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ORIGINAL ARTICLE – BREAST ONCOLOGY

Sentinel Lymph Node Biopsy in Pregnant Women with Breast Cancer

Adrienne B. Gropper, MD[1], Katherina Zabicki Calvillo, MD[1], Laura Dominici, MD[1], Susan Troyan, MD[1], Esther Rhei, MD[1], Katherine E. Economy, MD[2], Nadine M. Tung, MD[3], Lidia Schapira, MD[4], Jane L. Meisel, MD[1], Ann H. Partridge, MD, MPH[1], and Erica L. Mayer, MD, MPH[1]

[1]Dana-Farber/Brigham and Women's Cancer Center, Boston, MA; [2]Brigham and Women's Hospital, Boston, MA; [3]Beth Israel Deaconess Medical Center, Boston, MA; [4]Massachusetts General Hospital, Boston, MA

ABSTRACT

Background. Sentinel lymph node biopsy (SNB) in pregnant women with breast cancer is uncommonly pursued given concern for fetal harm. This study evaluated efficacy and safety outcomes in pregnant breast cancer patients undergoing SNB.

Methods. Patients who underwent SNB while pregnant were identified from a retrospective parent cohort of women diagnosed with breast cancer during pregnancy. Chart review was performed to tabulate patient/tumor characteristics, method/outcome of SNB, and short-term maternal/fetal outcomes.

Results. Within a cohort of 81, 47 clinically node-negative patients had surgery while pregnant: 25 (53.2 %) SNB, 20 (42.6 %) upfront axillary lymph node dissection, and 2 (4.3 %) no lymph node surgery. Of SNB patients, 8, 9, and 8 had SNB in the first, second, and third trimesters, respectively. 99 m-Technetium (99-Tc) alone was used in 16 patients, methylene blue dye alone in 7 patients, and 2 patients had unknown mapping method. Mapping was successful in all patients. There were no SNB-associated complications. At a median of 2.5 years from diagnosis, there was one locoregional recurrence, one new primary contralateral tumor, three distant recurrences, and one breast cancer death. Among patients who underwent SNB, there were 25 liveborn infants, of whom 24 were healthy, and 1 had cleft palate (in the setting of other maternal risk factors).

Conclusions. SNB in pregnant breast cancer patients appears to be safe and accurate using either methylene blue or 99-Tc. This is one of the largest reported experiences of SNB during pregnancy; however, numbers remain limited. SNB rates in this cohort were lower than in non-pregnant breast cancer patients.

In breast cancer surgery, sentinel lymph node biopsy (SNB) is an accepted standard of care in patients with localized, clinically node-negative disease. In 2005, 65.5 % of early-stage breast cancer patients in the US underwent SNB.[1] Multiple historic randomized phase III trials have shown that SNB, with conversion to axillary lymph node dissection (ALND) if the sentinel node is positive or not identified, is equivalent to upfront ALND in terms of survival endpoints.[2,3] More recently, the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial demonstrated that survival after positive SNB alone is non-inferior to survival after subsequent conversion to full ALND.[4] SNB is superior to ALND with respect to morbidity and quality of life. With SNB alone, breast cancer patients experience less arm pain, numbness, and lymphedema; improved arm mobility; and decreased length of perioperative hospitalization in comparison to undergoing ALND.[2,5] In major studies, as well as in current practice, sentinel node mapping is performed by either injection of a 99 m-Technetium (99-Tc) radiolabeled colloid with gamma probe detection, injection of blue dye with subsequent intraoperative visualization, or both.[3]

Breast cancer is the most common pregnancy-associated malignancy, with incidence estimated as high as 1 in 3,000 pregnancies.[6] This incidence is projected to increase as

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E. L. Mayer, MD, MPH
e-mail: emayer@partners.org

more women pursue child-bearing later in life.[7] Many of the treatment paradigms used in non-pregnancy-associated breast cancer can be used without complication in women diagnosed during pregnancy, but given consideration for fetal well-being, changes to standard paradigms may also be considered.[8] In striking a balance between optimal treatment for the mother and minimization of risk to the fetus, the role of SNB in pregnancy has been the subject of controversy. In 2001 and 2005, two consensus panels recommended against SNB in pregnancy, and in 2006 an international panel conceded that the method could be considered after informed discussion between surgeon and patient.[8–10] The potential concerns surrounding SNB in pregnant patients have been numerous, including fetal harm from radiation exposure in the context of radiocolloid use, fetal harm from possible teratogenicity of blue dyes, and fetal harm from maternal anaphylaxis to isosulfan blue dye, among others.[11–14] Despite concerns, SNB has been offered to women with breast cancer during pregnancy; however, there are only limited data to date describing the experience and safety of this procedure in pregnant women.

In prior analysis of a cohort of patients with breast cancer in pregnancy treated at the Dana-Farber/Harvard Cancer Center (DF/HCC: Dana-Farber/Brigham and Women's Cancer Center, Massachusetts General Hospital, Beth Israel Deaconess Medical Center), we have shown favorable obstetrical and fetal outcomes with the use of contemporary chemotherapy regimens and schedules.[15] In this analysis, we queried the DF/HCC breast cancer in pregnancy cohort for women who had undergone SNB while pregnant, to describe the type and result of sentinel node evaluations, maternal disease outcomes, and fetal well-being outcomes.

METHODS

A retrospective cohort of women diagnosed with breast cancer during pregnancy and treated at the DF/HCC between 1996 and 2013 was assembled as previously described through structured search of the DF/HCC clinical database.[15] In addition, medical oncologists, breast surgeons, and maternal-fetal medicine specialists at DF/HCC institutions were asked to identify patients in their practices with a history of breast cancer during pregnancy. Eligibility criteria included pathologically confirmed breast cancer diagnosed during pregnancy, two or more follow-up visits for breast cancer treatment at a DF/HCC institution, and age >18 years. Subsequently, patients from the full cohort who had undergone SNB during pregnancy were identified. Chart review of each SNB patient was used to tabulate patient demographics, breast cancer characteristics, method and outcome of SNB, procedural complications, obstetrical complications, and short-term maternal/fetal outcomes.

TABLE 1 Patient and tumor characteristics of 25 women who underwent SNB while pregnant

Patient/tumor characteristic	Number (N = 25)	Percent
Age at diagnosis (years)		
Median (range)	35 (26–41)	
Year of diagnosis		
2004–2008	10	40.0
2009–2013	15	60.0
Stage		
0	3	12.0
1	9	36.0
2A	7	28.0
2B	6	24.0
ER/PR positive	15	60.0
HER2 positive	9	36.0
Triple negative	7	28.0

SNB sentinel lymph node biopsy, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

Sentinel lymph nodes (SLNs) from patients whose operations were performed at outside institutions underwent central review at one of the DF/HCC pathology laboratories as part of standard clinical practice. If a patient delivered at an outside institution, she was contacted by mail for permission to acquire copies of the medical records from the outside institution. This study was approved by the Dana-Farber Cancer Institute Institutional Review Board. Analyses were descriptive in nature.

RESULTS

The parent cohort contained 81 women diagnosed with breast cancer during pregnancy between 1996 and 2013, 55 of whom underwent surgery for breast cancer while pregnant. Of 55 surgical patients, 47 were clinically node-negative, and 8 were clinically node-positive. Of the clinically node-negative patients, 20 (42.6 %) underwent upfront ALND, 25 (53.2 %) underwent SNB, and 2 (4.3 %) had no nodal evaluation during surgery, both of whom had invasive disease. All eight clinically node-positive patients had upfront ALND.

Table 1 shows the patient and tumor characteristics for the 25 women who underwent SNB while pregnant. Sixteen women (64.0 %) had 99-Tc sulfur colloid alone used to perform their SNB, whereas seven (28.0 %) had methylene blue dye alone used. No woman received both radiocolloid and methylene blue dye together. SNB method was unknown in two women (8.0 %). Table 2 documents SNB procedural details. Dose range for 99-Tc sulfur colloid was 3.7–48.1 MBq (average: 25.6 MBq); dose range for blue dye was 1–5 ml. There were no complications of SNB in any patients. All women had successful

TABLE 2 Surgical and sentinel lymph node biopsy characteristics

Procedure characteristic	Number (N = 25)	Percent
Gestational age at SNB (weeks)		
Median (range)	17 (4–32)	
0–12	8	32.0
13–23	9	36.0
24–40	8	32.0
Method of SNB		
99-Tc radiocolloid alone	16	64.0
Same-day injection	14	
Day-before injection	2	
Methylene blue alone	7	28.0
Radiocolloid + methylene blue	0	0.0
Unknown	2	8.0
SNB procedural complications	0	0.0
Number of SLN identified		
Median (range)	2 (1–10)	
≥1 SLN positive for macrometastases	5	20.0
≥1 suspicious intraoperative node positive for macrometastases[a]	1	4.0
Underwent subsequent axillary lymph node dissection[b]	6	24.0
Number of ALN removed		
Median (range)	18 (10–28)	
≥1 ALN positive for metastasis	3	12.0
Type of breast surgery		
Mastectomy	13	52.0
Lumpectomy	12	48.0

ALN axillary lymph node, *ALND* axillary lymph node dissection, *SLN* sentinel lymph node, *SNB* sentinel lymph node biopsy, *99-Tc* 99m-Technetium

[a] A single SLN was identified and was negative in this patient

[b] One woman underwent ALND 8 months after SNB, with 0/11 nodes positive. One woman underwent ALND 15 days after SNB, with 5/10 nodes positive

TABLE 3 Exposures during pregnancy

Systemic treatment	Number (N = 25)	Percent
Chemotherapy		
Any chemotherapy	14	56.0
AC	13	52.0
AC + T	1	4.0
Hormonal therapy	0	0.0
Radiation therapy	0	0.0

AC adriamycin/cytoxan, *T* paclitaxel

identification of at least one SLN. Five women had one or more sentinel node(s) positive for macrometastasis. One woman had one negative SLN, but a non-sentinel node that appeared clinically suspicious intraoperatively was excised and found to be positive for macrometastasis. These six women went on to have ALND, and three had further axillary metastases identified, including the woman with negative SLN. Non-surgical treatments received for primary breast cancer during pregnancy are listed in Table 3. Of the 34 women who underwent ALND (28 upfront plus 6 following SNB), 4 (11.8 %) subsequently developed lymphedema, compared with 1 of 19 women (5.3 %) who had SNB without ALND.

TABLE 4 Gestational outcomes

Gestational outcome	Number (N = 25)	Percent
Intrauterine complications		
Cord prolapse	1	4.0
SGA at delivery	2	8.0
Gestational age at delivery (weeks)		
Mean (range)	37 (34–40)	
Infant health		
Healthy at delivery	24	96.0
Cleft palate[a]	1	4.0
Apgar scores		
≤7 at 1 min	3	12.0
≤7 at 5 min	0	0.0
Unknown	9	36.0

SGA small for gestational age (<10th percentile for weight)

[a] In the setting of multiple maternal risk factors, i.e. smoking, methadone use

Gestational outcomes are shown in Table 4. Of the 25 pregnancies documented, 25 resulted in liveborn infants. A single episode of cord prolapse was the only intrauterine complication recorded. Twenty-four of the 25 liveborn infants were classified as healthy at delivery. One baby was born with cleft palate; of note, the mother in this case had additional risk factors, including smoking and methadone use. SNB method used in this case, and timing of SNB in relation to diagnosis of the fetal abnormality, was unknown. Of the 16 babies with known Apgar values, 3 had scores ≤7 at 1 min and none had scores ≤7 at 5 min.

At a median follow-up of 2.5 years from the time of diagnosis, there was one (4.0 %) new primary tumor in the contralateral breast, one (4.0 %) local recurrence, and three women (12.0 %) had distant breast cancer metastasis (locations of initial distant metastasis: femur, liver, pleura and liver). One woman (4.0 %) had died of breast cancer.

DISCUSSION

This is the largest single cohort to date of breast cancer patients who underwent SNB while pregnant. Women in this group had a lower rate of SNB (53.2 % of clinically

node-negative surgical patients) than that described in the general breast cancer population (65.5 % of early-stage breast cancer patients in the United States National Cancer Data Base in 2005),[1] and a significant proportion (42.6 %) of women with a clinically node-negative axilla underwent upfront ALND despite potentially being SNB candidates. Moreover, women undergoing ALND experienced postoperative lymphedema at a higher rate than those who underwent SNB alone (11.8 % vs. 5.3 %), an observation further supporting the benefit of SNB over ALND, especially in a young breast cancer population. The majority of patients in this cohort had SNB by the radiocolloid method, although many had methylene blue mapping. The selection of method mirrors our institutional practice for non-pregnant patients; isosulfan blue is generally not selected due to concern for allergic reactions. Regardless of method, SNB was successful in all patients, with at least one sentinel node retrieved, and was a safe procedure, with no maternal complications and generally excellent health in the infants born.

Four previously published case series have described maternal and/or fetal outcomes following SNB in pregnancy for any cancer. The first examines nine pregnant women who underwent SNB (six for melanoma, three for breast cancer), all of whom delivered healthy infants at term.[16] The majority (78 %) of patients in this series had SNB after the first trimester; SNB was performed using radiocolloid alone in four patients, isosulfan blue dye alone in two patients, and a combination in three patients. The second series describes ten SNBs in pregnant breast cancer patients, whose pregnancies resulted in one elective termination and nine healthy deliveries.[17] Average gestational age at SNB was 15.8 weeks, and SNB methods used were combined radiocolloid and dye (six patients), radiocolloid alone (two patients), and isosulfan blue dye alone (two patients). The third series evaluated 12 patients who underwent SNB during pregnancy, and went on to deliver 11 healthy babies.[11] One infant was born with ventricular septal defect, which had been suspected on ultrasound prior to SNB. At longer-term follow-up (median 32 months, range 6–83 months), all children were reportedly doing well. Radiocolloid alone was used for SNB in all patients. In the fourth and final series, 15 pregnant melanoma patients who underwent SNB are documented.[18] Median gestational age at SNB was 20 weeks, with only three patients having SNB during the first trimester. SNB methods used were combined radiocolloid and blue dye (nine patients), radiocolloid alone (five patients), and blue dye alone (one patient); both methylene blue and isosulfan blue dye were used. Two minor perinatal complications (hypertension/tachycardia and jaundice) were observed, but all children were healthy at median 54.4 months' follow-up.

The increasing preference for use of radiocolloid injection alone in SNB during pregnancy may reflect the results of studies proposing the safety of 99-Tc to an unborn fetus. General consensus suggests that fetal radiation doses of >200 mGy can lead to physical or cognitive developmental deficits,[19] while levels >100 mGy may confer some increased risk of fetal malformations or decreased intelligence quotient.[20,21] Some sources cite fetal doses as low as 10–50 mGy as potentially increasing risk for malignancy.[20] The International Commission on Radiation Protection states that <100 mGy of fetal radiation need not provide a basis for pregnancy termination.[19] Multiple groups have attempted to estimate the amount of radiation that a fetus could absorb from a standard SNB procedure, via a variety of methods: injecting radiocolloid into non-pregnant breast cancer patients and modeling its distribution in worst case scenarios ($N = 2$); [21] retrospective phantom-based internal dosimetric estimation in non-pregnant SNB/breast cancer patients ($N = 1021$);[19] and prospective study of calculated uterine radiation from SNB ($N = 14$).[12] Calculated or modeled fetal radiation exposure by these methods ranges from 1.14 μGy to 4.3 mGy, well below the threshold of concern for fetal harm, and in the realm of the background radiation absorbed on an average day in the US.[12,19,21] Practical means of minimizing fetal radiation should be implemented in pregnant patients, including injection of the lowest possible radiocolloid dose. In addition, one group's modeling implies that fetal radiation exposure may be lower with same-day as opposed to day-before radiocolloid injection.[19,20]

In contrast, two main areas of concern persist regarding the use of blue dyes (typically either isosulfan blue or methylene blue) in SNB procedures. First, isosulfan blue has been documented to cause allergic reactions in a small percentage of patients. Studies estimate the overall prevalence of allergic reactions of all types (comprising a spectrum from the dermatologic response of 'blue hives' to full anaphylaxis) at 0.8–2.0 %,[22] while anaphylactic reactions with cardiovascular effects are estimated at 0.25–1.1 %[2,23] prevalence. No patients in our cohort were mapped with isosulfan blue, which is standard institutional practice for non-pregnant patients as well, reflecting concern for allergic reactions. Second, both isosulfan blue and methylene blue are pregnancy class C drugs, with an unknown potential for teratogenicity.[12] In vitro, methylene blue has been shown to cause DNA damage at clinically used concentrations.[24] Moreover, the dye was previously used intra-amniotically, in which context it caused prenatal and neonatal complications. It is unknown whether this translates into any risk to a fetus from maternal lymphatic mapping with methylene blue, although one pharmacokinetic study demonstrated that up to 5 % of an administered dose could reach the fetus. The administered dose for sentinel node lymphatic mapping is 50–100 times less than that used intra-amniotically.[25] Of the 30 total pregnant patients documented in the literature (7 from this cohort,

plus a combined 23 from prior case series[16–18]) who received blue dye for SNB mapping, 1 electively terminated her pregnancy, and 29 gave birth to healthy infants. Thus, it remains unclear whether theoretical safety concerns around blue dye have true clinical implications.

Outside of concerns about methodological safety, a final category of apprehension toward SNB during pregnancy focuses on the accuracy of the procedure in the pregnant breast cancer population. Concern has been raised regarding the trend away from using dual methods (radiocolloid plus blue dye) for SLN mapping in pregnancy.[8] While one of the two large original trials documenting equivalency of SNB and ALND in terms of survival outcomes used radiocolloid alone,[2,3] some analyses have concluded that there is a greater chance of successful SLN localization with use of a combined method.[25,26] However, many surgeons at our institutions do not routinely utilize dual tracer for non-pregnant patients. Another hypothetical concern has been that physiologic modifications of breast glands' lymphatic drainage during pregnancy may decrease the accuracy of lymphatic mapping in SNB. In this cohort, there was one instance of what would be considered a false negative SLN result. Although the true false negative rate in the cohort is unknown, this single failure would certainly fall within the range of false negatives seen in studies of non-pregnant women.[27] Lastly, there is the question of whether disease profiles differ in pregnant as opposed to non-pregnant breast cancer patients.[13] Breast cancer diagnosed during pregnancy may tend to have aggressive features, but most recent analyses suggest no significant differences in disease-free or overall survival in patients with breast cancer diagnosed and treated during pregnancy compared with non-pregnant comparison groups, when controlled for stage.[6,7,28–30] Data on whether the incidence of axillary metastasis is higher in pregnant versus non-pregnant breast cancer patients are also conflicting.[14,31] Thus, there are no firm data suggesting that a clinical standard supporting upfront SNB over ALND cannot be applied to pregnant patients. Of note, the contemporary paradigm evaluated in the ACOSOG Z0011 and European Organisation for Research and Treatment of Cancer (EORTC) After Mapping of the Axilla: Radiotherapy Or Surgery (AMAROS) trials of deferral on completion ALND in those with positive SNB who will subsequently undergo regional irradiation may not be readily applicable to patients who are pregnant due to the need to defer on radiotherapy until after delivery, but deserves further study .[4,32]

CONCLUSIONS

This cohort study represents the largest series of pregnant patients undergoing SNB reported for any cancer, suggests favorable maternal and fetal outcomes, and highlights the use of upfront ALND in a population of patients who might otherwise have been SNB candidates, possibly related to practitioners' reluctance to perform SNB procedures during pregnancy. Given the relatively small number of patients diagnosed with cancer during pregnancy, it is not likely that large or randomized studies will ever definitively describe the safety of SNB in pregnancy. Thus, the strongest data available come from cohort studies such as the one presented here, which, although reassuring, is limited by small numbers and lack of follow-up of children's outcomes. Based on the presented data, as well as a lack of strong evidence to support theoretical concerns, SNB appears to be both a safe and accurate procedure in this population. Pregnant breast cancer patients and providers alike will benefit from continued focus on this topic in future investigations.

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