Intraoperative Gamma Detection Of 125I-Lanreotide in Women With Primary Breast Cancer

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Background: Somatostatin receptors are present in most human breast cancers. We performed a pilot trial of intraoperative tumor-gamma detection using the radiolabeled somatostatin analog 125I-lanreotide in 13 women with 14 primary breast carcinomas.

Methods: All patients were given 125I-lanreotide intravenously before surgery. Patients underwent lumpectomy, and postresection margins were evaluated with the gamma probe. Axillary dissection specimens were evaluated ex vivo.

Results: Seven of 13 women had gamma probe-positive or clinically suspicious margins re-excised at the time of lumpectomy. Four of six probe-positive margins were histologically positive, and two of six probe-positive margins were histologically negative; a single clinically suspicious margin was histologically positive. A total of 270 axillary lymph nodes were evaluated ex vivo by gamma probe and histology. McNemar’s contingency tests demonstrated a highly statistical correlation between histology and gamma probe counts (P < .0001).

Conclusions: The overall accuracy of nodal evaluation with 125I-lanreotide/Intraoperative gamma detection was 77%; the negative predictive value of this technique was 97%, however. This technique predicted the presence of tumor in 20% of axillary lymph nodes that were negative by routine histology. This technique appears safe and is able to detect positive tumor resection margins and accurately predict axillary lymph node negativity. Further trials of this technique are required to validate its utility.

Key Words: Somatostatin receptors—Gamma radiation—Breast cancer—Somatostatin analogs—125Iodine.

Women who present with a carcinoma of the breast often are offered a number of surgical options for the treatment of their cancer. Trends favoring minimally invasive breast cancer surgery have developed along two distinct surgical approaches. Treatment of the primary breast cancer has shifted from mastectomy to lumpectomy, and the evaluation of axillary lymph node status has shifted from complete axillary dissection (removal of levels I, II, and III nodes) to less complete dissections. Each of these trends has created new surgical dilemmas.

The shift from mastectomy to lumpectomy has led to a significant risk of ipsilateral tumor recurrence. Local recurrence rates may be increased by undetected positive tumor resection margins or multifocal disease that remains undiscovered following lumpectomy.1,2 Up to 45% of initial excisional breast biopsy margins are positive and require subsequent re-excision.2 In addition, some patients may have clinically and mammographically occult multifocal disease that is not discovered during lumpectomy. In a meta-analysis of 11 studies with 2657 cases, Carter et al. found that 32% of primary breast...
cancers were multifocal with residual tumor in other quadrants. This finding has been confirmed by Pittinger et al., who reported multifocal disease in 24% of patients with close margins and 44% in patients with positive margins.

Axillary dissection for breast carcinoma provides the most accurate staging data and is the most accurate determinant of patient prognosis. Unfortunately, complete axillary lymph node dissection also is a major source of postoperative morbidity associated with lumpectomy and axillary dissection or modified radical mastectomy. In an effort to decrease this postoperative morbidity, others have suggested that axillary sampling (level I nodes) provides accurate prognostic information and minimizes morbidity. Unfortunately, a significant number of patients have positive level II or III nodes in the face of negative level I nodes. The total number of positive nodes in an axilla is a critical determinant of a patient’s prognosis; thus, obtaining the most accurate prognostic information requires evaluation of all of the axillary nodes. However, the morbidity of complete axillary dissection and the absence of a survival advantage following complete axillary dissection have forced a reassessment of the role of axillary dissection.

A variety of techniques have been developed to evaluate axillary lymph nodes. These include the use of sentinel lymph node mapping, using Lymphazurin blue or Lymphazurin blue and technetium-99m (Tc 99m) sulfur colloid with intraoperative gamma detection, to identify sentinel nodes for excision. This technique does not evaluate all of the axillary lymph nodes, however, and cannot provide the operating surgeon information on the resection margins of the primary tumor. A technique that accurately evaluates all axillary lymph nodes and detects positive tumor resection margins would be a useful tool to guide intraoperative surgical decision-making in women with breast cancer.

Somatostatin receptors have been demonstrated to be present in a large proportion of breast carcinomas. van Eijck et al. demonstrated that 75% of all women with primary breast cancers have positive 111In-pentetreotide (a radiolabeled, somatostatin receptor subtype 2-prefering, somatostatin analog) scintigraphic scans. Parallel in vitro autoradiography demonstrated somatostatin receptor (sst) positivity in 28 of 30 (93%) of these patients. Positive scans are obtained more often in patients with ductal carcinomas than in those with lobular carcinomas (85% vs. 56%). Unfortunately, the relatively long distance from the tumor (radioactive source) to the camera (the inverse-square law) decreases the sensitivity of external scintigraphic scanning. As expected, T2 carcinomas are more commonly visualized than are T1 carcinomas (86% vs. 61%). In van Eijck’s study, 111In-pentetreotide scanning demonstrated nonpalpable, cancer-containing lymph nodes in only 4 of 13 patients (31%) with historically proven axillary lymph node metastases.

We have previously demonstrated that 125I-lanreotide, when used with intraoperative gamma detection, can detect very small tumor burdens, including occult lymph node metastases in patients with gastrinoma. We hypothesized that intraoperative gamma detection of the radiolabeled somatostatin analog 125I-lanreotide could detect positive breast cancer resection margins and accurately assess axillary lymph node tumor status.

MATERIALS AND METHODS

Preparation of 125I-lanreotide

Lanreotide was radiolabeled with 125I using previously published methods. Briefly, lanreotide was obtained from Kinerton, Ltd. (Dublin, Ireland) and radiolabeled with Na125I using a modification of the chloramine T method. Five micrograms (5 μg) of lanreotide in 100 μl of 0.05 M potassium sodium phosphate buffer (KNaPO4), pH 7.0, was added to 1.5 mCi of Na125I buffered with 100 μl 0.5 M KNaPO4, pH 7.0. After bounce mixing the buffered Na125I and peptide, 5.7 μg of chloramine T in 10 μl of 0.05 M KNaPO4, pH 7.0, was added and allowed to react for 45 seconds. The reaction was terminated immediately with the addition of 57 μg of sodium metabisulfite in 100 μl of 0.05 M KNaPO4, pH 7.0. Two milliliters (2 ml) of 0.0005% injectable human serum albumin (HSA) in 0.05 M acetic acid was added to the reaction vessel, and the material transferred to a se-Pak C18 cartridge to separate iodinated peptide from free iodine. The C18 cartridge had been prestereilized with 5 ml of 70% ethanol activated with 5 ml of 2-propanol and rinsed with 12.5 ml of HPLC-grade water prior to applying the reaction mixture. After loading the reaction mixture, the C18 cartridge was washed with 5 ml of HPLC-grade water followed by 5 ml of 0.5 M acetic acid. Finally, the radiolabeled peptide was eluted with 5 ml of 96% ethanol. The labeled lanreotide was evaporated with dry nitrogen and purified by reverse phase (RP) HPLC. Buffers used for (RP) HPLC were (A) HPLC-grade water, (B) HPLC-grade methanol, and (C) potassium phosphate, pH 6.9. The gradients were 50% A to 0% A, 2-minute linear; 30% B to 60% B, 2-minute linear; and 20% C to 40% C, 2-minute linear. Flow was 1 ml/min. Fractions were collected and counted in a radioisotope dose calibrator, and the purified moniodinated 125I-lanreotide fraction evaporated to dryness in a 40°C water bath using a gentle stream of dry nitrogen. The final product was reconstituted with 0.9% NaCl in 0.05 M acetic acid. This solution was passed through a