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A Systematic Review ofthe Safety of Nipple Sparing Mastectomy

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ABSTRACT

Background: Breast cancer is a complex disease, and local recurrence and cancer-related death is likely multifactorial.Over the past three decades there has been a move towards breast conservation and a focus on aesthetic outcomes while maintaining oncological safety. For some patients, mastectomy is the preferred option. There is growing interest in the potential use of nipple sparing mastectomy (NSM). However, oncological safety remains unproven, and the benefits and indications have not been clearly identified

Methods:A Systematic search in the scientific database (Medline, EMBASE , Google Scholer and Ovid) from 1980 to 2016 was conducted for all relevant retrospective studies including; randomized controlled trials, cohort studies and case–control studies involving women undergoing either NSM were analyzed and included based on the preset inclusion criteria.

Results: The search yielded 1193 articles, of which 55 studies with 9053 patients met our selection criteria. After a mean follow up of 41 months (range, 7.1–78 months), the overall pooled locoregional recurrence rate (LRR) was 3.25%, the overall complication rate was 21.8%(1309 of 6003) , and the overall incidence of nipple necrosis, either partial or total, was 6.6 % (561 of 8438). Significant heterogeneity was found among the published studies and patient selection was affected by tumor characteristics.

Conclusion: There is growing evidence that NSM has been marked as oncologically safe in women with small, peripherally located tumors, without multicentricity, or when performed as a prophylactic mastectomy. Hence, NSM has been recommended only if carefully selected for a particular group of patients.

Keywords: Mastectomy,Recurrence, NSM , NAC.

INTRODUCTION

Breast carcinoma is the leading cause among women in most developed countries [1]. It is not a single disease, which comprises of many biologically different entities with distinct pathological features and clinical implications[1,2].Accumulating evidence has suggested that breast cancers with different histopathological and biological features exhibit distinct behaviors that lead to different treatment responses and should be given different therapeutic strategies [3] .Thus, accurate grouping of breast cancers into clinically relevant subtypes is of particular importance for therapeutic decision making and thus urgently called for it[4].There is evidence that 40% of breast cancer undergo a masterctomy. This is due to various reasons (size or position of the tumour,

anticipating a bad cosmetic result, small breast, multifocal tumour, a woman's request, etc.) [5].

History of Mastectomy goes back in time to Halsted's radical mastectomy which had been the standard of care for patients since its inception in 1894 up to the 1960s. Patey described the modified radical mastectomy, which achieved a local recurrence rate of 10% after 10 years[6]. Skin sparing mastectomy (SSM) was first described in 1991 by Toth and Lappert; it involves removing the entire breast and nipple-areola complex (NAC) while maintaining the skin envelope and the native inframammary fold (IMF)[7]. A

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subsequent meta-analysis by Lanitis*et al*. in 2010 found that local recurrence rates after SSM are equivalent to those after modified radical mastectomy (MRM)[8].

Traditionally mastectomy has included resection of the NAC together with the gland. The concern being that the NAC may harbour occult tumour cells. Indeed, large trials have shown the NAC to be involved in 5–12% of cases. The earliest report of nipple sparing mastectomy (NSM) came from Hinton in 1984, who reported that NSM achieved comparable local recurrence rates and survival to that of MRM[9]. However, the technique did not achieve widespread use due to oncological concerns at the time, and these concerns persist still [10] .Previously, NSM was approached cautiously in the context of patients who had received neoadjuvant chemotherapy, but recent data suggested that this may be safe [11] .Similar concerns were raised over the oncological safety of breast conserving surgery for small tumours until Veronesi *et al* published their seminal randomized controlled trial (RCT) with 20-year follow-up showing equivalent oncological outcomes to mastectomy. The treatment of breast cancer has become more nuanced over the past few decades, and a gradual process of systematic improvement has taken place to improve outcomes, both oncologically and aesthetically[12]. Treatments are tailored to individuals and care is directed through multidisciplinary teams.

The nipple is one of the key defining visual features of a breast. With removal of the NAC, the point in the profile at which the most natural convexity occurs is lost[13]. Preserving the NAC also eliminates the need for staged nipple reconstruction and areola tattooing, after which there can be loss of projection and fading over time, respectively. The fundamental reason for attempting nipple preservation is aesthetics, with studies reporting psychological benefits and improved patient satisfaction [14].

Total skin-sparing mastectomy (TSSM), which preserves the nipple-areolar complex (NAC), results in better cosmesis when compared with standard skin-sparing mastectomy (SSM) and avoids the need for later NAC reconstruction. Although SSM is well-established as an oncologically safe procedure, nipple-sparing mastectomy is still avoided in many centers due to oncological concerns and the lack of long-term tumour recurrence data. Of the studies to date that have reported 5-years oncological data for the technique, however, the locoregional recurrence is less than 1% per year[15], which is acceptable when compared to simple modified radical mastectomy.

METHODS

The present systematic review isconducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16] .

- **Data source and time coverage:** Medline, EMBASE , Google Scholer and Ovid databases for studies evaluating NSM from 1980 to 2016.
- **Types of studies:**Retrospective and prospective studies **,**RCTs; cohort and case–control studies
- **Data terms :**'nipple sparing mastectomy' AND 'total skin sparing mastectomy' along WITH 'locoregional recurrence' AND 'outcomes.'
- **Inclusion Criteria :** clear statement of the procedure type NSM or SSM, and clearly stating the outcomes of the NSM cohort separately
- **Exclusion Criteria :**
  a. Articles that didn't specify the number of patients and the number of procedures involved, or
  b. Articles that didn't meet the outcomes of interest ; study endpoint.
  c. Reports, commentaries, reviews or letters or,
  d. Non- English language publications.

Data collection: authors, study name, publication year, location of the study, journal of publication, type of study, number of patients, number of procedures, inclusion criteria for NSM, type of reconstruction, number of overall complications, nipple necrosis, LR, and aesthetic results. Characteristics of the studies included are shown in **table 1.**

Data analysis

Inputs and outputs: The pooled analysis of the rate of LR, the nipple necrosis rate, and the rate of overall complications was performed based on the number of patients included in each study. **Outcome measures:** the rate of overall LR recurrence, the overall complication rate, and the overall rate of nipple necrosis.

Table 1: Characteristics of the included studies

Study	Year	Study type	Reconstruction Type	No. of patients	No. of procedures
Sookhan et al. [17]	2008	Retrospective	Implant	20	20
Garcia-Etienne et al. [18]	2009	Retrospective	Implant	25	42
Dao et al. [19]	2005	Retrospective	Autologous tissue	16	32
Denewer and Farouk [20]	2007	Retrospective	Autologous tissue	41	41
Caruso et al. [21]	2006	Prospective	Implant, autologous tissue	50	51
Benediktsson and Perbeck[22]	2008	Prospective	-	272	272
Voltura et al. [23]	2008	Retrospective	Autologous tissue	36	51
Gerber et al. [24]	2009	Retrospective	Autologous tissue	60	60
Stolier et al. [25]	2008	Prospective	Direct to implant, autologous tissue	58	82
Spear et al. [26]	2011	Retrospective	Direct to implant, autologous tissue	101	162
Colwell et al. [27]	2014	Retrospective	Direct to implant, tissue expander/implant, autologous tissue	285	500
Mustonen et al. [28]	2004	Retrospective	Direct to implant, tissue expander/implant, autologous tissue	34	34
Moyer et al. [29]	2012	Retrospective	Direct to implant, tissue expander/implant, autologous tissue	26	40
Warren Peled et al. [30]	2012	Prospective	Direct to implant, tissue expander/implant, autologous tissue	428	657
Wagner et al. [31]	2012	Prospective	Direct to implant, tissue expander/implant, autologous tissue	33	54
Tanna et al. [32]	2013	Retrospective	Autologous tissue	51	85
Lohsiriwat et al. [33]	2013	Retrospective	Direct to implant, tissue expander/implant, autologous tissue	934	934
de AlcantaraFilho et al. [34]	2011	Retrospective	Implant, autologous tissue	200	353
Kim et al.[35]	2010	Prospective	Autologous tissue	152	152
Paepke et al. [36]	2009	Prospective	Autologous tissue/ implant	96	109
Yang et al. [37]	2012	Prospective	Autologous tissue	92	92
Petit et al. [38]	2009	Prospective	Direct to implant	1,001	1,001
Chen et al. [39]	2009	Retrospective	Direct to implant, tissue expander/implant	66	115
Radovanovic et al. [40]	2010	Prospective	Direct to implant	205	214

Salgarello et al. [41]	2010	Retrospective	Direct to implant	33	42
Mladenov et al. [42]	2010	Retrospective	Direct to implant	52	57
Rawlani et al. [43]	2011	Retrospective	Direct to implant	20	37
Harness et al. [44]	2011	Retrospective	Direct to implant	43	60
Jensen et al. [45]	2011	Prospective	Tissue expander/implant, autologous tissue	99	149
Boneti et al.[46]	2011	Retrospective	Direct to implant, tissue expander/implant	-	281
Spear et al. [47]	2012	Retrospective	Direct to implant	15	24
Kneubil et al. [48]	2012	Retrospective	-	-	948
Peled et al. [49]	2012	Prospective	Tissue expander/implant	288	450
Verheyden[50]	1998	Retrospective	Tissue expander/implant	20	30
Algaithy et al. [51]	2012	Prospective	Direct to implant, tissue expander/implant	45	50
Sahin et al. [52]	2013	Retrospective	Direct to implant	21	41
Sakurai et al. [53]	2013	Retrospective	-	788	788
Fortunato et al. [54]	2013	Retrospective	Immediate, expaneders, prostheses, autologous flaps	121	138
Burdge et al. [55]	2013	Retrospective	Immediate with prostheses or delayed two stage	527	558
Rulli et al.[56]	2013	Retrospective	-	77	87
Romics et al. [57]	2013	Retrospective	Immediate reconstruction	253	253
Sakamoto et al. [58]	2009	Retrospective	-	87	89
Coopey et al. [59]	2013	Retrospective	-	370	645
Tancredi et al. [60]	2013	Retrospective	Immediate reconstruction	55	55
Chen et al. [61]	2013	Retrospective	Both immediate and delayed	56	56
Stanec et al. [62]	2014	Retrospective	Varied	252	252
Chattopadhyay et al. [63]	2014	Prospective	Immediate, autologous tissue, silicone implants	34	34
Leclere et al. [64]	2014	Retrospective	Immediate, prostheses, tissue expander or autologous tissue	41	41
Wang et al. [12]	2014	Retrospective	Immediate reconstruction	633	730
Kim et al. [65]	2016	Retrospective	-	19	19
Adam et al. [66]	2014	Retrospective	Immediate implant based reconstruction	67	69
Huston et al.[67]	2014	Retrospective	Implant based reconstruction	318	318
Peled et al. [68]	2014	Retrospective	-	106	212
Poruk et al. [69]	2015	Retrospective	-	130	205
Yao et al. [70]	2015	Retrospective	-	201	397
Totals			-	9053	12268

RESULTS

1193 studies were screened and assessed for eligibility. After applying inclusion and exclusion criteria , in addition to that 24 articles were manually searched and obtained, after removing duplicates, 1094 records were reassessed based on the title and abstract and further 503 records were excluded.

591 articles' full-text were again screened based on the inclusion and exclusion criteria(536 articles were excluded ; 43 of which could not be retrieved in addition to 431 articles with irrelevant endpoint and study outcome and 62 studies with the same cohort). Finally 55 studies with 9053 patients were selected for inclusion(**Figure 1**),

Which reported LR rates, complication rates, and/or nipple necrosis rate following NSM ,**table 2.**

The majority of the studies were retrospective (91%). The 55 studies yielded 12,268 procedures in 9053 patients, and the indications included invasive breast cancer, risk-reduction surgery, and carcinoma in situ. The mean follow-up period was 59 months, with a range of 10–156 months. Pooled analysis demonstrated an overall LR rate of 3.25%, The overall complication rate was 21.8% and the nipple necrosis rate was 6.6%. As reported by the majority of studies NSM has been very popular after 2011 . A small subgroup analysis was carried out examining the average complication rates before and after 2013, and the results was a clear reduction in the complication rate and the incidence of nipple necrosis after 2013 [78].

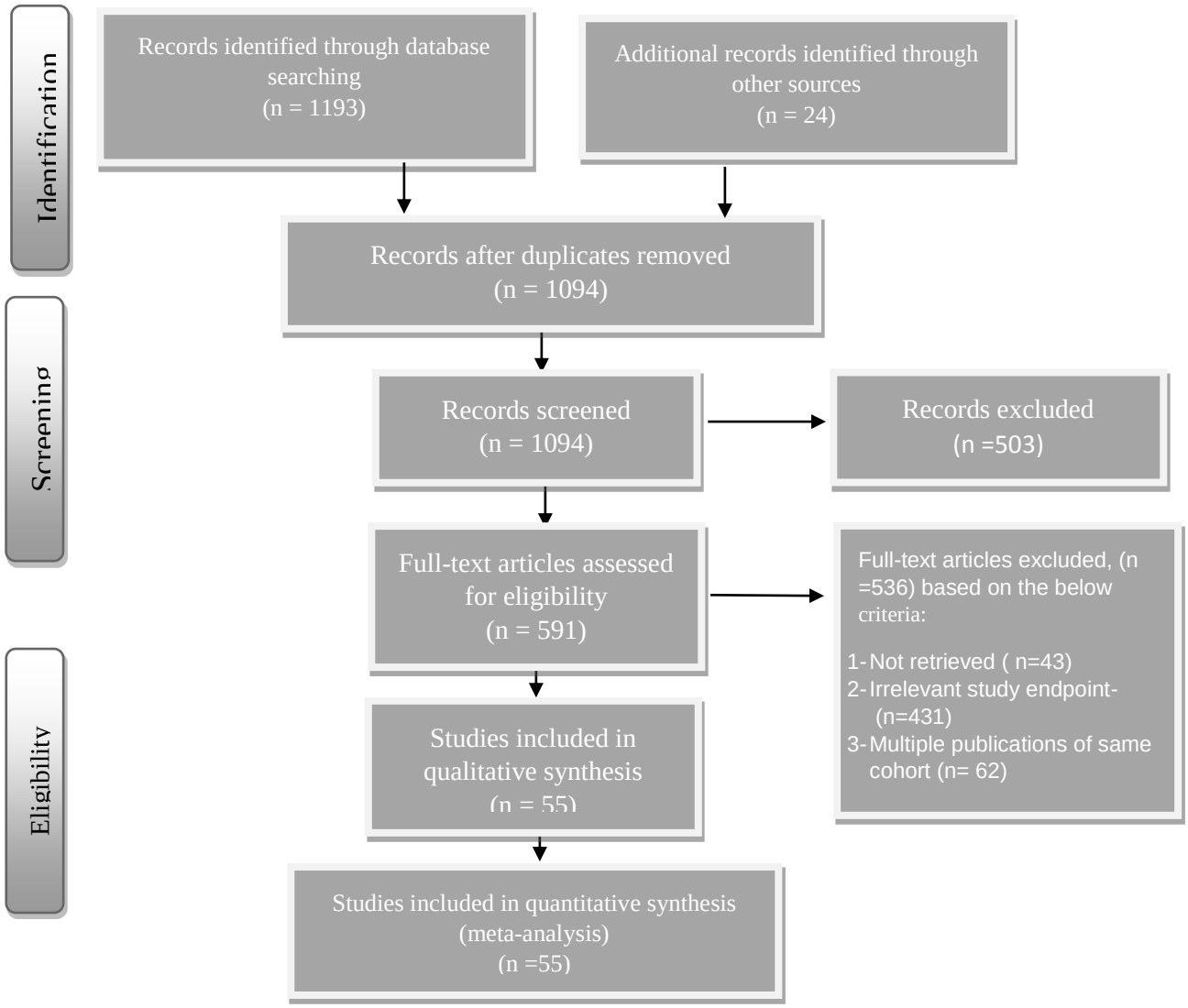

Figure 1: PRISMA flow diagram showing the selection process and steps of the literature search

Table 2 :**Output of the included studies interms of present study outcome measure ; locoregional recurrence rate (LRR), overall complication rate, and nipple necrosis rate.**

Study	Follow-up time (mo, mean)	LRR (%)	Complications (%)	Nipple necrosis (%)
Sookhan et al. [17]	10.8 (mean)	0 (0)	3 (15)	2 (10)
Garcia-Etienne et al. [18]	10.5 (median, range 0.4–56.4)	0 (0)	6 (14)	3 (7.1)
Dao et al. [19]	-	-	12 (37.5)	0 (0)
Denewer and Farouk [20]	7.9 (mean, range 4–11)	0 (0)	11 (26.8)	1 (2.4)
Caruso et al. [21]	66 (mean, range 9–140)	1 (1.9)	4 (8)	2 (4)
Benediktsson and Perbeck[22]	156 (median, range 2.4–210)	52 (19.1)	-	-
Voltura et al. [23]	18 (mean, range 2–68)	2 (3.9)	-	-
Gerber et al. [24]	-	7 (11.6)	-	-
Stolier et al. [25]	-	-	10 (7.2)	0 (0)
Spear et al. [26]	36.5 (mean, range 5–243)	0 (0)	46 (28.4)	7 (4.3)
Colwell et al. [27]	2.17 yr (mean)	-	62 (12.4)	22 (4.4)
Mustonen et al. [28]	45.6 (mean, range 28.8–69.6)	4 (11.8)	23 (67.6)	6 (17.6)
Moyer et al. [29]	-	-	16 (40)	15 (37.5)
Warren Peled et al. [30]	28 (median, range 3–116)	4 (0.6)	-	23 (3.5)
Wagner et al. [31]	15 (median, range 1–29)	0 (0)	-	16 (29.6)
Tanna et al. [32]	-	-	-	11 (12.9)
Lohsiriwat et al. [33]	64 (median, range 18–113)	0 (0)	-	40 (4.3)
de AlcantaraFilho et al. [34]	10.38 (median, range 0–109)	0 (0)	90 (25.5)	12 (3.3)
Kim et al.[35]	60 (median)	3 (2)	40 (22.6)	40 (22.6)
Paepke et al. [36]	34 (median)	1 (0.91)	-	27 (25)
Yang et al. [37]	18.1 (mean, range 5–34 months)	0 (0)	-	12 (13)
Petit et al. [38]	20 (median, range 1–69)	14 (1.4)	358 (35.8)	90 (9)
Chen et al. [39]	-	-	-	25 (21.7)
Radovanovic et al. [40]	-	-	35 (16)	9 (4.5)
Salgarello et al. [41]	-	-	10 (23.8)	4 (9.5)
Mladenov et al. [42]	13181	0 (0)	-	13 (22.8)
Rawlani et al. [43]	-	-	16 (43.2)	9 (24.3)
Harness et al. [44]	18.5 (mean, range 6–62)	1 (1.7)	12 (20)	5 (8.3)

Jensen et al. [45]	60.2 (median, range 12–144)	3 (2.01)	9 (6)	8 (6.3)
Boneti et al.[46]	25.3 (mean, range 3–102)	7 (2.5)	20 (7.1)	-
Spear et al. [47]	13 (mean)	0 (0)	10 (41.6)	7 (29)
Kneubil et al. [48]	64 (median, range 18–113)	10 (1.05)	-	-
Peled et al. [49]			252 (56)	4 (0.9)
Verheyden[50]	75.5 (mean, range 3–126)	0 (0)	24 (80)	11 (36)
Algaithy et al. [51]	-	-	-	13 (25)
Sahin et al. [52]	-	-	8 (19)	0 (0)
Sakurai et al. [53]	78 (median)	65 (8.2)	-	0 (0)
Fortunato et al. [54]	28 (median)	1 (0.72)	-	25 (18.1)
Burdge et al. [55]	18 (median)	4 of 39 (10.3)	93 (16.7)	-
Rulli et al.[56]	50.3 (mean)	3 (3.3)	-	4 (4.6)
Romics et al. [57]	112 (median)	21 (8.2)	-	-
Sakamoto et al. [58]	52 (median)	0 (0)	-	16 (18)
Coopey et al. [59]	22 (mean)	4 of 156 therapeutic cases (2.6)	-	11 (1.7)
Tancredi et al. [60]	21.7 (mean, range 3–55)	2 (3.6)	8 (14.5)	2 (3.6)
Chen et al. [61]	40 (median, range 14–88)	0 (0)	5 (8.9)	0 (0)
Stanec et al. [62]	63 (median, range 1–180)	6 (5.5)	-	29 (10.1)
Chattopadhyay et al. [63]	28.5 (median, range 18–38)	0 (0)	3 (8.8)	1 (2.9)
Leclere et al. [64]	7.1 ± 2.9 yr (mean, range 2–13 yr)	1 (5.3)	-	9 (22)
Wang et al. [12]	29 (median)	19 (3)	113 (11.6)	10 (1)
Kim et al. [65]	22.4 (mean)	1 (5.3)		
Adam et al. [66]	36 (median, range 4–162)	0 (0)	-	-
Huston et al.[67]	505 day (mean, range 7–1,504 day)	3 (2.5)	-	10 (8.2)
Peled et al. [68]	37 (mean)	1 (3.7)	-	-
Poruk et al. [69]	25.08+18 (mean)	2 (0.1)	-	-
Yao et al. [70]	32.6 (mean)	4 (1)	10 (2.5)	7 (1.8)
Totals	-	246/7558 (3.25)	1309/6003 (21.8)	561/8438 (6.6)

The findings of the present study are inline with a systematic review conducted by Heade*et al.* [77].

DISCUSSION

In this systematic review, we are attempting to assessthe oncological Safety of Nipple-Sparing Mastectomy.

Histological studies following conventional mastectomy have reported residual glandular tissue in 5% of all biopsies, indicating that more radical surgery may not be guaranteed of complete clearance [73] . In SSM performed in patients with invasive breast cancer, the prevalence of residual breast tissue has been reported to be as high as 59.5%, with residual disease in 9.5% [74] ,a finding echoed by Ho et al. [75] ,who reported that skin flaps exhibited residual malignancy in 23% of cases, most commonly in the skin overlying the tumour. However, a large systematic review from 2012 reported that the overall incidence rate of LR was only 0.9% after a mean follow-up of 38.4 months and that the skin flap recurrence rate was 4.2% following SSM , which was much lower than had been reported in single-centre studies.

Several authors have shown that certain incisions are associated with a decreased risk of necrosis, particularly if the surgeon ensures that the incision does not extend across the whole circumference of the NAC, loss of the nipple is less likely[35].Stolier et al. performed [25] NSMs without NA necrosis, and advocated a six-o'clock radial incision, or a lateral incision if excising a biopsy or BCT scar[39] .They also stressed the importance of lighting, use of headlamps, blended current cautery used only for pinpoint homeostasis, and the utility of bipolar dissecting scissors. Other authors also endorse the use of radial or lateral incisions, [18]noting that medial incisions seemed to compromise blood flow. Paepke et al. reported only a 1% NA loss with a periareolar incision, [58] however, Regolo et al. reported a 60% NA loss with periareolar incision, [24] which they abandoned in favor of a lateral incision. In summary, since there is no agreement on optimal approach, surgeons should be familiar with the literature and employ an approach they are familiar with for optimal outcomes.

Complications of NSM

The overall complication rate was 22.3% and the nipple necrosis rate was 6.6%. Due to the extensive undermining of the NAC during NSM, it is thought that NSM may lead to an increased incidence of necrotic complications. Many studies have reported data on nipple necrosis, with incidence rates ranging from 3.8% for total nipple necrosis to 13.4% for partial nipple necrosis [27,40]. Necrosis can occur as a quite early complication, with Radovanovic et al. [40] finding a major skin necrosis rate of 3% after just 6 weeks The concern with nipple necrosis is that it can lead to loss of the NAC at a later date [64] . Consequently, it would appear that despite the risk of necrotic complications, the actual incidence of necrosis remains low, meaning that NSM may still be a viable option. Those at a higher risk, such as those with a higher body mass index or large breast volume, should be individually assessed for suitability with the options of an autologous tissue flap or two-stage reconstruction discussed in order to minimize the possibility of revisional surgery. [78]

Adjuvant therapy (radiotherapy):

Benediktsson et al. [22]reported in their study that patients who underwent radiotherapy had a LR rate of 8.5% compared to 28.4% in those that did not undergo radiotherapy over a 13-year follow-up period.

Nevertheless, Radiotherapy incurs many complications - such as fat necrosis and volume loss in reconstructions using autologous tissueand capsular contracture in those using implants in the reconstructed breast. In terms of nipple necrosis, however, it appears that including radiotherapy in the treatment of the patient does not increase the risk of NAC necrosis [79] .

CONCLUSION

NSM is the surgery of choice for a particular group of patients and under a careful criteria which should be fully comprehended by the oncologic Surgeon prior to advising NSM for patients. Optimally , patient of choice for NSM should be those with early-stage IBC and DCIS. Also , Patients with a peripherally located tumour less than 5 cm in diameter, located more than 2 cm from the NAC, not showing HER2 overexpression, and exhibiting a positive ER and PR status may be considered for NSM with or without adjuvant radiotherapy.

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