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

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The author (HM) is a current resident at The University of Oklahoma and contributed to the study by constructing the protocol, performing 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. 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. 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 performed 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 heterogeneity 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**


Figure 1.

99 Articles generated from Initial Search Strategy

73 Studies excluded due to:
- Lack of primary cancer diagnosis reporting
- Pertaining to bone lesions in the face or skull

26 Studies assessed for eligibility

20 Studies excluded after full text review due to:
- Inclusion of patients with known cancer
- Exclusion of patients with Hematogenous Cancer

6 Studies included in review and analysis
### Table 2. Recommended Staging Work Up by Cancer Type

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

*Recommended Imaging is based on National Comprehensive Cancer Network guidelines*