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A Quantitative Multigene RT-PCR Assay For Predicting Recurrence Risk After Surgical Excision Alone Without Irradiation For Ductal Carcinoma in Situ (DCIS): A Prospective Validation Study of the DCIS Score From ECOG E5194

Background: We have previously reported the results of surgical excision without irradiation for selected patients with DCIS in ECOG E5194, where the 5-year rates of local recurrence varied with age, grade, and lesion size (Hughes et al. J Clin Oncol 2009; 27:5319). New methods are needed to provide more accurate and reproducible assessment of recurrence risk.

Methods: ECOG E5194 included 670 eligible patients with DCIS treated with surgical excision (≥ 3 mm negative margins) without irradiation, 228 of whom received tamoxifen. Patients had low or intermediate grade DCIS ≤ 2.5 cm, or high grade DCIS ≤ 1 cm. The Onco*type* DX® assay was performed by quantitative RT-PCR using formalin fixed paraffin embedded tumor specimens from 327 patients (49% of the parent study). Recurrence Score® (RS) was calculated using the published algorithm. A new, prespecified DCIS Score™ was designed to predict recurrence regardless of whether adjuvant tamoxifen was given. The primary objective was to determine whether there was a significant association between the risk of an ipsilateral breast event (IBE) and the continuous DCIS Score in Cox models. 46 patients had an IBE (defined as ipsilateral local recurrence of DCIS [n=20] or invasive cancer [n=26]). Median follow-up was 8.8 years.

Results: The 10-year IBE rates were 15.4% for low/intermediate grade DCIS and 15.1% for high-grade DCIS (as determined by central pathology review), and for invasive IBE, 5.6% and 9.8%, respectively. Comparison between local and expert grading showed substantial disagreement. Continuous DCIS Score was significantly associated with IBE (HR 2.34 per 50 units; 95% CI 1.15, 4.59; p=0.02) when adjusted for tamoxifen use (prespecified primary analysis) and with invasive IBE (HR 3.73; CI 1.34, 9.82; p=0.01). DCIS Score was significantly associated with outcome when evaluated by the prespecified risk groups (see Table). Similar results were observed with and without adjustment for tamoxifen use or for negative margin width. Features associated with IBE in multivariate models included menopausal status (HR 0.49; 95% CI 0.27, 0.90; p=0.02), tumor size (HR 1.52 per 5 mm; 95% CI 1.11, 2.01; p=0.01), and continuous DCIS Score (HR 2.41; 95% CI 1.15, 4.89; p=0.02). The standard RS, which

is calculated using thresholding of many genes, unlike the DCIS Score, was not associated with IBE or invasive IBE ($p > 0.6$).

Conclusions: We have prospectively validated a multigene assay that quantifies recurrence risk and complements traditional clinical and pathologic factors in selected patients with DCIS treated with surgical excision without irradiation. The DCIS Score provides a new clinical tool for individualized selection of treatment for patients with DCIS.

Table. 10-year Outcomes With the New DCIS Score

DCIS Score Risk Group	No. (%)	10-Year Kaplan-Meier Rate (95% CI)	
		Ipsilateral Breast Event (Invasive or DCIS)	Invasive Ipsilateral Breast Event
Low (<39)	246 (75%)	12.0% (8.1%, 17.6%)	5.1% (2.8%, 9.5%)
Intermediate (39-54)	45 (14%)	24.5% (13.8%, 41.1%)	8.9% (2.9%, 25.8%)
High (≥55)	36 (11%)	27.3% (15.2%, 45.9%)	19.1% (9.0%, 37.7%)
Log rank p-value		0.02	0.01