

# Nipple-Sparing Mastectomy – Extended Indications and Limitations

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## Key Words

Mastectomy · Nipple areola complex ·  
Skin-sparing mastectomy · Breast neoplasm surgery

## Summary

If mastectomy is indicated for removal of breast cancer, the nipple areola complex (NAC) is routinely excised during surgery followed by nipple reconstruction. Despite advances in reconstruction techniques, removal of the NAC often results in a sense of mutilation. However, recent studies regarding the tumorigenic involvement of the NAC have provided some evidence that in carefully selected patients the NAC could be preserved. Nipple-sparing mastectomy (NSM) preserves the breast skin envelope and the NAC, and has therefore emerged as an alternative to conventional radical mastectomies. Because NSM leaves no or sparse retroareolar ductal tissue, NSM is increasingly considered as oncologically safe both in patients with small and peripherally located tumors and in women with high breast cancer risk, who opt for prophylactic mastectomy. Moreover, NSM has been applied in patients with large and centrally located or multicentric invasive carcinomas but oncologic safety as well as postoperative complications such as NAC necrosis are still controversial. Since long-term data are limited, there is no general recommendation for NSM indications. To evaluate if indications for NSM may be rather enlarged under certain conditions, we performed a MEDLINE search for studies published between 2003 and 2009.

## Schlüsselwörter

Mastektomie · Mamillen-Areola-Komplex ·  
Hautsparende Mastektomie · Brustkrebsoperation

## Zusammenfassung

Ist zur Brustkrebsentfernung eine Mastektomie indiziert, wird der Mamillen-Areola-Komplex (MAK) üblicherweise entfernt und anschließend rekonstruiert. Trotz Fortschritten der Rekonstruktionstechniken wird der Verlust des MAK von vielen Betroffenen als Verstümmelung empfunden. Verschiedene Studien zur malignen Infiltration des MAK begründen jedoch die Ansicht, dass der MAK bei streng selektionierten Patientinnen erhalten werden kann. Die MAK-erhaltende Mastektomie erhält den gesamten Brusthautmantel und den MAK und wird daher als Alternative zur konventionellen Radikalmastektomie angesehen. Da kein oder nur sehr wenig duktales Gewebe zurückbleibt, wird die MAK-erhaltende Mastektomie zunehmend als onkologisch sicheres Verfahren bei der Entfernung kleiner, peripherer Tumoren oder bei prophylaktischen Mastektomien bei Hochrisikopatientinnen akzeptiert. Darüber hinaus wurde die MAK-erhaltende Mastektomie auch bei Patientinnen mit großen und zentral lokalisierten Tumoren oder multizentrischen invasiven Karzinomen angewandt, wobei die Frage der onkologischen Sicherheit sowie das Risiko postoperativer Komplikationen wie der Mamillennekrose zurzeit noch kontrovers diskutiert werden. Da bislang keine ausreichenden Langzeitdaten zur Verfügung stehen, existieren keine generellen Empfehlungen zu den Indikationen der MAK-erhaltenden Mastektomie. Die Frage, ob die MAK-erhaltende Mastektomie unter bestimmten Bedingungen auf weitere Indikationen ausgedehnt werden kann, ist das Thema der vorliegenden Übersichtsarbeit, für die wir Studien, die zwischen 2003 und 2009 publiziert wurden (MEDLINE-Suche), ausgewertet haben.

## Introduction

In the past decades, there have been significant advances in breast cancer surgery concerning oncologic safety and cosmetic outcome. Skin-sparing mastectomy (SSM) removes the nipple areola complex (NAC) but leaves the majority of the native skin envelope intact [1]. Thereby, SSM enables immediate reconstruction of the breast with preservation of the submammary fold and breast contour, along with avoidance of skin differences. Importantly, several studies have shown that SSM increases neither the rate of local recurrence [2–5] nor the incidence of distant metastasis [2, 3, 5] when compared to modified radical mastectomy. Although numerous techniques have been developed to reconstruct the nipple after mastectomy, removal of the NAC leads to an increased sense of mutilation [6]. Patients frequently report discontent with nipple projection, color match, shape, size, texture, and position of their reconstructed NAC [7]. The patient-driven desire for cosmetic improvements led to the question whether the NAC can be preserved. Since 1962, subcutaneous mastectomy (SCM) with preservation of the NAC has been occasionally performed for cystic disease [8, 9], prophylaxis in women at high risk for breast cancer [10], and less frequently for cancer [11]. However, generally, SCM was not considered as an oncologically safe procedure, and the NAC was routinely excised during mastectomy because of the presumed risk of malignant nipple involvement. The current technique of nipple-sparing mastectomy (NSM) differs from that of the historical SCM in that it preserves the NAC leaving only a 2–3 mm thick nipple areola flap with no or little ductal tissue. Therefore, it is worth considering whether the NAC could be treated the same way as other breast skin, and, consequently, whether NSM is as oncologically safe as SSM.

## Predictive Factors for Neoplastic NAC Involvement

Neoplastic involvement of the NAC usually occurs by direct tumor extension but there might also be de novo carcinomas arising from the NAC. However, the majority of ductal and lobular breast cancers arise from the terminal duct lobular units (TDLU) that are only infrequently found in the nipple [12]. Moreover, it has been reported that the incidence of invasive carcinomas developing after prophylactic SCM with NAC preservation (7 of 575) does not differ significantly from the incidence observed after prophylactic total mastectomy (0 of 64). In this study, only one lesion occurred within the NAC. In this context, Paget's disease of the nipple should be mentioned. Paget's cells arise in the breast ducts and spread from a lactiferous sinus into the nipple epidermis. However, the incidence of Paget's disease of the nipple ranges from 0.5 to 2.8%, and Paget's disease was reported to be associated with an underlying invasive ductal carcinoma or ductal carcinoma in situ (DCIS) in 92–100% of patients [13, 14]. Therefore, it

**Table 1.** Occult neoplastic involvement of the nipple areola complex (NAC)

Primary author(s) [ref.]	Year	Specimens, n	NAC involvement, %
Smith et al. [46]	1976	541	12.2
Parry et al. [47]	1977	200	8
Andersen and Pallesen [26]	1979	40	50
Lagios et al. [48]	1979	149	30
Wertheim and Ozzello [49]	1980	1,000	23.4
Quinn and Barlow [50]	1981	45	25
Morimoto et al. [51]	1985	141	31
Kissin and Kark [21]	1987	100	16
Luttges et al. [25]	1987	166	38
Santini et al. [52]	1989	1,291	12
Menon and Van Geel [16]	1989	33	58
Verma et al. [15]	1997	26	0
Vyas et al. [53]	1998	140	16
Laronga et al. [20]	1999	246	5.6
Simmons et al. [18]	2002	217	10.6
Sikand et al. [54]	2005	220	7
Petit et al. [39]	2006	106	10.4
Schechter et al. [55]	2006	31	42
Crowe et al. [56]	2008	149	6
Loewen et al. [19]	2008	302	10
Banerjee et al. [23]	2008	219	20
Volturna et al. [27]	2008	34	5.9

may be assumed that invasive carcinomas arising directly from the NAC are uncommon.

In breast cancer patients with invasive carcinomas, the incidence of occult NAC involvement ranges from 0% [15] to 58% [16] which is probably due to differences in both histological methods and tumor criteria (table 1). Several studies have suggested that the risk of NAC involvement could be assessed by certain criteria. In a retrospective study on 397 breast cancer patients, tumor location, number of positive axillary lymph nodes, and lymphatic vascular invasion were identified as conclusive risk factors for NAC involvement. In this study, overall NAC involvement was determined in 58 (14.6%) patients by histopathological examination. NAC involvement was found in 50% of patients with 2 or 3 risk factors. Importantly, incidence of NAC involvement dropped to 8.1% in patients with only 1 risk factor [17].

Most reports have consistently identified tumor location and tumor distance from the nipple as reliable predictors for neoplastic NAC involvement. Simmons et al. [18] found an overall frequency of 10.6% of NAC involvement in mastectomy patients. Prevalence increased if tumors were centrally located (27.3%) but decreased to 6.4% in patients with tumors located in the lower inner/lower outer, upper inner/upper outer quadrants. In a retrospective analysis on 302 women who had undergone mastectomies because of invasive breast cancer or DICS, NAC involvement was found in 10% of cases and was negatively correlated with tumor distance from the nipple. The authors concluded that if tumor distance from the nipple is less than 4.96 cm as determined by mammography, NAC involvement can be predicted with a sensitivity

of 82% [19]. Most studies combined tumor distance with additional predictors such as lymph node status [17, 20, 21] or tumor stage [22]. Tumor size [18, 23], nuclear grading [24], multicentricity and multifocality [25] have been published as further predictive factors. However, some surgeons who find a high frequency of nipple involvement in breast cancer patients generally doubt the reliability of predictive factors [16]. Andersen and Pallesen [26] detected involvement of the nipple and/or areola at a depth of 1 cm in 20 out of 40 breasts with primary carcinomas. Among these 20 cases, 11 were intraductal, 8 intraductal as well as stromal, and 1 purely stromal. From their analyses, the authors concluded that tumor location and tumor size would have predicted NAC involvement only in a minority of cases.

Currently, predictability of NAC involvement is still controversial. Therefore, intraoperative pathological assessment of the subareolar breast tissue during surgery is of the utmost importance and is widely accepted as the crucial decisional criterion for NAC preservation [27–29]. Intraoperative examination of frozen sections results in NAC excision in 0% [30, 31] to 45.5% [32] of cases. Govindarajulu et al. [33] recently described the technique of ultrasound-guided mammotome biopsy which might be considered as an alternative to the intraoperative surgical assessment of retroareolar tissue. In their study, biopsies of the ducts beneath the NAC were preoperatively taken from 33 breast cancer patients prior to nipple-preserving SCM. Mamotome biopsy revealed NAC involvement in 7 out of 36 specimens which correlated 100% with the histopathological evaluation of the mastectomy specimen.

It is unquestionably critical for oncologic safety that no or little mammary tissue remains after mastectomy. It has therefore been suggested that the NAC could be safely preserved if breast gland tissue and galactophoric ducts can be completely separated from the NAC [34–36]. Recently, Rusby et al. [37] provided anatomic details of nipple microvessels and lactifer-

ous ducts that might advance surgical techniques of NSM. They demonstrated that the duct bundle can be completely excised in 96% of cases if a peripheral rim of 2 mm of nipple skin and subcutaneous tissue is left during surgery whereas a peripheral rim of 3 mm results in complete excision in 87% of cases. The peripheral 2 and 3 mm of the nipple contain 50 and 66% of blood vessels, respectively. These measurements indicate that all galactophoric ducts and any subjacent tissue on the areola base can be precisely dissected while leaving the blood supply of the NAC intact.

### Local Recurrence

The fact that recurrence rate is inversely related to the amount of tissue removed during surgery implies that removal of as much breast tissue as possible would maximally diminish the breast cancer risk [38]. However, the outcome of NSM and other surgical treatment options cannot be compared in randomized trials, but several studies have considered the question of how frequently recurrence actually occurs after NSM (table 2).

NSM has been performed for risk reduction as well as for the treatment of invasive cancer, DCIS, phyllodes tumor, and pseudoangiomatous stromal hyperplasia [27, 30, 31]. NAC preservation may not increase the local recurrence rate if an intraoperatively examined frozen section from underneath the nipple is tumor-free [32]. Caruso et al. [22] enrolled breast cancer patients for NSM, who had early stage tumors more than 2 cm away from the NAC, no clinically visible involvement of the NAC, and no tumor cells in the retroareolar ducts intraoperatively proved by frozen section. Furthermore, only patients with small- and medium-size breasts with no or minimal ptosis and possibly healthy skin were included. Three patients were excluded due to positive intraoperative frozen sections. In the 50 women treated with NSM, 1 local recur-

**Table 2.** Outcome of nipple-sparing mastectomy (NSM) in studies with comparable patient selection criteria

Study				Outcome			
primary author(s) [ref.]	year	indication	cases, n	NAC excised <sup>a</sup> , %	follow-up, months	LR, %	LR within NAC, n
Gerber et al. [32]	2003	T	112	45.5	59	5.4	1
Caruso et al. [22]	2006	T	56	7.1	66	2 (overall: 12)	1
Petit et al. [39]	2006	T	114	7	13	1 (iRT)	0
Sacchini et al. [30]	2006	T/P	123	0	24.6	1.6 (overall: 2.4)	0
Sookhan et al. [31]	2008	T/P	18	0	10.8	0	0
Benediktsson and Perbeck [41]	2008	T	272	20.6	156	28.4 / 8.5 (RT)	NR
Voltura et al. [27]	2008	T/P	36	5.5	18	5.9	0
Petit et al. [57]	2009	T	1,001	13.1	19	1.4 (iRT) (overall: 5)	0
Paepke et al. [36]	2009	T/P	109	11.9	34	0.9	0

<sup>a</sup>NAC excised because of neoplastic involvement, insufficient blood supply of the nipple, or postoperative immediate nipple necrosis.

NAC = Nipple areola complex; LR = local recurrence; T = treatment of invasive and non-invasive cancer; P = prophylaxis; RT = radiotherapy; iRT = intraoperative radiotherapy; NR = not reported.

**Table 3.** Nipple necrosis following nipple-sparing mastectomy (NSM)

Study			Outcome	
primary author [ref.]	year	NSM completed, n	partial necrosis, %	total necrosis, %
Crowe et al. [58]	2004	48	6.3	0
Caruso et al. [22]	2006	50	2	0
Sacchini et al. [30]	2006	192	6.8	4.7
Komorowski et al. [44]	2006	38	5.3	7.9
Petit et al. [39]	2006	105	5.6	2.6
Bistoni et al. [59]	2006	14	14.3	0
Stolier et al. [43]	2008	82	2.4	0
Paepke et al. [36]	2009	97	0	1

rence and 5 distant metastases were diagnosed (overall recurrence rate: 12%), at a mean follow-up of 66 months. Local recurrence within the nipple occurred in 1 patient.

Table 2 summarizes the outcome of NSM in studies with comparable patient selection criteria. Some studies suggested that intra- or postoperative radiotherapy (RT) may further reduce the risk of local recurrence after NSM [39–41]. Petit et al. [39] included 102 patients with large, multicentric, peripheral tumors. During surgery, NSM was followed by RT (16 Gy) if frozen section showed the tissue under the areola to be disease-free. After an average follow-up of 13 months, 1 local recurrence occurred under the clavicle. Benediktsson and Perbeck [41] analyzed the outcome of 216 patients with NSM with endpoints of locoregional recurrence (LRR) or distant metastases, disease-free survival, and overall survival. All patients had large (> 3 cm) T1–T3 tumors, multifocal carcinoma (73%), and axillary lymph node involvement (40.3%). Forty-seven patients received postoperative RT. The frequency of LRR was 8.5% after NSM with postoperative RT and 28.4% after NSM without RT. After a median follow-up of 13 years, disease-free survival was 51.3%, and overall survival was 76.4%, which is comparable to the results of more radical mastectomies.

In our recent study, the NAC needed to be excised because of neoplastic NAC involvement in 13 out of 109 breasts as determined by examination of frozen sections. In the remaining 96 cases, no recurrence within the NAC was observed after a median follow-up of 34 months. Although neither sample size nor follow-up period were extensive, comparison with other studies suggests that the NAC might be preserved even in patients with large and centrally located tumors (table 2). Since most studies differ in inclusion criteria, follow-up length, and sample size, no correlation between indication and outcome can be currently established. Indications for NSM could be extended if a frozen section from underneath the nipple is examined during surgery. However, there is some consensus among surgeons that extensive tumor involvement of the skin, inflammatory breast cancer, Paget's disease, and clinically suspicious nipples are absolute contraindications for NSM.

## Necrosis

Potential postoperative complications which should be discussed with patients who consider NSM are complete or partial necrosis of the NAC due to disturbance of the NAC blood supply. However, there are surgical options for skin incisions that are intended both to provide adequate access to breast tissue and muscles and to ensure the viability of the NAC by preserving its blood supply [30, 42]. The choice of the appropriate surgical technique is critical and depends on biopsy scars, tumor location, reconstructive surgery, and NAC vascularization. Sacchini et al. [30] described 4 different skin incisions: periareolar, transareolar, transareolar and transnipple, and mammary crease incision. Although large studies are currently needed to determine the best approach, reduced NAC necrosis and improved surgical outcomes have been associated with radial transareolar incisions [35, 43]. Palmieri et al. [42] recently suggested a sophisticated 2-step surgery: In the first mini-invasive step, the galactophore stalk is detached from the nipple, and the deep vascular plexus is coagulated to initiate dermal revascularization and thereby 'autonomization' of the vascular supply to the NAC. After weeks, the actual NSM is performed as a second step. Fortunately, the incidence of necrosis after NSM is low and rarely requires surgical intervention in cases of partial or total necrosis (table 3). Generally, necrosis of the NAC occurs due to inadequate blood supply and therefore is promoted by factors affecting blood flow and vascularization. Komorowski et al. [44] analyzed such factors in patients who underwent NAC-sparing mastectomy. From their study on 38 patients, they concluded that age below 45 years is linked with a reduced risk of necrosis. In another study, adjuvant radiotherapy was identified as a risk factor for decreased cosmetic results, at least partially caused by necrosis [45].



## Conclusion

NSM is an option both for patients without proven breast cancer, who decide to undergo prophylactic surgery, and for patients with small and peripherally located tumors, who are candidates for breast-conserving therapy but prefer mastectomy. However, the range of indications for NSM might be extended. Recent findings regarding neoplastic involvement of the NAC and current advances in surgical techniques have led to the question of whether NAC preservation is feasible even in patients with large tumors close to the NAC and mul-

ticentric invasive carcinoma. Intraoperative frozen section analysis of the NAC enables accurate assessment. If the NAC is involved, it must be excised. Additional follow-up data are now required both to determine the long-term local recurrence rate for NSM performed with different indications and to assess the cosmetic outcome achieved by advanced surgical techniques.

## Conflict of Interest

The authors declare no conflicts of interest.

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