Diagnostic and treatment modalities in carcinoid tumours

Zuutendorst, J.M.

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Chapter 1

Evaluation of $^{111}$In-pentetreotide, $^{131}$I-MIBG and bone scintigraphy in the detection and clinical management of bone metastases in carcinoid disease

J.M. Zuitemhorst$^1$, C.A. Hoefnagel$^2$, H. Boot$^1$, R.A. Valdés Olmos$^2$, B.G. Taal$^1$

Departments of $^1$Gastroenterology and $^2$Nuclear Medicine

Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam

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Abstract

Background: Bone metastases are assumed to be rare in carcinoid disease and to be associated mainly with bronchial primaries. The aim of the present study was to evaluate the occurrence of bone metastases in patients with metastatic carcinoid tumours, and the role of various nuclear medicine modalities (bone scintigraphy, $^{111}$In-pentetreotide and $^{131}$I-MIBG) in its detection and clinical management.

Methods: Nine (2 women, 7 men, median age 65 years) out of 86 consecutive carcinoid patients treated between 1987 and 1998 developed bone metastases (10%) with a median interval of 37 months between the diagnosis of metastatic carcinoid and bone metastases. Seven of them had non-bronchial primaries.

Results: $^{111}$In-pentetreotide scintigraphy failed to detect the bone lesions in 50% of the cases, and $^{131}$I-meta-iodobenzylguanidine (MIBG) scintigraphy in almost 80% of cases. Standard bone scintigraphy, however, was positive in all. Pain relief of bone metastases by means of radiation therapy was obtained in 5 of 6 patients. In another patient palliation of pain symptoms was obtained with Rhenium-186-hydroxyethylidene diphosphonate. Octreotide, interferon or MIBG were ineffective for this purpose.

Conclusion: Bone metastases in carcinoid patients may be missed on $^{131}$I-MIBG and $^{111}$In-pentetreotide scintigraphy. Bone scintigraphy is a sensitive imaging technique. Diagnostic nuclear medicine modalities may be helpful in the clinical management of carcinoid disease.
Bone metastases in carcinoid tumours

Introduction

Carcinoid tumours are often indolent, slowly growing tumours. They predominantly originate in the gastrointestinal tract and bronchi. Carcinoid patients often present with metastatic disease in the liver, while the primary tumour does not cause symptoms. Carcinoid tumours derived from the midgut are well-known for their peptide hormone production, mainly serotonin. In the presence of liver metastases, this is leading to the characteristic symptoms of diarrhoea and flushing, i.e. the carcinoid syndrome. Other metastatic sites such as lung and skeleton, which are prominent in adenocarcinomas, are unusual. Information on skeletal metastases is scarce. They are most frequently associated with localisation of the primary tumour in the bronchial tree. We evaluated the occurrence, detection and clinical management of bone metastases in patients with metastatic carcinoid using tumour seeking radionuclide studies (\(^{111}\)In-pentetreotide and \(^{131}\)I-MIBG) as well as bone scintigraphy with \(^{99m}\)Tc-diphosphonate.

Patients and methods

Among 86 consecutive patients with carcinoid tumours and liver metastases treated in The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital between 1987 and 1998, bone metastases occurred in nine patients (10%). Bone metastases were identified by pain suggesting a clinical diagnosis of skeletal involvement or detected by coincidence during follow-up. Clinical data as well as diagnostic procedures were reviewed in these nine patients.

Radionuclide imaging was performed using a dual head gamma camera (ADAC) and a Pegasys system. Studies with \(^{131}\)I-MIBG and \(^{111}\)In-pentetreotide were performed following a previously described protocol. For \(^{131}\)I-MIBG 10-min images (256 x 256 x 16 matrix) were made at 24, 48 and 72 hours after intravenous injection of 37 MBq of the radiopharmaceutical. A potassium-iodide solution was administered orally for 5 days to prevent \(^{131}\)I concentration in the thyroid. For \(^{111}\)In-pentetreotide whole body acquisition (512 x 1024 matrix) during 50 min was performed at 24 hours after injection of 130 MBq of the tracer. Bone scintigraphy was performed 2 to 3 hours after injection of 500-700 MBq \(^{99m}\)Tc-MDP using whole body acquisition (9 cm/min).
Results

In nine patients (2 women and 7 men) with a median age of 65 years (range 50-81) bone metastases appeared based on localised pain in six and found by coincidence in three (Table 1). The median interval between the initial diagnosis of metastatic carcinoid and the detection of bone metastases was 37 months (range 0-95). The primary tumour was located in the foregut in two patients, in the midgut in two and in the hindgut in one patient. In 4 out of 9 patients the primary tumour remained unknown. Seven patients expressed the carcinoid syndrome with flushes and/or diarrhoea accompanied by an elevated urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion. In two patients without symptoms of carcinoid syndrome the urinary 5-HIAA excretion was not increased; the diagnosis was based on histology. In all nine patients liver metastases were diagnosed and in six of them metastases at other sites were also present.

X-rays of the skeleton revealed lesions in only three out of 8 patients, which were sclerotic in nature. In an additional patient the X-ray showed an irregular and difficult to interpret aspect of the thoracic and lumbar spine (Table 2). In eight patients a CT-scan of the abdomen was performed to evaluate liver metastases; in one case ultrasound was applied for this purpose. Although CT-scan gives only information on the pelvic area and not the complete skeleton, sclerotic lesions were seen in three patients. In one patient the lesions on the CT-scan were the first symptom of skeletal involvement. MRI was performed indicated by localised pain symptoms and revealed in an additional two patients, with negative findings on CT-scanning, sclerotic bone metastases.

Bone scintigraphy using \(^{99m}\text{Tc-MDP}\) showed multiple metastases in all patients. The axial skeleton and the pelvis were affected in all and the extremities were involved in more than half of the patients. Most of the patients with clearly positive findings on bone scintigraphy did not have skeletal abnormalities on other radionuclide imaging studies (Figure 1).

\(^{131}\text{I-meta-iodobenzylguanidine (MIBG)}\) scintigraphy showed retention in the liver metastases of all patients. However, uptake in bone metastases was only seen in two out of nine patients (Table 2).

\(^{111}\text{In-pentetreotide scintigraphy was available in eight cases, and showed the liver metastases in all eight patients. One patient (nr.8) was admitted in 1987, when}^{111}\text{In-pentetreotide scintigraphy was not yet performed on a regular basis. Bone metastases were detected with this technique in four out of 8 patients. In patient 2, the bone scintigraphy showed accumulations, which in retrospect were vaguely shown on the}^{111}\text{In-pentetreotide scintigram (Figure 2).}

In two patients the bone metastases could only be recognized because the localisation was proven before by bone scintigraphy (Figure 3).
<table>
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<tr>
<th>No.</th>
<th>Age at bone metastases (years)</th>
<th>Gender</th>
<th>Primary tumour</th>
<th>Metastatic sites</th>
<th>5-HIAA (normal &lt; 40 μmol/24h)</th>
<th>Carcinoid syndrome</th>
<th>Pain at bone metastatic sites</th>
<th>Diagnosis bone metastases after initial diagnosis (months)</th>
<th>Effect of local radiotherapy</th>
<th>Survival from bone metastases (months)</th>
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Table 2. Radiologic and scintigraphic findings by carcinoid patients with bone metastases

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<th>CT-scan abdomen (on X-ray or CT-scan)</th>
<th>Aspect of metastases</th>
<th>Bone scintigraphy</th>
<th>‹¹³¹-I-MIBG scintigraphy</th>
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*n.a.: not available
Figure 1. Bone scintigraphy (A) of patient 1 with carcinoid syndrome revealing multiple “hot spots” in the vertebral axis, the right and left humerus, the left femur and the right toe. $^{111}$In-pentetreotide scintigraphy (B) as well as the $^{131}$I-MIBG images (C) show metastases in liver, but no retention in the affected skeletal areas.

Medical treatment for the metastatic carcinoid tumour was given in all patients to achieve symptomatic improvement. MIBG, either non-radioactive or radioactive, was given in eight patients. Seven patients were treated with octreotide or long-acting octreotide and five patients received interferon injections. A combination of more than one treatment modality was given in eight patients. Although symptomatic improvement of symptoms of the carcinoid syndrome was achieved in most of the patients, no pain relief of the bone metastases was obtained. In six patients irradiation of the painful skeletal metastases was performed with a short schedule of one to five sessions. All but one experienced improvement of pain in a few weeks. In two patients a second course of radiotherapy was given because of new painful localisations with the same fair palliation of pain. A second course of radiotherapy at the same lesions was not needed in any patient. In one of the patients Rhenium-186- hydroxyethylidene diphosphonate (HEDP) led to some palliation of the pain symptoms (Figure 4).

After the diagnosis of bone metastases the median survival was 15 months (range 11-19) for the five patients who died. In the four patients still alive the median follow-up after the bone metastases were diagnosed was 27 months (range 15-38).
Figure 2. Bone scintigraphy (A) showing accumulations in ribs, vertebral axis, humeri and pelvis. $^{111}$I-MIBG (B) shows only intense accumulation in liver metastases. $^{111}$In-pentetreotide (C) shows intense uptake in liver metastases and faint activity in some affected skeletal areas of the thorax.

Figure 3. Bone scintigraphy (A) shows increased uptake in vertebral metastases and one of the left distal ribs. $^{111}$In-pentetreotide (B) show also uptake in bone metastases as well as in liver and right side of the neck. $^{131}$I-MIBG (C) show only uptake in non-skeletal metastases.
Figure 4. Posterior image of bone scintigraphy (A) showing increased accumulation of $^{99m}$Tc-MDP in bone metastases in vertebral spine, pelvis, ribs. A similar pattern of distribution is seen on Rhenium-186 HEDP image (B) which enables palliation of pain symptoms. By contrast, $^{131}$I- MIBG scintigraphy (C) shows extensive liver and lung metastases but only some of the affected skeletal areas.

**Discussion**

The diagnosis of bone metastases of carcinoid tumours may be difficult as is illustrated by the evaluation reported here. Bone metastases are reported to arise more often from bronchial or hindgut primaries compared with patients with midgut carcinoid tumours.\textsuperscript{6,7} In our patients there was no preferential primary site and in four out of 9 patients the primary tumour remained unknown. Recently the incidence of skeletal metastases in neuroendocrine tumours has been reported to be 13\%.\textsuperscript{9} In our series this figure is 10\% (nine out of 86), but probably underestimated as bone scintigraphy was mainly performed in case of symptoms.

The radiographic signs of bone metastases are often subtle and easily missed. They may appear as osteoblastic or osteolytic lesions similarly to metastatic deposits in other malignancies as prostate or breast cancer.\textsuperscript{5,10-13} They can even mimic a benign condition.
as osteomyelitis.\textsuperscript{14} In our patients the X-ray of the symptomatic sites showed sclerotic lesions in three patients. Literature data on the diagnostic impact of CT and MRI-scan is lacking. In the present series of nine cases the CT-scan performed to measure the liver metastases, accidentally detected sclerotic lesions in only two patients. The additional MRI-scan performed in two patients indicated by pain, detected lesions in both without positive findings on CT-scan.

In metastatic carcinoma bone scintigraphy is known to be a sensitive imaging technique to detect skeletal involvement before X-ray abnormalities appear. In metastatic carcinoid tumours, however, data are limited. In a French study\textsuperscript{9} in 19 patients with CT or MRI proven bone metastases from endocrine gastroenteropancreatic tumours (GEP) bone scintigraphy was positive in 17 (89\%). In our study all patients showed clear abnormalities on $^{99m}$Tc-MDP bone scintigraphy. The axial skeleton is the most commonly affected site, as is described in the literature.\textsuperscript{14,15} In all our patients, there were lesions in the axial skeleton on bone scintigraphy. In addition, the pelvis was positive in all nine patients too, a localisation that has not been described as a preferential site of skeletal lesions of carcinoid tumours.

The specific tumour seeking image technique of $^{131}$I-MIBG scintigraphy has shown a sensitivity of 60-75\%.\textsuperscript{16,17} Whether $^{131}$I-MIBG easily detects bone metastases is not clearly known from the literature as data are limited. A German study reported the diagnostic value of $^{131}$I-MIBG scintigraphy in a small group of 9 carcinoid patients as a staging procedure compared with abdominal CT-scanning.\textsuperscript{18} Only one patient was found with bone metastases at CT-scan and did not show clear $^{131}$I-MIBG retention. In our series the $^{131}$I-MIBG scintigraphy demonstrated the bone metastases in only two of the nine patients, despite the liver metastases did show clear retention. A possible explanation for the absence of $^{131}$I-MIBG retention in skeletal lesions may be a variation in differentiation of tumour cells at different sites or a different local blood supply to the bone cortex. This is also in line with the observations in $^{131}$I-MIBG therapy of neuroblastoma, pheochromocytoma and paraganglioma, that non-skeletal metastases respond better to $^{131}$I-MIBG therapy than bone metastases despite adequate scintigraphic detection of these lesions.\textsuperscript{19}

The somatostatin receptor imaging by $^{111}$In-pentetrotide scintigraphy is reported to have a sensitivity of 80-92\% in various endocrine tumours.\textsuperscript{20} A high sensitivity for bone metastases have been reported in a series of 19 patients, which were all positive.\textsuperscript{9} In contrast, in our series this modality picked up the skeletal metastases in only half of the patients. Whether this might be explained by a difference in technique is unlikely. The patient population, however, is different. Lebtahi et al. scanned mainly at presentation, while our patients were detected during follow-up; maybe there is a dedifferentiation in a later stage of the disease. A comparative study\textsuperscript{21} among 21 carcinoid patients, including two cases with bone metastases, described the superiority of scintigraphy with $^{111}$In-
Bone metastases in carcinoid tumours

pentetreotide over $^{131}$I-MIBG. In our present series both modalities, and specially MIBG, resulted less sensitive than bone scintigraphy to detect bone metastases. With respect to $^{111}$In-scintigraphy this is in agreement with the findings of Banzo et al.\textsuperscript{22}

In metastatic carcinoid, scintigraphy is important to manage therapy. In case of a positive $^{111}$In-pentetreotide scintigraphy octreotid is useful in the prevention of hormone release leading to improvement of symptoms as diarrhoea and flushes in 60-68%.\textsuperscript{23-25} A possible antiproliferative effect to induce tumour reduction, as needed for the treatment of bone metastases, has so far only occasionally been seen. If $^{131}$I-MIBG is positive, a therapeutic dose has been used for local irradiation based on selective concentration and prolonged retention of $^{131}$I-MIBG in the tumour cells. This resulted in fair palliation in 65% at the cost of minimal side effects.\textsuperscript{26} In our nine patients no palliative effect was observed for the pain of bone metastases by MIBG despite successful palliation of the carcinoid syndrome. Similarly, a therapeutic dose of octreotide can be applied. The preliminary data are promising.\textsuperscript{27} As the $^{111}$In-pentetreotide scintigraphy was often negative this was not an option in the presented cases.

The role of radiation therapy by external beam is thought to be limited in carcinoid disease, probably because the liver is the main site of metastases and not amenable for radiation. However, irradiation may be effective for several other metastatic sites such as skeletal localisations of carcinoid tumours.\textsuperscript{5,28,29} Schupak describes worthwhile palliation in a series of 44 patients with localised tumour in e.g. the lung, brain and the spinal cord, including 8 patients with bone metastases.\textsuperscript{30} In our present series a simple radiotherapy scheme, performed in six patients, proved effective in five of them. A second course of radiotherapy on the same site was not needed. In two patients new painful skeletal lesions developed with an interval of 9 and 14 months, they responded well to irradiation. One patient in our series was treated with Rhenium-186-HEDP with moderate result. Although external beam radiotherapy can be used in patients with limited localisation of skeletal symptoms, radioactive treatment with Rhenium-186-HEDP can be considered in patients with multifocal bone symptoms or with pain symptoms persisting after radiotherapy with external beam.

In conclusion, bone metastases may be underestimated and easily be missed by conventional radiography and even by scintigraphy using specific tumour seeking agents such as $^{111}$In-pentetreotide and $^{131}$I-MIBG. This in contrast with the detection of carcinoid metastases using these tracers in other organs, such as the liver, in which the findings of both radionuclide studies may be the key to treatment.\textsuperscript{8}

Bone scintigraphy is a very sensitive and reliable nuclear imaging technique to detect bone metastases in carcinoid disease and provides additional information to manage treatment for pain.


Chapter 1

References


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