

Scientific Article

Radiation Therapy After Surgical Resection Improves Outcomes for Patients With Recurrent Pleomorphic Adenoma



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Abstract

Purpose: Pleomorphic adenoma is a benign salivary tumor that may recur multifocally. In case series, the benefit of radiation therapy (RT) for recurrent pleomorphic adenoma remains unclear. We hypothesized that the combination of surgery and adjuvant RT reduces risk of subsequent recurrence compared with surgery alone for recurrent pleomorphic adenoma.

Methods and Materials: Patients who received diagnoses of recurrent pleomorphic adenoma between 1980 and 2016 were identified using an institutional pathology database. Medical records were retrospectively reviewed to determine clinical, operative, pathologic, and imaging characteristics. Kaplan-Meier methods were used to estimate local control after surgery, stratified by completeness of resection and receipt of adjuvant RT. The association of variables with risk of subsequent local recurrence was analyzed using Cox proportional hazards model, and variance estimates were calculated to account for multiple recurrences in the same patient. Toxicities were prospectively recorded in a departmental database.

Results: A total of 49 patients presented with at least 1 recurrence, of which 28 were managed with surgery alone, and 21 were treated with surgery and RT. The median follow-up time after the initial recurrence was 48 months (range, 6-531 months). There were 35 subsequent recurrences; 34 after surgery alone and only 1 after surgery with RT. On multivariate analysis, adjuvant RT was associated with decreased risk of recurrence (hazard ratio, 0.09; 95% confidence interval, 0.02-0.41, $P = .002$), whereas increasing number of prior recurrences was associated with increased risk (hazard ratio, 1.23; 95% confidence interval, 1.13-1.35, $P < .001$). Common toxicities of RT included dermatitis, xerostomia, and mucositis.

Conclusions: For patients with recurrent pleomorphic adenoma, the addition of adjuvant RT after surgery is associated with a significant decrease in risk of subsequent tumor recurrence.

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Introduction

Pleomorphic adenoma, or benign mixed tumor, is the most common parotid gland neoplasm, occurring in estimated 3.0/100,000 persons/y in the United States.¹ The standard of care for initial management is complete surgical resection, and the rate of recurrence after initial resection is less than 5% if the tumor is wholly removed with intact capsule.² Disruption of the capsule or tumor spillage may result in multifocal recurrences despite the benign nature of the disease. After the tumor recurs once, the rate of subsequent recurrence is approximately 50%.³ Surgical resection becomes increasingly difficult with each recurrence, both in terms of tumor resection and facial nerve preservation.^{4,5} In addition, there is increased risk of tumor-associated symptoms with recurrence.⁵ Furthermore, there is risk of transformation into carcinoma ex pleomorphic adenoma.⁶

There are limited data evaluating the role of radiation therapy (RT) in the management of recurrent pleomorphic adenoma. Several studies report good rates of local control for patients who received RT, but these are not compared with patients who underwent surgery alone.⁷⁻¹³ The few studies that do compare these treatment groups are inconsistent in whether the benefit of RT is statistically significant.¹⁴⁻¹⁶ Some studies suggest the importance of other factors such as completeness of resection, number of recurrences, and number of nodules.^{7,8} Furthermore, adjuvant RT is often deferred due to concerns for potential toxicities and risks, such as xerostomia, mucositis, and radiation-induced malignancy.¹⁷ We therefore explored the benefit and risks of adjuvant RT using a large institutional data set.

Methods and Materials

Upon approval by the Johns Hopkins University institutional review board, retrospective review of patient medical records was conducted. Patients with a histologic diagnosis of pleomorphic adenoma or benign mixed tumor were identified using a centrally collected institutional pathology database. Patients were excluded from this study if they had no recurrence, incomplete notes, or lack of follow-up after treatment. Charts were reviewed to identify patient age, sex, tobacco use (greater or less than 10-pack-years), number of prior recurrences, location of tumor, and type of surgery, as well as the details of all operative, pathology, and imaging reports.

Surgeries were classified by the completeness of resection as described in operative and pathology reports. Resections with reported complete and intact tumor removal were categorized as R0; positive margins, capsule rupture, tumor spillage, or fragmentation were categorized as R1; and incomplete, aborted, or postop residual disease were categorized as R2. Surgeries at

outside centers with insufficient records to classify the completeness of resection were coded as “unknown.” These surgeries were very likely R1 or R2 resections given the expertise required to achieve R0 resection for recurrent pleomorphic adenoma, and they were therefore included in the R1/R2 group for Kaplan-Meier and Cox hazard analyses. Radiation records were reviewed to determine total dose, fractionation, and technique.

The primary endpoint was recurrence or disease progression. Time-to-recurrence was calculated per surgery based on the absolute time between surgery and clinical, radiographic, or pathologic confirmation of subsequent recurrence. For patients who had R2 resection, time-to-progression (rather than recurrence) was calculated. Local control (ie, freedom from progression) was plotted using Kaplan-Meier methods. Note that patients who had multiple recurrences were included multiple times in this plot. Median time-to-recurrence and 95% confidence intervals (CIs) were generated for comparison using the generalized Brookmeyer-Crowley method based on log transformation. The association of variables with risk of subsequent local recurrence was analyzed using Cox proportional hazards model. The Andersen-Gill model together with the robust variance were used to account for recurrence events.^{18,19} All tests were 2-sided, and *P* values $\leq .05$ were considered significant. Variables tested for association with recurrence included receipt of RT, completeness of resection, number of prior recurrences (as a continuous variable), age at first surgery, sex, and tobacco use (greater than 10-pack-years).

Treatment toxicities associated with RT were recorded prospectively in Oncospace, a workflow-integrated database containing radiation treatment and clinical information for all patients treated in Johns Hopkins University Department of Radiation Oncology. Toxicities were graded as per Common Terminology Criteria for Adverse Events version 3.0.

Results

Between January 1980 and December 2016, 780 patients in our institutional pathology database had a diagnosis of pleomorphic adenoma. Of these, 731 were excluded for the following reasons: 357 had no recurrence, 356 had lack of clinical evaluation or follow-up (eg, outside pathology reviews), and 18 had carcinoma ex pleomorphic adenoma. The 49 patients who remained formed our study cohort with recurrent pleomorphic adenoma. Most of this cohort was female (65%), non-smokers (74%), and underwent their first surgery at ≤ 30 years of age (51%; Table 1). The median age at surgery for initial recurrence was 30 years, at surgery for any recurrence was 45 years, and at radiation was 44 years. The median follow-up time after the initial recurrence was 48 months (range, 6-531). The median follow-up time

Table 1 Patient characteristics

	Total	Surgery only	Surgery and adjuvant radiation
Age at first surgery	N = 49	n = 28	n = 21
≤30 years	25 (51)	15 (54)	10 (48)
>30 years	24 (49)	13 (46)	11 (52)
Sex			
Female	32 (65)	16 (57)	16 (76)
Male	17 (35)	12 (43)	5 (24)
Number of recurrences			
1	26 (53)	14 (50)	12 (57)
2	17 (35)	11 (39)	6 (29)
≥3	6 (12)	3 (11)	3 (14)
Tobacco			
No	31 (63)	14 (50)	17 (81)
Yes	11 (22)	8 (29)	3 (14)
Unknown	7 (14)	6 (21)	1 (5)

% indicates percentage out of n for each column.

after each surgery was 50 months (range, 0-534) and after radiation was 35 months (range, 3-174).

Of 49 patients, 28 (57%) received surgery/surgeries alone and 21 (43%) eventually received surgery and adjuvant RT. The majority had 1 (n = 26) or 2 (n = 17) recurrences and were multinodular.

Treatment records were available for 84 recurrences: 55 (65%) were treated with surgery alone, 21 (25%) were treated with surgery and adjuvant RT, and 8 (10%) were untreated. The 76 surgeries for recurrences were further classified by the completeness of the resection into R0 (21), R1 (33), R2 (9), and unknown (13; Table 2). Adjuvant RT was delivered in the more recent period of the study (date range 2000-2016, median 2013), whereas surgery alone was conducted throughout the study period (median 2002).

Adjuvant RT was delivered after surgery for the first recurrence for 12 patients, after the second recurrence for 7 patients, after the fourth for 1 patient, and after the 10th for 1 patient. The median radiation dose was 6000 cGy (range, 5000-7040 cGy) and the median fraction size was 200 cGy (range, 180-220 cGy). Intensity modulated therapy was used for 16 patients, 3-dimensional

conformal therapy was used for 1 patient, and unknown technique was used for 4 patients.

Table 2 presents the frequency of subsequent recurrences. There were a total of 35 subsequent recurrences: 34 after surgery alone (out of 55; 62%) and 1 after surgery and RT (out of 21; 5%; P value < .0001). The rate of recurrence after R0 resection alone was 50% compared with 0% after R0 resection with RT. The rate of recurrence or progression for R1 or R2 resection alone was 54% compared with 6% for R1 or R2 resection with RT. The rate of recurrence for the 14 cases of surgery performed at outside centers for which the completeness of resection was unknown was 92%. The single progression event that occurred after RT was in a patient who had been treated for a second multinodular recurrence. This patient had undergone an R2 resection (1 cm residual tumor on postoperative magnetic resonance imaging) with RT to 5940 cGy in 180 cGy fractions and experienced clinical progression 174 months after treatment.

Time-to-recurrence after each surgery for recurrent pleomorphic adenoma was evaluated using Kaplan-Meier methods in Figure 1. These results were stratified by the category of resection and by receipt of RT. The 10-year

Table 2 Number of recurrences by treatment type including completeness of resection and receipt of radiation

	Total surgeries N = 76	Surgery only n = 55	Surgery and adjuvant radiation n = 21
R0	8/21 (38)	8/16 (50)	0/5 (0)
R1	10/33 (30)	10/20 (50)	0/13 (0)
R2	5/9 (55)	4/6 (67)	1/3 (33)
Unknown	12/13 (92)	12/13 (92)	0/0 (0)
Total	35/76 (46)	34/55 (62)	1/21 (5)

“R0” indicates complete and intact tumor resection. “R1” indicates positive margins, spillage, or fragmentation. “R2” indicates resection was incomplete, aborted, or with gross residual disease. “Unknown” indicates that there were insufficient records to classify the surgery. % in parentheses indicates raw percentage of recurrences after each treatment type.

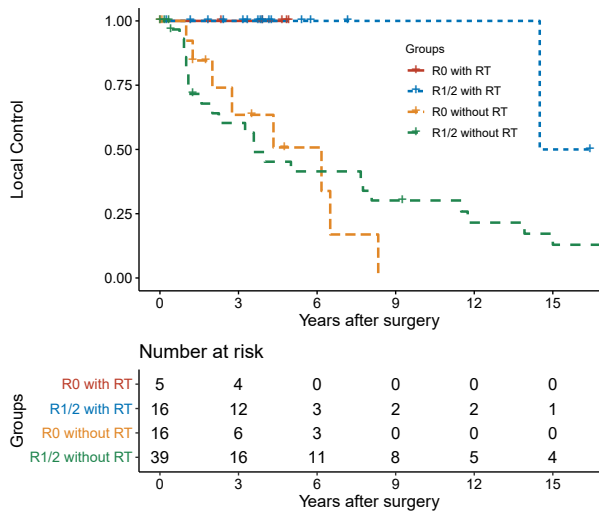


Figure 1 Kaplan-Meier plot of local control after each surgery, stratified by completeness of resection (R0 or R1/R2/unknown) and by receipt of radiation. Note that patients with multiple subsequent recurrences are included multiple times in this plot.

actuarial local control rate was 35% after surgery alone and 100% after surgery and RT. The median time to recurrence was 74 months (95% CI, 54-97 months) after surgery alone and 174 months (95% CI, undefined) after surgery and RT. The median time to recurrence after an R0 resection alone was 60 months (95% CI, 23-83 months) and after an R0 resection with RT was not reached. The median time to recurrence after an R1 or R2 resection alone was 43 months (95% CI, 26-58 months) and after an R1 or R2 resection with RT was 174 months (95% CI, undefined).

Factors associated with risk of recurrence were evaluated with Cox proportional hazards model (with variance estimates to account for multiple recurrences per patient) and are shown in Table 3. In univariate analysis, RT was associated with a significant decrease in the risk of subsequent recurrence (hazard ratio [HR], 0.08; 95% CI, 0.01-0.45; $P = .004$), along with lower age, male sex, and lower number of prior recurrences. Of note, after accounting for other clinically significant factors, radiation remained independently associated with a reduction in risk of recurrence (adjusted [a]HR, 0.09; 95% CI, 0.02-0.41; $P = .002$). Additionally, number of prior recurrences remained significantly associated with an increase in risk of recurrence (aHR, 1.23; 95% CI, 1.13-1.35; $P < .001$).

Detailed treatment toxicities associated with RT were available for review for 14 of 21 patients using the prospectively collected Oncospace database,²⁰ and treatment toxicities were reviewed retrospectively for the remaining 7 patients. Using Common Terminology Criteria for Adverse Events and Radiation Therapy Oncology Group criteria for dermatitis, xerostomia, and mucositis, dermatitis was reported in all patients (maximum grade 1 in 3

patients, grade 2 in 11 patients). Xerostomia was reported in all patients (maximum grade 1 in 5 patients, grade 2 in 9 patients). Mucositis was reported in 13 of 14 patients (maximum grade 1 in 2 patients, grade 2 in 4 patients, grade 3 in 7 patients). No dysphagia was reported. In long term follow-up, dermatitis and mucositis resolved and xerostomia improved gradually. One patient developed grade 3 osteoradionecrosis in the setting of prior mandibulotomy and plate with wound dehiscence requiring surgical debridement and repair before RT; she had persistent hardware exposure that was managed with hyperbaric oxygen at 1.5 years post-RT and hardware removal and flap reconstruction at 7 years post-RT. Importantly, no radiation-induced malignancies were reported during the follow-up period.

Discussion

The benefit of RT in the management of recurrent pleomorphic adenoma remains unclear. This is largely due to uncertainty regarding the efficacy and toxicities of RT relative to those of surgical resection alone. In analyzing the outcomes of 49 patients with recurrent pleomorphic adenoma, 21 of whom received RT, we found that RT was significantly associated with a decreased risk of subsequent recurrence (HR, 0.09; $P = .002$) and longer time to recurrence (median 174 months vs 74 months), with a median follow-up time of 48 months. We also found that risk of recurrence was significantly associated with the number of prior recurrences (HR, 1.23; $P < .001$) but not significantly associated with the completeness of resection (HR, 0.61; $P = .164$). Finally, the toxicities of RT were limited to acute dermatitis, acute mucositis, and subacute xerostomia.

This study is one of few to directly compare the outcomes for patients who received surgery and RT with those who received surgery alone. In addition, it is the only study to further analyze the outcomes by event, rather than by patient, and by the completeness of the preceding surgical resection. Using multivariate analyses with robust variance estimates, we demonstrated that RT was associated with a significant decrease in the risk of subsequent recurrence even after adjusting for other risk factors such as number of prior recurrences and completeness of surgical resection (Table 3). Out of 55 recurrences that were treated with surgery alone, 62% (34) were followed by another recurrence. In contrast, out of 21 recurrences that were treated with surgery plus RT, only 5% (1) were followed by another recurrence. We further found that local control at 10 years was maintained at 100% in cases treated with RT compared with 35% in cases treated with surgery alone. This rate of recurrence for RT is similar to those reported in previous studies,

Table 3 Univariate and multivariate analyses of risk of recurrence after surgery, calculated by Cox proportional hazards models

Variable	Univariate			Multivariate		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Radiation						
No	ref					
Yes	0.08	0.01-0.45	.004	0.09	0.02-0.41	.002
Age						
≤30 y	ref					
>30 y	2.37	1.03-5.46	.043	1.34	0.48-3.70	.576
Sex						
Female	ref					
Male	0.39	0.16-0.95	.038	0.59	0.18-2.00	.398
# Recurrences						
1-10 (Continuous)	1.31	1.23-1.40	<.001	1.23	1.13-1.35	<.001
Tobacco						
≤10 pack-years	ref					
>10 pack-years	1.50	0.76-2.95	.239	NA	NA	NA
Resection						
R1/R2/unk	ref					
R0	0.61	0.31-1.22	.164	NA	NA	NA

Abbreviations: CI = confidence interval; HR = hazard ratio.

Variables include age at surgery, number of prior recurrences as a continuous variable, and completeness of resection.

although the rate of recurrence for surgery alone is higher in this study than in previous studies.

Carew et al¹⁴ found that local control at 10 years was 100% for patients who received RT and 71% for patients who did not. Renehan et al²¹ found that local control at 15 years was 92% for patients who received RT and 76% for patients who did not. It is likely that the higher rate of recurrence for surgery alone in this study is affected by the inclusion of 60 cases with multiple recurrences, as local control with each additional recurrence is known to be increasingly difficult to achieve.^{4,5} In contrast, Renehan et al²¹ only analyzed patients with first recurrences. Furthermore, surgeries performed at outside institutions were included in our analysis and had higher rates of recurrence.

When we stratified by the completeness of the surgical resection, we found that RT was beneficial regardless of the completeness of the resection. R0 resections alone yielded a 50% rate of subsequent recurrence, whereas R0 resections with RT yielded a 0% rate. While it may be expected that complete resections (R0) would yield a lower rate of recurrence, our analysis was underpowered and did not reveal a significant association of recurrence risk with completeness of resection. However, the hazard ratio of 0.61 for R0 resection and the high recurrence rates of 67% after R2 resection and 92% after outside unknown surgery suggest the importance of complete resection. Importantly, only 3 patients in our study received RT after R2 resection, and other studies report limited success of RT in this setting. Specifically the series by Hodge et al⁷ shows only 43% local control with RT for gross disease. Overall, the available data reinforce the value of careful

resection of all gross disease at a high-volume surgical center.

Similar to other studies, our results show that a higher number of recurrences is associated with significantly higher risk of subsequent recurrence on multivariate analysis.^{4,6} We did not observe significant associations based on age or gender, which is consistent with the results of Robertson et al.⁷ We also did not observe significant associations based on tobacco use, which is consistent with previous studies showing an association of tobacco use with Warthin tumor but not with pleomorphic adenoma.²²

Given that the primary concern regarding RT is potential side effects, this study reports toxicities that were prospectively recorded in our institution's Oncospace database. Based on available data, the toxicities of RT were limited to acute dermatitis, acute mucositis, and subacute xerostomia. The single case of osteoradionecrosis was in the setting of complicated mandibulotomy with dehiscence, and delay of RT may be appropriate in the setting of postoperative complications. Chen et al⁸ reported similar side effect profiles: grade 1 or 2 acute dermatitis in all patients and subacute xerostomia in two-thirds of patients. Patel et al¹³ reported grade 1 and 2 dermatitis, grade 1 xerostomia, and grade 2 mucositis, but again all resolved within 3 months of treatment. Robertson et al¹⁷ noted occasional temporary hearing loss (1 of 25 patients) and persistent aural discharge (1 of 25 patients), in addition to dermatitis and xerostomia. Only Chen et al⁸ observed a radiation-induced malignancy, which occurred in 1 out of 34 patients. We assert that these toxicities do not outweigh the benefit of RT in the

setting of recurrent pleomorphic adenoma. Furthermore, the potential complications and morbidity of subsequent surgical resection must also be considered in weighing the benefits and risks of adjuvant radiation. Prior studies have shown an increased rate and extent of facial nerve sacrifice with repeat resection for recurrent parotid tumors.⁴ Finally, to further mitigate the risks of adjuvant radiation, proton therapy may be considered, particularly for young patients (median age in our cohort was only 44 years). Proton radiation has been shown to decrease acute toxicity of unilateral head and neck treatment compared with intensity modulated RT, as well as decrease risk of osteoradionecrosis and secondary malignancy.^{23,24}

Although this study is one of the largest series available on RT for recurrent pleomorphic adenoma, there are significant limitations when performing a retrospective study of a rare disease. Our small cohort of 49 patients was treated over a 36-year period with varying techniques of surgery and radiation and significant missing data regarding treatment details. As noted previously, this makes interpretation challenging. Further, adjuvant RT was delivered during the more recent period of the study (2000–2016), when surgical technique may have been more advanced. It would thus be valuable to conduct a prospective multi-institutional study of RT for recurrent pleomorphic adenoma. This study also has a median follow-up time of 48 months, which does not capture all delayed recurrences or radiation-induced malignancies that can occur beyond a decade.^{10,25} As such, the continued follow-up of these patients is essential.

Conclusions

For patients with recurrent pleomorphic adenoma, RT is associated with a significant decrease in risk of recurrence (HR, 0.09) relative to surgery alone, regardless of the completeness of the resection. The radiation-associated toxicities are limited and do not outweigh the potential benefit conferred by RT for recurrent pleomorphic adenoma.

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