Ductal Carcinoma-in-Situ: New Concepts and Controversies

James J. Stark, MD, FACP

Medical Director, Cancer Program and Palliative Care Maryview Medical Center

Professor of Medicine, EVMS



Case Presentation

- 51 y.o. woman referred for recent diagnosis of Ductal Carcinoma-in-Situ
- Presented to her surgeon with mass in right breast
 - Prior mammogram (two years earlier) negative
 - Current mammogram





Case Presentation

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- Presented to Dr. Chang with mass in right breast
 - Prior mammogram (two years earlier) negative
 - Current mammogram....
 - Needle biopsy....DCIS



Case, continued

- Past history unremarkable
- No history of hormone replacement therapy
- Natural menopause several years ago
- Exam: residual 2-3 cm mass adjacent to needle biopsy mark only abnormality
- Surgical therapy discussed with her surgeon
 - Calcifications extensive so he recommended mastectomy feeling that margins would be difficult to achieve
- Underwent modified radical mastectomy
- Pathology: sentinel LN negative but additional lymph node positive; no invasive cancer seen on mastectomy specimen



Case, continued

- Biochemical markers:
 - ER and PR both negative
 - Her-2/neu 6.9 interpreted as overexpressed
- Received therapy with Taxotere, Adriamycin and Cytoxan followed by Herceptin
- Ejection fraction fell from 75% to 60% after Herceptin but otherwise she feels well and is without evidence of cancer at present 18 months after initial diagnosis





- 50 y.o. lady developed breast mass which she watched for three years
- Mammogram...





Case #2

- 50 y.o. lady developed breast mass which she watched for three years
- Mammogram...
- Underwent lumpectomy
 - 3 cm tumor: all DCIS; margins close
 - Re-excision of margins....pathology: DCIS with microinvasion; margins now negative



Case #2

- Biochemistry of microinvasive component:
 - ER, PR negative
 - Her-2/neu overexpressed at 10.7
- Referred for medical oncology consultation; decision made not to treat further, e.g., with chemo or herceptin
- See subsequent discussion for rationale
- Pathology at issue.....



Normal Breast Architecture





Double cell layer: beginnings of atypia





Very cellular: Atypia





Ductal Carcinoma in-situ











Comedo necrosis





Microinvasive Ductal Carcinoma





DCIS -- Background

- <1% of all breast neoplasms in 1978 prior to widespread screening mammography
- Percentage of all breast neoplasms that are DCIS has skyrocketed in mammography era
- Now at least 20% of all breast neoplasms are in situ; most are picked up by mammography only and are not palpable



Background, continued

- Risk factors same as for invasive breast cancer (FH, nulliparity, etc.)
- Part of BRCA 1 and 2 syndromes
- Not related to hormone replacement therapy
- What is the natural history of this entity?
 - What percentage of these tumors would go on to develop full-blown invasive cancer?
 - No one knows the answer to this but there are powerful clues in the literature...



Natural history of 28 women with small low-grade DCIS tumors treated with biopsy only (path originally misread by current standards)



The Nurses Health Study

- Huge longitudinal health study conducted by the Harvard School of Public Health involving 237,000 female nurses over 20 years
- 1877 "benign" breast biopsies reviewed
- 13 cases of previously unrecognized DCIS uncovered
- All treated by biopsy only



Patient no.	Age at benign breast biopsy	DCIS nuclear grade	DCIS pattern	DCIS extent (no. of slides involved/no. reviewed)	Outcome, yrs after benign breast biopsy
1	39	Low	Micropapillary	2/5	DCIS, 4
2	62	Low	Cribriform	1/6	Invasive ca, 5
3	47	Low	Cribriform	1/2	Invasive ca, 18
4	55	Low	Cribriform	1/12	NED, 23
5	58	Intermediate	Micropapillary	2/2	DCIS, 4
6	48	Intermediate	Cribriform	1/2	Invasive ca, 5
7	63	Intermediate	Papillary	2/2	DCIS, 6
8	42	Intermediate	Cribriform	3/6	Invasive ca, 16
9	55	Intermediate	Solid	2/6	NED, 21
10	43	Intermediate	Cribriform	2/3	NED, 27
11	53	High	Solid	1/1	DCIS, 2
12	55	High	Cribriform	1/1	Invasive ca, 4
13	56	High	Solid	1/4	Invasive ca, 5

Table 1. Pathologic Findings and Outcome in 13 Women with DCIS Treated by Diagnostic Biopsy alone in the Nurses' Health Study I and II

DCIS: ductal carcinoma in situ; Invasive ca: invasive breast carcinoma; NED: no evidence of subsequent invasive breast carcinoma or subsequent DCIS.

Collins et al CANCER 103:1778, 2005



What happened to the women with recurrent DCIS?

Details of Outcome of Women with Subsequently Detected DCIS in the Nurses' Health Study I and II

Patient no.	Original DCIS nuclear grade	Original DCIS pattern	Subsequent DCIS nuclear grade	Subsequent DCIS pattern	Follow-up after subsequent DCIS (yrs)
1	Low	Micropopillary	Low	Micronanillary	Alizo 5
1	LOW	wheropapiliary	LOW	мистораршату	Allve, J
5	Intermediate	Micropapillary	High	Comedo	Alive, 10
7	Intermediate	Papillary	NA	NA	Alive, 9
11	High	Solid	High	Comedo	Alive, 8
DCIS: ductal carcinoma	in situ; NA: not available.				



What happened to the women who subsequently developed invasive cancer?

Details of Outcome of Women who Developed Invasive Breast Carcinoma Subsequent to Their Benign Breast Biopsy in the Nurses' Health Study I and II

Patient no.	DCIS nuclear grade	DCIS pattern	Histologic type/ size/grade of invasive carcinoma	Axillary lymph node status	Follow-up after diagnosis of invasive carcinoma (yrs)
2	Low	Cribriform	IDC/2 cm/3	Negative	Alive, 7
3	Low	Cribriform	IDC/2 cm/3	Positive	Alive, 9
6	Intermediate	Cribriform	IDC/4 cm/2	Positive	Dead, 7
8	Intermediate	Cribriform	IDC/4 cm/NA	Negative	Alive, 9
12	High	Cribriform	IDC/NA/2	Negative	Alive, 11
13	High	Solid	IDC/1 cm/3	Positive	Alive, 11

DCIS: ductal carcinoma in situ; IDC: infiltrating ductal carcinoma; NA: information not available.

Of 13 women whose tumors were misread, 10 developed subsequent events, 6 with invasive cancer; one died



Untreated DCIS, cont.

- Relative risk (versus biopsied patients with truly benign histology) in this group of 13 women of developing:
 - Subsequent invasive cancer: 13.5
 - Either DCIS or invasive cancer: 20

Take-home message from these two studies: DCIS is worth treating!



What About DCIS Treated "Properly" (to be defined)

- After simple lumpectomy only, the majority of patients never suffer a recurrence
- One half of all recurrences are with invasive cancer
- 90% of patients with invasive cancer and 100% of patients with pure DCIS recurrence survive the second event



How to Treat DCIS in 2008: Factors in Decision Making

- What determines likelihood of local recurrence:
 - Grade (high-grade or with necrosis)
 - Margin width (10 mm is usual cut-off)
 - Microinvasion
- How do the above contribute to treatment recommendations?



What is the Optimal Treatment for DCIS?

- Surgery: breast-conserving surgery is adequate if margins can be achieved; can be difficult in DCIS where disease is often multifocal (several foci in the same quadrant...versus multicentric)
 - Mastectomy virtually eliminates local recurrence but is too much treatment for most women



Results of Largest Series of DCIS treated non-randomly (1,115 pts): freedom from local recurrence



Optimal Treatment of DCIS, continued

- What about radiation?
- Several studies have addressed this issue
 - NSABP B-17: study with long follow-up
 - Radiation halves rate of in-breast invasive and noninvasive recurrence but has no impact on survival because salvage therapy is so good
 - Two other smaller studies from Europe and Asia confirm the above findings
 - Some authors believe that for highly favorable lesions (small, low-grade) radiation can be eliminated



Optimal Treatment of DCIS, continued

- What about the role of hormonal suppression?
- Tamoxifen vs. Placebo added to RT in large trial (NSABP B-24)
- Benefit of tamoxifen small
 - Largely confined to women whose DCIS expressed the estrogen receptor
- UK/ANZ trial failed to confirm
- Nonetheless most large centers recommend tamoxifen as an adjunct to lumpectomy and radiation for DCIS
- No data on Aromatase Inhibitors but two large trials are ongoing which will attempt to assess Tamoxifen vs. Arimidex in DCIS



The Van-Nuys Scoring System

	Size	Margin (mm)	Pathologic Classification	Age (yr)
Score				
1	<15 mm	>10	low-grade no necrosis	≥60
2	15-40 mm	1-9	low-grade with necrosis	40-60
3	>40 mm	<1	high-grade with necrosis	<50

Add up the score from the four columns: that is the "Van-Nuys" Score



Validation of Van-Nuys

Van Nuys Score	4-6	7-9	10-12
Average Size (mm)	8.6	17.3	36
Avg Nucl Grade	1.6	2.4	2.8
% Recurrences	2	22	52
% Inv. Recurrences	0	46	43
%10-year Survival	100	97	97



Van Nuys, contined

- Has stood up as best way to estimate risk of future "events"
- Useful as way to stratify patients for future randomized trials
- To some extent helps guide contemporary treatment, especially for women with the highest scores



What is the Significance of Microinvasive Cancer?

- Uncommon finding
- Hotly debated
- One large series...*
 - 425 patients: pT1a, pT1b and pT1mic
 - 24 had pT1mic:
- Of these 24 all had negative axillary or sentinel lymph node
 - 5/14 were Her-2/neu + (not done on the rest)
 - Ki-67 elevated in half
 - 15/23 were ER+ or PR + or both +
 - None of these patients received adjuvant chemotherapy
 - Patients who were ER or PR + were offered adjuvant hormones
 - All 24 patients were alive and cancer-free at the time the article was written; years at risk not stated in paper

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Colleoni et al Annals of Oncology 15:1633-2004

Survival of Three Groups





Colleoni et al Annals of Oncology 15:1633-2004



What about DCIS that overexpresses Her-2/neu?

- A high percentage of ER-negative DCIS tumors overexpress the Her-2/neu oncogene
- Associated with higher incidence of comedo necrosis (recall this predicts for local recurrence)
- Not yet standard-of-care to add Herceptin to treatment regimen of such patients but question is being actively studied at major institutions
- Editorial comment:
 - Expense and potential for cardiac toxicity limit value of this approach in patients in whom survival is already virtually assured with appropriate treatment

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What about DCIS with positive lymph node(s) – case 1

- Not a trivial issue as many as 10% of patients with DCIS have positive sentinel lymph node
- 11% of patients with DCIS on biopsy will have invasive component at mastectomy
- Most patients with + sentinel node did not have invasive cancer found at subsequent mastectomy
- What to do about all of this is unclear
- Argues for more liberal use of sentinel LN procedure in DCIS



What is in store long-term for patients with DCIS?

- Large MD Anderson study looking at 799 women with DCIS
- Characteristics...



Therapy Administered at MD Anderson 1997-2007

Surgery type		
Mastectomy	346	43.47
Segmental	450	56.53
Margins		
Close ($< 2 \text{ mm}$)	48	6.09
Negative	734	93.15
Positive	6	0.76
Adjuvant hormones		
No	526	65.83
Yes	273	34.17
Adjuvant radiation		
No	441	55.19
Yes	358	44.81

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Dawood et al Annals of Surgical Oncology 15:244, 2008

Number of patients	Percentage (%)
45	
2-22-3	
32	71.11
10	22.22
2	4.44
1	2.22
17	38.64
27	61.36
30	71.43
12	28.57
14	31.11
31	68.89
10	28.57
25	71.43
14	40.00
21	60.00
2	4.76
22	52.38
18	42.86
19	61.29
7	22.58
3	9.68
2	6.45
-	0.45
26	83 87
1	3 23
1	3 23
i	3 23
2	6.45
2	0.45
29	03.55
29	6.45
	Number of patients 45 32 10 2 1 17 27 30 12 14 31 10 25 14 21 2 22 18 19 7 3 2 26 1 1 1 2 29 2

TABLE 2. Patient characteristics at second event

45/799 patients had second event



Gradual Nature of Subsequent Events





Conclusions

- DCIS is a very common diagnosis
- Overall prognosis very good
- Even with subset analysis it is difficult to identify patient group with bad outcome
- Adequate surgery and radiation contribute to risk reduction for second event
- Role of adjuvant hormonal antagonism less certain
- Genetic subset analysis will become important in the future

