

Postoperative Radiation Therapy for Parotid Pleomorphic Adenoma with Close or Positive Margins: Treatment Outcomes and Toxicities

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Abstract. *Aim: To evaluate the locoregional control and treatment toxicity of patients with pleomorphic adenoma after resection with close or positive margins followed by postoperative radiation therapy (PORT). Patients and Methods: Between 2002 and 2011, twenty-one patients underwent PORT at the Mount Sinai Beth Israel Medical Center for pleomorphic adenoma of the parotid with close or positive margins. Four out of the 21 patients (19%) had recurrent lesions. The median dose was 57.6 Gy (range 55.8-69.96) delivered at 1.8-2.12 Gy/fraction. Treatment and follow-up data were retrospectively analyzed for locoregional control as well as acute- and late-treatment toxicities. Actuarial survival analysis was also performed. Results: Twelve women and 9 men with a median age of 46 (26-65) at PORT were included in this study. Eighty-one percent of the cohort had positive resection margins while 19% had close margins. At a median follow-up of 92 months, 19/21 patients (90%) had locoregional control. Two patients who failed had primary lesions which recurred locally, and initially had positive margins. The two recurrences occurred at 8 months*

and 12 months. Acute Radiation Therapy Oncology Group (RTOG) grade 1 and 2 toxicities were experienced by 11 (52%) and 4 (19%) patients, respectively, while 2 (10%) experienced late RTOG grade 1 toxicities. No patients experienced any grade 2-4 late toxicities. Actuarial survival was 100%. Conclusion: 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.

The most common salivary gland tumor is pleomorphic adenoma (1). Eighty percent of all salivary tumors are located in the parotid gland and 80% of these tumors will be benign. Additionally, approximately 80% of parotid tumors are located in the superficial lobe and 80% of these are pleomorphic adenomas. Although these are most often found in young to middle-aged women, they can occur in either sex and at any age. The current standard-of-care for treatment of pleomorphic adenoma is surgical resection. Optimal treatment with superficial or total parotidectomy results in local control exceeding 95% (2-5). For patients with gross residual disease, close or positive margins, multifocal recurrence, or with perineural invasion, postoperative radiotherapy (PORT) can provide long-term local control with minimal cosmetic and functional impairments (6). Thus, it has been our management philosophy to offer PORT to patients with close or positive margins in an effort to minimize the risk of local failure as well as the consequences of additional treatment on oncologic and functional outcome. In this report, we summarize our experience with PORT for this specific cohort of patients.

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Key Words: Postoperative radiation, postoperative radiotherapy, pleomorphic adenoma, benign, parotid, close margins, positive margins, local control, radiation toxicity.

Patients and Methods

Patients. Between 2002 and 2011, twenty-one patients with parotid pleomorphic adenoma with resection pathology revealing close or positive margins underwent PORT at Mount Sinai Beth Israel Medical Center. Patients were identified through systematic queries of our prospective, Institutional Review Board (IRB)-approved Head and Neck Database. Search results were subsequently verified with the Beth Israel Medical Center Tumor Registry. The resulting list of patients was analyzed through a review of individual consultation notes, surgical notes, radiation data and treatment planning notes, pathology reports, and follow-up reports on both digital and paper records. Our IRB deemed this study to be exempt from IRB review and compliant under the Health Insurance Portability and Accountability Act (under the provision of 45 CFR 46, Sec. 101[b]).

All patients underwent gross total resection of their parotid tumor, which may have entailed total vs. subtotal parotidectomy with facial nerve preservation and all patients completed their prescribed course of PORT. All patients had close (19%) or positive (81%) resection margins. A close margin was defined as tumor cells 5 mm from the inked margin. In cases where the tumor was peeled off cranial nerve VII, the margin status was coded as positive.

Postoperative radiation therapy was delivered using external beam in all 21 patients. Six patients were treated with a wedged pair technique or 3-dimensional conformal radiation therapy (3DCRT) using 6 MV photons, and 15 patients received 6 MV photons via an intensity-modulated radiation therapy (IMRT) approach. The range of doses to the parotid was 55.80 to 69.96 Gy, with a median dose of 57.6 Gy. All patients received daily fractions of 1.80 to 2.12 Gy. The intent of treatment was to cover a defined target volume that encompassed the surgical tumor bed alone with modest margins.

Follow-up. All patients underwent close follow-up; this was generally every 3 months for the first year, every 6 months for years 2 and 3, and every year from year 4 onward. Follow-up computed tomography (CT) or magnetic resonance imaging (MRI) was obtained from 3 to 6 months after completion of treatment. Additional imaging was carried out as clinically indicated but usually on an annual basis for the first 3 years. Median follow-up was 92 months (range 8-134) and no one was lost to follow-up.

Statistical methods. Data were analyzed using SPSS V21.0 (SPSS Inc., Chicago, IL, USA). Descriptive analysis was conducted. Frequencies and percentages were used for categorical variables and median and range for continuous variables. Actuarial relapse-free survival and overall survival curves were used to describe survival times.

Results

Twenty-one patients were included in this study. The median age of this cohort was 46 (26-65). Table I shows the baseline characteristics of these patients. Tumors were classified by size, with the majority of patients having lesions larger than 2 cm.

At a median follow-up of 92 months, 19/21 patients (90%) had locoregional control. Two patients who failed had primary lesions which recurred locally and initially had positive margins. There were no distant failures. The two recurrences occurred at 8 months and 12 months. Figure 1 shows the actuarial recurrence-free survival curve for the cohort.

Table I. Patient characteristics.

Factor	No. of patients
Age	
20s	2
30s	5
40s	6
50s	5
60s	3
Gender	
Female	12
Male	9
Tumor side	
Left	14
Right	7
Size	
≤2 cm	2
>2 cm	19
Recurrent tumor	
Yes	4
No	17
Margin status	
Close	4
Positive	17

The most common acute toxicities were dermatitis, xerostomia and mucositis. Six patients had grade 1 dermatitis and 3 patients had grade 2 dermatitis. Six patients had grade 1 xerostomia. Four patients had grade 1 mucositis and 1 patient had grade 2 mucositis. One patient had grade 1 alteration in taste. All acute reactions resolved within 3 months of treatment completion. All patients were evaluated for late toxicities including pain, fatigue, edema, xerostomia, altered taste, voice change, trismus, dysphagia, visual change or neurological sequelae, hearing loss, dental decay, osteoradionecrosis of the mandible and temporal bone, temporal lobe necrosis and radiation-induced malignancies. Only 2 patients had grade 1 xerostomia. No grade 2-4 late toxicities were noted. There were no secondary malignancies. The actuarial overall survival curve (Figure 2) shows the survival distribution of our patient cohort.

Discussion

Benign pleomorphic adenomas are the most common neoplasms of the parotid gland. It is widely accepted that surgery (parotidectomy) is the primary treatment for pleomorphic adenoma. We demonstrated the efficacy and tolerability of PORT for patients with this disease with positive or close margins after resection. A review of several series revealed that the recurrence rate was greater than 20% among patients who underwent enucleation compared to 1% in patients who underwent total parotidectomy (7). Still, the question as to how much parotid tissue should be resected

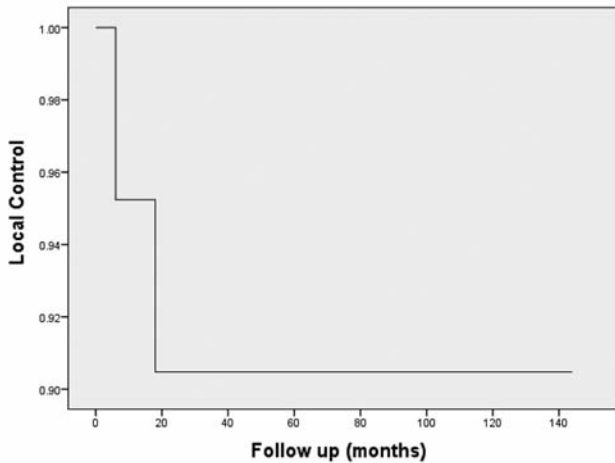


Figure 1. Actuarial relapse-free survival.

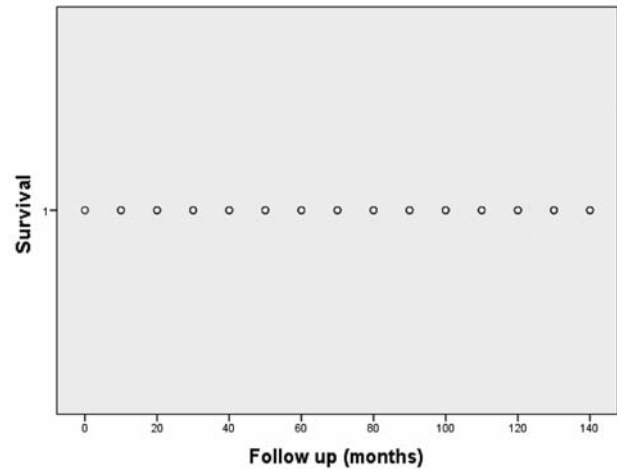


Figure 2. Actuarial overall survival.

remains and thus superficial, sub-total and total parotidectomy remain viable surgical options that can reduce the risk of local recurrence when compared to enucleation (3).

The role of PORT in the treatment of benign pleomorphic adenomas is controversial and some clinicians believe that radiation therapy should be avoided in the majority of these cases (6, 8-10). In malignant salivary gland tumors, matched-pair analysis with historical controls revealed no statistically significant benefit in local control in patients treated with PORT compared to surgery alone; however, Armstrong *et al.* (11) did find that PORT resulted in a significant improvement in survival and a benefit in local control in stage III and IV tumors. In malignant salivary gland neoplasms, there are factors other than stage that have been recognized as indicators for PORT, including close or positive surgical margins, perineural or perilymphatic invasion, intraparotid or regional nodal metastases and recurrent disease(12-15). Given the strength of evidence behind these factors, it would stand to reason that some of them may also represent applicable indicators for PORT in benign pleomorphic adenomas.

There have been a number of retrospective reviews of PORT for pleomorphic adenomas. Armitstead *et al.* (16) reported the first study that demonstrated the value of PORT in salivary pleomorphic adenomas. They reviewed 76 patients with a primary pleomorphic salivary adenoma treated with simple extra-capsular enucleation and high-energy radiation between 1963 and 1976. Only 1 patient had developed a recurrence after radiation. This study demonstrated the importance of PORT in cases where incomplete resections are performed.

Dawson *et al.* (17) reported on 29 patients with recurrent pleomorphic adenomas (mixed tumors) of the parotid treated

with excision and PORT. In this study, 18 of 20 (90%) patients with a first recurrence achieved local control comparing favorably with series employing surgery alone. PORT was thus found to be beneficial in cases of recurrent disease.

Samson *et al.* reviewed 21 cases of recurrent pleomorphic adenoma treated with subtotal excision and facial nerve preservation, followed by PORT (8). Of the 17 patients with microscopic residual tumor at completion of surgery, 16 (94%) remained free of recurrence at 6 years whereas only one of four patients (25%) with a large postoperative tumor load remained free of disease. Importantly, facial nerve function was normal in 20 of 21 patients. The authors recommended that facial nerve preservation with PORT should be considered as an alternative to nerve sacrifice in selected cases of recurrent pleomorphic adenoma. Liu reviewed 76 patients with pleomorphic adenoma of the parotid of which 55 received PORT between 1970 and 1987 at the Princess Margaret Hospital (9). These patients had been treated with total parotidectomy with facial nerve preservation. With a median follow up of 12.5 years, relapse-free survival was 62% and 93% for patients with gross residual disease and microscopic disease, respectively. While PORT was found to be most useful in cases of recurrent disease, the authors also recommended that it be considered in cases of tumor spillage or residual disease. Of note, no patient developed a secondary malignancy.

In another study, Barton *et al.* revealed the importance of immediate PORT *vs.* delayed radiation after an observed recurrence (18). They followed 187 patients with incomplete removal or tumor spillage of parotid pleomorphic adenomas treated with PORT. One hundred fifteen patients had radiotherapy immediately after their first resection while 72

patients underwent PORT after surgical treatment of one or more recurrences. Radiation was initially delivered with a radium needle implant prior to the 1960s and then with external beam. At a median follow-up of 14 years, recurrence rates were 0.9% (1/115) and 12.5% (9/115) in the immediate and delayed arms, respectively. The authors concluded that patients having an unsatisfactory surgery due to spill at operation or residual tumor should undergo PORT immediately because of the increased morbidity and higher incidence of a second recurrence with delayed radiation.

In an update on their experience with radiation for pleomorphic adenoma of the parotid, Wallace *et al.* reviewed 25 patients of which 23 were treated with resection followed by PORT (19). At a median follow-up of 10.5 years, local control was achieved in 13 (75%) of 16 patients with subclinical disease and 5 (56%) of 9 patient with gross disease. Two out of the 25 patients underwent definitive radiation therapy without resection and both experienced local recurrence, revealing yet again the oncologic necessity for surgical resection prior to radiation therapy.

The local control rates in the above studies are in general concordance with our findings; however, in our study, we focused solely on the patients with close or positive margins who received PORT after resection.

Malard *et al.* performed a retrospective review of 32 patients with parotid pleomorphic adenoma treated with resection at their institution with a 20-year follow-up (10). Eleven patients were treated with PORT. In contrast to prior studies, Malard *et al.* found no significant reduction in local recurrence with PORT but did note a delay in time-to-recurrence in cases of multifocal tumors. They noted that their sample size of patients receiving PORT was small (n=11) and this likely contributed to their findings.

One reason for the reluctance to use radiation therapy is the fear of inducing a second malignant tumor in the remaining gland or in other organs of the head and neck. However, series reviewing the outcomes of patients who underwent PORT for benign pleomorphic adenoma have found that the incidence of second primary tumors is low (18, 20, 21). We did not find any secondary malignancies in our patient cohort following radiation therapy.

Another concern with using PORT is the development of acute and late toxicities. As presented in our study, treatment toxicity was minimal. All significant acute toxicities resolved within 3 months of treatment completion and the only late toxicity was xerostomia, which was experienced by 2 (10%) of our patients.

There are minimal data on the toxicity of parotidectomy alone, but the available data suggest that radiation therapy does not add substantially to this toxicity (22). Chaushu *et al.* (23) reviewed salivary flow rates in preoperative and postoperative settings and reported decreased flow proportional to the volume of parotid resected. Nitzan *et al.* reported on 53 patients with

parotidectomy and found that 11 (21%) patients developed xerostomia (24). While it would be difficult in our series to separate late grade 1 xerostomia induced by resection, postoperative radiation, or both, this toxicity did not appear to be a major clinical problem in our cohort.

We believe that our levels of toxicity were low as a direct correlation to the limited anatomic contouring volumes (parotid bed with a modest margin) used to guide our treatment plans and because of the technology employed in treating the majority of these patients. IMRT has been found to decrease toxicity when used to treat parotid lesions in comparison to 3DCRT (25), and three fourths of our patient cohort was treated with IMRT. Because of our findings, we believe that the prospect of developing treatment-related toxicity should not sway the practitioner away from postoperative radiation in warranted cases.

There are certain limitations to our study. It is a retrospective study with a relatively small number of patients. While the median follow-up period was significant, longer follow-up would be needed to ensure that our local control rates and toxicity profiles are maintained.

Conclusion

Our experience demonstrates excellent long-term locoregional control with low morbidity after PORT for pleomorphic adenoma of the parotid gland with inadequate surgical margins. Our data, combined with findings from our review of the scant available literature, indicate that PORT is beneficial and feasible in these patients.

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