The Lobar Distribution of the Lesions in Breast Carcinoma: Ductoscopy and Surgery

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9.1 Introduction

Breast ductoscopy is an evolving field of surgical technical expertise and a new method of access to the earliest premalignant and malignant lesions for breast cancer researchers. Clinical endoscopy has rapidly improved over the last 40 years and offered researchers and clinicians access to many epithelial surfaces at risk for cancer. In the early 1990s, with the advent of submillimeter endoscopes, this approach could finally be used to examine the breast ductal epithelium. In a period of less than 2 decades, we have through clinical use been able to make direct observations of anatomy and the relationship of anatomy to the processes of breast cancer carcinogenesis. Whether unifocal or multifocal, breast cancers seem to arise within only a single ductal tree. The grade and presence or absence of angiogenesis seem to be associated with lesions in radically different regions of the ducto-lobular tree. Currently, our biopsy tools are rudimentary, but as these improve, the ability to genetically map the sequence of events during carcinogenesis up and down the ductal tree offers perhaps one of the most exciting avenues for increasing understanding or breast cancer carcinogenesis.

9.2 History of Early Ductoscopy

Early in the 1990s, Okazaki and others began to attempt breast ductoscopy for symptomatic pathologic nipple discharge using the first endoscopes less than 2 mm in diameter (Okazaki et al. 1991; Okazaki et al. 2007). As the technology improved and scopes about 1 mm in diameter could be fashioned, they met with greater success at actually canulating the offending orifice and successfully navigating to the lesion of interest present as a polyp or change in the intraluminal surface of the breast duct (Shen et al. 2000; Shao and Nguyen 2001; Matsunaga et al. 2001; Yamamoto et al. 2001a; Yamamoto et al. 2001b). In the Oriental population, nipple fluid abnormalities were a more common presenting symptom of breast cancer and these new scopes offered a way to superficially localize a lesion for diagnostic biopsy. Problems relating to poor image quality and glare/refraction related to air insufflation of the duct limited this new technology's use. Further, since most identified lesions could only be removed via open surgical biopsy, the ductoscopy was only serving as the equivalent of needle localization for a mammographic abnormality.

Important understandings of ductal involvement by cancer and the anatomy of these changes were however being revealed. Dr. Love and her colleagues went on to attempt ductoscopy using the Japanese scopes in the first US trial (Love and Barsky 1996; Love and Barsky 2004). This directly led to recognition of the ability to wash cells from intraductal proliferative lesions and the beginnings of modern attempts of ductal lavage. It was out of the evaluation trial of a ductal lavage system where I got involved. Quickly in the ductal lavage trial participants at my institution, we accumulated several with frankly malignant or suspicious cells reproducibly being lavaged from a single duct orifice. In spite of our best available imaging modalities, we were unable to identify the source of the cells more precisely. I searched for available submillimeter scopes and found one made by an American manufacturer. Using this scope and the principles of

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saline ductal distension developed during the ductal lavage trial, I was able to identify the lesion of interest in each of these cases (Dooley 2000). A short series of scope use in patients having surgery with pathologic nipple discharge abnormalities quickly demonstrated ductoscopy's potential value to a breast surgeon in diagnostic and therapeutic planning (Yamamoto et al. 2001a).

9.3 Ductoscopy in Breast Cancer Cases – Lessons Learned

When I first began ductoscopy in the routine management of early-stage breast cancer where a fluid-producing duct could be identified, I quickly learned some important anatomy of the breast and how to identify ducts and positions within the ductal tree containing cancer (Dooley 2002; Dooley 2003). First was the ductal anatomy and duct distribution, as has been described in Dr. Love's chapter. Most upper outer quadrant lesions would be associated with a large branching lobar-ductal complex with a single orifice on the periphery of the nipple papilla plateau from 8:00 to 2:00 o'clock positions. Lesions greater than 2 cm in size clinically or radiographically rarely had ducts that could be identified by breast massage and compression to contain fluid unless they were associated with extensive intraductal component. In general, these lesions with a large halo of peripheral proliferative changes were the easiest ducts to identify as fluid producing. Core biopsy or open biopsy could lead to difficulty in identifying the correct orifice of the lobar-ductal unit by fluid production on the nipple surface.

Once the target duct had been chosen for endoscopy, I used intraductal distension with local anesthetic. The ductal branches of the lobar unit, which dilated the most under this topical anesthetic use were almost always associated with the most proliferative subsegments of ductal breast tissue. Scoping the largest branches would take you to the cancer and precancerous changes quickly. Small side branches rarely if ever were found to have significant proliferative changes. Often invasive cancers would seemingly purse-string the duct shut but tapping the obstruction with the scope – the palpable or ultrasound visible tumor could be seen to move. Some invasive tumors would have grossly ulcerated lesions visible but this was rarer. Over 40% of early-stage breast cancers had significant intraluminal growths arising in the region of the known tumor and extending well beyond 1 cm beyond the known radiographic and or clinical target cancer (Dooley 2002). Most of these cases had frank extensive intraductal component (EIC) but some would have only multiple foci of atypical ductal hyperplasia (ADH) or of florid usual ductal hyperplasia. Unfortunately, the visual appearance of the intraductal growths on endoscopy did not perfectly correlate to the eventual histologic findings if that region was entirely removed.

In general, intraluminal growths fell into several categories, large spongiform lesions with a distinct stalk were usually solitary papillomas (Shen et al. 2000; Khan et al. 2002; Dooley 2005; Moncrief et al. 2005; Sauter 2005; Sauter et al. 2005; Valdes et al. 2005). Ridging and furrowing of the ductal wall usually occurred only in the larger and more central ducts. These abnormalities usually were either low-grade ductal carcinoma in situ (DCIS) or columnar or florid ductal hyperplasia. Intraductal growths that were peripheral and had evidence of angiogenesis by localized hyperemia were likely to be ADH or DCIS (solid or with comedonecrosis). Exophytic growths fitting these categories only occurred very distally in the ductal tree. Occasionally, sessile hyperemic patches were visible in larger ducts – where few and widely scattered ones were associated with ADH. In general, if lesions were numerous in a region, there was a high chance of diagnosis of DCIS when the entire region was excised. Rare patients had small frond like growths – usually white – resembling sea anemones. These could be either micropapillomas, micropapillary hyperplasia, or micropapillary DCIS. When present again, the multiplicity of lesions greatly increased the chances of DCIS diagnosis. Invasive ductal grade 3 cancers seemed always isolated to a small distal ductal branch. In contrast, grade 1 ductal, tubular, colloid, etc. seemed much more likely to be associated with a large central main ductal trunk.

For the purposes of lumpectomy, I mapped the proliferative activity and resected the known cancer and all intraluminal growths associated with it under ductoscopic guidance (Dooley et al. 2004). Most cancers were peripheral, and all visible proliferative activity was limited to a ductal subbranch, which could be easily resected to the periphery of the breast tissue. Some cancers had associated proliferative changes in several ductal subunits of the same lobar system. Usually, the extent and type of proliferative change was quite

different in each subunit. I theorized from this that there were stem cells scattered throughout the lobular unit having the same initiation events but responding locally differently to progression events. I saw a number of patients described radiographically as either multifocal or multicentric on mammography and MRI imaging. In over 1,500 cases, I have never found a single early-stage breast cancer where additional noncontiguous cancers were not endoscopically shown to be connected to the same lobar-ductal tree. This may be an important observation (Okazaki et al. 1991; Dooley 2002; Kapenhas-Valdes et al. 2008) supporting an alternative breast carcinogenesis model such as the lobar theory.

In follow-up of patients managed by endoscopically directed segmental lumpectomy removing all diseased branches of the same lobar-ductal tree as the primary cancer, I have been able to drop local recurrence to less than 1/10 that of traditional breast conservation in those patients without lympho-vascular invasion (LVI). This now actually leaves me with this subcategory of breast conservation patients approximating the local failure rates of mastectomy patients who also lack LVI.

German ductoscopists have been able to reproduce findings similar to mine in breast cancer lumpectomies (Hünerbein et al. 2006a; Hünerbein et al. 2006b; Hünerbein et al. 2007; Grunwald et al. 2007; Jacobs et al. 2007a; Jacobs et al. 2007b). Some American groups have not but each made I believe a classic assumption error (Louie et al. 2006; Kim et al. 2004). These groups believed that if routine pathology did not find either DCIS or invasive cancer – the other proliferative activity was unimportant. Their basis seemed reasonable in that older pathology series suggest that positive margins for ADH or usual ductal hyperplasia are unimportant to local recurrence. Unfortunately, pathologists are not examining but minute fractions of the epithelial surfaces of the ductal tree. Routine pathology then greatly underestimates coexistent proliferative disease so as to confuse these other series conclusions. Many times I find and photograph intraductal lesions and have to send my pathologist back several times for recuts before the visual findings I make can be histologically explained adequately. More recent studies suggesting the sinister nature of widespread noncontiguous ADH for future ipsilateral breast cancer events suggest that my endoscopically driven assumptions may be closer to reality.

9.4 Conclusions

Using the lobar hypothesis, data are now being generated, which would substantially change our approach to breast lumpectomy. When there is a field defect, there may be value in resection of the entire lobar unit or subunit involved. This cannot be defined well using mere pathologic distance measurements to prove adequacy of lumpectomy. We may need to genetically map the extent of carcinogenic changes within the lobe to develop the most rational approach to anatomic correct lumpectomy.

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