ORIGINAL ARTICLE

Pregnancy-Associated Breast Cancer Patients Can Safely Undergo Lymphatic Mapping

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■ **Abstract:** As more women put off pregnancy until their 30s and beyond, the possibility of pregnancy-associated breast cancer (PABC) will rise. Treatment options for patients with PABC need to consider possible harm to the fetus. The goal of this study is to review our institution's experience with sentinel lymph node (SLN) biopsies in patients with PABC. A prospectively accrued breast Institutional Review Board (IRB) approved data base was searched under separate IRB approval for cases of SLN biopsy in patients with PABC. Ten patients were identified between 1994 and 2006 out of 5,563 patients. A chart review was performed on all 10 patients. Ten patients with PABC and an average gestation age of 15.8 weeks underwent SLN biopsy. All patients successfully mapped. Positive SLN were identified in 5/10 patients (50%) while there was no evidence of metastases in 5/10 patients (50%). 9/10 (90%) of patients went on to deliver healthy children without any reported problems. One patient (10%) decided to terminate her pregnancy in the first trimester following surgery prior to the start of chemotherapy. SLN biopsy can safely be performed in patients with PABC with minimal risk to the fetus. By performing a SLN biopsy, a large proportion of patients with PABC may be spared the risk of a complete axillary lymph node dissection. ■

Key Words: breast cancer, lymphatic mapping, pregnancy, sentinel lymph node biopsy

Pregnancy-associated breast cancer (PABC) is diagnosed more frequently and is expected to become more common as women often delay bearing children into the fourth and fifth decades of their lives. PABC represents a small but complex group of patients requiring significant forethought regarding the trimester of pregnancy, fetal development, risk of miscarriage, and treatment plan as it may have profound effects on each of these considerations. Treatment options must consider possible harm to the fetus and safety for the mother. Documentation of the safe application of lymphatic mapping in PABC was the aim of this retrospective single institutional study.

METHODS

An Institutional Review Board (IRB)-approved Health Insurance Portability Accountability Act compliant breast cancer data base and electronic health record (IRB# 102554) was prospectively accrued on 5,563 patients undergoing SLN biopsy from 1994 to 2006. Under separate IRB approval (IRB# 14723), this data set was queried for all PABC patients in the Moffitt Cancer Center data base who underwent lymphatic mapping. Prior to surgery and injection with Tc-99m and/or isosulfan blue dye (Lymphazurin; US Surgical Corp, Norwalk, CT), all patients were separately consented for mapping injection with care in disclosure of the fact that the effects were unknown but thought to be safe to the mother and fetus of the doses and timing of the injection and use of these agents. The safety of administration of radioactive colloid was based on several factors. A small dose of 225–450 μCi was used (1/60th the dose for a normal bone scan) and the site of administration (breast) was physically removed with minimal calculated fetal exposure. The majority of Tc-99m was removed by surgery.

RESULTS

Ten PABC patients aged 24–42 years underwent lymphatic mapping and sentinel lymph node (SLN)

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biopsy (six with blue dye and Tc-99m, two with Tc-99m only, and two with blue dye only; see Table 1 for characteristics of each patient). The average gestational age of each baby was 15.8 weeks. All patients had successful mapping of a SLN. The average number of SLN excised was 4.3 with an average number of 0.8 positive SLN. Complete axillary lymph node dissection (CALND) was performed in three patients (30%) at the time of surgery. In two patients (25%), CALND was delayed until after chemotherapy completed. Five patients (50%) were spared an axillary dissection because the SLN was negative. Surgery included mastectomy 20% (2/10) or lumpectomy 80% (8/10). The average tumor size was 3.1 cm. Seven patients had an invasive ductal carcinoma and two patients had invasive lobular carcinoma. One patient, who was found to be pregnant on the day of surgery, underwent a prophylactic mastectomy with sentinel node biopsy at the time of a modified radical mastectomy on the opposite breast for a 2.5 cm invasive ductal cancer. Nine (90%) patients gave birth to healthy children and the one (10%) patient found to be pregnant at the day of her surgery terminated the pregnancy by her choice in the first trimester after surgery prior to starting chemotherapy. No problems have been reported in any of the delivered children. With an average follow-up of 1.82 years, three patients (30%) with PABC have passed away. There were no intra-operative complications such as allergic reactions to blue dye in any of these patients.

DISCUSSION

The surgical management of PABC is a challenge. Breast cancer incidence in pregnancy is rare (1:3,000 to 1:10,000) (1). Most cancers (including breast, cervical, thyroid, and other malignancies) (38/100,000) are diagnosed in the postpartum period and fewer are diagnosed prenatally and at delivery (18/100,000 and 15/100,000) (2). Although the incidence of PABC is low, it may be increasing because of many more women delaying child-bearing until a later age (3). The impact of BRCA1 and BRCA2 mutations upon the incidence of PABC is not clear. One small study showed that BRCA1 mutation carriers were more likely than BRCA2 mutation carriers to have PABC. However, since women who carry a BRCA1 or BRCA2 mutation are more likely to have breast cancer at a younger age, the association between these mutations and PABC may be coincidental (4).

Imaging of breast cancer diagnosed and treated during pregnancy has been studied and can be useful. A recent study showed that of 20 women who were imaged prior to surgery by mammography, findings were positive in 18 (90%), despite dense breast parenchymal patterns (Breast Imaging and Reporting System types 3 and 4). Ultrasound depicted a mass in all the 20 patients imaged with cancer (100%) (5).

Pathologic features of breast cancer diagnosed during pregnancy have been described. The majority of women have tumors that are diagnosed at a more advanced stage and have poor prognostic features. In one study of 39 patients with PABC, the mean age at presentation was 33 years and mean tumor size was 4.5 cm. Of these patients, 37 women had stage II, III, or IV disease. High-grade invasive ductal carcinoma was found in 32/38 (84%) of patients (6). Many tumors were estrogen and progesterone receptor negative (6,7). Her-2/neu expression was positive in 7/39 (18%) of patients and the proliferation rate as shown by Ki-67 staining was high in 60% of the cases (6). One study suggests that morphologic features might vary according to whether the patient is pregnant, lactating, or had recently terminated pregnancy or lactation (8).

Surgical management of the PABC patient can include mastectomy or breast conservation. However, the options must be tailored according to each individual patient's clinical presentation and proper consideration must be given to these options in order to avoid harm to the fetus. Mastectomy and complete axillary lymph node removal can be performed with minimal risk to the developing fetus or the continuation of the pregnancy and is the traditional treatment for PABC diagnosed during the first trimester (3). However, there is an increased risk of spontaneous abortions with general anesthesia in those in their first or second trimester of pregnancy (9). Breast conserving surgery in the PABC patient is technically possible but the radiation therapy required to complete local therapy is contraindicated during pregnancy because of the risk of harm to the fetus. Therefore, during the second or third trimester, breast conserving surgery may be performed and radiation therapy given during the postpartum period. Neo-adjuvant or adjuvant chemotherapy can be given during the second or third trimester with little risk to the fetus (3). This strategy has been employed in a number of patients in which an initial lumpectomy and SLN biopsy was performed and the patients then underwent their chemotherapy

Table 1. Characteristics of Each Pregnant Patient Undergoing SLN Biopsy

Patient	Age	Weeks gestation	Operation	Method SLN	Tumor type	Tumor size (cm)	Tumor Grade	Number SLN	SLN (+)	Number total nodes	Total nodes (+)	Follow-up (years)	Disease status	Pregnancy status	Notes
1	42	20	Lumpectomy, SLN, and CAND	TC-99 and Blue Dye	Lobular	3.0	Unknown	4	3	14	4	1.50	Dead	Delivered healthy child	Mastectomy performed secondary to inability to obtain negative margins
2	33	15	Lumpectomy, SLN, and CAND	Blue Dye only	Ductal	3.0	3	4	1	12	1	1.50	Dead	Delivered healthy child	
3	31	11	Lumpectomy and SLN	Tc-99 only	Lobular	1.7	1	2	0	2	0	2.90	Alive	Delivered healthy child	Re-excision lumpectomy performed
4	24	5	Lumpectomy and SLN	TC-99 and Blue Dye	Ductal	2.0	2	3	0	3	0	2.60	Alive with disease	Terminated pregnancy	Terminated pregnancy after surgery prior to chemo
5	27	19	Mastectomy, SLN, and CAND	TC-99 and Blue Dye	Ductal	8.2	3	10	2	21	2	2.10	Dead	Delivered healthy child	
6	27	32	Lumpectomy and SLN	TC-99 and Blue Dye	Ductal	3.5	3	2	0	5	0	1.40	Alive	Delivered healthy child	
7	39	16	Lumpectomy and SLN	TC-99 and Blue Dye	Ductal	2.9	3	6	1	6	1	0.50	Alive	Delivered healthy child	CAND performed after chemo (0/14 nodes positive)
8	37	28	Lumpectomy and SLN	TC-99 only	Ductal	2.5	2	5	1 (i+)	5	1 (i+)	0.48	Alive	Delivered healthy child	CAND planned for after chemo
9	33	4	Prophylactic mastectomy and SLN	Blue Dye Only	Prophylactic	2.5 (opposite breast)	3 (opposite breast)	4	0	4	0	2.81	Alive	Delivered healthy child	Modified radical mastectomy on opposite side for a 2.5 cm invasive ductal tumor
10	33	8	Lumpectomy and SLN	TC-99 and Blue Dye	Ductal	1.6	2	3	0	3	0	2.54	Alive	Delivered healthy child	
AVG	33	15.8				3.1	2.4	4.3	0.8	7.3	0.8	1.82			

after which a period of time between chemotherapy and the initiation of radiation the patient was able to deliver the child; nurse the child with the initial colostrum and then begin radiation therapy. A recent article by Gentilini *et al.* included 38 PABC patients (21 had breast cancer diagnosed during pregnancy and 17 presented with breast cancer during lactation) with a mean tumor size of 2.4–2.5 cm. Six women were in their first trimester and preferred termination of their pregnancy although other options were discussed. Five patients received anthracyclin containing chemotherapy during their second and third trimester with no complications for the patient or fetus (7). Breast conserving surgery is a potentially suitable option for all PABC patients and should be discussed with the patient whenever possible. Conservative surgery was performed for 15 of 21 patients during pregnancy with no recurrence after a 24-month median follow-up. Three women underwent lymphatic mapping and SLN biopsy (7).

According to our data and others, about half of PABC patients will have node negative disease and, therefore, would benefit from the use of the minimally invasive technique of lymphatic mapping and SLN biopsy (7). SLN biopsy and lymphatic mapping can be safely performed in the pregnant woman with breast cancer. Tc-99m localization has been shown to have minimal radiation exposure and low risk to the fetus (10,11). One study of lymphoscintigraphy after Tc-99m peritumoral injection in 26 premenopausal nonpregnant women showed no radioactive tracer concentration except in the injection site and in the sentinel node (12). The immediate surgical resection of the breast tissue and lymph nodes removes the majority of Tc-99m making this procedure safe and unique in PABC women. An additional study estimated the fetal dose of 99m Tc-sulfur colloid to be 0.014 mGy or less with an 18.5 MBq injection the day before surgery. This level is far less than the National Council on Radiation Protection and Measurements limit to pregnant women (13).

Isosulfan blue has a possible risk of an allergic/anaphylactic reaction, which can increase the risk of harm to the fetus. Although the incidence of severe anaphylactic reactions has been noted at or less than 1% (14–17), we believe that this risk should be avoided if the patient has good drainage on lymphoscintography or as detected with the gamma probe at the time of the surgical procedure. Furthermore, there are some reports of possible skeletal or neurologic defects in rat models (18). Isosulfan blue should be avoided in first trimester patients because of these concerns. For this reason, Tc-99m by itself may be safer than blue dye. However, isosulfan blue dye in the second and third trimesters was used without incident in the PABC patients in this series. Methylene blue has been used for sentinel node biopsies as an alternative to isosulfan blue with a lower anaphylactic reaction risk (14). Unfortunately, methylene blue is contraindicated in the pregnant patient because of known teratogenic and consequent effects of vascular accidents causing intestinal atresia. Historically, methylene blue was used by obstetricians to inject into the amniotic sac to detect rupture of membranes. However, there was a high incidence of jejunal atresia possibly due to the vasoconstrictive effects of methylene blue in blocking nitric oxide (19).

Our data produces a similar safety pattern to already published studies on SLN biopsies in PABC (20,21). For the nine women who carried their pregnancy forward, all delivered healthy children with no reported problems. The use 99m Tc-sulfur colloid and blue dye did not affect the decision of the one patient who decided upon abortion after surgery and prior to chemotherapy.

In conclusion, lymphatic mapping can be performed safely in PABC patients. Current consensus is that radiocolloid mapping is the preferred method to avoid fetal risk of dye exposure as isosulfan blue may have potential fetal effects in the first trimester and to avoid the potential for anaphylactic reactions in the mother further putting the fetus at risk. Our experience, however, emphasizes that the use of blue dye in selected patients without good radiocolloid mapping as determined intra-operatively may be safe in the second and third trimester with careful patient monitoring for dye reaction and fetal monitoring for overall safety during anesthesia. When compared with CALND, the SLN biopsy is a minimally invasive technique with less morbidity and can be performed under local anesthesia. SLN biopsy should be part of the standard surgical management of PABC.

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