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Intraoperative radiocolloid injection for sentinel node biopsy postneoadjuvant chemotherapy

Huan N. Vu, MD,[a,*] *Rebecca R. Shoemaker, MD,*[b] *Patricia F. O'Connor, MD,*[c] *Wen Wan, PhD,*[d] *and Melvin J. Fratkin, MD*[e]

[a] *Department of Surgery and Massey Cancer Center, Virginia Commonwealth University, Richmond, Virginia*
[b] *Department of Physical Medicine and Rehabilitation, Wayne State University Detroit Medical Center, Detroit, Michigan*
[c] *Department of Dermatology, Virginia Commonwealth University, Richmond, Virginia*
[d] *Department of Biostatistics and Massey Cancer Center, Virginia Commonwealth University, Richmond, Virginia*
[e] *Department of Radiology, Virginia Commonwealth University, Richmond, Virginia*

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ABSTRACT

Background: This study sought to determine significance of radiocolloid injection timing for sentinel node biopsy (SNB) after neoadjuvant chemotherapy (NAC).
Material and methods: A retrospective comparison of intraoperative (IRCI) and preoperative (PRCI) radiocolloid injection for SNB was performed in breast cancer patients who had completed NAC. The sentinel node identification rate (SNIDR) was tested for noninferiority by a two-proportion z-test. The differences between clinical demographics, pathologic demographics, and SNIDR were evaluated by Fisher exact test. The difference in the number of sentinel nodes removed was analyzed by two-sample t-test.
Results: In the 6-y study period, 120 SNB were performed after NAC: 84 received PRCI and 36 received IRCI. The two groups were similar except there were fewer clinical T2 and more clinical T3 and T4 with IRCI ($P = 0.0008$). The SNIDR was 92.9% with PRCI and 80.6% with IRCI. By two-proportion z-test, IRCI was not "noninferior" ($P = 0.5179$). By Fisher exact test, the SNIDR of the two groups did not differ. The SNIDR differs only in patients who experience T downstaging (100% *versus* 80%, $P = 0.0173$). The mean number of lymph nodes removed was higher with IRCI: 3.38 *versus* 2.49 nodes ($P = 0.0068$). There were more positive SNB with IRCI: 32.1% *versus* 55.2%, ($P = 0.0432$). The incidence of nontherapeutic axillary dissection was similar between the two groups (3.6% for PRCI *versus* 5.6% for IRCI).
Conclusions: IRCI for SNB after NAC may be inferior to PRCI.

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1. Background

For breast cancer, the axillary nodal status has been crucial in determining the prognosis and need for adjuvant systemic therapy. Routine axillary nodal staging with axillary dissection, however, has not been shown to affect survival but has been associated with increased risk for arm lymphedema. To avoid nontherapeutic axillary dissection and reduce the incidence of lymphedema, axillary sentinel node biopsy (SNB) has become the standard of care for axillary nodal staging of breast cancer. With SNB, only a few axillary nodes are selected and excised for pathologic evaluation rather than an anatomically directed axillary dissection. The selection of the sentinel node frequently requires a preoperative injection of

* *Corresponding author*. Department of Surgery and Massey Cancer Center, Virginia Commonwealth University, PO Box 980011, Richmond, VA 23298. Tel.: +1 804 828 9322; fax: +1 804 828 4808.
E-mail address: hnvu@vcu.edu (H.N. Vu).
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radiocolloid (PRCI). A hand-held radiation probe is then used intraoperatively to identify the sentinel nodes for excisional biopsy.

To permit sufficient time for the radiocolloid to travel from the injection site to the axillary sentinel node, the injection is usually performed before the patient is anesthetized for the operation. The injection is directed into the ipsilateral breast, frequently into the subareolar space and can be uncomfortable for patients. Many have reported intraoperative injection of radiocolloid (IRCI) is equivalent to PRCI in patients with breast cancer [1–8].

Although SNB has become the standard of care for nodal staging of breast cancer, there remains debate over the role and timing of SNB for patients who receive neoadjuvant chemotherapy (NAC). At many institutions, SNB is performed before NAC, while at others SNB is delayed until the definitive operative management of the breast. The NSABP B-27 trial has supported SNB for breast cancer patients post-NAC [9]. But when patients presented with positive axillary node, the ACoSOG Z1071 trial suggested SNB as an alternative to routine axillary dissection post-NAC may yield an unacceptably high rate of false negative SNB at 12.6% [10]. All these studies have used PRCI. None of the IRCI studies have included patients after NAC [1–8]. This study sought to determine whether IRCI would be comparable with PRCI for sentinel node identification rate (SNIDR) in patients who have received NAC.

2. Material and methods

2.1. Study design

This is a noninferiority retrospective study. The primary objective was to compare the SNIDR between those patients with IRCI *versus* PRCI. The hypothesis is that the identification rate (p_1) of sentinel node in patients with IRCI is not lower than the rate (p_0) in those with PRCI.

After institutional review board approval was obtained to collect data, eligible patients were identified through the Massey Cancer Center patient registry. Inclusion criteria included all patients undergoing SNB for breast cancer at Virginia Commonwealth University Health System (VCUHS) from January 1, 2005–December 31, 2010. Only patients who had received NAC before their SNB were included. Patients who were treated for breast cancer without SNB were excluded.

2.2. SNB techniques

The Division of Surgical Oncology manages all surgical care for breast cancer at VCUHS. The injection sites of radiocolloid for sentinel node localization vary among the five active surgical oncologists of the division. Sentinel node mapping at VCUHS consists of PRCI with 1 mCi in 0.5 mL of filtered (0.22 μ) Tc-99m sulfur colloid. All surgeons inject in the subareolar location; some surgeons also include peritumoral or intradermal injection. All but one surgeon usually inject the sulfur colloid agent preanesthesia in the preoperative holding area. One surgeon routinely injects after induction of anesthesia in the operating room and subareolar. Five milliliters of Lymphazurin (Covidien, Mansfield, MA) is also routinely injected by all surgeons postanesthesia and subareolar before surgical incision for visual localization of sentinel node. Intraoperative audio localization of the sentinel node uses the C-Trak Automatic Analyzer system and the OmniProbe with collimator (Care Wise Medical Products Corp, Morgan Hill, CA).

2.3. Definitions

SNIDR is defined as the identification of at least one sentinel node among the patients who underwent SNB. Sentinel nodes are defined as hot and blue, hot but not blue, not hot but blue, and any abnormal node palpable on SNB. "Hot" is defined as nodal tissue with greater than 10% of the *ex vivo* count of the "hottest" sentinel node. All sentinel nodes are removed as part of the procedure. The clinical T stage (cT) and clinical N stage (cN) were obtained from the preoperative clinical records. The pathologic T stage (pT) and pathologic N stage (pN) were obtained from the pathology record of the surgical specimen. Tumor (T) downstaging is defined as a reduction of one or more T stage values from clinical T stage to the pathologic T stage. Clinically positive axillary node (cN+) was defined as palpable and suspicious per the surgeon. Fine needle aspiration of clinically or radiographically abnormal nodes was frequently used for confirmation but was not required. Node (N) downstaging is defined as conversion from cN + disease before NAC to pN0 stage.

2.4. Statistical analysis

The difference of the identification rate between the two groups ($p_1 - p_0$) was estimated for noninferiority with a two-sided 95% confidence interval and a prespecified noninferiority margin of 10% was applied. If the lower bound of the 95% confidence interval for the estimated difference was determined to be above −10%, the IRCI would be considered noninferior to the PRCI. The noninferiority test through a two-proportion z-test was also used. If the P value was <0.05, then IRCI would be considered not worse than the PRCI group in terms of the identification rate. The Fisher exact test was used to compare the two groups in terms of demographic characters, cT and cN stages, pT and pN stages, SNIDR, identification rate by pT and pN stages, the overall rate of positive sentinel nodes, the rate of positive sentinel nodes by pT stages, and axillary dissection findings. The two-sample t-test was used to compare the number of sentinel nodes by pT stage and numerical demographic characters. A two-sided type 1 error of 0.05 was used for each test to define statistical significance. Statistical analysis was performed using SAS 9.3 (SAS Institute Inc, Rockville, MD) and GraphPad Prism 5.0 (GraphPad Software Inc, La Jolla, CA). Statistical analysis was reviewed and confirmed by a biostatistician.

3. Results

3.1. Study population

A total of 904 SNBs were performed at our institution from January 1, 2005–December 31, 2010. Of these, eleven SNBs had incomplete records and were excluded from analysis. Of the