Acta Oncologica 27 (1988) Fasc. 6a

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THE VALUE OF PRE-SCHEDULED BONE SCINTIGRAPHIES IN BREAST CANCER

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Abstract

During the first 10 years of Danish Breast Cancer Cooperative Group (DBCG), the subcommittee on bone scintigraphy has focused on the value of bone scintigraphy at the time of operation in all patients and then yearly in those considered to be primarily operable (stage I and II). Out of 1175 patients examined at time of operation, bone metastases could be verified by x-ray or histology in only 16, of whom the majority had bone pain and/or spread to other organs. Similarly, around 2.5% per year for the first 3 postoperative years and about 1% per year during the next 4 postoperative years had bone metastases verified by x-ray or histology within 12 months after the latest scheduled bone scintigraphy. It is concluded that bone scintigraphy is of no value in primarily operable patients with breast cancer, and that the examination should be reserved for patients with symptoms and/or signs of bone metastases and for patients with relapse.

Key words: Breast cancer, bone scintigraphy.

Autopsy reports have shown that 50–80% of females dying of breast cancer have bone metastases. Since the diagnosis of bone metastases indicates treatment with chemotherapeutics, which often have several side-effects, the diagnosis should be undebatable. In the early 1970s some reports (3, 4) indicated that bone scintigraphy was an ideal examination for screening patients operated for breast cancer, since it was considered to be very sensitive and since it could be positive up to several months before conventional bone roentgenography. According to Galasko (4), about 25% of breast cancer patients have bone metastases at the time of operation as determined by scintigraphy. These promising aspects led us to incorporate bone scintigraphy into the protocols of DBCG: 1) at time of operation for staging, and 2) yearly control of the primarily operable patients. Herein we report our experience with bone scintigraphy on these indications. Furthermore, we compared the readings at the local laboratories with those of the subcommittee as well as the results of multicenter studies with studies from a single center.

Bone scintigraphy at the time of operation. In 1978, 682 out of a total of 1888 Danish breast cancer patients had a bone scintigraphy performed (8). Fifty (7%) of these 682 were considered to be equivocal of bone metastases and 46 (7%) to be indicative, but in only 5 of the patients (0.7%), metastases were verified by conventional radiograms (these 5 patients also had metastases in other organs). This comparison, however, yields too high figures for false-positive scintigrams considering that bone x-rays may reveal osseous involvement later than bone scans (4) and only when as much as 50% of the mineral content has been displaced by malignant tissue. Recently, the study was repeated at one center over a 2-year period (12). Thirtyfour (7%) out of 493 scintigrams were equivocal or indicative of bone metastases, but for only 10 (2%) of them, bone metastases were verified by the corresponding conventional x-ray. Of the 10 patients, 8 had pain related to the bones and/or metastases in other organs, whereas 2 had no symptoms of bone metastases. However, the general health of these 2 patients was poor; the finding of bone metastases had no therapeutic consequence.

On the basis of these results from almost 1200 unselected patients we have concluded that due to the low cost/

Presented at the DBCG meeting, Copenhagen, January 22–23, 1988.

benefit, bone scintigraphy is not indicated in patients without clinically suspected bone metastases or spread to other organs at time of operation.

Yearly control of primarily operable breast cancer. Repeated pre-scheduled scintigraphy 6 and 12 months after operation was performed in 760 patients, who were representative of all primarily operable patients operated in 1978 and 1979. Only 37 of the 760 patients (4.9%) developed bone metastases verified by radiography and histology during the first 2 years after surgery (10). A single positive scintigraphy, especially performed 6 or 12 months after surgery, as well as 2 or 3 scintigraphies repeatedly staying or becoming positive was indicative of a significantly increased risk of developing bone metastases within 12 months after the latest scintigraphy. In 13 of 37 patients with otherwise proven bone metastases, the latest scintigram(s) were, however, negative. A delay between the 2 examinations could not explain this.

Out of the 760 patients, 231 continued to have a bone scintigraphy yearly to the 6th postoperative year until recurrences were diagnosed, irrespective of localization, another cancer was detected, or the patient refused further follow-up (13). During the observation period (12 months after the latest scheduled scintigraphy), 13 patients (5.6%) had bone metastases verified by x-ray or histology. The scheduled scintigraphy was positive in only 7 of these patients, whereas 9 other patients had a scintigram equivocal or indicative of bone metastases without subsequent (within 12 months of scintigraphy) verification by x-ray or histology.

Due to the low incidence and the low cost/benefit shown in these studies we conclude, that a fixed schedule or repeated scintigraphies or x-rays is not justified in primarily operable breast cancer patients otherwise free of apparent disease, at least not within the first 6 years of operation and probably not beyond the 6th year either.

Coordination of reading. The initial scans of the 1978 and 1979 cohorts were read both locally and by a re-reading group (the subcommittee). A surprisingly large variation of positive initial bone scans among 8 centers has been shown by others (1), whereas we could find no such large variation among the 1978 cohort between 12 centers (8). The number of positive scintigraphies were, however, high compared with the number of patients having bone metastases verified by x-ray or histology. Therefore, early in 1979 we initiated a coordination of the local interpretation (10). This resulted in a drastic decline in the frequency of positive bone scintigraphies read both locally *and* by the re-reading group, but an unchanged agreement measured by the kappa value. Furthermore, the frequency of bone metastases proven radiologically and histologically within 24 months after operation was almost the same for the 1978 (5.6%) and 1979 (4.1%) cohorts (10). Thus, the effect of issuing standardized guidelines for interpretation was not satisfactory. We conclude that instead of just a simple set of standardized guidelines, the technique and the evaluation must be better coordinated and optimized.

Single versus multicenter studies. Twice we have performed both a single center and a multicenter study. The first single center study was part of the multicenter study and included 165 of 760 patients (10, 11). Both groups were found to be representative of all patients entering the nationwide, randomized adjuvant therapy protocols of DBCG in 1978 and 1979. Almost identical results were found in the 2 studies. The second single center study was a repetition of the first study performed by the subcommittee (8, 12). The interval between the 2 studies was almost 6 years. Again similar results were obtained.

A multicenter study is more difficult, larger, and more time-consuming than that of the single center study. The result of the single center study (11) was available one year before that of the multicenter study (10). However, multicenter studies have been valuable in many relations. While a multicenter study is in progress, minor local center studies can be performed if the benefit is debatable, and through analyses it can be assessed whether the minor group is representative of all patients.

The gold standard. It is generally considered that bone scintigraphy is a sensitive, but rather unspecific examination (2, 6). False-negative and false-positive examinations occur (5). With increasing age, the frequency of benign changes of bone scintigraphy increased making the discrimination between benign and malignant lesions difficult. On the other hand, the use of conventional x-ray as the gold standard of bone metastases is not optimal because of its low sensitivity (2). CT-scanning may be a better choice, since it has been shown that conventional x-ray fails to see many metastases which on CT bone scans were clearly discernible (7). Until a radiopharmaceutical with special affinity to bone metastases is available, we have to accept that only the normal bone scintigram has a direct influence on the clinical decision.

Discussion

Our studies have clearly shown a very limited value of bone scintigraphy in staging at time of operation and in follow-up of primarily operable patients (stage I and II), simply because bone metastases occur infrequently in those patients. This leads to the question: Are there groups of breast cancer patients in whom bone scintigraphy can be used with a higher cost/benefit? The answer is confirmative. It has been shown that at the time of the *first* recurrence of breast cancer in 380 consecutive patients, 120 (32%) had bone metastases (6). Bone scintigraphy turned out to be an effective method to exclude metastatic bone disease (sensitivity 96%), whereas a positive scintigram requires radiologic confirmation (specificity 66%). In another study we found that 27% of patients at first relapse had bone metastases (13). Therefore, for the time being it is recommended that patients having

bone pain and/or any kind of relapse should have a bone scintigraphy made (9). In the next years, the subcommittee will evaluate this recommendation.

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