

Editorial

DNA Fingerprinting and Breast Cancer

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In this issue of the *Annals of Surgical Oncology*, Toth-Fejel et al.¹ present their initial experience with DNA fingerprinting of primary and metastatic breast cancer. To generate the DNA fingerprint, they used a polymerase chain reaction (PCR)-based technique involving the amplification of genomic DNA between *Alu* repeat sequences, which occur semi-randomly throughout the genome. When the PCR product is run on a gel matrix, a unique pattern of bands appears, reflecting the varying lengths between the *Alu* sequences. Genetic changes within breast cancer cells result in an altered DNA fingerprint specific for a patient's tumor and which should be conserved in metastatic deposits. Measuring broad alterations in DNA content by this method theoretically bypasses the need for the as yet elusive ideal tumor marker, one universally and uniquely expressed in breast cancer.

The authors compare the DNA fingerprint derived from peripheral blood samples and various breast and lymph node tissues from 45 women. Among the 33 patients with breast cancer, all of the DNA fingerprints from the breast tumors differed from their normal peripheral blood DNA and the altered DNA fingerprint pattern was conserved in all of the histologically positive lymph nodes. This yielded a 100% sensitivity of altered DNA fingerprint for the diagnosis of primary and axillary metastatic breast cancer. The specificity of the assay is somewhat lower as some non-neoplastic hypertrophic breast tissue from patients without cancer demonstrated an altered DNA fingerprint involving a single extra band. Two histologically negative lymph nodes also had an altered DNA fingerprint compared with peripheral blood. This finding likely reflects a greater sensitivity of the

assay compared with routine hematoxylin and eosin histologic examination. On the other hand, although not specifically mentioned, it seems unlikely that these nodes from axillary dissection were subjected to the more rigorous scrutiny (e.g., multiple hematoxylin and eosin [H&E] levels, cytokeratin immunostain) that pathologists generally apply to today's sentinel lymph nodes. The possibility of sampling error also remains because different halves of the bivalved lymph nodes were sent for DNA fingerprinting and standard histology. A single patient with advanced inflammatory breast cancer had an altered DNA fingerprint in her peripheral blood, presumably caused by circulating breast cancer cells. The authors propose that after further refinements, DNA fingerprinting can be helpful in the diagnosis of microscopic nodal metastases and even be useful in monitoring peripheral blood in patients at high risk for breast cancer recurrence.

Although it would be premature to propose monitoring patients with breast cancer with *Alu*-PCR, use of the technique in the diagnosis of microscopic lymph node metastases bears consideration. Several potential advantages exist to the use of PCR (or reverse transcription [RT]-PCR)-based techniques over standard histology or immunohistochemistry (IHC). Provided that an appropriate target has been identified, a PCR-based assay would be far more sensitive than standard histology or even IHC in its ability to detect as few as 10 tumor cells in an entire lymph node. PCR is also far less time-consuming and less expensive than multiple thin section evaluation of a lymph node by IHC or standard histology. In addition, PCR-based assays are fairly straightforward to perform and require significantly less training and manpower to interpret. *Alu*-PCR would be more widely applicable than available RT-PCR techniques, which rely on the presence of specific proteins.² Additionally, *Alu*-PCR does not suffer from the problem of false-positive findings that afflict PCR-based techniques that measure expression of tumor-associated genes because of the difficulty differentiating tumor-specific expression from

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nonpathologic background expression by normal tissues.³ Because PCR-based assays are so sensitive, DNA fingerprinting of lymph nodes as performed here might upstage a significant proportion of patients with breast cancer. Whereas the presence of micrometastases, identified by IHC alone, may predict outcome in some patients,⁴ it remains to be seen whether mini-micrometastases identified by PCR alone are clinically relevant.

In their article, Toth-Fejel et al.¹ describe a patient who developed brain metastases following primary surgery for breast cancer with DNA fingerprinting of the primary tumor. Both the primary tumor and the brain metastases had identical fingerprints, supporting the conclusion that the metastases were of breast origin. This anecdotal case suggests a clinical scenario wherein DNA fingerprinting may prove to be of great benefit. DNA fingerprinting might be helpful in determining the primary source of metastatic cancer in patients with a history of more than one primary tumor. DNA fingerprinting may also be helpful in determining whether a particular malignant lesion is a metastasis from a prior malignant primary tumor or is a new primary tumor itself. This question is commonly raised when malignant solitary pulmonary nodules are identified in patients with a history of antecedent malignancy. Knowledge of the

DNA fingerprint pattern of the original tumor for comparison, however, is a prerequisite for either determination. The clinical utility of DNA fingerprinting in this scenario would be greatly facilitated by a modification of the *Alu*-PCR technique, permitting it to be performed on formalin-fixed, paraffin-embedded tissues and allowing retrospective review. This may be problematic given the very large size (up to 2 kb) of DNA amplified in the *Alu*-PCR method, as currently described. Nevertheless, this fairly simple and straightforward method for creating a specific fingerprint of a tumor has several potentially useful applications in the diagnosis and monitoring of patients with cancer.

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