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Tumor Necrosis: Does it define the need for post operative radiotherapy in Ewing's sarcoma?

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Introduction: Though there is general consensus regarding surgical excision as being the optimal modality for local control in Ewing's sarcoma the role of post operative 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. While radiotherapy does add to local control in Ewing's sarcoma it also has its drawbacks. While an involved margin is a definitive indication for the addition of PORT, it is unclear if the presence of viable tumor in the excised specimen in the presence of clear margins always necessitates PORT.

Questions: We sought to correlate the rate of local control and overall survival after surgical excision in osseous Ewing' sarcoma with respect to chemotherapy induced percentage necrosis and PORT.

Method: We retrospectively reviewed the data for 94 consecutive surgically operated patients of localised Ewing's sarcoma between January 2006 to June 2010. All patients were non metastatic at presentation. There were 73 males and 21 females. The age ranged from 3 years to 33 years with a median of 15 years. We excluded the 7 tumors that arose in the soft tissue leaving 87 osseous lesions. Bones involved were femur and, tibia (24 each), humerus (15), radius and scapula (6 each), fibula (5), clavicle, metacarpal, ulna (2 each) and 1 talus.

All patients were treated on the institutional chemotherapy protocol. No patient received preoperative radiotherapy. Surgery was performed between week 9 and week 12 after initiation of chemotherapy. 83 patients had limb salvage while 4 had an amputation

The excised specimen was analysed for margins and chemotherapy induced percentage necrosis. Patients were divided into 2 groups based on the percentage necrosis as < 90 % and > 90%. Estimation of chemotherapy induced necrosis was available in 73 patients. Fourteen patients had reimplantation of the excised specimen for reconstruction after extracorporeal irradiation and hence percentage necrosis was not reported. The 4 patients who had an amputation were also not included in the analysis as there is little role for PORT after an ablative surgery. Thus 69 patients were eligible for analysis.

PORT was offered to patients on a case by case basis. Besides pathologic interpretation of margins and percentage necrosis the other factors that were considered included: presence of pathologic fractures, large soft tissue component at presentation, anatomic site and the surgeon's (subjective) evaluation of margin adequacy.

The primary objective was to correlate the rate of local control with respect to chemotherapy induced percentage necrosis and PORT. The secondary objective was to compare overall survival of the patients on similar parameters.

Results: One patient had involved margins. This patient received PORT. Though there was no local relapse, the patient eventually succumbed to the disease after 20 months due to distant relapse.

Of the 69 patients eligible for analysis, 19 had < 90 % and 50 had > 90 % necrosis. 20 of these patients received radiotherapy (in 7 patients with < 90 % necrosis and in 13 patients with > 90% necrosis). All patients were available for follow up. Currently 46 of these 69 patients are alive with a median follow up of 74 months (range 33 to 102 months). The overall survival (OS) of all patients was 68 % at 5 years. The patients with < 90 % necrosis had poorer OS than those with > 90 % necrosis; 47 % vs. 76 % ($p = 0.020$). Five patients developed local recurrence (Table: 1)

Table 1:

	Number	**Radiotherapy**	**No Radiotherapy**	
< 90 % necrosis	19	7 (37%)	12 (63%)	
	Local recurrence	2 of 7 (29%)	0	
	0S at 5 years	43 %	50 %	p = 0.957
> 90 % necrosis	50	13 (26%)	37 (74%)	
	Local recurrence	1 of 13 (8%)	2 of 37 (5%)	
	0S at 5 years	54 %	87 %	p = 0.019

Discussion: While the presence of involved margins is a definite indication to give PORT we have been reluctant to add PORT in all cases which have shown viable tumor in the excised specimen if the surgical margins have been reported as free. Our decision has been influenced by various additional factors. Viable tumor in the presence of a pathologic fracture is an indication for PORT irrespective of the surgical margins as we believe that the resultant fracture hematoma has the potential to leave microscopic residual contamination inspite of achieving surgically adequate margins. Similarly the presence of a large soft tissue mass with adjacent tissue edema at index presentation has often been a determining factor in the decision to add PORT if the surgical specimen demonstrates viable tumor. Certain anatomic sites like the forearm and the proximal fibula offer a surgical challenge to achieving conventional quantitative or qualitative wide margins. We have often favoured PORT in this situation in view of close surgical margins. We have also given credence to the surgeon's subjective impression regarding adequacy of margins. We accept that this "subjective impression" introduces an element of selection bias and is largely based on the surgeon's experience and maturity.

Our rate of local recurrence, 7 % (5 of 69) is in keeping with most series and indicates that our multi factorial approach to PORT appears valid. More local recurrences occurred in patients receiving PORT than those that did not (15 % vs. 4 %). This difference is possibly due to selection bias as those selected for PORT were patients believed to be at a "subjective" greater risk for local failure. In fact in our 12 patients with < 90 necrosis who did not receive PORT, none developed a local recurrence. This justifies our rationale for not offering PORT to all patients only on the basis of presence of viable tumor in the excised specimen.

Conclusion: Our data suggests that the decision to offer PORT after surgical excision in Ewing's sarcoma is multifactorial. The adequacy of surgical margins and percentage necrosis after chemotherapy though important should not be the sole governing factors when deciding on PORT and various additional factors also need to be considered.