

# SKELETAL METASTASES OF UNKNOWN ORIGIN : A RETROSPECTIVE ANALYSIS OF 29 CASES

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The objective of this study was to assess the diagnostic strategy in identifying occult primary carcinomas in metastatic bone disease. The records of 29 patients seen between 1983 and 1993 were reviewed retrospectively. The patients had been evaluated nonuniformly with a wide array of diagnostic procedures. The primary tumor was identified in 22 patients antemortem, and in 2 patients postmortem. In 5 patients a diagnosis of the primary tumor was never obtained. Eleven of the primary tumors were carcinomas of the lung, 3 were prostatic carcinomas, 2 were carcinomas of the breast and 2 were malignant lymphomas. In 4 patients respectively a carcinoma of the kidney, the pancreas, the ovary or the stomach was found. One patient had a carcinoid tumor of the small intestine, and one had a retroperitoneal rhabdomyosarcoma. The average survival time after clinical onset of skeletal metastases was 12 months.

We propose a flow sheet to evaluate this category of patients including a medical history, thorough physical examination, routine laboratory tests, chest radiograph, bone scintigram, ultrasonography or computed tomography of the abdomen and biopsy of the most accessible metastasis. These tests allowed premortem diagnosis of the primary tumor in 75% of the cases. Biopsy should be considered the last test to be performed.

**Keywords :** skeletal metastases ; metastatic carcinomas ; metastatic pulmonary carcinomas.

**Mots-clés :** métastases osseuses ; carcinomes métastatiques ; métastases de carcinome pulmonaire.

## INTRODUCTION

Most skeletal malignancies are metastatic rather than primary, as the ratio between primary bone tumors and visceral metastases to the skeleton is

from 1:17 to 1:25 (4, 5). Autopsies have documented skeletal metastases in approximately 20 to 30% of all patients with visceral carcinomas (1, 10). In 3 to 4% of all patients with metastatic carcinomas, the type and site of the primary tumor is unknown ; 10 to 15% of these patients with unknown primary site have skeletal lesions. If the unknown primary tumor is indeed detected, it most frequently appears to be a carcinoma of the lung, kidney or pancreas ; whereas the sources of skeletal metastases in patients in whom the primary tumor is known typically are carcinomas of the breast and prostate (8, 12).

Even if extensive diagnostic procedures are employed in patients with skeletal metastases, the unknown primary tumor often remains unknown, and it is important to use a rational diagnostic approach to this difficult problem from the onset. Treatment of patients with skeletal metastases is often limited to palliative measures ; in some cases, however, the successful identification of a primary carcinoma opens up opportunity for specific therapy.

In this study we analyzed the clinical evaluation of 29 cases of skeletal metastases from occult primary tumors to formulate a diagnostic strategy.

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Table I. — Patient data, metastatic presentation, evaluations, biopsy results, final diagnosis, survival

Case	A	B	C	D	E	F	G	H	I	J
1	47	M	Scapula	N	Malignant disease	Scapula	N	—	—	—
2	65	F	Femur	N	Malignant disease	—	—	—	—	—
3	59	M	Humerus	N	Atelectasis	Humerus	—	—	—	—
4	81	F	Femur	N	N	Spine ribs, femurs	—	—	—	—
5	56	F	Spine	N	N	Spine	Malignancy of pancreas	—	—	—
6	77	M	Femur	N	Malignant disease	Femur tibia, pelvis	—	—	—	—
7	75	F	Spine	Pelvic tumor	N	—	Retroper. tumor	—	—	—
8	45	F	Spine	Breast tumor	Costal metastases	Spine, ribs	—	—	—	—
9	58	M	Spine	N	N	—	—	—	—	—
10	59	F	Pelvis	N	Malignant disease	Pelvis	—	—	—	—
11	82	M	Tibia	N	N	Tibia, femur	—	—	—	—
12	81	M	Scapula	N	Malignant disease	Scapula, clavicle, ribs	N	—	—	—
13	20	M	Femur	N	N	—	N	—	—	—
14	62	M	Pelvis	N	N	—	N	N	—	—
15	72	M	Spine	N	Malignant disease	Spine, pelvis, ribs	—	—	—	—
16	76	M	Spine	N	N	—	—	—	—	—
17	77	M	Spine	N	Malignant disease	Spine	Hepatic metastases	—	—	—
18	78	M	Femur	N	N	Femur, spine, pelvis	N	—	—	—
19	63	F	Spine	N	N	Spine, costals, pelvis	Ovarian tumor	N	—	—
20	58	M	Humerus	Axillary node	N	—	—	—	—	Abdominal : normal
21	42	M	Femora	N	Pleural thickening	Femurs, ribs, spine	N	N	—	—
22	79	M	Spine	N	N	Spine	N	—	—	—
23	45	M	Thorax	N	Costal metastases	Thorax, spine, pelvis	Hepatic metastases	—	—	—
24	82	M	Femur	N	N	Femur, pelvis	N	—	—	—
25	58	F	Spine	Breast tumor	N	—	—	—	—	—
26	56	F	Pelvis	N	Malignant disease	Pelvis, cranium	N	—	Malignant disease	—
27	58	M	Spine	N	Malignant disease	Spine	Hepatic metastases	—	—	—
28	46	M	Femur	N	Lung metastases	—	Hepatic metastases	N	—	—
29	47	F	Pelvis	N	Malignant disease	—	N	—	Malignant disease	—

## Headings and abbreviations.

A Age (years).

B Sex (M = male, F = female).

C Metastatic site of presentation.

D Physical examination (N = normal).

E Chest radiograph.

F Radionuclide Tc-99-scintigram ; sites of abnormal uptake.

G Abdominal ultrasonogram.

H Thyroid ultrasonogram.

I Computed tomogram of chest.

J Computed tomogram of other regions.

Case	K	L	M	N	O	P	Q	R
1	—	—	—	—	Squamous cell carcinoma	Lung	—	13
2	—	—	—	—	Carcinoma	Lung	—	10
3	—	—	—	—	Non Hodgkin lymphoma	Generalized	—	—
4	—	—	—	—	Carcinoma	?	—	2
5	—	—	—	—	Carcinoma	Pancreas	—	30
6	—	—	—	—	Squamous cell carcinoma	Lung	—	2
7	—	—	—	—	—	Retroperitoneal	Rhabdomyosarcoma	2
8	—	—	—	Malignant disease	Ductal carcinoma	Breast	—	14
9	—	—	Hypernephroma	—	Clear cell Carcinoma	Kidney	—	24
10	Proctoscopy :N	—	—	—	—	Lung	Carcinoma of the lung	9
11	—	—	—	—	Prostatic carcinoma	Prostate	—	21
12	—	—	—	—	Carcinoma	Lung	—	16
13	—	N	—	—	Non Hodgkin lymphoma	Generalized	—	—
14	Proctoscopy:N Lower GI	—	—	—	Carcinoma	?	—	8
15	—	Carcinomatosis	—	—	—	Lung	—	10
16	—	—	—	—	Prostatic Carcinoma	Prostate	—	21
17	—	—	—	—	—	Lung	—	1
18	—	Carcinomatosis	N	—	—	?	—	4
19	Lower GI contrast:N	Carcinomatosis	—	N	—	Ovarian	Carcinoma of the ovary	13
20	—	—	—	—	Squamous cell carcinoma	Lung	—	—
21	Endoscopy of the stomach:N	—	—	—	Carcinoma	?	—	13
22	—	Carcinomatosis	—	—	—	?	Carcinoma of the prostate	5
23	—	—	—	—	Carcinoma	?	Carcinoma of the stomach	2
24	Lower GI contrast:N	—	—	—	Carcinoma	?	—	22
25	—	—	—	Malignant disease	Duct carcinoma	Breast	—	4
26	—	—	—	—	Squamous cell carcinoma	Lung	—	4
27	Lower GI contrast:N	Carcinomatosis	—	—	Carcinoma	Lung	—	15
28	Upper GI contrast : multiple tumors	—	—	—	Carcinoid tumor	Small intestine	—	43
29	—	—	—	N	—	Lung	—	5

K Gastrointestinal evaluation.

L Bone marrow aspiration (Carcinomatosis = nonspecific, malignant tumor cells).

M Intravenous pyelogram.

N Mammography.

O Biopsy of osseous metastasis.

P Antemortem site of primary tumor.

Q Postmortem site of primary tumor at autopsy.

R Survival (months).

## PATIENTS AND METHODS

The records of 29 patients seen between 1983 and 1993 with skeletal metastases as first manifestation of an occult primary tumor were reviewed.

The patients were evaluated at the orthopedic departments of the University Hospitals of the County of Copenhagen. In no case was the histologic diagnosis of the metastasis or the primary carcinoma known at the time of referral. We recorded the age, sex, initial physical examination, metastatic sites, diagnostic procedures, histologic diagnosis antemortem and postmortem and survival from the date of referral.

## RESULTS

There were 19 men and 10 women with an average age of 62 years (range 20 to 82 years). All patients were evaluated nonuniformly, and no preestablished protocol existed. Eighteen patients had bone metastases in the axial skeleton, 11 patients in the appendicular skeleton. Initial symptoms were most often pain, tumor or pathological fracture. Diagnosis of the primary tumor was obtained in 22 patients antemortem and in 2 patients postmortem. In 5 patients the primary tumor was not identified. Carcinoma of the lung was the primary tumor in 11 cases, 3 were carcinomas of the prostate, 2 were carcinomas of the breast and 2 were malignant lymphomas. In 4 patients a carcinoma of the kidney, pancreas, ovary or stomach was found. One patient had a

carcinoid tumor of the small intestine, and one had a retroperitoneal rhabdomyosarcoma (table I).

Twenty-six patients were dead at the time of follow-up (April-June 1994); the average survival time was 12 months.

## DIAGNOSTICS

### Physical examination

In 2 patients palpable tumors of the breast were found (table II). Carcinomas were subsequently identified by mammography and mastectomy.

### Laboratory studies

In 3 patients with biopsy-verified carcinomas of the prostate, the levels of the prostate-specific antigen (PSA) were significantly elevated, and one patient with a carcinoid tumor had a corresponding elevation of 5-hydroxyindolacetate. A majority of the patients had an elevated sedimentation rate, white blood cell count and alkaline or acid phosphatase. No other tumor markers than the above-mentioned were obtained.

### Chest radiograph

A chest radiograph was obtained in all patients, and a carcinoma of the lung was identified as the primary tumor in 10 patients. In 2 of these 10 pa-

Table II. — Test revealing localization of primary tumors antemortem

Diagnostic test	Primary tumor
Physical examination and mammography	2 carcinomas of the breast
Chest radiograph	10 carcinomas of the lung
Ultrasonogram of abdomen	1 retroperitoneal rhabdomyosarcoma
	1 carcinoma of the pancreas
	1 carcinoma of the ovary
Intravenous pyelogram	1 hypernephroma
Biopsy of metastasis	2 carcinomas of the prostate
	2 malignant lymphomas
	1 carcinoid tumor
	1 carcinoma of the lung
	Total : 22 primary tumors out of 29, or 75%

tients the diagnosis was confirmed by computed tomography of the chest, and in 3 patients by biopsy of a bone lesion. In 3 other cases the chest radiographs revealed metastases of the ribs, in one case lung atelectasis and in one case thickening of the pleura. In 14 other patients the chest radiographs were normal; in one of these biopsy of the metastasis revealed squamous cell carcinoma corresponding to an occult pulmonary primary.

#### **Tc-99-radionuclide bone scintigram**

A bone scintigram was performed in 18 patients and showed abnormal findings in all the patients at the suspected site of initial metastatic presentation and additionally at multiple sites in 11 of those patients.

#### **Abdominal ultrasonography**

Ultrasonography was performed in 17 patients and revealed a retroperitoneal tumor, a tumor of the ovary or a tumor of the pancreas in 3 patients. In 4 patients ultrasonography showed additional metastases of the liver; in 10 cases the test was normal.

#### **Thyroid ultrasonography**

It was performed in 4 patients in whom it was negative.

#### **Computed tomography of the chest**

Chest CT was used in 2 patients, in whom it showed a primary tumor of the lung, thereby confirming earlier radiographs.

#### **Gastrointestinal evaluation**

Seven patients were evaluated by protoscopy, endoscopy of the stomach, or upper and lower intestinal contrast studies. In one patient upper intestinal contrast study revealed elements corresponding to carcinoid tumors verified by biopsy of a skeletal metastasis. The other gastrointestinal tests were normal.

#### **Bone marrow biopsy**

Aspiration of the bone marrow was performed in 5 patients, the histology showing nonspecific carcinomatosis in 4 instances. In one case the aspiration was normal.

#### **Intravenous pyelogram (IVP)**

An IVP was performed in 2 patients, in one of whom it was diagnostic for hypernephroma.

#### **Mammography**

A mammogram was performed in 4 patients; it detected a carcinoma in two instances, later verified by mastectomy and histologic evaluation.

#### **Biopsy of skeletal lesions**

A biopsy was performed in 23 patients, yielding a specific histologic diagnosis in 12 cases, a nonspecific diagnosis of disseminated adenocarcinoma in 11 cases. In 6 patients the biopsy alone was diagnostic; in 13 patients the biopsy confirmed the diagnosis of other tests (tables I, II).

#### **Autopsy**

Five patients underwent autopsy, revealing the site of the unknown primary in two instances, and confirming the diagnosis provided by other ante-mortem tests in 3 patients.

### **DISCUSSION**

The distribution of skeletal metastases, survival after referral, the sites of the detected primary tumors and the ages of the patients are comparable to other series (12, 7, 11). The metastases occurred in the axial and diaphyseal appendicular skeleton, whereas primary bone tumors usually develop in the metaphyses of long bones. All visceral carcinomas can metastasize to bone, although carcinomas of the breast and prostate have particular affinity for the skeleton and are highly represented in series in which the primary origin of the skeletal

metastases is known (4, 10). In case of an unknown primary tumor the organs to suspect are the lung, kidney and pancreas (7, 2). Apart from the kidney and pancreas, which were present in our series in only 2 cases, the diagnosis of the lung as the primary site of metastatic carcinoma in 11 out of 24 patients is in agreement with similar studies.

Diagnosis of an occult primary tumor rarely results in an improved prognosis or life expectancy for the patient. We believe, however, that it is important to verify the extent of the metastatic disease in regard to impending fractures, neurologic compromise of the spinal medulla and dysfunction of the hematopoietic system, which lead to anemia, thrombocytopenia and neutropenia (11).

In our series the primary tumor was diagnosed antemortem in 22 patients (75%), using a variety of tests in a nonuniform manner, the most successful of which were chest radiograph, ultrasonography of the abdomen and biopsy from osseous site of metastatic presentation, whereas laboratory studies (except PSA), bone marrow aspiration and various gastrointestinal evaluations were of lesser specificity and diagnostic value.

Simon and Bartucci (12), in a retrospective series of 46 patients, identified the unknown primary tumor in 43% of the patients evaluated by physical examination, routine laboratory studies, chest radiographs, Tc-99-radionuclide scintigrams, IVP and biopsy from skeletal metastases. Computed tomography of the abdomen was performed in a few patients. Nottebaert *et al.* (7) identified the primary in 29% of 172 patients antemortem using a similar program of evaluation. Shih *et*

*al.* (11) diagnosed the primary tumor in 54% of the patients in a series of 52 patients.

In a prospective study of 40 patients, Rougraff *et al.* (9) obtained a diagnosis of the primary in 85% of the patients, supplementing the above-mentioned tests by computed tomograms of the chest and abdomen. Interestingly, plain radiographs of the chest revealed the lung as primary site in 17 patients (43%), and CT scan of the chest showed an additional 6 carcinomas of the lung (15%), missed on plain radiographs. Therefore, computed tomograms of the chest and abdomen seem to constitute the major difference in the success rate in obtaining a diagnosis of the primary tumor.

Our own data and those from similar studies then suggest a flow-sheet for the evaluation of this not often encountered but clinically difficult group of patients :

- a. Complete patient history (smoking habits, etc.).
- b. Physical examination, i.e. thyroid, breasts, skin, genitalia rectal examination, etc.
- c. Routine laboratory studies, i.e. red and white blood cell count, sedimentation rate, PSA in men, urinalysis.
- d. Chest radiographs, to be supplemented with computed tomography of the chest.
- e. Tc-99-radionuclide scintigrams to assess the extent of metastatic disease and to reveal metastases more accessible to biopsy than the initial site of metastatic presentation.
- f. McMillan *et al.* (6) prefer computed tomography of the abdomen to ultrasonography in these patients.

Table III. — Diagnostic strategy

Medical history	
Physical examination	Breasts, thyroid, skin, external/internal genitals, rectal examination
Laboratory tests	Red and white blood cell count, sedimentation rate, PSA.
Radiology	Chest radiograph, Computed tomogram of chest Tc-99-scintigram, ultrasonography/computed tomography of the abdomen.
Biopsy of most accessible bone metastasis.	

g. Biopsy of the most accessible skeletal metastasis. This must be done cautiously at the end of the evaluation in the event that it is in reality a sarcoma of bone one is evaluating, for an ill-planned biopsy can compromise subsequent limb-sparing procedures. If previous tests have shown a hypernephroma as the primary tumor, one is best advised to avoid biopsy because the metastases are abundantly vascularized (9) (table III). Moreover, other tests (i.e. computed tomography, magnetic resonance) can make biopsy superfluous.

Such a protocol would probably have had the same diagnostic efficiency as the array of nonuniformly applied diagnostic procedures analyzed in the present study.

## REFERENCES

1. Abrams H. L., Spiro R., Goldstein N. Metastases in carcinoma. *Cancer*, 1950, 3, 74-85.
2. Didolkar M. G., Fanous N., Elias E. G., Moore R. H. Metastatic carcinomas from occult primary tumors. *Ann. Surg.*, 1977, 186, 625-630.
3. Frassica F. J., Sim F. H. Metastatic bone disease. *Orthopedics*, 1992, 5, 599-604.
4. Johnston A. D. Pathology of metastatic tumors in bone. *Clin. Orthop.*, 1970, 73, 8-32.
5. Lote K., Walløe A., Bjersand A. Bone metastasis. *Acta Radiol.*, 1986, 25, 277-332.
6. McMillan J. H., Levine E., Stephens R. H. Computed tomography in the evaluation of metastatic adenocarcinoma from an unknown primary site. *Radiology*, 1982, 143, 143-146.
7. Nottebaert M., Exner G. U., von Hochstetter A. R., Schreiber A. Metastatic bone disease from occult carcinoma : a profile. *Int. Orth.*, 1989, 13, 119-123.
8. Osteen R. T., Kopf G., Wilson R. E. In pursuit of the unknown primary. *Am. J. Surg.*, 1978, 135, 494-497.
9. Rougraff B. T., Kneisl J. S., Simon M. A. Skeletal metastases of unknown origin. *J. Bone Joint Surg.*, 1993, 75-A, 1276-1781.
10. Sherry H. S., Levy R. N., Siffert R. S. Metastatic disease of bone in orthopedic surgery. *Clin. Orthop.*, 1982, 169, 44-52.
11. Shih L.-Y., Chen T.-H., Lo W.-H. Skeletal metastasis from occult carcinoma. *J. Surg. Onc.*, 1992, 51, 109-113.
12. Simon M. A., Bartucci E. J. The search for the primary tumor in patients with skeletal metastases of unknown origin. *Cancer*, 1986, 58, 1088-1095.

## SAMENVATTING

*S. JACOBSEN, S. L. STEPHENSEN, B. P. PAASKE, P. G. LIE, G. S. LAUSTEN. Botmetastasen van onbekende origine : retrospectieve studie van 29 gevallen.*

Doel van de studie was een evaluatie van de diagnostische procedure bij de identificatie van de occulte primitieve tumoren die aanleiding geven tot botmetastasen. De dossiers van 29 patiënten, gezien tussen 1983 en 1993, werden retrospectief onderzocht. De patiënten waren aanvankelijk op een niet-uniforme wijze geëvalueerd door middel van meerdere diagnostische middelen. De primitieve tumor werd ante mortem bij 22 patiënten en post mortem bij 2 andere patiënten geïdentificeerd ; zij werd nooit bepaald bij 5 patiënten. Onder de primitieve tumoren waren 11 longtumoren, 3 prostaatacarinomen, 2 borstcarcinomen en 2 maligne lymfomen. Bij 4 patiënten werd een maligne tumor gezien ter hoogte van respectievelijk de nier, de pancreas, het ovarium en de maag. Bij 1 patiënt was er een carcinoïde tumor van het ileon en bij een andere een retroperitoneale rhabdomyosarcoom. De gemiddelde overleving na het diagnosticeren van botmetastase beliep 12 maanden. De auteurs stellen een evaluatie protocol voor met onder meer een anamnese, een volledig klinisch onderzoek, de gebruikelijke labo onderzoeken, Röntgenopnamen van de thorax, een botsintigrafie, een echografie of een CT-scan van het abdomen en een biopt van de gemakkelijkst te benaderen metastase. Met deze technieken wordt het mogelijk een pre mortem diagnose te bekomen in 75% der gevallen. Het biopt, voor zover het onderzoek noodzakelijk blijkt, komt pas als laatste diagnosemiddel.

## RÉSUMÉ

*S. JACOBSEN, S. L. STEPHENSEN, B. P. PAASKE, P. G. LIE, G. S. LAUSTEN. Métastases osseuses d'origine inconnue : analyse rétrospective de 29 cas.*

L'objectif de cette étude était d'évaluer la stratégie diagnostique pour l'identification des tumeurs primitives occultes à l'origine de métastases osseuses. Les dossiers de 29 patients examinés entre 1983 et 1993 ont été revus rétrospectivement. Les patients avaient été évalués d'une façon non uniforme en recourant à un large éventail de moyens de diagnostic. La tumeur primitive a été identifiée ante mortem chez 22 patients et post mortem chez 2 autres ; elle n'a jamais pu être identifiée chez 5 patients. Parmi les tumeurs primitives,

11 étaient des tumeurs du poumon, 3 étaient des carcinomes prostatiques, 2 des carcinomes mammaires et 2 des lymphomes malins. Quatre patients ont été reconnus porteurs d'une tumeur maligne touchant respectivement le rein, le pancréas, l'ovaire et l'estomac. Un patient présentait une tumeur carcinoïde de l'intestin grêle et un autre un rhabdomyosarcome rétropéritonéal. La survie moyenne après le diagnostic de métastases osseuses a été de 12 mois.

Les auteurs proposent un protocole d'évaluation pour cette catégorie de patients, comprenant une anamnèse,

un examen clinique complet, les examens de laboratoire habituels, une radiographie du thorax, une scintigraphie osseuse, une échographie ou un CT Scan de l'abdomen et une biopsie de la métastase la plus facilement accessible. Ces tests ont permis d'obtenir un diagnostic pre mortem dans 75% des cas. La biopsie, pour autant qu'elle soit jugée nécessaire, ne doit être envisagée qu'en dernier lieu.