Radioisotope-Guided Surgical Biopsy of Suspected Osseous Metastases

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The gamma probe shows promise as an effective technique to locate bone metastases.

Background: Radioisotope bone scanning is frequently used to stage patients with suspected or proven malignancies. Since false-positive results are common, especially in the ribs, open biopsy is often necessary. The conventional approach of visual inspection of the bone scan image to guide the surgeon usually requires excision of a large area of one or two ribs to assure that the biopsy was performed on the correct rib. A more precise method to guide the biopsy is desirable.

Methods: One technique to localize the suspicious area of bone intraoperatively for accurate biopsy involves percutaneous injection of the bone abnormality with a radioisotope followed by injection of methylene blue into the periosteum and subsequent open surgical biopsy. A more recent technique uses a handheld gamma probe in a sterile sleeve in the operating room to locate the bone "hot spot" directly in the wound to guide the biopsy.

Results: Both techniques are effective in pinpointing the bone scan abnormality, but use of the gamma probe is less cumbersome and consumes less time and fewer resources. In one series of 10 patients undergoing gamma probe-guided biopsies of 13 rib and 1 sternal bone scan lesions, this technique showed a sensitivity of 100% in locating the area of abnormal radioisotope uptake. All biopsies yielded an abnormal diagnosis to account for the bone scan abnormality, but only 4 of 14 (29%) demonstrated metastatic tumor.

Conclusions: Techniques described for radioisotope-guided localization of areas of increased tracer uptake in asymptomatic suspected bone metastases are accurate, sensitive guides to the open biopsy of these bony abnormalities. Due to the high false-positive rates in these asymptomatic but suspicious bone scan abnormalities, a diagnosis should be histologically confirmed.

Introduction

Accurate staging of malignancies is essential to guide the clinician in selecting the most appropriate therapy for that patient. The presence of metastatic disease from solid tumors in bone is considered as distant metastases and classifies the tumor as advanced stage IV. Since stage and survival are strongly correlated, precise staging is critical to avoid over- or under-treatment. Special importance is attached to staging with regard to surgery since the presence of bone metastasis effectively eliminates resection as a curative option. In addition, the documented presence of bone metastases generally mandates a chemotherapy-only approach in most malignancies, with radiotherapy being reserved only for treatment of symptomatic lesions. However, suspected bony metastases must be histologically confirmed because of the high frequency of false-positive results, particularly when discovered only on radioisotope bone scans.

Bone Metastases

Although primary bone malignancies are rare, metastatic disease to the bone is common, particularly in patients over 45 years of age. The most common sites of metastases are sites of persistent red marrow, especially the axial skeleton (spine, pelvis, ribs, and skull). In a study of 2,001 patients with bone metastases, the most common eight sites of metastatic disease in descending frequency are the vertebrae, pelvis and sacrum, femur, ribs, skull, humerus, scapula, and sternum.

Carcinomas of the breast and prostate account for most of the bone metastases, with cancers of the kidney, thyroid, and lung following in descending frequency. In all cases, bone metastases will occur in 67% of breast cancer patients, in 50% of prostate cancer cases, in 25% of lung and kidney cancer patients, and in less than 10% of cases with all other malignancies. Cancers of the gastrointestinal and genital tracts and sarcomas rarely metastasize to bone.

Metastases to bone are often symptomatic, presenting with new onset bone pain over the metastatic site and swelling. An occasional patient presents with a pathologic fracture. Most metastases are destructive and cause osteolytic changes, with an occasional case demonstrating increased density that is characteristic of an osteoblastic lesion. An elevated serum alkaline phosphatase level may be seen in some patients with bone metastases, but this enzyme may be elevated in a variety of conditions such as hyperparathyroidism, osteomalacia, osteitis deformans, osteogenic sarcoma, rickets, healing fractures, pregnancy, normal growth, and various hepatobiliary conditions.

Some patients have clinically silent bone metastases, and the presence of bony spread is suspected only from a screening radioisotope bone scan performed during a staging workup. In some malignancies, bone scanning is routine in the initial workup, and asymptomatic abnormalities may be found. In other cancers such as non-small-cell lung cancer, bone scanning is recommended only if there is some clinical indicator of bone disease such as bone pain, elevated level of serum alkaline phosphatase, or elevated serum calcium level. Bone metastases are rarely found in non-small-cell lung cancer patients who are entirely free of clinical indicators.

Most bone metastases are destructive and cause osteolytic changes. Therefore, the typical plain radiograph appearance is decreased density at the site of the metastatic lesion. In some patients, an area of increased density may be seen, indicating an osteoblastic metastatic site and swelling. An occasional patient presents with a pathologic fracture.
Radioisotope Bone Scan

The radioisotope bone scan is a much more sensitive indicator of metastatic disease. The scan may be positive when as little as 5% to 15% of trabecular bone is destroyed, often demonstrating the metastatic tumor much earlier than plain radiographs. In fact, only 3% of patients with radiographically proven bone metastases will have no evidence of increased uptake ("hot spot") on bone scan.

Radioisotope Bone Scan

The mechanism leading to an increased uptake of the radiopharmaceutical used in a bone scan, most commonly $^{99m}$technetium-labeled diphosphonate, is incompletely understood and involves multiple steps. Generally, localization of the radioisotope will occur in areas of increased blood flow and/or areas of increased bone formation. Most tumors cause both osteoclastic bone resorption, but there is new bone formation as well. The technetium-diphosphonate complex appears to bind onto the surface of the hydroxyapatite crystal during new bone growth and not to the tumor itself.

A localized area of decreased uptake of the radioisotope (photopenic lesion) may be rarely seen with decreased blood flow or with reduced or absent reactive new bone formation. In rapidly growing tumors, the bone matrix may be resorbed before mineralization occurs such that there is no increased uptake of isotope in an area of metastatic disease. These instances are infrequent, and most bone scan lesions appear as areas of increased uptake.

Although the bone scan is sensitive in demonstrating metastatic bone involvement, this test is not especially specific. A number of normal or benign conditions may also result in a hot spot on bone scan, which can lead to a false-positive result in the staging of the primary cancer. Some of these benign conditions that cause local increased uptake of tracer on bone scan are listed in the Table. Considering the nonspecific nature of a positive bone scan, particularly when the plain radiographs are normal, histologic confirmation of the bony metastasis is mandatory prior to implementing treatment.

Bone Localization Techniques

For the symptomatic patients, the presence of bone metastases will be readily apparent and proving their existence will be relatively easy. In the patient with bone pain or local swelling, plain radiographs are usually obtained first, and the bone scan is obtained only if the radiograph results are negative or equivocal. In addition, a bone scan may be obtained in a patient with known bone metastases on plain radiographs to look for asymptomatic metastases in weight-bearing bones such as the femur to locate and treat prior to a pathologic fracture. Computed tomography (CT) or especially magnetic resonance imaging (MRI) with gadolinium contrast appears to be a sensitive technique, particularly in the spine or pelvis, to document bone metastases when the bone scan is positive and the plain radiographs are negative. MRI of the spine also has special use in patients with neurologic abnormalities or vertebral body collapse to visualize a tumor mass extending from or around the vertebral body that may impinge on the spinal cord.

Histologic confirmation of the metastasis often can be obtained in symptomatic patients who have imaging abnormalities by using CT scan-guided percutaneous biopsy of the vertebral body in question or by a needle biopsy of a lytic lesion or soft-tissue mass in other bones. However, the possibility of a sampling error exists when the needle biopsy result returns as negative or nondiagnostic. When treatment and/or a diagnosis depends on a positive malignant histology, an open biopsy is necessary. In the setting of a locally symptomatic probable metastasis with a corresponding plain radiograph abnormality, intraoperative localization of the bony abnormality is generally not difficult, particularly when the target bone for biopsy is a rib.

Among radiologists, it is commonly believed that a positive bone scan abnormality with negative plain radiographs in an asymptomatic patient with known cancer indicates a probable bone metastasis. However, there is a documented high incidence of false-positive bone scan results seen in this setting, ranging from 47% to 71% in various studies. Therefore, a confirmatory open bone biopsy is mandatory, but increased technical difficulties are encountered in locating the lesion in these patients when only the bone scan serves as the guide.

Conventional Open Bone Biopsy

The presence of a positive bone scan in an asymptomatic patient with normal plain radiographs presents a difficult clinical problem to the surgeon planning a bone biopsy. Ribs, when positive on bone scan, are probably the easiest bones, technically, on which to perform a biopsy, but localization of the exact site of the bone scan hot spot is generally difficult. Depending on the quality and definition of the bone scan image, establishing exactly which rib is "hot" can be challenging. Likewise, localizing the precise anterior-posterior location of the rib abnormality based on the scan alone also can be difficult when the plain bone radiographs are normal. As a result, the surgeon is often forced to remove a large, grossly normal-appearing area of one or even two ribs to be sure that the bone scan abnormality is contained in the specimen.

In the muscular or obese patient, it may be difficult to measure and actually count at surgery (within one or two ribs) which is the target rib for removal, especially in the lower ribs posteriorly. Consequently, most patients require one or often many intraoperative radiographs (usually cross-table lateral radiographs, which are technically difficult to complete on the first try) with a radiopaque marker adherent to the rib in the wound to verify that the biopsy will be performed on the correct-numbered rib. Since a frozen section analysis on bone with a thick cortex, such as a rib, is not possible intraoperatively and the final histologic diagnosis awaits lengthy decalcification and processing, seven to 10 days may pass before the surgeon can determine if the biopsy was performed on the correct area. If the final diagnosis is "normal bone," then there is even more uncertainty about the accuracy of the biopsy site.

Methylene Blue "Tattooing" of the Target Rib

Due to this difficult and often frustrating clinical problem of precisely locating the rib abnormality by the operating surgeon, Little and associates developed a technique published in 1983 that involves preoperative marking of the target rib. With this technique, the radioactive tracer ($^{99m}$technetium diprophosphonate) is injected intravenously in the patient six to 12 hours before the patient is brought to the nuclear medicine department. The patient is positioned below the gamma camera to image the appropriate area. An external $^{99m}$technetium point source is placed over the scan image abnormality and is imaged on the scintiview screen. If the external point source corresponds to the abnormal scan area, the skin is marked with an indelible pen. The area is anesthetized with lidocaine, and a needle is inserted to the rib in that area, followed by injection of a small amount of the tracer to mark the hot spot more deeply. With the needle still left in place, the patient is repositioned several times under the gamma camera to ensure that the percutaneously injected tracer is superimposed over the bone scan abnormality. Several injections may be needed until the correct area is imaged. Methylene blue is then injected into the same needle to stain the underlying periosteum and soft tissue up to the skin. The patient is taken promptly to the operating room for an open biopsy of the methylene blue-stained rib so that the stain does not diffuse away.
In the experience of Little and associates, this technique was used successfully in 15 patients with known cancer (12 lung cancer, one breast carcinoma, and two gastrointestinal carcinomas) to perform biopsies on 13 ribs, one skull, and one scapula. An abnormal diagnosis was found in all patients, but only eight of 15 (53%) had metastatic cancer, and the others (bone scan false-positive rate = 47%) had a variety of benign diagnoses (two old rib fractures, two hypercellular marrow, one Paget’s disease, one granuloma, and one osteoporosis). Although this tattooing technique appears to work in experienced hands, the operative episode is prolonged and complicated. The nuclear medicine department schedule must be carefully coordinated with the availability of the operating room in order to immediately accept the patient for surgery before the blue dye spreads to other ribs. Due to the considerable experience and operative coordination needed by the nuclear medicine department, the surgeon performing only an occasional bone biopsy guided by this technique might find it difficult to duplicate the excellent results of Little and associates.

**Intraoperative Radioscintigraphic Localization**

The most direct method to localize the bone scan hot spot for open biopsy in the asymptomatic patient became possible with the development of a hand-held, high-resolution gamma camera, which is capable of providing real-time gamma counting from the intravenously injected tracer. This device has been successfully used for intraoperative radiolymphoscintigraphy for sentinel lymph node identification in melanoma and breast cancer patients. It has been adapted at our center for intraoperative localization of areas of increased uptake of tracer in ribs and the sternum for open biopsy in 10 patients suspected of having bone metastases.

Six to twelve hours prior to surgery, each patient received an intravenous injection of 28 mCi technetium-99m oxidronate, the standard dosage for a radioisotope bone scan. The six-hour interval from injection until surgery provided the best intraoperative results. After general anesthesia was administered and the patient was prepared and draped, the hand-held gamma probe in a sterile plastic sleeve was used to localize the area of greatest tracer activity (measured in counts per second) on the skin of the chest wall. A 3- to 4-cm incision was made over this area, and the targeted rib or sternum was exposed. The probe in the sterile sleeve was then used to localize precisely in the surgical wound the area of increased tracer activity in comparison to background counts (Fig 1). In the initial few patients, an intraoperative cross-table lateral radiograph was obtained with a radiopaque marker on the rib in the wound to verify that the biopsy was performed on the correct rib. As the experience with the gamma probe grew, these time-consuming and costly radiographs were eliminated. A 3-cm portion of the targeted rib or the outer table of the sternum was removed subperiosteally and was decalcified and histologically studied. Patients were discharged after obtaining a chest radiograph in the recovery room to verify the absence of a pneumothorax and to confirm that the biopsy was performed on the proper rib.

This series of 10 patients consisted of a variety of known or suspected underlying primary cancers (five had carcinoma of the lung, two had carcinoma of the prostate, and one each had carcinoma of the breast, lymphoma, and melanoma). Biopsies of 14 bones (13 ribs and one sternum) were all positive for pathologic processes, although metastatic cancer was diagnosed in only four of the 14 (29%) patients. The other 10 bone biopsies (71% bone scan false-positive rate for diagnosing a malignancy) showed various benign processes: localized hypercellular marrow (one rib), medullary fibrosis/Paget’s disease of the bone (two ribs), localized fibrosis/granulatation tissue (one rib), enchondroma (three ribs), and chondroma (two ribs and one sternum).

Using this technique, localization and detection of the bone scan hot spot were easily accomplished with the gamma probe. A typical radioisotope bone scan from this population of patients is shown in Fig 2. Intraoperatively, the rib or sternum appeared grossly normal to the surgeon, even after resection of the abnormal area. When using the gamma probe to count directly on the rib in the wound, the mean ratio of hot spot activity measured in counts per second in the targeted rib to background counts (count ratio) on other ribs or elsewhere on the same rib was 1.63 ± 0.06 (range = 1.35–2.05; median = 1.59), and the difference was easily discernible intraoperatively. That is, the number of counts measured over the hot spot was a mean 63% higher than background counts.

Interestingly, six of the 14 biopsies (43%) in this series demonstrated the benign cartilaginous tumor, a chondroma. Chondromas are relatively common, representing 13.4% of benign tumors in bone, although the real incidence is unknown since they are generally asymptomatic. Chondromas usually occur sporadically, most commonly in the small bones of the hands and feet, although they may occur in thin bones such as the ribs or scapulae and rarely in the sternum. Unless they become very large, chondromas are asymptomatic and generally are either not seen on plain radiographs or are seen as a subtle, localized area of central rarefaction in the bone. Most chondromas are found incidentally as a hot spot on a radioisotope bone scan performed during the metastatic workup of a patient with a known or suspected malignancy. A biopsy often follows, and the diagnosis of chondroma is made. Fig 2 shows the radioisotope bone scan from one patient from this series who had biopsy-proven chondromas.

No mortality or morbidity was specifically associated with this intraoperative radioscintigraphy technique. With the open rib biopsy, inadvertent entry into the pleural cavity in two patients during rib resection required an intravenous injection, followed by a short convalescence and hospitalization. In the remaining 10 patients, the operative episode was uncomplicated. The nuclear medicine department schedule must be carefully coordinated with the availability of the operating room in order to immediately accept the patient for surgery before the blue dye spreads to other ribs. Due to the considerable experience and operative coordination needed by the nuclear medicine department, the surgeon performing only an occasional bone biopsy guided by this technique might find it difficult to duplicate the excellent results of Little and associates.

**Conclusions**

The presence of an asymptomatic area of increased uptake of tracer in a bone scan of a patient with a malignancy does not necessarily indicate the presence of metastatic tumor in the bone. Histologic confirmation of metastatic disease is necessary since the incidence of false-positive scans is high, ranging from 46% to 71% in this setting.

The technique of methylene blue tattooing of the rib for biopsy appears to be effective but is much more time consuming than the more recently described intraoperative gamma probe method. This latter technique requires only an intravenous injection of radioisotope four to 12 hours preoperatively, followed by a short operative procedure to precisely pinpoint the target hot spot. The extreme accuracy of this technique obviates the need for time-consuming intraoperative localizing radiographs.

Use of the gamma probe to guide the biopsy of ribs is quicker, more direct, less cumbersome (especially in obese patients), and likely to provide more cost-effective bone biopsies. Although the technique was used in this study only to localize rib or sternal abnormalities for biopsy, this same gamma probe method could no doubt be adapted by orthopedic surgeons to localize bone lesions for biopsy in other areas (e.g., long bones of the appendicular skeleton). This method has no side effects and is 100% sensitive in finding bony abnormalities. The hand-held intraoperative gamma counter is gaining widespread application for multiple uses in surgical practice; for example, the hand-held gamma probe can be used to site the biopsy of ribs and sternal lesions, as well as for sentinel lymph node identification in melanoma and breast cancer patients.
oncology such as nodal mapping in breast cancer and melanoma and is becoming a common fixture in most major hospitals. The gamma probe appears to be the most accurate and cost-effective technique to localize bone scan abnormalities and should be considered for use by the surgeon in guiding the open biopsy of suspected asymptomatic osseous chest metastases.

References