Intraductal Approach to Breast Cancer: The Role of Mammary Ductoscopy

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Abstract Mammary ductoscopy is a recent advance enabling direct visualisation and sampling of human mammary ducts using a micro endoscope. The majority of pre malignant and malignant changes in the breast arise from the epithelium lining the duct lobular unit, and access to this region by ductoscopy has the potential to revolutionise breast cancer diagnosis and treatment. The ability to sample ductal epithelium may allow identification of early malignant and pre-malignant cytological changes and assist surgical excision, facilitating diagnosis of non palpable cancer before detection on current imaging modalities. Presently, there are three main indications for ductoscopy in clinical practice viz. determining extent of resection for breast cancer, assessment of high risk individuals and in the management of patients with pathological nipple discharge. Our initial experience with ductoscopy in patients with nipple discharge undergoing surgery has been rewarding. Ductoscopy was feasible in 92% of patients. Abnormal findings on ductoscopy were associated with DCIS in 37% and DCIS with early invasive breast cancer in 21%, while normal ductoscopy correlated with a normal pathological assessment.

Keywords Mammary ductoscopy · Intraductal · Breast cancer · Nipple discharge

Introduction

There are two main approaches to minimising morbidity and mortality related to breast cancer viz. prevention and early detection. Unfortunately, true prevention of breast cancer still remains elusive. Thus early detection remains the most important approach to managing breast cancer.

Breast cancer is known to originate in the epithelial lining of milk ducts or lobules. Moreover once early pre-malignant or malignant changes take place in the ductal lining there is a long latent period before these ductal changes manifest symptoms or are detected on imaging. The inability of current imaging techniques to detect these early lesions made it logical to develop methods which would allow direct approach to the breast ductal system [1]. Till recently access to the ductal tree was limited to fine needle aspiration and cytological evaluation or blind removal of tissue. Evolution in micro endoscope technology finally provided researchers with a direct approach to breast ductal epithelium. The procedure called “mammary ductoscopy”, “ductoscopy” or “breast endoscopy” refers to a technique which allows introduction of a micro endoscope in to breast milk ducts facilitating inspection of the ductal epithelial lining and recovery of cells for analysis by lavage and biopsy. This has led to development of the “Intraductal Approach” to breast cancer.

The field of ductoscopy has rapidly progressed over the last 20 years. Initial developments occurred in Europe and the Far East [2–4]. The following article traces the development of this technique, its current and future applications and our preliminary experience with ductoscopy in patients with nipple discharge.

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Evolution of Breast Ductoscopy

The earliest report of ductoscopy was by Teboul in 1988 [2]. He used a rigid endoscope to observe breast ducts using ultrasound assistance. Since then the technique has progressed rapidly. The early scopes were of large calibre, had limited optics, and were single-lumen. These limitations precluded cannulation of small ductal openings which were millimetres in size and the single lumen prevented insufflations of ducts for navigation of the ductal tree, resulting in limited access. The lack of a working channel precluded sampling of the tree under vision and the limited optics did not generate clear images.

Advances in technology addressed these short comings. Newer generation of scopes are now available which allow excellent images and have a working channel. The working channel allows insufflations, lavage of the ductal tree for cytological evaluation and biopsy of intra ductal lesions. Initial scopes were flexible, fibre optic with a limited life. Semi flexible scopes are now available which have a longer life. Furthermore, scopes in varying sizes ranging from an outer calibre of 1.2 mm to as small as 0.45 mm are now available. A video link allows recording of the procedure.

We have been using a semi rigid, flexible scope with a 1.1 mm external diameter and a working length of 8 cm. It has a separate channel for lavage, insufflation and a working channel for brush sampling and a basket for intra ductal biopsy (Fig. 1).

Ductoscopy Procedure

Ductoscopy can be performed as an office procedure in the out patient clinic or under anaesthesia in the operating room. Under sterile conditions the breast is massaged to

identify the discharging ductal orifice. The ductal orifice of interest on the nipple is dilated and the scope gently inserted into the ductal orifice. Using saline insufflations, the scope is gently advanced into the ductal tree under vision with the help of a video monitor which allows recording of the procedure. After assessment of the main ducts, side ducts or branches are evaluated till further advancement is limited by size of the scope. The ductal appearance is visualised and recorded using the attached video equipment. Ductal washings are collected for cytology (Fig. 2). Abnormality identified during ductoscopy can be addressed by ductoscopy directed surgical removal for definitive diagnosis. Appearances during ductoscopy are shown in Fig. 3.

Indications for Ductoscopy

Feasibility of ductoscopy was initially demonstrated in human mastectomy specimens by Dietz et al. [5] using a 1.2 mm rigid scope with a 350 μ m working channel. Dilatation and cannulation of at least one major duct was possible in all the 42 mastectomy specimens studied. Visualisation of the proximal duct was achieved in 81% of specimens and distal sub-segmental ducts could be studied in 52%.

The role of ductoscopy is currently being evaluated in directing excision in patients with breast cancer undergoing lumpectomy, in the evaluation of women at high risk for developing breast cancer, and in the management of patients with symptomatic nipple discharge. Dooley [6] evaluated the role of ductoscopy in patients undergoing definite surgery for atypical ductal hyperplasia (ADH), ductal carcinoma in situ (DCIS), and breast cancer to assess intra ductal extent of disease and in achieving disease free surgical margins. Using a flexible fibre optic scope he

Fig. 1 Mammary ductoscope with 1.1 mm external diameter, 8 cm length, 0.4 mm working channel and separate irrigation channel

Fig. 2 Ductal lavage cytology showing the presence of atypical cells

Fig. 3 Appearance of ducts on mammary ductoscopy
a Normal main duct, **b** Normal ductal bifurcation, **c** Intra ductal bleeding, **d** Bleeding with growth, **e** Intraductal growth

studied 201 patients undergoing lumpectomy for ADH ($n=16$), DCIS ($n=52$) and 133 patients with breast cancer. Following massage of the index quadrant ductoscopy was performed to identify the extent of the disease in the breast and to direct complete excision. He termed the technique “routine operative breast endoscopy” (ROBE). The procedure was successful in 150 patients (74.6%). Additional lesions outside the anticipated lumpectomy were identified in 41% ($n=83$) of cases. Successful ROBE decreased the chances of a positive margin for cancer from 23.5% to 5.0%. Conversely, Kim et al. [7] prospectively evaluated 30 patients undergoing therapeutic partial mastectomy for in situ and invasive cancer and failed to find any benefit with per-operative ductoscopy.

Another area of current interest is the role of ductoscopy in the assessment of high risk patients with normal clinical examination and imaging. The use of ductal lavage for risk assessment and random peri-areolar fine needle aspiration cytology has resulted in identification of high risk patients with no identifiable site of malignant change on current imaging. Although the clinical significance of these findings is unclear reports suggest identification of atypical cells on random periareolar fine needle aspiration is associated with a significant near term risk (<3 years) of subsequent breast cancer [8]. There is no defined approach to these patients and current options include MRI, ductography, chemoprevention and mammary ductoscopy. However the exact role of ductoscopy in high risk states still remains to be defined.

Pathological nipple discharge is a relatively common symptom noted in approximately 5% of patients attending a breast clinic. Although, usually benign in origin it can, in fact, be the earliest sign of malignant change within the

ductal system. The cancer risk associated with nipple discharge is reported to vary from 1.3% to 47% [9]. The presence of a single duct discharge and dilated ducts makes identification of the ductal orifice and insertion of the scope in to the ducts technically easy. Identification of an intra ductal lesion and its excision under ductoscopic direction is then feasible [10]. Advantages include accurate identification of intraductal abnormalities, and their excision, limiting volume of excision to abnormal ducts, and assessment of the rest of the ductal tree.

Shen et al. [11] reported on their results with ductoscopy in 415 patients with nipple discharge. They found an intraductal lesion in 166 patients (40%). They found the majority of benign lesions to be present in the main segmental ducts and the first branch while DCIS lesions were situated more peripherally in the first and second branches. The average distance for a DCIS lesion was 3.3 cm, and the most distant lesion was situated 5 cm from the nipple. In contrast benign papillomas were situated at an average distance of 2.7 cm and the nearest at 0.5 cm. DCIS lesions were associated with bleeding, circumferential ductal obstruction, and gross fungating projections. The positive predictive value with ductoscopy in detecting DCIS was 80% which increased to 100% when combined with ductal lavage cytology.

In an earlier study Okazaki et al. [12] studied 46 patients with nipple discharge and were able to successfully scope 90% of the patients. Thirteen patients subsequently underwent surgical resection and four of whom were found to have carcinoma (31%). They identified white flat spreading lesions on the ductal wall, bleeding and fragile bridging structures of a pale yellow colour to be associated with malignant change. In a more recent study Tekin et al. [13] found abnormal findings in 20 patients (66%) of 30 who

could be successfully evaluated by ductoscopy. Of the 20 patients with abnormal findings they identified the presence of malignant change in three patients (15%) while 45% had benign papillomas and 40% had changes suggestive of inflammation.

Our Preliminary Results with Mammary Ductoscopy in Patients with Nipple Discharge

We started evaluating the role of ductoscopy in patients with nipple discharge in July 2004 at the P.D. Hinduja National Hospital, Mumbai. Over the last 5 years more than 50 patients have undergone ductoscopy and guided excision for nipple discharge. Our preliminary analysis evaluated patients treated between July 2004 and October 2007. During this period, 26 patients underwent ductoscopy with ductoscopy directed surgical excision for pathological nipple discharge. Ductoscopy could be successfully performed in 24 patients (92%) while cannulation of the ducts failed in two patients (8%). Ductoscopy was normal in five (19%) and abnormal in 19 (73%) of the patients (15 had intraductal growth, two had intraductal bleeding with an abnormal ductal epithelial lining, and two had intraductal bleeding without obvious ductal pathology). Pathological assessment correlated with normal duct appearance on ductoscopy, proving to be normal in four patients and associated with moderated epithelial hyperplasia in one patient. In presence of abnormal ductal appearance however ($n=19$), pathology revealed benign papilloma in 11 patients (42%), seven (27%) of which were associated with hyperplasia of varying degree. Seven patients (27%) had DCIS of which four (15%) had early invasive breast cancer. The remaining patient with an abnormal finding had mild ductal hyperplasia.

Thus, in this selected group of patients with nipple discharge, the presence of an abnormal finding on ductoscopy ($n=19$) was associated with DCIS in as high as 37%, while 21% had early invasive breast cancer. Interestingly, preoperative mammography and sonography did not suggest malignant change in any of these patients. Our results add to the growing body of evidence indicating the usefulness of ductoscopy in the assessment of nipple discharge and diagnosis of early breast cancer.

Future Directions

Ductoscopy has come a long way since the pioneering efforts of the 1980's. However like all nascent technologies there is scope for further development. While the current generation of scopes are excellent, scopes with better

optics, smaller size, with an ability to negotiate tight turns, with better biopsy and working channels are being developed. Attempts are being made to identify ductal epithelium at risk of harbouring atypical changes, using technological advances such as auto fluorescence, to allow accurate direct tissue sampling. Detailed analysis of retrieved ductal cells using modern genomic techniques, to evaluate the presence of tumour suppressor gene methylation or other biomarkers, has the potential to transform the way high risk states are being assessed and may facilitate diagnosis of early breast cancer [14]. Finally intraductal mapping of the extent of breast cancer and administration of intra ductal therapy to ablate small lesions may obviate the need for surgical intervention.

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