

Prevalence of Terminal Duct Lobular Units in Nipple to Assess the Safety of Nipple Sparing Mastectomy

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ABSTRACT

Background: Nipple sparing mastectomy is widely used for both treatment and risk reduction of breast cancer. Terminal duct lobular units (TDLU) are considered as the basic reacting unit in all neoplastic lesions arising from the breast. TDLU is the basic anatomic unit of breast parenchyma, studies revealed that it also exists in the nipple whose frequency is not widely researched. Our objective is to study the frequency of TDLUs in nipple along with its location, number and association with age and laterality of breast.

Methods: The descriptive study involved entire submission of nipples from 191 consecutive therapeutic mastectomy specimens from a reputed cancer institute in India between January 2015 and June 2016. The nipple is divided into two parts, nipple papilla and nipple base and presence of TDLU were recorded separately.

Result: From the specimens submitted, 38% were observed to have TDLU in the nipple. While 45.2% were in the papillae and 26% in the base the remaining 28.8% were in both the papillae and base with maximum number of TDLU counted at 5 and mean age of subjects at 53.56 years, 57.5% from the left and 42.4% from the right breast respectively. There was no significant association between age ($p=0.59$), laterality of breast ($p=0.37$) with presence of TDLU whereas a significant negative linear correlation observed between age and number of TDLUs ($r=-0.237$, $p=0.043$).

Conclusion: Nipples show a high frequency of TDLU and is observed more in papilla than in the base.

Keywords: Terminal Duct Lobular Units, Breast Cancer, Nipple, Mastectomy

Introduction

Breast cancer is the most common cancer in women worldwide, representing about 25 per cent of all cancers in women. Incidence rates vary widely across the world, from 27 per 100,000 in Middle Africa and Eastern Asia to 92 per 100,000 in Northern America. According to the Union health ministry of India, breast cancer ranks as the number one cancer among Indian females with rate as high as **25.8 per 100,000** women and mortality of **12.7 per 100,000** women. The age-standardized **incidence rate of breast cancer in Kerala** has been stated as 30.5 in urban areas and 19.8 in rural areas per 100,000 female population. Increased general awareness among population along with advancements in screening modalities enabled detection of breast cancer in the early stages. The advances produced a revolutionary change in the treatment of breast cancer from the conventional radical mastectomy of Halstedian to less debilitating breast conservation surgeries such as nipple sparing mastectomy (NSM), subcutaneous mastectomy, skin sparing mastectomy etc.^[1,2] Among individuals who had undergone breast reconstruction, a good percentage opt for nipple reconstruction, with the reconstructed nipple being usually insensate and non – erectile.^[3] Multiple series

of studies with skin sparing mastectomies^[4-7] and nipple sparing mastectomies^[8-12] does not show any oncological disadvantages compared with the radical mastectomies. Nowadays people who test positive for a deleterious mutation of BRCA1 and BRCA2 elect to undergo prophylactic mastectomy. Nipple sparing mastectomy is now considered as a good choice for young individuals undergoing prophylactic mastectomies and mastectomies for early breast cancer or small volume disease. Nipple sparing mastectomy offers an opportunity to preserve native breast envelope without mutilation of nipple-areola complex (NAC) and avoids multiple surgical procedures required for reconstruction.^[13] Nipple sparing mastectomy is associated with an increased oncological risk due to de novo cancer development from TDLUs in nipple. The lobule, together with its terminal duct, has been called the terminal duct lobular unit (TDLU) which represents the structural and functional unit of the breast. Research on the anatomic origin of breast cancer carried out by Wellings, Jensen and associates^[14, 15] observes that all neoplastic lesions arise from TDLU with the exception of intraductal papilloma and epithelial hyperplasia arising in the larger ducts. These studies concludes that both ductal and lobular

carcinoma share a common origin in terminal duct lobular units. Literature saying that the occurrence of TDLU in nipple is infrequent, which supports the oncological safety of nipple sparing mastectomy. Aim of this study is indirect assessment of safety of nipple sparing mastectomy by measuring the prevalence of an anatomical structure in nipple named terminal duct lobular units along with its association with age and laterality of breast. Objectives are to assess the prevalence TDLUs in nipple, location of TDLUs in nipple, its number and its association with age and laterality of breast. All mastectomy specimen removed for breast cancer are included in the study. Mastectomy specimen following neoadjuvant chemotherapy and mastectomy specimens removed for male breast cancer are excluded from the study.

Materials and Methods

Mastectomy specimens received in the Department of Pathology at Amala Institute of Medical Sciences were collected for a period of 18 months (01 January 2015 – 30 June 2016). This study was approved by institutional review board and ethics committee. Post chemotherapy mastectomy specimens and mastectomy specimens of male patients were excluded. The clinical and relevant investigative details required for the study were obtained from the subjects themselves as well as from their medical records. Specimens are sliced immediately after surgery and fixed in 10 times the bulk of 10% formol saline. A modified grossing protocol is applied (Figure 1), which includes amputation of the nipple at the level of the areolar skin with a 0.5 cm areola around it. Nipple base is submitted as an en face section, which was a circular section perpendicular to lactiferous ducts. Nipple papilla (top portion elevating above the areolar skin) as 4 serial sections parallel to the lactiferous ducts. Each section measures approximately 2- 3mm in thickness.

All representative tissue were submitted for routine tissue processing following which they were cut into sections of 5 micron thickness, stained using routine haematoxylin and eosin (H and E) stain and examined using a microscope. Three serial sections of 5 micron thickness from each block is examined microscopically. Terminal duct lobular unit (TDLU) is defined as a terminal duct surrounded by a lobule containing acini.^[16]

Data analysis was performed using SPSS 22.0 (IBM Inc., Chicago, Illinois, USA). Chi – square analysis and independent sample ‘t’ test were used to evaluate the association between age, laterality of breast with presence of TDLU. The p-values less than 0.05 were considered statistically significant. In subjects with bilateral mastectomy, each breast was considered as a separate statistical event.

Result

A total of 252 mastectomies from 251 subjects (one woman had bilateral mastectomy) were received in the department and all were therapeutic mastectomies. Among these cases, 61 cases were excluded based on the exclusion criteria. The remaining 191 mastectomies constituted study cohort with subjects in the range of 22 to 87 years with mean age at 54.9 years. 101 cases were left side mastectomies and 90 were right side mastectomies (Table 1). Nipple sections show skin with sebaceous and apocrine glands with underlying stroma showing lactiferous ducts. Out of 191 cases, 38% (73) cases showed terminal duct lobular units in nipple (Table 2). Terminal duct lobular units show lactiferous duct surrounded by lobule containing acini in a dense fibromuscular stroma (Figure 2).

Of the 38% cases that were observed to have TDLU in the nipple, 45.2% (33 cases) were observed in the papillae, 26% (19 cases) were observed in the base and the remaining 28.8% (21 cases) were observed in both base and papillae (Table 3). Patients observed to have TDLUs in nipple were in the age between 35 to 87 years. Mean age was 53.56 (SD: 9.98) years. And the mean age of the cases without TDLUs in the nipple was 55.86 (SD: 11.79) years. The pattern of presence of TDLUs in various decades of age were also analyzed (Figure 3). There was no statistically significant difference in age between the patients with and without TDLU in the nipple ($p=0.59$). There was no statistical significance between right and left side of breast with patients having with or without TDLU in nipple ($p=0.37$). Number of TDLUs in nipple varies from 1-5. There was a significant negative linear correlation between the age and number of TDLUs present in the nipple ($r=-0.237$, $p=0.043$). It means with increase in age there is reduction in number of TDLUs.

In addition to the TDLUs in nipple, of the 191 cases examined, 22 cases (11.51%) showed neoplastic involvement of nipple. 19 cases showed invasive neoplasm as direct extension of underlying malignancy and 3 cases showed Paget disease. All Paget diseases show malignancy in underlying breast parenchyma. One of the nipple sections show a usual ductal hyperplasia in lactiferous duct.

Discussion

Pathological characteristics of breast tumours with increased risk of occult neoplastic involvement of nipple have been proposed by different studies. The importance of our study is that we are analysing an anatomical structure in nipple known as TDLU which has been proved as the basic reacting unit in breast neoplasms. This is very important in the setting of nipple sparing mastectomy especially when it is done for risk reduction/prophylaxis. When TDLUs are

Table 1: Site of distribution of total cases.

Site	Frequency	Percent
Left	101	52.9
Right	90	47.1
Total	191	100.0

Table 2: Terminal duct lobular units (TDLU) frequency among study group.

TDLU	Frequency	Percent
Absent	118	61.8
Present	73	38.2
Total	191	100.0

Table 3: Location of terminal duct lobular units in nipple.

Location of TDLU	Frequency	Percent
Base	19	26.38
Papillae	33	45.83
Both base and papillae	21	27.77
Total	73	100.0

Table 4: Summary of selected studies and our study describing frequency and location of terminal duct lobular units in nipple.

Source	No. of mastectomies		Cases with TDLU (%)	TDLU location	Nipple submission
	Prophy-lactic	Therapeutic			
Rosen and Tench,^[20] 1985	None	101	17(17)	NA	1 vertical section
Luttges et al,^[18] 1987	None	166	NA	NA	3 verticals sections
Menon and van Geel,^[24] 1989	None	33	NA	NA	Entirely submitted
Stolier and Wang,^[21] 2008	22	10	3(9)	Base (3)	Entirely submitted
Voltura et al,^[19] 2008	17	34	NA	NA	Entirely submitted
Gulben et al,^[17] 2009	None	397	NA	NA	1 vertical section
Brachtel et al,^[23] 2009	84	232	NA	NA	Entirely submitted
Reynolds et al,^[22] 2011	33	29	15(24)	Papilla & retro Areolar (5), Retro areolar (10)	Entirely submitted
Kryvenko et al,^[25] 2013	15	90	17(26%)	Base (6), Papilla (6), Both (5)	Entirely submitted
Present study	None	191	72(38.2)	Base (26) Papillae (46) Both (28)	Entirely submitted

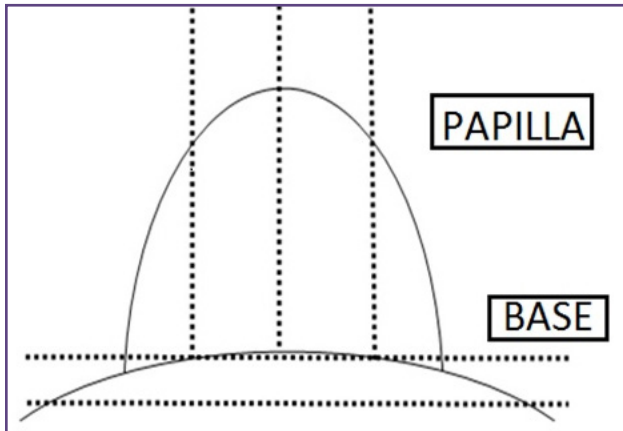


Fig. 1: Grossing protocol of nipple. [—] - Nipple areola complex [.....] - Plane of sectioning.)

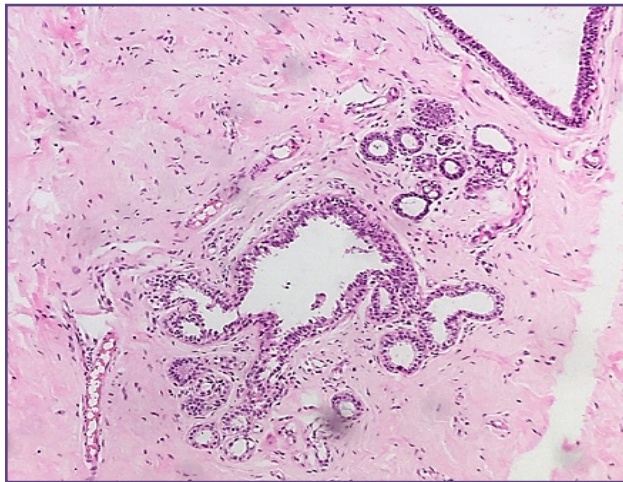


Fig. 2: Photomicrograph of Terminal duct lobular unit in nipple. (H and E stain, 10x).

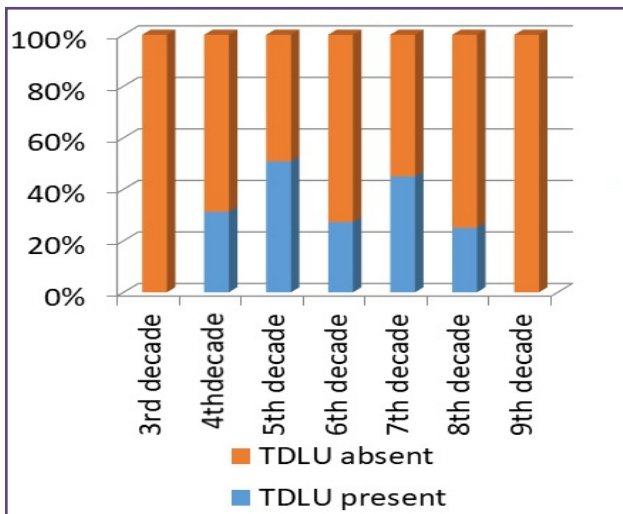


Fig. 3: Presence of TDLUs in the nipple across the decades (age group). (p=0.087).

present in the nipple, there is always a risk for de novo development of cancer in nipple tissue. Our study observed a frequency of 38.2% TDLU in nipple which is higher value compared to other studies. The reported frequency of TDLU in nipple in literature review shows a significant variation from 10% to 24%, whose difference may be explained by the different method of nipple submission. Studies by Gulben et al, Luttges et al, Voltura et al and Rosen and Tench included only a single sagittal section or partial embedding of nipple^[17, 18, 19, 20] while studies by Stolier and Wang, Reynolds et al, Brachtel et al, Menon and van Geel and Kryvenko et al included multiple sections and entire submission.^[21, 22, 23, 24, 25] A comparison of these studies and our study was done (Table 4).

In this study , dominant location of TDLU was in papillae, i.e. in 33 out of 72 cases (45.2%). While 19 cases (26%) showed TDLU location in nipple base, 21 cases (28.8%) TDLU was present in both base and papillae. Most of the studies report dominant location of TDLU in base of the nipple. But in this study dominant location was found in nipple papilla. Location of the TDLU is of utmost important because in nipple sparing mastectomy, some surgeons will dissect base of the nipple and leave behind nipple papilla.^[26] In such scenarios, dominant location of TDLU in nipple papillae is significant because there is risk for deno vo development of cancer from the residual TDLUs in nipple papilla. To overcome this risk, some surgeons attempt to remove tissue within nipple papillae, known as ‘coring’ during which, entire content of nipple is removed to ensure complete eradication of ductal system.^[27] But these surgeries are compromised by vascularity of nipple. Hence most of the surgeons now prefer to leave a small amount of tissue in sub areolar location to maintain vascular supply. Studies by Petit JY, Veronesi U, Orecchia R, et al recommend intraoperative radiotherapy to the remaining tissue in nipple to reduce the recurrence rate.^[28, 29]

In this study, number of TDLUs in a nipple varies from 1 to 5. We found no association between ages of the patient with presence of TDLU. But we found a significant reduction in number of TDLUs in nipple as the age advances, implying an increased risk for younger individuals undergoing nipple sparing mastectomy. This reduction in number may be due to hormonal influences. There was no association between laterality of breast with prevalence of TDLU. Recently studies are published for pre-operative radiological evaluation of nipple for occult neoplastic involvement, but none of these studies propose the radiological identification of terminal duct lobular units in nipple.

TDLUs in glandular breast tissue usually show loose lobular stroma. In contrast to that the terminal duct lobular

units we found in nipple show a dense stroma. It is unclear how this dense stroma can affect the development of cancer from TDLUs in nipple.

Our data supports a significant percentage of TDLU in nipple which indirectly indicating the risk of nipple sparing mastectomy. But the value obtained in this study cannot directly be applied to the cohort undergoing prophylactic mastectomy due to the fact that all cases were therapeutic mastectomy. Due to limited number of data, there needs to be more long term follow up, study and clinical research to prove the significance of residual TDLUs in nipple especially in young women.

Conclusion

38.2% of patients showed TDLUs in nipple, which is a higher frequency and is questioning the safety of nipple sparing mastectomy. Most of the TDLUs were found in nipple papilla which also discouraging the type of nipple sparing mastectomy surgery with base dissection and papilla preservation. Age and laterality of breast show no significant association with presence of TDLU, but there was a significant significant reduction in number of TDLUs as the age advances. This indicating the importance of future long-term clinical trials in young women undergoing prophylactic mastectomy for risk reduction.

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Competing Interests

None declared.

Reference:

1. Cady B, Stone MD, Wayne J. New therapeutic possibilities in primary invasive breast cancer. *Ann Surg.* 1993; 218(3):338–347.
2. Cady B. Traditional and future management of nonpalpable breast cancer. *Am Surg.* 1997; 63(1):55–58.
3. Jabor MA, Shayani P, Collins DR Jr, Karas T, Cohen BE. Nipple – areola reconstruction: satisfaction and clinical determinants. *Plastic Reconstr Surg* 2002; 110:457 – 463.
4. Carlson GW, Styblo TM, Lyles RH, Bostwick J, et al. Local recurrence after skin-sparing mastectomy: tumour biology or surgical conservatism? *Ann Surg Oncol* 2003; 10:108–12.
5. Newman LA, Kuerer HM, Hunt KK, Kroll SS, et al. Presentation, treatment, and outcome of local recurrence after skin sparing mastectomy and immediate breast reconstruction. *Ann Surg Oncol* 1998; 5:620–6.
6. Medina-Franco H, Vasconez LO, Fix RJ, Heslin MF, et al. Factors associated with local recurrence after skin-sparing mastectomy and immediate breast reconstruction for invasive breast cancer. *Ann Surg* 2002; 235:814–9.
7. Foster RD, Esserman LJ, Anthony JP, Hwang ES, et al. Skin sparing mastectomy and immediate breast reconstruction: a prospective cohort study for the treatment of advanced stages of breast carcinoma. *Ann Surg Oncol* 2002; 9:462–66.
8. Stanec Z, Zic R, Stanec S, Budi S. Skin-sparing mastectomy with nipple-areola conservation. *Plast Reconstr Surg* 2003; 111:496–8.
9. Crowe JP, Kim JA, Yetman R, Banbury J, et al. Nipple sparing mastectomy: technique and results of 54 procedures. *Arch Surg* 2004; 139:148–50.
10. Gerber B, Krause A, Reimer T, Muller H, 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.
11. Sacchini V, Pinotti JA, Barros AC, Luini A, et al. Nipple sparing mastectomy for breast cancer and risk reduction: oncologic or technical problem? *J Am Coll Surg* 2006; 203:704– 14.
12. Paepke S, Schmid R, Fleckner S, et al. Subcutaneous mastectomy with conservation of the nipple-areola skin: broadening the indications. *Ann Surg.* 2009; 250(2):288–292.
13. Rusby JE, Smith BL, Gui GP. Nipple-sparing mastectomy. *Br J Surg.* 2010; 97(3):305–316.
14. Wellings SR, Jensen HM. On the origin and progression of ductal carcinoma in the human breast. *J Natl Cancer Inst* 1973; 50:1111-8.
15. Wellings SR. A hypothesis on the origin of human breast cancer from the terminal duct lobular unit. *Pathol Res Pract* 1980; 166:515-35.
16. Schnitt SJ, Collins LC. Breast. In: Mills SE, ed. *Histology for Pathologists.* Philadelphia, PA: LWW; 2007:57–75.)
17. Gulben K, Yildirim E, Berberoglu U. Prediction of occult nipple-areola complex involvement in breast cancer patients. *Neoplasia.* 2009; 56(1):72–75.
18. Luttgies 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(5):481–487.
19. Voltura AM, Tsangaris TN, Rosson GD, et al. Nipple-sparing mastectomy: critical assessment of 51 procedures and implications for selection criteria. *Ann Surg Oncol.* 2008; 15(12):3396–3401.
20. Rosen PP, Tench W. Lobules in the nipple: frequency and significance for breast cancer treatment. *Pathol Annu.* 1985; 20(pt 2):317–322.
21. Stolier AJ, Wang J. Terminal duct lobular units are scarce in the nipple: implications for prophylactic nipple-sparing

- mastectomy: terminal duct lobular units in the nipple. *Ann Surg Oncol*. 2008; 15(2):438–442.
22. Reynolds C, Davidson JA, Lindor NM, et al. Prophylactic and therapeutic mastectomy in BRCA mutation carriers: can the nipple be preserved? *Ann Surg Oncol*. 2011; 18(11):3102–3109.
 23. Brachtel EF, Rusby JE, Michaelson JS, et al. Occult nipple involvement in breast cancer: clinicopathologic findings in 316 consecutive mastectomy specimens. *J Clin Oncol*. 2009; 27(30):4948–4954.
 24. Menon RS, van Geel AN. Cancer of the breast with nipple involvement. *Br J Cancer*. 1989; 59(1):81–84.
 25. Oleksandr N. Kryvenko, Ji Yoon, Dhananjay A. Chitale, Min W. Lee. Prevalence of Terminal Duct Lobular Units and Frequency of Neoplastic Involvement of the Nipple in Mastectomy. *Arch Pathol Lab Med* 2013; 137: 955- 960.
 26. Paepke S, Schmid R, Fleckner S, et al. Subcutaneous mastectomy with conservation of the nipple-areola skin: broadening the indications. *Ann Surg*. 2009; 250(2):288–29.
 27. Randall P, Dabb R, Loc N. “Apple coring” the nipple in subcutaneous mastectomy. *Plast Reconstr Surg*. 1979; 64(6):800–803.
 28. Petit JY, Veronesi U, Orecchia R, et al. Nipple-sparing mastectomy in association with intra operative radiotherapy (ELIOT): a new type of mastectomy for breast cancer treatment. *Br Breast Cancer Res Treat*. 2006; 96(1):47–51.
 29. 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(2):333–338.

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