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Excellent Local Control With Preoperative Radiation Therapy, Surgical Resection, and Intra-Operative Electron Radiation Therapy for Retroperitoneal Sarcoma

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Purpose: To examine the value of surgical resection combined with preoperative external beam radiation therapy and intraoperative radiation therapy (Surg-RT) for retroperitoneal sarcoma (RPS).
Methods: Review of 63 consecutive patients with RPS from 1996 to 2011.
Results: Thirty-seven patients (59%) underwent Surg-RT and 26 (41%) had surgery alone. 51% of tumors were high grade and 36% of patients had locally recurrent disease. Final margin status was: R0 73%, R1 16%, R2 6%, and unknown 5%. Of those with R0 resections, 67% received Surg-RT. Median follow-up was 45 months. The 5-year local control rate was 89% for Surg-RT patients and 46% for surgery alone patients ($P = 0.03$). On multivariate analysis, Surg-RT was the only variable associated with a lower risk of LR (HR 0.19; CI 0.05–0.69, $P = 0.003$). The actuarial 5-year OS was 60% for patients receiving either Surg-RT or surgery alone.
Conclusions: The combination of pre-operative radiation, surgical resection, and intraoperative radiation produces excellent local disease control for RPS. Combination therapy was associated with improved local control but not with overall survival.

KEY WORDS: **sarcoma; retroperitoneal; intraoperative radiation; radiation therapy**

BACKGROUND

Retroperitoneal sarcomas (RPS) are a rare form of soft tissue sarcoma typically treated with surgical resection. These tumors often infiltrate or surround retroperitoneal organs and complete surgical excision frequently requires en bloc removal of surrounding organs and tissues. Unlike many malignancies, the leading cause of death in these patients is local disease progression rather than distant metastases. Despite many years of accumulated treatment experience, local recurrence rates are often >50% even after complete surgical resection alone or plus external beam irradiation [1–5]. Efforts to improve local control rates have included more aggressive en bloc surgical resection, but this approach has not been widely adopted [1–3,6–8]. Unfortunately, even with aggressive surgical intervention, local recurrence rates can remain stubbornly high [1].

External beam radiation therapy (EBRT) can improve the local control of extremity soft tissue sarcomas when utilized as an adjuvant treatment with surgical resection [9]. However, the relative radiosensitivity of the small bowel, stomach, and other intra-abdominal organs limits the dose of EBRT that can be safely delivered in the setting of RPS [5,10–12]. Preoperative EBRT is preferred in this setting due to the fact that the mass provides a target for radiation while displacing the other intra-abdominal organs. The role of EBRT in RPS is currently being evaluated in a prospective, randomized, phase III trial through the European Organization for Research and Treatment of Cancer (*EORTC 62092 STRASS trial*) which opened in 2012. Intraoperative radiation therapy allows precise delivery of either high-dose rate brachytherapy or electron radiation (IOERT) to the site determined to be at the highest risk for local recurrence while limiting morbidity by excluding or shielding uninvolved organs or structures. A phase III NCI trial demonstrated that following gross total resection of RPS, the combination of 20 Gy IOERT plus 35–40 Gy post-operative EBRT was superior to 50–55 Gy post-operative EBRT alone in terms of improved local control and gastrointestinal morbidity (local recurrence rate was 40% in the surgery + IOERT/EBRT group vs. 80% in the surgery + EBRT group, $P < 0.01$) [5].

Combined modality therapy sequencing preoperative EBRT, surgical resection, and IOERT has emerged as a potential strategy to improve the local control of RPS while limiting the morbidity from EBRT [8,11,12]. We undertook this study to assess the effectiveness of combination therapy defined as preoperative EBRT, aggressive surgical resection and IOERT (Surg-RT) and compare outcomes to those patients treated with surgical resection alone.

METHODS AND MATERIALS

After Institutional Review Board approval was obtained, all patients treated at the Mayo Clinic in Arizona for RPS were identified via the Cancer Registry Database. Those patients with distant metastatic disease at the time of presentation were excluded from the study. Patients who underwent planned palliative debulking and therefore were treated with

Conflict of Interest: None.

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intentional R2 resection were also excluded from this study. A retrospective review was then performed of 63 consecutive patients with primary or locally recurrent RPS treated with curative intent from 1996 to 2011. Data analysis included patient, tumor, and treatment characteristics as well as outcomes including local recurrence (LR), distant metastasis (DM), and overall survival (OS).

When possible, tumors were further classified based on grade and histologic subtypes. Detailed review of the surgical, medical and radiation treatment was performed. Margin status was defined according to the following criteria: R0 = gross total resection with microscopically negative margins (no tumor on inked surface); R1 = gross total resection with microscopically positive margins (tumor extending to inked surface); R2 = less than gross total resection. When the pathology report did not discuss the margins of resection and the operative report made no explicit mention of complete gross resection, the margin status was classified as unknown.

Follow-up schedule was based on the nature of the tumor with high risk patients (high grade, large tumors, or close margins of resection) undergoing cross-sectional imaging and physical examination at 3-month intervals for the first 2 years postoperatively, then biannually until year 5, and then annually. Lower risk patients underwent cross-sectional imaging and physical examination at 6-month intervals for the first 2 years then annually. Disease recurrence was determined by radiographic imaging. If radiographic imaging was not clearly representative of recurrent sarcoma features, but recurrence was suspected, then either radiographically-guided biopsy or surgical resection was performed to obtain a pathological diagnosis.

Surgical Approach

All patients underwent pre-operative radiologic staging and were deemed to be at least potentially resectable. Exploratory laparotomy was undertaken and evidence of peritoneal metastases or unresectability assessed. Complete en-bloc resection was carried out for all patients, including adjacent organs as necessary. The aggressiveness of achieving wide margins of excision was at the discretion of the operating surgeons, though our general approach in the past 10 years has been an aggressive attempt at achieving gross total resection with microscopically negative resection margins (R0). However, in the cases where adjacent structures were functionally unresectable, R0 resection margins may have been quite narrow.

Radiation Therapy

Patient selection for Surg-RT was determined by the multidisciplinary team and no randomization occurred. Criteria for Surg-RT versus Surgery alone were subjective and not prospectively defined. The decision was largely based on the perception of the surgeon as to the ability to achieve adequate margins of resection (with patients having areas of anticipated close margins more likely to receive Surg-RT), primary versus recurrent disease (with recurrent disease more likely to receive Surg-RT), and time period (as our experience grew with Surg-RT this strategy became more widely applied). Patients undergoing EBRT received 4,500–5,000 cGy in 180–200 cGy fractions over 5 weeks preoperatively, followed by surgical resection with IOERT applied to any close or high-risk margin. Intraoperative electrons were delivered using the Mobetron mobile linear accelerator (Intraop Medical Corporation, Sunnyvale, CA). The IOERT dose ranged from 1,000 to 2,000 cGy based on both the EBRT dose that could be delivered preoperatively and the amount of residual disease after maximal surgical resection. The circular applicator sizes ranged from 5 to 12 cm and rectangular applicator sizes ranged from 7 cm × 12 cm to 9 cm × 12 cm. IOERT energy was selected intraoperatively and was based on the depth of the tumor bed after review of electron energy depth dose tables and pre-operative imaging, and IOERT applicator size included the targeted at-risk portion of the tumor bed with a 1-cm margin (e.g., 7 cm targeted at-risk tumor bed = 9 cm applicator). Two patients received IOERT using abutting applicators with caution taken to avoid overlap.

Statistical Analyses

Univariate analysis was performed using chi-squared analyses for categorical variables and Fisher's exact tests for continuous variables as appropriate. Logistic regression analysis was performed to identify predictors of LR. Patients with R2 resection were not included in the LR analyses since, by definition, they would not have a LR but rather persistent disease. Estimates for local disease control and survival were derived by the Kaplan–Meier product-limit method and log-rank analysis. Multivariate analysis using Cox proportional hazards model was used to determine significant independent prognostic factors. Factors that were significant on univariate analysis ($P < 0.1$ considered significant for this analysis) were included in the multivariate analysis. The statistical software SPSS 16.0 (Chicago, IL) was used for this study.

RESULTS

Patient, Tumor and Treatment Characteristics

Patient, tumor, and treatment characteristics for 63 patients presenting with primary or locally recurrent RPS are presented in Table I. The median age was 67 years (range 4–84 years), and 59% of the patients were male. Forty patients (64%) presented with primary RPS, and 23 patients (36%) were treated for locally recurrent disease. One patient was diagnosed with a metastasis to the abdominal wall at the time of surgical intervention. The metastasis was completely resected at the time of initial surgery and the patient was included in the analysis.

Median tumor size was 10 cm (range 2–50 cm). Tumors most frequently involved or abutted the kidney, colon, and psoas muscle. High-grade liposarcoma (38% of patients) and low-grade liposarcoma (30%) represented the most common final histology followed by leiomyosarcoma (13% of patients). The histologic grade (based on highest grade within a given tumor) was high/de-differentiated in 57% of patients, intermediate in 10%, low/well-differentiated in 30%, and unknown in 3% The final margin status was: R0 73%, R1 16%, R2 6%, and unknown 5%. In the three patients with R2 resection, complete gross total resection was the intention at the time of surgery but could not be achieved because of the extent of disease.

Thirty-five patients (55%) underwent surgical resection combined with preoperative EBRT and IOERT. Two (3%) patients received resection and IOERT without preoperative EBRT for locally recurrent disease because they had previously been treated with surgical resection and maximum dose EBRT at other institutions. These patients were included in the Surg-RT group for analysis purposes for a total of 37 patients. EBRT median dose was 4500 cGy (range 4,000–5,550) and IOERT median dose was 1250 cGy (range 1,250–1,750) and median energy was 9 MeV (range 9–12). Twenty-six patients (41%) had resection without any form of radiation therapy (Table II). There were important differences between the patients treated with Surg-RT and those treated with surgery alone which are presented in Table II. Aggressive combined modality treatment with Surg-RT was used in 86% of patients initially presenting with recurrent disease (19/23 patients), versus 48% of patients (18/37 patients) presenting with primary disease ($P = 0.004$). Of the patients with R0 resections, 67% received Surg-RT; for R1 patients, 70%; and for unknown, 0% ($P = 0.16$). Tumor resection included adjacent organs in 86% of Surg-RT patients and 83% of those having surgery alone ($P = 0.69$). Among

TABLE I. Demographic, Tumor, and Treatment Characteristics of the Retroperitoneal Sarcoma Cohort (n = 63)

	N	% of Total
Age (years)		
<50	19	30%
≥50 <70	19	30%
≥70	25	40%
Gender		
Male	37	59%
Female	26	41%
Presentation		
Primary	40	64%
Recurrent	23	36%
Tumor grade		
High	36	57%
Intermediate	6	10%
Low	19	30%
Unknown	2	3%
Histologic subtype		
Low-grade Liposarcoma	19	30%
High-grade Liposarcoma	24	38%
Leiomyosarcoma	8	13%
Undifferentiated/unclassified	8	13%
Pleomorphic undifferentiated	4	6%
Margin status		
R0	46	73%
R1	10	16%
R2	4	6%
Unknown	3	5%
Stage		
I	16	25%
II	25	40%
III	18	29%
IV[a]	1	1%
Unknown[a]	3	5%
Preoperative therapy		
None	27	43%
Chemotherapy	1	2%
Radiation	22	35%
Chemo-radiation	13	20%
Intraoperative radiation		
Yes	37	59%
No	26	41%
Survival		
Died of disease	9	14%
Alive with disease	11	18%
Died of other cause	9	14%
Died of unknown cause	7	11%
Alive with no evidence of disease	20	32%
Lost to follow-up	7	11%

[a]One patient had distant metastases unknown until discovered at surgery. Three patients with unknown stage because either grade or tumor size not reported.

patients undergoing resection of adjacent organs, 57% had multiple organs resected. The rate of multi-organ resection was 56% of all Surg-RT patients and 30% of all surgery alone patients ($P = 0.10$, Table II). The most common organs resected were the colon and kidney. A comparison of completeness of resection was made between patients treated between 1996 and 2003 and those treated between 2004 and 2011 and patients in the latter time period were more likely to receive an R0 resection ($P = 0.02$).

Radiation Toxicity

Of all patients undergoing radiation therapy, 12 experienced toxicity (34%). Six patients (16%) developed neuropathy (all six grade 2), three (8%) developed gastrointestinal toxicity/radiation enteritis (all three grade 2), and three (8%) developed genitourinary toxicity. Of the patients with genitourinary toxicity, two had grade 2 dysuria or bladder spasms (including one patient who also had grade 2 erectile impotence), and one patient had grade 4 toxicity consisting of ureteral stricture requiring stent placement.

TABLE II. Comparison of the Characteristics of Patients Undergoing Surg-RT and Those Undergoing Surgery Alone

Characteristic	Surg-RT patients	Surgery alone patients	*P*
n	37	26	—
Male gender	54%	65%	0.38
Median age (years)	56	74	<0.01
Recurrent disease	51%	13%	0.002
Low-grade tumor[a]	30%	16%	0.50
Treatment in later time-period (2004–10)	86%	54%	0.03
R0 resection	84%	65%	0.02
Adjacent organ resection	86%	83%	0.69
Multi-organ resection	56%	30%	0.10
Median tumor size (cm)	9.3	12.0	0.28
Median follow-up (months)	45	48	0.53

[a]Grade defined by the highest grade within the resected specimen.

Recurrence Rates

The median follow-up time was 45 months (range 6–196) from diagnosis; median follow-up for Surg-RT patients was 45 months and for surgery alone patients it was 48 months ($P = 0.53$, Table II). Disease recurrence was observed in 27 patients overall (46%). LR was the only site of disease recurrence in 15 patients (25%). The median time to LR was 21 months (range 3–141) after resection. The 5-year actuarial rate of local control was 66% for the entire cohort. The 5-year rate of local disease control was 89% for patients treated with Surg-RT. The 5-year rate of local control was 46% for those treated with surgery alone ($P = 0.03$ vs. Surg-RT; Fig. 1). The median LR-free survival was 94 months (95% CI = 65.2–123.4) for the Surg-RT patients and 54 months (95% CI = 33.6–75.0) for the patients having surgery alone ($P = 0.01$).

Univariate analysis of all patients treated for RPS in this series demonstrated that lower rates of LR were associated with receipt of Surg-RT ($P = 0.004$) and treatment in the later (2004–10) time-period ($P = 0.004$; Table III). In addition, female gender and non-Caucasian race were associated with lower risk of developing LR ($P = 0.05$ and 0.096, respectively). The association of race with LR is likely spurious given the predominantly Caucasian population of the cohort. Factors not associated with LR rates were R0 versus R1 margins of resection, histologic type of sarcoma, grade of tumor, and presentation with locally recurrent disease (Table III).

Significant variables were then used for multivariate analysis to determine independent factors predicting for lower risk of developing LR (Table IV). The only statistically significant variable associated with lower risk of LR on multivariate analysis was the use of Surg-RT (OR = 0.19; 95% CI 0.05–0.69, $P = 0.01$). When margin status (R0, R1, and unknown) and tumor grade were forced into the multivariate analysis, the receipt of Surg-RT remained the only variable significantly associated with LR.

Survival

DM was the only site of disease recurrence in six patients (10%), and both LR and DM were observed in six patients (10%). Median OS for the entire cohort was 81.4 months (95% CI = 30.1–132.7). Among patients with complete resection (i.e., R0/R1), the median survival for the surgery

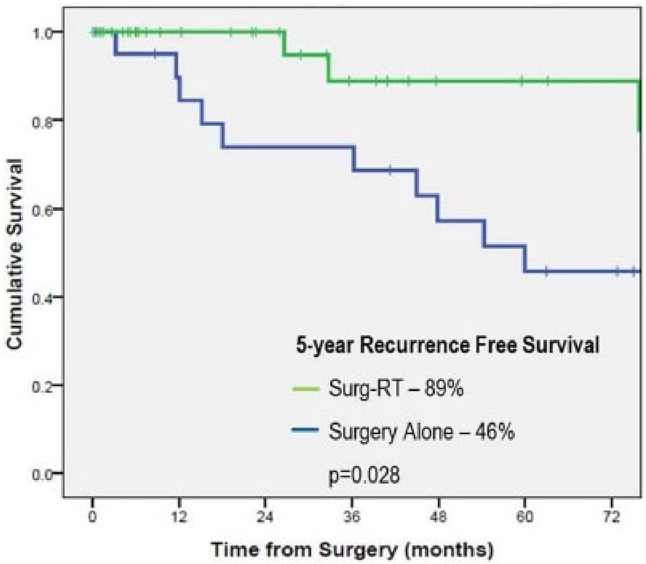

Fig. 1. Recurrence-free survival for patients receiving combination surgery + external beam radiation therapy + intraoperative radiation therapy and for those receiving surgery alone.

only patients was 79.3 months (95% CI = 69.8–88.8 months) and the mean survival for this group was 80.3 months (95% CI = 53.4–107.1). For the Surg-RT patients, median survival was not yet reached (>50% still alive at last follow-up) and mean survival for this group was 101.8 months (95% CI = 72.8–130.9, $P = 0.95$ vs. surgery alone patients). The actuarial 5-year OS was 60% for both patients receiving Surg-RT and patients receiving surgery alone (Fig. 2).

DISCUSSION

Local recurrence continues to be the predominant pattern of failure in RPS. Although surgical resection remains the most important factor in treatment, adjunct therapy such as EBRT and IOERT may enhance local control. Few studies have explored the benefit of preoperative EBRT plus surgical resection with IOERT, and the results have been mixed. The largest study of RPS patients receiving IOERT was reported by the Mayo Clinic in Rochester [12]. This study concluded that local control in both primary and locally recurrent disease may be improved with a combined approach of aggressive surgical resection, EBRT and IOERT. However, they did not compare outcomes with patients treated with surgery alone. Studies from the Massachusetts General Hospital (MGH) also reviewed their results using IOERT in the multimodality treatment of RPS [8,10]. Pierie et al. [8] demonstrated that the use of IOERT plus EBRT in 14 patients significantly lowered the risk of disease-specific death as well as time to local and distant recurrence on multivariate analysis versus EBRT alone. However, the use of IOERT did not significantly improve OS. Yoon et al. [10] described recurrence and survival results in 28 patients treated with intensity-modulated radiation therapy, proton-beam radiation therapy, and/or IOERT. They concluded that these forms of radiation therapy may sufficiently control microscopic residual disease, but similar to the previous Mayo study, they did not specifically evaluate the predictive value of IOERT on LR or survival [8,10,12].

In the current analysis, outcomes of 37 patients treated with Surg-RT as well as the outcomes of 26 patients treated with surgery alone are reported. The treatments were not randomized and the groups significantly differed in several areas that could influence LR risk (Table II). Some of these factors may have lowered the LR risk in the Surg-RT group, while a greater proportion of patients treated for recurrent disease may have increased the LR risk in this group. Similar to the MGH study of 2006, we demonstrate that patients undergoing

TABLE III. Univariate Analysis of Clinical, Tumor, and Treatment Variables Associated with Local Recurrence in Retroperitoneal Sarcomas Excluding R2 Patients

Variables	Local recurrence (n = 21)	*P*-value[a]
Age (years)		0.906
<50 (N = 19)	6 (32%)	
≥50 <70 (N = 16)	6 (38%)	
≥70 (N = 24)	9 (38%)	
Gender		0.050
Male (N = 35)	16 (46%)	
Female (N = 24)	5 (21%)	
Race		0.096
White (N = 50)	20 (40%)	
Non-white (N = 9)	1 (11%)	
Time-period		0.004
1996–2003 (N = 22)	12 (55%)	
2004–2010 (N = 37)	7 (19%)	
Presentation with recurrent tumor		0.641
Yes (N = 22)	7 (32%)	
No (N = 37)	14 (38%)	
Tumor grade		0.270
High/intermediate (N = 37)	16 (43%)	
Low (N = 20)	5 (30%)	
Histology		0.134
Well-differentiated Liposarcoma (N = 18)	4 (22%)	
De-differentiated Liposarcoma (N = 22)	11 (50%)	
Leiomyosarcoma (N = 8)	2 (25%)	
Others (N = 11)	3 (27%)	
Surgery + radiation		0.004
Yes (N = 37)	8 (22%)	
No (N = 22)	13 (59%)	
Margin status		0.120
R0 (N = 46)	14 (30%)	
R1 or unknown (N = 13)	7 (54%)	
Stage[b]		0.156
Stage I (N = 16)	3 (19%)	
Stage II (N = 25)	12 (48%)	
Stage III (N = 14)	6 (43%)	

[a]Pearson's chi-square or Fisher's exact test as appropriate.
[b]Stage for 55 patients (Stage IV & Unknown patients left out of analysis).

TABLE IV. Predictors of Local Recurrence by Multivariate Analysis

	Multivariate analysis		
	Odds ratio	95% CI	*P*-value
Surgery + radiation			0.003
No			
Yes	0.19	0.05–0.69	
Gender			0.053
Male	3.18	0.85–11.90	
Female			
Time-period			0.068
1996–2003	0.34	0.17–1.28	
2004–2010			
Race			0.12
Non-White			
White	6.00	0.49–73.3	

Logistic regression analysis.

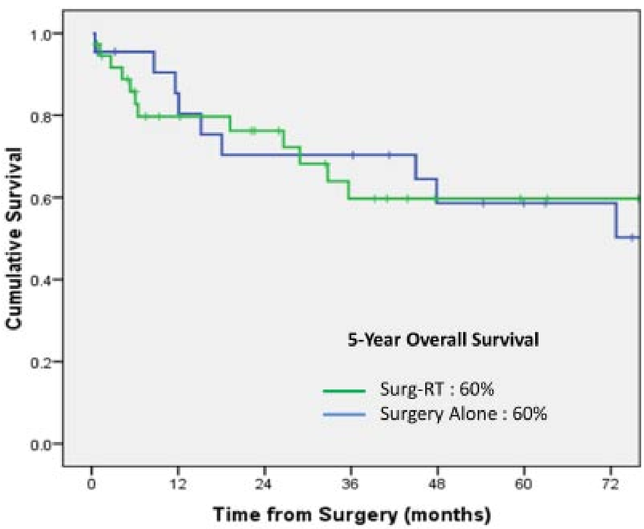

Fig. 2. Overall survival for patients receiving combination surgery + external beam radiation therapy + intraoperative radiation therapy and for those receiving surgery alone.

combined modality treatment had excellent local disease control: in the present series, the combination of EBRT, aggressive surgical resection, and IOERT was associated with an 89% five-year local control rate. While acknowledging the multiple variables that are different between these groups, the rate of local control was better for the Surg-RT patients and the median time to LR was longer than with surgery alone. Receipt of combination therapy was the sole independent factor significantly associated with local control on multivariate analysis, suggesting this may be a significant factor in improved outcomes for patients with RPS.

Although others have demonstrated an association between LR and grade, margin status, histologic type, and recurrent disease [13–15], we did not find these factors to be predictive of LR in this cohort. This may be due to both an insufficient number of patients in this cohort and a weighting of patients with recurrent disease to the Surg-RT treatment strategy. As found in the current analysis and prior analyses, patients with locally recurrent disease presentation can be salvaged successfully with aggressive combined modality treatment including maximal resection plus EBRT/IOERT.

Unlike the MGH study, we did not detect a significant improvement in survival with combination therapy including the use of IOERT. While this is consistent with several previous studies, OS may simply be a lagging indicator since death from RPS is typically a result of LR and we have shown that Surg-RT is associated with a lower risk of LR. Our cohort has an unexpectedly high actuarial 5-year survival rate and, over time, a larger difference in mortality rates may emerge to match the differences in LR rate. At a minimum, there is no evidence of increased mortality from the addition of radiation therapy to counteract the benefit of an improved local control rate.

Several limitations of our study must be acknowledged. First, patients were not randomized and there were differences in subsequent recurrence risks between those treated with the combination of radiation therapy and resection and patients treated with surgery alone. Patients treated with Surg-RT were younger, were more likely to be treated in the later time period, and had a trend toward undergoing more multi-organ resections ($P = 0.10$, Table II). On the other hand, there were higher rates of presentation with locally recurrent disease in the Surg-RT group ($P = 0.002$, Table II). Due to power limitations secondary to a small sample size, the influence of locally recurrent disease at the time of treatment could not be assessed. There may have also been other factors that are different between the groups that were not accounted for since, again, the treatment assignment was not randomized. A second limitation is that nearly all of the patients receiving IOERT also received EBRT so that the relative benefits of each modality cannot be individually assessed. A third limitation is that the extent of surgical resection was not standardized between groups and, as our practice shifted to more multimodality therapy, this time period also may have been associated with a more aggressive surgical approach as evidenced by an increased rate of R0 resection in the later time period. Ideally a prospective, randomized trial of the addition of EBRT and IOERT would control for surgical approach. Thus it is best to take the data presented in the present cohort as a demonstration of the absolute achievable rate of local control with such multimodality therapy rather than trying to determine the interval gain in local control verus surgery alone.

In conclusion, a well-planned surgical approach combined with preoperative EBRT and IOERT can achieve excellent 5-year local control rates of 89% for patients presenting with either primary or locally recurrent RPS. Although a difference in OS could not be detected in the current analysis, we believe that the significant improvement in local disease control supports the continued use of multimodality therapy that includes both EBRT and IOERT.

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