HIGHLIGHT

by Peter M. Anderson, MD, PhD*

# Futility Versus Utility of Marrow Assessment in Initial Ewing Sarcoma Staging Workup

In the early days of Ewing sarcoma staging work-ups for chemotherapy planning and risk stratification in clinical trials, bone involvement with the primary tumor and/or metastases was assessed with (a) $^{99m}$Tc-MDP bone scan which detect metastatic bone lesions that cause remodeling, and (b) bone marrow aspiration and biopsy. Currently there are many non-invasive methods to assess bone and/or marrow involvement including $^{99m}$Tc-MDP bone scan $^{18}$FDG-PET-CT, and MRI [1]. The study by Newman et al. demonstrated that 0/57 patients without osseous metastases on $^{18}$FDG PET-CT had bone marrow involvement [1].

The contribution by Kopp et al. in this issue of Pediatric Blood and Cancer analyzed staging workup outcomes in patients with Ewing sarcoma from University of Arizona, Phoenix Children's Hospital, and the MD Anderson Cancer Center [2]. These authors showed that a pelvic primary site was not more likely to have bone marrow aspirate and/or biopsy involvement than a non-pelvic primary site. They also conclusively show that patients without osseous metastases detected using modern radiologic imaging also do not have marrow involvement; in this study 0/85 patients without imaging evidence of bone metastases had marrow involvement on bone marrow aspirates and biopsies [2]. Thus combined score of Kopp et al. and also the Seattle Children's and University of Washington series is 0/142 [1,2]. These data indicate futility (not utility) of looking for marrow metastases in standard-risk Ewing sarcoma regardless of location in those without radiologic evidence of metastatic disease. Hopefully these data will spare future newly diagnosed patients with Ewing sarcoma without radiologic evidence of distant disease, from having unnecessary marrow procedures during work-up and/or at time of central line placement.

What about patients with evidence of distant metastases on $^{18}$FDG PET-CT, chest CT, MRI, or $^{99m}$Tc-MDP bone scans? $^{18}$FDG PET-CT has the highest specificity (96%) and sensitivity (92%) of imaging modalities to detect bone metastases [3]. In the study by Kopp et al., only 42% of patients with metastases on imaging had positive marrow exams. Currently, demonstration of marrow involvement is unlikely to significantly affect overall clinical decision making. It is more important to make the effort in the initial work-up to use imaging to locate all sites that will need local control. Principles of adequate therapy for Ewing sarcoma include: (1) pre-adjuvant chemotherapy; (2) local control of primary tumor; (3) adjuvant chemotherapy to reduce microscopic disease burden; and (4) adequate local treatment of known distant metastases [4].

Would knowledge of initial marrow involvement in those with distant metastases influence assessment of adequate control? This is patient, location, and modality specific. However, as patients with metastases do so poorly [5], such information may be of benefit in determining speed of response to standard and/or new modalities as well as risk stratification, for example, in the context of clinical trial or too numerous to count (TNTC) metastases in which high dose therapy and a stem cell transplant when in clinical complete remission may become a possible option to consider [6]. Curiosity is no reason to do marrow analysis, but if data will be analyzed in the context of attempts to improve outcomes in high-risk, metastatic situations, it may possibly be worth obtaining. The same is true of other means to assess Ewing sarcoma disease burden and response to therapy (e.g., circulating tumor cells by RT-PCR and/or flow cytometry [7,8]).

Thus Newman, Jones, and Hawkins and now Kopp et al. have provided a much better idea of not only how much to do, but also how much is enough [1,2]. My recommendations are to first do modern imaging staging studies; this should include CT and/or MRI of the primary tumor, chest CT to look for lung metastases, and $^{18}$FDG PET-CT to detect bone metastases. If no metastases are detected using imaging, marrow analysis can be considered unnecessary. However, if imaging detects metastases, additional attention to imaging and discussion can sometimes provide a plan concerning following efficacy of therapy and also, more importantly, future local control options such as whole lung, standard, or stereotactic radiotherapy to lung and/or bone metastases [9,10]. In those with metastatic disease, utility of marrow analysis is uncertain to add value to current chemotherapy or local control treatment planning but may help understand future treatment efficacy.

[1]Department of Pediatrics, Director Pediatric Hematology/Oncology and Bone Marrow Transplant, Levine Children's Hospital and Levine Cancer Institute, Carolinas HealthCare System, 1001 Blythe Blvd, Medical Center Plaza Suite 601, Charlotte 28203, North Carolina

Conflict of interest: The author has no conflicts of interest relevant to this PBC Highlight to disclose.

*Correspondence to: Peter M. Anderson, Levine Children's Hospital and Levine Cancer Institute, Department of Pediatrics, Director Pediatric Hematology/Oncology and Bone Marrow Transplant, Carolinas HealthCare System, 1001 Blythe Blvd, Medical Center Plaza Suite 601, Charlotte, NC 28203.
E-mail: peter.anderson@carolinas.org

Received 8 August 2014; Accepted 8 August 2014


DOI 10.1002/pbc.25246
Published online 12 October 2014 in Wiley Online Library (wileyonlinelibrary.com).

## REFERENCES


1. Newman EN, Jones RL, Hawkins DS. An evaluation of [F-18]-fluorodeoxy-D-glucose positron emission tomography, bone scan, and bone marrow aspiration/biopsy as staging investigations in Ewing sarcoma. Pediatr Blood Cancer 2013;60:1113–1117.
2. Kopp L, Hu C, Rozo B, et al. Utility of bone marrow aspiration and biopsy in initial staging of Ewing sarcoma. Pediatr Blood Cancer 2014; doi: 10.1002/pbc.25212. [Epub ahead of print].
3. Treglia G, Salsano M, Stefanelli A, et al. Diagnostic accuracy of (1)(8)F-FDG-PET and PET/CT in patients with Ewing sarcoma family tumours: A systematic review and a meta-analysis. Skeletal Radiol 2012;41:249–256.
4. Haeusler J, Ranft A, Boelling T, et al. The value of local treatment in patients with primary, disseminated, multifocal Ewing sarcoma (PDMES). Cancer 2010;116:443–450.
5. Luksch R, Tienghi A, Hall KS, et al. Primary metastatic Ewing's family tumors: Results of the Italian sarcoma group and Scandinavian sarcoma group ISG/SSG IV study including myeloablative chemotherapy and total-lung irradiation. Ann Oncol 2012;23:2970–2976.
6. Rasper M, Jabar S, Ranft A, et al. The value of high-dose chemotherapy in patients with first relapsed Ewing sarcoma. Pediatr Blood Cancer 2014;61:1382–1386.
7. Schleiermacher G, Peter M, Oberlin O, et al. Increased risk of systemic relapses associated with bone marrow micrometastasis and circulating tumor cells in localized Ewing tumor. J Clin Oncol 2003;21:85–91.
8. Wagner LM, Smolarek TA, Sumegi J, Marmer D. Assessment of minimal residual disease in Ewing sarcoma. Sarcoma 2012;2012:780129.
9. Rusthoven KE, Kavanagh BD, Burri SH, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. J Clin Oncol 2009;27:1579–1584.
10. Wang XS, Rhines LD, Shiu AS, et al. Stereotactic body radiation therapy for management of spinal metastases in patients without spinal cord compression: A phase1-2 trial. Lancet Oncol 2012;13:395–402.