

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

Maria C. Cuntz, MD, Edward A. Levine, MD, Thomas M. O'Dorisio, MD, James C. Watson, MD, Dawn A. Wray, MS, MA, Gregory D. Espenan, MS, Connie McKnight, MS-RN, J. Ralph Meier, MD, Luke J. Weber, MD, Robertino Mera, MD, PhD, M. Sue O'Dorisio, MD, PhD, and Eugene A. Woltering, MD

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 ^{125}I -lanreotide in 13 women with 14 primary breast carcinomas.

Methods: All patients were given ^{125}I -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 ^{125}I -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— ^{125}I iodine.

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

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From the Departments of Surgery (MCC, EAL, JCW, CM, EAW), Radiology (GDE), and Pathology (JRM) and The Stanley S. Scott Cancer Center (EAL, DAW, LJW, RM, EAW), Louisiana State University Medical Center, New Orleans, Louisiana; The Veterans Administration Medical Center (EAW), New Orleans, Louisiana; and The Departments of Medicine (TMO, MSO) and Pediatrics (MSO), The Ohio State University, Columbus, Ohio.

Address correspondence to: Eugene A. Woltering, MD, Chief, Section of Surgical Endocrinology, Director, Surgical Research, Louisiana State University Medical Center, 1542 Tulane Avenue, New Orleans, LA 70112.

cancers were multifocal with residual tumor in other quadrants.³ 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.²

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.⁴ 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.^{5,6} 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.⁷ 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 histologically 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.⁸ 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.⁸ Briefly, lanreotide was obtained from Kinerton, Ltd. (Dublin, Ireland) and radiolabeled with Na¹²⁵I using a modification of the chloramine T method.⁸ Five micrograms (5 μ g) of lanreotide in 100 μ l of 0.05 M potassium sodium phosphate buffer (KNaPO₄), pH 7.0, was added to 1.5 mCi of Na¹²⁵I buffered with 100 μ l 0.5 M KNaPO₄, pH 7.0. After bounce mixing the buffered Na¹²⁵I and peptide, 5.7 μ g of chloramine T in 10 μ l 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 μ g of sodium metabisulfite in 100 μ l 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 presterilized 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 monoiodinated 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

low protein binding 0.22 μm Millex-GV (Millipore Corp, Milford, MA) filter that had been preflushed with 2% injectable HSA (0.4 ml) in sterile 0.9% NaCl (4.6 ml). The injectable product was subjected to endotoxin and sterility tests before intravenous administration.

Fifteen patients with fine-needle aspiration- or core biopsy-proven primary breast cancers were identified. They signed an informed consent according to the guidelines set out by the Louisiana State University Human Subjects Review Board (LSU-IRB #2361) and the Federal Food and Drug Administration (IND #40,477). After signing an informed consent, the women were started on Lugol's iodine solution, 10 drops a day for 7 days prior to their breast cancer surgery. This therapy, along with Synthroid (0.1 mg/day for seven days postoperatively), was utilized to minimize any possible effect of ¹²⁵I on their thyroids. One woman was subsequently shown to have a false-positive fine-needle aspirate and had the excision of a benign (atypical hyperplasia) breast mass at the time of definitive surgery. This patient was excluded from further evaluation. An additional patient was studied who had a breast and axillary recurrence of her primary breast cancer. This patient's repeat axillary dissection yielded only three lymph nodes, and she was excluded from statistical evaluation in this trial. One woman had bilateral breast cancer, and each primary tumor and each axilla were evaluated independently. There were 13 evaluable women with 14 tumors, with a mean age of 58.6 years. The mean ¹²⁵I-lanreotide activity was 171.8 μCi, and the mean ¹²⁵I-lanreotide activity per kilogram was 2.18 μCi/kg (range, 0.89–3.57 μCi/kg). Three primary tumors were pathologically staged as T1, eight were T2, two were T3, and one woman had a T4

lesion. Estrogen-progesterone receptor status, ploidy, and S-phase fractions were evaluated (Table 1). On the day of surgery, women were injected with ¹²⁵I-lanreotide either in the preoperative holding area or in the operating room. A single surgeon (EAL) performed all of the surgical procedures, and another surgeon (EAW) independently performed all of the intraoperative scanning. In all patients the primary tumor was removed as a lumpectomy, independent of the tumor size or the patient's ultimate surgical procedure (lumpectomy with axillary dissection or modified radical mastectomy). Following resection of the primary tumor, the lumpectomy cavity was scanned using the hand-held gamma detector in scanning mode. In this mode, counts from normal breast tissue are obtained and stored in the hand-held gamma detector's computer. If tissue counts exceeding background $x + 3 \sqrt{x}$ background counts are discovered, an audible alarm is sounded. If the intraoperative gamma detector signaled a positive margin in the lumpectomy site, this was re-excised and sent for permanent pathology. To obtain pharmacokinetic and bio-distribution data, triplicate 10-second counts were obtained over the thyroid, four quadrants of each breast, nipple, stomach, liver, spleen, and heart at set intervals ranging from 5 minutes to 180 minutes (Table 2). The patients then underwent completion of their surgical procedure (axillary dissection or modified radical mastectomy). Following resection, the gamma detector was used to scan resection margins on the chest wall and in the axilla. Positive margins were excised and histologically analyzed. The gamma detector, when used in scanning mode, routinely issued positive signals over the ribs in the highest portion of the axilla. These areas were not

TABLE 1. Patient demographics^a

Patient	Age (y)	Weight (kg)	¹²⁵ I-lanreotide activity (μCi/kg)	Pathology stage	ER/PR	DNA index	S phase
1	50	128	.889	T3N1M0	-/-	1.4	16.5
2	46	73	1.46	T2N1M0	+/-	1.4	*
3	60	98	1.18	T4N1M0	+/-	1.9	4.9
4	66	64	3.57	T1N0M0	+/+	1.0	3.
5	48	104	1.03	T2N0M0	+/-	1.	*
6	64	71	1.69	T2N0M0	-/-	1.2	7.4
7	71	71	1.74	T2N0M0	-/-	1.0	7.1
8	52	75	1.55	T2N0M0	-/-	1.1	*
9	----- Recurrent cancer -----						
10	55	79	3.16	T2N0M0	+/-	0.7	*
11	74	84	3.14	T2N1M0	+/+	1.0	1.3
12	----- Benign disease -----						
13	51	59	2.75	T2N0M0	+/+	1.0	5.7
14	58	130	2.95	T1N0M0	+/-	1.0	*
15	76	74	2.85	T2N0M0	+/+	1.0	*

*. Specimen not evaluated.

^aPatients 9 and 12 were not part of this statistical evaluation.

TABLE 2. Gamma detection probe (counts/ μ Ci/10 seconds)

Organ	Time (after injection)					
	15 min	30 min	60 min	90 min	120 min	160 min
Normal Organs						
Thyroid	492 \pm 125	474 \pm 152	368 \pm 67	354 \pm 178	363 \pm 90	456 \pm 107
Heart	607 \pm 98	567 \pm 2760	791 \pm 681	394 \pm 103	455 \pm 200	395 \pm 111
Liver	2301 \pm 1086	4420 \pm 2992	12,160 \pm 1714	8869 \pm 8056	7684 \pm 5635	4550 \pm 4075
Spleen	476 \pm 198	717 \pm 509	691 \pm 140	278 \pm 49	616 \pm 171	612 \pm 204
Stomach	710 \pm 359	952 \pm 724	817 \pm 122	423 \pm 93	903 \pm 306	1018 \pm 422
Normal breast ^a						
12:00	365 \pm 116	412 \pm 215	348 \pm 99	296 \pm 9	345 \pm 109	NA
3:00	533 \pm 296	499 \pm 322	506 \pm 241	428 \pm 129	437 \pm 134	NA
6:00	801 \pm 614	665 \pm 534	719 \pm 659	549 \pm 484	536 \pm 357	NA
9:00	458 \pm 285	498 \pm 323	579 \pm 569	359 \pm 132	455 \pm 221	NA
Nipple	438 \pm 191	465 \pm 220	574 \pm 351	410 \pm 16	436 \pm 179	NA
Affected breast ^a						
12:00	444 \pm 156	440 \pm 168	390 \pm 130	195 \pm 9	464 \pm 5	400 \pm 171
3:00	531 \pm 199	559 \pm 302	705 \pm 322	236 \pm 97	595 \pm 203	245 \pm 159
6:00	460 \pm 198	446 \pm 238	296 \pm 108	250 \pm 59	639 \pm 295	334 \pm 142
9:00	527 \pm 107	502 \pm 191	525 \pm 35	229 \pm 90	472 \pm 288	221 \pm 137
Nipple	493 \pm 142	505 \pm 168	575 \pm 242	259 \pm 98	NA	NA

NA, not available.

^aProbe positions for breast counts are expressed using a clock axis.

excised, and these signals were felt to be due to distribution of the radiotracer in the bone marrow of the upper lateral thoracic ribs. Biodistribution studies of ¹²⁵I-lanreotide demonstrated high levels of uptake of this tracer in the liver, which is consistent with our previous reports on the liver as the primary organ of excretion of iodinated lanreotide and octreotide.^{8,9} Intense uptake of ¹²⁵I-lanreotide by the liver mandated that right lower breast and tumor cavities in this location be scanned with the detector parallel to the long axis of the body, rather than the normal perpendicular orientation.

Following completion of the modified radical mastectomy or the axillary lymph node dissection, the axillary contents were taken to the histology laboratory, and triplicate ex vivo counts of normal axillary fat were obtained (10 seconds \times 3) and meaned. The mean counts from the background fat (\bar{x}) were used for subsequent comparison to the counts obtained from each individual lymph node. Two hundred seventy (270) lymph nodes from these 14 axillas were evaluated. An average of 19.2 nodes (range, 9–41) were removed per axillary dissection. Each node was counted three times for 10 seconds and the counts meaned. Nodes were considered positive if their mean counts per 10 seconds exceeded axillary fat counts (\bar{x}) by three times the square root of the mean axillary fat background count ($\bar{x} + 3\sqrt{\bar{x}}$). The use of this formula paralleled the method used by the hand-held gamma counter (in scanning mode) to detect positive tumor resection margins. Comparisons of nodal histology and probe counts were done using McNemar's contingency test.

RESULTS

Thirteen women with 14 primary breast cancers had their tumor resected with the use of ¹²⁵I-lanreotide and intraoperative gamma detection. Seven of 13 women had either probe-positive or clinically suspicious margins re-excised. Of these seven suspicious margins, six were probe-positive, and one probe-negative area was re-excised on a clinical suspicion of tumor. Four of the six probe-positive margins were histologically positive, and two of six probe-positive margins were histologically negative. The single clinically suspicious margin was histologically positive.

A total of 270 lymph nodes were evaluated by the gamma probe and histology. Comparisons of gamma probe and histologic results were performed using McNemar's test for correlated proportions (Fig. 1). Results of McNemar's testing demonstrate a highly statistically significant correlation between histologic and gamma probe results ($\chi^2=31.9$, $P < .0001$). The overall sensitivity of ¹²⁵I-lanreotide and intraoperative gamma detection was 77%; the negative predictive value of this technique was 97%, however.

DISCUSSION

The use of minimally invasive breast cancer surgery has been increasing in popularity. Mammography traditionally has been used to guide primary tumor localization and resection for nonpalpable lesions. Mammography has a specificity of 87% to 97%, a sensitivity of 78%

		Histology	
		+	-
Probe	+	11 (4.1%)	55 (20.3%)
	-	6 (2.2%)	198 (73.3%)

FIG. 1. Results of McNemar's test for comparisons of histology and gamma probe data (percents) represent the fraction of nodes in each category (x/270).

to 96%, and a positive predictive value of 15% to 30%.¹⁰ Other tumor localizing techniques, such as Tc-99m sestamibi injection with prone breast imaging, have been used to guide primary tumor resection and have demonstrated a sensitivity of 92%, a specificity of 89%, and a negative predictive value of 95.8%.¹¹ Axillary lymph node evaluation with Tc 99m-sestamibi demonstrated a sensitivity of 60% and specificity of 90%.¹¹ Unfortunately, these techniques cannot help the surgeon to intraoperatively identify and localize tumor in resection margins or in all individual lymph nodes.

Furthermore, the surgeon's ability to detect positive resection margins is limited by his or her ability to see or feel the tumor. The use of frozen sections often helps with intraoperative assessment of tumor resection margins but lacks sensitivity compared to permanent section histology. Positive tumor resection margins seen on permanent sections require as many as 45% of women to undergo re-excision of their lumpectomy cavity.¹ In this age of cost containment, this is not cost effective. None of the women undergoing intraoperative gamma detection of ¹²⁵I-lanreotide were subsequently discovered on permanent histologic sections to have additional positive resection margins requiring re-excision. This technique may prove to be a cost-effective way to limit the need for reoperation. Other authors have determined that women with positive resection margins are at increased risk of developing local recurrence.¹⁻³ A technique that local-

izes positive tumor resection margins may initially be cost effective and may subsequently decrease the incidence of local recurrences, further increasing cost-effectiveness.

Bertsch et al. noted that, using the gamma probe as an intraoperative adjunct, surgeons could better identify the extent of recurrent colorectal disease. Occult metastatic disease was identified by ¹²⁵I anti-TAG 72 murine monoclonal antibody and the hand-held gamma detector.¹² In a recent study using ¹²⁵I-labeled CC49 murine monoclonal antibody for detection of histologically occult colon cancer by a hand-held gamma detector,¹³ this technique detected tumor in 40% of lymph nodes originally believed to be tumor-free on standard histological evaluation. Confirmation of the accuracy of the probe determination of positivity required serial section of each node and immunohistochemical evaluation. This suggests that the gamma probe can detect tumor burdens not seen by routine histology.¹⁴ Support for this concept is provided by a study by Oredipe et al. in which the limit of detection of an ¹²⁵I-labeled monoclonal antibody (17-1a and its F(ab=)5 fragment) was determined to be 4 × 10⁴ cells. This number of cells represents a tumor volume much less than 0.01 mm.² Unfortunately, ¹²⁵I-labeled monoclonal antibodies must be injected several weeks before surgery to allow clearing of background counts.¹⁴

The incidence of detection of micrometastases in axillary lymph nodes depends on the aggressiveness of the histologic evaluation. Commonly, lymph nodes are bisected and a single 5-μm section from each node is evaluated. In series in which serial sections or serial step sections are used, occult micrometastases are discovered in 9% to 24% of "negative" lymph nodes. The false-positive rate of our series (20%) is consistent with the results one might expect if negative nodes were subjected to serial sectioning.¹⁵⁻¹⁷ We currently are evaluating histologically negative but probe-positive nodes in this series by serial sections and immunohistochemistry.

CONCLUSIONS

This pilot trial had several significant limitations. Nodal negativity and positivity were defined by standard histologic techniques (all nodes bisected, single 5-μm sections evaluated). Other techniques such as serial step sectioning or immunohistochemical techniques are much more accurate than standard histology at defining the presence of micrometastasis. Techniques such as reverse transcriptase polymerase chain reactions (RT-PCR), immunohistochemical methods, or autoradiography may discover histologically undetectable axillary lymph node

metastasis and may more accurately predict nodal positivity or negativity.¹⁸

The activity of radiolabeled analog in this pilot trial varied from 100 to 260 μCi (0.89 to 3.57 $\mu\text{Ci}/\text{kg}$). This variation may have produced variation in nodal counts based on node size and low, but finite, background tracer uptake. A standard radioligand (2.5 $\mu\text{Ci}/\text{kg}$) activity may lessen variability in nodal counts. The volume (weight) of a lymph node also may affect the total counts obtained from a node. Future trials of this technique should weigh all lymph nodes, allowing expression of tracer distribution as (counts/ $\mu\text{Ci}/\text{kg}$ of patient weight)/(mg wet tissue weight).

This pilot trial included few women with positive lymph nodes. This significantly limits our ability to make positive predictive statistical statements but does not limit our ability to perform accurate power calculations. Sample size calculations for this pilot trial have been performed. We have made the assumption that the false-negative rate of a new technique should be less than 10%, a rate consistent with the reported false-negative rate of routine histology. In the pilot study, the probability of a false-negative node was 2.6%. The sample size required to detect an unacceptable level of false-negatives (>10%), which would invalidate the results of this pilot series, would be 900 lymph nodes, or 57 women (assuming resection of 16 nodes per woman). If a future validation study in a larger group of patients has a false-negative rate below 10%, there should be compelling evidence to conclude that histology and ¹²⁵I-lanreotide assessment of nodal status are comparable. This may allow the development of axillary sampling technique which excises only probe-positive nodes rather than performing a complete resection of the axillary contents.

In this pilot trial we have demonstrated the potential utility of ¹²⁵I-lanreotide and intraoperative gamma detection in the intraoperative management of women with primary breast carcinomas. This technique is safe and appears to be able to detect positive tumor resection margins in vivo and to accurately predict nodal negativity ex vivo. The intraoperative identification of positive nodes with radiolabeled tumor markers and gamma detection has been the subject of recent interest not only in patients with breast cancer, but also in patients with colorectal tumors and melanoma. Phase III trials of intraoperative gamma detection of ¹²⁵I-lanreotide are required to validate the utility of this technique for the intraoperative management of breast carcinoma.

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REFERENCES

- Gwin JL, Eisenberg BL, Hoffman JP, et al. Incidence of gross and microscopic carcinoma in specimens from patients with breast cancer after re-excision lumpectomy. *Ann Surg* 1993;218:729-34.
- Pitinger TP, Maronian NC, Poulter CA, Peacock JL. Importance of margin status in outcome of breast-conserving surgery for carcinoma. *Surgery* 1995;116:604-9.
- Carter D. Margins of "lumpectomy" for breast cancer. *Human Pathology* 1986;17:330-2.
- Montani MC, Levine EA, Watson JC, et al. Intraoperative gamma detection ¹²⁵I-lanreotide in women with primary breast carcinoma. Abstract. *Regul Pept* 1996;64:131.
- Morton DL, Wen D-R, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1993;127:392-9.
- Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994;220:391-401.
- van Eijck CHJ, Krenning EP, Bootsma A, et al. Somatostatin receptor scintigraphy in primary breast cancer. *Lancet* 1994;343:640-3.
- Woltering EA, Barrie R, O'Dorisio TM, O'Dorisio MS, Nance R, Cook DM. Detection of occult gastrinomas with iodine 125-labeled lanreotide and intraoperative gamma detection. *Surgery* 1994;116:1139-47.
- Woltering EA, O'Dorisio MS, O'Dorisio TM. The role of radiolabeled somatostatin analogs in the management of cancer patients. In: DeVita VT, Hellman S, Rosenberg SA (eds). *Principles and Practice of Oncology Updates*. Philadelphia: Lippincott-Raven Publishers, 1995;9(8):1-16.
- Kopans D. The positive predictive value of mammography. *Am J Roentgenol* 1992;158:521-6.
- Khalkhali I, Cutrone J, Mena I, et al. Technetium-99m-sestamibi scintimammography of breast lesions: clinical and pathological follow-up. *J Nucl Med* 1995;36:1784-9.
- Bertsch A, Burak WE Jr, Young DC, Arnold MW, Martin EW Jr. Radioimmunoguided surgery system improves survival for patients with recurrent colorectal cancer. *Surgery* 1995;118:634-9.
- Cote R. Intraoperative detection of occult colon cancer micrometastases using ¹²⁵I-radiolabeled monoclonal antibody CC49. *Cancer* 1996;77:613-20.
- Oredipe OA, Barth RF, Tuttle SE, et al. Limits of sensitivity for the radioimmunodetection of colon cancer by means of a hand held gamma probe. *Nucl Med Biol* 1988;15:595-603.
- Fisher ER, Swamidoss S, Lee CH, Rockette H, Redmond C, Fisher B. Detection and significance of occult axillary node metastasis in patients with invasive breast cancer. *Cancer* 1978;42:2025-31.
- International (Ludwig) Breast Cancer Study Group. Prognostic importance of occult axillary lymph node micrometastases from breast cancers. *Lancet* 1990;335:1565-8.
- Apostolikas N, Petraki C, and Agnantis NJ The reliability of histologically negative axillary lymph nodes in breast cancer. *Pathol Res Pract* 1989;184:35-8.
- Trojani M, DeMascara I, Bonichant F, Coindre JM, and Delsol G. Micrometastasis to axillary lymph nodes from carcinoma of breast: Detection by immunohistochemistry and prognostic significance. *Br J Cancer* 1987;55:303.