

Recurrent Pleomorphic Adenoma of the Parotid Gland: Treatment Outcomes and Risks of Ulterior Recurrence

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ABSTRACT

Background: Surgical management of recurrent pleomorphic adenoma (RPA) of the parotid gland has a considerable risk of facial nerve injury and a high re-recurrence rate. To obtain more insight into this issue we evaluated our experiences.

Materials and methods: A retrospective analysis of all patients treated surgically for recurrent pleomorphic adenoma (RPA) of the parotid gland was performed. Clinical examination included the site and nature of the RPA, facial nerve status and so on. The extent of clinically suspected recurrences was determined by CT and sometimes with MRI. The surgical treatment included local excision, partial or total superficial parotidectomy with preservation of the facial nerve, and total parotidectomy with sacrifice of the facial nerve. Patients were followed regularly at 3, 6 and 12 months interval for the first year followed by once annually during a period ranging from 1 to 9.

Result: 20 out of 48 patients were included. Mean age at the time of the first surgery was 44.5 years, 65% were female and 35% were male. Mean time between IPS and I-RPA was 15.7 years. Mean interval between recurrences was 10.6 years for first recurrence, 9.5 years for the second, 3.2 years for the third and 2 years for the fourth. Tumor recurrence lateral to the facial nerve (superficial lobe) was 85% and medial to the nerve (deep lobe) was 15%. Multinodular recurrence was 80%, with the largest nodule ranging from 0.7 to 6 cm (mean 2.3cm). IPS with local excision ($P=0.04$), surgery other than parotidectomy at I-RPA ($P=0.006$), detection of microscopic multinodular disease at I-RPA ($P=0.003$) and age of 30 years or less at the time of IPS ($P=0.001$) were associated with an increased risk of new recurrence.

Conclusion: In treatment of RPA, PSP has a better local control rate than LE and has results similar to those of SP or TP. Thus, we recommend that PSP with careful dissection of facial nerve should be considered for the treatment of RPAs.

Keywords: parotid gland, parotidectomy, pleomorphic adenoma, recurrence.

INTRODUCTION

Recurrence of the pleomorphic adenoma of the parotid gland is the most serious outcome of parotidectomy because of the considerable risk of facial nerve injury and the high rerecurrence rate. The treatment of recurrent pleomorphic adenoma (RPA) has never been appropriately defined mainly because of the absence of

sufficiently large series and randomized control trials evaluating this topic.

At this point, surgery remains the most common approach.¹ Parotidectomy with facial nerve preservation is the standard surgical procedure for the management of pleomorphic adenoma of the parotid gland.²

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Recurrence rates have been reported to be about 3% after total parotidectomy and about 5% after superficial parotidectomy, which is an option for superficially located adenomas.³ Local excision by simple enucleation was tried initially, but the reported high recurrence rate, above 25%, and up to 45% was unacceptable.^[4] Secondary surgery is less likely to control the tumor than the initial surgery and carries a higher risk of facial nerve damage since the nerve is less well-defined due to the scarring of the operative field. Facial nerve paralysis, although a known complication after parotidectomy,⁽⁵⁾ is a severely disfiguring problem that is not followed by satisfactory restoration and rehabilitation. Intraoperative facial nerve injury occurs in 7% to 50% during the surgery for recurrence.^{2,6-8} On the other hand, there is still a risk of ulterior recurrence (UR) even after wide surgery which ranges from 10% to 70%.⁹⁻¹²

In this study, we reviewed our experience with the treatment and outcomes of RPA of parotid gland. In addition, we evaluated the factors associated with an increased risk of rerecurrence of RPA of parotid gland.

Patients and methods

A retrospective analysis of all patients treated surgically for recurrent pleomorphic adenoma (RPA) of the parotid gland at the Department of Oral and Maxillofacial Surgery, the 1st Affiliated Hospital of Dalian Medical University between 2005 and 2012 was performed. The data such as clinical and pathologic features, types of initial surgery and surgery for the recurrence and complications were derived from medical records, interviews, and physical examinations of all living patients and the pathologic materials of all patients were revised. Only the cases with RPA of parotid gland with sufficient data from the initial surgery to the surgery for the recurrence/s were included in the study while the cases with insufficient data and cases with malignant transformation of RPA of parotid gland were excluded.

Preoperative examination

All patients underwent both clinical and radiographic examination. Clinical examination

included the site and nature of the RPA, facial nerve status and so on. The extent of clinically suspected recurrences was determined by CT and sometimes with MRI. CT scan was carried out as a primary imaging in all patients with RPA while MRI is the choice of imaging to evaluate the deep lobe involvement of the tumor. Ultrasonography (USG) and preoperative fine-needle aspiration cytology (FNAC) are not routinely performed in our institution and were not carried out in any of the patients in this study.

Surgical technique

The surgical treatment used depended on previous surgical interventions. The operative procedures for the recurrence included –

- Local excision (LE),
- Partial superficial parotidectomy (PSP) with preservation of the facial nerve,
- Superficial parotidectomy (SP) with preservation of the facial nerve,
- Total parotidectomy (TP) with preservation of the facial nerve and
- TP with sacrifice of the facial nerve.

LE was defined as removal of the tumor from the parotid gland along with some amount of normal gland tissue without exposure of the main trunk of the facial nerve; if the main trunk is exposed, the procedure is designated as partial parotidectomy (PSP) as parts of the superficial lobe of the gland is left in place; superficial parotidectomy involves removal of the parotid tissue superficial to the facial nerve and its branches after identification and dissection of the facial nerve branches; consequently, removal of the entire gland is total parotidectomy. In this operation, the entire parotid gland is supposed to be removed, and the facial nerve is preserved.

Postoperative management and follow-up

All patients remained in the hospital for an average period of 3 to 6 days after the operation in order to regularly monitor their general condition as well as wound healing. All patients were followed regularly at 3, 6 and 12 months interval for the first year followed by once annually during a period ranging from 1 to 9

years with a mean of about 4 years (median: 3 years).

Analysis of outcome

We analyzed the surgical treatment results and the risk of ulterior recurrence. Statistical analyses were performed using SPSS version 17.0 software. Data were summarized according to frequency and percentage for categorical variables. Mean, standard deviation, median, and range were computed for continuous variables. All survival times were calculated from date of study entry. Local control rates or Relapse-free survival (RFS) rates were estimated by Kaplan–Meier method. For calculation of RFS, an event was defined as a local recurrence. The log-rank test was performed to compare groups. All statistical tests were two-sided, and *P* value of <0.05 was considered statistically significant.

RESULTS

Characteristics of primary pleomorphic adenoma (PPA) and RPA

From 2005 to 2012, 48 patients had been treated for RPA of the parotid gland. In 46 patients, the primary pleomorphic adenoma (PPA) was resected elsewhere. 2 patients were treated initially at this hospital. 28 of the 48 patients were excluded from this study either due to lack of sufficient information or due to malignant transformation of the RPA.

Mean age of patients at the time of the first surgery for RPA in our department was 44.5 years, with median age of 42.5 years (range 22-66 years) (Table I). There were 13 female (65%) and 7 male (35%) patients, with a sex ratio of 1.8:1. Mean age at the time of initial surgery for the pleomorphic adenoma (IPS) was 28.7 years, with median age of 28.5 years (range 12-50 years).

Table I. Descriptive statistics of the continuous variables.

	Age at IPS (yrs)	Age at 1RPA-DMU (yrs)	Tumor size at 1RPA-DMU (cm)	Time between IPS and 1RPA-DMU (yrs)	Follow-up time from 1RPA-DMU (yrs)
N	20	20	20	20	20
Mean	28.7	44.4	2.32	15.7	3.95
Median	28.5	42.5	2.0	14.5	3.0
SD	9.92	12.61	1.35	9.54	2.66
Minimum	12.0	22.0	0.7	1.0	1.0
Maximum	15.0	50.0	6.0	42.0	9.0

N – number; *SD* – standard deviation

Mean time between IPS and I-RPA was 15.7 years (median 14.5 years; range 1-42 years). Mean interval between recurrences was 10.6 years for first recurrence, 9.5 years for the

second, 3.2 years for the third and 2 years for the fourth (Table II). It was the first recurrence for 12 patients (60%) and second or more for 8 patients (40%).

Table II. Descriptive statistics of the recurrence intervals (RI)

	1RI (yrs)	2RI (yrs)	3RI (yrs)	4RI (yrs)
N	20	8	4	2
Mean	10.57	9.55	3.2	2.0
Median	8.0	6.0	4.0	2.0
SD	7.6	9.04	2.04	0.0
Minimum	0.5	1.04	1.0	2.0
Maximum	26.0	28.0	5.0	2.0

N – number; *SD* – standard deviation

Tumor recurrence was lateral to the facial nerve (superficial lobe) in 17 patients (85%) and medial to the nerve (deep lobe) in 3 (15%). Multinodular recurrence was present in 16 patients (80%), with the largest nodule in each patient ranging from 0.7 to 6 cm (mean 2.3cm; median 2 cm).

Initial parotid surgery (IPS) consisted of local excision in 16 cases (80%) and superficial parotidectomy in 4 cases (20%). (Table III)The

operative procedures for recurrence depended largely on patient's previous surgical history. Local excision (LE) was performed in 3 patients (15%) including excision of the involved skin in one, partial superficial parotidectomy (PSP) in 8 patients (40%) with skin excision in two, superficial parotidectomy (SP) in 6 patients (30%) including skin excision in one and total parotidectomy (TP) in 3 patients (15%) including skin excision and facial nerve sacrifice in one.

Table III. Description of qualitative variables.

Variable	Modality	No.	%
IPS	LE	16	80%
	SP	4	20%
	TP	-	
No. of previous interventions	1	12	60%
	2	4	20%
	3	2	10%
	4	2	10%
1RPA-DMU	LE	3	15%
	PSP	8	40%
	SP	6	30%
	TP	3	15%
Site of recurrence at 1RPA-DMU	SL	17	85%
	DL	3	15%
multinodular disease on HP at 1RPA-DMU	Y	16	80%
	N	4	20%
Definitive facial palsy 1 year after 1RPA-DMU	Y	3	15%
	N	17	85%
New recurrence after 1RPA-DMU	Y	2	10%
	N	18	90%

HP – histopathology; SL – superficial lobe; DL – deep lobe; Y – yes; N – no.

Functional Results

Two patients had abnormal facial nerve function before surgery, presumably due to prior surgery, which involved a single branch (buccal) in one patient and two branches (buccal and marginal mandibular) in the other. During the surgical extirpation of the RPA, nerve-sparing surgery was possible in both of these cases. The main trunk of the facial nerve had to be sacrificed in 1 of the other patients because it was encased by the tumor.

After the surgery for the recurrence (I-RPA), transient facial nerve paresis was present in 8 patients (40%) while permanent facial nerve

dysfunction was present in 3 patients (15%) one year after the surgery. Of the three patients, one showed paresis of the buccal branches, functional loss of the buccal and mandibular branches both occurred in one patient while the other patient with facial nerve resection had complete paralysis on the side of resection.

Recurrence

Two patients (10%) had ulterior recurrence (UR) after I-RPA. Mean time between I-RPA and UR was 4.5 years (median 4.5 years; range 2-7 years). Mean age at time of ulterior recurrence was 46.5 years. Initial surgery involved local excision in both cases. It was the second

recurrence for one patient and the third for the other. The new recurrence was treated surgically by superficial parotidectomy in both cases.

In order to evaluate the local control (relapse-free survival) rates and the factors associated with increased anterior recurrence risk, we

studied the following factors (Table IV): age at time of I-RPA, gender, initial parotid surgery procedure (IPS), number of recurrence/s before I-RPA, I-RPA surgical technique, microscopic multinodular disease in I-RPA, and age at initial surgery.

Table IV. Variables studied to identify the risk factors for UR after surgery for RPA: p value (log-rank test)

Variable	Modality 1 versus 2	P-value
Age at 1RPA-DMU (yrs)	>40 vs ≤40	0.288
Gender	M vs F	0.473
IPS	LE vs SP	0.04
No. of recurrence before 1RPA-DMU	≥1 vs 0	0.806
	>1 vs ≤1	0.519
1RPA-DMU		
1. LE	1 vs 2+3	0.006
2. PSP/SP	1+3 vs 2	0.404
3. TP	1+2 vs 3	0.496
Multiple nodules at 1RPA-DMU	No vs Yes	0.03
Age at IPS (yrs)	>30 vs ≤30	0.001

Statistically significant factors for new recurrence risk were IPS extension, surgical technique at I-RPA, detection of multiple nodules in pathologic examination of I-RPA specimens and age at IPS. IPS with local excision ($P=0.04$), surgery other than parotidectomy at I-RPA ($P=0.006$), detection of microscopic multinodular disease at I-RPA ($P=0.003$) and age of 30 years or less at the time of IPS ($P=0.001$) were associated with an increased risk of new recurrence.

Anterior recurrence occurred in 2 patients yielding the overall local control rate of 90% at 4 years. Better local control was observed when

- the initial surgery was a conventional parotidectomy (superficial parotidectomy) with facial nerve dissection (75% vs 56.3% with local excision at 15 years) (Fig. A)
- the age at I-RPA was 40 years or less (100%).
- the number of recurrence before I-RPA was 0 (100% vs 77.8% when it was 1 or more).
- the surgery at I-RPA was some form of parotidectomy (94% vs 66.6% with local excision).
- the recurrence at I-RPA was uninodular (100%).

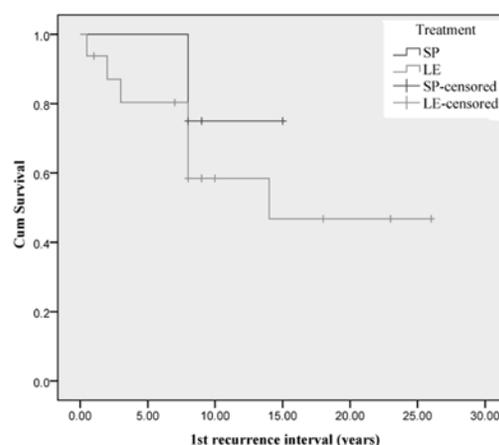


Fig. A. Kaplan–Meier graph: relapse-free survival (RFS) rates in the two groups of patients: LE versus SP at IPS ($P = 0.04$, log-rank test). At 15 years, the local control (RFS) rate was 75% with SP and 56.3% with LE.

DISCUSSION

Initial treatment

The technique of enucleation of primary pleomorphic adenoma was based on the idea that these tumors were encased in a firm capsule. However, recurrence rates after enucleation were as high as 45%.^{13,14} Microscopic anatomic studies showed that

pleomorphic adenoma presents often with a focal absence of a capsule; furthermore, capsular herniation, pseudopodia, and satellite nodules are frequently observed.^{7,15-18} During surgery, especially with the enucleation technique, small lobulations or pseudopodia of tumor outside the presumed capsule can be detached and left within the normal salivary gland tissue.^{7,15,17}

The high recurrence rate after enucleation led to a change in treatment philosophy. The enucleation technique was replaced by a superficial parotidectomy for tumors in the superficial lobe. Since the introduction of this technique, the recurrence rate decreased to 2% to 5% in the last decades.¹⁶ However, several investigators have reported that the recurrence rate after extracapsular dissection of pleomorphic adenoma is the same as that after superficial parotidectomy.^{19,20} They advocated that a few millimeters of surrounding parotid tissue might be sufficient for complete resection of a pleomorphic adenoma. In addition, in a large number of patients even a superficial or total parotidectomy with facial nerve preservation incorporates the principle of limited enucleation or capsular dissection at some point during the procedure.²¹ Intraoperative tumor spill during parotidectomy, when properly managed, did not seem to be associated with an increased rate of tumor recurrence.^{22,23}

Some surgeons consider superficial parotidectomy as an ideal procedure^(18, 20) which is also supported by this study in which only 25% of the patients treated initially with SP had more than one recurrences in contrast to about 44% with LE. So, we, speaking in support of SP, advocate that enucleation/LE for pleomorphic adenoma should be avoided.

Age at first presentation and recurrence interval

Several investigators have reported that the mean age of initial presentation of pleomorphic adenoma among patients who later developed multiple recurrences was significantly lower than the mean age of those who remained relapse-free after the surgery for the first recurrence on

long-term follow-up.^{14,24} We can confirm this observation because all of the patients with multiple recurrences in our study had had initial surgery at the age of below 30 years while 83.3% of the patients with a single recurrence were above 30 years at the time of IPS.

The median interval between the initial surgery and tumor recurrence is reported to be between 3 and 15 years^{15,25} which is similar to our results i.e. the median interval in our study was 8 years. Similarly, the mean interval for the 2nd and 3rd recurrences has been reported as 4 years and 4.5 years respectively¹² which were 9.5 years and 3.2 years respectively in this study.

Surgical treatment of recurrent pleomorphic adenoma

RPA is a clinical entity that encompasses lesions with different clinical characteristics and different degrees of difficulty for surgical treatment.¹² The surgical treatment of RPA is a challenge and has never been standardized.^{26,27} The type of surgery applied in our series was based on the extent and location of the recurrence as well as the type of surgical procedure done initially.

With appropriate initial parotid surgery, i.e., total or superficial parotidectomy, the recurrence rate is less than 5%, but this rate rises to 10–70% after revision surgery.^{10, 13, 20, 25,}

²⁸ It was 10% in this study after I-RPA. Despite improvements in initial surgical management of PPA, cases of RPA are still reported. Microscopic multinodular disease and the impossibility of achieving a 2 cm margin could explain the recurrence of PPA even after total parotidectomy.¹²

In case of recurrence, complete removal of all salivary gland tissue reduces the probability of a new recurrence (10). However, we prefer only partial removal of the salivary gland as far as possible but of course with complete removal of the recurrent tumor along with a generous amount of normal gland tissue. In this study, PSP was the most commonly performed surgery during I-RPA (40%) with a 100% local control rate. If partial parotidectomy had been attempted already for one or more times, then we would go for complete removal of the

superficial lobe (SP) or both superficial and deep lobes (TP) which in this study were 30% and 15% respectively both with 100% local control rates. PSP has already been adopted as the standard treatment for the RPAs with recurrence rate of <1%.^{29,30} Since the outcome of PSP was similar with the SP and TP in this study, we would suggest that PSP should be considered in the treatment of the RPAs whenever feasible.

Dealing with the facial nerve

Permanent partial facial nerve injury is a pertinent risk when treating RPA of the parotid gland. The incidence in this study was 15%, which is comparable with the incidence of 15% to 29% published elsewhere.²⁶ However, without the cases in which the facial nerve was dysfunctional before surgery (two) or intentionally sacrificed (one), permanent facial nerve dysfunction was not noted in other patients.

The facial nerve can be very difficult to identify because of the presence of scar tissue, especially after an initial superficial or total parotidectomy. Conley and Clairmont⁷ estimated the necessity of having to sacrifice the facial nerve during surgery of RPA in 14% of patients which in our study was 5%. Nevertheless, total parotidectomy with facial nerve sacrifice does not prevent a further recurrence in all patients.^{27,31} Most investigators express reservation about sacrificing the facial nerve for a benign tumor.^{11,27} Currently, and related to the use of an operating microscope and intraoperative facial nerve monitoring, nerve dissection and preservation is possible in most cases of first recurrence surgery.^{32,36} However, we have no experience with the intraoperative facial nerve monitoring. Because our results are similar with the other published results, we would conclude that facial nerve monitoring is a very useful tool but it is not a must. Witt³⁵ also concluded in his study that "intraoperative facial nerve monitoring for a mobile parotid mass of the superficial lobe is not the standard of care." Olsen and Daube³⁶ used facial nerve monitoring in 7 patients operated on for recurrent pleomorphic adenoma and concluded that "facial nerve monitoring is not a replacement for

an experienced surgeon but as an adjunct, it has proved extremely beneficial."

Characteristics of recurrent tumors

Whereas primary tumors are extremely rarely multinodular,^{17,18} 33% to 98% of RPAs are multinodular,^{10, 11, 23, 25, 26, 37, 38} thus rendering radical treatment difficult. The incidence of recurrence with microscopic multinodular disease in our study was 80% which is within the range of the published reports. MRI use is now systematic. It aids in evaluation of remnants of parotid tissue after previous procedures, leading to discovery of multinodular tumors especially situated in the deep lobe of the parotid gland which most often might be missed by clinical examination alone.¹²

Follow-up

In our study, the median first re-recurrence interval was 6 years, and re-recurrence occurred as long as 28 years. It means that 6 years is necessary to detect one half of failures, and up to 28 years is necessary to capture all recurrences. This is similar to the results of Carew et al 1999¹⁰ in which the median disease-free interval was 9 years and treatment failure was observed as long as 30 years.

The local control rate after treatment of RPAs is also difficult to estimate for the same reasons. Recent reports indicate that the local control rate varies from 37% to 89.5%.³⁹⁻⁴³ As would be expected, the studies with longer follow-up usually have higher rates of recurrence. The median time to recurrence in the treatment of RPAs in most of these studies is similar to the time to recurrence noted after initial surgery: 6.0 to 9.9 years.^{31,42} In one report, none of the patients followed up for less than 10 years had recurrence, whereas 43% of patients followed up more than 10 years had recurrences⁽⁴²⁾. In our study, mean follow-up after I-RPA was 4 years (range 1-9 years) which is quite short. Tumor control rate of 90% at 4 years in our study, however, is comparable with that described by others with similar lengths of follow-up.

In our experience, there is risk of UR even after wide surgery. This risk was found to be higher if the IPS was local excision ($P = 0.04$). Detection of

microscopic multinodular disease in I-RPA was associated with an increased risk of UR ($P = 0.003$). Surgery other than parotidectomy at I-RPA ($P=0.006$) and age of 30 years or less at the time of IPS ($P=0.001$) were also associated with increased risk for UR. However, unlike M. Makeieff (2010) (12) who found that patients with more than one recurrences had a higher risk of UR, we couldn't establish this association in this study. Similarly, in contrast to our results, he didn't find any association between the surgical technique at the time of first intervention at their centre and the risk of UR. This conflicting result of ours might be due to the small study sample and the short follow-up.

CONCLUSION

RPAs of parotid gland are usually located in the superficial lobe (85%) and are often multinodular (80%). It occurs frequently in young patients with initial pleomorphic adenoma treated by local excision; therefore, a pleomorphic adenoma in the superficial lobe, especially in young persons, should be treated by superficial parotidectomy with careful dissection of the facial nerve whereas local excision should be avoided for PPA. Revision surgery is challenging, time consuming, and difficult. The mean interval between the first recurrence and re-recurrence was 6 years. Good results with acceptable morbidity can be achieved by parotidectomy even though a more tailored approach is recommended to reduce the individual risk of complications. But further recurrence is still possible (10% in this study). Factors associated with an increased risk of ulterior recurrence are IPS with local excision, surgery other than parotidectomy at I-RPA, detection of microscopic multinodular disease at I-RPA and age of 30 years or less at the time of IPS. In treatment of RPA, PSP has a better local control rate than LE and has results similar to those of SP or TP. Thus, we recommend that PSP should be considered for the treatment of RPAs.

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