Intraoperative central nipple biopsy in nipple-sparing mastectomy— A retrospective analysis of 211 patients

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Abstract

Subcutaneous nipple sparing mastectomies (NSM) are an important tool in modern oncoplastic surgery. Especially when an immediate implant-based reconstruction (IBR) is desired, clean margins are of the utmost importance. Central nipple biopsies during surgery serve two main purposes. Most importantly, it is hypothesized that intraoperative pathological evaluation of this biopsy may increase clean margin resection rates. In addition, a general recurrence risk reduction may occur due to the elimination of glandular and ductal components within the nipple. This analysis is a single center, multi-surgeon, retrospective, head to head analysis. Starting in March 2015, intraoperative central nipple biopsy in NSMs with IBR was introduced at the Municipal Breast Cancer Centre Cologne, Holweide, Germany. This trial retrospectively evaluates global complication rates, clean margin status and local recurrence rates for cohort 1 (NSM/no nipple biopsy, n = 103) vs. cohort 2 (NSM with nipple biopsy, n = 108) Median follow-up was 15 months. All implant-based reconstruction procedures used an epipекторal implant pocket. Cohorts were comparable. Global complication rates slightly favored the nipple biopsy cohort with respects to implant loss rate. An involved central nipple biopsy was found in 4.6% (n = 5/108) of the performed NSM procedures leading to the immediate removal of the nipple areola complex. All positive retro- areolar biopsies correlated with a positive nipple biopsy. However, in n = 1 case we found DCIS discontinual proliferation with an involved nipple biopsy, without a correlating positive retro-areolar biopsy (ie, 1 false-negative case was prevented). For the 15 month follow-up, there was no case of local recurrence within nipple areola complex for both cohorts. With this retrospective head to head analysis of 211 patients, it was shown that the central nipple biopsy correlates well with the retro-areolar biopsy. There may be a reduction in false negative rates. The procedure is safe to use and should be offered to NSM patients.

KEYWORDS

breast cancer, mastectomy, nipple biopsy, subcutaneous
1 | INTRODUCTION

The nipple sparing subcutaneous mastectomy (NSM), that is, retaining the nipple-areola complex (NAC)\(^1,2\) is a common procedure in breast cancer patients. Previous trials showed that the psychosocial and sexual well-being of patients with nipple sparing mastectomies is higher than that of patients with modifying radical mastectomy a constant effort to improve this oncoplastic option is required.\(^3-7\)

When retaining the NAC, there is an increased risk of local recurrence since minimal glandular tissue is retained and/or cancerous tissue remains due to discontinuous proliferation. This is known as NAC involvement and is generally ruled out by intraoperative frozen section of the retro-areolar area.\(^8-10\) An additional central nipple biopsy during surgery may serve two main purposes. It is hypothesized that a general recurrence risk is reduced due to elimination of glandular and ductal components within the nipple.\(^11\) In addition, intraoperative pathological evaluation of the biopsy may increase clean margin resection rates and represent the actual nipple involvement more accurately than only performing the retro-areolar biopsy intra-surgically.\(^12\) This trial evaluates complication rates, clean margin rates and local recurrence rates for subcutaneous mastectomies with and without central nipple biopsies.\(^13-16\)

2 | PATIENTS AND METHODS

This head-to-head analysis is a retrospective evaluation of a single center experience from March 2015 until February 2018. The intraoperative central nipple biopsy in NSMs with immediate implant-based reconstruction was first introduced at the Municipal Breast Cancer Centre in Cologne, Holweide, Germany in 2015.

Prior to March, 2015 all patients only received the gold standard of a retro-areolar biopsy, with immediate pathological intra-surgical evaluation (control group, cohort 1). If involved, the nipple-areolar complex would be removed. Beginning in March 2015 a central nipple biopsy, using a circular biopsy tool, was performed in addition to a retro-areolar biopsy (nipple biopsy group, cohort 2). This yielded two intraoperative, corresponding biopsies regarding the same area of interest.

For this analysis, the following parameters were documented: age, BMI, resection/margin-status (central nipple biopsy positive or negative), TNM classification and prior therapy (chemotherapy, radiation).\(^17,18\) Primary endpoints were complication rates with major complication rates involving an implant loss and minor complications which were managed conservatively. Secondary endpoints were clean margin status and long-term local recurrence. The two trial cohorts were cohort 1 (control) with 103 SSM cases without central nipple biopsy versus cohort 2 with 108 SSM cases with nipple biopsy. For all implant-based reconstructions, an epiprosthetic implant pocket was used. The median follow-up for both cohorts is 15 months. Naturally, the follow-up for the control group could be longer, however in order to maintain comparability a 15 month cutoff was chosen.

2.1 | Surgical procedures

The nipple biopsy was performed with a 4 mm diameter circular scalpel at the beginning of the surgery. Afterward, the nipple was closed by a tobacco pouch suture. These steps are shown in Figure 1.

2.2 | Statistics

The statistical calculations of the data have been produced by VassarStats (Vassar College, Poughkeepsie, NY, USA) and Excel. Pearson’s Chi-Quadrat-Tests and t-tests were when appropriate.

**FIGURE 1** This image shows a step by step of taking a 4 mm central nipple core biopsy. Step 1: a circular 4 mm scalpel is used to remove the central core of the nipple. (2) The core is removed resulting in a 4 mm diameter cylinder (3). Step 4: a tobacco pouch suture closes the defect resulting in a closed and aesthetically adequate NAC (5). [Color figure can be viewed at wileyonlinelibrary.com]
Ethics committee approval was obtained, the reference number is 19-1204, ethics committee of the University of Cologne, Cologne Germany.

3 | RESULTS

No statistically significant differences were shown between both cohorts regarding the tumor type and prior therapies. There is slightly higher conversion to radical mastectomy in the cohort having received a nipple biopsy. These were not related to the nipple core biopsy. Cohort 1 (NSM/no nipple biopsy) includes 103 patients with a median age of 50 (range 24–75) years of which 48.5% were premenopausal. Cohort 2 (NSM with nipple biopsy) includes 108 patients with a median age of 49 (range 30–71) years of which 57.4% had a premenopausal status. (Table 1) Comparable TNM stages and histological subtypes were given.

3.1 | Primary endpoints

Overall complication rates are low. Major complications (implant loss) occurred in 4.6% (n = 5) for the nipple biopsy cohort and 12.6% (n = 13) for the control cohort. There is a statistically significant difference favoring the nipple biopsy cohort. This is not thought to be caused by the nipple core biopsy itself.

Minor complication rates were higher. 38.8% (n = 40) of all cases showed some sort of minor complication in the control cohort and 41.7% (n = 45) of all cases experience minor complications in the nipple biopsy cohort. All minor complications were managed conservatively (ie, no implant loss). Subgroup analyses are shown in Table 2.

Secondary endpoints: This trial was able to show a R1 status, that is, involved margins in 15.5% (n = 16) for the control cohort and 20.4% (n = 44) for the nipple biopsy cohort. There was no statistically significant difference. This led to 3.9% (n = 4) and 12.0 (n = 13) radical mastectomies, respectively. Not all R1 patients received a re-operation, as some patients refused a re-operation. For the sake of this analysis, the relevant data relates only to the ventral R1 status. Results are shown in Tables 3 and 4.

For the trial group, Table 4 shows five patients who had an involved nipple core biopsy. Within this group, the retro-areolar biopsy, which was performed for all 211 patients, was positive in only 4 of the 5 patients. This means that 1 patient showed a discontinual DCIS growth. For this patient, a false R0 statement would have been issued meaning that the free-margin pathology evaluation would have been a falsely negative. Subgroup analyses are shown in Table 4. Also noteworthy is the fact that all positive retro-areolar biopsies correlated with a positive nipple biopsy, but not all positive nipple biopsies had a corresponding positive retro-areolar result (Table 5).

For the 15 month follow-up, there was no case of local recurrence within nipple areola complex for both cohorts.

4 | DISCUSSION

Overall comparability between the two cohorts was given.

4.1 | Primary endpoints

A core nipple biopsy seems to be a safe procedure which does not negatively impact the overall outcome in NSM procedures. Implant loss rates were low and compare well to literature. Minor complication rates such as seroma, mild capsular fibrosis, infection, red breast syndrome etc. also compare well to literature and do not differ significantly between the two cohorts. Therefore, a central nipple biopsy may be safely performed in addition to a retro-areolar intraoperative frozen section in order to improve pathological evaluation of the resected tissue.

4.2 | Secondary endpoints

A clean margin status (ie, R0) also compares well with literature as approximately 15.5% (control) and 20.4% (nipple biopsy) of the
procedures yielded a R1 situation. Within the nipple punch cohort, a re-operation lead to 13 patients who opted for a mastectomy. In comparison, only 4 of the control group received a subsequent mastectomy. For the sake of this analysis, this difference is not relevant. This is due to the fact that the ventral R1 situations did not differ significantly (6.8% vs. 8.3%).

More interestingly however, of all 5 involved central nipple biopsies, only 4 patients showed a correlating involved retro-areolar biopsy.

| Gender (w) | Patients | % | Patients | % | p-value |
|------------|----------|---|----------|---|---------|
| Male       | 103      | 100.0 | 108      | 100.0 |         |

| Histology                                      | Standard NSM | NSM with central nipple biopsy | p-value |
|------------------------------------------------|--------------|--------------------------------|---------|
| NST                                            | 43           | 108                            | 0.791   |
| Invasive lobular                               | 10           | 13                             |         |
| DCIS                                           | 12           | 19                             |         |
| No pathology (prophylactic)                    | 21           | 22                             |         |
| Not available/other                            | 17           | 3                              | 0.015   |

| Size                                           | Patients | % | Patients | % | p-value |
|------------------------------------------------|----------|---|----------|---|---------|
| pTis                                           | 14        | 13.6 | 22       | 20.4 |         |
| ypT0                                           | 8         | 7.8  | 5        | 4.6  |         |
| pT1m                                           | 0         | 0    | 2        | 1.9  |         |
| pT1a                                           | 2         | 1.9  | 6        | 5.6  |         |
| pT1b                                           | 5         | 4.9  | 8        | 7.4  |         |
| pT1c                                           | 18        | 17.5 | 15       | 13.9 |         |
| pT2                                            | 21        | 20.4 | 23       | 21.3 |         |
| pT3                                            | 1         | 1.0  | 3        | 2.8  | 0.67    |
| Unknown                                        | 34        | 33.0 | 24       | 22.2 | 0.33    |

| Nodalstatus                                    | Patients | % | Patients | % | p-value |
|------------------------------------------------|----------|---|----------|---|---------|
| pN0                                            | 57       | 71.3 | 63       | 70.8 |         |
| pNX                                            | 9        | 11.3 | 6        | 6.7  |         |
| pN positive                                    | 14       | 17.5 | 20       | 22.5 | 0.32    |

| Ki67 (%)                                        |          |     |          |     |         |
|------------------------------------------------|----------|---|----------|---|---------|
| ≤14                                            | 23       | 28.8 | 23       | 25.8 |         |
| >14                                            | 9        | 11.3 | 16       | 18.0 |         |
| ≥25                                            | 31       | 38.8 | 31       | 34.8 | 0.42    |

| Grading                                        |          |     |          |     |         |
|------------------------------------------------|----------|---|----------|---|---------|
| G1                                             | 5        | 4.9  | 9        | 8.3  |         |
| G2                                             | 38       | 36.9 | 45       | 41.7 |         |
| G3                                             | 26       | 25.2 | 28       | 25.9 | 0.71    |
| Not reported                                   | 2        | 1.9  | 2        | 1.9  |         |
| Benign/prophylactic                            | 32       | 31.1 | 24       | 22.2 |         |

| Hormone receptor status                        |          |     |          |     |         |
|------------------------------------------------|----------|---|----------|---|---------|
| Positive                                       | 54       | 67.5 | 69       | 77.5 | 0.32    |

| HER2/neu-Expression                            |          |     |          |     |         |
|------------------------------------------------|----------|---|----------|---|---------|
| Positive                                       | 10       | 12.5 | 19       | 21.3 | 0.14    |

| Side/Breasts                                   |          |     |          |     |         |
|------------------------------------------------|----------|---|----------|---|---------|
| Left                                           | 29       | 28.2 | 34       | 31.5 |         |
| Right                                          | 26       | 25.2 | 28       | 25.9 |         |
| Bilateral                                      | 48       | 46.6 | 46       | 42.6 | 0.82    |

| TABLE 2 Patient overview, TNM and histology |
### TABLE 3 Primary Endpoints, Major/Minor Complication Rates * (sub-group p-value only listed when significant)

|                          | Standard NSM |NSM with central nipple biopsy |
|--------------------------|--------------|-------------------------------|
|                          | Number of patients | % | Number of patients | % | p-value |
| **Total (n = 211)**      | 103 | 100 | 108 | 100 | |
| **Minor complications**  |               |   |               |   |       |
| Overall                  | 40 | 38.8 | 45 | 41.7 | 0.67* |
| Seroma                   | 13 | 12.6 | 18 | 16.7 | |
| Capsular Fibrosis        | 1 | 1.0 | 2 | 1.9 | 0.04 |
| Infection (no operative revision) | 1 | 1.0 | 1 | 0.9 | |
| Hematoma (operative revision) | 6 | 5.8 | 4 | 3.7 | |
| Implant rotation/dislocation | 2 | 1.9 | 3 | 2.8 | |
| Red-Breast-Syndrome      | 13 | 12.6 | 10 | 9.3 | |
| Nipple necrosis (no operative revision) | 1 | 1.0 | 1 | 0.9 | |
| Impaired wound healing   | 1 | 1.0 | 5 | 4.6 | |
| Abscess                  | 0 | 0 | 1 | 0.9 | |
| Exanthema                | 2 | 1.9 | 0 | 0 | |
| **Major Complications (implant loss)** |               |   |               |   |       |
| Overall                  | 13 | 12.6 | 5 | 4.6 | 0.04 |
| Infection of expander/breast implant with implant loss | 10 | 9.7 | 5 | 4.6 | |
| Implant loss because of allergy | 1 | 1.0 | 0 | 0 | |
| Nipple necrosis which lead to DIEP or Ablatio | 2 | 1.9 | 0 | 0 | |
| **Late Complications (>6 months)** |               |   |               |   |       |
| Capsular fibrosis which led to implant change or DIEP | 6 | 5.8 | 1 | 0.9 | 0.05 |

*Sub-group p-value only listed when significant.

### TABLE 4 Patient overview (margin status)

|                       | Standard NSM |NSM with central nipple biopsy |
|-----------------------|--------------|-------------------------------|
|                       | Patients | % | Patients | % | p-value |
| **Positive nipple biopsy** | 103 | 100 | 108 | 100 | |
| R1 after NSM          | 16 | 15.5 | 22 | 20.4 | 0.36 |
| Follow-up resection   | 12 | 11.7 | 13 | 12.0 | |
| Follow-up resection ventral/retromam. | 7 | 6.8 | 9 | 8.3 | |
| Radical Mastectomy    | 4 | 3.9 | 13 | 12.0 | 0.03 |

*Sub-group p-value only listed when significant.

### TABLE 5 Patient overview correlation between retro-areolar involvement and nipple biopsy

|                       | Positive nipple biopsy | Corresponding positive retro-areolar biopsy | Corresponding negative retro-areolar biopsy |
|-----------------------|------------------------|--------------------------------------------|--------------------------------------------|
| **Overall**           | 5 | 4 | 1 (20%) | |
| DCIS                  | 2 | 1 | 1 | |
| LCIS                  | 1 | 1 | - | |
| M. Paget + Carcinoma  | 1 | 1 | - | |
| Carcinoma             | 1 | 1 | - | |
We must therefore ask ourselves if a simple retro-areolar biopsy sufficiently represents the involvement of this area. Although numbers are low as only 1 patient would have been falsely classified as R0 (ie, false negative) the authors consider this additional biopsy necessary in order to give a clearer overall picture. Furthermore, we have found 15.5% (control) and 20.4% (nipple biopsy) to have had an R1 status regardless of the nipple biopsy. Of these patients 6.8% (control) and 8.3% (nipple biopsy) were ventrally R1 despite a benign retro-areolar frozen section ± a nipple punch biopsy. This R1 status is thus ventral, but not in the area of the NAC. In summary, we can therefore say the increased level of pathological confidence gained through intraoperative nipple biopsy is evident and can safely be offered to most patients.

We therefore answered the following questions.

1. Is the central core nipple biopsy a safe procedure? Yes. Implant loss rates seem to favor central nipple biopsies.
2. Is there an advantage in performing central a core nipple biopsy versus retro-areolar biopsies during surgery? Nipple biopsies seem to be more accurate in representing NAC involvement.
3. Should both be performed? Yes, evidence that retro-areolar biopsies may be omitted in favor of only performing nipple biopsies is immature.

5 | CONCLUSION

This analysis showed that intraoperative evaluation of the ductal components of the nipple is a safe procedure. A slight benefit was shown for the nipple biopsy since implant loss rates are lower in this cohort. At least 1 patient showed an immediate advantage of this procedure since clean margins were obtained by removing the nipple areola complex during the same surgery. For the minimum median 15 month follow-up, we found no significant difference in local recurrence.

We therefore strongly recommend a central nipple biopsy for all NSM procedures where a DCIS component or an invasive component may be found in close proximity to the nipple areolar complex.

DATA AVAILABILITY STATEMENT

All data is openly available upon request by the corresponding author via email.

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