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Original Paper

The Role of Bone Scintigraphy in the Follow-up of Osteogenic Sarcoma

D. Körholz,[1] I. Wirtz,[1] H. Vosberg,[2] W. Rüther,[3] H. Jürgens[1] and U. Göbel[1]

Departments of [1]Paediatric Haematology and Oncology, [2]Nuclear Medicine and [3]Orthopaedics, Heinrich-Heine University Medical Center, Düsseldorf, Germany

The role of bone scintigraphy in the follow-up of osteosarcoma patients is still controversial. It is not yet clear whether bone scintigraphy results in early detection of relapse nor whether this can improve the survival rate of relapsed patients. In this study, results of scintigraphies obtained from 78 patients treated for osteosarcoma between 1978 and 1992 were analysed. 28/78 patients presented with 61 relapse sites, including 34 lung metastases, 20 distant relapses and 7 local recurrences. More than 90% of relapses were detected within 4 years after primary diagnosis of the tumour. A total of 489 bone scintigraphies were performed routinely during follow-up of these patients. 66/489 scintigraphies showed increased uptake of tracer. In 7/66 positive scintigraphies, a relapse was detected: lung metastases (3), local recurrence (1) and distant bone or soft tissue relapses (3). These relapses occurred between 1 and 4 years after primary diagnosis. In these cases, scintigraphies showed areas with increased uptake, although these patients had neither clinical symptoms nor positive X-rays or CT scans. At an observation period of 2.5 or 3.5 years, a second or third remission was induced in 2/6 patients in whom scintigraphy allowed an early diagnosis of the relapse. In conclusion, these data show that only a small number of routinely performed bone scintigraphies indicate a relapse. However, since bone scintigraphy is able to detect relapses early, the outcome of future relapsed patients might be improved. Therefore, bone scintigraphies should be included in a follow-up programme for patients with osteosarcoma. Since most relapses detected by scintigraphy occurred during the first 4 years after initial diagnosis, bone scintigraphy should be limited to this time frame.

Key words: bone scintigraphy, osteosarcoma, relapse, survival, metastases, follow-up, prognosis
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INTRODUCTION

OSTEOGENIC SARCOMA is the most frequent malignant bone tumour in adolescence. Since in 80–90% of patients occult micrometastases exist at the time of diagnosis, prognosis was poor until introduction of polychemotherapy. Treatment regimens including pre-operative and postoperative chemotherapy have led to a relapse-free survival of 60–70% [1–3]. Early detection of relapse might further improve life expectancy of these patients.

Rieden and associates [4] found that bone scintigraphy was the most sensitive searching method for analysis of metastatic bone tumours in patients with diverse tumours. In 93%, bone infiltrations were detected by scintigraphy. In patients with osteogenic sarcoma, scintigraphy shows a typical pattern of tracer uptake which allows the determination of response to chemotherapy [5–9]. Bielack and colleagues [8] as well as Edeline and associates [9] were able to show that tumour regression demonstrated by scintigraphy correlated strongly with histological tumour response in over 90% of examined osteosarcomas. In addition to bone infiltrates, scintigraphy can also detect certain soft tissue metastases of osteosarcomas. Ozarda and colleagues [10] demonstrated a brain metastasis in an osteosarcoma patient by conventional bone scintigraphy. Thus, the routinely performed total body bone scintigraphy is a very sensitive method for detecting osteosarcomas and metastatic disease. Therefore, it might allow early recognition of local as well as distant bone relapse. However, only a few studies are available which document the value of scintigraphy for detection of relapses.

Reviewing 55 patients with osteogenic sarcoma, McKillop and coworkers [11] found that bone relapses were detected by

Correspondence to U. Göbel.
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bone scintigraphy in approximately 50%, although the tumours were clinically asymptomatic. Therefore, the authors concluded that routinely performed bone scintigraphy is necessary during follow-up in all patients after completion of chemotherapy. In contrast, Rees and associates [12] found lung metastases in 18/27 patients. However, bone metastases occurred only in patients who presented with lung metastases. Since detection of bone metastases did not alter the therapeutic strategies in this study, the authors recommended restricting regular bone scintigraphy only to patients with clinical symptoms or detection of lung metastases by other procedures. The burden of radiation from scintigraphy is comparable to an X-ray of the abdomen. However, in children and adolescents, the radiation burden might be 2–4 times higher than in adults. Thus, it is necessary to clarify the controversy over the value of bone scintigraphy in the follow-up of osteosarcoma patients. Therefore, it is important to know whether early detection of relapse by bone scintigraphy can improve survival in these patients.

Since, in some cases of small or hidden metastases, scintigraphy might be more sensitive for detecting relapse than X-ray or CT-scans, here, the data of 78 patients with osteosarcoma were retrospectively reviewed to evaluate the role of routinely performed bone scintigraphy in the follow-up of these patients.

PATIENTS AND METHODS

The clinical records of 78 patients with osteogenic sarcoma were reviewed in this study. Patients had been treated at the Department of Paediatric Haematology and Oncology of the Heinrich-Heine University Medical Centre between 1978 and 1992. The study group included 36 female and 42 male patients between 2 and 21 years of age (median 14 years). Patients were treated according to the current T-7 and COSS 77, 82, 85 and 89 protocols [13–17], including polychemotherapy and tumour resection. Until December 1994, the mean follow-up time of these patients was 6.3 years (range 0.7–15.11 years). 3 patients died of complications. 21/28 patients with relapse eventually died from metastatic disease.

During follow-up, patients received bone scintigraphy using 99m-technetium methylene diphosphonate every 3–6 months during the first and second year off therapy. During the third to fifth year off therapy, bone scintigraphy was performed once a year (Table 1). In addition to bone scintigraphy, CT scans of the lung and chest X-rays were arranged as indicated in Table 1.

The results of bone scintigraphy were classified into three different categories: positive, tracer enhancement due to relapse; positive unconfirmed as relapse, positive due to trauma or malactivity; negative, no tracer uptake and no signs of bone relapse.

Table 2. Relapses in patients with osteosarcoma

Localisation of relapses	Number of patients	Number of relapses
Lung metastasis	9	18
Lung metastasis + distant relapse	8	28
Lung metastasis + local relapse	2	4
Distant relapse only	4	6
Local relapse only	5	5

RESULTS

In 28/78 patients, a total of 61 relapse sites were diagnosed. 9/28 patients presented with 18 lung metastases. In 4 patients, 6 distant extrapulmonary relapses were diagnosed. In an additional 5 patients, only local recurrences were observed. In 10 patients, relapses occurred in the lungs (16 metastases) and other sites (local recurrence 2, distant relapse 14; Table 2). First relapses were found in 11/28 patients. In 4/11 patients with a first relapse (lung metastases 3 patients, local relapse 1 patient) a second continuous remission was obtained (mean observation time: 9.1 years). In 1/7 patients with a second relapse, a third remission was induced by chemotherapy (observation period: 4 years). In 10 patients, third or further relapses were observed. In 2/10 patients who presented with third or further relapse with lung metastases, a remission (observation time: 3.7 or 4.1 years) was induced by surgical removal of recurrent disease (Table 3).

Most relapses occurred during the first 4 years after primary diagnosis of osteosarcoma (54/61; Figure 1). Distant relapses peaked during the second year (10 relapses). However, only two relapses were first recurrences of the tumour. Lung metastases occurred mostly during the first 2 years. After 3 years lung metastases almost halved compared to the previous year, and were reduced after 4 years compared with years 1 and 2 (Figure 1). The incidence of local relapses was almost equal during the first 4 years. Differences in the incidence of relapses are explained by the different distribution of primary, second, third or fourth relapses.

Table 3. Number of relapses in patients with osteosarcoma

Number of relapses	Number of patients	Number of alive patients
1	11	4
2	7	1
3	4	1
4	6	1

Table 1. Follow-up investigations in patients with osteosarcoma

	Time off therapy			
	1st year	2nd year	3rd–5th year	6th–10th year
Bone scintigraphy	3 monthly	6 monthly	annually	no further investigation
Chest X-ray	monthly	2 monthly	4–6 monthly	annually
Local X-ray	3 monthly	6 monthly	annually	no further investigation

CT-scan of the lung once after completion of therapy.

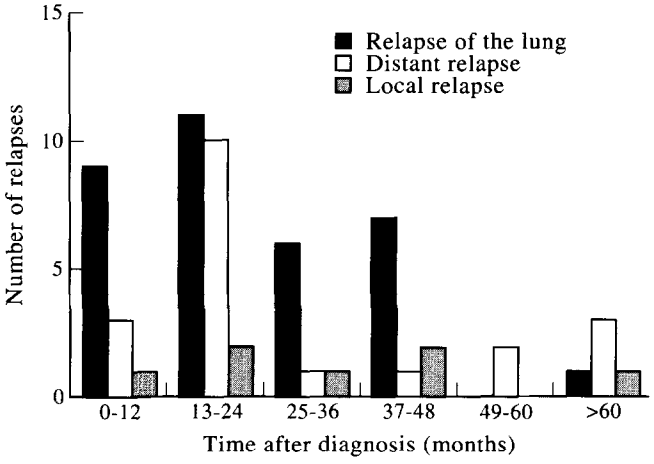

Figure 1. Correlation between time of diagnosis and occurrence of relapses. In 28 patients with osteosarcoma, 61 relapses were diagnosed during follow-up. Occurrence of relapse was correlated to the time after initial diagnosis.

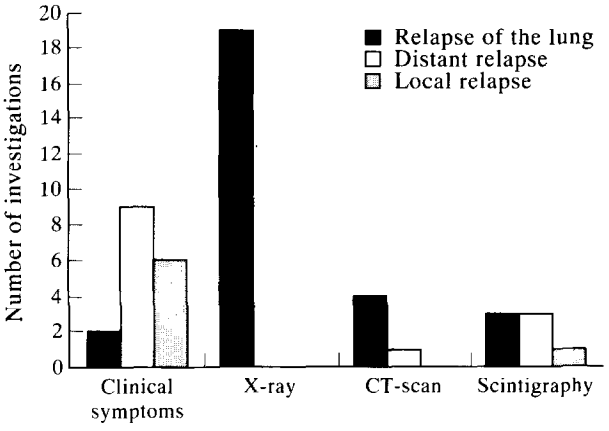

Figure 3. Early detection of relapse by bone scintigraphy. In 28 patients with osteosarcoma, 61 relapses were diagnosed. The relapses were first diagnosed by clinical symptoms, chest X-ray or CT-scan as well as bone scintigraphy as indicated on the *x*-axis.

During follow-up of 78 patients with osteosarcoma, 489 bone scintigraphies were routinely performed (Figure 2). 423 scintigraphies were negative. In 7/423 patients with negative bone scans, a lung metastasis was diagnosed by X-ray. 7/66 scintigraphies showed tracer enhancement and a relapse was subsequently diagnosed by biopsy. 59/66 scans showed tracer enhancement due to reasons other than metastatic disease, such as trauma or malactivity. Infections which might be another explanation for increased tracer uptake in bones were not observed in these patients. Thus, although only 1.4% of all scintigraphies indicated a relapse, more than 10% of all relapses were diagnosed by bone scintigraphy.

Comparing the value of bone scintigraphy, chest X-ray or chest CT-scan and clinical symptoms for early detection of relapse, the results show (Figure 3) that lung metastases were predominantly diagnosed by routine chest X-ray or routine CT-scan (23/28) compared to scintigraphy (3/28) or clinical symptoms (2/28). Local relapses were diagnosed by clinical symptoms (6/7) or scintigraphy (1/7). Distant relapse was first diagnosed by bone scintigraphy (3/13), clinical symptoms (9/13) or CT studies (1/13). Seven distant relapses and six lung metastases were detected by scintigraphy (six distant relapses), CT-scan (one distant relapse, one lung metastasis) or chest X-ray (five lung metastases) during restaging of relapsed patients. Thus, 7/61 relapse sites were first detected by regular bone scintigraphy.

In 2/6 patients with positive regular scintigraphy, early detection of a lymph node metastasis in the mediastinum or recurrence of a lung metastasis allowed induction of a continuous remission by surgery or salvage chemotherapy. The observation time in these patients was 2.7 or 3.5 years. In addition the life of a third patient was extended for 2.7 years by intensified relapse treatment after early relapse diagnosis by scintigraphy.

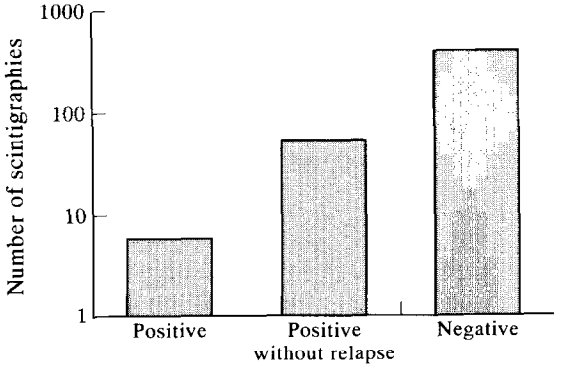

Figure 2. Results of routine bone scintigraphy in patients with osteosarcoma. In 78 patients, 489 scintigraphies were performed during follow-up. Results were graded as tracer enhancement due to relapse, tracer uptake for reasons other than metastatic disease, negative scintigraphy without detection of bone relapse.

DISCUSSION

The event-free survival rates of patients treated for osteosarcoma according to protocols of the German Society of Paediatric Haematology and Oncology (COSS 77 to COSS 91) improved from 46% (COSS 77) to about 75% (COSS 86) after introduction of ifosphamide. Early detection of relapses might further improve life expectancy.

Prior to the introduction of polychemotherapy into treatment strategies of osteosarcoma, distant relapses only occurred in patients with lung metastases. Therefore, McNeil and associates [18] suggested the use of follow-up investigations which allowed detection of lung metastases, such as X-ray or CT scans of the chest. For the same reason, Rees and colleagues [12] did not perform scintigraphies during follow-up. Our own analysis showed that a few isolated local relapses as well as distant relapses occurred in patients without lung metastases. These results were comparable to those of McKillop and associates [11] and Goldstein and associates [19].

Scintigraphy is a very sensitive method for detecting metastatic bone disease or soft tissue metastasis of an osteosarcoma. It allows detection of even small infiltrates. In comparison to chest X-ray, local X-ray or CT-scan of the chest, scintigraphy has the major advantage of being a screening method which detects relapses within the total body. Thus, it is not surprising that in 6/28 patients, routinely performed bone scintigraphies detected the first sign of relapse. The

same spectrum could only be expected from other broad investigations, such as total body MRI, which is performed in metastatic Ewing's sarcoma. However, this method is much more expensive than bone scintigraphy.

Goldstein and associates [19] as well as McKillop and colleagues [11] recommended the routine use of bone scintigraphy during follow-up of osteosarcoma patients, although it was not clear if relapsed patients would benefit from early relapse detection by scintigraphy. In our study, 7/61 relapse sites were detected primarily by scintigraphy. In 2/6 relapsed patients, a continuous remission was induced after early detection of the relapse by scintigraphy. The life of another patient was extended for 2.7 years by intensified relapse therapy.

In conclusion, our results demonstrate that a small number of routine bone scintigraphies will indicate relapses during follow-up of osteosarcoma. In addition, there is a high incidence of positive scintigraphies due to trauma or malactivity. Thus, many patients receive the burden of radiation without benefit. However, our results also demonstrate that bone scintigraphy is able to detect relapses early with evidence for a better chance of successful salvage therapy. Thus, since most relapses occurred within the first 4 years after primary diagnosis, bone scintigraphies should routinely be performed within this time frame.

1. Edmonson JH, Green SJ, Ivins JC. Methotrexate as adjuvant treatment for primary osteosarcoma (letter). *N Engl J Med* 1980, **303**, 642–648.
2. Rosen G, Marcove RC, Caparros B, Nirenberg A, Kosloff C, Huvos A. Primary osteogenic sarcoma—the rational for preoperative chemotherapy and delayed surgery. *Cancer* 1979, **43**, 2163–2167.
3. Winkler K, Beron G, Delling G, *et al.* Neoadjuvant chemotherapy of osteosarcoma: results of a randomized cooperative trial (COSS 82) with salvage chemotherapy based on histological tumor response. *J Clin Oncol* 1988, **6**, 329–337.
4. Rieden K, Adolph J, Mende U, Georgi P. Radiologische Diagnostik von Knochenmetastasen. *Röntgen B1* 1989, **42**, 95–103.
5. McLean RG, Murray IPC. Scintigraphic patterns in certain primary malignant bone tumors. *Clin Radiol* 1984, **35**, 379–383.
6. Knop J, Stritzke P, Montz R, Delling G, Winkler K. Knochenszintigraphie zur Erfolgsbeurteilung einer Chemotherapie beim Osteosarkom. *Nucl Med* 1985, **24**, 75–81.
7. Knop J, Delling G, Heise U, Winkler K. Scintigraphic evaluation of tumor regression during preoperative chemotherapy of osteosarcoma. *Skeletal Radiol* 1990, **19**, 165–172.
8. Bielack S, Knop J, Delling G, Winkler K. Szintigraphische Verlaufskontrolle von Osteosarkomen während neoadjuvanter Chemotherapie. *Nucl Med* 1988, **27**, 237–241.
9. Edeline V, Froulin F, Bazin JP, *et al.* Factor analysis as a means of determining response to chemotherapy in patients with osteogenic sarcoma. *Eur J Nucl Med* 1993, **20**, 1175–1185.
10. Ozarda AT, Legaspi JR, Haynie TP. Detection of a brain metastasis from osteosarcoma with 99 m Tc-methylene diphosphonate bone scanning. *Eur J Nucl Med* 1993, **8**, 552–554.
11. McKillop JH, Etcubanas E, Goris ML. The indications for and limitations of bone scintigraphy in osteogenic sarcoma. A review of 55 patients. *Cancer* 1981, **48**, 1133–1138.
12. Rees CR, Siddiqui AR, duCret R. The role of bone scintigraphy in osteogenic sarcoma. *Skeletal Radiol* 1986, **15**, 365–367.
13. Bielack S, Beck J, Delling G, *et al.* Neoadjuvant Chemotherapie des Osteosarkoms. Ergebnisse der kooperative Studien COSS 80 und COSS 82 nach 7 bzw. 5 Jahren. *Klin Pädiatr* 1989, **201**, 275–284.
14. Winkler K, Jürgens H. Experience of the German–Austrian cooperative osteosarcoma study group. *Monogr Paediatr* 1986, **18**, 264–278.
15. Winkler K, Bielack S, Delling G, *et al.* Effect of intraarterial vs. intravenous cisplatin in addition to systemic doxorubicin, high-dose methotrexate and ifosphamide on histologic tumor response in osteosarcoma (study COSS 86). *Cancer* 1990, **66**, 1703–1710.
16. Bieling P, Bielack S, Delling G, *et al.* Neoadjuvante Chemotherapie des Ostcosarkoms. Vorläufige Ergebnisse der kooperativen Osteosarkomstudie COSS 86. *Klin Pädiatr* 1991, **203**, 220–230.
17. Rosen G, Nierenberg A, Capparros B, *et al.* Osteogenic sarcoma. Eighty percent three year, disease-free survival with combination therapy (T-7). *Natl Cancer Inst Monogr* 1981, **56**, 213–220.
18. McNeil BJ, Cassydy JR, Geiser CF, *et al.* Fluorine-18 bone scintigraphy in children with osteosarcoma and Ewing's sarcoma. *Radiology* 1977, **109**, 627–631.
19. Goldstein H, McNell BJ, Zufall E, Jaffe N, Treves S. Changing indications for bone scintigraphy in patients with osteosarcoma. *Radiology* 1980, **135**, 177–180.