resection combined with chemotherapy. *Cancer* 1975, **35**, 618–621.
113. Rosen G, Huvos AG, Mosende C, *et al.* Chemotherapy and thoracotomy for metastatic osteogenic sarcoma: a model for adjuvant chemotherapy and the rationale for the timing of thoracic surgery. *Cancer* 1978, **41**, 841–849.
114. Ward WG, Mikaelian K, Dorey F, *et al.* Pulmonary metastases of stage IIB extremity osteosarcoma and subsequent pulmonary metastases. *J Clin Oncol* 1994, **12**, 1849–1858.
115. Saeter G, Hoie J, Stenwig AE, Johansson AK, Hannisdal E, Solheim OP. Systemic relapse in osteogenic sarcoma: prognostic factors for long term survival. *Cancer* 1994, **75**, 1084–1093.
116. Cade S. Osteogenic sarcoma: a study based on 133 patients. *J R Coll Surg Edin* 1955, **1**, 79–111.
117. Bruland OS, Skretting A, Solheim OP, Aas M. Targeted radiotherapy of osteosarcoma using 153-Sm-EDTMP. A new promising approach. *Acta Oncol* 1996, **35**, 381–384.
118. Marina NM, Pratt CB, Rao BN, Shema SJ, Meyer WH. Improved prognosis of children with osteosarcoma metastatic to the lung(s) at the time of diagnosis. *Cancer* 1992, **70**, 2722–2727.
119. Meyers PA, Heller G, Healey JH, *et al.* Osteogenic sarcoma with clinically detectable metastasis at initial presentation. *J Clin Oncol* 1993, **11**, 449–453.
120. Ferrari S, Bacci G, Briccoli A, *et al.* Osteosarcoma of the extremities with synchronous metastases: results in 67 patients treated with chemotherapy and simultaneous resection of primary and metastatic lesions. 2nd Osteosarcoma Research Conference, Bologna, 1996, 77.
121. Bacci G, Picci P, Ferrari S, *et al.* Synchronous multifocal osteosarcoma: results in twelve patients treated with neoadjuvant chemotherapy and simultaneous resection of all involved bones. *Ann Oncol* 1996, **7**, 864–866.
122. Marangolo M, Tienghi A, Fiorentini G, *et al.* Treatment of pelvic osteosarcoma. *Ann Oncol* 1992, **3**(Suppl. 2), 19–21.
123. Fahey M, Spanier SS, Vander Griend RA. Osteosarcoma of the pelvis. A clinical and histopathological study of twenty-five patients. *J Bone Joint Surg Am* 1992, **74**, 321–330.
124. Estrada Aguilar J, Greenberg H, Walling A, *et al.* Primary treatment of pelvic osteosarcoma. Report of five cases. *Cancer* 1992, **69**, 1137–1145.
125. Bielack SS, Wulff B, Delling G, *et al.* Osteosarcoma of the trunk treated by multimodal therapy: experience of the Cooperative Osteosarcoma Study Group. *Med Ped Oncol* 1995, **24**, 6–12.
126. Glasser DB, Lane JM, Huvos AG, Marcove RC, Rosen G. Survival, prognosis, and therapeutic response in osteogenic sarcoma. The Memorial Hospital experience. *Cancer* 1992, **69**, 698–708.

Acknowledgement—I, like many others, am indebted to the wisdom and guidance of Professor R.L. Souhami.

PII: S0959-8049(97)00400-0

Commentary

V.H.C. Bramwell

London Regional Cancer Centre, 790 Commissioners Road East, London, Ontario, Canada N6A 4L6

THE OUTCOME for 'classic' high grade osteosarcoma of extremities has improved dramatically over the past 25 years. Limb salvage surgery is widely used, employing metal protheses or allografts, although in his update (pp. 1611–1619) Dr Whelan is right to highlight concerns about their durability in young active individuals. In addition, the less widely used Van Ness procedure, which converts an above knee to a below knee amputation, provides an excellent functional outcome in selected patients willing to tolerate the unusual appearance.

The relative merits of randomised controlled trials (RCTs) versus innovative pilot studies is particularly hotly debated in the setting of adjuvant chemotherapy for osteosarcoma. I feel that both types of studies are important, but that certain questions can only be answered by RCTs. Unfortunately results of some RCTs have been inconclusive because of inadequate size. Dr Whelan outlines some key unresolved issues regarding adjuvant chemotherapy, and these can best be addressed in RCTs. However, the logistics of performing such studies in this rare tumour are formidable and would need not only multi-centre but multi-cooperative group collaboration.

The relationship between a 'good response' (histopathological necrosis $\geq 90\%$) after neoadjuvant chemotherapy and outcome is convincing, based on several reported studies. However, the percentage of tumours showing a 'good response' ranged from 27–41% in the three studies shown in Table 1 of Dr Whelan's update. The group from the Memorial Sloan Kettering Center, U.S.A. [1] found that longer pre-operative treatments produced higher rates of histological response, but the correlation with outcome decreased. More recent studies, using dose intensive multi-agent regimens, including ifosfamide, have shown 'good responses' in 72–87% of patients [2, 3]. When survival data are available from these studies it will be interesting to see if histological response is still of prognostic importance.

Necrosis after chemotherapy, similar to that seen in the primary tumour, also occurs in pulmonary metastases, as illustrated by two series of patients from Bologna, each comprising 23 patients with synchronous primary tumours and pulmonary metastases, treated with neoadjuvant chemotherapy between 1983–1989 [4] and 1993–1995 [5]. The latter cohort received pre-operative ifosfamide in addition to high dose methotrexate/cisplatin/doxorubicin. 'Good responses' were more frequent both in primary tumours (73 versus 26%) and in metastases (89 versus 24%) in the second series and there was a better correlation, within patients, of histopathological response between primary and metastases.

As noted by Dr Whelan, a Pediatric Oncology Group randomised trial showed no survival disadvantage for

postoperative versus neoadjuvant chemotherapy. With a total accrual of 106 patients though, this study can detect only a 20% difference in event-free survival with 80% power, and median follow-up (2 years) is still short.

There is substantial controversy, both for sarcomas and other tumours, as to whether local recurrence is merely a marker of biological aggressiveness or the seed for subsequent metastases. I think that the data favour the former hypothesis and more radical local treatments may not improve outcome.

Dr Whelan describes the controversy surrounding the role, dose and scheduling of high dose methotrexate. Although regarded as essential components of therapy, there are still questions about the optimal use of doxorubicin and cisplatin. A meta-analysis [6] of 16 published regimens found that doxorubicin dose intensity was the most important determinant of a good histological response to pre-operative chemotherapy ($P=0.01$). As discussed earlier, there may be problems with using histological response as a surrogate for survival. Bacci and associates [7], on the basis of a non-randomised comparison between consecutive Bologna studies, concluded that maintenance of dose intensity of doxorubicin was critical. Similarly, in the COSS-82 [8] study, 'good responses' were seen less frequently (71 versus 55%) when doxorubicin administration was changed from bolus to 48 h continuous infusion. For cisplatin, rates of 'good response' increase with intra-arterial versus intravenous administration, but whether this translates into improvements in local control and/or survival remains uncertain.

Craniofacial osteosarcomas are as rare as the pelvic and vertebral osteosarcomas discussed by Dr Whelan, but historically outcome has been somewhat better (30–50%, 5 year survival) than for 'classic' extremity osteosarcoma. Chemotherapy has been used increasingly in these tumours but, not surprisingly, there have been no RCTs. A meta-analysis [9] of 201 patients from 20 uncontrolled series suggests that chemotherapy, as well as complete surgical removal, improves outcome. Although there may have been biases in selecting individual patients for chemotherapy, the fact that 'good responses' can be achieved by neoadjuvant chemotherapy supports its use.

Dr Whelan's excellent and comprehensive update leads me to one further comment: better understanding of the genetic alterations associated with this rare tumour should lead to the development of novel therapies that target specific abnormalities.

1. Meyers PA, Heller G, Healey J, *et al.* Chemotherapy for non-metastatic osteogenic sarcoma: the Memorial Sloan Kettering experience. *J Clin Oncol* 1992, **10**, 5–15.
2. Miser J, Arnt C, Smithson W, *et al.* Treatment of high-grade osteosarcoma (OGS) with ifosfamide (IFOS), Mesna (MES), adriamycin (ADR), high-dose methotrexate (HDMTX) with or without cisplatin (CDDP). Results of two pilot trials. *Proc Am Soc Clin Oncol* 1994, **13**, 41.
3. Bacci G, Picci P, Ferrari S, *et al.* Neoadjuvant chemotherapy for the treatment of osteosarcoma of the extremities: excellent response of the primary tumor to pre-operative treatment with methotrexate, cisplatin, adriamycin and ifosfamide. Preliminary results. *Chir Organi Mov* 1995, **LXXX**, 1–10.
4. Biagani R, Bacci G, Picci P, *et al.* Osteosarcoma of the extremities metastatic at presentation (OEMP). *Proc Am Soc Clin Oncol* 1992, **11**, 415.
5. Bacci G, Mercuri M, Briccoli A, *et al.* Osteogenic sarcoma of the extremity with detectable lung metastases at presentation. Results of 23 patients with chemotherapy followed by simultaneous resection of primary and metastatic lesions. *Cancer* 1997, **79**, 245–254.
6. Smith MA, Ungerleider RS, Horowitz ME, *et al.* Influence of doxorubicin dose intensity on response and outcome for patients with osteosarcoma and Ewing's sarcoma. *J Natl Cancer Inst* 1991, **83**, 1460–1470.
7. Bacci G, Picci P, Ferrari S, *et al.* Influence of adriamycin dose in the outcome of patients with osteosarcoma treated with multi-agent neoadjuvant chemotherapy: results of two sequential studies. *J Chemo* 1993, **5**, 237–246.
8. Bieling P, Winkler K, Bielack S, *et al.* Continuous infusion (CI) versus short-term infusion (SI) of doxorubicin (DX) in osteosarcoma (OS). *Proc Am Soc Clin Oncol* 1991, **10**, 308.
9. Smeele LE, Kostense PJ, van der Waal I, *et al.* Effect of chemotherapy on survival of craniofacial osteosarcoma: a systematic review of 201 patients. *J Clin Oncol* 1997, **15**, 363–367.