Article:
Kanatas, A orcid.org/0000-0003-2025-748X, Ho, MWS orcid.org/0000-0001-9810-3136 and Mücke, T (2018) Current thinking about the management of recurrent pleomorphic adenoma of the parotid: a structured review. British Journal of Oral and Maxillofacial Surgery, 56 (4). pp. 243-248. ISSN 0266-4356

https://doi.org/10.1016/j.bjoms.2018.01.021

Current thinking about the management of recurrent parotid pleomorphic adenoma: a structured review.

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Key words: Pleiomorphic adenoma, parotid gland, parotid surgery, recurrence

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Abstract

Introduction

Pleomorphic adenoma (PA) is the most frequent salivary gland tumour of the parotid gland and can recur following surgical excision. Recurrent pleomorphic adenoma (RPA) of the parotid gland can be a challenge to the clinical team and has variable outcomes. The aim of this work is to present the current thinking in the management of this disease. This may be helpful to clinical teams and could improve the health-related quality of life of patients.

Materials and methods

A search of several online databases was devised using the following key terms: Pleomorphic adenoma, recurrent pleomorphic adenoma, parotid gland tumours, parotid surgery, radiotherapy and parotid pleomorphic adenoma, parotid surgery outcomes. Information was collected relating to the topic of the paper, sample size, recurrence rate, facial nerve status, types of surgery, adjuvant treatments relating to recurrence, clinical outcome.

Results

2301 papers were screened, of which 49 articles eligible; There is no consensus amongst the clinical teams for the management of RPA of the parotid gland. There is a lack of randomised studies and hence conclusions in most papers are coherent arguments.

Discussion

RPA of the parotid gland tends to occur after long intervals, with propensity towards multifocal disease. The risk of recurrence depends on the initial surgical technique, is higher

when the initial surgery was at young age, after enucleation and after initial positive margins. Based on the published papers accepted management varies from observation of selected cases to total parotidectomy with/without postoperative radiotherapy.

Introduction

The management of recurrent pleomorphic adenoma (RPA) of the parotid gland presents a challenge to clinicians. This is because surgery is difficult, it is often multinodular[1] and can be associated with facial nerve compromise. Following recurrence there is an increased risk for further recurrences and a risk of malignant transformation that is recently reported as 3.3%[3]. The time interval from the initial treatment can be as long as 15 years[1.] The recurrence rates reported in the literature are depended on the initial surgery type. When a superficial parotidectomy has been performed, the recurrence rate may be below 3%[4]. Tumour factors that may have an influence on recurrence include tumour size[5] pathological subtype[6], satellite nodules[2,] incompleteness of encapsulation[7]. In contemporary surgical practice, PA enucleation is not performed anymore; partial/total parotidectomy or extra-capsular dissection are the operations of choice at initial presentation. When surgical factors are examined in detail, tumour spillage and / or positive margins are associated with recurrences[2]. When examining patient factors, some published papers indicated that the younger patients at initial presentation are those that are associated with later recurrences. However, this conclusion is not robust at present[5]. There is paucity of well-designed studies that defines the role of radiotherapy in the management of RPA of the parotid. Surgeons have a reluctance to advocate the routine use of radiotherapy due to the risks associated with radiation induced malignancies, especially in young patients[8]. The published experiences have been derived from studies on the use of radiotherapy in patients with incomplete margins after their first episode of surgery. Radiotherapy appeared to reduce recurrence with incomplete excision[8]. Chen et al[9] (2006) evaluated the role of radiation therapy in the management of recurrent pleomorphic adenoma of the parotid gland. In that study, the 20-year local control rate was 94%. One patient (1 patient out of 34) developed a second malignancy at approximately 14 years after completion of therapy. The aims of this review

include evaluation of current practice and evidence-based understanding of the management of RPA of the parotid in order to provide guidance to clinical teams.

Material and Methods

A search strategy was devised using the following key terms: Pleomorphic adenoma, recurrent pleomorphic adenoma, parotid gland tumours, parotid surgery, radiotherapy and parotid pleomorphic adenoma, parotid surgery outcomes. The following databases were examined: PubMed, Handle-on-qol, Medline, Ebase (Excerpta Medica), Science Citation Index/Social Sciences Citation Index, Ovid Evidence-Based Medicine databases.
Only manuscripts written in English were included. All instruments included in PRISMA guidance was considered in the search and presentation of the results[10]. A total of 2301 papers were identified. From an evaluation of the abstracts and available full text, 49 relevant papers were closely examined (Figure 1). Information was collected relating to the topic of the paper, sample size, recurrence rate, facial nerve status, types of surgery, adjuvant treatments relating to recurrence, clinical outcome (current clinical status).

Results

The authors found 49 papers, which satisfied our inclusion criteria (Figure 1). Most studies were retrospective case series. A detailed description has been presented in Table 1[1,2,9,11-56].
A superficial or a total parotidectomy are the operations of choice in RPA of the parotid given the multicentricity of the lesions and the risk of further recurrences[12,35]. In selective cases with small volume recurrent disease an extracapsular dissection may be employed. A superficial or a total parotidectomy is the gold standard for the management of RPA but may be inadequate to control disease. There is evidence from retrospective series that postoperative radiation therapy improves local control[15]. Clear margins are essential but

cannot guarantee a cure in RPA[12,25]. There is evidence now that PAs slowly gain malignant characteristics after repeated recurrences[21]. Myxoid subtypes of PA tend to have incomplete and thinner capsules and to recur more frequently. Larger PA tend not only to exhibit incomplete capsules but in addition are associated with more numerous satellite nodules[46]. Larger tumours seem, in most studies (Table 1), to be associated with more frequent recurrences. The use of Intraoperative Facial Nerve Monitoring during RPA parotidectomy reduced the duration of surgery and the incidence of postoperative facial paralysis ($P < .01$ and $P = .01$, respectively) and reduced recovery time[18].

A promising tool might be the intraoperative use of sodium fluorescein in case of recurrent PA with a risk of damaging the facial nerve. With the help of this tool, which is integrated into the microscope, nerve fibres can become visible for the surgeon, making dissection of the nerve easier and allow for facial nerve preservation[57,58]. This technique is used by the authors and allows for identification of nerve fibres if a standardized protocol is used[57,58]. The correct timing of sodium fluorescein application makes nerve fibres visible, even in situations of actual wound healing or patients who received radiotherapy [58,59]. Although this technique is new and needs further prospective evaluation, it might be suitable for patients with RPA allowing facial nerve preservation.

Discussion

The management of RPA presents a challenge to the clinical team. Often there are multiple local recurrences- that may not necessarily all be 'visible' during pre-operative imaging due to their size- that may become apparent during the surgical intervention or during histopathological examination. Despite the lack of randomized studies and the paucity of prospective studies, the available data in this structured review seem to point toward a series of coherent arguments.

Controversies are evident from this work and mostly relate to the type of operation and the use of post-operative radiotherapy. Often clinicians adopt a pragmatic view that takes into account the location of the recurrent tumour, whether it is a multinodular or uninodular recurrence, the size and the rate of growth as well as the patient's co-morbidities. Selected cases can be observed. Conservative surgical management can include partial superficial parotidectomy or extracapsular dissection. In patients that are symptomatic but unfit for a surgical intervention, radiotherapy could be suggested as an alternative for surgery. Total parotidectomy, is appropriate in many patients, but may be inadequate to control recurrent pleomorphic adenomas. Adjuvant radiotherapy seem to significantly improved control in multinodular recurrences [56]. Sometimes the clinical scenario may include elderly patients with multifocal recurrences where the facial nerve is engulfed by scar and tumour. Limited data[55,60] suggested a role for radical parotidectomy with immediate nerve reconstruction. Most clinicians though, will preserve the facial nerve whenever possible. Lumpectomy is not the operation of choice for the management of RPA and this is reflected in the literature[1,2,3], but there may be clinical situations that can be considered. This is little talked about but it may be an entirely rational approach for the older, frail patient who may now have another multi-focal recurrence, many years after primary treatment which spilled tumour, had radiotherapy and then had recurrence with multiple nodules. The risk in this group is that some of the nodules may undergo stochastic malignant change. In our experience, these were usually the rapidly expanding nodules which could be safely excised as a lumpectomy, clearing early carcinoma ex PSA and causing 'minimal damage' to patients with somewhat limited life-expectancy. A radical parotidectomy with nerve reconstruction rather than a 'lumpectomy' may be inevitable in the latter scenario in a patient that is fit for an extensive operation.

It is evident from this work that we are lacking appropriately designed and powered prospective multicentre randomised controlled studies that would better inform the clinical teams and provide an improved patient outcome. This in part, is due to the nature of the disease, its growth characteristics and often a long period between initial surgery and recurrence. Despite the lack of level I evidence, using the current data a flow pathway may be suggested (Figure 2). Another aspect of the management of RPA relates to the long term clinical outcome. Although RPA metastases are rare[13], we need to keep in mind that a high percentage of RPA are incurable[12]. Patients need to be informed well about the potential need of multiple operations over time, the adverse effect on the facial nerve and the rate of malignant transformation[3]. In some circumstance (elderly patients with significant comorbidities), best supportive care may be the only option.

A clear resection margin cannot guarantee a cure in RPA, and it seems that parotid pleomorphic adenomas slowly gain malignant characteristics after repeated recurrences. When marginal clearance is of clinical concern, options include further surgery or post-operative radiotherapy. Patel et al (2014) demonstrated improved locoregional control for patients with close or positive margins[16]. One reason for the reluctance –from the surgical teams-to use radiation therapy is the fear of inducing a second malignant tumour in the remaining gland or in other organs of the head and neck. However, the incidence and side effects appeared to be low [16] with IMRT, this is something that need to be discussed in detail especially in young patients. Recurrent operations are challenging and can result in poor aesthetic or functional outcome in RPA, especially when the facial nerve is at increased risk of damage due to previous extent of surgery or multifocal recurrences. The data is limited specifically to RPA, but the use of intraoperative facial nerve monitoring seem to reduce the duration of surgery, enhance recovery and reducing the incidence of long term paralysis. This appears to be a logical argument and a current practice in RPA surgery.

Conclusions

The management of RPA of the parotid gland is challenging. There is a lack of randomised and prospective studies but there is a large volume of retrospective studies that included practises indicating good clinical outcomes. There is a need for some flexibility in the management of this condition in order to accommodate current patient health, the natural history of the disease and the effect of the treatment modalities in the patient's quality of life. Because of the complexity of the condition, there is need for tailored treatment. Surgeons should be prepared to offer , in addition to a superficial / total parotidectomy , a radical parotidectomy with immediate reconstruction or even a 'lumpectomy' on selective cases. The relative low incidence of RPA and the requirement of a prolong follow-up, has adversely affected progress.

Conflict of interest: the authors have no conflict of interest to declare

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Conflict of interest: The authors have no conflict of interest to report

Figure 1 Search results included in the review

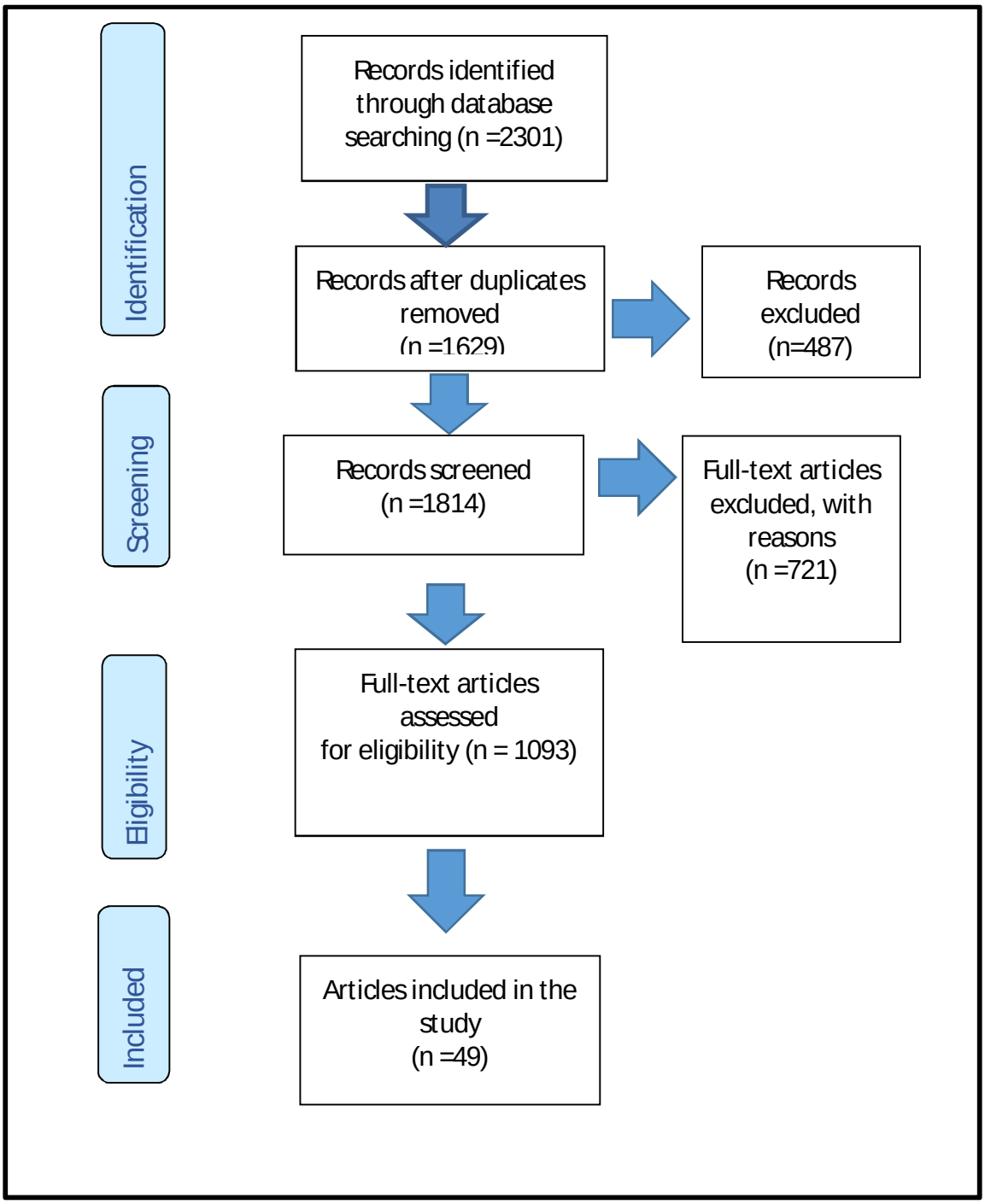

Figure 2: A guide for the management of recurrent parotid PA

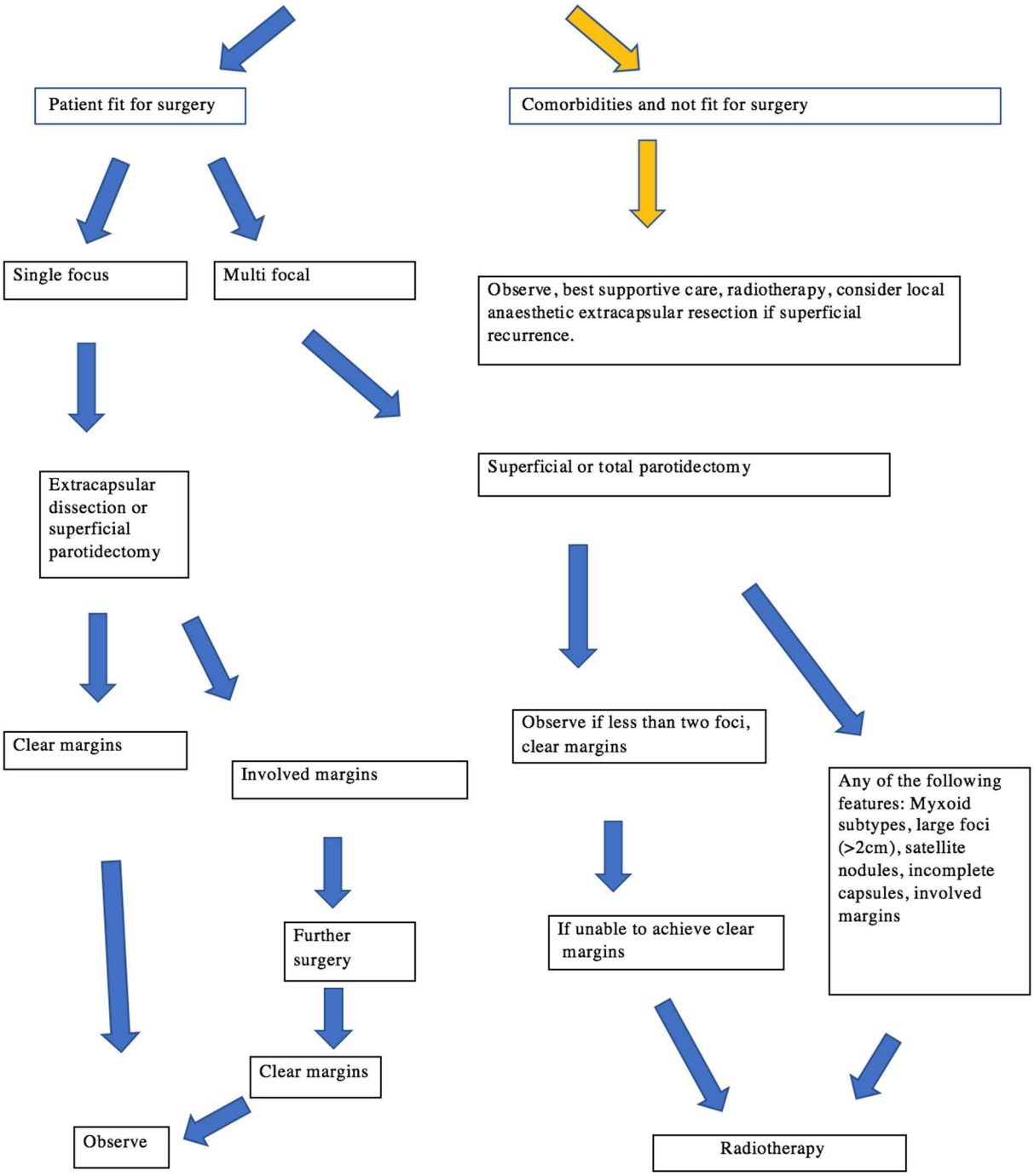

Table 1: Details from studies included in this paper

Authors	**Sample size and type**	**Recurrence rate**	**Surgery type**	**Adjuvant treatment**	**Main Conclusions**
Espinosa et al[11] 2017	198 Retrospective study	Enucleation -78.6% Superficial Parotidectomy-6%	Enucleation and Total / superficial parotidectomy	No mention	Young age, enucleation, and positive margins are risk factors for residual PA. Surgical technique and histomorphologic features are associated with increased facial nerve dysfunction.
Abu-Ghanem et al[1] 2016	22 patients with RPA Retrospective study	All these were patients with recurrence		Radiotherapy given to 9 patients	Recurrent PA of the parotid gland tends to occur in long intervals in a multifocal pattern
Witt RL et al[12] 2016	Review				The most important causes of recurrence of benign pleomorphic adenoma are enucleation with intraoperative spillage and incomplete tumour excision
Mc Garry et al[13]	1 Case report				RPA of parotid

2016					with pulmonary metastasis
Andreasen S et al[14] 2016	Danish Pathology Data Bank was searched	2.86%			The rate of malignant transformation in recurrent pleomorphic adenoma was 3.3%.
Witr RL[15] 2015	Review		Total parotidectomy		Most recurrent pleomorphic adenoma are multinodular
Patel S et al[16] 2014	21 Retrospective study	21 patients with close or positive margins		Post-operative radiotherapy routinely	PORT for patients with pleomorphic adenoma of the parotid gland after resection with close or positive margins results in excellent locoregional control and low treatment-related morbidity.
Philouze P et al[17] 2014	Case Report	1		Post-operative radiotherapy	Adjuvant radiotherapy can be given in recurrent multifocal PA.

Liu H et al[18] 2014	58 Cohort study	58 RPA	Total and superficial Parotidectomy		The use of IFNM during total or wide resection RPA parotidectomy reduced the duration of surgery and the incidence of postoperative facial paralysis and enhanced recovery. However, there was little impact on facial nerve outcomes when IFNM was used during superficial RPA parotidectomy.
Causevic VM et al[19] 2014	60 patients Retrospective study	After enucleation (88.9%), then after excision (46.9%), and the least after superficial (4%) and total parotidectomy (0%).		No	Total or superficial parotidectomy were optimal surgical procedures
Strub GM et al[20] 2012	1 patient Case study		Total parotidectomy	Yes	Transcranial RPA, recurred after 30 years

Becelli R et al[21] 2012	1 patient Case report		Conservative parotidectomy	Yes	
Park GC et al[2]	110 patients Retrospective study	10 patients	Superficial parotidectomy		Satellite nodules and tumor rupture increase the risk of recurrence in patients with pleomorphic adenomas treated by superficial parotidectomy
Papadogeorgakis N et al[22] 2012	1 Case report				The probability of subsequent recurrence increases with each recurrent episode, thus making local control difficult and damage to the facial nerve more likely.
Soares AB et al[23]	39 cases in total, 29 with RPA				This study showed that recurrences were multinodular

2011	Immunohistochemical study				
Makeieff M et al[24] 2010	62 consecutive patients with RPA		New recurrence after surgery is less frequent if the initial treatment for pleomorphic adenoma is total parotidectomy.		Surgery is recommended in pleomorphic adenoma recurrence because of the high rate of carcinoma ex pleomorphic adenoma (16.1%)
Suh MW et al[25]	270 patients retrospective study				A clear resection margin cannot guarantee a cure in RPA
Soares AB et al[26] 2009	A total of 19 cases of PA and 24 cases of RPA Immunohistochemical study				RPA presents more aggressive clinical behaviour than PA
Bhutta MF et al[27] 2010	1 case report				Case of renal metastasis of a recurrent pleomorphic adenoma

Ghosh A et al[28] 2008	1 case report				PA of the parotid gland that metastasized to the scapular region
Redaelli de Zinis LO[29] 2008	33 patients Retrospective study	The estimated tumour recurrence rates were 14.1+/-6.6% at 5 years, 31.4+/-9.4% at 10 years, 43.0+/-10.8% at 15 years, and 57.2+/-14.8% at 20 years.	A total or extended total parotidectomy was performed in 16 cases (48.5%), a superficial parotidectomy in 10 cases (30.3%), and a local excision in 7 cases (21.2%).		RPAs are prone to new recurrences, especially when multinodular and treated with a local excision. Surgical treatment should include facial nerve resection in selected cases
Wittekindt C et al[30] 2007	134 RPA	All RPA patients	Extended parotidectomy		Extended parotidectomy seems to be the best approach for the reoperation to reduce the risk of recurrence.
Steele NP et al[31]	1 case report				Case of pleomorphic adenoma of the parotid gland

2007					metastasizing to a mediastinal lymph node
Chen AM et al[9] 2006	34 patients treated with post-operative radiation	With a median follow-up of 17.4 years (range, 2.3-28.9 years), 2 patients had local recurrences at a median of 3.4 years after completion of radiation		Yes	The use of postoperative radiation therapy leads to excellent long-term local control for the treatment of recurrent pleomorphic adenoma with acceptable late toxicity.
Leonetti JP et al[32] 2006	42 patients with RPA		Total parotidectomy or subtotal petrosectomy with facial nerve resection		Two of 42 patients were found to have carcinoma ex-pleomorphic adenoma, both of these patients underwent prior radiotherapy, and both died of metastatic disease.
Maxwell EL et al[33] 2004	35 RPA patients	Locoregional control rate of 77%.	Total parotidectomy	No	Local excision of recurrent disease is sufficient in controlling further recurrence.
Zbären P et al[34]	33 patients with RPA	Multifocal recurrence and carcinoma in pleomorphic adenoma were observed in 73% and 9%	Enucleation and superficial parotidectomy		To evaluate the re-recurrence rate, a follow-up of at least 10 years is necessary.

2005		of patients, respectively.			
Stennert E et al[35] 2004	31 patients with RPA prospective study	Most recurrences were multinodular	Total parotidectomy		The myxoid subtype was predominant.
Koral K et al[36] 2003	15 patients retrospective study				The lesions were multiple in 73.3% of patients
Glas AS[37] 2002	52 patients with RPA				Progesterone receptor seems to be a prognostic factor in RPA
	7 patients retrospective study		Total parotidectomy with facial nerve preservation		Tumour control rates and facial nerve preservation are enhanced with formal parotidectomy

Becelli R et al[38] 2001					
RowleyH et al[39] 2000	12 patients with RPA retrospective study		Superficial parotidectomy	Three patients required adjuvant radiotherapy.	Type of recurrence was uninodular or multinodular
Carew JF et al[40] 1999	31 patients retrospective study		More than half of these patients underwent total parotidectomy.	Better local control was seen in 11 patients who received postoperative irradiation (100% at 10 years) than in 20 patients who did not (71% at 10 years; $P < 0.28$)	Postoperative radiation therapy may improve control in patients at high risk for another recurrence.
Yasumoto M et al[41] 1999	15 patients with RPA retrospective study				Most recurrent pleomorphic adenomas were well delineated with smooth margins, like most primary tumours.
Patel N et al[42] 1998	24 RPA patients retrospective study	Recurrence rates are between 0-4%		Yes	Radiotherapy is controversial, it should be considered if there has been tumour

					spillage following re-operation.
Yugueros P et al[43] 1998	39 patients with RPA retrospective study			Yes	When previous parotidectomy has been performed, simple excision with a margin of surrounding tissue would seem appropriate.
Laskawi R et al[44] 1998	94 RPA patients retrospective study				Adequate initial operation to avoid recurrences of pleomorphic adenomas in the parotid gland.
Leverstein H et al[45] 1997	40 patients with RPA.			16 received postoperative radiotherapy	Recurrent disease tends to be multifocal in origin, prolonged routine follow-up is required.
Renehan A et al[46] 1996	114 RPA patients retrospective study			Yes	Multinodular tumours have a high risk of relapse-advised radiotherapy

Phillips PP et al[47] 1995	126 patients with RPA retrospective study.	Recurrence was 32.5%			These results suggest low morbidity and good success in tumour eradication with an aggressive surgical approach.
Natvig K et al[48] 1994	346 patients	Six (2.5%) patients had a recurrence 7 to 18 years postoperatively		No	We also question the justification and benefit of postoperative radiotherapy for patients with this benign disease.
Jackson SR et al[49] 1993	209 patients retrospective study	38 RPA	Total / Superficial parotidectomy		
Buchholz TA[50]	6 RPA retrospective study			Yes	Neutron radiation also carries a low risk of facial nerve

1992					damage, a consideration that may argue for limiting the extent of surgical resection of recurrent disease.
Dawson AK[51] 1989	29 patients were treated by excision and post-operative irradiation following RPA Retrospective study	Eighteen of 20 (90%) patients with a first recurrence were controlled comparing favourably with series employing surgery only.		Yes	Radiation therapy has a role to play as a surgical adjuvant in the management of these tumors
Fleming WB[52] 1987	19 RPA patients			No	Radiotherapy does not seem to be an appropriate alternative to repeated surgical excision.
Niparko JK et al[53] 1986	48 RPA patients	Malignant conversion developed in three (6%) of 48 cases	Formal partial or total parotidectomy		En bloc total parotidectomy offers effective, though not absolute, control of extensive recurrence.

Maran AG et al[54] 1984	19 RPA retrospective study			No	The suggested treatment of recurrence is total parotidectomy with preservation of the facial nerve.
Stanley RE et al[55] 1984	19 RPA retrospective study				Eighteen out of the 19 patients did not have further recurrences after revision parotidectomy.
Conley J et al[56] 1979	Review	The recurrence rate for benign mixed tumour in the parotid gland is variously reported in the ranges of 0.5% to 10%			