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CHEMOTHERAPY INDUCED NECROSIS AS A PROGNOSTIC MARKER IN OSTEOSARCOMA - DO WE NEED TO RAISE THE BAR?

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Introduction: The degree of chemotherapy induced histological necrosis has proven to be one of the most robust prognostic markers in osteosarcoma. Currently a cut off using < / > 90 % necrosis is employed as the determinant for classifying the response as poor or good.

Questions: We asked if the traditional cut off using < / > 90 % necrosis for classifying the response as poor or good was valid or a new benchmark needed to be established

Methods: We reviewed the data for 192 consecutive patients of localised extremity osteosarcoma enrolled in a prospective randomized trial for surveillance between January 2006 to June 2010. All patients had a histologically confirmed diagnosis of osteosarcoma and were non metastatic at presentation. There were 145 males and 47 females. The age ranged from 5 years to 49 years with a median of 17 years. Sites involved were femur (105), tibia (54), humerus (21), radius (3) and fibula (9). All patients received neoadjuvant chemotherapy as per the existing hospital protocol. Patients then underwent appropriate surgical resection with an attempt to achieve clear oncologic margins followed by adjuvant chemotherapy. 168 patients had limb salvage while 24 had an amputation. The excised specimen was analysed for margins and chemotherapy induced percentage necrosis. Margins were reported as free in all cases. Patients were divided into 3 groups based on the percentage necrosis as < 90 %, 90 – 99 % and 100%.

The primary objective was to correlate overall survival of the patients with respect to chemotherapy induced percentage necrosis. The secondary objective was to compare disease-free survival (time to recurrence).

Results: Eight patients had reimplantation of the excised specimen for reconstruction after extracorporeal irradiation and hence percentage necrosis was not reported. Estimation of chemotherapy induced necrosis was hence available in 184 patients. Six of these patients died during chemotherapy or due to unrelated causes. A total of 178 patients were therefore analysed. Necrosis was reported as < 90 % necrosis in 73, between 90 – 99 % necrosis in 62 and 100 % necrosis in 43. 173 of these patients were available for follow up. Currently 84 patients are alive. All survivors had a minimum follow up of at least 2 years (range 31 to 88 months, median 50 months).

The overall survival of all patients was 48 % at 5 years and the disease free survival was 39 %. The survival figures for the various groups based on percentage necrosis are shown in Table 1.

Table 1: Survival outcomes based on response to chemotherapy

% necrosis	Number	Overall survival	Disease free survival
Group I = < 90	73	46	32
Group II = 90 – 99	62	34	29
Group III = 100	43	73	67
Grouped as 90% or greater (Group II + III)	105	50	45
Grouped as < 100 % (Group I + II)	135	41	31

Table 2: Survival outcomes between various groups based on response to chemotherapy

Comparison based on % necrosis	Numbers	Overall survival	Disease free survival
< 90 % vs. > 90 %	73 vs. 105	46 % vs. 50 % p = 0 .139	32 % vs. 45 % p = 0 .139
< 100 % vs. 100 %	135 vs. 43	41 % vs. 73 % p = 0 .001	31 % vs. 67 % p < 0 .001

Conclusions: Our data suggests that the traditional cut off "< / > 90 % necrosis" may not be the appropriate benchmark when deciding to modulate post surgery chemotherapy in patients. Patients with necrosis between 90 – 99 % appear to fare as poorly as those who have < 90 % necrosis. More accurate prognostic indicators may have the potential to improve survival by tailoring post operative adjuvant chemotherapy regimens for patients. It may be better to use the presence of any viable tumor (i.e. < 100 necrosis) as the benchmark to grade a patient as a poor responder as only patients with a complete absence of any viable tumor in response to neoadjuvant chemotherapy have shown better survival outcomes.

An additional advantage of classifying the response as 100% or < 100% (absence or presence of any viable tumor) is the removal of inter observer variability while grading patients as good or poor responders thus establishing more consistency among centres in multi centre studies.