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Abstract Title: Local Recurrence In The Euramos-1 Trial – Risk Factors, Management And Outcome

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on behalf of the EURAMOS-1 investigators

Background:

The EURAMOS-1 trial was the largest randomised trials for patients with osteosarcoma, registering 2260 patients from 17 countries of whom 1334 were randomised. Recruitment started in April 2005 and ended in June 2011. All patients had preoperative MAP (methotrexate, doxorubicin, cisplatin), followed by surgery; Poor responders (≥10% viable tumor) were randomised to ongoing MAP vs MAP plus postoperative ifosfamide, etoposide (IE); good responders (<10% viable tumor) to maintenance interferon-alpha 2b or MAP only.

Questions / Purposes:

This report documents the rate of local recurrence at the primary site, the risk factors, treatment and significance of local recurrence on patient survival.

Patients and Methods:

All registered patients were included in the analyses unless they were: (a) ineligible following central pathology review; (b) ineligible at registration due to other reasons; or (c) reported local recurrence prior to surgery. Kaplan-Meier method was used to estimate time from surgery (or planned surgery) to local recurrence or date last contact, and time from local recurrence to death, or date of last contact. Cox model was applied to explore risk factors for local recurrence. Completion of surgery data was not mandatory for non-randomised patients; missing dates of surgery were estimated as a median time from registration to surgery in patients from the same group (COG, COSS, EOI, SSG) and the same metastases status at registration. The following risk factors for local recurrence after

surgery were included in the multivariate Cox model: age, sex, site, type of surgery, histological response, metastases status at registration, fracture at surgery, surgical margins, randomisation status.

Results:
Of the 2,260 registered patients, 2,140 were included in this analysis. This excludes 84 eligible patients with local recurrence reported prior to or on the date of surgery, and 36 patients ineligible due to pathology or other reasons.

Median follow-up from surgery was 51 months (IQR 35-70). Of the 2,140 patients, 152 (7%) were reported to have local recurrence by 6 years after surgery. Ignoring competing risks, the local-recurrence-free rate was 92% (95%CI 91%-93%) at 5 years from surgery. For randomised patients, the local-recurrence-free rate was 93% (95%CI 92%-95%) at 5 years from surgery and for registered (but not randomised patients) it was 90% (95%CI 87%-92%).

Of 152 patients with local recurrence (LR), 23 had (resectable) metastases at baseline, 11 developed new metastases prior to local recurrence, 42 reported synchronous new metastases (+/-4 weeks from local recurrence), 6 were reported to develop metastases after local recurrence and metastases status was unknown for 2 patients; 68 patients with reported LR had no metastases yet, but not all participating trials groups reported disease events after the first. Of these patients, 35/68 died without reported metastases and 33/68 were alive. The statistically significant prognostic characteristics were tumour site (axial worse, HR 4.35, 95%CI (2.56-7.39)) and histological response (poor responder worse, HR 1.58, 95%CI (1.09-2.29).

At 2-years after local recurrence, overall survival was 36% (95%CI 28%-44%); 48% (95%CI 38%-60%) in those with isolated local recurrence alone and 24% (95%CI 15%-34%) in patients with synchronous or pre-existing metastases.

Conclusions:
The results show that the key risk factors for local recurrence are tumour site and histological response among the factors we were able to assess. One limit of our work is that reporting and interpretation of local recurrence after metastatic progression or secondary malignancy is complicated. Data will be presented using these as competing risks.