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Frequency of Skeletal Metastases as Revealed by Routinely Taken Bone Marrow Biopsies

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Summary. In a total of 581 patients with the presumptive clinical diagnosis of bone marrow metastases, core biopsies of the iliac crest were performed to evaluate the frequency of infiltrates in routinely taken samples. The frequency of metastases depends greatly on the varying clinical indications to perform an examination. Staging procedures will result in a decline in positive findings whereas overt signs and symptoms of tumor spread naturally increase the rates. Thus, the annual rates have decreased from 45 to 28% during the last 5 years. The mean frequency of metastases in 501 patients with known primaries was 24%; related to particular tumors the rates were 49% in prostate, 41% in breast, 19% in thyroid and 7% in bronchogenic cancer. The patterns of bone marrow involvement displayed an overwhelming focal infiltration of the marrow space in carcinomas of the thyroid gland and bronchus, and a more diffuse extension in tumors of the prostate and breast.

It was demonstrated that neither the width or the total area of the marrow biopsies nor the site of the core is decisive in determining the yield of positive results, but the length of the cylinder may be. No differences could therefore be observed between Jamshidi's dorsal and Burkhardt's anterior crest biopsy method. The results of histopathology were compared with the findings of total body bone scanning in 209 patients. In 49% of all cases scintigrams showed lesions suggestive of metastatic spread and therefore higher frequency of occurrence than the trephine biopsy. Conversely in 23% of the patients with marrow involvement the scintigrams were negative. It is concluded that the core biopsy of the bone marrow is a most valuable aid for an early detection of bone metastases together with radiological methods and is a basal requirement for clinical staging procedures and choice of therapeutic regimens.

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Introduction

Dissemination of cancer cells is generally thought to be widespread prior to any recognizable appearance of gross metastases in lymph nodes or parenchymal organs. One should probably anticipate a very early growth of small clusters of tumor cells in or around the capillaries or sinuses within tissues which are not detectable by conventional clinical screening methods. In addition to x-rays and scintigrams of the skeleton, biopsies of the bone marrow have gained a favoured position among diagnostic tools, since they sample extensive areas of a vascular compartment which is easily available for examination (Dick et al. 1974; Brunning et al. 1975). The recognition of tumor spread is essential for clinical staging and the choice of therapeutic regimen. Consequently one of the basic requirements is to estimate the value and particularly the yield of bone marrow biopsy in the course of diagnostic procedures in patients with malignancies. Further, investigations of routinely taken specimens are necessary to evaluate whether the size of the removed sample or the site of the biopsy has any influence on the results. Finally we wished to study the clinical usefulness of the two most widely applied search methods for metastases – the bone scintigram and the trephine biopsy – and to compare the findings with both techniques.

Patients and Methods

In a total of *581 patients* with the presumptive clinical diagnosis of bone metastases with or without a known primary tumor core biopsies of the iliac crest had been performed by the clinicians during routine diagnostic procedures. The bone marrow specimens were collected from our files in the period ranging from January 1976 to July 1980 and have been processed by plastic embedding and semithin sectioning (Vykoupil et al. 1976). 267 cores were taken by the method of Jamshidi and Swaim (1971), 224 obtained as myelotomies (Burkhardt 1966) and 90 by different methods. It should be noted that in patients with carcinomas of the bronchus and thyroid gland most trephines were made by the Jamshidi technique (102/145 or 70% and 22/27 or 81% respectively), whereas in cases with malignancies of the breast and prostate gland the biopsy method of Burkhardt was more frequently used (113/191 or 59% and 20/35 or 57%). These differences in the distribution of the biopsy technique used are due to the referral of patients from outside, mainly university affiliated hospitals (see acknowledgements). A further statistical problem has to be mentioned: There is an almost continuous decrease of positive findings of bone metastases in later years (see results, Table 1).

Measurements of the cross-sectional areas of total bone cylinders and the fraction of their marrow spaces available for diagnostic evaluation were obtained by television microscopy (Micro-Videomat, Zeiss, Germany). By this method electronic frames were adjusted to coincide with the boundaries of the image of the specimen. The estimated values represent the percentage of the biopsy area with the monitor area corresponding to 100%. The length of the specimens were estimated by a slide gauge lying on the coverslip adjusted to the ends of the biopsy cylinder. The statistical calculation of means were made by Student's t-test and of frequencies by the chi-sqare test. Differences were considered to be significant if p was less than 0.05.

In 209 patients total body bone scanning had been performed as a screening procedure for localizing metastatic involvement, using 99 m Tc-pyrophosphate intravenously. This investigation was done approximately at the time of the trephine biopsy of the bone marrow.

Table 1. Frequency of metastases in relation to the year of examination: there is a decrease of incidence during the five years which correlates with increasing frequency of crest biopsies

Year of examination	Frequency of metastases	
	Ratio	Percentage
1976	19/ 42	45
1977	43/101	43
1978	44/123	36
1979	51/158	32
1980	44/157	28
Total	201/581	35

Table 2. Frequency of metastases in relation to the site of primary cancer as revealed by 501 trephine biopsies of bone marrow

Primary cancer	Frequency of metastases	
	Ratio	Percentage
Prostate	17/ 35	49
Breast	78/191	41
Thyroid	5/ 27	19
Bronchus	10/145	7
Others	9/103	9
Total	119/501	24

Results

Histological evaluation of the 581 core biopsies of the bone marrow revealed a 35 percent frequency of metastases, including those cases in which no primaries were known (Table 1). There is a gradual decrease of frequency during the five years period of observation which seems to be correlated with the increasing frequency of crest biopsies. After exclusion of 80 cases with unknown primaries the total incidence of metastases declines to 24% (Table 2).

However, there were remarkable differences with regard to the frequency of neoplastic involvement of the marrow by various primary tumors (Table 2). In our material metastases of carcinomas of the prostate gland (49%) occurred most frequently whereas those of the bronchus were only rarely encountered (7%). A quantitative histological evaluation of the spread of malignancy in the bone marrow showed a diffuse involvement in about 61% and in only 15% minimal or more focal growth. Extension of neoplastic proliferation further depended on the type of tumor: carcinomas of the prostate displayed an overwhelmingly diffuse infiltration (79%) in contrast to tumors of the thyroid gland with only 40% (Table 3). Methods of trephine biopsy were compared with each other with regard to the yield of positive results in the two most frequently observed carcinomas of breast and bronchus. In patients with mammary carcinomas both commonly applied techniques of Jamshidi and Burkhardt yielded in 43% (24/56) or 39% (44/113) positive results and in bronchial carcinomas the corresponding values were 7% (7/104) or 8% (2/24) respectively. Thus there were no significant differences in the occurrence of metastases according to

Table 3. Patterns (percentage) of bone marrow involvement by metastases in trephine biopsies

Primary cancer	Pattern of marrow involvement (percentage)		
	Focal	Extended	Diffuse
Prostate	10	10	79
Breast	9	24	67
Thyroid	40	20	40
Bronchus	30	20	50
Others	56	11	33
Unknown	14	30	56
Total	15	24	61

Table 4. Frequency (percentage) of metastases in bone marrow in relation to the length of biopsy cylinders

Primary cancer	Length of bone marrow core (mm)					
	<10		10–15		>15	
	Ratio	Percentage	Ratio	Percentage	Ratio	Percentage
Prostate	3/ 5	60	7/14	50	7/16	44
Breast	11/28	39	33/84	39	34/79	43
Thyroid	0/ 5	0	1/ 5	20	4/17	24
Bronchus	1/37	3	6/66	9	3/42	7
Others	1/21	5	4/40	10	4/42	10
Total	16/96	17	51/209	24	52/196	27

these two procedures. The mean length of the bone cylinders obtained by Jamshidi's method was 14.2 ± 5.6 mm and of those in Burkhardt's method 14.9 ± 3.7 mm. This correlates well with the length of the bone cylinder in patients with breast and bronchial carcinomas, where no significant differences were detectable. In addition core biopsies of the bone marrow displayed the same length irrespective of whether they contained metastases or not: the rate was $14.3 \pm 6.1/14.0 \pm 5.6$ mm (Jamshidi's needle) compared with $15.1 \pm 4.2/14.7 \pm 3.5$ mm (Burkhardt's myelotomy). Biopsies with a length of less then 10 mm contain fewer metastases than those with a length of more than 10 mm, but the difference is not significant. This statement is limited, since in our study short biopsy-cylinders were presented more frequently in bronchogenic carcinomas, which generally have a lower incidence of metastases in the biopsies (see Discussion). A comparison of cylinders with different lengths in cases with same tumors was not possible because of the small numbers of patients in each group (Table 4). However, these mean values, which were measured for the total length of the bone cylinders produced by both techniques of coring the iliac crest, do not really refer to the space of the bone marrow available

Table 5. Total body bone scanning: Frequency of positive fingings in comparison with the results of trephine biopsies in a total of 209 patients with various malignancies

Primary cancer	Total bone scintigram		Trephine biopsy	
	Ratio	Percentage	Ratio	Percentage
Prostate	7/ 7	100	4/ 7	57
Breast	52/75	69	31/75	41
Thyroid	2/10	20	2/10	20
Bronchus	16/60	27	5/60	8
Others	11/40	28	7/40	18
Unknown	15/17	88	17/17	100
Total	103/209	49	66/209	32

Table 6. Core biopsy versus scintigram: Comparison of results obtained in 209 patients showing differences in 67 patients or 32%

Biopsy / Scintigram	Number	Percentage
Both positive	51	24
Both negative	91	44
Biopsy: positive Scintigram: negative	15	7
Biopsy: negative Scintigram: positive	52	25
Total	209	100

for diagnostic evaluation. A calculation of the total area of the cylinder in 30 controls demonstrated that Jamshidi's cylinders exhibited a mean area of 32.2 ± 12.8 mm^2 in contrast to the significantly larger area of the Burkhardt specimens with 50.7 ± 12.4 mm^2 ($P < 0.01$). From these normal values of marrow extension the overall mean area of the cylinders was 28.3 ± 11.3 mm^2 after Jamshidi's method and 55.1 ± 14.6 mm^2 as the result of the Burkhardt technique in all patients measured. A comparison of both methods revealed no significant differences when calculating the results of bone metastases in carcinomas of breast and bronchus. The total extension of the biopsy cylinder, after subtraction of the cortical area, did not have any decisive influence on the results.

Total body bone scanning was performed in 209 patients and compared with the results of histopathology of the corresponding trephine biopsies. In 49% the scan showed lesions suggestive of metastatic spread and thus a 17% higher occurrence than the bone marrow biopsies (Table 5). Further evaluation showed that in about two thirds of the cases examined, there was a coincident positive or negative result in scan and biopsy. Nevertheless in about 25% of all cases the scintigram was positive but the trephines did not reveal any malignancy, whereas in 23% of the patients with positive biopsies the scintigrams showed no suspicious signs. In those 15 patients with negative findings in the total body bone scan, neoplastic infiltration was mostly diffuse. In only 4 cases was a focal involvement observed (Table 6).

Table 7. Trephine biopsy: Frequency of metastases in bone marrow as recorded in the pertinent literature. Own results differ in carcinomas of the bronchus but not in breast cancer

Reference	Primary tumor	Frequency of metastases	
		Ratio	Percentage
Own results 1980	Bronchus	10/145	7
Renner et al. 1975	Bronchus	10/116	9
Hansen and Muggia 1972	Bronchus	25/150	17
Burkhardt et al. 1980	Bronchus	$n=128$	22
Hirsch et al. 1979	Bronchus	20/ 89	22
Dick et al. 1974	Bronchus	9/21	43
Ridell and Landys 1979	Breast	51/532	10
Dick et al. 1974	Breast	11/ 33	33
Own results 1980	Breast	78/191	41
Burkhardt et al. 1980	Breast	$n=255$	41

Discussion

The frequency and significance of bone marrow involvement by metastatic tumors are closely related to prognosis and choice of therapeutic regime (Anner and Drewinko 1977). Marrow infiltration clearly indicates advanced spread which may not be as easily recognizable as when occurring as metastases to lymph nodes or parenchymal organs. Diagnosis of metastases in the bone marrow is occasionally possible by clinical, laboratory or hematological methods which, however, offer uncertain data and are only suggestive for tumor spread in most instances (Chernow and Wallner 1978). The commonly applied and favoured procedures to detect these lesions in the skeleton are radiological techniques, x-ray examination and total body bone scanning. These indirect methods used in the search for tumor involvement should always be accompanied by a direct approach, i.e., the histopathology of the bone marrow. Examinations of the marrow may be performed by puncture and aspiration with smear preparation, but it is well established that cytology is inferior to core biopsy and sections of the marrow with regard to the sensitivity for metastases (Landys and Stenram 1975; Singh et al. 1977).

In the present study these two routinely used techniques for tracing metastases are considered: the core biopsy of the bone marrow and the scintigram. No special emphasis was directed towards the histological classification of the primary tumor or growth of metastases (osteoplastic – osteolytic).

The frequency of metastases in routinely performed biopsies of the bone marrow in tumor patients is reported to occur over a wide range, as listed in Table 7. Significant differences exist when reviewing the results from various authors, which may not be easily explained by the small number of patients examined alone. For example the selection of the patients may depend on and be influenced by clinical indications and the feasibility of the biopsy method. The frequency of metastases seems to decline with increasing use of modern instruments (i.e., Jamshidi's technique) and introduction of clinical staging (Ta-

Table 8. Scintigram: Frequency of metastases as revealed by total body bone scan in relation to the site of the primary tumor according to the pertinent literature

Reference	Primary tumor	Frequency of metastases	
		Ratio	Percentage
Robbins et al. 1972	Breast	61/321	19
Joo et al. 1979	Breast	81/170	48
Corcoran et al. 1976	Breast	150/280	54
Own results 1980	Breast	52/ 75	69
Own results 1980	Bronchus	16/ 60	27
Corcoran et al. 1976	Bronchus	141/266	53
Corcoran et al. 1976	Prostate	60/134	45
Own results 1980	Prostate	7/ 7	100

ble 1). Series of patients from therapeutic trials with clinical staging procedures have a significant influence on the percentual rates of bone marrow metastases. Our material of bronchial carcinomas is composed mostly of patients with clinical staging, and therefore the incidence is far below other results. In comparison the specimens of patients with breast cancer are randomly submitted and do not include protocol studies and therefore correspond with other authors, particularly Burkhardt et al. (1980) (Table 7), while others show striking differences. Hansen and Muggia (1972) as well as Anner and Drewinko (1977) stressed a high frequency of bone marrow involvement in bronchial carcinomas particularly of the small cell type, but this could not be supported by our findings.

Our evaluation and comparison of the core biopsies obtained by Jamshidi's method and the technique of Burkhardt suggest that neither the site (anterior or posterior iliac crest) nor the width, or the total marrow area of the biopsy is decisive for the result. The length of the biopsy cylinder is probably the critical point regarding the production of representative material. Although core biopsies which have been performed as so called myelotomies (Burkhardt 1966) exhibit almost a doubling of the marrow space available for study it should be emphasized that metastases are *not* found more frequently in these specimens. This result has implications for practical reasons: In recent years the Jamshidi trephine biopsy (Jamshidi and Swaim 1971) has gained increasing use in the course of clinical investigations for hematological and various other disorders, as a technique for staging and other diagnostic procedures.

It should be remembered that the length of the bone cylinder must be adequate, since a focal infiltrate, which often occurs in bronchial or thyroid carcinomas, may not be detected (see also Table 3).

In scintigrams the frequency of positive results is reported to vary in larger series (see Table 8) which is similar to the results of histopathology (Table 7). The same uncertainty about frequency is encountered when evaluating the differences between suspicious findings in the total body bone scan (49% in our series) and the positive results of histopathology (32% in bone marrow biopsies). A comparable gap between positive findings by these two methods has been

recorded by Broghamer and Keeling (1977) and amounts to 67% or 31%, respectively. Nevertheless in 68% of our cases both techniques reveal the same results for positive and negative findings, which demonstrates, that both techniques have a practical value (Table 6).

Negative histological findings in patients with suspicious lesions in the scintigram may be as high as 50%, at least for carcinomas of the prostate (Graber et al. 1971), but the results also seem to be dependent on the radiological techniques applied: Joo et al. (1979) stressed the clinical usefulness of bone scanning in patients with breast carcinomas and considered it superior to x-ray examination. Finally it should be mentioned that this discrepancy of results may be related to false positive scintigrams and to false negative biopsies, particularly if the last are too short or are heavily distorted and squeezed.

Bilateral biopsy of the iliac crest may result in a decrease in negative results in metastazing tumors. Autopsy studies in patients with advanced cancer (mostly of the bronchus and breast) revealed only a 10% improvement (Brennecke et al. 1980), whereas Hirsch et al. (1979) reported a 30% gain in anaplastic bronchial carcinomas. In contrast false negative results of total bone scanning have been described by Renner et al. (1975) and Dick et al. (1974) for oat-cell carcinomas of the bronchus. Di Steffano et al. (1979) confirmed these findings for bone metastases of mammary carcinomas. In our study with 15 patients having negative scintigrams and positive biopsies there was a strikingly diffuse involvement of the bone marrow in the majority of cases. This may account for the absence of a localized enrichment of radionucleotids, since it is highly dependent on the activity of osteoblasts (for further details see Joo et al. 1979).

Our results are in general agreement with the conclusions of Nagel (1980) who emphasized x-ray, scintigram and biopsy are the currently optimal search methods for the detection of metastases and are a most valuable aid for the establishment of exact tumor staging. In extension to this review we would like to press for a more frequent use of the biopsy technique of Jamshidi (Jamshidi and Swaim 1971) for the early recognition of metastazing tumors. Scintigrams should also be used, since both methods are complementary and together may reach a high reliability of diagnosis.

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