Ann Surg Oncol (2014) 21:2237–2244
DOI 10.1245/s10434-013-3446-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

The Role of Radiation Therapy after Nipple-Sparing Mastectomy

Caitlin Gomez, MD[1], Chirag Shah, MD[2], Susan McCloskey, MD[1], Nova Foster, MD[3], and Frank Vicini, MD, FACR[4]

[1]Department of Radiation Oncology, University of California, Los Angeles, Los Angeles, CA; [2]Department of Radiation Oncology, Summa Health System, Akron, OH; [3]Department of General Surgery, University of California, Los Angeles, Los Angeles, CA; [4]Michigan HealthCare Professionals/21st Century Oncology, Farmington Hills, MI

ABSTRACT

Purpose. The aim of this review was to examine the incidence of nipple-areola complex (NAC) involvement, the rates of NAC recurrence, and the data regarding the role of radiation therapy (RT) following nipple-sparing mastectomy (NSM).

Methods. A literature review was performed using the PubMed search engine, with articles selected based on standardized criteria. Additional articles included those known to the authors and those obtained by review of references from key studies.

Results. The reported incidence of NAC involvement ranges from 0 to 58 %. The most commonly associated factors with NAC involvement include tumor-to-NAC distance, tumor size, central location of the primary tumor, multicentricity/multifocality, and positive axillary lymph nodes. Following NSM, in the setting of proper patient selection, rates of NAC recurrence are generally low, with the majority of studies reporting rates ranging from 0 to 4 %. There is a paucity of data evaluating the role of RT after NSM and a lack of level I evidence, with the largest series documenting low rates of local recurrence with RT but failing to provide a control arm without radiotherapy.

Conclusions. Optimal preoperative patient selection for NSM and intraoperative assessment of the NAC result in acceptably low rates of NAC involvement/recurrence. NSM alone is not adequate justification for post-mastectomy radiation. NSM should be taken into consideration to inform radiation decision making only when preoperative imaging, clinical features, or pathologic findings suggest higher risk for NAC involvement.

Surgical techniques in the management of breast cancer have evolved significantly since the introduction of the radical mastectomy by Halsted in the 1800s.[1] While mastectomy was once considered the standard of care for all stages of breast cancer, several phase III trials have shown equivalent breast cancer-specific survival with breast conserving surgery and radiation compared with mastectomy.[2–8] While this data led to an increase in the use of breast conservation, more recently mastectomy rates have been steadily rising.[9] With these increased rates of mastectomy, cosmetic outcomes after mastectomy have become a growing concern. The nipple-areola complex (NAC) has traditionally been included in the mastectomy specimen given concern for a risk of NAC recurrence or new primary breast cancer in the remaining breast tissue. This concern may have been based on early descriptions of centripetal lymphatic drainage towards the subareolar plexus, as described by Sappey in 1885.[10] However, removal of the NAC impairs cosmesis and women may feel a greater sense of mutilation with the loss of the NAC.[11] An alternative to the modified radical mastectomy (MRM) or simple mastectomy is the nipple-sparing mastectomy (NSM), which has been found to have a positive impact on patient satisfaction and body image, compared with mastectomy and nipple reconstruction.[11] While several studies have addressed the incidence of NAC involvement in breast cancer and the incidence of NAC recurrence following NSM, these studies were limited by small numbers and a lack of prospective data. Furthermore, there are limited data on the role of radiation therapy (RT) in the setting of NSM. Therefore, the purpose of this review is to examine the incidence of NAC involvement, the rates of NAC recurrence, and the data regarding the role of RT following NSM.

First Received: 7 September 2013;
Published Online: 1 April 2014

F. Vicini, MD, FACR
e-mail: fvicini@rtsx.com

MATERIALS AND METHODS

A literature review was performed using the PubMed search engine with combinations of the following keywords: 'nipple sparing mastectomy', 'breast cancer', 'radiation therapy', 'nipple areola complex involvement', and 'predictors of nipple involvement'. No official review protocol was created for this review. Based on an initial search, 357 articles were found and, after duplicates were removed, 30 articles were ultimately selected based on abstract relevance. Additional studies were identified based on a review of the references from these articles, as well as studies known to the authors. When multiple updates were available from a single institution, the most recent data was utilized. References were included from 1976 to 2012, in addition to a single reference from 1885 for historical context. All searches were completed by 23 July 2013.

RESULTS

Nipple Involvement in Breast Cancer

The reported incidence of NAC involvement in mastectomy specimens varies significantly in the literature, ranging from 0 to 58 % (Table 1).[12–34] This wide range of reported incidence is likely due to variations in specimen processing, patient populations, and the definition of NAC involvement, as well as the inclusion of specimens with clinically suspicious nipples in multiple studies.

The incidence of nipple involvement in studies that explicitly excluded patients with clinical suspicion of nipple involvement was 0–31 %.[18,22,24,27] In studies that specifically included patients with clinical suspicion of involvement, the incidence of pathologic nipple involvement was 8–58 %.[12,13,15,16,19–21,27,28,30–32] Laronga et al.[24] evaluated 286 skin-sparing mastectomy (SSM) specimens and found NAC involvement in 16 (5.6 %) of the specimens. The histology associated with positive specimens was either ductal carcinoma in situ (DCIS) or pagetoid spread in the majority of cases. Of the 16 positive cases, only four would have been identified on the frozen section of the retroareolar region and in three of those cases, the NAC involvement was contiguous with the primary tumor. Furthermore, location of the primary tumor (subareolar or multicentric vs. peripheral) and positive axillary lymph nodes were associated with occult NAC involvement; however, larger size, higher nuclear grade, and ER/PR receptor status were not associated.[24] Brachtel et al.[27] examined 232 mastectomy specimens and found 49 (21 %) to have nipple involvement (defined as involvement up to 5 mm below areolar skin). The majority of the 49 involved NAC specimens had DCIS histology (62 %). Similar to Laronga et al. the retroareolar tissue was evaluated to determine if NAC involvement could reliably be predicted at the time of surgery. Unlike Laronga et al.[24] however, Brachtel et al. found that 45 of the 49 involved nipples had involvement of the retroareolar margins, with a sensitivity for retroareolar tissue sampling of 0.8, and a negative predictive value of 0.96. Larger tumor size, shorter tumor-to-nipple distance, and Her-2/neu amplification were significantly associated with occult NAC involvement on multivariate analysis.[27] Morimoto et al. evaluated the NAC in 141 mastectomy specimens up to 20 mm below the skin and found 44 cases (31 %) with NAC involvement, 22 (16 %) of which occurred within the first 5 mm.[18] Larger tumor size, shorter tumor-to-areola distance, 'cancerous extension' and, to a lesser extent, positive lymph node involvement and papillotubular carcinoma tumor histology were associated with occult NAC involvement. Older data have found lower rates of NAC involvement; Verma et al. [22] examined 26 simple mastectomy specimens, to a depth of 1 cm from the areolar skin, and found 0 % NAC involvement. The low incidence of NAC involvement was likely due to the very small cohort and the inclusion criteria of tumor-to-NAC distance of at least 2.5 cm. Several studies have found that tumor-to-NAC distance less than 2.5 cm is significantly associated with a higher incidence of NAC involvement.[15,18,19,23,27,28,30,33]

In addition to shorter tumor-to-NAC distance, multiple studies have identified other factors associated with NAC involvement.[12–29] The most commonly associated factors include tumor size (14 of 19 studies), central location of the primary tumor (9 of 11 studies), multicentricity/multifocality (5 of 9 studies), and positive axillary lymph nodes (12 of 19 studies; Table 1). Other factors include higher tumor or overall stage (3 of 5 studies), higher grade (4 of 10 studies), various histologies (DCIS,[16] papillotubular carcinoma,[18] or invasive ductal carcinoma[28]) [3 of 9 studies], ER/PR receptor status (1 of 6 studies), lymphvascular invasion (LVI) [2 of 4 studies], and age under 50 years (1 of 4 studies; Table 1). Clinical suspicion of disease and HER-2 amplification were evaluated in a limited number of studies, but were associated with higher risk of NAC involvement in all of those studies.[12,13,15,16,27–29,32,33] In addition to these factors, recent studies have attempted to use preoperative imaging to predict NAC involvement.[30–33] D'Alonzo et al.[30] performed a retrospective review of 78 patients who had undergone preoperative mammogram, and 54 patients who had undergone preoperative magnetic resonance imaging (MRI). On multivariate analysis, a tumor-to-NAC distance of less than or equal to 10 mm was significantly associated, with a 100 % negative predictive value on MRI and 94 % negative predictive value on mammogram. Billar et al.[31] performed a retrospective review of 392 mastectomy

TABLE 1 Incidence of nipple involvement and factors associated with nipple-areola complex involvement

Authors	No. of specimens	% Nipple involvement	Tumor size (cm)	Tumor-to-NAC distance	Location of primary tumor	Multicentric/ multifocal	Nodal status	Stage	Grade	Histologic subtype	Receptor status	LVI	Clinical suspicion of disease	HER-2	Age
Smith et al.[12]	541	12.2[a]	+ (2)		+	+	+			−			+		
Parry et al.[13]	200	8[a]					−						+		−
Andersen and Pallesen[14]	40	50													
Lagios et al.[15]	149	30.2[a]	+ (2)	+		−							+		
Wertheim and Ozzello[16]	1,000	23.4[a]	+ (2)		+		+			+			+		
Quinn and Barlow[17]	44	25	+ (2)				+								
Morimoto et al.[18]	141	31[b]	+	+			+			+					
Lüttges et al.[19]	166	38[a]		+	+	+	+	+	−						
Santini et al.[20]	1,291	12[a]	+				−		−	−					
Menon and van Geel[21]	33	58[a]	−			+	−								
Verma et al.[22]	26	0	−	−			−			−					
Vyas et al.[23]	141	16	+	+ (2.5 cm)			+								
Laronga et al.[24]	286	5.6[b]	−		+	+	+		−	−	−				
Lambert et al.[25]	458	12	+ (4)[c]		+		+	+	+						
Simmons et al.[26]	217	10.6	−		+		−	−	−						
Brachtel et al.[27]	232	21[b]	+ (2)	+ (4 cm)		−	+[c]		+[c]		−	+[c]		+	−
Weidong et al.[28]	2,323	14.2[a]	+ (2.5)	+ (3 cm)	+	+	+		+[c]	+	+[c]	+		+	+[c]
Wang et al.[29]	787	9.5[a]	+ (5)		+	−	+		+	−	−			+	−
D'Alonzo et al.[30]	132	14[a]	+[c]	+ (10 mm)[d]	+		−	+	−		−				
Billar et al.[31]	392	16[a] (7[b])	+[c]	+[c]			+[c]								
Sakamoto et al.[32]	81	21[a]	− (2)		−	−	−	−		−		−	+		

TABLE 1 continued

Authors	No. of specimens	% Nipple involvement	Tumor size (cm)	Tumor-to-NAC distance	Location of primary tumor	Multicentric/multifocal	Nodal status	Stage	Grade	Histologic subtype	Receptor status	LVI	Clinical suspicion of disease	HER-2	Age
Schecter et al.[33]	31	42	+	+[a]	–				–		–	–	+		

NAC nipple-areola complex, *LVI* lymph-vascular invasion, *HER-2* human epidermal growth factor receptor 2, + indicates significant correlation, – indicates no correlation

[a] Included patients with clinical suspicion of nipple involvement

[b] Excluded patients with clinical suspicion of nipple involvement

[c] On univariate analysis only

[d] Tumor-to-NAC distance on imaging

specimens that had preoperative imaging (ultrasound, mammogram, or MRI) and, unlike D'Alonzo, found that NAC involvement on preoperative imaging had only a 62 % positive predictive value and 89 % negative predictive value for predicting NAC involvement on final pathology. Of the 37 cases with evidence of NAC involvement on imaging, 38 % were false positives. Additionally, 59 % of tumors less than 2 cm from the nipple on imaging did not ultimately involve the NAC. Mammogram was the most sensitive study, followed by MRI, then ultrasound.[31] Sakamoto et al.[32] performed a retrospective review of 81 patients in which a preoperative MRI was performed prior to mastectomy with NAC resection. They determined that MRI is a useful tool to predict NAC involvement, particularly unilaterally enhancing nipples with continuous enhancement extending from the index lesion. No positive predictive value was provided for these MRI findings.

Nipple Recurrence after Nipple-Sparing Mastectomy

Reported rates of nipple recurrence following NSM in retrospective and prospective studies range from 0 to 12 % (Table 2), with a pooled review estimating the rate of recurrence at 0.9 % for 2,314 patients.[34–42] Nipple recurrence rates in patients who did not receive RT ranged from 0 to 12 %, compared with 0–2 % in patients who did receive RT. The highest rates of both nipple recurrence and locoregional recurrence (LRR) were seen in the studies from Bishop et al. and Cheung et al.,[35,40] but there is insufficient information to determine if those populations had a higher overall baseline risk of recurrence. Cheung et al.[40] performed a retrospective review comparing 134 patients who underwent subcutaneous mastectomy (SCM) and 535 patients who underwent simple mastectomy. Similar to NSM, SCM leaves all skin intact, including the nipple. With 122 months of median follow-up for the SCM patients, the nipple recurrence rate was 4 %, which was not significantly different from the simple mastectomy recurrence rate.[42] Gerber et al.[41] completed a prospective, non-randomized study of 286 patients, comparing SSM, with and without NAC preservation, and MRM. Of 112 patients who opted for SSM with NAC conservation, the NAC was ultimately conserved in only 61 patients as 51 patients had either a tumor-to-NAC distance of less than 2 cm or suspicious cells on the frozen section of the NAC base during surgery. With a mean follow-up of 59 months, one patient (1 %) who underwent SSM with nipple conservation was found to have nipple recurrence.[41] Other prospective and retrospective studies have found similarly low rates of NAC recurrence in patients with limited risk factors for NAC recurrence.[35,36,38]

Radiation of the Nipple-Areolar Complex

The majority of patients in studies evaluating rates of nipple recurrence following NSM did not receive any form of RT. Among patients who did receive RT after NSM, nipple recurrence rates were 0–2 %.[32,36,41,42] Only one published series could be found in the literature in which RT was specifically used to address the NAC. Petit et al.[42] published a series of 1,001 patients treated with NSM and perioperative RT to the NAC. RT consisted of electrons, 16 Gy, prescribed to the point of maximum dose using an intraoperative technique primarily. Patients who were unable to receive intraoperative RT (IORT) due to technical problems or poor nipple vascularization received the same dose with external beam RT a few days after surgery. A local relapse rate of 1.4 % was seen with 20 months of follow-up. None of these local relapses occurred in the preserved NAC. Based on their results, it is unclear if RT reduced the risk of nipple recurrence, or whether this was a result of low-risk patients who would have had good local control and NAC control regardless of the addition of RT. It is, however, notable that 79 patients were found to have retroareolar involvement on final pathology, yet no NAC recurrences were noted, suggesting that RT was able to control microscopic disease in the NAC.[42]

Following NSM, there is a risk for NAC loss due to necrosis or infection, and there may be concern about increased rates of NAC loss with RT. Petit et al.[42] examined this and found that removal of the nipple for necrosis was seen in 5 % of cases following surgery and RT, which is comparable to rates reported by other series without RT.[36,43] In a series of 25 patients who underwent 42 NSMs without RT, reported by Garcia-Etienne et al.[43] the NAC was entirely preserved in 39 (93 %). In the series of 216 patients reported by Benediktsson and Perbeck,[36] 47 patients received RT, and the overall rate of nipple preservation, excluding cases of NAC involvement, was 90 %. Overall, it appears that the rates of nipple-sparing following NSM and RT are comparable to the rates of nipple-sparing after surgery alone.

DISCUSSION/CONCLUSIONS

Based on our review of the available literature, factors associated with higher rates of NAC involvement include clinical suspicion of nipple involvement, large tumor size, short tumor-to-NAC distance, central primary tumor location, multicentricity/multifocality, and positive axillary lymph nodes. Published rates of nipple recurrence following NSM without RT are low in patients without these risk factors, with 0–4 % reported for the majority of studies. Given that the risk of NAC recurrence can be modified with appropriate patient selection for NSM, it is difficult to justify additional toxicity from RT with minimal clinical benefit in the absence of additional risk factors.

The factors identified to predict for NAC involvement should inform surgical decision making. The data reviewed here would suggest that women with high-risk features (summarized in Table 3) should be advised against NSM. MRI may be a useful tool to assist with surgical decision making. With proper surgical decision making, rates of nipple recurrence are low and the performance of NSM should not influence radiation decision making.

In the setting of NSM, it would be advisable for the radiation oncologist to review preoperative imaging and clinical features, as well as pathologic factors from surgery, to best gauge the risk of NAC and LRR. NSM performed in a post-menopausal female with a small, low grade, peripherally located primary tumor with widely negative margins and negative nodes would be considered appropriate, should be associated with very low risk of recurrence, and therefore, would not warrant post-mastectomy RT (PMRT). In contrast, NSM performed in a young, pre-menopausal, node-positive woman with a larger tumor located within 2 cm of the NAC with unfavorable biology would be considered inappropriate, is likely associated with a significant risk of recurrence, and should invoke consideration of PMRT or an alternative surgical technique. For women with standard indications for PMRT, i.e. tumor size >5 cm and/or positive lymph nodes, PMRT is advisable regardless of the performance of NSM.[44,45] In women for whom PMRT decision making is controversial, i.e. those with T1–2N0 or T1–2N1a disease, multiple risk factors are taken into account to inform radiation decision making. These risk factors include tumor size greater than 2 cm, close or positive margins, the presence of LVI, high grade, pre-menopausal status, age less than 50 years, and no systemic therapy.[46–50] The performance of NSM should be considered as a potential risk factor for recurrence only if it was performed in the setting of imaging or clinical factors that would suggest a higher risk of NAC involvement, as noted above.

The management of breast cancer is multidisciplinary in nature. Radiation is most commonly one of the last treatment modalities delivered and thus radiation decision making is influenced by a multitude of physician and patient decisions that have preceded it. In the modern management of breast cancer, with a multitude of imaging modalities and surgical approaches available, a radiation oncologist would be remiss to look only at the surgical pathology report to inform decision making. Preoperative imaging findings and operative reports may also inform risk. This review would suggest that the radiation oncologist presented with a patient having undergone NSM should review preoperative imaging and clinical features as well as pathologic factors to gauge if the NSM was done in

TABLE 2 Locoregional recurrence and nipple recurrence rates after nipple-sparing mastectomy

Authors	No. of patients	Type of surgery	XRT	Absolute LRR (%)	Nipple recurrence (%)	Median follow-up
Bishop et al.[35]	63	Total mastectomy with nipple preservation	Yes[a]	3	0	3.9 years
	24		No[b]	17	12	3.8 years
Cheung et al.[40]	134	Subcutaneous mastectomy	No	16	4	122 months
	535	Simple mastectomy	No	14	NA	93 months
Gerber et al.[41]	61	Skin-sparing mastectomy with NAC conservation	Some[c]	5.4	2	59 months
	51	Skin-sparing mastectomy without NAC conservation	Some[d]		NA	
	134	Modified radical mastectomy	Some[e]	8.2	NA	
Caruso et al.[38]	50	Nipple-sparing mastectomy	Some[f]	2	2	66 months
Petit et al.[42]	1,001	Nipple-sparing mastectomy	Yes	1.4	0	20 months
Sacchini et al.[39]	123	Nipple-sparing mastectomy	No	3[g]	0	24.6 months
Benediktsson and Perbeck[36]	216	Nipple-sparing mastectomy	Overall	5-year: 16.2 10-year: 20.8	0	13 years
			Yes[h]	8.5	0	
Crowe et al.[37]	83	Nipple-sparing mastectomy	Unknown	3.4	0	41 months

XRT radiation therapy, *LRR* locoregional recurrence rate, *NAC* nipple-areola complex

[a] Mastectomy performed for recurrent disease

[b] Mastectomy performed for multifocal disease

[c] 27.9 % received XRT

[d] 31.4 % received XRT

[e] 23.9 % received XRT

[f] An unknown number of patients received radiation therapy

[g] Local recurrence rate in patients who underwent nipple-sparing mastectomy for cancer treatment

[h] 47 patients received radiation therapy

TABLE 3 Risk factors associated with higher incidence of NAC involvement

Clinical suspicion of nipple involvement
Large tumor size (greater than 2 cm)
Short tumor-to-NAC distance (less than 2 cm)
Central primary tumor location
Multicentricity/multifocality
Positive axillary lymph nodes

NAC Nipple-areola complex

an appropriately low risk context for NAC involvement. If so, the performance of NSM should not affect radiation decision making. If the NSM was potentially done in a higher risk context for NAC involvement, the radiation oncologist would be advised to take the performance of NSM into consideration, in the context of other potential risk factors, when rendering a radiation decision.

FINANCIAL DISCLOSURES None.

CONFLICT OF INTEREST None.

REFERENCES

1. Maddox WA, Carpenter JT Jr, Laws HL, et al. A randomized prospective trial of radical (Halsted) mastectomy versus modified radical mastectomy in 311 breast cancer patients. *Ann Surg*. 1983;198:207–12.
2. Forrest AP, Stewart HJ, Everington D, et al. Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. *Lancet*. 1996;348:708–13.
3. Liljegren G, Holmberg J, Bergh A, et al. 10-year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. *J Clin Oncol*. 1999;17:2326–33.
4. van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 Trial. *J Natl Cancer Inst*. 2000;92:1143–50.
5. Veronesi U, Marubini E, Mariani L, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. *Ann Oncol*. 2001;12:997–1003.
6. 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.
7. Veronesi U, Cascinelli N, Mariani 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.
8. Holli K, Hietanen P, Saaristo R, Huhtala H, Hakama M, Joensuu H. Radiotherapy after segmental resection of breast cancer with favorable prognostic features: 12-year follow-up results of a randomized trial. *J Clin Oncol*. 2009;27:927–32.
9. Dragun AE, Huang B, Tucker TC, Spanos WJ. Increasing mastectomy rates among all age groups for early stage breast cancer: a 10-year study of surgical choice. *Breast J*. 2012;18:318–25.
10. Sappey PC. Anatomie, physiologie, pathologie des vaisseaux lymphatiques considere chez l'homme et les vertebres. Paris: Leconsier; 1885.
11. Didier F, Radice D, Gandini S, et al. Does nipple preservation in mastectomy improve satisfaction with cosmetic results, psychological adjustment, body image and sexuality? *Breast Cancer Res Treat.* 2009;118:623–33.
12. Smith J, Payne WS, Carney JA. Involvement of the nipple and areola in carcinoma of the breast. *Surg Gynecol Obstet.* 1976;143:546–8.
13. Parry RG, Cochran TC Jr, Wolfort FG. When is there nipple involvement in carcinoma of the breast? *Plast Reconstr Surg.* 1977;59:535–7.
14. Andersen JA, Pallesen RM. Spread to the nipple and areola in carcinoma of the breast. *Ann Surg*. 1979;189:367–72.
15. Lagios MD, Gates EA,Westdahl PR, Richards V, Alpert BS. A guide to the frequency of nipple involvement in breast cancer. A study of 149 consecutive mastectomies using a serial subgross and correlated radiographic technique. *Am J Surg.* 1979;138:135–41.
16. Wertheim U, Ozzello L. Neoplastic involvement of nipple and skin flap in carcinoma of the breast. *Am J Surg Pathol.* 1980;4:543–9.
17. Quinn RH, Barlow JF. Involvement of the nipple and areola by carcinoma of the breast. *Arch Surg*. 1981;116:1139–40.
18. Morimoto T, Komaki K, Inui K, Umemoto A, Yamamoto H, Harada K, et al. Involvement of the nipple and areola in early breast cancer. *Cancer*. 1985;55:2459–63.
19. Lüttges J, Kalbfleisch H, Prinz P. Nipple involvement and multicentricity in breast cancer. A study on whole organ sections. *J Cancer Res Clin Oncol.* 1987;113:481–7.
20. Santini D, Taffurelli M, Gelli MC, Grassigli A, Giosa F, Marrano D, et al. Neoplastic involvement of nipple-areolar complex in invasive breast cancer. *Am J Surg.* 1989;158:399–403.
21. Menon RS, van Geel AN. Cancer of the breast with nipple involvement. *Br J Cancer.* 1989;59:81–4.
22. Verma GR, Kumar A, Joshi K. Nipple involvement in peripheral breast carcinoma: a prospective study. *Indian J Cancer.* 1997;34:1–5.
23. Vyas JJ, Chinoy RF, Vaidya JS. Prediction of nipple and areola involvement in breast cancer. *Eur J Surg Oncol*. 1998;24:15–16.
24. Laronga C, Kemp B, Johnston D, Robb G, Singletary SE. The incidence of occult nipple-areola complex involvement in breast cancer patients receiving a skin-sparing mastectomy. *Ann Surg Oncol*. 1999;6:609–13.
25. Lambert PA, Kolm P, Perry RR. Parameters that predict nipple involvement in breast cancer. *J Am Coll Surg*. 2000;191:354–9.
26. 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.
27. Brachtel EF, Rusby JE, Michaelson JS, Chen LL, Muzikansky A, Smith BL, et al. Occult nipple involvement in breast cancer: clinicopathologic findings in 316 consecutive mastectomy specimens. *J Clin Oncol*. 2009;27:4948–54.
28. Weidong L, Wang S, Guo X, et al. Nipple involvement in breast cancer: retrospective analysis of 2,323 consecutive mastectomy specimens. *Int J Surg Pathol*. 2011;19:328–34.
29. Wang J, Xiao X, Wang J, et al. Predictors of nipple-areola complex involvement by breast carcinoma: histopathologic analysis of 787 consecutive therapeutic mastectomy specimens. *Ann Surg Oncol*. 2012;19:1174–80.
30. D'Alonzo M, Martincich L, Biglia N, et al. Clinical and radiological predictors of nipple-areola complex involvement in breast cancer patients. *Eur J Cancer*. 2012;48:2311–8.
31. Billar JAY, Dueck AC, Gray RJ, Wasif N, Pockaj BA. Preoperative predictors of nipple-areola complex involvement for patients undergoing mastectomy for breast cancer. *Ann Surg Oncol*. 2011;18:3123–8.
32. Sakamoto N, Tozaki M, Hoshi K, Fukuma E. Is MRI useful for the prediction of nipple involvement? *Breast Cancer.* 2013;20:316–22.
33. Schecter AK, Freeman MB, Giri D, Sabo E, Weinzweig J. Applicability of the nipple-areola complex-sparing mastectomy: a prediction model using mammography to estimate risk of nipple-areola complex imvolvement in breast cancer patients. *Ann Plast Surg*. 2006;56:498–504.
34. Mallon P, Feron JG, Couturaud B, et al. The role of nipple-sparing mastectomy in breast cancer: a comprehensive review of the literature. *Plast Reconstr Surg*. 2013;131:969–84.
35. Bishop CC, Singh S, Nash AG. Mastectomy and breast reconstruction preserving the nipple. *Ann R Coll Surg Engl*. 1990;72:87–9.
36. 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.
37. Crowe JP, Patrick RJ, Yetman RJ, Djohan R. Nipple-sparing mastectomy update: one hundred and forty-nine procedures and clinical outcomes. *Arch Surg*. 2008;143:1106-10.
38. Caruso F, Ferrara M, Castiglione G, Trombetta G, De Meo L, Catanuto G, et al. Nipple sparing subcutaneous mastectomy: sixty-six months follow-up. *Eur J Surg Oncol*. 2006;32:937–40.
39. Sacchini V, Pinotti JA, Barros AC, et al. Nipple-sparing mastectomy for breast cancer and risk reduction: oncologic or technical problem? *J Am Coll Surg*. 2006;203:704–14.
40. Cheung KL, Blamey RW, Robertson JF, Elston CW, Ellis IO. Subcutaneous mastectomy for primary breast cancer and ductal carcinoma in situ. *Eur J Surg Oncol*. 1997;23:343–7.
41. Gerber B, Krause A, Reimer T, et al. Skin-sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction is an oncologically safe procedure. *Ann Surg*. 2003;238:120–7.
42. Petit JY, Veronesi U, Orecchia R, et al. Nipple sparing mastectomy with nipple areola intraoperative radiotherapy: one thousand and one cases of a five years experience at the European Institute of Oncology of Milan (EIO). *Breast Cancer Res Treat*. 2009;117:333–8.
43. Garcia-Etienne CA, Cody Iii HS 3rd, Disa JJ, Cordiero P, Sacchini V. Nipple-sparing mastectomy: initial experience at the Memorial Sloan-Kettering Cancer Center and a comprehensive review of the literature. *Breast J*. 2009;15:440–9.
44. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. *N Engl J Me*d. 1997;337:949–55.
45. 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 Randomized Trial. *Lancet*. 1999;353:1641–8.
46. Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. *J Natl Cancer Inst*. 2005;97:116–26.

47. Abi-Raad R, Boutrus R, Wang R, Niemierko A, Macdonald S, Smith B, et al. Patterns and risk factors of locoregional recurrence in T1-T2 node negative breast cancer patients treated with mastectomy: implications for postmastectomy radiotherapy. *Int J Radiat Oncol Biol Phys*. 2011;81:151–7.
48. Yildirim E, Berberoglu U. Can a subgroup of node-negative breast carcinoma patients with T1-2 tumor who may benefit from postmastectomy radiotherapy be identified? *Int J Radiat Oncol Biol Phys*. 2007;68:1024–9.
49. Jagsi R, Raad RA, Goldberg S. Locoregional recurrence rates and prognostic factors for failure in node-negative patients treated with mastectomy: implications for postmastectomy radiation. *Int J Radiat Oncol Biol Phys*. 2005;62:1035–9.
50. Truong PT, Lesperance M, Culhaci A, Kader HA, Speers CH, Olivotto IA. Patient subsets with T1-T2, node-negative breast cancer at high locoregional recurrence risk after mastectomy. *Int J Radiat Oncol Biol Phys*. 2005;62:175–82.