# Tumour necrosis and prognosis in Ewing's sarcoma

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Over the last 20 years major advances have been made in the treatment of Ewing's sarcoma and osteosarcoma. The combined treatment of preoperative chemotherapy-radiotherapy followed by surgical resection of the tumour has resulted in a remarkable improvement in prognosis.

The surgical treatment has also made possible a histopathological examination of the tumour response to the preoperative therapy. The correlation of the histopathologic tumour response with clinical outcome is a well established routine investigation in patients with osteosarcoma and the grading of the tumour response is based on definable histopathologic criteria.

Widely used is the grading system proposed by Huvos (1991). Another system for histologic response grading of osteosarcoma has been suggested by Picci et al. (1985) They divided the response into three grades; good, fair and poor, based on the percentage of necrosis in the specimen. Good corresponded to necrosis in more than 80%, fair 50–80% and poor necrosis less than 50%.

These histologic response gradings of osteosarcoma are based on necrosis, diminuition or total disappearance of the sarcomatous tissue. Bone trabeculae may be retained as well as ossified tumor osteoid and primitive tumor bone. Thus in a favorable response the tumour volume is in the main unaltered and composed of fibrous tissue between trabeculae of tumour osteoid, more or less ossified or calcified.

Ewing's sarcoma cells do not produce stroma (osteoid, cartilage or collagen) and when they respond satisfactory to the chemotherapy they disappear completely and unlike osteosarcoma, there may be a substantial decrease in tumour volume after the preoperative chemotherapy. This difference in effect on the tumour has led many investigators to consider that the Huvos grading may not be applicable in Ewing's sarcoma. This has lead to a search for a histopathologic response grading which differs from that suggested by Huvos for osteosarcoma.

Picci et al. (1993) described a histopathologic response grading specifically applicable for Ewing's sarcoma. Their approach was a three Grade system but instead of estimation of the amount of non-viable tumour they proposed the evaluation of the amount of remaining viable tumour. Grade I is defined as the response when the tumour specimen contains at least one remaining macroscopic nodule of viable tumour. A macroscopic nodule is defined as a viable tumour mass which is larger then one 10x magnification field or scattered smaller tumour nodules whose area together exceeds one 10x field.

Grade II is defined when isolated small nodules of viable tumour are found, the total areas of these nodules not exceeding one 10x field and Grade III is defined as the response when no viable tumour nodules are identified within the surgical specimen.

Specimens with scattered individual tumour cells but without nodules are also defined as Grade III. Operative specimens without viable nodules but with scattered cells which are difficult to identify as tumor cells are also included as Grade III (Figure 1).

A reliable response grading is dependent on a thorough macroscopic as well as microscopic examination of the surgical specimen. The fresh specimen should be examined soon after surgery. It is important that multiple sections are saved from the following areas: the subperiosteal region, the intramedullary canal, the soft tissue mass over the tumor, if any, and areas of haemorrhage. When the site for a diagnostic open biopsy is included in the specimen, several sections are also cut from that area. It is advantageous to saw the specimen into halves and use one half for the multiple sections and the other as a whole tumour section. A drawing of the tumour specimen should be done indicating the cuts and their reference. It is then easy for the pathologist to report the different areas with viable tumour.

Picci et al. (1993) were able to show the importance of this regional mapping of the specimen. In Ewing's sarcoma viable tumour was more often encountered in the soft tissue mass, subperiosteal region and in areas of haemorrhage than in the central part of the tumour. In their investigation of 68 patients they found the following 5-year disease free survival; Grade I 32%, Grade II 53% and Grade III 90%.

We have, however, used the Huvos response grading system for osteosarcoma in two trials of Ewing's

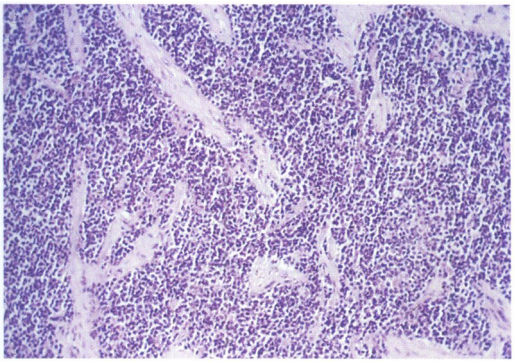

*Figure 1. A. Histologic response Grade I. Viable Ewing's sarcoma tumour mass larger than one 10x magnification field. HE, ×25.*

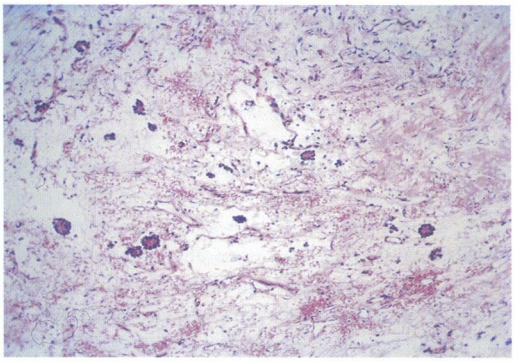

*Figure 1. B. Histologic response Grade II. Isolated small nodules of viable Ewing's sarcoma, not exceeding one 10x magnification field. HE, ×25.*

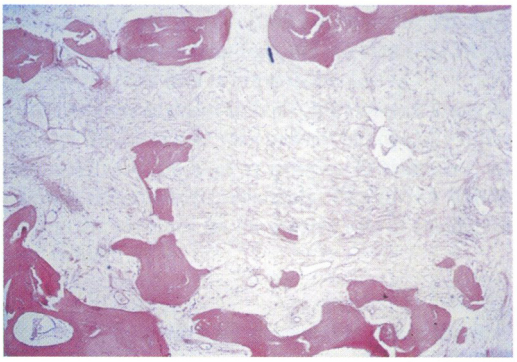

*Figure 1. C. Histologic response Grade III. No viable tumour. Loose fibrous tissue surrounded by degenerated bone trabeculae. HE, ×25.*

sarcoma initiated by the Scandinavian Sarcoma Group SSGIV 1984 comprising 53 patients and SSGIX 1990 and ongoing, comprising 84 patients. The tumour was not resectable in all patients, in 78 of the resectable tumours information of the response grading and clinical follow up was registered in September 1996. The follow up time varied between 144–5 months and disease free survival was 24% in Grade I tumours, 65% in Grade II, 45% in Grade III and 85% in Grade IV. Grades I–II are considered an unfavorable response and Grades III–IV a favorable. The disease free survival rates in these two trials were for the unfavorable 44% compared to 73% for the favorable group (Alvegård et al. 1989, Åkerman and Stenwig 1996).

We also had the opportunity to re-examine 42 specimens from the above material according to the Picci 3-Grade system. 27 tumour specimens were considered to have a Grade I response, 6 a Grade II response and in 9 a Grade III response was diagnosed. The disease free survival was 30% in Grade I tumours and 89% in Grade III tumours.

Our survival figures in the total material, graded according to the Huvos system, are inferior to those of Picci et al. but in the smaller material graded after the Picci system essentially the same. The Picci material was collected from one centre where all patients were primarily diagnosed, clinically and radiographically investigated, treated and operated and the surgical specimens prepared and histologically evaluated according to the same protocol while the SSG patients originated from at least 10 centres with a variable experience in diagnosing and treating Ewing's sarcoma.

In spite of this decentralized management the histologic response grading was of importance in the monitoring of these patients and it was also possible to confirm that the regional mapping of the surgical specimen is most important. Viable tumour was very often found in the soft tissue extensions even when the Ewing's sarcoma in central parts of the bone was totally obliterated (Figure 2).

## *Summary*

The type of grading system used appears to be less important than the protocol of regional mapping and histologic evaluation.

## *References*

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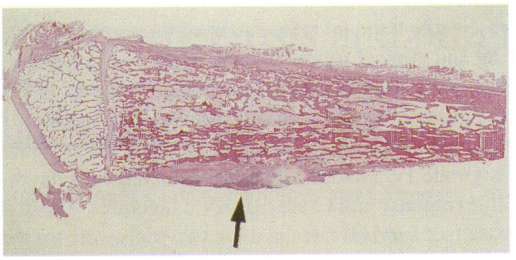

*Figure 2. A. Whole tumour section . No viable tumour within the bone corresponding to Grade III Picci, but viable tumour in the soft tissue extension outside the bone (arrow). HE, ×2.5.*

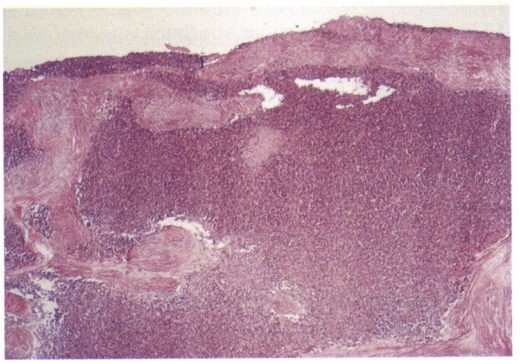

*Figure 2. B. Higher magnification of the viable tumour area, corresponding to Grade I Picci. HE, X25.*

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