Does Radiotherapy after Surgery Affect Outcomes in Ewing's Sarcoma of the Pelvis?

Abstract

Background: The impact of postoperative radiotherapy (PORT) on outcomes has been a matter of debate after adequate resection in Ewing's sarcoma of the pelvis. We evaluated our cases after surgical excision in pelvic Ewing's sarcoma and assessed local control and overall survival (OS) with respect to PORT and chemotherapy-induced percentage necrosis. **Materials and Methods:** Forty four surgically operated patients (June 2002–November 2014) of localized Ewing's sarcoma were retrospectively reviewed. There were 31 males and 13 females. Age ranged from 2 to 53 years. All patients received institutional chemotherapy protocol. No patient received preoperative radiotherapy. Specimen was analyzed for margins and chemotherapy-induced percentage necrosis. PORT was offered to patients on case-by-case basis. Presence of a large preoperative soft-tissue component, margin evaluation, and percentage necrosis were factors considered. At time of the last followup, 29 patients were alive, 11 died, and 4 were lost to followup. Survivors had a minimum followup of 2 years (range: 31–118 months, mean = 69 months). **Results:** One of twenty (5%) patients with PORT had a local recurrence as against 2 of 24 (8%) without PORT. OS of all patients was 76% at 5 years. Twelve patients with <90% necrosis had OS of 56% and 32 with >90% necrosis had OS of 83% (P = 0.040). OS of patients with PORT was 74%, without PORT was 78% (P = 0.629). **Conclusions:** The decision to offer PORT after surgical excision in pelvic Ewing's sarcoma is multifactorial; the absence of PORT in selected cases is not detrimental to local control. Poor responders to chemotherapy had poorer survival while PORT did not impact on outcomes.

Keywords: *Bone tumor, Ewing's sarcoma, local recurrence, radiotherapy, survival*
MeSH terms: *Pelvis, tumor, Ewing's tumor, recurrence, radiotherapy*

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Introduction

In the last few decades, the advantages of surgery as compared to radiotherapy alone for local control in Ewing's sarcoma have been demonstrated.[1,2] Although there is general consensus regarding surgical excision as being the optimal modality for local control, the role of postoperative radiotherapy (PORT) has been a matter of debate. Most protocols recommend using the adequacy of surgical margins and the amount of chemotherapy-induced necrosis as parameters on which to base the decision to add PORT.[3,4] While radiotherapy may add to local control in Ewing's sarcoma, it also has its drawbacks.[5,6] In the pelvis, close proximity of visceral structures, an increased incidence of wound complications, fertility issues, and the risk of second cancers in these young patients are additional areas of concern.[7]

The role of PORT in influencing outcomes after surgery still remains undefined.[8] It is unclear if the failure to completely remove the tissues involved by prechemotherapy volume in good responders or the presence of viable tumor in the excised specimen in the presence of clear margins always necessitates PORT.[1-4,8]

We evaluated our cases after surgical excision in pelvic Ewing's sarcoma and sought to determine the impact of PORT. The primary objective was to correlate local control and overall survival (OS) with PORT. We also looked at the effect of chemotherapy-induced percentage necrosis on these outcomes. We are hopeful that this could help shed further light on the indications for PORT in surgically operated pelvic Ewing's sarcoma.

Materials and Methods

We retrospectively reviewed the data for 44 consecutive surgically operated patients of localized Ewing's sarcoma between June 2002 and November 2014. All patients had a histologically confirmed diagnosis of Ewing's sarcoma and were nonmetastatic at presentation.

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There were 31 males and 13 females. The median age was 15 years (range 2-53 years). All patients were treated on the institutional chemotherapy protocol for Ewing's sarcoma family of tumors which included two courses of vincristine, ifosfamide, and etoposide (VIE) couplet 3 weekly followed by two courses of vincristine, adriamycin, and cyclophosphamide (VAC) couplet administered every 2 weeks as neoadjuvant/induction chemotherapy. Maintenance therapy was continued after surgical excision and consisted of 12 courses of chemotherapy administered every 3 weeks [VAC, 4 courses; VIE, 2 courses, and VCD (vincristine, cyclophosphamide, actinomycin D) 6 courses with actinomycin D substituted for doxorubicin after a total dose of 360 mg/m^2]. Vincristine was administered weekly through the chemotherapy schedule.

No patient received preoperative radiotherapy. Surgery was performed between week 9 and week 12 after initiation of chemotherapy. The primary goal of surgery was complete excision of the tumor. The decision to offer surgical excision to these patients was taken at a multidisciplinary tumor board meeting based on the possibility of achieving tumor-free resection margins as evaluated on preoperative imaging.

The excised specimen was analyzed for margins and chemotherapy-induced percentage necrosis. The amount of chemotherapy-induced necrosis was expressed in a semi-quantitative manner by grading the extent of necrosis relative to the percentage of residual viable tumor. Patients were divided into two groups based on the percentage necrosis as <90% necrosis and >90% necrosis. Twelve patients (27%) had <90% necrosis and 32 had >90% necrosis.

PORT was offered to patients on a case-by-case basis. Presence of a large soft-tissue component at presentation, pathologic interpretation of margins, and percentage necrosis were the factors considered before deciding on PORT at a multidisciplinary meeting. Of the 44 patients, twenty (45%) cases received PORT [Table 1] which was delivered at a dose of 45 Gy delivered in 25 fractions over 5 weeks (1.8 Gy/fraction). A 5.4 Gy boost was delivered in cases with positive microscopic margins. Followup ranged from 0 to 118 months (mean = 50 months and median = 47 months). At the time of the last followup, 29 patients were alive, 11 had died, and 4 were lost to followup. All survivors had a minimum followup of 24 months (range 31–118 months, mean = 69 months, and median = 64 months).

We assessed local control and OS of the patients with respect to PORT and chemotherapy-induced percentage necrosis. The end point for OS was defined as the time from registration to death from all causes. The survival curves were calculated according to the Kaplan–Meier method and compared by means of the long-rank test using Statistical Package for the Social Sciences software version 20.0 (SPSS, Chicago, IL, USA). Hazard ratios and 90% confidence intervals were estimated by Cox proportional hazard regression. The log-rank test was used to compare survivals. Significance was set at $P < 0.05$.

Results

Four (9%) patients had involved margins. Their eventual outcomes are detailed in Table 2.

Three (7%) patients had local recurrence; 1 (25%) of 4 with involved margins and 2 (5%) of 40 with free margins. Their eventual outcomes are detailed in Table: 3. The overall survival of all patients was 76% at 5 years. Patient outcomes with respect to PORT and chemotherapy induced percentage necrosis are detailed in Table 4.

Discussion

The role of radiotherapy in local control of Ewing's sarcoma is well established.[1,4,9] With the increasing use of surgery in Ewing's sarcoma, the indications for radiotherapy are being revaluated.[8,10] Although there is a consensus that the presence of involved margins is an indication for the addition of PORT, various series have

Table 1: Reasons for patients receiving postoperative radiotherapy

Reason for PORT (*n*=20)	*n*
>90% necrosis + PORT	**11**
Large soft tissue component	11
<90% necrosis + PORT	**9**
Large soft tissue component	7
Involved margin	2

PORT=Postoperative radiotherapy

Table 2: Outcomes of patients with involved margins

Percentage necrosis	PORT	Comment
<90	Yes	Local recurrence, distant metastasis - dead
<90	Yes	Alive with no evidence of disease
<90	No	PORT not given because of perioperative mortality - dead
>90	No	PORT not given because of local wound complications, distant metastasis - dead

PORT=Postoperative radiotherapy

Table 3: Outcomes of patients with local recurrence

Number	Margin	Percentage necrosis	PORT	Comment
1	Involved	<90	Yes	Distant metastasis - dead
2	Free	>90	No	Distant metastasis - dead
3	Free	>90	No	Received radiotherapy for local recurrence - alive

PORT=Postoperative radiotherapy

Table 4: Patient outcomes with respect to postoperative radiotherapy and chemotherapy-induced percentage necrosis

Variable	*n*	LR (%)	5 year OS (%)	*P*	HR	95% CI
PORT	20	1 (5)	74	0.628	1.3	0.4-4.5
No PORT	24	2 (8)	78		1	
>90% necrosis	32	2 (6)	83	0.040	1	1-11
<90% necrosis	12	1 (8)	56		3.3	
>90% necrosis + PORT	11	-	81	0.129	1	-
>90% necrosis without PORT	21	2 (10)	85		0.8	0.1-4.4
<90% necrosis + PORT	9	1 (11)	67		2.3	0.4-13.6
<90% necrosis without PORT	3	-	33		4.6	0.6-32.8

LR=Local recurrence, OS=Overall survival, HR=Hazard ratio, CI=Confidence interval, PORT=Postoperative radiotherapy

used differing amounts of viable tumor in the excised specimen to recommend PORT.[4,10]

At our institute too, we have favored surgical excision as the preferred modality for local control in nonmetastatic pelvic Ewing's sarcoma if preoperative imaging suggests that tumor-free resection margins are possible.[11] Our decision to add PORT has been decided on a case-to-case basis and is multifactorial. While the presence of involved margins is a definite indication to give PORT, we have not always added PORT in cases which have shown a viable tumor in the excised specimen if the surgical margins have been reported as free. Other series have expressed similar views.[1,2] This reluctance stems from the disadvantages associated with PORT, especially in the pelvis.[5,6,12] The presence of a large soft-tissue mass with adjacent tissue edema at index presentation has often been a determining factor in our decision to add PORT even if the surgical margins are free and chemotherapy necrosis >90%. As the pelvis offers a surgical challenge to achieve conventional quantitative or qualitative wide margins, it is a possibility that the tissues involved by prechemotherapy volume may not always have been completely removed in spite of the margins being reported as free.[8,13] In addition, the histological evaluation of the resected specimen in a single slice may underestimate the proportion of viable tumor cells in large tumors.[8] Majority of our pelvis patients do not undergo reconstruction with bone grafts or implants as we favor hip transposition where reconstruction is required.[11] Hence, some of the major early complications associated with PORT are relatively less relevant.

We had a local recurrence (LR) in 7% of our patients. This is comparable to the recent series from the Mayo clinic but less than the 26% reported by Dramis and 18% reported in the Euro-E.W.I.N.G study.[7,8,14] This could be a reflection of the fact that advances in current imaging technology help the surgeon plan surgical margins with greater accuracy compared to series which spanned many decades.[14] In addition, a specialized sarcoma service in a single institute can plan and execute a multidisciplinary treatment approach for a patient with more consistency compared to series that collate data from multiple institutions with varying levels of expertise.[8] Minimizing local failure is important as patients with LR have a dismal prognosis as is evident in our series too [Table 2].[8,15] Only one of twenty (5%) of the patients receiving PORT had LR. It is a matter of conjecture whether the addition of PORT in these "at-risk" patients aided in adequate local control. Only 8% of the patients not receiving PORT had LR. This is in contrast to the 23% patients with pelvic tumors without PORT who developed LR in the Euro-E.W.I.N.G study.[8] Our three patients with <90 necrosis who did not receive PORT did not develop LR. The number of LR s is too small to make definitive recommendations regarding PORT and/or the response to chemotherapy, but it appears that our multifactorial approach balancing the pros and cons of PORT appears valid and is not detrimental to achieve adequate local control.[4,9]

Our OS for all patients was 76% at 5 years. This is comparable to other series of surgically operated nonmetastatic pelvic Ewing's sarcomas.[7,16] Patients with <90% necrosis fared worse than those with >90% necrosis (56% vs. 83% [P = 0.04]), a fact that has been commented on in other series of pelvic Ewing's sarcoma as well.[14] Patients receiving PORT had similar outcomes to those that did not receive PORT. Similar results have been documented by others.[8] In our series in patients with <90 necrosis; those who did not receive PORT seemed to have poorer survival compared to the group receiving PORT [Table 3]. The numbers are too small to form any definite conclusions. Although the addition of PORT is not known to improve survival in surgically operated Ewing's sarcoma of the pelvis, this subgroup will need to be the focus of further studies to determine if the addition of PORT can impact on survival in patients with pelvic tumors who are poor responders to chemotherapy.[8]

Our retrospective series has its limitations. The numbers are small. This paucity of numbers is unavoidable in a single institutional study reporting on these uncommon tumors in a specific location.[7] The evaluation of the impact of PORT on outcome was performed in an observational setting as PORT was not randomly allocated. It is highly unlikely that evidence for similar cases will arise from a randomized setting. Larger numbers from multicenter studies can help formulate guidelines, though we accept that there is an element of subjectivity in the decision-making for PORT in our series that may be difficult to standardize when formulating guidelines applicable across different centers.[14] A much longer followup would be necessary to comment whether the addition of PORT impacts on the incidence of second cancers in our patients.

In spite of these shortcomings, we believe that this study does add to the understanding of indications for PORT in surgically treated pelvic Ewing's sarcomas. Compared to studies where all local control options including definitive radiotherapy were evaluated together, our study focuses on the impact of PORT exclusively in patients of pelvic tumors who underwent surgery.[7,14,16] Its strength lies in the fact that it presents the results of a group of patients who were managed by the same multidisciplinary team. The cases were seen and treated at a specialist oncology center over a relatively short period of time where treatment philosophy was consistent and not affected by the popularity of various therapeutic modalities in different eras.[8]

Conclusions

Our data suggest that the decision to offer PORT after surgical excision in pelvic Ewing's sarcoma is multifactorial. Poor responders to chemotherapy have poorer survival. The adequacy of surgical margins and percentage necrosis after chemotherapy though important should not be the sole governing factors when deciding on PORT. Although the absence of PORT in selected cases does not seem to be detrimental to local control, its role in survival in patients with <90 necrosis will need to be studied further.

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Conflicts of interest

There are no conflicts of interest.

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