INTEND II randomized clinical trial of intraoperative duct endoscopy in pathological nipple discharge

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Background: The majority of lesions resulting in pathological nipple discharge are benign. Conventional surgery is undirected and targeting the causative lesion by duct endoscopy may enable more accurate surgery with fewer complications.

Methods: Patients requiring microdochectomy and/or major duct excision were randomized to duct endoscopy or no duct endoscopy before surgery. Primary endpoints were successful visualization of the pathological lesion in patients randomized to duct endoscopy, and a comparison of the causative pathology between the two groups. The secondary endpoint was to compare the specimen size between groups.

Results: A total of 68 breasts were studied in 66 patients; there were 31 breasts in the duct endoscopy and 37 in the no-endoscopy group. Median age was 49 (range 19–81) years. Follow-up was 5.4 (i.q.r. 3.3–8.9) years in the duct endoscopy group and 5.7 (3.1–9.0) years in no-endoscopy group. Duct endoscopy had a sensitivity of 80 (95 per cent c.i. 52 to 96) per cent, specificity of 71 (44 to 90) per cent, positive predictive value of 71 (44 to 90) and negative predictive value of 80 (52 to 96) per cent in identifying any lesion. There was no difference in causative pathology between the groups. Median volume of the surgical resection specimen did not differ between groups.

Conclusion: Diagnostic duct endoscopy is useful for identifying causative lesions of nipple discharge. Duct endoscopy did not influence the pathological yield of benign or malignant diagnoses nor surgical resection volumes. Registered as INTEND II in CancerHelp UK clinical trials database (https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-changes-inside-the-breast-ducts-of-women-who-have-nipple-discharge).

Introduction

In 5–21 per cent of patients, breast cancer presents with nipple discharge as the primary symptom[1–6]. The majority of women with nipple discharge, however, have benign conditions. This underlines the importance of an accurate diagnosis of an uncommon early presentation of breast cancer while not overtreating the vast majority of women with benign disease. In the presence of nipple discharge, a higher risk of breast cancer is recognized when the patient is aged over 50 years with a palpable mass, or a defined abnormality is observed on imaging or in cytology of the nipple discharge fluid[3–7]. Blood-stained nipple discharge carries a higher risk of being associated with malignancy than discharge of any colour or serous/clear nipple discharge, with odds ratios of 2.27 (95 per cent c.i. 1.32 to 3.89) and 2.49 (1.25 to 4.94) respectively[8].

The current diagnostic standard for nipple discharge is histology of the affected duct[7,8]. The cytology of nipple discharge has variable sensitivity (23–73 per cent) and limited specificity (59–76 per cent)[6,9,10]. The presence of red blood cells in nipple discharge, either on stick testing or cytology, is not a reliable marker for breast cancer[6,7,11]. The sensitivity and specificity of mammography in identifying breast cancer in patients with pathological nipple discharge are 18–57 and 33–94 per cent, whereas those for ultrasound examination are 73– 83 and 18–29 per cent, respectively[8,10]. MRI is not currently recommended as a standard investigation for nipple discharge[12]. As a research tool, MRI in combination with ductal contrast has modest sensitivity (55 per cent), specificity (67 per cent), positive predictive value (PPV) (85 per cent) and negative predictive value (NPV) (31 per cent)[13].

These widely used imaging investigations do not necessarily help the surgeon to localize the pathological lesion within the ductal tree of the breast unless wire localization of a definitive lesion is feasible and undertaken before surgery. Ductography is used less often but has the advantage of highlighting the anatomy in three dimensions. This enables the surgeon to determine the surgical strategy in

terms of identifying the affected duct, the distance from the nipple surface and the identification of potential multiple lesions. Ductography also distinguishes duct ectasia from space-occupying lesions, allowing non-surgical intervention in patients with minimally symptomatic nipple discharge. Ductography has acceptable sensitivity but limited specificity (79 and 12 per cent respectively) in the identification of cancer[8]. Although ductography may enable direct visualization of the causative lesion, it does not allow real-time planning for surgical intervention.

Developments in fibre-optic technology and the evolution of microendoscopic instruments have been revolutionary over the past two decades. Endoscopy allows direct visualization of the breast ducts, enabling distinction between normal and abnormal areas, and targeting of visible lesions that correlate with subsequent postoperative surgical pathology with a sensitivity of 71.2 per cent and specificity of 49.4 per cent[10]. The most common recognizable lesions are duct ectasia and benign polyps. Raised flat lesions, erythema and stranding are often benign, but can also be associated with atypical ductal lesions. The efficiency of duct endoscopy in improving preoperative diagnosis is reported variably. A range of indications for endoscopy, non-uniform classification of recognizable abnormalities, different methods for localization of any visualized lesion for surgery and different surgical techniques for removal have been described. Despite these limitations, a meta-analysis[14] of 20 studies concluded that duct endoscopy provides an accurate means of identifying surgical pathology. Duct endoscopy has been proposed as a way of selecting which women with pathological nipple discharge require surgery[15–17]. The use of interventional duct endoscopy in resection of papillomas has been described[18,19], but its efficacy and cost-effectiveness is controversial in the context of what is essentially a benign disease.

Patients with single-duct persistent nipple discharge requiring surgery, but without any clinical mass or suspicious lesions on imaging, were included in this RCT. The hypothesis was that targeting a visualized causative lesion by duct

endoscopy before standard surgical excision would enable smaller resection volumes, resulting in improved aesthetic outcome and a lower risk of complications. The primary endpoints were to assess the rate of successful visualization of a pathological lesion before a standard microdochectomy or major duct excision; and to compare the causative pathology between the duct endoscopy and no-endoscopy groups. The secondary endpoint to compare the volumes of the resection specimens.

Methods

The study was approved by the institutional Committee for Clinical Research (CCR2747) and registered in the CancerHelp UK clinical trials database (https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-changes-inside-the-breast-ducts-of-women-who-have-nipple-discharge). Patients who met the inclusion criteria were invited to participate and informed consent was obtained. Women were randomized to undergo either diagnostic duct endoscopy or no endoscopy before admission to hospital. A random allocation sequence was computer-generated at the Institute of Cancer Research – Clinical Trials Statistics Unit randomization centre. Patients were allocate in a 1 : 1 ratio stratified by site using block sizes of four and six.

All operations were performed as a day-case procedure by a single surgical team. Women randomized to duct endoscopy underwent the procedure immediately before the start of the planned open resection under the same general anaesthetic.

A consistent duct endoscopy protocol was applied. Endoscopy was performed initially on the symptomatic discharging duct, systemically inspecting first-order and subsequent branches, before proceeding to any identifiable additional fluid yielding ducts worthy of inspection. Findings at duct endoscopy were classified as: papilloma, duct ectasia, flat raised lesion, irregular raised plaque, stricture, erythema and stranding. Localization of any abnormality before surgical excision was achieved

using an expanding rhomboid guidewire passed down the working channel of the microendoscope. A semirigid endoscope with an external diameter of 0.95 mm was used for viewing and a 1.1-mm endoscope with a working channel to pass the guidewire (Laduscope®; Polydiagnost, Pfaffenhofen, Germany). The localization procedure allowed precise excision of the visualized target. The wire was retrieved through a periareolar incision and the targeted duct dissection commenced at the base of the nipple, following the duct proximally to the position of the rhomboid, excising the duct system beyond the identified lesion. If no lesion was identified, a lacrimal probe was used to cannulate the fluid-yielding duct and standard surgery performed to excise the offending duct system to a depth deemed appropriate by the operating surgeon (*Fig. 1*).

Patients randomized to no duct endoscopy proceeded directly to standard surgery. The lacrimal probe cannulation and excision method described for the duct endoscopy group was used when no lesion was identified. Patients aged over 40 years requiring major duct excision had a disc of subareolar tissue resected in addition to the offending duct cannulated by the lacrimal probe; the size of the disc and depth of the duct were determined by the operating surgeon.

Resected specimens were orientated by marking sutures for pathological assessment. In all patients, the defect created by open surgery was approximated to enable repair with direct apposition of adjacent parenchymal tissue using absorbable sutures, avoiding any space for haematoma or seroma formation. The surgical incision was closed in layers with local anaesthetic infiltration comprising 20–40 ml of 0.25 per cent chirocaine as preemptive analgesia before reversal of the general anaesthetic.

Statistical analysis

The histopathology findings after standard surgery for nipple discharge in the authors' department showed a specific diagnosis to account for the nipple discharge

(such as papilloma or duct ectasia) in around 50 per cent of breasts. It was expected that duct endoscopy might increase the yield to 85 per cent. The study was designed to randomize 71 patients and on this basis to have over 83 per cent power based on a two-sided 5 per cent □ significance level for the primary outcome.

The primary endpoint was the sensitivity of successful visualization by duct endoscopy, aimed at 80 per cent in the duct endoscopy group; conversely, the procedure would be considered unsuccessful if the rate of visualization of a lesion fell to below 60 per cent. Based on this level of successful visualization, with 80 per cent power and one-sided 5 per cent □, 33 breasts were to be examined using duct endoscopy.

Test characteristics of duct endoscopy in identifying any lesion were expressed as sensitivity, specificity, PPV and NPV in comparison with findings at pathology. Volume of the surgical resection specimen in the two groups was described using median (i.q.r.) and assessed for significant differences using the Mann–Whitney *U* test. The χ^2 test was used to compare histological findings between the groups. Stata® version 13 (StataCorp, College Station, Texas, USA) was used for statistical analysis.

Results

Of 78 patients assessed for eligibility, seven decided not to participate in the study; the remaining 71 patients were randomized, accounting for 73 breasts with nipple discharge. Four women were withdrawn from from the study, either because of cancellation of the surgical procedure (2) or equipment failure (2). Complete analyses included 66 patients and 68 breasts for study, 31 breasts in the duct endoscopy group and 37 in the no-endoscopy group (*Fig. 2*). The median age overall was 49 (range 19–81, i.q.r. 44–60) years, 49 (i.q.r. 44–60) years in the duct endoscopy group and 51 (46–58) years in the no-endoscopy group. Median follow-up in the two groups was 5.4 (i.q.r. 3.3–8.9) and 5.7 (3.1–9.0) years respectively.

Overall, there was only one complication: a haematoma in the no-endoscopy group that needed surgical evacuation. There were no wound infections in either group after surgery. No toxicities or serious adverse events were recorded.

Outcome of duct endoscopy

Of the 32 duct endoscopies performed, a single duct as the only fluid-yielding duct was examined in 22 breasts, two ducts in eight breasts, and more than three ducts were examined in two breasts. The index lesion was identified at a median distance of 2.5 (range 1–6) cm from the nipple surface. The median depth of inspection of all ducts studied was 5.5 (range 1–10) cm. Details of the number and order of ducts studied are shown in *Table 1*.

Duct endoscopy (32 breasts) identified any lesion with a sensitivity of 12 of 15 (80 (95 per cent c.i. 52 to 96) per cent), specificity of 12 of 17 (71 (44 to 90) per cent), PPV of 12 of 17 (71 (44 to 90) per cent) and NPV of 12 of 15 (80 (c.i. 52 to 96) per cent. Data on histopathology were missing for one patient in the duct endoscopy group and further analyses with regard to specific lesions identified were therefore based on 31 patients. The most common benign lesions identified were papilloma and duct ectasia; these specific entities were identified with overall accuracy of 90 and 65 per cent respectively (*Tables 2* and *3*). Three patients had papillomas with atypia, two in the duct endoscopy group; both papillomas were identified by endoscopy and the atypical features of one were predicted by the presence of stranding.

Adjunctive duct endoscopy, however, did not contribute to an increase in the correct histological yield to account for the nipple discharge between the two randomized groups (any lesion, $P = 0.213$; papilloma, $P = 0.435$; duct ectasia, $P = 0.806$) (*Table 4*).

Five patients were identified with ductal carcinoma *in situ* (DCIS), three in the duct endoscopy group and two in the no-endoscopy group. Duct endoscopy

successfully identified the DCIS as a flat lesion in two of three patients. The five DCIS cases comprised three of low grade and two of intermediate grade. None required adjuvant radiotherapy. One patient needed no further treatment whereas the other four required further surgery because of involved or close excision margins. Two patients had a wider excision and two a mastectomy. The latter patients included one woman in the no-endoscopy group who had low- and intermediate-grade DCIS extending to 45 mm, and one in the duct endoscopy group diagnosed with intermediate-grade DCIS larger than 50 mm and a 10-mm grade 2 invasive breast cancer. None of the patients with DCIS or invasive cancer had developed recurrence or progressed with any further malignant diagnosis at the time of census. The numbers of DCIS and breast cancer events were too small to evaluate test characteristic values for accuracy of duct endoscopy in identifying a malignant cause or predicting the extent of such disease.

The median volume of the surgical resection specimen in the duct endoscopy group was 4875 (i.q.r. 2016–8280) mm^3 compared with 4455 (2400–7000) mm^3 in the no-endoscopy group (P = 0.577).

Follow-up

Two patients subsequently developed ipsilateral nipple discharge on follow-up, both in the duct endoscopy group. One was a single episode that resolved with no treatment; the second patient developed a new papillary lesion that was excised by vacuum excision biopsy as an interventional radiological procedure with no further recurrence of symptoms. Another patient in the duct endoscopy group developed contralateral nipple discharge during follow-up. No ipsilateral breast cancers formed in the follow-up period, but one contralateral cancer was diagnosed in a patient who had not undergone ductal endoscopy.

Discussion

In this randomized trial of pathological nipple discharge, duct endoscopy was successful in the identification and localization of the causative lesion with high sensitivity, specificity, PPV and NPV. Duct endoscopy additionally offers the potential advantage of localization of unexpected deeper lesions within the breast. Duct endoscopy was found to be safe; no significant complications or adverse effects were observed.

Benign papillomas were the commonest identifiable source of nipple discharge by direct view. Duct endoscopy was very accurate in diagnosing the presence of a papilloma, with a PPV and NPV of at least 90 per cent. Duct ectasia can be a gradation of dilatation and, unless the ducts are particularly tortuous, this finding may by under-reported by duct endoscopy as the duct under investigation is distended with saline infused through the working channel during the endoscopic procedure. Although duct endoscopy accurately recognized duct ectasia in this study (PPV 100 per cent), the NPV was only 52 per cent.

There were only three instances of atypia by histopathological criteria in the entire study cohort of 68 breasts, a finding compatible with reports in the current literature[13]. The rate of DCIS was similar in both groups and the yield of a malignant or atypical diagnosis was not increased by duct endoscopy. Duct endoscopy identified two of three instances of DCIS, but was not predictive of disease extent. The relatively low rate of DCIS and atypia observed may be explained by the strict inclusion criteria.

Duct endoscopy is a costly and skilled procedure with a learning curve, which in most countries remains unfunded or not reimbursed. Consideration needs to be given to how the results of the present RCT can be used in the context of intraductal approaches generally and the future of duct endoscopy specifically.

Early work focused on developing predictive and prognostic factors for breast cancer by assessing the internal milieu of the breast, and the breast duct fluid in direct contact with breast epithelial cells. Abnormal cells in duct fluid are a predictive

factor for future breast cancer risk[20,21], and repeated access to breast duct fluid is feasible with high compliance, especially in populations at risk, such as *BRCA1/2* gene carriers or women attending family history clinics[22,23]. The limited cellularity of nipple aspirate cytology fluid can be overcome by ductal lavage[24,25], but the reproducibility of cellular atypia on repeated sampling and subsequent correlation with pathology of the excised specimen can be variable[26,27]. Cellular and molecular techniques have identified cell products such as carbohydrates and proteins, along with a range of epigenetic and metabolomic markers from methylation and detailed quantitative PCR[28–33], as potential markers. However, despite refining these methods to account for small volumes of pure duct fluid, or the effects of dilution from lavage, there remains no single marker, or panel of markers, that can be used as a reliable predictive or prognostic breast cancer biomarker.

The fibre-optic technology underpinning microendoscopy is well established[34]. Most endoscopes have a light channel, an irrigation channel and a working channel through which microinstrumentation can be passed. Developments in microinstruments include forceps to biopsy, snares to extract papillomas and laser technology to treat target lesions. Successful interventional duct endoscopy has been reported in selected case series from enthusiastic centres[16–19]. Although the present study has shown no additional benefit in the adjunctive use of duct endoscopy to evaluate patients with persistent nipple discharge at the time of standard surgery, the trial results have demonstrated that duct endoscopy is a reliable means of identifying papillomas. Interventional duct endoscopy targeting resection through the endoscope is thus a reasonable next step in technological advancement. It remains unknown whether nipple discharge symptoms will relapse if the papilloma alone is treated, but not the duct. The fact that pathological nipple discharge is an essentially benign condition that can be treated as a simple surgical day case has to be weighed against the health economics of high-technology intervention if endoscopic

management of treating papillomas is to progress. The ability to offer therapy by intraductal means remains a theoretical goal[35].

The present study has shown that duct endoscopy is accurate in identifying a target lesion causative of pathological nipple discharge, but does not improve the diagnostic yield compared with standard surgery. The future of duct endoscopy may lead to interventional approaches that avoid open surgery. Such intervention needs to be evaluated carefully and supported by evidence-based comparative studies of cost efficiency, particularly in the context of benign disease.

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Disclosure: The authors declare no conflict of interest.

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Figure Legends

Fig. 1 Surgical procedure: **a** duct endoscope *ex vivo* showing wire and rhomboid that expands to fill the duct; **b** periareola surgical approach for microdochectomy or major duct excision; **c** surgical resection of wire-localized excision, with the proximal end of the wire emerging from the nipple end of the duct and the rhomboid within the specimen showing the distal duct containing the target lesion; and **d** surgical specimen following standard surgery with no localization wire

Fig. 2 CONSORT flow diagram for the trial

Table 1 Technical information on duct endoscopic examination in the 32 breasts randomized to duct endoscopy

	No. of breasts*
No. of ducts cannulated	
1	22
≥ 2	10
Deepest order of duct inspected	
First order	6
Second order	14
Third order	10
Fourth order	2
First-order ducts examined‡	32
Second-order ducts examined	27
No. per breast†	2 (2–4)
Third-order ducts examined	17
No. per breast†	2 (2–3)
Fourth-order ducts examined	7
No. per breast†	2 (2–3)
Limit of inspection among all ducts examined (cm)†	5.5 (1–10)

*Unless indicated otherwise; †values are median (range). ‡In five women, the first-order duct was the only accessible duct.

Table 2 Identification of papilloma by duct endoscopy compared with histopathological findings in the duct endoscopy group

	Papilloma identified on histopathology		
	Yes	No	Total
Papilloma identified on duct endoscopy			
Yes	10	1	11
No	2	18	20
Total	12	19	31
Sensitivity	10 of 12 (83; 52, 98)		
Specificity	18 of 19 (95; 74, 100)		
PPV	10 of 11 (91; 59, 100)		
NPV	18 of 20 (90; 68, 99)		

Values in parentheses are percentages with 95 per cent confidence intervals. PPV, positive predictive value; NPV, negative predictive value.

Table 3 Identification of duct ectasia by duct endoscopy compared with histopathological findings in the duct endoscopy group

	Duct ectasia identified on histopathology		
	Yes	No	Total
Duct ectasia identified on duct endoscopy			
Yes	8	0	8
No	11	12	23
Total	19	12	31
Sensitivity	8 of 19 (42; 20, 67)		
Specificity	12 of 12 (100; 74, 100)		
PPV	8 of 8 (100 (63, 100)		
NPV	12 of 23 (52; 31, 73)		

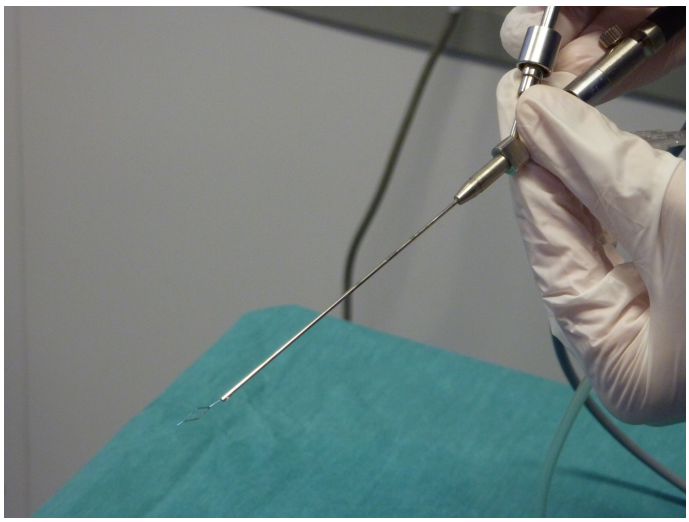
Values in parentheses are percentages with 95 per cent confidence intervals. PPV, positive predictive value; NPV, negative predictive value.

Table 4 Comparison of histological yield in the two groups

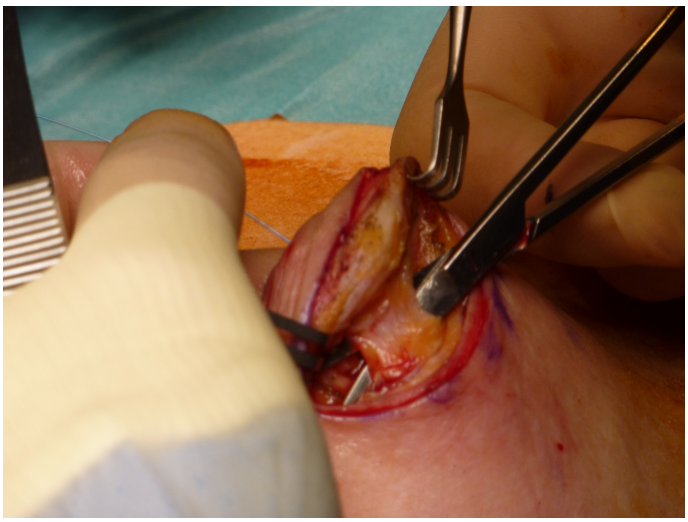
	Duct endoscopy (*n* = 32)	No duct endoscopy (*n* = 37)	*P**
Any lesion on histology			0.213
Yes	15	11	
No	17	26	
Papilloma on histology			0.435
Yes	12*	10	
No	19*	27	
Duct ectasia identified by duct endoscopy			0.806
Yes	20	21	
No	12	16	

*Data missing for one patient in the duct endoscopy group. †Fisher's exact test.

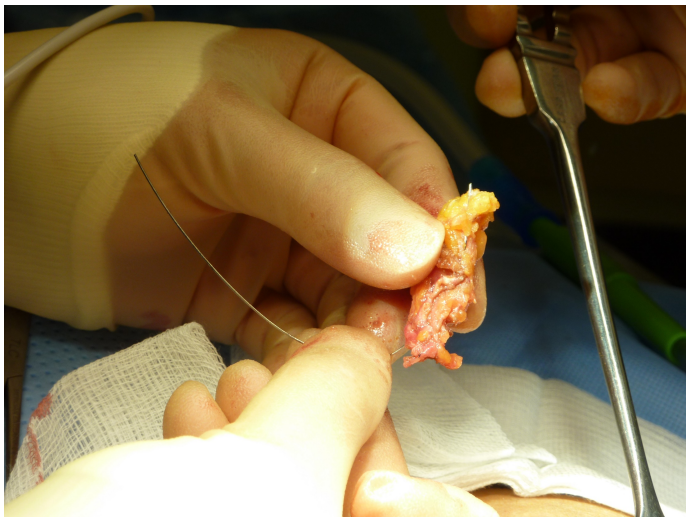
Figure 1



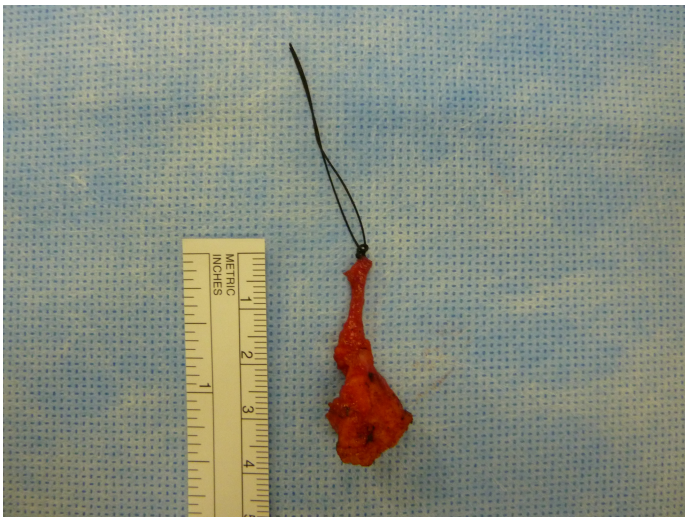
a Duct endoscope



b Periareola surgical approach

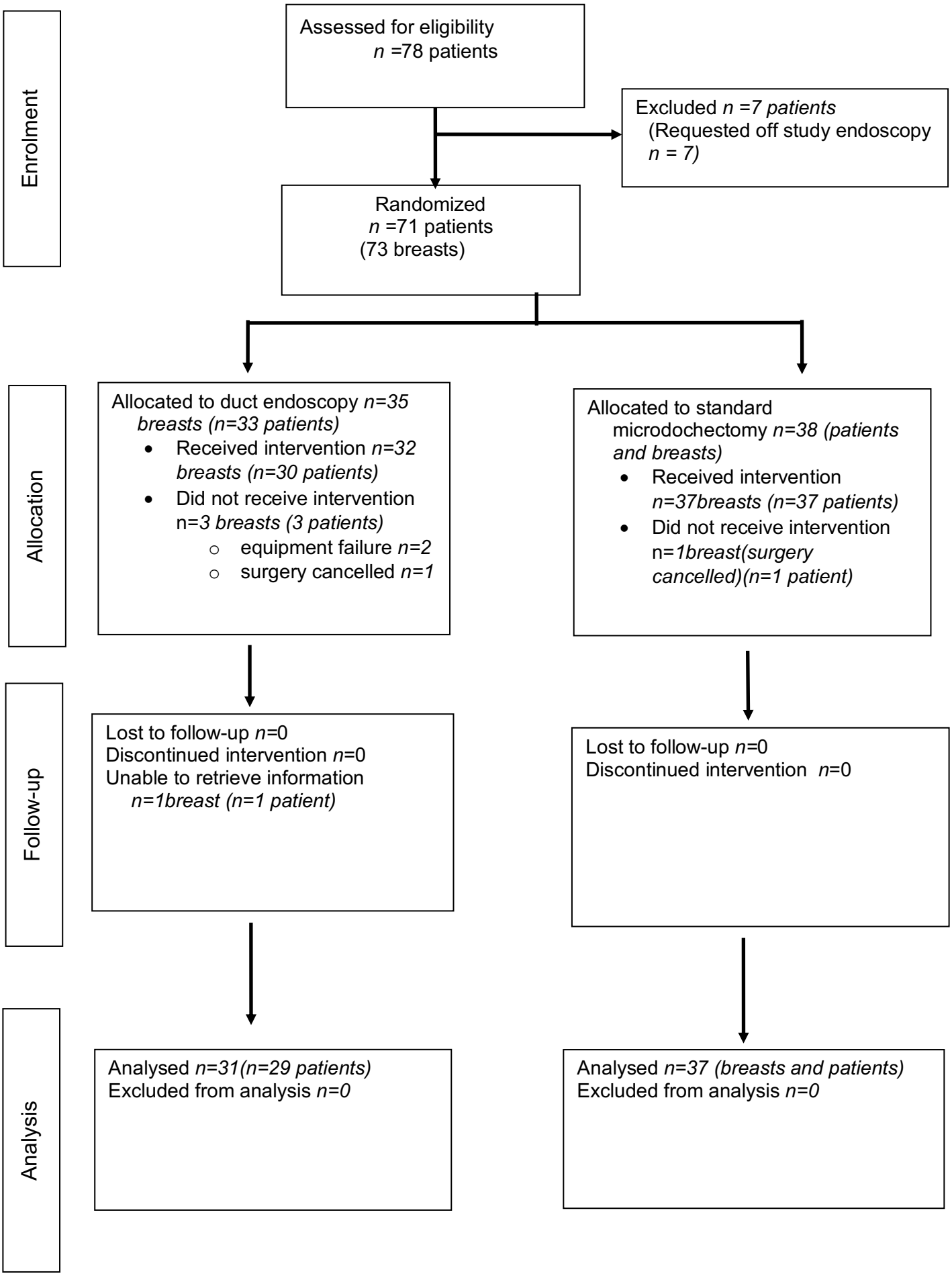


c Surgical excision of lesion



d Surgical specimen

Figure 2


Enrolment
Assessed for eligibility
n =78 patients
Excluded n =7 patients
(Requested off study endoscopy
n = 7)
Randomized
n =71 patients
(73 breasts)
Allocation
Allocated to duct endoscopy n=35 breasts (n=33 patients)
Received intervention n=32 breasts (n=30 patients)
Did not receive intervention n=3 breasts (3 patients)
equipment failure n=2
surgery cancelled n=1
Allocated to standard microdochectomy n=38 (patients and breasts)
Received intervention n=37breasts (n=37 patients)
Did not receive intervention n=1breast(surgery cancelled)(n=1 patient)
Follow-up
Lost to follow-up n=0
Discontinued intervention n=0
Unable to retrieve information n=1breast (n=1 patient)
Lost to follow-up n=0
Discontinued intervention n=0
Analysis
Analysed n=31(n=29 patients)
Excluded from analysis n=0
Analysed n=37 (breasts and patients)
Excluded from analysis n=0