Osseous Metastases Missed by Bone Scan in Hepatocellular Carcinoma: A Retrospective Analysis

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A. Study Background, Rationale, and Objectives

Background:

Incidence estimates in 2008 demonstrate that hepatocellular carcinoma (HCC) is the 5th most common cancer in men and the 8th most common cancer in women worldwide.[1] It is estimated that 8500 to 11,500 new cases of HCC occur annually in the United States.[2] Because methods for diagnosing and treating HCC have improved over the last few decades, the survival of patients with HCC has been prolonged. As a consequence, extrahepatic metastases are now observed more frequently. Furthermore, it has been shown that a significant number of patients with HCC have extrahepatic metastases at initial presentation.[7] The detection of extrahepatic metastases is crucial in determining appropriate therapy for HCC; those with disease limited to the liver will be considered for curative surgical treatment, while those with extrahepatic disease will offered palliation. Early and accurate detection of extrahepatic metastases is therefore imperative to avoid unnecessary surgical intervention.

Imaging used to detect extrahepatic metastases in the staging of HCC includes imaging of the abdomen and pelvis (usually with a triphasic CT scan or MRI), a CT of the chest, and a bone scan. Except in rare cases where the presenting symptom of HCC was bone metastases[6], clinicians rely on the bone scan alone to detect osseous metastases in patients with otherwise nonmetastatic disease. The bone metastasis is almost always an osteolytic lesion, sometimes with a hypervascular expansile soft tissue mass, most commonly occurring in bones with red marrow.[5] The most frequent osseous metastatic sites are vertebrae, rib, and long bone, with more than half of the patients having multiple bone metastases.[3] Osseous metastases in HCC were shown to be a significant source of morbidity, causing pathologic fractures,[5] complete spinal cord injury,[3,6] and severe pain.[3]

Rationale for the Proposed Trial:

The prevalence of bone metastases in HCC has been poorly described in the literature, with published estimates ranging from 2% to 38.5%.[3] Although the incidence of osseous metastases in HCC may be increasing due to prolonged survival[4], the observed prevalence in very recent studies continues to vary greatly; for example, published estimates were as low as 9.8% in a 2003 prevalence study[7] and as high as 38.5% in a 2005 prevalence study[3]. Part of the problem in ascertaining the prevalence of osseous metastases in HCC may be that bone scans do not always detect osteolytic lesions. Bone scans involve identifying intensity of bone response, or osteoblastic activity. An incredibly destructive lesion will not show up on a bone scan because it is so lytic that

there is no osteoblastic response.[8] As mentioned above, the bone metastases in HCC is almost always osteolytic. Many of the patients in the aforementioned studies underwent other imaging such as CT, MRI, or plain radiography at their physician's discretion; these studies may have revealed the bone metastases. We suspect that bone scan may be underestimating the prevalence of osseous metastases given the osteolytic nature of most bone metastases in HCC. Because treatment decisions, survival, and prognosis are affected by extrahepatic spread, false negatives on bone scan could have dire consequences and result in unnecessary surgery, inappropriate listing for OLT, or increased morbidity due to untreated bone metastases. We propose that if bone scans are missing at least 5% of osseous metastases in HCC, an additional or alternative imaging strategy should be used to screen for osseous metastases in HCC.

Study Objective:

Primary objective: To determine whether the prevalence of bone metastases in HCC that are not detected by bone scan exceeds 5%.

Secondary objective: To describe what other imaging studies detected bone metastases in HCC that were missed by bone scan.

B & C. Study Design, Study Procedure, and Statistical Analysis

Study Design, Procedure, and Operational Definitions:

The study will be a retrospective review of 462 HCC patients seen at the NYPH-Columbia Center for Liver Disease and Transplantation between 1/1/02 and 12/31/06. We will review the electronic and paper charts of these patients and determine which patients had osseous metastases that were not detected by routine bone scan. The chart review will include review of imaging reports including plain radiography, MRI, and CT scan, as well as review of pathology reports. The following 3 columns will be entered into our preexisting research database where every individual patient has a row: the presence or absence of bone metastases noted on any imaging (yes/no), the result of the bone scan (positive/negative), and a third column indicating the presence or absence of another imaging study diagnosing osseous metastases (yes/no). The percentage of HCC patients with bone metastases that were missed by bone scan (defined as those with "negative" in second column and "yes" in the first and third columns) will be divided by the total number of HCC patients (n=462). This percentage will be used in the statistical analysis described below. A fourth column with the type of study (Xray, CT, MRI, etc) will be added to the database for the purposes of the secondary objective.

Statistical Analysis:

Statistical analysis will be performed using a one-sample chi-square test. The sample size of 462 subjects provides a statistical power of 90% to detect a 5% prevalence of missed bone metastases in HCC (alpha = 0.05). We can detect $p<0.021$ and $p>0.089$; in other words, if the study prevalence of missed bone metastases exceeds 8.9%, we will

have demonstrated that the prevalence of missed bone metastases in this HCC population exceeded 5% (and that the difference was not due to chance).

Sample Size:

The sample size of 462 patients was predetermined according to the size of our database of HCC patients. This sample size was used in the power analysis described above.

D. Study Drugs

There are no drugs required for this study.

E. Medical Devices

There are no medical devices required for this study.

F. Study Questionnaires

There are no questionnaires required for this study.

G. Study Subjects

Subject Selection:

The database of 462 patients that will be used in this study consists of HCC patients who were evaluated at the NYPH-Columbia Center for Liver Disease and Transplantation between 1/1/02 and 12/31/06.

Inclusion Criteria:

- Confirmed diagnosis of hepatocellular carcinoma
- Bone scan report available (in paper or electronic chart)

Exclusion Criteria:

All 462 patients in our preexisting database were diagnosed with hepatocellular carcinoma. However, any patient who does not have a bone scan report available will be excluded from the study.

H. Recruitment of Subjects

No further recruitment is necessary as the study will be conducted with the 462 subjects currently in the database.

I. Confidentiality of Study Data

Each study subject has been assigned a unique numeric ID for the purposes of confidentiality.

J. Potential Conflict of Interest

There are no potential conflicts of interest for the investigators or CPMC.

K. Location of the Study

The retrospective review will be performed at CPMC.

L. Potential Risks

There are no potential risks or discomforts for the subjects of this study.

M. Potential Benefits

There are no potential benefits for the subjects of this study, but there may be benefit to future HCC patients as described above.

N. Alternative Therapies

Not applicable.

O. Compensation to Subjects

The study subjects will not receive any compensation.

P. Costs to Subjects

The subjects will not incur any costs as a result of participating in this study.

Q. Minors as Research Subjects

This study does not involve the participation of minors.

R. Radiation or Radioactive Substances

This study does not involve radiation or radioactive substances.

References

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