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Analysis of local control outcomes and clinical prognostic factors in localized pelvic Ewing sarcoma patients treated with radiation therapy: A Report from the Children's Oncology Group

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Abstract

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Conflict of interest

PSR serves on the board of directors of the Sacral Tumor Society. KJM receives royalties as a co-author in Up to Date. RLR receives royalties from Onkos, Zimmer Biomet, and Daichii Sankyo; consulting fees from Onkos, Zimmer Biomet, and Daichii Sankyo; honoraria for presentations from Onkos; and has a leadership role in the Sarcoma Foundation of America and the Musculoskeletal Tumor Society. SGD has received consulting fees from Amgen, Bayer, and Jazz as well as travel expenses from Loxo, Roche, and Salarius. RGG has received consulting fees from Jazz Pharmaceuticals.

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Clinical trial information:

Patients in this analysis were treated on the INT-0091, INT-0154, and AEWS0031 clinical trials.

Purpose: To identify potential clinical prognostic factors associated with a higher risk of local recurrence in localized pelvic Ewing sarcoma (ES) patients treated with radiation therapy.

Methods: Data for 101 patients treated with definitive radiotherapy (RT) or both surgery and radiation (S+RT) to primary pelvic tumors on INT-0091, INT-0154, and AEWS0031 were analyzed. Imaging data for patients who did not receive radiation were not available for central review, so surgery alone patients were not included. Cumulative incidence rates for local failure at 5-years from time of local control were calculated accounting for competing risks.

Results: The most common pelvic subsite was sacrum (44.6%). RT was utilized in 68% of patients and S+RT in 32%. The local failure rate was 25.0% for RT and 6.3% for S+RT (p=0.046). There was no statistically significant difference in local control modality by tumor characteristics. Tumors originating in the ischiopubic-acetabulum region were associated with the highest local failure incidence, 37.5% (p=0.02, vs. sacrum and iliac/buttock tumors), particularly those treated with RT (50.0%, p=0.06). A higher incidence of local failure was seen with each additional 100 mL of tumor at diagnosis (p=0.04). Multivariable analysis demonstrated RT alone (HR 5.1, p=0.04), tumor subsite (particularly ischiopubic-acetabulum tumors, HR 4.6, p=0.02), and increasing volume per 100 mL (HR 1.2, p=0.01) were associated with a higher incidence of local recurrence.

Conclusions: Combination surgery and RT is associated with improved local control in patients with pelvic ES compared to definitive RT. Tumors involving the ischiopubic-acetabulum region and increasing tumor volume at diagnosis are associated with inferior local control. Tumor characteristics did not correlate with choice of local therapy modality suggesting an opportunity to develop best local therapy practices guidelines for future studies based on tumor features.

Introduction

Pelvic Ewing sarcoma (ES) has long been associated with a higher rate of local recurrence compared to non-pelvic sites.[1–4] Large size and proximity to or infiltration of critical pelvic organs, nerves and vasculature can make resection or definitive radiation challenging. The 5-year local failure rate for all pelvic tumors treated on the INT-0091, INT-0154, and AEWS0031 trials was 13% compared to less than 9% at other tumor sites.[1] The challenges associated with local therapy at this site for both surgeons and radiation oncologists probably contribute to these suboptimal outcomes. Definitive radiation therapy, however, is associated with the highest local failure rates.[1,2] The recent local failure report from the Children's Oncology Group (COG) documented a local recurrence rate of 22.4% in pelvic tumors treated with radiation therapy compared to 3.9% for tumors treated with surgery.[1]

Recent studies suggest local tumor control may be improved with treatment intensification such as definitive radiation therapy dose escalation or with combined surgery and radiation therapy approaches.[2,5,6] Currently, the exact subpopulation at highest risk for local failure and the potential associated clinical prognostic factors for local recurrence in pelvic ES are unknown. Tumor size or volume at diagnosis, pelvic subsite, and response to neoadjuvant chemotherapy are associated with event-free and overall survival, and accordingly warrant further analysis with local tumor control outcomes.[2,7–9] Identification of clinical prognostic

factors for local recurrence is essential in determining patients most likely to benefit from different local treatment strategies.

We analyzed localized pelvic ES patients treated with radiation therapy on the INT-0091, INT-0154, and AEWS0031 trials to identify potential clinical prognostic factors associated with a higher risk of local recurrence. We postulated that pelvic tumor subsite is associated with differential local failure risk, and tumor size at diagnosis and pelvic tumor subsite likely influence choice of local therapy modality.

Methods

Patients and Treatment

Patients with pelvic ES (n=176) who received ifosfamide and etoposide (IE) based chemotherapy and were included in the previously published COG local failure analysis of the INT-0091, INT-0154, and AEWS0031 trials were eligible for inclusion in this retrospective cohort study.[7] Ethics approvals were provided by the institutional review boards for all participating sites. Only patients who received IE based chemotherapy were analyzed because this regimen is associated with improved local tumor control.[10] Imaging submission was not required for surgery alone patients, so only patients with radiation therapy as a component of local therapy were included in this analysis. Radiation treatment case report forms, baseline tumor diagnostic imaging, and pre-local therapy diagnostic imaging were reviewed at Imaging and Radiation Oncology Core (IROC) Rhode Island, Quality Assurance Review Center (QARC). IROC QARC stores diagnostic imaging and radiation therapy clinical trial data for the COG.

The final cohort consisted of 101 patients, after excluding patients treated with surgery alone (n=51) and patients without information to categorize pelvic subsite (n=24). Local therapy modalities were defined as definitive radiation therapy (RT) or surgery plus radiation therapy (S+RT). Local therapy details are published in the primary manuscripts.[10–12] Treating physicians determined the method of local therapy for each case. In general, radiation was combined with surgery for incompletely resected tumors (gross or microscopic residual disease) or less than minimal surgical margins. The relevant reason for combined modality therapy was not routinely documented in the IROC QARC radiation treatment case report forms and therefore not included in this analysis.

Statistical Analysis

Tumor size was classified in maximum dimension and volumetrically. Baseline size measurements in three perpendicular tumor dimensions were obtained by reviewing imaging reports. If imaging reports did not state three-dimensional measurements, the measurements were obtained directly from the baseline cross sectional imaging (MRI or CT). Tumor volume was subsequently calculated using the three perpendicular tumor dimensions according to the volume calculation method currently used on the COG ES protocols: $0.52 d_1 d_2 d_3$. This same approach was used to calculate tumor size with imaging prior to local therapy. Tumor size was then categorized as </≥ 8 cm in maximum dimension and </≥ 200 mL volumetrically.

Percent volume change was calculated by: [(tumor volume prior to local therapy − tumor volume at baseline) / tumor volume at baseline] *100. Given that the median percent volume change for the cohort was −76%, local failure incidence based on </≥ −75% volume change was calculated. Local failure incidence based on </≥ −50% volume change was also calculated given that </≥ −50% was the cutoff used with volume regression on the French EW93 study and correlated with event-free survival.[13] Pelvic subsites were determined by reviewing imaging and categorized as sacrum, iliac/buttock, or ischiopubic-acetabulum.

The primary outcome was local failure incidence, considering other events (distant failure, death, or secondary malignancy) as competing risks. The five-year cumulative incidence of local failure from time of local treatment is reported, and the association of clinical and treatment variables with local failure was assessed using the Fine and Gray method extending the Cox model. Categorical patient and tumor characteristics were compared among the two local treatment modalities using chi-square tests or Fisher's exact test as appropriate. Multiple variable models considered those variables with a univariate significance of <0.2 and used a backward selection method. A p value <0.05 was considered statistically significant.

Results

Table 1 lists patient, tumor, and local therapy characteristics. The median age at diagnosis was 13 years (range: 1–42 years). Most patients (56%) were treated on AEWS0031. The most common primary pelvic subsite was sacrum (44.6%). The median tumor size at diagnosis was 9.7 cm (range: 2.4–16.0 cm) in maximum dimension and 215.9 mL (range: 3.7–1400.0 mL) volumetrically. T4 tumors (per the American Joint Committee on Cancer (AJCC) 8th edition pelvis bone sarcoma staging[14]) accounted for 40.6% of the cohort. The median tumor size prior to local therapy was 7.0 cm (range: 1.4–15.0 cm) in maximum dimension and 53.7 mL (range: 0.0–990.0 mL) volumetrically; translating to a median percent volume reduction of 76.0 % (range: 15.4 – 100.0 %).

RT was utilized in 68% of patients and S+RT was utilized in 32% of patients. There was no obvious difference in local therapy modality (RT vs. S+RT) employed based on tumor size prior to local therapy or percent volume change (Table 1). Given that the median tumor size in maximum dimension at diagnosis was 9.7 cm, approximately 75% of tumors treated with RT and S+RT were ≥8 cm in maximum dimension (Table 1, p=0.81). Though not statistically significant, more tumors ≥200 mL at diagnosis were treated with S+RT (62.1%, p=0.31, Table 1) compared to a roughly even split based on tumor volume </≥ 200 mL for RT patients (Table 1). Most tumors were <8 cm in maximum dimension (63%) and <200 mL (91%) prior to local therapy. There was no statistically significant difference in local therapy modality employed based on tumor subsite (Table 1, p=0.86 for sacrum vs. iliac/buttock vs. ischiopubic-acetabulum). On the other hand, more T2 tumors were treated with S+RT (46.9%) and more T4 tumors were treated with definitive RT (46.4%, p=0.08).

The five-year cumulative incidence of local failure for the entire cohort was 19.0% (95% confidence interval (CI), 12.7–28.5%). There was no difference in local failure outcomes by tumor size at diagnosis or prior to local therapy, or T stage (Table 2). RT was associated

with a significantly higher incidence of local failure at 25.0% compared to 6.3% for S+RT (p=0.05). RT quality control data were available in all patients. Minor or major protocol deviations were documented in 21 patients. The local failure incidence was 28.6% for patients without a protocol deviation and 16.5% for patients with a protocol deviation (p=0.17).

Though </≥ 200 mL tumor volume at diagnosis was not associated with local failure incidence, a higher incidence of local failure was seen with each additional 100 mL volumetrically at diagnosis (p=0.04; Figure 1A). For RT only patients, there was no difference in local failure incidence based on tumor size at diagnosis (18.8%, <8 cm versus 27.4%, ≥8 cm; p=0.6) or tumor volume at diagnosis (18.8%, <200 mL versus 29.4%, ≥200 mL; p=0.33). However, similarly to all patients, there was a higher incidence of local failure with each additional 100 mL volumetrically at diagnosis (HR 1.28, 95% CI 1.08–1.52, p=0.005, Figure 1B). There was no difference in local failure incidence based on tumor size at local therapy, tumor volume at local therapy, and percent volume change for RT only patients (data not shown).

The local failure incidence by pelvic subsite is listed in Table 2. Tumors originating in the ischiopubic-acetabulum region were associated with the highest local failure incidence at 37.5% (p=0.02; Figure 2A). Correlation of tumor size in maximum dimension revealed more iliac/buttock and ischiopubic-acetabulum tumors were ≥8 cm (p=0.03, Table 3). Volumetrically, more sacral tumors were <200 mL and more iliac/buttock tumors were ≥200 mL (p=0.03, Table 3). There was no statistically significant difference in local failure incidence by local therapy modality and subsite; however, there was a trend for higher local failure incidence for ischiopubic-acetabulum tumors treated with RT (Table 4, 50.0%, p=0.06, Figures 2B and 2C).

Multivariable analysis for local recurrence risk was performed with local therapy modality, tumor subsite, and increasing tumor volume at diagnoses per 100 mL variables (Supplementary Table 1). RT (HR 5.1, p=0.04), tumor subsite (specifically ischiopubic-acetabulum tumors, HR 4.6, p=0.02), and increasing volume at diagnosis per 100 mL (HR 1.2, p=0.01) were statistically significantly associated with higher incidence of local recurrence.

Discussion

Local therapy is an essential component of definitive treatment for ES. The choice of local therapy is individualized and dependent on multiple factors including patient age, tumor location, associated treatment morbidity, and patient and provider preferences. The preferred local therapy modality for pelvic ES has been the subject of many investigations over the past several decades given the high rate of local relapse in this cohort.[1–4,7,15–18]

The COG local failure analysis of 956 patients treated on INT-0091, INT-0154, and AEWS0031 demonstrated a 13% local failure rate for all pelvic tumors, with the highest local failure rate seen in definitive RT patients at 22.4%.[1] Similarly, the Euro-EWING99 local control analysis of pelvic tumors reported local failure rates as high as 40% for tumors

treated with RT only.[2] Our results again show that pelvic tumors treated with RT alone are associated with the highest local failure rates in ES. Accordingly, additional analyses of potential clinical factors associated with these high local failure rates is warranted to help identify the RT patients most likely to benefit from local treatment intensification strategies, such as RT dose escalation or combined modality therapy with S+RT.[5,6] We analyzed a subset of localized pelvic ES patients treated with radiation therapy as a component of local therapy on the INT-0091, INT-0154, and AEWS0031 trials to identify potential prognostic factors associated with a higher risk of local recurrence. Specifically, we were interested in investigating whether pelvic subsite correlates with local failure risk and whether pelvic subsite and tumor size at diagnosis influenced choice of local therapy modality.

Our study demonstrated that non-sacral tumors, specifically tumors originating in the ischiopubic-acetabulum region, were associated with a higher local failure incidence at 37.5% compared to 11.4% for sacral tumors. The significance of anatomic subsite for pelvic ES tumors has been illustrated in a few prior series.[2,7,9] The Scandinavian Sarcoma Group first reported sacral tumors to be associated with improved disease-free survival compared to non-sacral tumors. The authors postulated the reason for the improved prognosis was a higher likelihood of diagnosing sacral tumors while small, given the proximity to nerves and tendency to cause symptoms earlier.[9] Additionally, the authors concluded RT to be an adequate local therapy for sacral tumors as 79% of this subsite was treated with RT in their series.[9] The Euro-EWING99 pelvic local tumor control analysis also demonstrated better outcomes for sacral tumors, specifically with local failure rate.[2] The local recurrence rate was 12% for sacral tumors versus 28% for non-sacral tumors.[2] Furthermore, the investigators found no difference in outcomes for sacral tumors based on local treatment modality but noted a lower local recurrence rate for non-sacral tumors treated with S+RT (14%) versus RT (40%).[2]

Of the non-sacral tumors, our results are the first to suggest there may even be differences in outcomes between the non-sacral sites. The highest local failure incidence was seen in ischiopubic-acetabulum tumors at 37.5% in our series. Though we found no statistically significant difference in outcomes based on local treatment modality and subsite, ischiopubic-acetabulum tumors treated with RT trended toward the highest local failure incidence (50.0%, p=0.06). Taken together, these results strongly suggest pelvic subsite in ES is a crucial clinical prognostic factor for outcomes in this cohort and accordingly may be helpful in determining optimal local therapy for these cases. For instance, non-sacral tumors may be a subgroup of pelvic tumors most likely to benefit from combined modality therapy with surgery and RT or RT dose escalation.

Tumor size at diagnosis has previously been shown to correlate with local control outcomes., with larger tumors having a higher local recurrence rate.[3,8,19] The COG local failure analysis of patients treated on INT-0091, INT-0154, and AEWS0031 did not associate tumor size with local recurrence rates.[7] However, 60% of the cohort did not have tumor size recorded.[7] Tumor volume was collected for all patients on AEWS1031, and tumor volume ≥ 200 mL was significantly associated with lower event-free survival (EFS).[20] Analyses including tumor volume and local control outcomes from this study, however, have not yet been published. In our study, we analyzed outcomes based on tumor size in both maximum

dimension and volume. We did not find an association with local recurrence based on tumor size with cutoffs of </≥8 cm in maximum dimension or </≥ 200 mL volumetrically. The analysis of pelvic tumors treated on Euro-EWING99 also did not find an association between tumor volume at diagnosis and local control outcomes.[2]

Our data instead demonstrate a higher incidence of local failure with each additional 100 mL of tumor volumetrically at diagnosis for all patients and RT only patients (Figure 1). Additionally, our data demonstrate association between tumor subsite and size. Sacral tumors were more likely to be <200 mL at diagnosis in our series, corresponding to the postulation made by the Scandinavian Sarcoma Group that sacral tumors likely have improved outcomes as they may be diagnosed when smaller. On the other hand, ischiopubic-acetabulum tumors in our series were more likely to be ≥8 cm and this tumor subsite was associated with the highest incidence of local recurrence. These results strongly suggest tumor size at diagnosis correlates with local control outcomes; however, the previously established tumor size cutoffs are likely antiquated in the modern era and new benchmarks to evaluate tumor burden may be warranted.

Radiographic response to neoadjuvant chemotherapy may be an important prognostic factor for oncologic outcomes. The French EW93 study evaluated outcomes based on risk factor adapted chemotherapy.[13] Radiographic response to neoadjuvant chemotherapy defined as </≥50% regression of the soft tissue mass was incorporated into the study schema to help determine which patients would receive intensified treatment.[13] Event-free survival was higher in patients with at least 50% radiographic response to neoadjuvant chemotherapy.[13] The Euro-EWING99 analysis demonstrated S+RT to be associated with improved survival in nonsacral tumors with a persistent extraosseous tumor component following induction therapy.[2] These results suggest radiographic response to neoadjuvant chemotherapy may be an important corollary prognostic factor to help determine the tumors at highest risk for poorer outcomes. We did not find any correlation with local failure rate and tumor response to neoadjuvant chemotherapy in our series; however, 35 patients did not have pre-local therapy size information for review. As such, this warrants further investigation with analysis of patients treated on AEWS1031 and AEWS1221.

The cases most likely to benefit from S+RT remain ill-defined.[21–23] Traditionally within the COG, RT is added to surgery for incompletely resected tumors or inadequate surgical margins. With this approach, the local recurrence rate has been comparable to that for surgery alone, including pelvic tumors, as evidenced in the previously published local failure analysis of patients treated on the INT-0091, INT-0154, and AEWS0031 trials.[1] The local failure incidence was 3.9% for all patients treated with surgery versus 6.6% for S+RT; and for pelvis tumors 3.9% treated with surgery versus 5.1% with S+RT.[1] These results indicate that adequate local control can be achieved with combined modality therapy in higher risk cases. For instance, the Euro-EWING99 group concluded from their analysis that non-sacral tumors are best treated with S+RT, even in cases with wide surgical margins and a good histologic response to neoadjuvant chemotherapy.[2] There may also be a role for centralized discussion of optimal local therapy approaches for pelvic ES cases in future COG trials given the complex interplay of potential prognostic tumor and treatment factors as evidenced

in our analysis. The Euro-EWING99 trial offered central guidance for local therapy planning based on interdisciplinary tumor board discussions in the coordinating data center.[2]

North American practice generally favors one modality of local therapy to minimize risk of long-term toxicity. Additionally, as discussed, post-operative radiation is generally reserved for unexpected close or positive margins. It was hypothesized that S+RT would be more likely for patients with smaller tumors or tumors in more favorable locations compared to patients treated with definitive RT. In our series, there was no difference in use of S+RT versus RT based on tumor subsite or volume. As there is no generally accepted practice for local therapy based on tumor features within the pelvis, this finding is consistent with North American practice. However, a significant limitation of our analysis is selection bias as we were unable to review the surgery-only cases. Future efforts should include mandatory submission of diagnostic imaging for all patients which would allow more detailed analysis of local control patterns of care.

Additionally, further investigation into the optimal sequencing of S+RT is warranted. Lex et al. evaluated 49 pelvic ES patients treated with preoperative RT or selective postoperative RT.[24] Patients who received preoperative RT were noted to have a higher proportion of wide surgical margins achieved (81.5% vs. 59.1%, p=0.08) and a significantly higher histological response to neoadjuvant therapy (96.3% vs. 63.6%, p=<0.01).[24] However, a higher rate of wound complications was seen with all tumors ≥250 mL in the cohort.[24] AEWS1031 permitted preoperative RT (36 Gy) in resectable tumors expected to be at a higher risk of a microscopic positive margin resection. Further analysis of this subpopulation will help determine cases most likely to benefit from preoperative RT, factoring in risk of wound complications, versus postoperative RT.

Given the challenges in standardizing local therapy modality recommendations, it may be helpful to utilize a consistent system that risk stratifies based on tumor characteristics. For this reason, we assigned tumors in our cohort a T stage based on the AJCC 8th Edition Bone Staging system.[14] This staging system takes into account the number of pelvic segments involved (sacrum; iliac wing; acetabulum/periacetabulum; and pubic rami, symphysis and ischium), tumor size (</≥8 cm in maximum dimension), whether tumor crosses the sacroiliac joint, and whether the tumor encases iliac vessels.[14] Though statistically not significant, more T4 tumors in our cohort were treated with RT. This trend is logical as T4 tumors are characterized as spanning three pelvic segments, crossing the sacroiliac joint, and/or encasing major pelvic vessels. As such, a margin-negative resection by itself may not be feasible and/or result in significant morbidity for the patient. In view of this, the AJCC Bone Staging system may be a helpful, standardized tool for oncologists to identify pelvic tumors most suitable for RT based on tumor extent and expected morbidity if surgery is pursued and vice versa. The exact utility of the AJCC Bone Staging system, however, and its potential correlation with outcomes and guidance with local therapy recommendations warrants further investigation and corroboration, especially with the surgery only cohort.

In summary, our analysis strongly suggests that pelvis tumor subsite is associated with local failure rate and may help determine the pelvic ES cases most likely to benefit from local treatment intensification strategies. On the other hand, we could not identify tumor

characteristics most likely to correlate with choice of local therapy modality. As such, there is an opportunity to develop guidelines for consistent and optimal local therapy practices. This study has many limitations including its retrospective nature, incomplete data points, and analysis in a patient population treated without the most contemporary systemic and local therapy approaches. The recently published AEWS1031 analysis demonstrated no statistically significant difference in EFS by local therapy modality. However, unlike prior studies, patients who received RT alone had a numerically higher EFS (82%) compared to patients who underwent surgery alone (79%) and patients who received S+RT (70%) indicating the current landscape for local therapy is different than before.[20] As such, our data warrant further investigation in a cohort of patients treated with modern chemotherapy and local therapy techniques, i.e. pelvic patients treated on AEWS1031 and AEWS1221.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing statement:

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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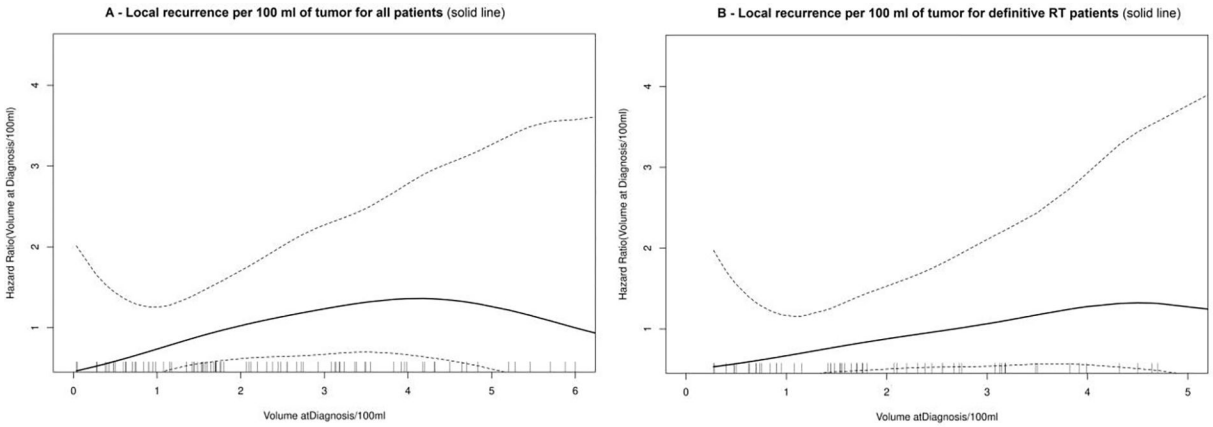
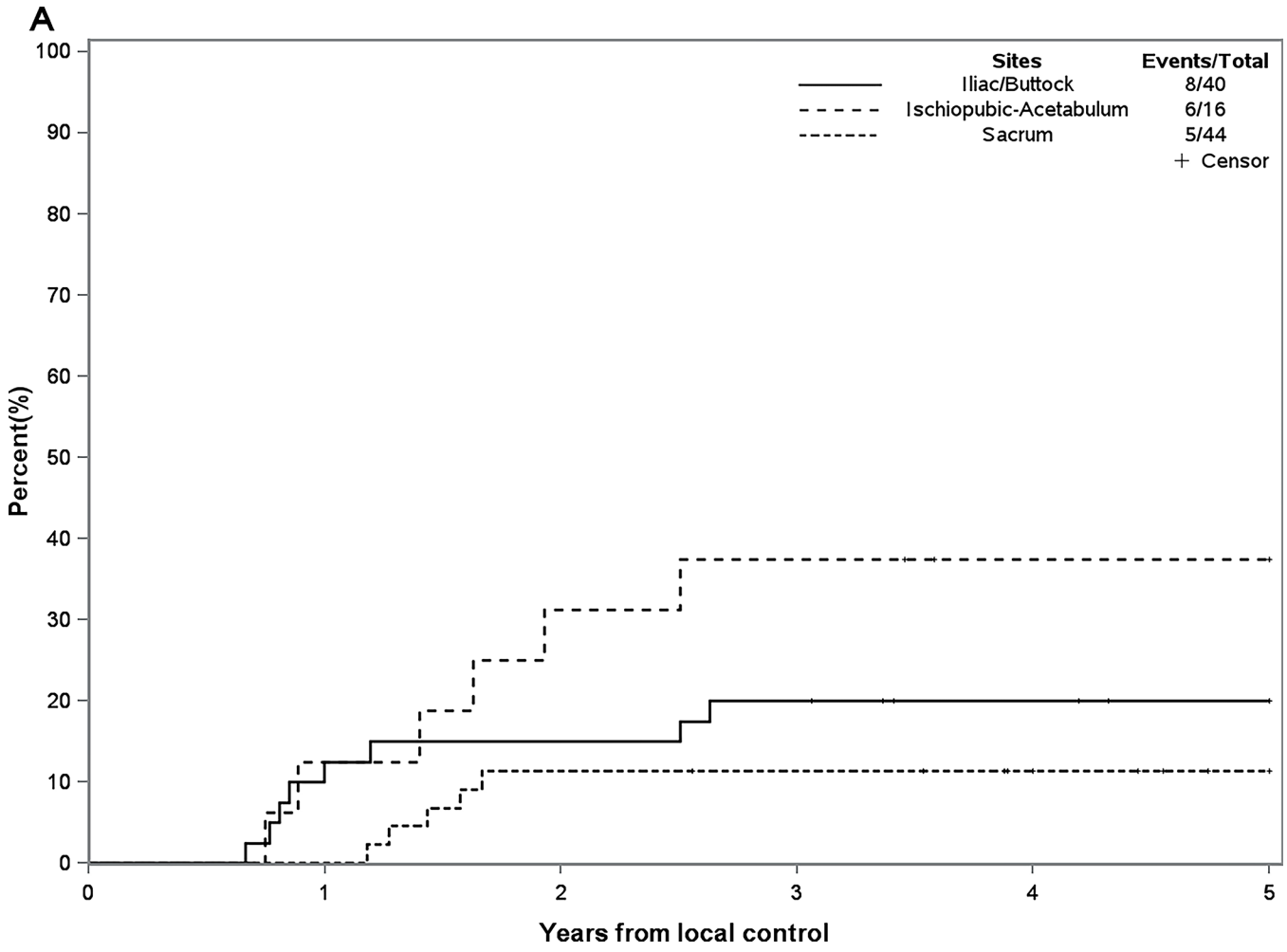
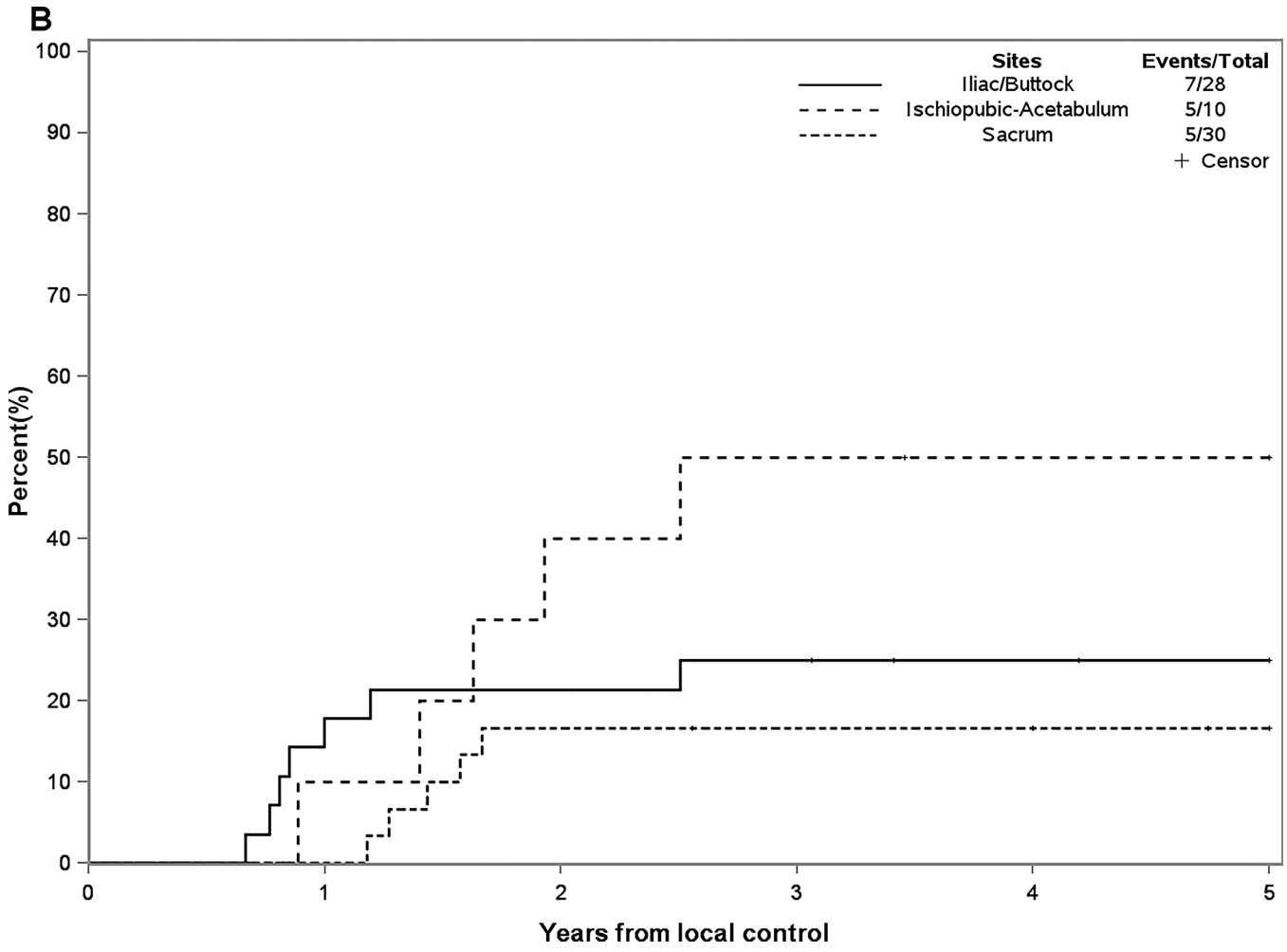


Figure 1. Probability of local recurrence per 100 ml of tumor volume at diagnosis.

A) Probability of local recurrence for all patients (solid line). 95% confidence interval depicted as dashed lines. Distribution of patients by tumor volume at diagnosis noted on y-axis as tick marks. B) Probability of local recurrence for definitive RT patients (solid line). 95% confidence interval depicted as dashed lines. Distribution of patients by tumor volume at diagnosis noted on y-axis as tick marks.





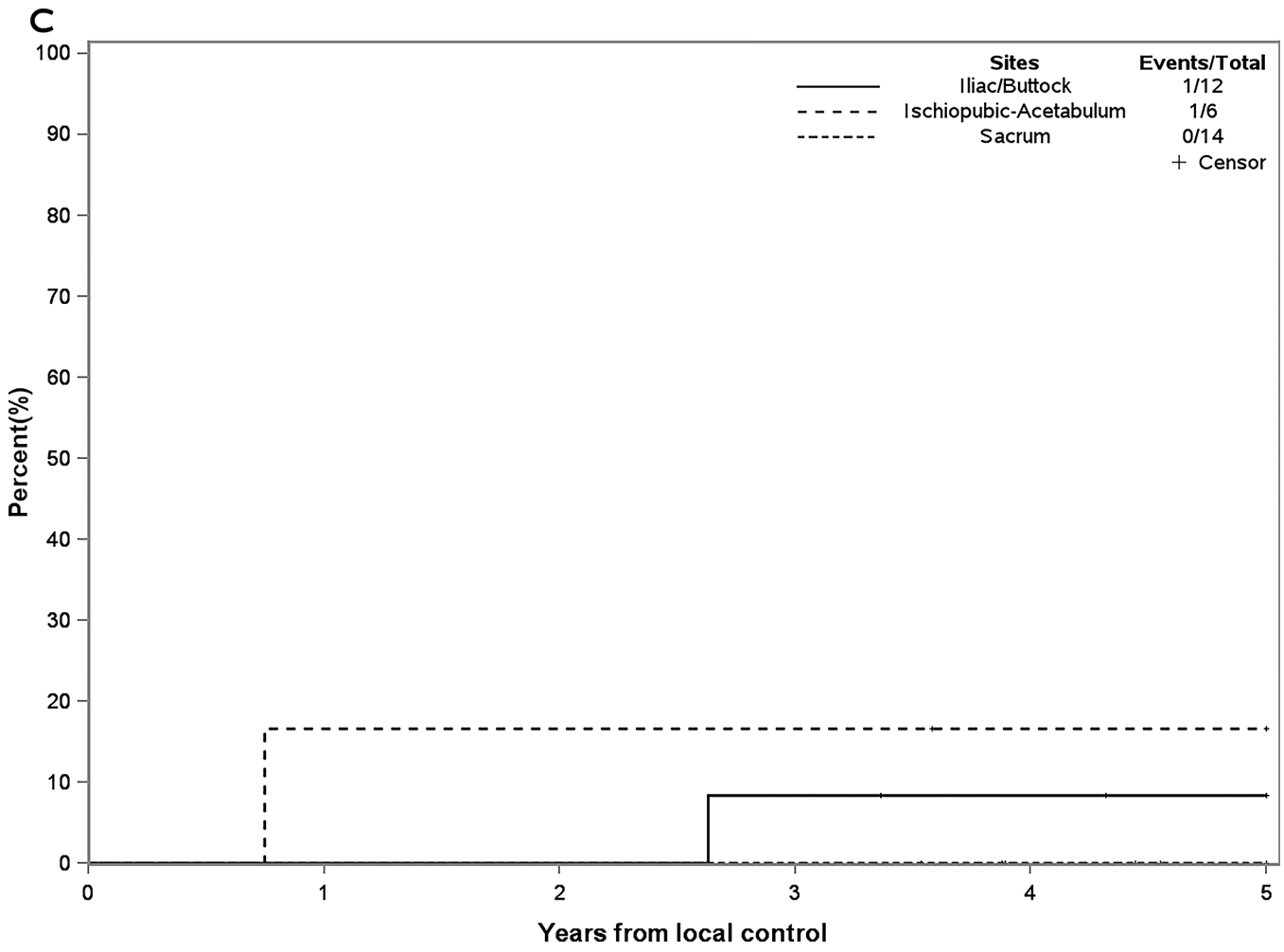


Figure 2. Five-year cumulative incidence of local failure by tumor subsite.

A) All patients, B) Definitive RT patients, C) S+RT patients.

Table 1.

Patient, tumor, and treatment characteristics for the entire cohort and by local treatment modality.

	All patients (N=101)	Radiation (N=69; 68%)	Surgery + radiation (N=32; 32%)	*p*
Sex				
Male	48 (47.5%)	32 (46.4%)	21 (65.6%)	0.07
Female	53 (52.5%)	37 (53.6%)	11 (34.4%)	
Age				
Median (range)	13 years (1.0 – 42.0 years)			
<13 years	46 (45.5%)	28 (40.6%)	18 (56.3%)	0.14
≥13 years	55 (54.5%)	41 (59.4%)	14 (43.8%)	
<18 years	90 (89.1%)	59 (85.5%)	31 (96.9%)	0.09
≥18 years	11 (10.9%)	10 (14.5%)	1 (3.1%)	
Study				
INT0091	9 (8.9%)	7 (10.1%)	2 (6.3%)	0.10
INT0154	35 (34.7%)	28 (40.6%)	7 (21.9%)	
AEWS0031	57 (56.4%)	34 (49.3%)	23 (71.9%)	
Tumor Subsite				
Sacrum	45 (44.6%)	31 (44.9%)	14 (43.8%)	0.91
Non-sacrum	56 (55.4%)	38 (55.1%)	18 (56.3%)	
Tumor Subsite				
Sacrum	45 (44.6%)	31 (44.9%)	14 (43.8%)	0.86
Iliac/buttock	40 (39.6%)	28 (40.6%)	12 (37.5%)	
Ischiopubic-acetabulum	16 (15.8%)	10 (14.5%)	6 (18.8%)	
Tumor Size at Diagnosis				
<8 cm	24 (24.2%)	16 (23.5%)	8 (25.8%)	0.81
≥8 cm	75 (75.8%)	52 (76.5%)	23 (74.2%)	
Missing	2	1	1	
Tumor Volume at Diagnosis				
<200 mL	44 (45.8%)	33 (49.3%)	11 (37.9%)	0.31
≥200 mL	52 (54.2%)	34 (50.7%)	18 (62.1%)	
Missing	5	2	3	
Tumor Size at Local Therapy				
<8 cm	43 (63.2%)	28 (60.9%)	15 (68.2%)	0.56
≥8 cm	25 (36.8%)	18 (39.1%)	7 (31.8%)	
Missing	33	23	10	
Tumor Volume at Local Therapy				
<200 mL	60 (90.9%)	39 (88.6%)	21 (95.5%)	0.65
≥200 mL	6 (9.1%)	5 (11.4%)	1 (4.5%)	
Missing	35	25	10	
Percent Volume Change				

	All patients (N=101)	Radiation (N=69; 68%)	Surgery + radiation (N=32; 32%)	*p*
N	71	49	22	0.16
Median	−76.0	−74.7	−79.1	
Range	−100.0 – −15.4	−100.0 – −15.4	−98.3 – −35.6	
≤ −75%	34 (48.0%)	25 (51%)	9 (41%)	0.43
> −75%	37 (52%)	24 (49%)	13 (59%)	
< −50%	10 (14.1%)	8 (16.3%)	2 (9.1%)	0.71 †
≥ −50%	61 (85.9%)	41 (83.7%)	20 (90.9%)	
Missing	30	20	10	
AJCC T Stage				
T1	3 (3.0%)	2 (2.9%)	1 (3.1%)	0.08
T2	30 (29.7%)	15 (21.7%)	15 (46.9%)	
T3	27 (26.7%)	20 (29.0%)	7 (21.9%)	
T4	41 (40.6%)	32 (46.4%)	9 (28.1%)	

† Using Fisher exact test

Table 2.

Five-year cumulative incidence of local failure for the entire cohort and by patient, tumor, and treatment characteristics.

	N	Local Failure	Hazard Ratio (95% CI)	*p*
All patients	101	19.0%	--	--
Sex				
Female	48	18.8%	1.0	0.90
Male	53	19.3%	0.95 (0.38 – 2.33)	
Age				
<13 years	46	15.6%	1.0	0.38
≥13 years	55	21.9%	1.51 (0.60 – 3.84)	
<18 years	90	18.0%	1.0	0.38
≥18 years	11	27.3%	1.73 (0.50 – 5.96)	
Local control modality				
RT	69	25.0%	4.45 (1.03 – 19.25)	0.046
S+RT	32	6.3%	1.0	
Tumor Subsite				
Sacrum	45	11.4%	1.0	
Non-sacrum	56	25.0%	2.41 (0.87 – 6.72)	0.09
Tumor Subsite				
Sacrum	45	11.4%	1.0	
Iliac/buttock	40	20.0%	1.84 (0.60 – 5.63)	0.29
Ischiopubic-acetabulum	16	37.5%	4.16 (1.27 – 13.66)	0.02
Tumor Size at Diagnosis				
<8 cm	24	12.5%	1.0	
≥8 cm	75	21.7%	1.76 (0.51 – 6.05)	0.37
Tumor Volume at Diagnosis				
<200 mL	44	14.0%	1.0	
≥200 mL	52	23.1%	1.80 (0.68 – 4.81)	0.24
Tumor Size at Local Therapy				
<8 cm	45	21.6%	1.0	
≥8 cm	25	24.0%	1.34 (0.18 – 3.75)	0.24
Tumor Volume at Local Therapy				
<200 mL	60	21.7%	1.0	
≥200 mL	6	33.3%	2.28 (0.51 –10.11)	0.58
Percent Volume Change				
≥ −75%	34	25.0%	1.0	
< −75%	37	17.6%	0.77 (0.27 – 2.16)	0.62
≥ −50%	10	20.0%	1.0	
< −50%	61	30.0%	2.06 (0.58 – 7.32)	0.26

	N	Local Failure	Hazard Ratio (95% CI)	*p*
AJCC T Stage				
T1	3	0.0%	1.36 (0.07 – 27.90)	0.84
T2	30	20.2%	1.0	
T3	27	25.9%	2.0 (0.10 – 41.28)	0.64
T4	41	15.0%	0.99 (0.05 – 20.37)	0.99

Table 3.

Correlation of tumor size in maximum dimension and tumor volume at diagnosis with tumor subsite.

	Sacrum (N=45)	Iliac/buttock (N=40)	Ischiopubic-acetabulum (N=16)	*p*
Tumor Size at Diagnosis				
<8 cm	16 (35.6%)	4 (10.5%)	4 (25.0%)	0.03
≥8 cm	29 (64.4%)	34 (89.5%)	12 (75.0%)	
Missing	0	2	0	
Tumor Volume at Diagnosis				
<200 mL	27 (60.0%)	11 (28.9%)	6 (46.2%)	0.02
≥200 mL	18 (40.0%)	27 (71.1%)	7 (53.8%)	
Missing	0	2	3	

Table 4.

Analysis of cumulative incidence of local failure at 5-years by local therapy modality and tumor subsite.

Local Therapy & Subsite	N	Local Failure	Hazard Ratio (95% CI)	*P* value
S+RT & Sacrum	14	0.0%	1.0	
S+RT & Iliac/buttock	12	8.33%	3.3 (0.1–103.6)	0.50
S+RT & Ischiopubic-acetabulum	6	16.67%	10.2 (0.3–320.9)	0.20
RT & Sacrum	30	16.67%	5.6 (0.3–126.2)	0.28
RT & Iliac/buttock	28	25.00%	9.0 (0.4–195.3)	0.17
RT & Ischiopubic-acetabulum	10	50.00%	19.6 (0.8–443.6)	0.06