ORIGINAL ARTICLE – BREAST ONCOLOGY

Nipple-Sparing Mastectomy in 99 Patients With a Mean Follow-up of 5 Years

J. Arthur Jensen, MD, Jay S. Orringer, MD, and Armando E. Giuliano, MD

Department of Surgical Oncology, John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, CA

ABSTRACT

Background. The safety and practicality of nipple-sparing mastectomy (NSM) are controversial.

Methods. Review of a large breast center's experience identified 99 women who underwent intended NSM with subareolar biopsy and breast reconstruction for primary breast cancer. Outcome was assessed by biopsy status, postoperative nipple necrosis or removal, cancer recurrence, and cancer-specific death.

Results. NSM was attempted for invasive cancer (64 breasts, 24 with positive lymph nodes), noninvasive cancer (35 breasts), and/or contralateral prophylaxis (50 breasts). Twenty-two nipples (14%) were removed because of positive subareolar biopsy results (frozen or permanent section). Seven patients underwent a pre-NSM surgical delay procedure because of increased risk for nipple necrosis. Reconstruction used transverse rectus abdominis myocutaneous flaps (56 breasts), latissimus flaps with expander (35 breasts), or expander alone (58 breasts). Of 127 retained nipples, 8 (6%) became necrotic and 2 others (2%) were removed at patient request. There was no nipple necrosis when NSM was performed after a surgical delay procedure. At a mean follow-up of 60.2 months, all 3 patients with recurrence had biopsy-proven subareolar disease and had undergone nipple removal at original mastectomy. There were no deaths.

Conclusions. Five-year recurrence rate is low when NSM margins (frozen section and permanent) are negative. Nipple necrosis can be minimized by incisions that maximize perfusion of surrounding skin and by avoiding long flaps. A premastectomy surgical delay procedure improves nipple survival in high-risk patients. NSM can be performed safely with all types of breast reconstruction.

The observation that nipple-sparing mastectomy (NSM) produces a cosmetic outcome superior to traditional non-NSM can be traced in the modern era to a presentation by Bromley Freeman in 1961. In his published report, Freeman denied that his idea was original and cited a work from 1882 to support the contention that NSM is an inherently less mutilating procedure than total mastectomy.[1] NSM achieves a better cosmetic outcome, but is it practical and safe for the patient with breast cancer?

As early as 1984, Hinton et al. reported that NSM achieved local recurrence and early survival rates equivalent to those for modified radical mastectomy.[2] Nonetheless, the oncologic community has remained skeptical. Prominent surgeons have concluded that "nipple sparing is not a reasonable option for mastectomy patients" and that "nipple areolar complex-sparing mastectomy may carry an unacceptable high risk for local relapse and should therefore not be advocated."[3,4]

The controversy over the safety of NSM may be similar to the early controversy over the safety of breast-conserving procedures. Only a generation ago, the medical community was divided over the question of whether lumpectomy was as safe as mastectomy.[5] In 2002, Veronesi et al. and Fisher et al. reported 20-year follow-up data for two independent multicenter trials comparing lumpectomy, lumpectomy followed by radiation, and mastectomy for breast cancers 4 cm and smaller.[6,7] Although the trials had different designs, both included two treatment arms in which the nipple was preserved and one treatment arm in which the nipple was removed. The fact that neither of these prospective randomized trials identified a treatment-related difference in long-term survival is evidence that removal of the nipple is not associated with a survival advantage in the initial treatment of breast cancer.[8,9]

A. E. Giuliano, MD
e-mail: giulianoa@jwci.org

Starting in 1997, we offered NSM to selected cancer patients who were considering mastectomy and breast reconstruction. This study describes the oncologic criteria for patient selection and reviews the surgical results of NSM with respect to its practicality and safety.

METHODS

Candidates for NSM included women who had a diagnosis of invasive or noninvasive breast cancer and were interested in the possibility of preserving the nipple-areolar complex (NAC). Patients who had known or suspected lymph node involvement were eligible. Those with tumor involvement of the skin or nipple, invasive or noninvasive tumors immediately under the NAC, or bloody nipple discharge were not eligible. Also excluded were patients who believed that the risk of NAC recurrence outweighed the projected benefit of nipple preservation.

During the informed consent process, subjects were fully informed that the long-term risks of NAC preservation were not certain but that the breast conservation literature showed no survival advantage for immediate removal of the nipple. All women were told that the NAC would be preserved as a full-thickness flap, if possible, and a subareolar biopsy specimen would be obtained at the time of mastectomy. If frozen section analysis of the subareolar tissue showed cancer, the nipple would be removed at the time of mastectomy. If frozen section analysis showed no cancer but permanent section showed disease postoperatively, subsequent removal of the nipple would be performed. Nipples were not removed for borderline pathologic changes such as atypia. All subjects were cautioned that the blood supply to the nipple comes largely from the breast tissue itself and an attempt at nipple preservation might result in postoperative necrosis of the nipple, requiring subsequent removal even with no sign of cancer. This study was approved by the Human Investigations Institutional Review Board of the John Wayne Cancer Institute.

During the 10-year study period, surgical incisions for NSM evolved from periareolar to lateral or even inframammary incisions to maximize perfusion of the nipple. Mastectomies were performed as for any breast cancer; the goal was to remove as much glandular tissue as possible with flaps as thin as possible. Only a thin layer (<2 mm) of subdermal tissue with only the subdermal plexus was retained behind the NAC (Fig. 1). All fat and glandular tissue was removed. Postoperative radiation or systemic adjuvant treatments were determined by patient-related and tumor-related characteristics and were not altered by the presence or absence of the NAC.

As we gained more experience with NSM, we recommended a premastectomy surgical delay procedure for women with a perceived higher chance of postmastectomy nipple necrosis.[10] Indications for the delay procedure included an active history of cigarette smoking, preexisting surgical scars that would restrict blood supply to the nipple after mastectomy (such as circumareolar scars; Fig. 2), or a suprasternal notch-to-nipple distance of 28 cm or greater (ptotic breast). During our outpatient delay procedure, the skin of the anterior breast and the NAC is surgically separated from the blood supply of the underlying breast tissue. This is performed in the same plane as a standard mastectomy; the ducts going to the nipple are cut at the thickness of the subdermal plane of mastectomy. The delay procedure differs from a circumareolar biopsy because a biopsy is not undertaken to separate the nipple from its underlying vascular supply. The purpose of surgical separation is to stimulate blood flow from the surrounding skin to the NAC in the days before mastectomy and thereby reduce the risk of nipple necrosis after mastectomy. The delay procedure also allows premastectomy subareolar biopsy, the results of which can aid plans for breast reconstruction. NSM is performed 7 to 10 days after the delay procedure.

Standard procedures were performed for breast reconstruction. These included tissue expansion followed by placement of a permanent silicone gel or saline-filled breast
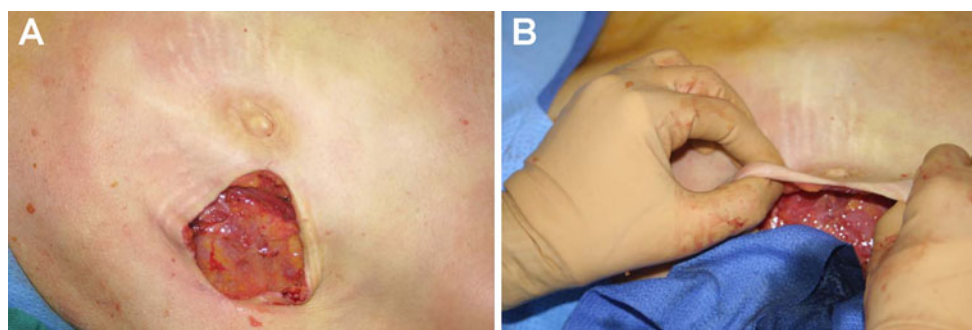
FIG. 1 Nipple-sparing mastectomy performed using a lateral incision (**a**) that allows excellent exposure of the axillary tail. Patients without long flaps or other risk factors tolerate thin subareolar flaps (**b**) as long as perfusion of the nipple-areolar complex approaches 360 degrees
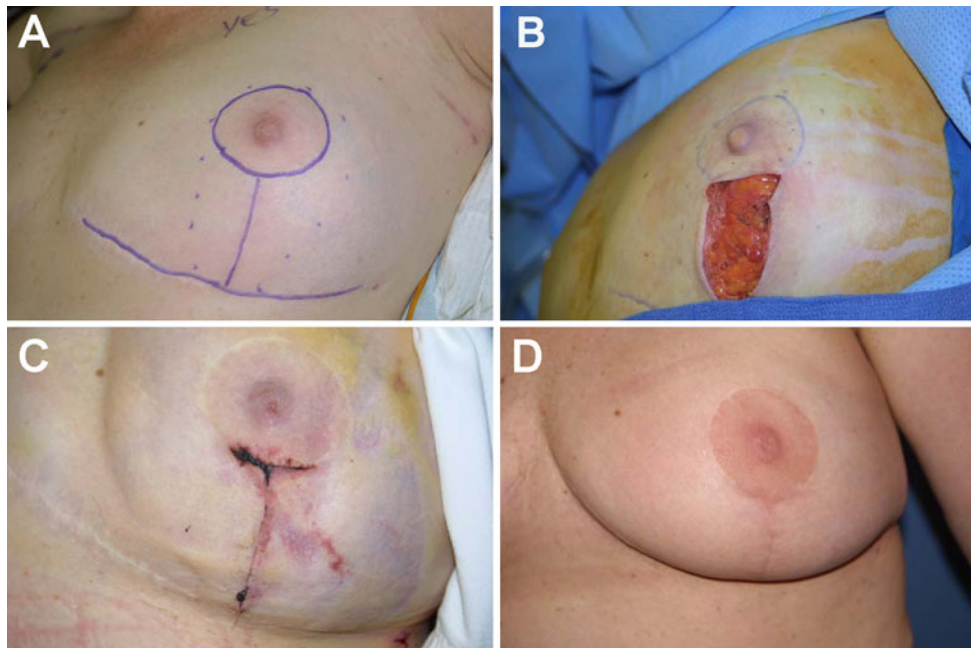
FIG. 2 Planned nipple-sparing mastectomy (NSM) after previous mastopexy (circumareolar inverted T scar) (**a**). An outpatient surgical delay procedure (**b**) performed 1 week before NSM ensured maximum perfusion of the nipple-areolar complex (**c**). Final reconstruction preserved all nipple tissue without loss of pigment (**d**)

implant, latissimus dorsi myocutaneous flap reconstruction with an expander/implant, or a microvascular muscle-sparing free transverse rectus abdominis myocutaneous (TRAM) flap.

Outcome measures included subareolar biopsy results with intraoperative nipple removal, viability of the retained nipple (postoperative nipple necrosis), postmastectomy removal of the nipple, postoperative reconstructive flap loss, infection requiring implant removal, local recurrence of breast cancer, and death.

RESULTS

Between October 1997 and September 2008, a total of 149 NSM procedures were undertaken in 99 women who had invasive ductal cancer ($n = 48$), invasive lobular cancer ($n = 16$), or ductal carcinoma in situ ($n = 35$). Of the 149 NSM procedures, 50 were contralateral mastectomies performed at the patient's request for risk reduction, prophylaxis and/or symmetry of reconstruction.

The 99 subjects had a mean age of 51 years, mean height of 65 inches, and mean weight of 142 pounds (mean body mass index 23.3). Five subjects were smokers. Of 21 patients who had undergone prior lumpectomy for their breast cancer, 19 also had received postoperative radiotherapy.

Mean diameter of the primary breast tumor was 2.4 cm (range 0.2–6.8 cm) for invasive cancer and 3.7 cm (range 0.5–10.0 cm) for ductal carcinoma in situ. Of the 64 patients with invasive cancer, 28 had American Joint Committee on Cancer (AJCC) stage I disease, 26 had stage II disease, and 10 had stage III disease; 24 (37%) of 64 patients had axillary lymph node metastasis, with 1 to 18 tumor-positive nodes.

At the time of mastectomy, frozen section analysis of the subareolar biopsy specimen demonstrated invasive or noninvasive cancer in 21 patients (15% of mastectomies, 21% of patients, and 21% of breasts with cancer); in each case the NAC was sacrificed. (One of these patients, who underwent successful NSM in the contralateral breast, subsequently requested removal of her noninvolved nipple for symmetry; this nonnecrotic nipple was removed several months later.) One subareolar biopsy specimen was tumor-free on frozen section analysis but positive for ductal carcinoma in situ on permanent section analysis. This was the only false-negative frozen section examination (false-negative rate <1%). There were no false-positive frozen section evaluations.

Of the 127 NACs that were preserved (because the subareolar biopsy specimen was negative on frozen and permanent sections), 8 (6.3%) developed ischemic necrosis during the early postoperative period. Seven of these cases were associated with ptotic breasts (nipple-to-notch distance of ≥28 cm), one of which had undergone prior irradiation. In one case the breast was not ptotic (nipple-to-notch distance of 22 cm) but the mastectomy incision was along the superior margin of the NAC, allowing only 180 degrees of perfusion.

A premastectomy surgical delay procedure was performed in 7 of the 99 subjects, who were believed to be at high risk for postoperative nipple necrosis because of identified risk factors. None of these subjects developed nipple necrosis after mastectomy.

Breast reconstruction consisted of 56 TRAM flaps (37%) (54 muscle-sparing free flaps, 2 "delayed" unipedicle flaps), 35 latissimus dorsi myocutaneous flaps plus tissue expanders (23%), and 58 expander/implant reconstructions (40%). Of the 149 procedures, only one (1.7%) required a return to the operating room, to repair vascular occlusion of a microvascular free flap. All TRAM and latissimus dorsi flaps survived. No tissue expanders or implants were removed because of infection, skin necrosis, or exposure.

Of the 99 subjects in this study, 16 (16%) underwent subsequent radiotherapy to the reconstructed breast. At a mean postoperative follow-up of 60.2 months (range 12–144 months), there have been no deaths and no nipple recurrences. Mastectomy skin flap recurrence developed in 3 (14%) of 22 patients who underwent NAC removal because of a positive subareolar biopsy specimen, as compared with 0 recurrences in the 77 patients whose NAC was preserved because the subareolar biopsy specimen was negative ($P = 0.0034$). One of the 3 patients developed a distant metastasis 5 years after her non-NSM. In all 3 of these cases, the breast cancer recurred within 2 cm of the original mastectomy incision. Because none of the recurrences occurred in patients whose NAC was retained, surgical exposure in these cases was no different than in a standard non-NSM.

DISCUSSION

Our 5-year mean follow-up data indicate a low rate of breast cancer recurrence in the chest wall and NAC when NSM is performed in patients with a tumor-free subareolar biopsy specimen. Indeed, the only chest wall failures observed in this study were in patients who had tumor involvement of subareolar tissue and underwent nipple removal at mastectomy. Radiotherapy may have been important in achieving the low rate of local recurrence because 16% of the patients in this study underwent postoperative radiotherapy.

Hinton et al. compared patients treated with NSM and implant reconstruction to a control group of patients treated by simple mastectomy alone.[2] At 56 months of follow-up, they concluded that local "flap" recurrence and overall survival rates were not greatly different between the two treatment groups. Attention should be drawn to the description of "subcutaneous" mastectomy specified by this study: "The skin flaps…are of the same thickness as in simple mastectomy…. Thus subcutaneous mastectomy differs from simple only in that no skin is excised and the nipple remains intact."

Gerber et al. reported remarkably similar results in a study of comparable size (61 patients vs. 70 patients reported by Hinton et al.).[2,11] Mean duration of follow-up was 56 months in the Gerber study and 59 months in the Hinton study; recurrence rates were 5.7% and 5.4%, respectively. The percentage of patients with AJCC stage II/III breast cancer was 81% in the Gerber study vs. 49% in the Hinton study; corresponding rate of postoperative radiotherapy was 27% vs. 0. Both groups concluded that NSM did not result in marked differences in local recurrence or survival rates compared to nonrandomized controls. In a recent update, Gerber et al. showed that with a mean follow-up of 101 months, NSM seems safe.[12]

A comparison of various reports of NSM (Table 1) demonstrates some unsurprising conclusions.[2,11–18] First, when NSM is performed in patients with stage II and stage III disease, local recurrence increases; and second, when patients with NSM are followed up for longer periods, more local recurrences will be found. In a study reported by Petit et al., intraoperative radiotherapy of the retained NAC did not increase nipple necrosis.[13] However, because reported local recurrences rarely involve the retained nipple, it is unclear whether intraoperative radiotherapy is necessary.[19] In patients with stage II and stage III disease, consideration should be given to postoperative radiotherapy, as for procedures that sacrifice the nipple.

Two lines of data converge to support the safety of NSM. The assertion that initially aggressive surgery does not improve breast cancer survival has been examined in randomized, prospective studies with extended follow-up.[5–7] These breast conservation studies found no difference in survival if nipples were removed, as they were in the mastectomy groups, or retained, as they were in the lumpectomy groups. Smaller, nonrandomized studies focused on NSM.[14,16,17,20] These studies found low rates (0% to 1.7%) of local recurrence within the NAC at approximately 5 years of follow-up. Recurrence within the skin flaps of patients with 5-year follow-up and comparable disease ranges from 3% to 6%.[2,11,12,16,17,20]

Higher local failure is reported by Benediktsson and Perbeck in their study from Sweden, which accumulated 216 patients treated from 1988 to 1994.[18] Patients were followed up for a minimum of 11.6 years, with a median follow-up of 13 years. Local failure rate was 24% but there were only 8 recurrences (4%) in the retained NAC. The surgical procedure left a 5-mm layer of glandular tissue beneath the NAC, which had a diameter of 2 cm. In their study, 53% of patients had stage II or stage III breast cancer and 40.3% had tumor-involved lymph nodes. The rate of local failure was 8.5% in patients who received pre-

TABLE 1 Reported rates of recurrence after nipple-sparing mastectomy for breast cancer

Study	No. of cancer patients	Duration of follow-up (months)	Rate of NAC necrosis (%)	Rate of recurrence (%)		Patients with stage II/III disease (%)
				Skin flap	NAC	
Hinton[2]	70	56	4	5.7	0	49
Gerber[11,12]	60	101	10	11.7	1.7	81
Crowe[14,15]	58	41	2	3	0	17
Margulies[16]	28	8	4	0	0	29
Petit[13]	102	13	5	1	0	NA
Sacchini[17]	64	25	11	3	0	16
Benediktsson[18]	216	156	8	24	4	53
Current study	99	60	6	3	0	36

NAC nipple-areolar complex, *NA* not available

or postoperative radiotherapy, as compared with 28.4% in patients who did not receive radiotherapy. Locoregional recurrence was independent of lymph node status or clinical stage, and it compared favorably with the locoregional recurrence rates reported in studies of modified radical mastectomy from Scandinavia.[21,22]

NSM should be considered not only for patients with breast cancers but also for women who seek risk reduction. Subcutaneous mastectomies were performed at the Mayo Clinic from 1960 to 1993. Of the more than 1,000 women treated, 639 sought prophylactic mastectomy because of a family history of breast cancer.[23] The risk of developing breast cancer was reduced 90% by this treatment. Such an impressive study addresses the well-intentioned concerns of earlier critics of this procedure.[24,25] Of the 639 women, only 7 developed breast cancer, and only 1 of the 7 developed breast cancer in a retained nipple. Blood samples were collected from 176 women thought to be at highest risk and genetic tests were performed.[26] *BRCA* abnormality was identified in 26 women; at a mean follow-up of 13.4 years none of these women had developed breast cancer. These data argue strongly that NSM has a role in the *BRCA*-positive patient. If the cosmetic outcome of mastectomy were improved, more women might choose to have such risk-reduction surgery. We are currently investigating NSM for women with *BRCA* mutations.

Some patients would not seem to be good candidates for nipple preservation because of well recognized risk factors for flap necrosis: history of cigarette smoking, previous incisions restricting postmastectomy blood supply to the retained nipple (Fig. 2), or breast ptosis.[27] Indeed, in our early experience, nipple necrosis was observed most commonly in patients with long, thin flaps as demonstrated by a preoperative nipple to suprasternal notch distance of greater than 28 cm. In 7 of the patients reported in this study who had one or more of these risk factors, a premastectomy surgical delay procedure was recommended to maximize the chances of postmastectomy NAC survival. This procedure also had the benefit of allowing

premastectomy evaluation of subareolar tissue. A surgical delay allows NSM to be offered to patients who might seem to be poor candidates for nipple preservation because of concerns about postoperative NAC perfusion.[28]

NSM results in a conflict for the oncoplastic team. A good NSM must be performed using incisions that allow adequate surgical exposure and are in the thin surgical plane to avoid future occurrence or local recurrence of breast cancer, but long thin mastectomy flaps are at higher risk for postoperative necrosis. Our operation is similar to that described by Hinton et al.[2] It is a mastectomy differing from a total mastectomy only in the amount of skin preserved and preservation of the NAC. Thick flaps and retained breast tissue must be avoided. Subcutaneous mastectomies often leave thick flaps with breast tissue under the NAC and in the low axilla. This amount of retained breast is likely to lead to recurrent or new cancer. Attention to detail with careful construction of thin flaps, "complete" glandular resection, and cooperation and planning between surgical oncologist and plastic surgeon will result in a safe, aesthetic mastectomy.

REFERENCES

1. Freeman BS. Subcutaneous mastectomy for benign breast lesions with immediate or delayed prosthetic replacement. *Plast Reconstr Surg.* 1962;30:676–82.
2. Hinton CP, Doyle PJ, Blamey RW, et al. Subcutaneous mastectomy for primary operable breast cancer. *Br J Surg.* 1984;71:469–72.

3. Simmons RM, Brennan M, Christos P, King V, Osborne M. Analysis of nipple/areolar involvement with mastectomy: can the areola be preserved? *Ann Surg Oncol.* 2002;9:165–8.

4. Cense HA, Rutgers EJ, Lopes Cardozo M, Van Lanschot JJ. Nipple-sparing mastectomy in breast cancer: a viable option? *Eur J Surg Oncol.* 2001;27:521–6.

5. Crile G Jr, Esselstyn CB Jr, Hermann RE, Hoerr SO. Partial mastectomy for carcinoma of the breast. *Surg Gynecol Obstet.* 1973;136:929–32.

6. Veronesi U, Cascinelli N, Mariaani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med.* 2002;347:1227–32.

7. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* 2002;347:1233–41.

8. Jensen JA. When can the nipple-areolar complex safely be spared during mastectomy? *Plast Reconstr Surg.* 2002;109:805–7.

9. Jensen JA. Breast cancer: is nipple-sparing mastectomy safe? *Ann Surg.* 2009;250:657.

10. Palmieri B, Baitchev G, Grappolini S, Costa A, Benuzzi G. Delayed nipple-sparing modified subcutaneous mastectomy: rationale and technique. *Breast J.* 2005;11:173–8.

11. Gerber B, Krause A, Reimer T, et al. Skin-sparing mastectomy with conservation of the nipple-areolar complex and autologous reconstruction is an oncologically safe procedure. *Ann Surg.* 2003;238:120–7.

12. Gerber B, Krause A, Dieterich M, Reimer T, Kundt G. The oncological safety of skin sparing mastectomy with conservation of the nipple-areolar complex and autologous reconstruction: an extended follow-up study. *Ann Surg.* 2009;249:461–8.

13. Petit JY, Veronesi U, Orecchia R, et al. Nipple-sparing mastectomy in association with intra operative radiotherapy (ELIOT): a new type of mastectomy for breast cancer treatment. *Breast Cancer Res Treat.* 2006;96:47–51.

14. Crowe JP Jr, Kim JA, Yetman R, et al. Nipple-sparing mastectomy: technique and results of 54 procedures. *Arch Surg.* 2004;139:148–50.

15. Crowe JP Jr, Patrick RJ, Yetman RJ, Djohan R. Nipple-sparing mastectomy update: one hundred forty-nine procedures and clinical outcomes. *Arch Surg.* 2008;143:1106–10.

16. Margulies AG, Hochberg J, Kepple J, et al. Total skin-sparing mastectomy without preservation of the nipple-areolar complex. *Am J Surg.* 2005;190:907–12.

17. Sacchini V, Pinotti JA, Barros A, et al. Nipple-sparing mastectomy for breast cancer and risk reduction: oncologic or technical problem? *J Am Coll Surg.* 2006;203:704–14.

18. Benediktsson KP, Perbeck L. Survival in breast cancer after nipple-sparing subcutaneous mastectomy and immediate reconstruction with implants: a prospective trial with 13 years median follow-up in 216 patients. *Eur J Surg Oncol.* 2008;34:143–8.

19. Rusby JE, Kirstein LJ, Brachtel EF, et al. Nipple-sparing mastectomy: lessons from ex vivo procedures. *Breast J.* 2008;14:464–70.

20. Caruso F, Ferrara M, Castiglione G, et al. Nipple sparing subcutaneous mastectomy: sixty-six months follow-up. *Eur J Surg Oncol.* 2006;32:937–40.

21. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med.* 1997;337:949–55.

22. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet.* 1999;353(9165):1641–8.

23. Hartmann LC, Schaid DJ, Woods JE, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N Engl J Med.* 1999;340:77–84.

24. Goodnight JE Jr, Quagliana JM, Morton DL. Failure of subcutaneous mastectomy to prevent the development of breast cancer. *J Surg Oncol.* 1984;26:198–201.

25. Goldman LD, Goldwyn RM. Some anatomical considerations of subcutaneous mastectomy. *Plast Reconstr Surg.* 1973;51:501–5.

26. Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in *BRCA1* and *BRCA2* gene mutation carriers. *J Natl Cancer Inst.* 2001;93:1633–7.

27. Spear SL, Hannan CM, Willey SC, Cocilovo C. Nipple-sparing mastectomy. *Plast Reconstr Surg.* 2009;123:1665–73.

28. Jensen JA. Nipple-sparing mastectomy: what is the best evidence for safety? *Plast Reconstr Surg.* 2009;124:2195–7.