Assessing the Role of Imaging in Primary Breast Cancer Staging

By

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Date
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ABSTRACT

Background: In the United States, there is no well-established staging protocol for new breast cancer patients. With various imaging modalities available, we performed the following systematic review and original retrospective study to better characterize the utility of bone scan, liver ultrasound, chest radiograph, and computed tomography (CT) of the abdomen. For our systematic review, we determined the pooled detection rates of distant metastases using bone scan, liver ultrasound, and chest radiograph by clinical stage. In our study, we determined the utility of further imaging with abdominal CT when there is no detected disease beyond the ipsilateral axillary lymph nodes by CT of the chest.

Methods: As part of our systematic review, we searched PubMed and EMBASE databases for relevant articles using detection rate, defined as the number of patients with an abnormal test result divided by the total number of patients tested, as the primary outcome of interest for bone scan, liver ultrasound, and chest radiograph. Additionally, for our retrospective study, we reviewed medical charts for 440 patients and used cross tabulation bivariate analysis to characterize the relationship between detection of disease in the chest and disease in the abdomen.

Conclusion: Based on our systematic review, we believe that the routine use of bone scan, liver ultrasound, and chest radiograph in the staging evaluation of primary breast cancer patients is of little value in detecting metastatic disease in women with clinical stage I and stage II cancer due to very low detection rates. Furthermore, we determined that of patients with no detectable disease in the chest beyond the ipsilateral axillary lymph nodes according to chest CT, 99.7% of them will have no detectable disease in the abdomen based on CT.
Staging Evaluation with Bone Scan, Liver Ultrasound, and Chest Radiograph in Primary Breast Cancer Patients

By

Stuart-Allison M. Staley
ABSTRACT

Background: Routinely, radiological investigation with bone scan, chest radiograph, and liver ultrasound are employed as baseline staging tests. The aim of this review was to examine indications for this costly routine screening, and, thus, we posed the following question: Among women with newly diagnosed breast cancer who are otherwise asymptomatic, does evaluation with bone scanning, liver ultrasound, and chest radiograph help to determine the extent of metastatic disease?

Methods: We searched PubMed and EMBASE databases to find articles using detection rate, defined as the number of patients with an abnormal test result divided by the total number of patients tested, as the primary outcome of interest. In order to obtain overall estimates of detection rates in each test, the results from the studies were pooled and summed according to pathological stage.

Results: Eight articles out of 232 reviewed were included in the final analysis. The following pooled detection rates for bone scan were calculated according to stage: Stage I 7 of 544 (1.29%), Stage II 29 of 938 (3.09%), Stage I & II 36 of 1,482 (2.43%), and Stage III 39 of 312 (12.5%). For liver ultrasound: Stage I 1 of 213 (0.47%), Stage II 4 of 400 (1.00%), Stage I & II 5 of 613 (0.82%), and Stage III 6 of 143 (4.20%). And, for chest radiograph: Stage I 0 of 223, Stage II 2 of 473 (0.42%), Stage I & II 9 of 1,782 (0.51%), and Stage III 8 of 175 (4.57%).

Conclusion: The routine use of bone scan, liver ultrasound, and chest radiograph in the staging evaluation of primary breast cancer patients is of little value in detecting metastatic disease in women with clinical stage I and stage II cancer, and therefore, should not be performed.
INTRODUCTION

Staging is pivotal in the management of cancer and describes the extent and severity of the patient’s disease. By classifying a person’s stage, a more accurate treatment plan and estimate of the patient’s prognosis may be determined.\(^1\)\(^,\)\(^2\) Carcinoma of the breast commonly metastasizes to bone, lung, liver, and brain.\(^1\) To detect the presence of disease at these distant sites, many expensive imaging modalities with increasing sensitivity and specificity are utilized by providers; however, as the care of cancer patients becomes more complex, the need for cost containment is paramount to the health care system. In response, providers must find areas to eliminate expensive staging techniques, while also protecting patient safety and providing accurate staging and diagnosis of disease.

Routinely, radiological investigation with bone scan, chest radiograph, and liver ultrasound are employed as baseline staging tests and are commonly referred to as “conventional diagnostic procedures”.\(^3\)\(^,\)\(^4\) The aim of this review was to examine indications for this costly routine screening, and, thus, we posed the following question: Among women with newly diagnosed breast cancer who are otherwise asymptomatic, does evaluation with bone scanning, liver ultrasound, and chest radiograph help to determine the extent of metastatic disease?\(^5\)

METHODS

Search Design & Study Criteria

PubMed and EMBASE databases were searched without language restriction or limitations on publication date, using the terms “bone scan”, “bone neoplasms/radionuclide imaging”, “liver ultrasound”, “chest radiograph”, “chest x-ray”, “diagnosis metastatic”, “detection metastatic”, “primary breast cancer”, and “primary breast neoplasm” as keywords.
Specifically, in EMBASE, the term “bone scintiscanning” was added to the search. Bibliographies from relevant articles were also reviewed. Only retrospective case series were included. To account for the rapid progression of the sensitivity and specificity of imaging modalities and in order to provide more accurate results from current technology, articles were reviewed if published after 1990. Furthermore, studies unavailable in English were excluded from the study.

Abstracts of relevant articles were reviewed if they reported number of women with newly diagnosed breast cancer who had disease detected by bone scan, liver ultrasound, or chest radiograph. Studies were included only if they reported rates of positive tests by patient’s pathological stage by the TNM staging system. These tests could be performed prior to or after surgical intervention.

**Study Evaluation**

A single author evaluated the articles selected for full review. The pertinent study data was extracted and organized into Tables 1 and 2, including setting, study method, total population, outcome measure, and total pooled results by method. The study’s quality was assessed using a grading criteria consisting of 4 categories: (1) reporting of all disease stages, (2) applicability to population of interest, (3) sufficient protocol detail, and (4) sufficient reporting of results with confidence limits. Each criterion was weighted equally and assigned a grade of good, fair, or poor (good = 2, fair = 1, poor = 0). These categorical scores were then averaged to give a final quality score that is presented in Table 2 (good > 1.5, fair 1.0 – 1.49, poor < 1.0).
Data Synthesis

The primary outcome of interest was the detection rate, defined as the number of patients with an abnormal test result divided by the total number of patients tested. In order to obtain overall estimates of detection rates in each test, the results from the studies were pooled and summed according to pathological stage.\(^5\)

RESULTS

As seen in Figure 1, results from PubMed and EMBASE searches yielded a total of 232 articles, without duplicates. These 232 articles were screened on the basis of title and abstract relevance, which provided 6 articles for full study review. Of the 226 articles excluded from the review, 207 articles did not measure detection rate as their outcome, 3 articles were not provided in English, and 15 articles were published prior to 1990.

The bibliographies of the 6 articles were reviewed for relevant titles, which yielded 5 additional articles. After review of the full manuscripts, 8 articles were included for the final analysis. Three articles were excluded. Two studies did not provide the detection rate by pathological stage,\(^6,7\) and one study did not report detection rate as the outcome measure.\(^8\)

Of the studies present in the final analysis, four studies analyzed only bone scanning; one study analyzed only chest radiography; three studies reviewed all three imaging modalities.

Bone Scanning

As seen in Table Three, seven studies reported the detection rate of bone metastasis using routine bone scan. The calculated rate was reported by stage (Stage I, Stage II, Stage I & II, Stage III) for each study. The pooled rates for all studies are provided by stage as well. For patients with Stage I disease, only 1.29% (7/544) were found to have metastatic or possible
metastatic disease to the bone as detected by bone scintigraphy. Similarly, only 3.09% (29/938) of patients with Stage II tumors had detectable or possible disease spread to bone as detected by bone scan. A pooled detection rate of only 2.43% (36/1,482) was determined for Stage I and II cancers. Patients with Stage III tumors had a larger number of detected bone metastasis at 12.50% (39/312). In total, across all three stages, bone scan detected disease spread in 4.18% (75/1,794) of new breast cancer patients.

Liver Ultrasound

As seen in Table Four, three studies reported the detection rate of liver metastasis using routine liver ultrasound. The calculated rate was reported by stage (Stage I, Stage II, Stage I & II, Stage III) for each study. The pooled rates for all studies are provided by stage as well. For patients with Stage I disease, only 0.47% (1/213) were found to have metastatic or possible metastatic disease to the liver as detected by ultrasound. Similarly, only 1.00% (4/400) of patients with Stage II tumors had detectable or possible disease spread to the liver as detected by ultrasound. A pooled detection rate of only 0.82% (5/613) was determined for Stage I and II cancers. Patients with Stage III tumors had only 4.20% (6/143) of patients with detected liver metastasis. In total, across all three stages, liver ultrasound detected disease spread in 1.34% (11/822) of new breast cancer patients.

Chest Radiograph

As seen in Table Five, four studies reported the detection rate of pulmonary metastasis using routine chest X-ray. The calculated rate was reported by stage (Stage I, Stage II, Stage I & II, Stage III) for each study. The pooled rates for all studies are provided by stage as well. For patients with Stage I disease, none of the study patients were found to have metastatic or possible metastatic disease to the lung as detected by radiograph. Similarly, only 0.42% (2/473) of
patients with Stage II tumors had detectable or possible disease spread to the lung as detected by chest X-ray. A pooled detection rate of only 0.51% (9/1,782) was determined for Stage I and II cancers. Patients with Stage III tumors had a higher percentage of patients with potential lung metastasis at 4.57% (8/175). In total, across all three stages, a routine chest radiograph detected possible disease spread to the lung in 0.87% (17/1,957) of new breast cancer patients.

CONCLUSION

Many previous studies have evaluated the use of CDPs (bone scanning, liver ultrasound, and chest radiograph) in primary breast cancer staging. With all methods, the detections rates increased with tumor size; however, the overall detection rates remain low for all three modalities, particularly in asymptomatic patients, which questions the utility of these imaging exams. Moreover, these techniques do not include many of the other common sites of metastasis. Many studies have recommended limited use of CDPs, particularly in patients with smaller tumor sizes.5, 6, 8, 13, 15

Future Research

The strength of this study is mainly a result of the number of patients studied – 1,794 for bone scan, 822 for liver ultrasound, and 1,957 for chest radiograph – and the consistently low detection rates seen for each method; however, further research to determine the false negative and false positive rates are needed to fully ascertain the usefulness of these methods as baseline staging exams. Moreover, the differences in rates of detection in patients who are clinically symptomatic versus asymptomatic would be helpful in determining if particular subgroups of cancer patients would benefit from these types of screening techniques.
**Recommendations**

Based on this data, the detection rates in patients with Stage I & Stage II tumors are incredibly low, with 0.50% to 3.00% detection rates among the three methods. With such a low number, we question if there is significant utility in performing any CDP on patients with small tumors, T1 and T2, who are clinically asymptomatic. Further research can more clearly answer this question, but the consensus of this research group is that patients with clinically early cancers do not benefit from bone scanning, chest radiograph, or liver ultrasound. It is our recommendation that asymptomatic patients proceed with only a screening chest CT scan. Further evaluation with abdominal and pelvic CT scans should only be performed in the presence of disease spread beyond the axillary lymph nodes or if the patients presents with specific symptomatology concerning for metastatic disease in these regions.\(^5\)
REFERENCES


TABLES & FIGURES

Figure One: Literature Search Flow Diagram

Literature Search:
Databases: PubMed & EMBASE
Limitations: None

Search Results: (n = 232)
PubMed: 223
EMBASE: 9
Duplicates: 0

Articles screened on basis of title and abstract (n = 6)

Articles provided from screened bibliographies (n = 5)

Included: 11

Excluded: (n = 226)
Different outcome measure: 208
Articles not provided in English: 3
Articles published before 1990: 15

Manuscript review and application of inclusion criteria

Included: 8

Excluded: (n = 3)
Did not meet inclusion criteria:
Gerber, et. al. (2003)6
Hadley, et. al. (1998)8
Müller, et. al. (2008)7

Bone Scan:
Ahmed, et. al. (1990)9
Brar, et. al. (1991)10
Glynne-Jones, et. al. (1991)11
Kennedy, et. al. (1991)12
Yeh, et. al. (1995)13
Barry, et. al. (1999)14
Schneider, et. al. (2002)16

Liver U/S:
Glynne-Jones, et. al. (1991)11
Barry, et. al. (1999)14
Schneider, et. al. (2002)16

CXR:
Glynne-Jones, et. al. (1991)11
Barry, et. al. (1999)14
Chen, et. al. (2000)15
Schneider, et. al. (2002)16
<table>
<thead>
<tr>
<th>Source</th>
<th>Method*</th>
<th>Patients, $n$</th>
<th>Bone Scan</th>
<th>Liver Ultrasound</th>
<th>Chest Radiograph</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 Ahmed, et. al. (United Kingdom, 1990)</td>
<td>RCR</td>
<td>389</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 Brar, et.al. (USA, 1991)</td>
<td>RCR</td>
<td>131</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 Glynne-Jones, et. al. (United Kingdom, 1991)</td>
<td>RCR</td>
<td>389</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>12 Kennedy, et. al. (United Kingdom, 1991)</td>
<td>RCR</td>
<td>84</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Yeh, et. al. (USA 1995)</td>
<td>RCR</td>
<td>316</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 Barry, et. al. (Ireland, 1999)</td>
<td>RCR</td>
<td>82</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>15 Chen, et. al. (USA, 2000)</td>
<td>RCR</td>
<td>1,085</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 Schneider, et. al. (Switzerland , 2002)</td>
<td>RCR</td>
<td>485</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

*RCR = Retrospective Chart Review
<table>
<thead>
<tr>
<th>Study</th>
<th>Population*</th>
<th>Method</th>
<th>Outcome Measure</th>
<th>Results (%, n)</th>
<th>Quality Rating$</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 Ahmed, et. al</td>
<td>Asymp. new BRCA pts.</td>
<td>RCR</td>
<td>Detection Rate</td>
<td>Bone Scan: 18.77 (24/389)</td>
<td>1.75</td>
</tr>
<tr>
<td>10 Brar, et.al.</td>
<td>Asymp. new BRCA pts.</td>
<td>RCR</td>
<td>Detection Rate</td>
<td>Bone Scan: 3.10 (4/131)</td>
<td>1.25</td>
</tr>
<tr>
<td>12 Kennedy, et. al</td>
<td>Asymp. new BRCA pts.</td>
<td>RCR</td>
<td>Detection Rate</td>
<td>Bone Scan: 3.57 (3/84)</td>
<td>1.75</td>
</tr>
<tr>
<td>13 Yeh, et. al.</td>
<td>Asymp. new BRCA pts.</td>
<td>RCR</td>
<td>Detection Rate</td>
<td>Bone Scan: 2.20 (7/316)</td>
<td>1.25</td>
</tr>
<tr>
<td>14 Barry, et. al</td>
<td>Asymp. new BRCA pts.</td>
<td>RCR</td>
<td>Detection Rate</td>
<td>Bone Scan: 1.26 (1/79) Liver U/S: 0.00 (0/76) Chest X-ray: 1.22 (1/82)</td>
<td>1.25</td>
</tr>
<tr>
<td>15 Chen, et. al.</td>
<td>Asymp. new BRCA pts.</td>
<td>RCR</td>
<td>Detection Rate</td>
<td>Chest X-ray: 0.60 (6/1,004)</td>
<td>1.25</td>
</tr>
<tr>
<td>16 Schneider, et. al</td>
<td>Asymp. new BRCA pts.</td>
<td>RCR</td>
<td>Detection Rate</td>
<td>Bone Scan: 2.68 (13/485) Liver U/S: 1.03 (5/485) Chest X-ray: 0.41 (2/485)</td>
<td>1.75</td>
</tr>
</tbody>
</table>

*Asymptomatic, new breast cancer patients

The study’s quality was assessed using a grading criteria consisting of 4 categories: (1) reporting of all disease stages, (2) applicability to population of interest, (3) sufficient protocol detail, and (4) sufficient reporting of results. Mean score is reported as the Quality Rating (good > 1.5, fair 1.0 – 1.49, poor < 1.0).
### Table 3: Bone Scan Results by Stage of Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage I &amp; II</th>
<th>Stage III</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmed, et. al.</td>
<td>1990</td>
<td>2.50 (2/80)</td>
<td>4.00 (9/226)</td>
<td>3.59 (11/306)</td>
<td>15.66 (13/83)</td>
<td>18.77 (24/389)</td>
</tr>
<tr>
<td>Brar, et. al.</td>
<td>1991</td>
<td>0 (0/21)</td>
<td>3.00 (2/67)</td>
<td>2.27 (2/88)</td>
<td>4.70 (2/43)</td>
<td>3.10 (4/131)</td>
</tr>
<tr>
<td>Kennedy, et. al</td>
<td>1991</td>
<td>0 (0/13)</td>
<td>1.67 (1/60)</td>
<td>1.37 (1/73)</td>
<td>18.18 (2/11)</td>
<td>3.57 (3/84)</td>
</tr>
<tr>
<td>Yeh, et. al.</td>
<td>1995</td>
<td>1.00 (2/204)</td>
<td>4.50 (5/112)</td>
<td>2.20 (7/316)</td>
<td>---</td>
<td>2.20 (7/316)</td>
</tr>
<tr>
<td>Schneider, et. al.</td>
<td>2002</td>
<td>1.30 (2/159)</td>
<td>0.80 (2/233)</td>
<td>1.02 (4/392)</td>
<td>9.70 (9/93)</td>
<td>2.68 (13/485)</td>
</tr>
<tr>
<td><strong>All studies</strong></td>
<td></td>
<td><strong>1.29 (7/544)</strong></td>
<td><strong>3.09 (29/938)</strong></td>
<td><strong>2.43 (36/1,482)</strong></td>
<td><strong>12.5 (39/312)</strong></td>
<td><strong>4.18 (75/1794)</strong></td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Stage I</td>
<td>Stage II</td>
<td>Stage I &amp; II</td>
<td>Stage III</td>
<td>Total</td>
</tr>
<tr>
<td>------------------</td>
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<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Glynne-Jones</td>
<td>1991</td>
<td>1.80 (1/54)</td>
<td>1.80 (3/167)</td>
<td>1.80 (4/221)</td>
<td>4.00 (2/50)</td>
<td>2.30 (6/261)</td>
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<td>Barry, et. al.</td>
<td>1999</td>
<td>---</td>
<td>---</td>
<td>0.00 (0/76)</td>
<td>---</td>
<td>0.00 (0/76)</td>
</tr>
<tr>
<td>Schneider, et. al.</td>
<td>2002</td>
<td>0 (0/159)</td>
<td>0.40 (1/233)</td>
<td>0.26 (1/392)</td>
<td>4.30 (4/93)</td>
<td>1.03 (5/485)</td>
</tr>
<tr>
<td>All studies</td>
<td></td>
<td>0.47 (1/213)</td>
<td>1.0 (4/400)</td>
<td>0.82 (5/613)</td>
<td>4.20 (6/143)</td>
<td>1.34 (11/822)</td>
</tr>
</tbody>
</table>
Table 5: Chest Radiography Results by Stage of Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage I &amp; II</th>
<th>Stage III</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glynne-Jones</td>
<td>1991</td>
<td>0 (0/64)</td>
<td>0.80(2/240)</td>
<td>0.65 (2/304)</td>
<td>7.30 (6/82)</td>
<td>2.07 (8/386)</td>
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<tr>
<td>Barry, et. al.</td>
<td>1999</td>
<td>---</td>
<td>---</td>
<td>1.22 (1/82)</td>
<td>---</td>
<td>1.22 (1/82)</td>
</tr>
<tr>
<td>Chen, et. al.</td>
<td>2000</td>
<td>---</td>
<td>---</td>
<td>0.60 (6/1,004)</td>
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<td>0.60 (6/1,004)</td>
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<tr>
<td>Schneider, et. al.</td>
<td>2002</td>
<td>0 (0/159)</td>
<td>0 (0/233)</td>
<td>0 (0/392)</td>
<td>2.20 (2/93)</td>
<td>0.41 (2/485)</td>
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<tr>
<td>All studies</td>
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<td>0 (0/223)</td>
<td>0.42(2/473)</td>
<td>0.51 (9/1,782)</td>
<td>4.57(8/175)</td>
<td>0.87(17/1,957)</td>
</tr>
</tbody>
</table>
Assessing the Role of Computed Tomography of the Abdomen in the Staging Evaluation of Primary Breast Cancer

By

Stuart-Allison M. Staley
ABSTRACT

**Objective:** As there is currently no well-established staging protocol for primary breast cancer, we sought to evaluate the role of computed tomography (CT), a commonly used imaging modality. The purpose of this study was to determine the utility of routine abdominal CT in the staging evaluation of women with newly diagnosed primary breast cancer given no detectable disease beyond the ipsilateral axillary nodes on chest CT.

**Methods:** The chest and abdominal CT scans from 440 patients over a 10-year period were reviewed. The presence of definite or possible metastatic disease in the axillary nodes, chest wall, internal mammary nodes, mediastinal nodes, lungs, liver and adrenals were recorded for each patient. Cross tabulation bivariate analysis as well as a chi-square test were performed to characterize the relationship between detection of disease in the chest and disease in the abdomen.

**Results:** Of the 440 patients reviewed, the following were found to have detectable metastatic disease by CT scan: axillary nodes 258 of 440 (56.5%), chest wall 40 of 440 (9.1%), internal mammary nodes 8 of 440 (1.8%), mediastinal nodes 29 of 440 (6.6%), lung 25 of 440 (5.7%), liver 12 of 437 (2.7%), and adrenals 8 of 440 (1.8%). In total, 81 patients had disease detectable in the chest beyond the ipsilateral axillary nodes (ie, chest wall, internal mammary nodes, mediastinal nodes, and lung), and only 12 patients had detectable disease spread in the abdomen (ie, liver and adrenals). Of the 359 patients who had a negative chest CT, only 1 patient had detectable or possible metastatic disease spread on abdominal CT, resulting in a 99.7% negative predictive value (p < 0.001).

**Conclusion:** The routine use of abdominal CT in women with newly diagnosed primary breast cancer and no detectable disease beyond the ipsilateral axillary nodes on staging chest CT scan has a 99.7% negative predictive value. Based on this information, we recommend that if a negative CT scan of the patient’s chest yields no detectable disease beyond the axillary nodes, then further CT imaging of the abdomen is of no additional benefit to the patient and should not be performed.
INTRODUCTION

Primary Breast Cancer Staging in the United States

Breast cancer is the most frequent malignant tumor in women of the Western countries.\(^1\) In 2011, an estimated 230,000 women were diagnosed with a new invasive breast cancer in the United States.\(^1\) These patients will receive some form of staging evaluation at the time of their diagnosis. Staging describes the extent and severity of the patient’s disease and is pivotal in the management of cancer. A patient’s specific stage is based on the invasiveness of the cancer, the size of the tumor, the number of lymph nodes involved, and presence of distant metastasis.\(^2\) By classifying a person’s stage, a more accurate treatment plan and estimate of the patient’s prognosis may be determined.\(^3\)

Several imaging techniques are among the various tests that are used during a staging evaluation. Imaging technology is advancing at a rapid pace, with tests available that are increasingly more sensitive and specific in detecting morphologic as well as functional changes in anatomy.\(^4\) With these advances, however, comes the added expense to the medical system as well as to the patient, additional time consumption, and emotional toll. In the U.S., there is no clearly defined and accepted protocol for staging of primary breast cancers. Positron emission tomography (PET) and computed tomography (CT) are commonly used in addition to less advanced techniques such as ultrasound and radiography.\(^4,5\) Moreover, to our knowledge, no variations in imaging protocols exist based on the patient’s initial tumor size and axillary lymph node metastasis.\(^6\)

Sites of Distant Metastasis

Roughly 45%-50% of new breast cancer patients will develop detectable distant metastases.\(^7\) A woman’s individual risk for distant metastases may be based on various tumor
factors, but most particularly, the presence and extent of disease spread to the axilla. Moreover, these findings have a significant impact on determining the therapeutic plan. The most common sites for distant metastasis include lung, liver, brain, bone, and adrenals. Effective staging evaluation must utilize imaging or laboratory techniques that can assess these locations in totality.

Conventional Diagnostic Procedures (CDPs)

The conventional diagnostic procedures (CDPs) include chest radiograph (posterior/anterior and lateral), ultrasound of the liver, and bone scan. In many institutions, these modalities are commonly used to determine presence of metastases in the lung, liver, and bone, respectively. The documented cumulative sensitivity of these tests may range from 36% to 51%, with a greater specificity ranging from 81% to 95%. One possible explanation for these suboptimal results is that metastases may be too small to detect with these methods. Moreover, these conventional techniques do not examine other common sites of disease spread, including other thoracic lymph nodes or the adrenal glands. However, one study estimated the positive predictive value of CDPs to be as high as 91%, but a negative predictive value of 53%.

Because CDPs are often inconclusive with low sensitivities, additional imaging may be needed to achieve a final diagnosis. To further assess suspicious findings, providers may pursue computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and/or bone scanning. With this additional imaging comes added financial cost, radiation exposure, and an increase in a patient’s anxiety. Regardless, CDPs continue to be mainstays in staging options as other imaging modalities are very costly, with longer scanning times and may not be available in all institutions.
**Positron Emission Tomography (PET)**

Positron emission tomography (PET) is a more advanced form of imaging that has been shown to be useful in detecting many tumors as well as distant metastases. It is well-established in radiologic research that there is increased uptake of $2-[^{18}\text{F}]$fluoro-2-deoxy-D-glucose (FDG) in numerous malignancies.\(^5\) This increased uptake is evidence for enhanced glycolytic rate compared to the surrounding benign tissue. As a result, FDG PET is another method used for whole-body staging evaluation.\(^5\)

Few studies report data concerning use of FDG PET in detection of distant disease spread; however, results from one prospective study indicate that FDG PET has a superior sensitivity to CDPs (78.6%-100%) as well as higher specificity (89.4%-100%).\(^5\) Compared to CDPs, FDG PET has a comparable positive predictive value of 93% and a higher negative predictive value (83% vs. 53%).\(^5\) Although superior in disease detection, FDG PET is a costly method with long scanning times. Furthermore, depending on the location, PET may not be widely available to all patients.\(^5,9\)

Generally, based on few studies reviewing PET for whole-body staging, FDG PET is not recommended in patients with small primary tumors on imaging (defined as < 3cm) and negative lymph nodes, as determined by surgical dissection or sentinel lymph node biopsy.\(^5,9\) In contrast, it is recommended for those with locally advanced disease, extended lymph node metastases and those scheduled to undergo intense chemotherapy. Furthermore, scanning is recommended in cases of uncertain radiographic results or rising tumor markers.\(^5\) In spite of these recommendations, many institutions continue to utilize PET in various ways, depending on availability and established practice.
The Role of Computed Tomography (CT) in Breast Cancer Staging

The clinical experience of members of our multidisciplinary breast oncology program has been that CT is a commonly utilized modality at the University of North Carolina Hospitals (UNCH) as well as referring institutions for breast cancer staging. Computed tomography is used to evaluate the chest, abdomen, and pelvis. With CT of the chest, the following structures may be evaluated for disease spread: axillary lymph nodes, chest wall, mediastinal nodes, internal mammary nodes, and lung. An abdominal CT will allow evaluation of the liver and adrenal glands, and the pelvic CT will allow visualization of the ovaries, endometrium, and pelvic bone.

In 2000, retrospective research from authors at Memorial Sloan-Kettering reported that patient treatment was not substantially altered based on findings from pelvic CT scans.10 Moreover, findings were reported to lead to additional examinations and procedures that yielded normal, benign, or indeterminate results that were not relevant to the patient’s cancer therapy. Specifically, out of 2426 new primary breast cancer patients, only 17 patients (0.7%) were found to have metastatic disease isolated to the pelvis. Of the 17 patients, eleven had metastasis present only in the pelvic bone, which was simultaneously detected by concomitant bone scanning. Pelvic CT only contributed relevant information for six patients, who had disease present in the adnexa and/or endometrium. As a result, routine scanning of the pelvis by CT was non-contributory in nearly all new cancer patients and, therefore, was not recommended based on these findings.10

Likewise, it has been our anecdotal experience that evaluation of the abdomen yields no further information when no metastases are detected in the chest beyond the ipsilateral axillary lymph nodes. Hence, we reviewed the evidence and indications for the extent of routine CT scanning in the context of the following hypothesis: If CT does not detect suspected spread of
disease beyond the ipsilateral axilla in the chest, then CT will not detect the spread of disease in the abdomen. In other words, if a negative CT scan of the patient’s chest yields no detectable disease beyond the axilla, then further CT imaging of the abdomen is of no additional benefit to the patient and should not be performed.

METHODS

Patient Selection and Data Collection

With Internal Review Board (IRB) approval, we performed a retrospective case series of all patients seen in the multidisciplinary breast oncology program at the University of North Carolina Hospital (UNCH) between 1998 and 2011. We reviewed clinical records in order to identify all patients referred for diagnosis of suspected breast cancer or treatment of a newly diagnosed primary breast cancer by fine needle aspiration, core biopsy, or excisional biopsy. Male patients, patients with a previous diagnosis of breast cancer, those with a diagnosis of benign breast disease, as well as those with a metastatic breast carcinoma from another primary cancer were excluded. Patients referred after surgical intervention were also excluded. There was no age exclusion.

Patients with a CT scan of the chest and abdomen within 30 days of diagnosis were included in the review. Patients evaluated with a CT chest or abdomen greater than 30 days after diagnosis were excluded. Those referred with imaging studies from outside institutions that could not be reviewed were not included in the study. Likewise, patients imaged at UNCH whose imaging exams could not be retrieved were excluded. Furthermore, those evaluated for staging purposes using Positron Emission Tomography/Computed Tomography (PET/CT) scans,
either at UNCH or referring institutions, were excluded. This provided a final study group of 440 subjects.

CT scans were all performed on helical scanners and reconstructed with 5mm or 8mm slice thickness and table incrementation. Between 1999 and 2002, patients were imaged on a Siemens® Plus 4 scanner, which has a single detector with helical acquisition. After 2002, all patients were imaged on a multidetector scanner, also with helical acquisition. All CT scans were reviewed by a board certified chest radiologist with fellowship training in body computed tomography. Scans of the chest were reviewed for the presence, questionable presence, or absence of axillary, mediastinal, and internal mammary adenopathy; chest wall invasion; and pulmonary metastases. Scans of the abdomen were reviewed for presence, possible presence, or absence of hepatic and adrenal metastases. Information from patient medical records included initial clinical stage, final pathologic stage post-operatively (if available), results of liver function tests (if determined), and findings from bone scan (if performed).

**Data Analysis**

We used descriptive statistics to tabulate patient staging distribution and the presence of disease in the chest and abdomen as detected by CT scan. The total number of patients included in the final analysis were calculated and categorized by their clinical stage. Within each clinical stage, the number and percentage of patients with metastases to the axillary nodes, chest wall, internal mammary nodes, lung, mediastinal nodes, liver, and adrenal glands were also calculated. Additionally, for each clinical stage, the total number and percentage of patients who had detected presence of disease in either the chest or the abdomen were summed. Cross tabulation bivariate analysis was performed to characterize the relationship between detection of disease in
the chest and detection of disease in the abdomen. The following contingency tables provide matrix displays of each variable based on location of disease. For contingency Table Two, a chi-square test was performed as a test for statistical significance.

RESULTS

*Presence of Metastases by Anatomical Sites and Clinical Stage*

For analysis, 440 patient scans were reviewed. Each patient received a chest CT and an abdominal CT. As seen in Table One, most patients were classified as stage IIB (129 of 440). The distribution by stage was as follows: Stage IIIA (90), Stage IIA (83), Stage IIIB (63), Stage I (40), and Stage IV (33). Two patients diagnosed with in situ carcinoma by core biopsy underwent staging evaluation by CT.

In total, 258 (56.46%) patients had disease spread to the axillary lymph nodes as detected by CT chest. Of note, axillary lymph node data was unavailable for 31 patients, as their CT evaluation was performed following surgical dissection. By stage, data was missing for the following: in situ (0), Stage I (3), Stage IIA (10), Stage IIB (14), Stage IIIA (2), Stage IIIB (2), Stage IV (0). These 31 patients were subtracted from the study population when calculating the percentage of metastases by stage and in total.

For other sites beyond the axillary lymph nodes, disease spread was less frequent: chest wall 40 (9.10%), internal mammary nodes 8 (1.82%), mediastinal nodes 29 (6.59%), lung 25 (5.68%), liver 12 (2.73%), and adrenals 8 (1.82%). For three patients, liver data was unavailable due to lack of contrast administration. By stage, data was missing for the following: in situ (0), Stage I (0), Stage IIA (0), Stage IIB (1), Stage IIIA (1), Stage IIIB (1), Stage IV (0). These
patients were subtracted from the study population when calculating the percentage of metastases by stage and in total.

**Comparison of Disease Detection in the Chest versus Abdomen**

As seen in Table Two, 359 of the 440 patients scanned did not have disease detected in structures beyond the axillary lymph nodes (i.e., chest wall, internal mammary nodes, mediastinal nodes, lung) based on CT imaging. Of these 359 patients without detectable disease in the chest, only 1 patient was found to have disease spread to the abdomen. This patient had metastatic disease spread to the liver, but not detectable disease to the adrenals as noted in Tables Three and Four. Moreover, PET/CT scanning of this patient found detectable disease spread in the supraclavicular, which was not present on chest CT.

From these data, a 99.7% negative predictive value was calculated. In other words, of those who did not have disease detected beyond the axillary lymph nodes in the chest, 99.7% did not have detectable disease in the liver or adrenals (p<0.001).

**Comparison of Disease Detection by Individual Chest Structures versus Abdomen**

As additional information, Tables Five through Eight display the contingency tables for each individual chest structure and disease spread to the abdomen. Of note, out of the 12 patients with detected abdominal metastases, 8 had detectable lung metastasis on CT scan. The other chest structures had detectable disease with concomitant abdominal metastasis seen in the following number of cases: chest wall invasion (4), mediastinal nodes (4), and internal mammary nodes (2).
DISCUSSION

Once the initial diagnosis of invasive breast cancer is made, the extent of disease spread is assessed in order to inform appropriate therapy, patient prognosis, and formally stage the tumor. This assessment includes a number of imaging modalities, such as chest radiograph, liver ultrasound, bone scintigraphy, MRI, PET, and CT scan of the chest, abdomen, and pelvis. Results from these various tests may also inform further imaging to reach a final diagnosis. To our knowledge, the routine use of many of these staging techniques is not standardized with no well-established protocol. Our goal was to assess the role of abdominal computed tomography in staging primary breast cancer patients.

Our study showed that pursuing a CT abdomen provides little to no additional information in light of a negative chest CT scan. Among the 359 patients who had no detectable disease spread to the chest wall, lung, mediastinal or internal mammary lymph nodes, only 1 had detectable disease to the abdomen.

Harms and Costs

With the benefits of additional knowledge achieved with CT, there are still many risks with ordering this test. These risks are further reasoning for why standard staging protocol is necessary for quality improvement, cost-effective medicine, and reducing patient exposure to potentially harmful testing. First, although there is some data that suggests hormesis at low levels of exposure, the generally accepted theory is the Linear No Threshold (LNT) theory based on extrapolated data from Hiroshima and Nagasaki. Using this theory and the “As Low As Reasonably Possible” principle, diagnostic imaging with ionizing radiation is done when the risk/benefit ratio shows there is a clear benefit to the patient in terms of medical management
based on the information gained from the test.\textsuperscript{11} Furthermore, without a standardized protocol, patients risk multiple forms of testing that may lead to additional follow-up imaging. This cumulative exposure may sum to a greater radiation risk for breast cancer patients.\textsuperscript{10,12}

Secondly, in order to appropriately image liver metastases, patients will receive contrast material intravenously prior to CT scanning. In some cases, contrast material may cause an allergic reaction or nephrotoxicity.\textsuperscript{12} Third, the financial cost of additional scanning, travel time, and work time lost are growing expenses to the U.S. health care system and the individual patient. Even though pricing for scans are variable between insurance providers and hospital systems, the most current hospital charges at UNC for a chest CT with contrast is $2890 with professional fee of $155, totaling over $3000 for one scan. An abdominal and pelvic CT scan totals to $2756 with an additional professional fee of $281. In this study, if the 358 patients with negative scans had not undergone abdominal CT in light of their negative chest CT, the total savings amounts to $1,087,246. The cumulative cost and time associated with pursuing abdominal CT scans in large numbers of patients are substantial, as exemplified by this value.

\textit{Study Limitations}

This study was a retrospective review of patient medical records. Several factors may have biased our results. Primarily, it is inherently difficult to fully determine retrospectively why a CT may have been ordered for a certain patient; however, to counteract this potential bias, only patients with CT scans performed within one month of diagnosis and listed as evaluations due to breast cancer diagnosis were included. It is our belief that the included subjects were scanned as part of routine cancer evaluation as opposed to concurrent medical problems or preoperative evaluation.
Additionally, CT scans performed at other institutions and reviewed by outside physicians were excluded from the study. This limited a large number of imaging studies that could be added to the analysis. Nevertheless, our sample size was significant, representing patients seen at UNCH over a 13-year time period, various presenting stages and symptomatology.

As this study is retrospective, assessing the clinical impact of the test result, even when negative, cannot be fully evaluated. Furthermore, the effect of routine abdominal CT scanning on patient survival cannot be assessed through this database.

**Future Research**

The need for routine imaging with CT chest, abdomen, and pelvis should be reconsidered when developing staging protocol based on our study results. A prospective study including a cost-effectiveness analysis as well as well-documented physical examination findings is needed to determine if a particular subset of new cancer patients could benefit from CT scanning beyond the chest. Furthermore, additional information concerning routine use of CT pelvis can inform future protocol.

**Recommendations for CT Imaging and Staging**

Based on our study results and those of Drotman et. al.\textsuperscript{10} in 2000, we believe that routine CT imaging protocol does not require scanning of the chest, abdomen, and pelvis for all new breast cancer patients. In fact, according to our findings, patients with no disease detected in the chest wall, lung, mediastinal or internal mammary nodes do not benefit from further imaging (including addition of contrast administration for liver evaluation) of the abdomen. Moreover,
routine CT of the pelvis has shown to be of benefit to less than 1% of new breast cancer patients. The results from these CT scans are rarely relevant to cancer therapy and, therefore, of no benefit to patients. In fact, the exposure to and cost of the testing may be greater potential harm to women.

CONCLUSION

The routine use of abdominal CT in women with newly diagnosed primary breast cancer and no detectable disease beyond the ipsilateral axillary nodes on staging chest CT scan has little value with a 99.7% negative predictive value. Based on this information, we recommend that if a negative CT scan of the patient’s chest yields no detectable disease beyond the axillary nodes, then further CT imaging of the abdomen is of no additional benefit to the patient and should not be performed.
REFERENCES


6. Based on systematic literature review of PubMed and EMBASE performed in conjunction with assistance from science information specialists at the UNC Health Sciences Library


**TABLES**

**Table One:** Presence of Metastasis as Detected by CT Scan by Pre-Operative Clinical Stage (n, %)

<table>
<thead>
<tr>
<th>Clinical Stage (n)</th>
<th>Axillary Nodes*</th>
<th>Chest Wall</th>
<th>Internal Mammary Nodes</th>
<th>Lung</th>
<th>Mediastinal Nodes</th>
<th>Liver**</th>
<th>Adrenal</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Situ (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>I (40)</td>
<td>9 (24.32)</td>
<td>1 (2.50)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (5.00)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>II A (83)</td>
<td>27 (36.99)</td>
<td>3 (3.61)</td>
<td>1 (1.20)</td>
<td>4 (4.82)</td>
<td>1 (1.20)</td>
<td>2 (2.41)</td>
<td>1 (1.20)</td>
</tr>
<tr>
<td>IIB (129)</td>
<td>67 (58.26)</td>
<td>8 (6.20)</td>
<td>1 (0.78)</td>
<td>2 (1.55)</td>
<td>6 (4.65)</td>
<td>2 (1.56)</td>
<td>2 (1.55)</td>
</tr>
<tr>
<td>III A (90)</td>
<td>75 (85.23)</td>
<td>4 (4.44)</td>
<td>1 (1.11)</td>
<td>3 (3.33)</td>
<td>4 (4.44)</td>
<td>0 (0)</td>
<td>1 (1.11)</td>
</tr>
<tr>
<td>III B (63)</td>
<td>51 (83.61)</td>
<td>11 (17.46)</td>
<td>4 (6.35)</td>
<td>4 (6.35)</td>
<td>4 (6.35)</td>
<td>1 (1.61)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>IV (33)</td>
<td>29 (87.88)</td>
<td>13 (39.39)</td>
<td>1 (3.03)</td>
<td>12 (36.36)</td>
<td>12 (36.36)</td>
<td>7 (21.21)</td>
<td>4 (12.12)</td>
</tr>
<tr>
<td>Total (440)</td>
<td>258 (56.46)</td>
<td>40 (9.10)</td>
<td>8 (1.82)</td>
<td>25 (5.68)</td>
<td>29 (6.59)</td>
<td>12 (2.73)</td>
<td>8 (1.82)</td>
</tr>
</tbody>
</table>

*Axillary Node data was missing for the following number of patients by stage: in situ (0), Stage I (3), Stage II A (10), Stage II B (14), Stage III A (2), Stage III B (2), Stage IV (0). These patients were subtracted from the study population when calculating the percentage of metastases by stage, respectively.

**Liver data was unavailable for three patients due to lack of contrast for imaging: in situ (0), Stage I (0), Stage II A (0), Stage II B (1), Stage III A (1), Stage III B (1), Stage IV (0). These patients were subtracted from the study population when calculating the percentage of metastases by stage, respectively.**
**Table Two: Comparison of Disease Detection in the Chest versus Disease Detection in the Abdomen (n)**

<table>
<thead>
<tr>
<th>Disease in the Chest</th>
<th>Detected</th>
<th>Not Detected</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected</td>
<td>11</td>
<td>70</td>
<td>81</td>
</tr>
<tr>
<td>Not Detected</td>
<td>1</td>
<td>358</td>
<td>359</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>423</td>
<td>440</td>
</tr>
</tbody>
</table>

Detection of disease in the chest is defined as disease detected beyond the axillary nodes.

Positive detection of disease in the chest was defined as disease detected beyond the ipsilateral axillary nodes and present in the chest wall, internal mammary nodes, lung, and/or mediastinal nodes. Positive detection of disease in the abdomen was defined as disease detected in the liver and/or adrenals.
**Table Three**: Comparison of Disease Detection in the Chest versus Disease Detection in the Liver (n)%

<table>
<thead>
<tr>
<th>Disease in the Chest</th>
<th>Disease in the Liver</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Detecte</td>
<td>9</td>
<td>70</td>
</tr>
<tr>
<td>Not Detece</td>
<td>1</td>
<td>357</td>
</tr>
<tr>
<td>10</td>
<td>427</td>
<td>437</td>
</tr>
</tbody>
</table>

Liver data was unavailable for three patients due to lack of contrast for imaging. Their results are not included in the above table. Of these three patients, two had disease present and one did not have disease present in the chest. None had disease detected in the adrenals.
**Table Four:** Comparison of Disease Detection in the Chest versus Disease Detection in the Adrenals (n)

<table>
<thead>
<tr>
<th>Disease in the Chest</th>
<th>Detected</th>
<th>Not Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected</td>
<td>4</td>
<td>77</td>
</tr>
<tr>
<td>Not Detected</td>
<td>0</td>
<td>359</td>
</tr>
</tbody>
</table>

4 436 440
**Table Five:** Comparison of Disease Detection in the Chest Wall versus Disease Detection in the Abdomen (n)

<table>
<thead>
<tr>
<th>Chest Wall Invasion</th>
<th>Disease in the Abdomen</th>
<th>Detected</th>
<th>Not Detected</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected</td>
<td>4</td>
<td>36</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Not Detected</td>
<td>8</td>
<td>392</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>428</td>
<td>440</td>
<td></td>
</tr>
</tbody>
</table>
**Table Six:** Comparison of Disease Detection in the Internal Mammary (IM) Nodes vs. Disease Detection in the Abdomen (n)

<table>
<thead>
<tr>
<th>Disease in the IM Nodes</th>
<th>Disease in the Abdomen</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Detected</td>
<td>2</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Not Detected</td>
<td>10</td>
<td>422</td>
<td>432</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td>423</td>
<td>440</td>
</tr>
</tbody>
</table>
**Table Seven:** Comparison of Disease Detection in the Lungs vs. Disease Detection in the Abdomen (n)

<table>
<thead>
<tr>
<th>Disease in the Lungs</th>
<th>Disease in the Abdomen</th>
<th>Detected</th>
<th>Not Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected</td>
<td></td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Not Detected</td>
<td>4</td>
<td>411</td>
<td>415</td>
</tr>
<tr>
<td></td>
<td><strong>12</strong></td>
<td><strong>428</strong></td>
<td><strong>440</strong></td>
</tr>
</tbody>
</table>
**Table Eight:** Comparison of Disease Detection in the Mediastinal (MD) Nodes vs. Disease Detection in the Abdomen (n)

<table>
<thead>
<tr>
<th>Disease in MD Nodes</th>
<th>Disease in the Abdomen</th>
<th>Detected</th>
<th>Not Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected</td>
<td>4</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>Not Detected</td>
<td>8</td>
<td>403</td>
<td>411</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>12</strong></td>
<td><strong>428</strong></td>
<td><strong>440</strong></td>
</tr>
</tbody>
</table>