PAPER 12

Re-evaluating the Workup of an Aggressive Bone Lesion of Unknown Etiology in Adults: A Systematic Analysis

Harrison Miner, MD[a], Jeremy White, MD[a]

a. Department of Orthopedic Surgery, The University of Oklahoma College of Medicine, 800 Stanton L Young Blvd, AAT-3400, Oklahoma City, OK 73104

Corresponding Author:

Harrison Miner, MD
Department of Orthopedic Surgery
The University of Oklahoma
College of Medicine
800 Stanton L Young Blvd, AAT-3400
Oklahoma City, OK
USA 73104
Phone: 254-495-8812
Email: Harrison-miner@ouhsc.edu

Author email contacts:

JW: jeremy-white@ouhsc.edu

Running title: PET/CT for Work Up of Bone Lesion of Unknown Etiology

This study was performed at The University of Oklahoma College of Medicine

This study was determined exempt from board review by the Institutional Review Board at The University of Oklahoma

The authors (HM, JW) certify that they, or any members of their immediate families, have no commercial associations (such as consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

The author (HM) is a current resident at The University of Oklahoma and contributed to the study by constructing the protocol, preforming the analysis, writing the abstract, and writing the manuscript.

Background The standard of care for the workup of adults presenting with an aggressive bone lesion of unknown etiology (BLUE) has remained consistent over the last 30 years. In 1993, Rougraff et al. demonstrated the good diagnostic capability of an algorithm including Computed Tomography of the Chest, Abdomen, and Pelvis (CT CAP), full body bone scintigraphy (bone scan), and labs.[1] However, since this time, the preferred staging for many of the cancers that results in an aggressive BLUE have been modified to include a Positron Emission Tomography/Computed Tomography (PET/CT). While there has been some evidence for the benefits of PET/CT in the initial work up of a BLUE, there has been hesitation in its adoption due to concerns of cost and the lack of clear diagnostic superiority over the standard of care.[2-4] Yet, often patients will require a PET/CT as a part of staging work up, once the primary cancer has been identified, leading to duplication of imaging and delay in care. Additionally, traditional PET/CT protocols include a low radiation, nondiagnostic full body CT scan. Recently, PET/CT protocols have been developed which combine a full body, diagnostic quality CT scan with PET imaging to improve the quality and specificity of the imaging. These protocols may expand the indications and capabilities of PET/CT in diagnosis and staging of various cancer types by avoiding the need for a diagnostic CT after the PET/CT has been completed.

Questions/Purposes (1) What are the most common cancer diagnoses associated with presentation with an aggressive BLUE in an adult? (2) Is the utilization of PET/CT as the initial imaging modality for the workup an aggressive BLUE cost effective?

Methods A systematic review was preformed to identify studies that list the diagnosis of adult patients who present with an aggressive BLUE. Studies that did not include patients with diagnoses of multiple myeloma and lymphoma were excluded. The data from the qualifying studies were pooled and the heterogenicity was analyzed via descriptive statistics. Next, the National Comprehensive Cancer Network (NCCN) guidelines were reviewed for each cancer type identified as presenting with an aggressive BLUE. The recommended staging imaging modalities were recorded for each cancer type. A mathematical model was then constructed using the distribution of diagnoses determined by systematic review, the staging work up recommended by NCCN, and the cost of the traditional work up (CT CAP and Bone Scan) and PET/CT based on the mean national 2022 Medicare Physician Fee Schedule. If the preferred initial staging study was not performed initially, then the new study was added to the total cost.

Results The distribution of primary cancer diagnoses for patients presenting with an aggressive BLUE were fairly consistent among the analyzed studies. Lung cancer was the most common (27% [CI 23-31]), followed by myeloma (15% [CI 12-18]), prostate cancer (11% [CI 8.3-14]), unknown (10% [CI 7.6-13]), and lymphoma (8.3% [CI 5.9-11]). Utilizing a traditional PET/CT protocol as the initial imaging modality yields a reduced cost of on average $176.27 per patient in our model. When utilizing a protocol that combines a Diagnostic quality CT with a PET scan, savings improve to $334.76 per patient.

Conclusion The presence of an aggressive BLUE in an adult often represents the initial manifestation of a cancer that is appropriately staged with a PET/CT. Therefore, its use as the initial imaging modality may be more efficient and cost effective than the traditional workup of a CT CAP and bone scan. Additionally, the utilization of modern protocols which combine a diagnostic quality full body CT scan with PET imaging sequences may prove to be superior both diagnostically and monetarily. Further study, including a prospective trial, will be required to better elucidate the breakdown of diagnoses that are responsible for a new destructive bone lesions in adults and to compare the diagnostic quality and value of a PET/CT versus a CT CAP and bone scan in the evaluation of the adult with an aggressive bone lesion of undetermined etiology.

Level of Evidence: III

References

1.	Rougraff BT, Kneisl JS, Simon MA. Skeletal metastases of unknown origin. A prospective study of a diagnostic strategy. *J Bone Joint Surg Am*. Sep 1993;75(9):1276-81. doi:10.2106/00004623-199309000-00003

2.	Lawrenz JM, Gordon J, George J, et al. Does PET/CT Aid in Detecting Primary Carcinoma in Patients with Skeletal Metastases of Unknown Primary? *Clin Orthop Relat Res*. Nov 2020;478(11):2451-2457. doi:10.1097/CORR.0000000000001241

3.	Budak E, Yanarates A. Role of (18)F-FDG PET/CT in the detection of primary malignancy in patients with bone metastasis of unknown origin. *Rev Esp Med Nucl Imagen Mol (Engl Ed)*. Jan - Feb 2020;39(1):14-19. Papel de la PET/TC con (18)F-FDG en la deteccion del tumor primario en pacientes con metastasis oseas de origen desconocido. doi:10.1016/j.remn.2019.06.002

4.	Park SB, Park JM, Moon SH, et al. Role of 18F-FDG PET/CT in patients without known primary malignancy with skeletal lesions suspicious for cancer metastasis. *PLoS One*. 2018;13(5):e0196808. doi:10.1371/journal.pone.0196808

Figure 1.
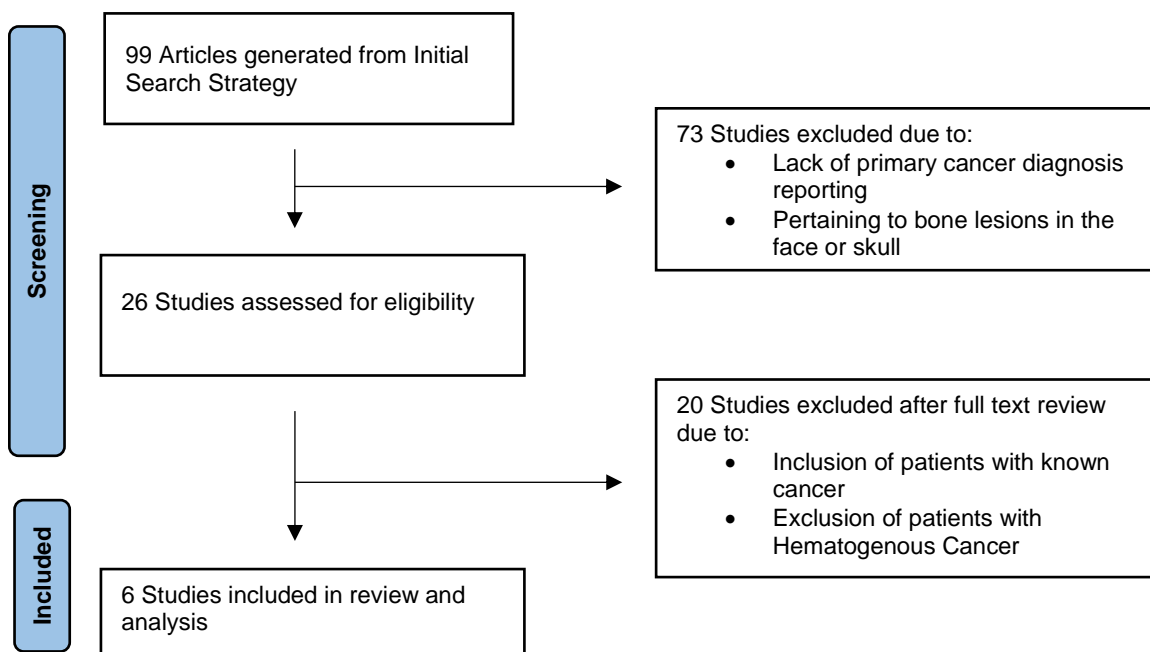
Table 2. Recommended Staging Work Up by Cancer Type

Primary Cancer	Percentage	95% Confidence Interval	Stage at Diagnosis	Recommended Imaging
Lung	27	(23-31)		
Small Cell			Stage IV	MRI Brain
Non-Small Cell			Stage IVA/B	PET/CT and MRI Brain
Multiple Myeloma	15	(12-18)	Stage I-III	PET/CT or Full Body CT
Prostate	11	(8.3-14)	Stage IVB	Bone Scan
Cancer of Unknown Primary	10	(7.6-13)	-	-
B-Cell Lymphoma	8.3	(5.9-11)	Stage IV	PET/CT or Contrast CT
Kidney	6.1	(4.0-8.2)	Stage IV	Abdominal CT
Hepatobiliary	5.1	(3.7-7.0)	Stage IVB	-
Breast	3.9	(2.3-5.6)	Stage IV	CT CAP and Bone Scan
Foregut	3.9	(1.7-6.3)	Stage IVB	PET/CT
Pancreas	2.8	(1.3-4.2)	Stage IV	Pancreas CT and CT CAP
Thyroid	2.4	(1.0-3.7)	Stage IVC	-
Colon	2.6	(1.2-3.9)	Stage IV A-C	CT CAP

Recommended Imaging is based of National Comprehensive Cancer Network guidelines