasis could not be operated due to skull base and dural infiltration.

In terms of complications, two of the twelve patients managed on a palliative basis did not present any treatment-related complications, 4 presented mild digestive/hematologic toxicity (which did not require treatment interruption), and 6 patients presented cutaneous fistulisation by the recurrent tumor in the course of their evolution.

Oncological outcome

Median overall survival in all patients was 28.94 months after recurrence, and median progression-free survival was 20.86 months. When comparing survival in patients that underwent salvage surgery vs. patients that were managed palliatively, we found an overall survival of 31.70 vs. 20.73 months ($p=0.3301$), and a progression- free survival of 28.70 vs. 13.61 ($p=0.4424$), respectively (Fig. 2a, b).

Specifically regarding salvage surgery outcomes (Table 2), out of the four patients operated for isolated local recurrences, only one was alive without disease progression

Table 3 Treatment characteristics of patients managed with salvage surgery ($n=8$)

Characteristic	Nr., [%]
Approach to the primary tumor	None (4, [50%]) Extended salvage parotidectomy (4, [50%])
Approach to the neck	None (4, [50%]) Salvage neck dissection (3, [37.5%]) Salvage radical neck dissection (1, [12.5%])
Adjuvant therapy post-salvage	None (4, [50%]) Irradiation (2, [25%]) Re-irradiation (2, [25%])
Reasons for failure	Successful salvage (3, [37.5%]) Persistent tumor (3, [37.5%]) DM post-salvage surgery (3, [37.5%])

DM distant metastasis, *extended salvage parotidectomy* parotidectomy with resection of other facial structures, mastoid, facial nerve, or mandible

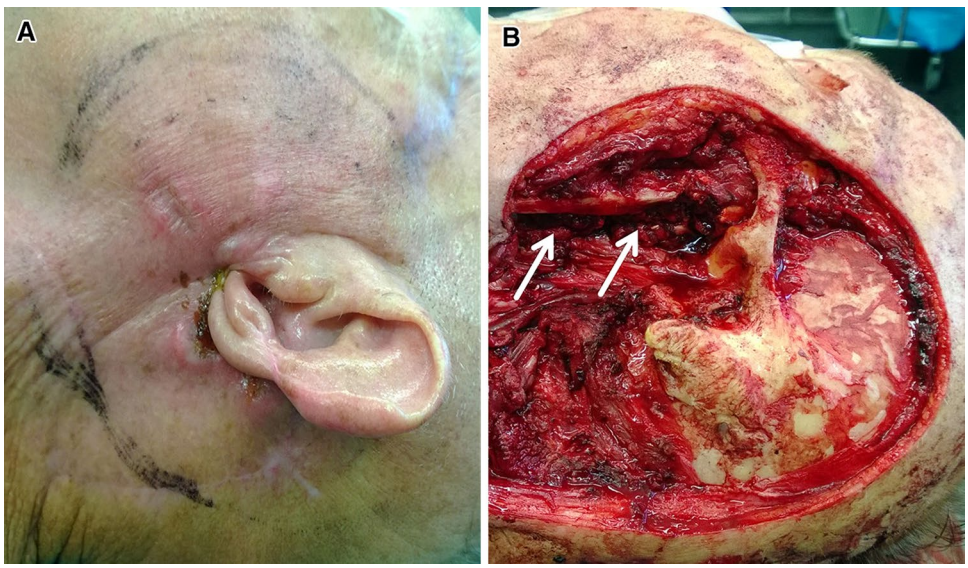
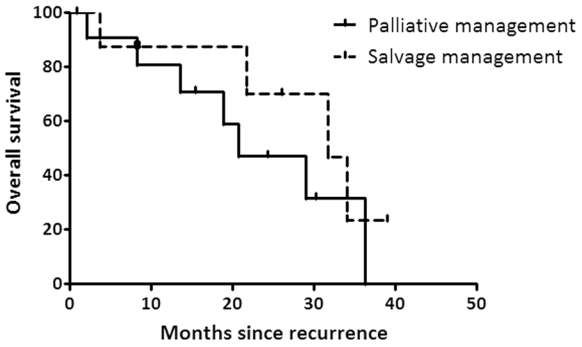
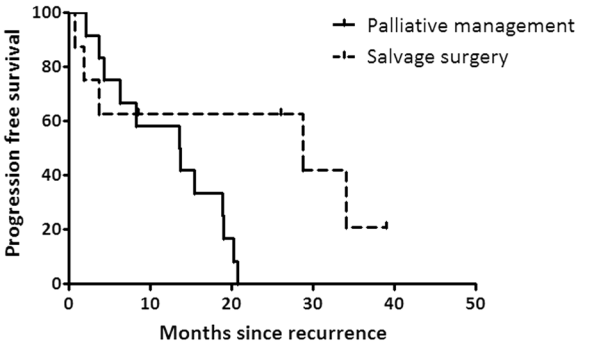


Fig. 1 Example of a recurrent carcinoma managed with extended parotidectomy and partial mandibular resection (arrows). Reconstruction with myocutaneous pectoralis major flap. **a** Preoperative status; **b** status at the end of resection





Group	Median survival (months)	p-value
Palliative	20.73	0.3301
Salvage	31.70	

Group	Median survival (months)	p-value
Palliative	13.61	0.4424
Salvage	28.70	

Fig. 2 Kaplan–Meier plots illustrating overall (**a**) and progression-free survival (**b**)

more than 6 month post-salvage (initial histology: acinic cell carcinoma). Two other patients had persistent disease despite surgery, and another one developed distant metastases after surgery but was loco-regionally disease-free. With respect to regional recurrences, two patients were successfully salvaged and one received postoperative re-irradiation. Moreover, two patients successfully salvaged in the neck developed distant metastases more than 2 years after salvage. At last follow-up, 3/8 surgically salvaged patients were without disease and 5/8 with disease (Table 2).

Discussion

In this study, we reviewed the clinical features and management approaches of recurrent PGCs in a cohort of 20 patients. Our main findings were that: (a) recurrent PGCs are aggressive neoplasms and present with significantly more advanced stage when compared with the initial tumors; (b) there is a high rate of distant metastases developing after the initial treatment and even following successful salvage surgery; (c) limited local or regional recurrences can be managed surgically, but the high tendency to widespread infiltration of recurrent PGCs often renders surgical salvage impracticable; and (d) we did not find significant differences in terms of survival in patients managed surgically vs. non-surgically in our cohort.

PGCs represent an heterogeneous group of malignancies with a relatively low incidence. Consequently, there is substantial debate about ideal approaches and such approaches depend in part on the histological subtypes [2]. Publications specifically focusing on recurrent PGCs are rare, and recommendations regarding the management of such tumors emanate mostly from expert consensus, with limited levels of evidence.

A first aspect to stress is that recurrent PGCs are to be considered high-risk neoplasms. In our own cohort, this is illustrated by the fact that re-staging after recurrence resulted in significantly higher T- and overall stage. Clinical follow-up after the initial therapy is, therefore, essential, with the primary goal to identify treatment failure, but also to address treatment complications/toxicity, and providing support [16]. In the present series, 20% of the patients were asymptomatic at recurrence and up to 45% of recurrences were diagnosed within the frame of regular follow-up. Such figures emphasize the importance of patient's education on self-awareness, especially whenever a slowly enlarging mass at the former site of the primary tumor or the neck appears.

With respect to specialized follow-up, it is important to note that anatomical modifications due to previously operated PGC along with aberrant scarring following radiotherapy may render diagnosis of recurrent PGCs difficult on a purely clinical basis. Consequently, different imaging techniques play important roles in the follow-up. It is worth pointing out that the absence of high levels of evidence in this sense precludes the development of standardized follow-up imaging protocols. Nevertheless, following standard strategies in other head and neck cancers, a post-therapeutic CT-scan or ideally an MRI at 3–4 months is useful as baseline assessment. Follow-up imaging during the first 36–48 months after the initial treatment seems equally recommended, as most recurrences will occur during this period. Nevertheless, it is essential to keep in mind that certain histological subtypes such as adenoid cystic carcinomas require longer follow-up period [16]. Given the high rate of distant recurrences found by us and others

[15], PET-CT in the setting of recurrent PGCs should be considered, especially in histological high-risk subtypes [17]. The interest of ultrasound is limited to superficial and well-defined recurrences, and eventually to guide fine needle aspiration to obtain cytopathological diagnosis [16].

The therapeutic choice for recurrent PGCs ought to take into consideration several aspects, including disease extension with an emphasis on distant metastases, ability of surgery for gross complete removal, and patient's demands. Surgical salvage is theoretically the approach that provides a higher chance of oncological success. However, involvement of structures such as the skull base, facial bones, and the orbit, along with the tendency of recurrent PGCs to be ill-defined and use atypical routes of invasion (such as those created by the previous surgery), are likely to limit the feasibility of certain resections [7]. In addition, the morbidity and functional impact of such approaches has to be stressed when discussing with the patient. As mentioned above, careful preoperative assessment is of utmost importance, since complete gross resection should be carried out, especially in patients who can no longer be irradiated.

In the present cohort, only patients with isolated local or regional recurrences underwent salvage surgery. As previously reported, local salvage often required thorough resection of involved facial tissues such as the skin, the facial nerve, and bone [7, 10, 14, 15]. Given that resection with healthy margins is a recognized prognostic factor in recurrent head and neck cancer, preservation of the facial nerve in locally recurrent PGCs is most often not possible and arguably even not recommended from an oncological perspective [16]. It is, therefore, essential to stress once more the importance of discussing potential functional and cosmetic consequences of salvage surgery with the patient. Facial reanimation techniques either at the time of salvage or later should be kept in mind when facial nerve sacrifice is required [10, 14].

In cases of recurrent PGCs with skull base invasion, some authors have reported good outcomes following the use of lateral skull base approaches and reconstruction mainly with regional flaps [10, 14]. Skull base approaches were not suitable in our cases as almost all T4b recurrences presented skull base invasion with either dural infiltration without or with extension to the brain, or extensive invasion of orbital bones and soft tissues which precluded any resection with curative intent (Table 2).

Surgically salvaged regional neck lymph node recurrences in our cohort were isolated. All cases but one had previously undergone some type of neck dissection, and salvage neck dissection implied more or less radical revision neck dissection with removal of recurrent tumor and not previously operated levels. All recurrences in our series were ipsilateral.

Regarding adjuvant therapy in surgically salvaged patients, 4/8 (50%) in our series received radiation therapy: re-irradiation in a local recurrence and in a regional recurrence, and irradiation in two regional recurrences that initially did not undergo neck irradiation. The feasibility of irradiation/re-irradiation must be a key element in the decision-making process for patients with recurrent PGCs.

Literature on adjuvant therapy in the context of recurrent PGC is seldom. As an example, Pederson et al. evaluated the effects of re-irradiation with concomitant chemotherapy following salvage surgery in a cohort of 14 patients with recurrent salivary gland tumors (including 6 PGCs). They found an overall survival of 57.1% and 35.7% at 1 and 3 years, respectively, with acceptable toxicity rates [15].

The aggressive nature of loco-regionally recurrent PGCs and the high rate of distant metastases impose a non-curative approach in a substantial number of patients with recurrent PGCs. Diverse combinations of chemotherapeutic agents with the goal to palliate tumor-related symptoms and in the best case-scenario impairing disease progression have been evaluated. Combinations of agents such as cyclophosphamide/fluorouracil, doxorubicin, and cisplatin have been reported to yield stabilization rates of up to 50%, although only for restricted time span [18, 19]. Vinorelbine was tested in a phase II clinical trial, showing moderate activity in recurrent PGCs [20]. Finally, a systematic review of clinical trials assessing the impact of systemic agents (cytotoxic agents and molecular targeted therapy) in adenoid cystic carcinomas by Laurie et al. revealed that, while major objective responses were rarely seen, stable disease was common [21]. As discussed in this review, it is difficult to determine whether such outcome was due to drug activity or to the inherent behavior of this disease, which is characterized by prolonged periods of slow indolent progression. In addition, a number of completed and ongoing phase II clinical trials evaluate several molecular targeted therapy agents (e.g., cetuximab, lapatinib, sunitinib, and sorafenib), but the indications of such agents are unfortunately not well codified [22, 23]. Therefore, the role of molecular targeted therapy agents needs to be further explored. Nevertheless, it is important to note that some authors have shown some benefit of surgical removal of isolated metastases, especially in adenoid cystic carcinoma [24, 25].

Even though oncological results in surgically salvaged PGCs are poor, it is important noting that in our series 6/8 patients where loco-regionally disease-free after 2 years, and half of these patients did not present systemic metastases at all. Surgical salvage for recurrent PGCs must be individually considered in patients with limited local and/or regional recurrences.

The main limitation of the present study is its retrospective design and the relatively low number of patients. A further inherent backdrop is the histological heterogeneity of

PGCs. This could account for the lack of statistical differences in survival between patients salvaged surgically and non-surgically. As discussed, studies focusing specifically on the approach and management of recurrent PGCs are rare and always include only small series of patients. Our present study further emphasizes the importance of thorough assessment and personalized treatment choices. Therefore, further studies analyzing the specific features of this group of patients are needed, to better understand recurrent PGCs as well as to provide elements for treatment discussions and patient counseling.

Conclusion

We report the presentation, management, and outcome of a series of 20 patients with recurrent PGCs. Recurrent PGCs are aggressive and highly infiltrative neoplasms, with a high rate of distant metastases. Only patients with either isolated local or regional relapse could be surgically salvaged with either extended parotidectomy or revision neck dissection. The other patients were managed on a palliative basis with different chemotherapeutic regimens or best supportive care. Overall and progression-free survival were not significantly different between patients surgically salvaged or treated palliatively. Correct assessment of the recurrent disease is essential to personalize treatment strategies in patients with recurrent PGCs.

Compliance with ethical standards

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

Ethical approval For this retrospective study, we obtained approval from our Institutional Review Board and National Ethic Committee. No procedures were performed on patients; only paper- and computer-based records of patients treated between January 1997 and June 2012 were reviewed. All are in accordance with the above-mentioned research committees and with the 1964 Helsinki declaration and its later amendments.

Informed consent General informed consent was obtained from all individual participants included in the study.

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