Original article

Radioisotope bone scans in the preoperative staging of hepatopancreatobiliary cancer

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Background: **The aim of the study was to determine the value of radioisotope bone scans in the preoperative staging of patients with hepatopancreatobiliary (HPB) cancer.**

Methods: **Bone scanning was performed as part of a routine staging protocol in 402 consecutive patients with HPB cancer over a period of 5 years. Patients with positive bone scans underwent coned radiography, computed tomography with review on bone windows, or a bone biopsy. Bone scans were reviewed along with staging investigations, surgical and histological findings. Patients were followed for a minimum of 6 months.**

Results: **There were 171 patients with colorectal liver metastases, 106 with suspected pancreatic cancer, 47 with hepatocellular cancer, 52 with gallbladder cancer or cholangiocarcinoma, and 26 with other types of HPB cancer. Bone scans were negative in 377 patients (93·8 per cent) and positive in 25 patients (6·2 per cent). Of the 25 positive scans, 16 were falsely positive as a result of degenerative bone disease. Of nine patients with a true-positive bone scan, four had locally irresectable disease and four distant metastases. In only one patient did the bone scan result alone influence the decision to resect the HPB cancer. Overall sensitivity was 100 per cent, specificity 95·9 per cent, positive predictive value 36·0 per cent and negative predictive value 100 per cent.**

Conclusion: **Bone scanning should not be included in the routine staging protocol for HPB cancer.**

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Introduction

Surgical resection is the optimal treatment for patients with cancer of the liver, biliary tract or pancreas who have localized disease and are fit for major surgery[1–3]. These surgical procedures are associated with significant morbidity (20–30 per cent) and mortality (0·6–5 per cent), even in specialist centres[4–7]. Detection of metastatic bone disease from these cancers is associated with a life expectancy of 6–12 months[8] and is a contraindication to surgery[9,10].

Radionuclide bone scanning is a sensitive and rapid method for the detection of bone metastases[11]. It can identify an alteration as small as 5–15 per cent in local bone homeostasis resulting from tumour involvement[11,12]. The clinical value of routine preoperative bone scintigraphy before resection of hepatopancreatobiliary (HPB) cancer is frequently discussed in the literature, but there are few supportive data[8,9,13–16]; no published study has evaluated the role of routine bone scanning in the preoperative staging of asymptomatic patients with HPB cancer. This prospective study evaluated a group of patients with HPB cancers who underwent bone scintigraphy as a part of a preoperative staging protocol. The influence of bone scintigraphy on patient management was reviewed.

Patients and methods

Isotope bone scanning was performed in all patients referred to a regional hepatobiliary referral centre for

surgical assessment of known or suspected HPB cancer over a 5-year interval. There were 402 patients (210 men) of mean(s.d.) age 63(12) years.

The staging protocol for the various HPB cancers is summarized in *Table 1*. Computed tomography (CT) was done with a HI Speed helical CT™ scanner (GE, Slough, UK). Magnetic resonance imaging (MRI) of the abdomen including the pelvis was performed using a 1·0-T Intera™ scanner with a quadrature phased-array body coil (Phillips, Best, The Netherlands). The same protocol was used for all tumour types and comprised axial/coronal fast spin echo T2, axial STIR (short tau inversion recovery), axial fat-saturated T1, axial dual echo T1, and axial dynamic gadolinium-enhanced T1 with and without delayed post-gadolinium.

All bone scans were performed more than 3 h after intravenous injection of 550–600 MBq ^{99m}Tc-radiolabelled methylene diphosphonate. Images were recorded as eight planar spot images using a Siemens Zlc Orbiter™ instrument (Siemens, Erlargen, Germany) or Scintronix gamma camera™ (Scintronix, Livingston, UK) interfaced to a Hermes™ computer system (Nuclear Diagnostics, Stockholm, Sweden). Alternatively, anterior and posterior whole-body imaging was performed with a Picker XP2000™ dual-headed γ camera (Picker, Cleveland, Ohio, USA). All the images were reported from hard-copy film with review on workstations by consultant nuclear medicine physicians.

Table 1 Staging protocols for individual diagnostic groups

Diagnostic group	Staging protocol
Colorectal liver metastasis	Triple-phase spiral CT (chest and abdomen with pelvis), colonoscopy, MRI of liver, laparoscopy (selective)
Pancreatic cancer	Unenhanced + reduced field-of-view thin-section dual-phase (arterial dominant + portal venous) spiral CT (chest and upper abdomen), laparoscopy and, selectively, mesenteric angiography, endoscopic ultrasonography and MRCP
Hepatocellular carcinoma	Triple-phase spiral CT (chest and abdomen with pelvis), MRI, laparoscopy, Lipiodol angiography (selective), post-Lipiodol CT (selective)
Cholangiocarcinoma or gallbladder cancer	Unenhanced + reduced field-of-view thin-section dual-phase (arterial dominant + portal venous) spiral CT (chest and abdomen), MRCP, MRA or selective angiography, laparoscopy

CT, computed tomography; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; MRA, magnetic resonance angiography.

Bone scans were reported as: (1) positive for metastases (defined as focal uptake at a non-physiological site not explained by recent trauma or known degenerative disease); (2) negative for metastatic disease (uptake that was physiological or in a distribution consistent with known recent trauma or known degenerative disease); or (3) suspicious for metastatic disease (increased uptake at a non-physiological site that was not characteristic of bone metastases, that is isolated focal uptake).

Patients with lesions considered suspicious for metastatic disease on the bone scan were investigated further by coned local radiography and CT with review on bone windows. Bone biopsy was performed in equivocal cases.

Patients whose scans were reported as positive were subsequently categorized as either true positives or false positives. True positives had clinical (bone pain) and/or radiological (coned local radiographs and/or CT with review on bone windows) or histological (bone biopsy) evidence of metastatic disease. False positives had abnormal bone scans but lacked clinical and/or radiological evidence of metastasis and showed no evidence of bone metastases over the following 6 months.

Patients whose scans were initially reported as negative were subsequently categorized as either true negatives (no clinical evidence of metastasis (bone pain) at initial scanning and no clinical or radiological evidence of metastatic disease within 6 months of surgical resection) or false negatives (clinical and radiological evidence of bony metastases within 6 months of surgical resection).

Sensitivity, specificity, positive predictive value and negative predictive value were calculated for the overall data and for individual diagnostic groups.

Results

The case-mix of patients referred for consideration of resection of HPB cancer is shown in *Table 2*. No patient had new-onset bone pain at the time of presentation. The bone scan results for the individual diagnostic groups are summarized in *Table 3*.

Of the 171 patients with colorectal liver metastases, one patient (0·6 per cent) had bone metastases. This patient had synchronous liver, pulmonary and bony metastases.

Of 106 patients with suspected pancreatic cancer, four had true-positive bone scans. Of these, two had locally advanced disease (biopsy confirmed) with portal vein involvement (identified by CT) and two had pulmonary metastases (identified by CT).

Of 47 patients with hepatocellular cancer, one had a true-positive bone scan. This patient had locally advanced disease (identified on abdominal CT and confirmed

Table 2 Diagnostic groups

Diagnosis	No. of patients	Age (years)*	Sex ratio (M : F)	No. resected†
Colorectal liver metastasis	171	61(11)	1 : 1	91 (53.2)
Pancreatic cancer	106	66(11)	1·2 : 1	44 (41.5)
Hepatocellular carcinoma	47	54(16)	1·6 : 1	22 (47)
Gallbladder carcinoma and cholangiocarcinoma	52	62(12)	1 : 1	11 (21)
Other‡	26	56(15)	0·7 : 1	10 (38)
Total	402	63(12)	1 : 1	178 (44.3)

*Values are mean(s.d.); †values in parentheses are percentages. ‡Neuroendocrine tumour, 14; leiomyosarcoma, three; stromal cell tumour, two; soft tissue sarcoma, one; paraganglionoma, one; endometrioid carcinoma, one; unknown primary with liver metastases, two; suspected pancreatic cancer without histological confirmation, two.

by percutaneous biopsy of the primary) that precluded surgery.

Of 52 patients with gallbladder cancer or cholangiocarcinoma, there were three with true-positive bone scans (two cholangiocarcinomas, one gallbladder carcinoma). Of the two patients with cholangiocarcinoma, one had locally advanced disease (biopsy confirmed) with vascular involvement (identified by CT) and the other had pulmonary metastases (seen on CT). The patient with gallbladder cancer had isolated asymptomatic bone metastases detected by bone scanning and confirmed by bone biopsy. Spiral CT showed no evidence of disease in the abdomen or lungs. The bone scan findings were considered a contraindication to further surgery.

Twenty-six patients had other types of HPB cancer (14 neuroendocrine tumours, three leiomyosarcomas, two stromal cell tumours, one soft tissue sarcoma, one paraganglionoma, one endometrioid carcinoma, two unknown primaries with liver metastases, two suspected pancreatic cancers with no histological confirmation). None of these patients had a true-positive bone scan.

The sensitivity, specificity, positive predictive value and negative predictive value of radioisotope bone scans for each diagnostic group are shown in *Table 3*. Of the 402 patients referred with either suspected or confirmed HPB cancer, 377 (93·8 per cent) had a negative scan and 25 (6·2 per cent) a positive scan at the initial assessment. The overall sensitivity was 100 per cent, specificity 95·9 per cent, positive predictive value 36·0 per cent and negative predictive value 100 per cent.

Of the 25 patients with a positive scan, 16 were false positives (one patient had a negative bone biopsy) and nine were true positives. In the whole series, a positive bone scan affected surgical management in only one patient with gallbladder cancer.

Discussion

Radioisotope bone scanning is frequently used as the major and sometimes the only diagnostic test for detecting bone metastasis[11,13,17,18]. Methylene diphosphonate was used in the present study and is the most commonly used agent for routine bone scanning. Bone-seeking agents accumulate in the hydroxyapatite crystal matrix as new bone is formed in response to tumour destruction of the bone mineral matrix[12]. Bone scanning is more sensitive than routine radiography in the detection of bony metastases. A slight increase in osteoblastic activity results in a positive isotope scan, whereas at least 50 per cent loss of cancellous bone has to occur for detection by conventional radiography[11,19–21]. Radioisotope bone scans can detect metastasis at least 6 months before clinical presentation[12,19,20].

In the present study 16 false-positive scans were due to degenerative changes in the spine. This is likely to reflect the advanced age of patients presenting with HPB cancer and the incidence of asymptomatic osteoarthritis in elderly patients[22,23]. Both the overall sensitivity and the negative predictive value were 100 per cent. This exceptional sensitivity confirms the ability of bone

Table 3 Bone scan results according to diagnostic group

	No. of patients	Bone scan			Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
		Negative	True positive	False positive				
Colorectal liver metastasis	171	165	1	5	100	97·0	16·7	100
Pancreatic cancer	106	96	4	6	100	94·1	40·0	100
Hepatocellular carcinoma	47	43	1	3	100	93	25	100
Gallbladder carcinoma or cholangiocarcinoma	52	48	3	1	100	98	75	100
Other	26	25	0	1	100	96	–	–
Total	402	377	9	16	100	95·9	36·0	100

PPV, positive predictive value; NPV, negative predictive value.

scintigraphy to detect a change as small as 5–15 per cent in local bone homeostasis[11]. In addition to alterations due to metastatic cancer, increased accumulation of ^{99m}Tc-labelled phosphate can result from increased calcium metabolism[17], increased vascularity[17], trauma[24] or arthritic changes[25,26]. Accurate clinical information is thus vital when interpreting radioisotope bone scans in patients with cancer.

The value of isotope bone scans in the staging algorithm has not been evaluated adequately in either primary or metastatic colorectal cancer. Isolated bone metastases in patients with primary colorectal cancer are considered a rare occurrence (0·9–1·3 per cent)[8,27,28]. Only one reported series included bone scanning as a part of a routine staging protocol in patients being considered for resection of colorectal liver metastases[29]; no patient had a positive bone scan. The present study of 171 patients with potentially resectable colorectal liver metastases also showed a low incidence of bone metastasis (0·6 per cent). There was only one asymptomatic patient with a true-positive bone scan, and resection of liver metastases was precluded in this patient owing to the presence of lung metastases.

The incidence of bone metastases in patients with carcinoma of the pancreas being considered for resection has not been reported previously. The incidence in the present series was 3·8 per cent. None of these patients had bony symptoms at presentation. A review in 1976 revealed a similar incidence of bone metastasis (5 per cent) in patients with pancreatic cancer[14]. All four patients with true-positive bone scans identified by the present preoperative staging protocol had evidence of extrapancreatic spread identified by other staging investigations.

Bone metastasis is rare in patients with hepatocellular carcinoma[16,30]. In the present series a 2 per cent incidence of bone metastasis was found in asymptomatic patients with hepatocellular cancer who were being considered for liver resection. There have been no previous reports identifying the incidence of bone metastases in asymptomatic patients being considered for resection. Taki *et al.*[16] reported an incidence of 3·1 per cent in 323 consecutive patients with hepatocellular carcinoma who underwent liver resection, but these metastases were detected only on postoperative follow-up when the scans were performed in symptomatic patients with bone pain and/or neurological deficit. In the present study only one of 47 patients was found to have bony metastases. This patient was precluded from a potentially curative liver resection because of locally advanced disease identified by other staging investigations.

Among patients with cholangiocarcinoma or gallbladder carcinoma there was a 5·8 per cent incidence of bone metastases. Again, no previous reports have been made of the incidence of bone metastases in asymptomatic patients with these cancers being considered for resection. Isolated asymptomatic bone metastases detected by bone scanning and confirmed by bone biopsy were found in only one patient with gallbladder cancer in the present series; bony metastases are rare in patients with gallbladder carcinoma[31].

Patients undergoing staging before resection of liver, biliary tract and pancreatic cancers had a 2·2 per cent incidence of bony metastases detectable by radioisotope bone scanning. Most of these patients also had locally advanced or metastatic disease. Surgical management is therefore rarely affected by the results of radioisotope bone scans, and the present data do not support the use of bone scanning as part of routine preoperative investigation. Similar results have been reported for bone scanning in cancers that more commonly metastasize to bone, such as breast, lung and kidney tumours[32–34], when used in patients with no bony symptoms.

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