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Biomarker resolution of uterine smooth muscle tumor necrosis as benign or malignant

Uterine leiomyosarcomas are rare malignant tumors with a poor prognosis, while leiomyomas are common benign tumors unrelated to their malignant counterparts. Diagnostic features commonly present in leiomyosarcoma include cytologic atypia, high mitotic index, and a sarcoma-specific geographic cell death designated as tumor cell necrosis (TCN). TCN has a sharp viable–nonviable boundary lacking inflammation, fibrosis, or the granulation tissue seen in nonspecific infarction. These characteristics are sometimes difficult to interpret on routine hematoxylin-and-eosin slides and can lead to diagnostic errors. The authors conducted a study in which they used extracellular matrix stains to test the hypothesis that the host response that characterizes nonspecific infarction may degrade the matrix in infarcted tumor more than in TCN. A honeycomb pattern of reticulin highlighted individual tumor cells in viable regions of all cases. Nonviable areas of reticulin patterns differed significantly by diagnosis ($P<.001$), with a honeycomb pattern maintained (91 percent; 20 of 22) in leiomyosarcomas and lost (61 percent; 11 of 18) in leiomyomas. Retention of honeycomb reticulin in nonviable areas of leiomyosarcoma occurred irrespective of the presence of inflammation, hemorrhage, fibrosis, or diffuse hyalinization. Fibrosis/hyalinization as evidenced by trichrome stain was significantly ($P<.001$) more common in nonviable areas of benign leiomyomas (100 percent; 18 of 18) compared with leiomyosarcomas (36 percent; eight of 22). Where viable tissues contained discernable polarization of mitotic activity, these decreased toward the nonviable interface in leiomyosarcomas and increased toward the interface in leiomyomas. There is a significant difference in the reticulin and collagen networks of nonviable areas of leiomyosarcoma compared with leiomyoma. Both retain reticulin at the time of early injury, but this is cleared over time in benign, but not malignant, areas of necrosis. The authors concluded that proliferative repair of leiomyomas at the viable–nonviable interface includes remodeling of the extracellular matrix, in contrast to the static preservation of extracellular matrix, or mummification, in nonviable areas of leiomyosarcomas.

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Cost factors for ER/PR/HER2 analysis of breast cancer in needle core

biopsy

Estrogen receptor/progesterone receptor/human epidermal growth factor receptor 2 (ER/PR/HER2) are often reflexively assessed in core needle biopsies containing invasive mammary carcinoma so neoadjuvant therapy can be considered. ER/PR/HER2 can be heterogenous, and there is growing consensus that negative results for any of these markers in small core needle biopsies should be repeated in larger excision specimens. To the authors' knowledge, the frequency and added cost of repeat testing of excision specimens containing untreated invasive mammary carcinoma with negative ER/PR/HER2 core needle biopsy results had not been studied. The authors reviewed 198 core needle biopsies containing invasive mammary carcinoma that had reflex ER/PR/HER2 testing and for which there was an excision specimen for review. They determined the number of cases in which ER/PR/HER2 immunohistochemistry and HER2 fluorescence in situ hybridization were negative on core needle biopsy. Twenty-seven (13.6 percent) patients received neoadjuvant chemotherapy, and eight (four percent) patients did not have invasive mammary carcinoma on follow-up excision specimens, so for them, core needle biopsy testing was necessary. Of the remaining 163 invasive mammary carcinomas, 17 percent were ER negative and 26 percent were PR negative, whereas 85 percent were HER2 negative or equivocal. At the authors' institution, ER/PR were repeated on slightly more than half of ER/PR-negative tumors and HER2 on less than one-third of HER2-negative/equivocal tumors. Had all negative tests been repeated, the increased cost of testing the core needle biopsies and excision specimens would have been $100,821. Extrapolating to 230,000 new cases of invasive mammary carcinoma in the United States each year, the increased cost of repeat testing of all negative ER/PR/HER2 core needle biopsy results would be more than $117 million. Limiting reflex testing to ER would decrease the cost of repeat testing to $10 million. The authors suggested that ER/PR/HER2 should not be reflexively performed on all core needle biopsy specimens containing invasive mammary carcinoma, but instead be routinely performed on excision specimens and only selectively on core needle biopsy specimens if neoadjuvant chemotherapy is a serious consideration for a particular patient.

VandenBussche CJ, Cimino-Mathews A, Park BH, et al. Reflex estrogen receptor/progesterone receptor/human epidermal growth factor receptor 2 (ER/PR/Her2) analysis of breast cancers in needle core biopsy specimens dramatically increases health care costs. *Am J Surg Pathol.* 2015;39:939–947.

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Prognosis and targetable pathways for high-risk endometrial cancer

The authors investigated whether molecular analysis can be used to refine risk assessment, direct adjuvant therapy, and identify actionable alterations in high-risk endometrial cancer. Transportec, an international consortium related to the PORTEC-3 trial, was established for translational research in high-risk endometrial cancer. In this explorative study, routine molecular analyses were used to detect prognostic subgroups: p53 immunohistochemistry, microsatellite instability, and *POLE* proofreading mutation. Furthermore, DNA was analyzed for hotspot mutations in 13 additional genes—*BRAF, CDKNA2, CTNNB1, FBXW7, FGFR2, FGFR3, FOXL2, HRAS, KRAS, NRAS, PIK3CA, PPP2R1A,* and *PTEN*—and protein expression of estrogen receptor, progesterone receptor, PTEN, and ARID1a was analyzed. Rates of distant metastasis, recurrence-free survival, and overall survival were calculated using the Kaplan-Meier method and log-rank test. Samples from 116 high-risk endometrial cancer patients were included: 86 endometrioid, 12 serous, and 18 clear cell. For the endometrioid, serous, and clear cell cancer patients, five-year recurrence-free survival rates were 68 percent, 27 percent, and 50 percent (P=.014), respectively. Distant metastasis rates were 23 percent, 64 percent, and 50 percent (P=.001), respectively. Four prognostic subgroups were identified: a group of p53-mutant tumors, microsatellite instable tumors, *POLE* proofreading-mutant tumors, and a group with no specific molecular profile (NSMP). In patients in group three (*POLE* mutant; n=14) and group two (microsatellite instable; n=19), no distant metastasis occurred, compared with a 50 percent distant metastasis rate for patients in group one (p53 mutant; n=36) and 39 percent in group four (NSMP; P<.001). Five-year recurrence-free survival was 93 percent and 95 percent for group three (*POLE* mutant)

and group two (microsatellite instable) versus 42 percent (group one, p53 mutant) and 52 percent (group four, NSMP; *P*<.001). Targetable FBXW7 and FGFR2 mutations (six percent), alterations in the PI3K-AKT pathway (60 percent), and hormone receptor positivity (45 percent) were frequently found. The authors concluded that molecular analysis of high-risk endometrial cancer identifies four distinct prognostic subgroups, with potential therapeutic implications. High frequencies of targetable alterations were identified and may serve as targets for individualized treatment.

Stelloo E, Bosse T, Nout RA, et al. Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. *Mod Pathol*. 2015;28:836–844.

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An international study to increase concordance in Ki-67 scoring

Although an important biomarker in breast cancer, Ki-67 lacks scoring standardization, which has limited its clinical use. The authors previously conducted a study that found variability when laboratories used their own scoring methods on centrally stained tissue microarray slides. In this more current study, 16 laboratories from eight countries calibrated to a specific Ki-67 scoring method and then scored 50 centrally MIB-1–stained tissue microarray cases. Simple instructions prescribed scoring pattern and staining thresholds for determining the percentage of stained tumor cells. To calibrate, laboratories scored 18 “training” and “test” Web-based images. Software tracked object selection and scoring. Success for the calibration was prespecified as root-mean-square error of scores compared with reference less than 0.6 and maximum absolute deviation from reference less than 1.0 (log2-transformed data). Prespecified success criteria for tissue microarray scoring required intraclass correlation significantly greater than 0.70 but aiming for observed intraclass correlation of 0.90 or greater. Laboratory performance showed nonsignificant but promising trends of improvement through the calibration exercise (mean root-mean-square error decreased from 0.6 to 0.4 and maximum absolute deviation from 1.6 to 0.9; paired t test: P=.07 for root-mean-square error, 0.06 for maximum absolute deviation). For tissue microarray scoring, the intraclass correlation estimate was 0.94 (95 percent credible interval, 0.90–0.97), markedly and significantly greater than 0.70, the prescribed minimum target for success. Some discrepancies persisted, including with clinically relevant cutoffs. The authors concluded that after calibrating to a common scoring method via a Web-based tool, laboratories can achieve high interlaboratory reproducibility in Ki-67 scoring on centrally stained tissue microarray slides. Although these data are potentially encouraging, suggesting that it may be possible to standardize scoring of Ki-67 among pathology laboratories, clinically important discrepancies persist. Before this biomarker could be recommended for clinical use, future research would need to extend this approach to biopsies and whole sections, account for staining variability, and link to outcomes.

Polley MY, Leung SC, Gao D, et al. An international study to increase concordance in Ki67 scoring. *Mod Pathol.* 2015;28:778–786.

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