Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2008 June 1; 71(2): 435–440. doi:10.1016/j.ijrobp.2007.10.025.

RISK OF SUBCLINICAL MICROMETASTATIC DISEASE IN THE SUPRACLAVICULAR NODAL BED ACCORDING TO THE ANATOMIC DISTRIBUTION IN PATIENTS WITH ADVANCED BREAST CANCER

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Abstract

Purpose—To determine the anatomic distribution of gross supraclavicular nodes within the supraclavicular fossa using 2-deoxy-2-[F-18] fluoro-d-glucose (FDG) positron emission tomography/computed tomography (PET/CT) scans, and to evaluate likely coverage of specific regions of the supraclavicular fossa using standard radiation fields.

Methods and Materials—We identified 33 patients with advanced or metastatic breast cancer who had a PET/CT scan demonstrating hypermetabolic supraclavicular lymph nodes in 2005. The locations of the involved lymph nodes were mapped onto a single CT set of images of the supraclavicular fossa. These lymph nodes were also mapped onto the treatment-planning CT dataset of 4 patients treated in our institution (2 patients with biopsy-proven supraclavicular nodes and 2 patients with clinically negative supraclavicular nodes).

Results—We were able to determine the distribution of 52 supraclavicular lymph nodes in 32 patients. Of 32 patients, 28 (87%) had a history of metastatic disease, and 2 patients had isolated nodal recurrences. Five patients had supraclavicular nodes posterior to the vertebral body transverse process, and several lymph nodes were in close proximity to the medial field border, raising the possibility of geographic miss in these areas.

Conclusions—In patients with locally advanced disease, increased coverage of the supraclavicular fossa medially and posteriorly may be warranted.

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Conflict of interest: none.

Keywords

Positron emission tomography; Computed tomography; Breast cancer; Supraclavicular nodes

INTRODUCTION

Radiation to the supraclavicular region is frequently administered to patients with breast cancer at a high risk of locoregional recurrence. In a series of 1031 patients treated with mastectomy and doxorubicin-based chemotherapy without radiation, 71 of 1031 patients (6.9%) recurred in the supraclavicular region, accounting for 41% of all locoregional recurrences (1). The Eastern Cooperative Oncology Group reported a study on 2016 patients with histologically involved axillary nodes treated with mastectomy and cyclophosphamide/methotrexate/fluorouracil chemotherapy without radiation. In this series between 3.9% and 18.2% of patients had a supraclavicular recurrence, depending on tumor and nodal stage (2).

It is desirable to define the areas at risk for disease in the supraclavicular region, so that these areas can be treated with an adequate radiation dose. Typical radiation coverage does not extend to the posterior supraclavicular fossa. We hypothesized that if these areas were at risk for subclinical disease, gross disease would be evident in patients with advanced disease. Here we describe the distribution of supra-clavicular lymph nodes in patients with advanced disease according to 2-deoxy-2-[F-18] fluoro-d-glucose (FDG) positron emission tomography/computed tomography (PET/CT) and analyzed the location of these nodes in relationship to the supraclavicular radiation fields used in our institution.

METHODS AND MATERIALS

This retrospective review was approved by the institutional review board at The University of Texas M. D. Anderson Cancer Center. Reports from all PET/CT scans performed for breast cancer patients in a single year (2005) were reviewed. A total of 404 breast cancer patients had 754 PET/CT scans performed in 2005. Twenty-four patients from this group had involved supraclavicular lymph nodes according to PET/CT. Nine additional patients were included if the PET/CT report from 2005 did not mention FDG-avid supraclavicular nodes but a PET/CT report in 2004 or 2006 noted FDG-avid supraclavicular nodes, for a total of 33 patients. The PET/CT scans with FDG-avid supraclavicular nodes were then reviewed by nuclear medicine physicians (J.L.C and H.Y.) and a radiation oncologist (V.K.R.). The locations of the involved supraclavicular nodes were then transferred onto a template CT (CT scan of a patient without neck adenopathy) using vertebral body and soft-tissue landmarks. During this process we determined the location of the supraclavicular lymph nodes in relation to a specific vertebral body on the PET/CT scan and mapped the node to the template CT using vertebral body anatomy. We further revised the location of the lymph node on the template CT by relating the node to blood vessels and muscles. All PET/CT scans reviewed, as well as the template CT, were performed with both of the arms above the head. We classified the location of the lymph nodes according to the Danish Head and Neck Cancer Group, European Organization for Research and Treatment of Cancer (EORTC), French Head and Neck Oncology and Radiotherapy Group, National Cancer Institute of Canada (NCIC), and Radiation Therapy Oncology Group consensus guidelines (3).

We then identified 4 consecutively treated patients with comprehensive chest wall/breast radiation including a left supraclavicular field (2 patients with a history of biopsy-proven left supraclavicular lymph nodes and 2 patients with clinically negative supraclavicular nodes). At our institution the supraclavicular field is treated with a slightly oblique field (15°) to

avoid the spinal cord and esophagus. For patients with clinically negative supraclavicular nodes, the superior field border flashes the shoulder, the medial border is midline with a medial block to shield the larynx and esophagus, and the lateral border is lateral to the humeral head with a block to shield the majority of the humeral head. In patients with supraclavicular disease at presentation, the superior field border is typically raised to the mastoid process. Patients with clinically negative supraclavicular nodes are prescribed 50 Gy in 25 fractions. A standard prescription point is not used. The physician contours the supraclavicular nodal basin, and a calculation point is placed depending on patient anatomy to ensure that the clinical target volume is covered by the 45-Gy isodose line (90% of the prescribed dose). The supraclavicular nodal distribution as described above was mapped onto the planning CT data set for each case. The Phillips Pinnacle Treatment Planning System (Phillips Medical Systems, Bothell, WA) was used to generate all treatment plans.

RESULTS

Patient characteristics

Of the 33 patients we identified with a history of FDG-avid supraclavicular lymph nodes on the report, we were able to map out the location of the nodes in 32 patients. Characteristics of these 32 patients subdivided into three groups (patients presenting with *de novo* disease, patients with recurrent disease who had known or unknown supraclavicular radiation, and patients with recurrent disease with no history of supra-clavicular radiation) are described in Table 1. The median age was 53 years, and 26 of 32 (81%) received chemotherapy and/or radiation before the PET/CT with FDG-avid supraclavicular nodes. Twenty-eight patients (87%) had metastatic disease at the time of PET/CT. The median number of involved axillary lymph nodes at the time of axillary dissection was 1.5, and the most common T stage was T2 (34%). Two patients (1 with a history of supraclavicular radiation and 1 with an unknown history of supraclavicular radiation) had isolated nodal recurrences.

Anatomic distribution of supraclavicular nodes

The distribution of the supraclavicular nodes is shown in Fig. 1. Three nodes were located inferior to the clavicle but were included here for completeness. Five patients had nodes posterior to the vertebral transverse process (Fig. 2). Neither history of metastatic disease, number of involved axillary lymph nodes, nor inflammatory breast cancer predicted for an increased risk of posterior nodes in this small group.

Five of 52 nodes (9.6%) were located in level III, 33 of 52 (63%) in level IV, and 11 of 52 (21%) in level V. Three lymph nodes located below the clavicle could not be classified according to the Danish Head and Neck Cancer Group, EORTC, French Head and Neck Oncology and Radiotherapy Group, NCIC, and Radiation Therapy Oncology Group consensus guidelines. However, these lymph nodes would be considered infraclavicular according to the guidelines proposed by Madu *et al.* (4). Two patients in this study had isolated locoregional recurrences. One of these patients had a history of supraclavicular radiation and recurred in a level V supraclavicular lymph node at the depth of the vertebral body transverse process. The other patient had an unknown history of supraclavicular radiation and recurred in levels III and V. The level V node was posterior to the vertebral body transverse process.

Location of supraclavicular nodes in relationship to radiation field

The digital reconstruction radiographs of the four supraclavicular fields used in this study are shown in Fig. 4. Three of the patients were simulated with their left arm abducted and maintained by a Vac-Lok patient immobilization system (MEDTEC, Orange City, IA). One patient with biopsy-proven supraclavicular involvement was simulated with both arms up to

treat the right breast, as well as the left chest wall and the left supraclavicular region. As seen in Fig. 4, several of the lymph nodes are in close proximity to the medial field border. Figure 3 is a PET/CT of a patient with a medial supraclavicular lymph node.

DISCUSSION

Three randomized trials have demonstrated an overall survival benefit with postmastectomy radiation (5–7). In all of these trials, patients were treated with comprehensive chest wall radiation, which included a supraclavicular field. Additionally, the clinical practice guidelines of the American Society of Clinical Oncology recommend postmastectomy radiation (including supraclavicular radiation) in patients with four or more involved lymph nodes (8). However, these guidelines state that “there are no clear data on the impact of supraclavicular irradiation on overall survival.” The panel recommended a supraclavicular field in patients with four or more involved axillary lymph nodes owing to the risk of clinical failure in the region.

This is the first study, to our knowledge, to determine the anatomic distribution of supraclavicular nodes in breast cancer patients according to PET/CT. It is important to define the areas at risk for disease. Patients treated with a supraclavicular field usually have no evidence of gross supraclavicular disease and are treated to the region with the intent that radiation will eliminate potential micrometastatic disease. The anatomic nodal distribution of nodes at risk extends over the axillary vessels into the supraclavicular fossa, and this area is the predicted target of the supraclavicular field. Here we examine the specific location of these nodes according to disease progression in patients with advanced disease. As seen in this study, supraclavicular nodes occur in a variety of locations. The area at risk may sometimes be posterior or medial to typical treatment volumes. Other investigators have noted that traditional supraclavicular fields can result in inadequate dosimetric coverage of the supraclavicular nodes (9, 10).

This study has several limitations. The majority of patients in this study had metastatic disease at the time of the PET/CT scan, and it is unclear whether these findings are applicable to patients with localized disease being treated to the supraclavicular field for presumed micrometastatic disease (the majority of cases). The information in the nodes transferred to the planning CT from the template CT should be viewed qualitatively. The nodes were transferred from the template CT (both arms up) to planning CTs in patients who underwent simulation with different arm positions. Dijkema *et al.* (11) demonstrated a change in position in all breast regional lymph nodes when the arm was abducted, with the exception of the medial supraclavicular and internal mammary nodes. Additionally, there is a small, inherent source of error in transferring the involved supraclavicular nodes from each individual patient to a template CT, then transferring the nodes from the template CT to the radiotherapy planning CT. This study focused on FDG-avid lymph nodes. Although PET/CT is more sensitive than CT for nodal metastases (12), it is unable to identify micrometastatic disease. Nanoparticles could be used to identify micrometastatic lymph nodes, as was done in a study mapping pelvic lymph nodes (13).

As demonstrated in Fig. 4, several of the mapped supraclavicular nodes were in close proximity to the medial field border, which raises the possibility of geographic miss in this area. On the basis of this study, it may be reasonable to extend the radiation field medially, even if this means including a portion of the esophagus in the treatment field, for patients with high-risk disease including gross nodes in the supraclavicular fossa at presentation. It will be interesting to review the results of the EORTC and the NCIC trials, which randomized patients to receive or not receive both supraclavicular and internal mammary nodal radiation, when they become available. In the EORTC study the supraclavicular field

was defined with a medial border 1 cm across midline with a block in the upper medial border to protect laryngeal structures (14). This extension beyond midline provides greater margin on the most medial supraclavicular nodes demonstrated in our study. Given the medial location of the supraclavicular lymph nodes and the potential for a narrow dosimetric margin on these nodes using standard supraclavicular fields, extension of the field medially similar to that described by the EORTC warrants consideration in patients treated to the supraclavicular fossa to avoid geographic miss. Use of CT-based simulation facilitates evaluation of the dosimetry on a case-by-case basis, such that the benefits and risk of additional coverage can be considered. Minimizing setup error is clearly critical to obtain adequate coverage without substantially extending the medial field margin.

Despite our study's limitations, we consider this an important first step in further defining the regions at risk in the supraclavicular region. Further studies are indicated to determine which patients benefit from more aggressive supraclavicular coverage.

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Fig. 1.

Location of 52 supraclavicular nodes transferred to the template patient according to bony and soft-tissue anatomy. All of the right supraclavicular nodes have been transferred to the left in this figure. Yellow = patients with *de novo* disease, green = patients with known or unknown history of supraclavicular radiation, red = patients with no history of supraclavicular radiation.

Fig. 2. Positron emission tomography/computed tomography of a patient with a left posterior node. The hypermetabolic region in the right supraclavicular fossa was considered hypermetabolic brown fat.

Fig 3.
Positron emission tomography/computed tomography of a patient with a medial supraclavicular node.

A. Fields from patients with biopsy-proven
involved supraclavicular nodes

B. Fields from patients without a history of
involved supraclavicular nodes

Fig 4.

Digital reconstruction radiographs of the four supraclavicular fields used in this study. The supraclavicular nodes from the template patient were transferred to each of the 4 patients according to bony and soft-tissue anatomy. The color code is the same as in Fig. 1.

Table 1

Patient characteristics

Characteristic	Entire group (n = 32)	Patients with <i>de novo</i> disease (n = 6)	Patients with recurrent disease that had known or unknown supraclavicular RT (n = 10)	Patients with recurrent disease with no history of supraclavicular RT (n = 16)
Age (y)				
Median	53	51	48	59
Range	23–82	23–82	34–54	40–73
Pathology differentiation (modified Black's nuclear grade)				
Well	0	0	0	0
Moderate	12 (37)	3 (50)	2 (20)	7 (44)
Poor	14 (44)	3 (50)	5 (50)	6 (38)
Unknown	6 (19)	0	3 (30)	3 (19)
Chemotherapy/radiation before PET/CT	26 (81)	0	10 (100)	16 (100)
Metastatic disease at time of PET/CT	28 (87)	4 (67)	9 (90)	15 (94)
Inflammatory breast cancer	5 (16)	4 (67)	0	1 (6)
Bilateral supraclavicular nodes	2 (6)	0	1 (11)	1 (6)
No. of involved axillary lymph nodes at initial axillary dissection				
Median	1.5	13	3	1
Range	0–28	2–18	0–28	0–5
No. of removed axillary lymph nodes				
Median	12	20	13	10.5
Range	2–34	16–22	6–34	2–20
T stage				
T1	8 (25)	1 (17)	2 (20)	5 (31)
T2	11 (34)	1 (17)	1 (10)	9 (56)
T3	4 (13)	0	4 (40)	0
T4	6 (19)	4 (67)	1 (10)	1 (6)
TX	3 (9)	0	2 (20)	1 (6)
History of supraclavicular radiation before PET/CT				
Yes	3	0	3 (30)	0
No	22	6 (100)	0 (0)	17 (100)
Unknown	7	0	7 (70)	0

Abbreviation: PET/CT = positron emission tomography/computed tomography.

Values are number (percentage), unless otherwise noted.