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Original contribution

Mucinous breast carcinomas lack *PIK3CA* and *AKT1* mutations☆

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Summary Activating point mutations in the phosphatidylinositol-3-kinase catalytic subunit (*PIK3CA*) are among the most common molecular defects in invasive breast cancer. Point mutations in the downstream kinase *AKT1* are seen in a minority of carcinomas. These mutations are found preferentially in estrogen receptor–positive and Her2-positive breast carcinomas; however, special morphologic types of breast cancer have not been well studied. Twenty-nine cases of pure invasive mucinous carcinoma and 9 cases of ductal carcinoma with mucinous differentiation were screened for a panel of point mutations (>321 mutations in 30 genes) using a multiplex polymerase chain reaction panel with mass spectroscopy readout. In addition, associated ductal carcinoma in situ, hyperplasia, or columnar cell lesions were separately tested where available (25 lesions). In 3 invasive cases and 15 ductal carcinoma in situ/proliferative lesions, *PIK3CA* hotspot mutations were, instead, tested by direct sequencing. No point mutations were identified in invasive mucinous breast carcinoma. This contrasts with the 35% frequency of *PIK3CA* mutations in a comparative group of invasive ductal carcinomas of no special type. Interestingly, *PIK3CA* hotspot point mutations were identified in associated ductal carcinoma in situ (3/14) and hyperplasia (atypical ductal hyperplasia [2/3], usual ductal hyperplasia [2/3], columnar cell change [1/5]), suggesting that *PIK3CA* mutations may play a role in breast epithelial proliferation. This series represents the largest study, to date, of *PIK3CA* genotyping in mucinous carcinoma and supports the unique pathogenetics of invasive mucinous breast carcinoma.

1. Introduction

Phosphatidylinositol-3-kinase (PI3K) is situated at a key node in epithelial cell signal transduction. PI3K is activated by receptor tyrosine kinases at the cell membrane or by RAS family members and catalyzes the formation of the second messenger phosphatidylinositol (3,4,5) triphosphate (PIP_3) [1-3]. PIP_3 transduces signals through AKT1 at the cell

Abbreviations: ADH, atypical ductal hyperplasia; CCC, columnar cell change; DCIS, ductal carcinoma in situ; LCM, laser-capture microdissection; UDH, usual ductal hyperplasia.

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membrane, which, in turn, activates or inhibits elements of downstream signaling, resulting in cell growth, cell proliferation, inhibition of apoptosis, and so on [1-3]. The PI3K pathway is one of the most commonly altered in breast cancer, most frequently by mutation of the catalytic subunit *PIK3CA*; other mechanisms include loss of the inhibitor PTEN (phosphatase and tensin homolog deleted from chromosome 10) by various mechanisms, gene amplification or point mutation of *AKT1*, or mutation of the PI3K regulatory subunit *PIK3R1*. Activating point mutations of *PIK3CA* are found in more than 25% of invasive breast cancers and are further enriched in estrogen receptor–positive tumors [3-6]. Somewhat paradoxically, among estrogen receptor–positive tumors, carcinomas with *PIK3CA* mutations have a favorable prognosis as compared with *PIK3CA* wild-type carcinomas [7-11]. The activating *AKT1* point mutation E17K is found in 3% to 5% of breast carcinomas and is generally mutually exclusive with *PIK3CA* mutation [4,12].

The mutational profiles of special morphologic types of invasive breast cancer have not been thoroughly studied, other than invasive lobular carcinoma [4,13]. Mucinous breast carcinomas have long been recognized as a unique morphologic subtype of invasive carcinoma, characterized by clusters of tumor cells floating in pools of mucin [14-16]. Clinicopathologic studies have revealed a favorable prognosis of pure mucinous carcinomas, relative to invasive ductal carcinomas, not otherwise specified (IDC-NOS) [14-16]. We screened a cohort of 38 invasive mucinous carcinomas and accompanying proliferative lesions, for a large panel of point mutations including activating point mutations in *PIK3CA* and *AKT1*.

2. Methods

After institutional review board approval, pathology files of Oregon Health & Science University were searched for breast resection specimens harboring invasive mucinous carcinoma or invasive carcinoma with mucinous features (2002-2010). Slides were reviewed to confirm the diagnosis and to select an appropriate block for testing. According to the standard criteria, *pure mucinous carcinoma* is defined as a tumor composed entirely of clusters of malignant epithelial cells "floating" in pools of mucin, without tumor cells directly invading stroma. A minor conventional invasive ductal component together with mucinous carcinoma is defined as a *ductal carcinoma with mucinous differentiation* (synonymous with mucinous component, with mucinous features, or mixed mucinous tumor) [15-17]. Where available, associated proliferative epithelial lesions from the same specimen, including ductal carcinoma in situ (DCIS), atypical ductal hyperplasia (ADH), usual ductal hyperplasia (UDH), and columnar cell change (CCC), were also identified for testing. Data on patient age at surgery, tumor size, lymph node status, and hormone receptor status were abstracted from pathology reports. Twenty-three cases were similarly identified from the University of Michigan Department of Pathology. A comparative group of IDC-NOS was derived from the infiltrating carcinomas analyzed by Troxell et al [18] and our additional unpublished cases (a total of 31 cases).

Five-micrometer unstained sections from the formalin-fixed, paraffin-embedded blocks were prepared, and lesional tissue was macrodissected with a clean scalpel blade or needle, using an hematoxylin and eosin–stained slide as template. In 2 cases, the mucinous and invasive ductal components were separately dissected. For 5 proliferative lesions, epithelial cells were isolated by laser-capture microdissection from slides counterstained with methyl green (ArcturusXT Applied Biosystems, Foster City, CA); however, 2 of these failed further analysis. Lesional tissue from the comparative group of IDC-NOS was isolated by coring the paraffin tissue block with a punch device; then further processing was identical [18]. DNA was extracted from paraffin using standard protocols (Qiagen Qiamp Mini kit, Valencia, CA; for laser-capture microdissection cases, Picopure, Arcturas/Applied Biosystems).

DNA extracts were screened for a panel of point mutations using a multiplex polymerase chain reaction (PCR) panel with a mass spectroscopy readout (Sequenom MassArray) as previously described [19,20]. The mutation panel covers 321 mutations in 30 genes including *ABL*, *AKT1/2/3*, *BRAF*, *CDK4*, *CTNNB1*, *EGFR1*, *ERBB2*, *FBX4*, *FBXW7*, *FGFR1/2/3*, *FLT3*, *GNAQ*, *HRAS*, *JAK2*, *KIT*, *KRAS*, *MAPK2K1/2*, *MET*, *NRAS*, *PDGFRA*, *PIK3CA*, *PTPN11*, *RET*, *SOS1*, and *TP53*. The panel includes 41 substitutions in 23 codons of the *PIK3CA* gene [20]. Twenty-two specimens (MUC-23–MUC-45) were tested with an updated mutation panel encompassing 643 mutations in 53 genes including the same hotspots in *PIK3CA* and *AKT1* present in the original panel. For 3 invasive carcinomas with low cellularity and 15 proliferative lesions, DNA yield was inadequate for full-mutation panel screening; thus, *PIK3CA* exon 9 and exon 20 hotspots were tested by direct sequencing. Point mutations identified by mass spectroscopy screening were confirmed by direct sequencing on an ABI3130 sequencer using the BigDye terminator method (Applied Biosystems, Carlsbad, CA), with or without the use of a locked nucleic acid probe to suppress amplification of the wild-type allele (Ang et al, unpublished data). After accounting for assay failures, the final group for analysis included 29 pure invasive mucinous carcinomas and 9 invasive ductal carcinomas with mucinous differentiation. Accompanying proliferative epithelial lesions included 14 DCIS, 3 ADH, 3 UDH, and 5 columnar cell lesions (see Table 1 and Supplementary Table 1, which includes full details of cases analyzed by targeted sequencing and/or laser-capture microdissection).

Statistical comparisons between mutation status of mucinous carcinoma and IDC-NOS, were made using Fisher exact test with Statview software version 5.0.1 (SAS Institute, Cary, NC).

Table 1 Clinicopathologic data

Parameter	Mucinous carcinoma, total	Pure mucinous carcinoma	Ductal carcinoma with mucinous differentiation
Patient age (y), average (range)	58 (31-83)	59.5 (31-83)	55.7 (37-70)
Invasive carcinoma size (cm), average (range)	2.2 (0.4-14)	2.2 (0.4-14)	2.2 (1.4-6)
Carcinoma grade, 1/2/3	25/12/1		
Estrogen receptor positive	38/38 (100)	29/29	9/9
Her-2/neu positive [a]	0/37 (0)	0/28	0/9
Nodal status, N0/N1/N2 [b]	32/4/1	26/2/0	6/2/1
AJCC stage (7th edition) [b] IA/IIA/IIB/IIIA	22/12/1/2	17/9/1/1	5/3/1/0

[a] Her-2/neu data not available for 1 carcinoma (MUC-6).
[b] Lymph node data not available for 1 carcinoma, a recurrence (MUC-20).

3. Results

3.1. Patients and cases

Forty-five cases of invasive breast carcinoma with mucinous differentiation, including pure and mixed mucinous carcinoma, were identified for mutational analysis; in 7 cases, mutational analysis was unsuccessful, usually due to a low DNA yield, leaving 38 cases of invasive carcinoma in the study group, including 29 pure invasive mucinous carcinomas and 9 cases of invasive ductal carcinoma with mucinous differentiation. Details of patient age, tumor size, grade, and hormone receptor status are listed in Table 1 and Supplementary Table 1. As is typical of mucinous carcinomas, most cases were estrogen receptor–positive, Her-2/neu–negative, low-grade carcinomas, with infrequent nodal metastasis.

3.2. Invasive carcinoma mutational analysis

DNA extracts from pure invasive mucinous carcinoma or mixed invasive mucinous carcinoma with a minor invasive ductal component were screened for a large panel of point mutations using a multiplex PCR panel with mass spectroscopy readout. In 3 pure mucinous carcinomas with low cellularity, DNA yield was low, and these cases were tested for *PIK3CA* exon 9 and exon 20 hotspot mutations only by direct sequencing. Interestingly, only one single nucleotide pleomorphism was identified (MUC-4, *FBX4* S8R), but no activating point mutations were identified in this extensive panel; specifically, no *PIK3CA* or *AKT1* mutations were found (Fig., Table 2). The conventional invasive ductal carcinoma components of 2 cases of mixed mucinous carcinoma were also tested, yielding no mutations (MUC-8, MUC-16).

The mutation profile of mucinous carcinomas was compared with the *PIK3CA/AKT1* mutation status of IDC-NOS, previously analyzed in our laboratory, in which 11 (35%) of 31 carcinomas harbored *PIK3CA* or *AKT1* hotspot mutations [18] (Ang and Troxell, unpublished). In comparison, the lack of mutations in mucinous carcinomas was a statistically significant difference (total mucinous cohort: 0/38 versus IDC-NOS: 11/31 [$P < .0001$]; pure mucinous carcinomas: 0/29 versus IDC-NOS: 11/31 [$P = .003$]).

3.3. In situ carcinoma mutational analysis

Fourteen cases of DCIS accompanying mucinous carcinoma were separately isolated and successfully analyzed for point mutations. Of the DCIS lesions, 6 were mucinous DCIS; all were nuclear grades 1 to 2. Six cases were screened using the full multiplex panel, and 8 were analyzed by direct sequencing of *PIK3CA* exons 9 and 20 only. Interestingly, *PIK3CA* exon 20 kinase domain mutations were identified in 3 DCIS lesions including H1047R and H1047Y point mutations, 2 of which were mucinous DCIS (Table 2). Two of these mutation-positive DCIS lesions accompanied wild-type invasive carcinoma (Table 3, Supplementary Table 1). No other point mutations were identified in the 6 DCIS lesions screened with the multiplex panel.

3.4. Proliferative breast epithelium mutational analysis

ADH in association with mucinous carcinoma was separately isolated and tested for mutations in 3 specimens; *PIK3CA* exon 20 mutations were identified in 2 (H1047R and H1047Y, both analyzed by targeted sequencing only; Table 2). Interestingly, both mutation-positive ADH lesions were associated with *PIK3CA* wild-type DCIS and invasive carcinoma (Table 3, Supplementary Table 1).

Likewise, 2 instances of UDH were analyzed by targeted sequencing; a third case was analyzed with the full-mutation panel. *PIK3CA* H1047R mutations were identified in 2 cases (Table 2); both of these cases failed *PIK3CA* exon 9 analysis, yet were included in the data set based on the exon 20 mutation finding and the relative rarity of multiple *PIK3CA* mutations in the breast cancer literature [2]. One *PIK3CA* exon 20 mutation was discovered among 5 cases of CCC, from a specimen that harbored the same mutation in UDH but not in the invasive mucinous carcinoma (Fig., Table 3, Supplementary Table 1).

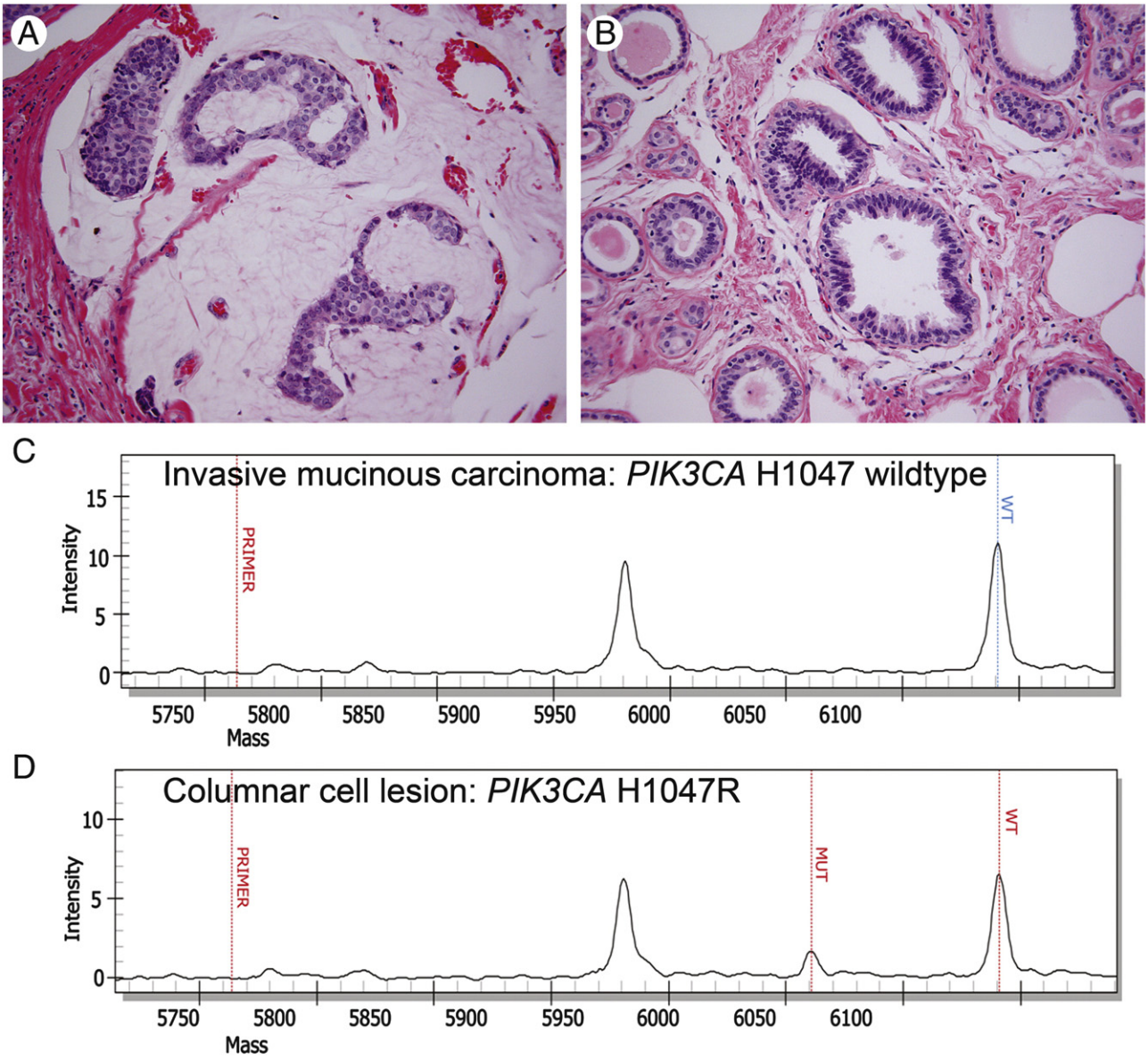

Fig. Histopathologic lesions and mutational analysis. A, Invasive mucinous carcinoma, wild-type (WT) for *PIK3CA*. B, Accompanying columnar cell lesion with *PIK3CA* exon 20 H1047R kinase domain mutation, shown in panel D. C, Invasive mucinous carcinoma, as shown in panel A, has a single WT peak for *PIK3CA* codon H1047 by PCR–mass spectroscopy assay. The peak present in the middle of the profile is from an unrelated assay multiplexed in the same assay well. D, Columnar cell lesion (see panel B) shows a WT and smaller H1047R mutant (MUT) peak by PCR–mass spectroscopy analysis. The relatively small mutant peak is due to sample heterogeneity, including lesional columnar cell epithelium, myoepithelial cells, and stroma.

Overall, *PIK3CA* exon 20 mutations were identified in 5 of 11 breast epithelial hyperplastic lesions (45%, ADH/UDH/CCC), all associated with concurrent *PIK3CA* wild-type invasive carcinoma (Table 3).

4. Discussion

Invasive mucinous (colloid) carcinoma represents a distinctive morphologic pattern that may manifest in breast carcinoma, as well as carcinomas of other organs (colon, stomach, etc). Mucinous breast carcinoma is characterized by a relative large volume of extracellular mucin, in which malignant epithelial cells are floating. Invasive mucinous carcinoma of the breast is a rare variant, comprising ~2% of invasive breast carcinomas, and is often estrogen receptor positive, Her-2/neu negative, low grade, with a favorable prognosis [14-16]. Fujii et al [21] first looked at the unique molecular characteristics of mucinous carcinomas by loss of heterozygosity markers (12 chromosomal segments, 18 cases) and full comparative genomic hybridization in a subset of 6 cases. They found a paucity of large-scale genomic changes in mucinous carcinomas [21]. More recently, Lacroix-Triki et al [17] confirmed these findings

Table 2 Mutation status of invasive carcinoma and associated lesions

Lesion	*PIK3CA* mutation	*AKT1* mutation
Invasive carcinoma		
Mucinous carcinoma, total	0/38	0/35
Mucinous carcinoma, pure	0/29	0/26
Invasive ductal carcinoma, mucinous differentiation	0/9	0/9
IDC-NOS	10/31	1/31
Carcinoma in situ		
DCIS	3/14 (H1047R-2, H1047Y-1)	0/6
Epithelial lesions associated with mucinous carcinomas		
Epithelial lesions, total	5/11 (H1047R-3, H1047Y, H1047L)	0/4
ADH	2/3 (H1047R, H1047Y)	0/1
UDH	2/3 (H1047R, H1047L)	0/1
Columnar cell lesion	1/5 (H1047R)	0/2

NOTE. See Table 3 and Supplementary Table 1 for further details.

in an array-comparative genomic hybridization study of 22 mucinous carcinomas. They found a relatively low level of genomic instability, including less frequent gains of 1q and 16p and losses of 16q and 22q, as compared with grade-matched estrogen receptor–positive invasive ductal carcinomas, which, thus, also revealed relative homogeneity of the molecular profiles of mucinous carcinomas [17]. They also showed that the mucinous and invasive ductal components of mixed mucinous tumors had closely similar comparative genomic hybridization profiles [17]. In 2 publications encompassing at least 18 cases analyzed by messenger RNA microarray expression and immunohistochemical analysis, Weigelt et al [22,23] demonstrated that mucinous breast carcinomas cluster together and generally cluster within the luminal A intrinsic subtype, with the more cellular tumors clustering with mucinous neuroendocrine carcinomas. However, systematic point mutational analysis of mucinous carcinomas has not been previously performed, to our knowledge.

Table 3 *PIK3CA* mutation status in specimens with multiple tested lesions

Case no.	Invasive carcinoma	DCIS	Other
MUC-1	WT	WT [a]	ADH-WT
MUC-3	WT		CCC-WT
MUC-4	WT	H1047R [a]	
MUC-5	WT		CCC-H1047R UDH-H1047R
MUC-7	WT	H1047R [a]	
MUC-8	WT	WT	ADH-H1047R [a]
MUC-11	WT	WT [a]	CCC-WT [a]
MUC-12	WT	WT	CCC-WT [a]
MUC-13	WT	WT [a]	
MUC-15	WT	WT [a]	ADH-H1047Y [a,b]
MUC-18		H1047Y [a]	
MUC-21	WT	WT [a]	UDH-H1047L [a]
MUC-23	WT	WT [a]	CCC-WT [a]
MUC-24	WT	WT	
MUC-25	WT	WT [b]	
MUC-33	WT	WT	
MUC-43	WT		UDH-WT

Abbreviation: WT, wild type.
[a] Analyzed by *PIK3CA* exon 9, exon 20 sequencing only (exon 20 only for MUC-18 DCIS; MUC-21 UDH).
[b] Papillary features.

It has been well established that activating point mutations in *PIK3CA* are common in invasive breast cancer (>25%) and, in fact, enriched in estrogen receptor–positive breast cancer [3-6]. Given that invasive mucinous carcinoma is often estrogen receptor positive, low grade, and of good prognosis, one might predict a high rate of *PIK3CA* mutations in mucinous carcinomas. However, our data and those of few smaller studies in the literature show a strikingly lower *PIK3CA* mutation frequency in mucinous carcinoma (Table 4). We found no mutations in 38 tested cases, a difference that is statistically significant in comparison with a group of IDC-NOS analyzed in our laboratory ($P < .003$). Furthermore, a meta-analysis of other published studies revealed only 5 mutations in 55 cases of mucinous carcinoma (total, 5/93 [5%]) [13,24-28], and no other mutations in mucinous carcinoma were identified with our large screening panel, including analysis of *AKT1*. The pathogenetic role of *PIK3CA/AKT1* mutations in breast epithelial proliferation and carcinogenesis remains incompletely understood; however, these data add further support to the unique genetic profile and pathogenesis of invasive mucinous carcinoma, as compared with low-grade invasive ductal or lobular carcinoma.

Interestingly, we did find *PIK3CA* exon 20 kinase domain point mutations in small numbers of DCIS (3/14, or 21%) and proliferative lesions (5/11, or 45%) separately isolated from the same breast specimens harboring *PIK3CA* wild-type invasive mucinous carcinoma or carcinoma with mucinous features (Table 3). Although this finding is

Table 4 Mutational analysis of invasive mucinous carcinoma: literature review

Study	*PIK3CA* mutation	*AKT1* mutation
Campbell et al [24]	0/1	
Buttitta et al [13]	1/22	
Maruyama et al [25]	1/4	
Bleeker et al [26]	2/17	0/17
Michelucci et al [27]	0/3	
Li et al [28]	1/8	
Present study	0/38	0/35
Total	5/93 (5%)	0/52 (0%)

unusual, it is not entirely unexpected because we have previously demonstrated a high percentage of *PIK3CA* mutations in benign nonatypical papillary lesions as well as columnar cell lesions (±atypia), with many of the latter having mutation status discordant with that of accompanying invasive carcinoma [4,18,19].

In summary, we have found a remarkable paucity of *PIK3CA/AKT1* mutations in invasive mucinous carcinoma of the breast. These genetic data further support the notion that mucinous carcinoma is an entity with unique genetic and pathologic features.

Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.humpath.2012.03.012.

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