



ORIGINAL ARTICLE

Breast duct micro-endoscopy: A study of technique and a morphological classification of endo-luminal lesions

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Received 1 March 2005; received in revised form 22 July 2005; accepted 11 August 2005

KEYWORDS

Endoscopy;
Ductoscopy;
Nipple discharge;
Mammary/breast ducts;
Early diagnosis

Summary Endoscopic visualisation of the human mammary ductal system has been sporadically reported over the last decade. Recent rapid and groundbreaking developments in the field of optics have made the previously unseen labyrinth of mammary ducts more easily accessible to direct visualisation and examination. The emphasis so far has been on visualisation of ectatic ducts with pathological nipple discharge. The purpose of this study was to assess the feasibility of mammary duct epithelium in patients with a range of other pathologies. Based on our findings we have developed a morphological classification of endo-luminal lesions seen on endoscopy.

We successfully conducted ex vivo mammary duct micro-endoscopy on 115 ducts in 35 mastectomy specimens. Visualisation of mammary duct epithelium was achieved using a solid rod depth of field imaging micro-minimally invasive (DOFI^R MMI, Acueity Inc., USA) and more recently the LaDuScope^R (PolyDiagnost GmbH, Germany) system. Both these systems consist of 0.9 mm maximum outer diameter micro-endoscope, with working channels 0.35 and 0.45 mm, respectively. Saline or air insufflation was used to keep the mammary ducts from collapsing.

An average of 3.3 (median 3) mammary ducts could be identified and cannulated in all 35 mastectomy specimens (total of 115 ducts). Visualisation beyond 2 cm of the ductal system was possible in 23/35 (66%) of specimens. Abnormalities were visualised in 40% of the ducts. The maximum depth we could negotiate to was 8.9 cm and in doing so manoeuvred past eight duct divisions. In 34% of ducts cannulated, we were able to navigate the scope beyond at least one bifurcation of the principal duct and in 16% of cases extensive intra-ductal navigation was possible. Peripheral ducts were visualised in 16% of cases. False passages were created in 16% of cases. Previous history of smoking, parity, breastfeeding and radiotherapy offered neither significant

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advantages nor disadvantages for the technique nor did they increase or decrease the number of normal ducts visualised per specimen.

This study showed that mammary duct micro-endoscopy is a practical and technically feasible procedure even in the absence of nipple discharge, in normal non-ectatic milk ducts. A simple morphological classification of endoscopically visualised intra-ductal abnormalities is suggested.

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Introduction

With more than one million cases being diagnosed worldwide each year, breast cancer has assumed truly pandemic proportions. Research into prevention and cure may provide the answers eventually, for the present, however, the early detection and treatment of primary breast cancer offers the best chance of reducing mortality.

Unfortunately, none of the array of investigative procedures currently available to us is able to reliably detect DCIS. Holland et al.¹ demonstrated that only 50% of micro-papillary or cribriform DCIS is associated with micro-calcification and it fails to show *in situ* malignancy in the region of the nipple in 70% of the cases. It follows, therefore, that an imaging modality, which offers direct visualisation of the mammary ductal epithelia, should provide valuable information that may facilitate the diagnosis of benign, pre-malignant and malignant pathology.

Mammary duct endoscopy evolved as a means to achieving these very objectives more than a decade ago, but until recently progressed only slowly and sporadically. Earlier attempts to establish this technique include reports from Okazaki et al.,² Love and Barsky,³ Makita et al.⁴ and Berna et al.⁵

Large endoscopes, limited optics and the inability to biopsy and insufflate have previously been the technical obstacles to successful mammary duct endoscopy. Technology has progressed a great deal since these early experiments, leading to the development of a new generation of dedicated breast micro-endoscopes with high-resolution optics along with the ability to insufflate/irrigate and biopsy package into extremely small external diameters. The depth of field imaging micro-minimally invasive (DOFI^R MMI, Acueity Inc., California, USA) system consists of a 0.89 mm external diameter solid rod endoscope with a 0.35 mm working channel that provides depth of perception during visualisation. Dietz et al.⁶ used similar, albeit larger, endoscopes of 1.2 mm diameter to successfully conduct feasibility studies on sowbelly mammary ductal systems, before proceeding to human models. The LaDuScope^R (PolyDiagnost GmbH, Pfaffenhofen, Germany) was the second

system that the authors used towards the end of this study along with DOFI. This package includes endoscopes ranging from 1.1 to 0.5 mm in external diameter. The endoscope used in this study measured 0.9 mm in external diameter with fibreoptic imaging and a working channel of 0.45 mm.

We have undertaken a study to determine the feasibility of human mammary duct endoscopy in patients with normal calibre mammary ducts in the absence of nipple discharge.

Methods

Local ethical committee approval for this study was obtained and all patients gave informed consent. Women taking part in this study were undergoing a modified radical or simple mastectomy for DCIS, invasive carcinoma or for prophylactic reasons. None of the women had a history of recent nipple discharge. Thirty-five *ex vivo* breasts were subjected to endoscopy in the pathology laboratory. Each specimen was examined fresh within 15 min of excision and was free from any form of fixative.

Mammary duct endoscopy was only carried out in those mastectomy specimens where sufficient tissue was available pre-operatively for routine and specialised histopathology. This was done to safeguard against loss of tissue architecture and staining characteristics that may occur on account of *ex vivo* specimens being left exposed to air at room temperature for 30–45 min with the subsequent denaturation of critical proteins such as the oestrogen receptor. Due care was taken to avoid postmortem tissue degeneration by keeping the mastectomy specimen on ice and restricting the procedure to a maximum of 45 min. A detailed individual patient history including information on smoking, parity and breastfeeding was recorded in every case. The size and morphological characteristics of each nipple were recorded and the weight of the breast specimen was obtained from the pathology reports.

Breast duct micro-endoscopy (BDME) was carried out using the DOFI^R MMI 0.89 mm endoscope (Acueity Inc., USA). A xenon light source, Raster

image screen, and a video camera provide excellent quality images at a focal length of 2 mm, while providing the sensation of a three-dimensional depth of visual field.

The LaDuScope^R (PolyDiagnost GmbH, Pfaffenhofen, Germany) was the second system that was used towards the end of this study along with DOFI. The endoscope used in this study measured 0.9 mm in external diameter with fibreoptic imaging and a working channel of 0.45 mm. This system is now in regular use; however, for this particular study, it was used only in last few cases with other scope.

The mastectomy specimen was mounted on a flat surface such as a dissecting board in a position similar to its anatomical lie in a supine body under good illumination. The nipple was cleaned with saline and then squeezed to express any unexpected discharge. The visible external ostia of mammary ducts were visualised with the naked eye and also with the use of magnifying loops ($\times 3.5$ magnification). In those specimens where the visualisation of external duct ostia was difficult, we used a solution of methanol to gradually de-epithelialise the nipple epidermis.

An atraumatic nipple duct dilator was used to gently enlarge the duct orifice at the level of the skin. The mammary endoscope was at first oriented and focussed and then inserted and advanced in the ductal system under direct vision. We tried both saline and air, injected through the working channel, to insufflate and thereby distend the mammary ducts. The location and number of ducts cannulated in each specimen were noted and care was exercised so as not to cannulate the same duct more than once, in the same specimen. The distance of scope advancement was recorded for each duct in each specimen, as was the number of bifurcations passed. For the purpose of clinical utility, we have defined the first two centimetres of the mammary ducts as the "proximal ducts". The epithelial morphology of each procedure was recorded and catalogued separately on a VHS video recorder and this was used to re-check features at the time of data analysis. A record of any false passages caused during the procedure along with possible contributing factors was also made in each case.

Results

A total of 35 women consented to make their specimens available for the study. The same trained investigators conducted the micro-endoscopic evaluation on each occasion. The median age of the

cohort was 45 (range 32–92 years). Twenty-nine mastectomies were carried out for operable carcinoma, two for DCIS, two for a locally advanced breast cancer and two were prophylactic mastectomies. The median nipple diameter was 1.4 cm (range 0.8–2.1 cm), with four nipples being inverted, one flattened, one hyper-keratotic, two being involved by malignancy, while 27 were entirely normal.

Cannulation of the ductal system with the endoscope was achieved in all the 35 specimens. A total of 115 ducts were cannulated, with the median number of ducts cannulated per specimen being 3 (range 1–8). Visualisation restricted to the proximal duct only occurred in 12/35 (34%) (Table 1), while distal navigation beyond two centimetres was achieved in 23/35 (66%) specimens.

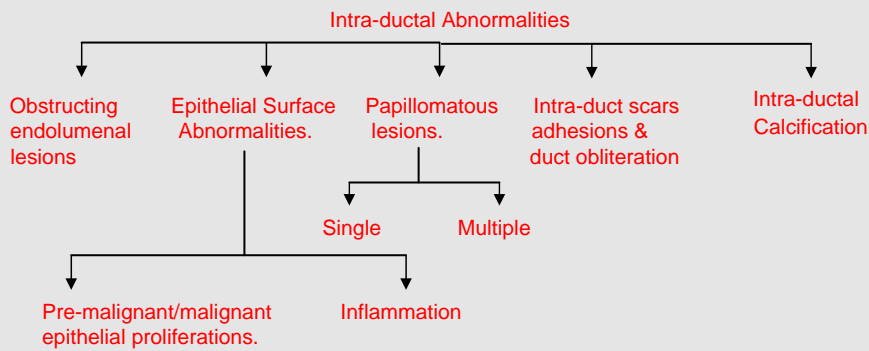
Imaging of the duct system deeper than 5 cm was possible in 18/115 ducts (16%). While visualising ductal systems we were able to navigate past at least one major bifurcation in 28/83 (34%) (Table 2) of all ducts and in one specimen we passed eight bifurcations. False passages were created in 16% of

Table 1 Visualisation of ductal system.

Results Ducts	
<i>Proximal (<2 cm from skin)</i>	<i>Distal (>2 cm from skin)</i>
12/35	23/35
34% of specimens	66% of specimens
Minimum depth of 0.5 cm	Maximum depth 8.9 cm

Table 2 Duct divisions visualised $N = 115$.

Number of divisions	Number of ducts	Percentage
1	14	34
2	6	21
3	11	20
4	11	12.3
5	4	8.6
6	2	3.7
7	1	1.2
8	1	1.2

Table 3 Morphological classification of endo-luminal lesions.

duct examinations and in many of these cases further attempts at negotiating that duct were unsuccessful and abandoned. We have divided the results into two groups, Group I (12/35) are those breast specimens where duct visualisation was not achieved beyond a depth of 2 cm in any duct, and Group II (23/35) where navigation beyond 2 cm was possible in at least one duct. Patient variables such as weight of the specimen, age, effect of smoking, parity and breastfeeding, the presence of pathological discharge and ipsilateral breast biopsy had no significant impact on success of endoscopy.

Abnormalities of the mammary ducts were seen in 40% of breast specimens examined. A morphological classification of these observed abnormalities was developed (Table 3).

Discussion

It was possible to pass beyond the proximal duct in two-thirds cases in this series. Duct endoscopy in ex vivo specimens is more difficult than in live patients due to less distensible ducts, which make visualisation of pathology difficult, and hence we believe that results of this study are an underestimation of the percentage of cases that can be successfully investigated. We found no difference between the ability to cannulate the duct or progress in the duct when air or saline is used for insufflation. However, picture quality is somewhat better with saline and so we quickly changed over to saline irrigation (Fig. 1).

The morphologically visualised abnormalities are classified into five main categories, namely epithelial surface abnormalities (Fig. 2), intra-ductal scars/adhesions/duct obliteration (Fig. 3), endo-luminal obstructing lesions (Fig. 4), intra-ductal

**Figure 1** Normal duct.

calcification (Fig. 5) and papillomatous lesions (Fig. 6). Papillomatous lesions may be sub-divided into single or multiple.

This classification includes signs of inflammation and hence has wider application, considering the fact that 5% of patients presenting to breast clinic have nipple discharge and more than 90% of these patients have benign inflammation of the ducts.

This is a morphological classification, but now with the availability of scopes with working channels and micro-instruments, it should be possible in future to take precise biopsy from endo-luminal lesions and establish pathological correlation.

We defined a papillomatous lesion as a discreet, rounded endo-luminal lesion that was adherent to the duct wall at only one point of its circumference.



Figure 2 Epithelial abnormality.

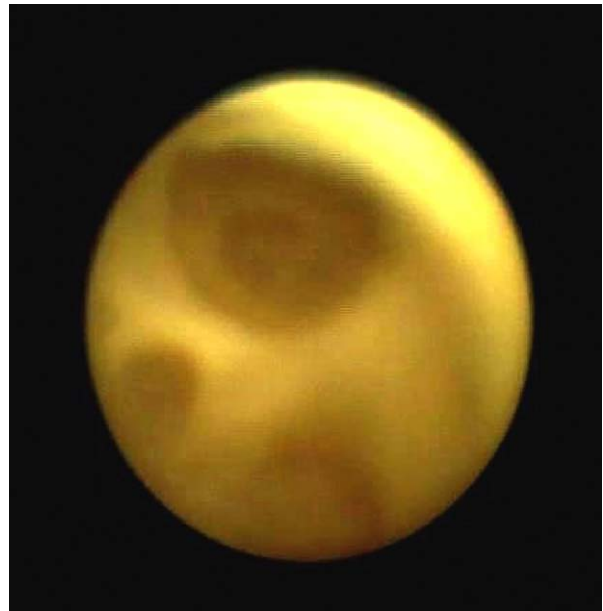


Figure 4 Blocked ducts.



Figure 3 Intra-ductal adhesions.



Figure 5 Intra-ductal calcification.

Obstructing lesions, on the other hand, are endo-luminal abnormalities that fill or obliterate the duct lumen sufficient to prevent further passage of the scope and appear adherent to, or part of, the duct wall at more than one point or circumferentially. Obstructing lesions have been reported as being most often a result of malignancy.⁷ It is important, therefore, to differentiate endo-luminal obstructing lesions from duct obliteration which is classified with scars and adhesions. Epithelial surface changes may be defined as an irregular alteration of the

character of the duct wall in either surface colour or texture. Intra-ductal calcification is identified as coarse roughened lumps of white calcium lying freely within the duct lumen. Intra-ductal scarring/ adhesions appear as relatively flimsy fibrous white bands running across the lumen of the duct in a random pattern. Included in this category, however, are dense adhesions that obliterate the duct lumen and prevent further passage of the endoscope.

The external openings of mammary ducts on the nipple are not well demarcated. In practice, it is



Figure 6 Papillomatous lesions.

usually possible to locate between 2 and 6 ostia per nipple. It is apparent that duct ostia are random and not placed in any sort of symmetrical pattern on the nipple. A search of literature did not give an agreed number of duct openings that one should encounter on the nipple, with figures ranging from 8 to 20. We found that the use of magnifying surgical loops ($\times 3.5$ magnification) did not add to our pick-up rate of the number of duct orifices identified per specimen.

The most crucial point in the entire endoscopic process is the dilation of the appropriate nipple orifice without disturbing the integrity of the duct system.

The first part of each duct is the lactiferous sinus, which is comparatively wide, and about 1 cm in length. At its distal end (away from the nipple skin) the lactiferous sinus narrows significantly as it becomes the main duct proper, and at this point there is a noticeable narrowing or sphincter that may prove troublesome to negotiate particularly with larger endoscopes. Normal ductal epithelium has a pearlescent white shiny, smooth appearance (Fig. 1).

It is not always immediately apparent that the duct wall has been perforated since the scope readily creates its own plausible channel, which may be mistaken for a duct with ragged adhesions. The transition from white, shiny, smooth ductal epithelium to a grey ragged surface (fibrous breast parenchyma) or to a yellow cavernous honeycomb appearance (breast adipose tissue) should always alert the investigator to a false passage especially in areas where force may have been used to

continue navigation. Another indication that the scope has extravasated is that the pressure required to irrigate is less decreased when the scope is outside the ducts. In the literature, there have been no major scope-related complications in patients throughout the last decade.

As the scope is navigated through the ductal tree bifurcations are encountered, there is no predictability or uniformity with regard to the depth when the ducts begin to arborise, but, in general, the first division of ducts is not encountered for approximately 1.5–2.5 cm. Occasionally, a bifurcation is encountered as close as 2 cm from the surface and on other occasions it is possible to traverse up to 4 cm within a major duct without encountering any sub-divisions. We also regularly noted duct trifurcations, but with less frequency than we encountered duct bifurcations. We were unable to detect any sort of spatial pattern that would allow us to predict the site or mode of duct division.

We were able to clearly visualise duct papillomas. While visualising ducts in the quadrant of the malignancy we sometimes encountered the tumour coming up along the duct in a solid irregular mass that occluded the duct. In cases where lumpectomy had been previously carried out, we were frequently able to navigate down to a seroma-filled cavity.

The ability to consistently access and comprehensively examine normal calibre ducts is of vital importance if we want to use this technique in detection of pre-invasive malignancy.

We have established the feasibility of BDME. With the advances in optical field and availability of smaller scopes with working channel and micro-instruments for precise sampling of lesions, it should be possible in the future to establish correlation between visualised endo-luminal lesions and histopathology. It is also a challenge for future studies to develop a technique to identify same duct and mark it in some way, so as to facilitate repeated periodic endoscopic examination. It is important if this technique is to be used for screening for high-risk women. The aim of BDME in the future should be to detect early changes in the lining ductal epithelium and thus help prevent invasive malignancy.

Conclusion

This study showed that mammary duct micro-endoscopy is a practical and technically feasible procedure even in normal calibre non-ectatic milk ducts in the absence of nipple discharge.

At present, a precise pathological identification of any endoscopic abnormality is difficult. The nature of intra-ductal pathology will only be clarified when good biopsy instruments are available. In the interim period, we suggest a simple morphological classification of endoscopically visualised endo-luminal abnormalities.

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