Letters to the Editor

CORRESPONDENCE RE: LACK EE, ASKIN FB, DEHNER LB, PAGE DL, WEISS LM. RECOMMENDATIONS FOR REPORTING OF TUMORS OF THE ADRENAL CORTEX AND MEDULLA. MOD PATHOL 1999:12:835–9.

To the Editor: Because tumors of adrenal cortex are uncommon in general surgical pathology practice, we think that our experience could be helpful to the members of the *ad hoc* committee on adrenal tumors and to other pathologists.

We evaluated 76 adrenocortical tumors (ACT) for prognostic factors. Tumors were analyzed according to Weiss's nine histologic features (1) and for the presence of broad fibrous bands (2). We also studied proliferation assessed by means of mitosis counting, MIB-1 expression, and AgNOR (mean counting, area and pattern). AgNOR and MIB-1 were quantitated by image analysis. These parameters were evaluated comparing tumors of children ($\leq$15 years; $n = 24$) and adults (>15 years; $n = 52$) and comparing clinically benign (CB; follow-up, >24 months; $n = 24$) and clinically malignant (CM; $n = 12$) tumors in the adult group ($n = 36$). According to our observations, the AgNOR were visually classified into the following four morphologic patterns on the basis of number, shape, and position in the nucleus: type I, a few (1 to 3) uniform, medium-size, and round-shaped AgNOR dots at the center or at the periphery of the nucleus; type II, one or two big, round-shaped, and uniform AgNOR with a tendency for location in the nuclear center accompanied by several smaller ones; type III, AgNOR particles polymorphic in size and shape distributed diffusely throughout the nucleoplasm; type IV, a few (1 to 3) small, dense, uniform size, and round-shaped AgNOR dots at the center or at the periphery of the nucleus.

Our results showed that ACT of children had a different morphologic spectrum and higher proliferative activity than those of adults. Weiss's criteria in children's ACT were not sufficient to distinguish CB-ACT and CM-ACT, as they were in adults' ACT and in this last group; a cutoff value of 4 had better correlation with malignant biologic behavior ($P = .004$). In the adults, MIB-1 labeling index (cutoff, 10%) had influence in the disease-free survival ($P = .037$) as did the AgNOR pattern ($P < .001$). The AgNOR pattern type I was associated with CB-ACT, and the AgNOR pattern type II was associated with CM-ACT. The AgNOR pattern type III was characteristic of children's ACT, and type IV was characteristic of non-neoplastic adrenal glands (in preparation).

Our experience points to the fact that ACT in children are still a challenge and most effort should be directed to understanding better their biology.

Simone Treiger Sredni, Ph.D., M.D.
Maria Claudia Nogueira Zerbini, Ph.D., M.D.
University of São Paulo, School of Medicine
São Paulo, Brazil

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ABSTRACTS. MOD PATHOL 2000;13:17A,19A,22A,24A,25A,27A.

To the Editor: We read with great interest the many abstracts in your January 2000 issue regarding Her-2/*neu* and its value in the evaluation of breast carcinoma (1–9). More than one of these abstracted studies compared the immunohistochemical and fluorescence *in situ* hybridization (FISH) techniques for semiquantitation of Her-2/*neu* (5, 6). These studies reflect the substantial debate now occurring as to which technique is the superior methodology for evaluating Her-2/*neu* status in breast carcinomas. The answer seems unclear, in part because the question is two questions, neither of which we believe has been precisely framed. Her-2/*neu* status seems to have both prognostic and predictive value. The answer as to which assay methodology is superior may depend on whether one is interested in Her-2/*neu* as a prognostic or as a predictive marker. We believe that the preponderance of evidence indicates the superiority of direct assessment of the genetic material for

prognostic stratification (10). Current data support a significant association between amplification of the Her-2/*neu* oncogene and a poor prognosis. This link has been most reproducibly demonstrated by the polymerase chain reaction and FISH techniques rather than by immunohistochemistry (IHC) (10).

The picture is less clear when Her-2/*neu* analysis is used as a predictive marker for response to Herceptin therapy (6). Herceptin therapy uses an antibody directed against the protein product of the Her-2/*neu* oncogene as a specific delivery system for a cytotoxic agent. The Her-2/neu protein product is expressed on the cell membrane surface in increased amounts in a subset of breast carcinomas. Theoretically, the greater the amount of Her-2/neu protein on the cell surface, the greater the amount of cytotoxic agent that can be delivered to the neoplastic cell. Hence, Herceptin therapy would be most effective against cancers that express high levels of cell membrane Her-2/neu protein. In the majority of Her-2/neu–positive cases, increased protein is secondary to amplification of Her-2/*neu* oncogene, but other pathways for overexpression exist, including posttranscriptional and posttranslational events. It is also possible that amplification of the Her-2/*neu* oncogene may not result in overexpression of a protein product recognizable by antibodies used in an IHC assay. Thus, one would not expect perfect correlation between FISH and IHC assay results.

From these observations, two conclusions can be drawn. First, assay of the Her-2/neu protein on the cell surface by IHC is a potentially superior technique for the prediction of Herceptin binding and response to Herceptin therapy than is measurement of DNA amplification by FISH techniques. Second, the IHC methodology would be most predictive of response if the assay antibody had *in vitro* binding characteristics identical to the Herceptin-carrying antibody's *in vivo* binding characteristics. Although similar, the antibody used in the HercepTest kit is a different clone than the carrying antibody used in the therapeutic agent Herceptin (11, 12). We are unaware of any published data comparing the binding properties of these two antibodies or the superiority of the clone used in the HercepTest over other commercially available clones for the prediction of response to Herceptin therapy.

Large long-term clinical studies are needed to document the superiority of FISH or IHC in the prediction of response to Herceptin therapy. The abstract by Kaptain *et al.* (6) addressed this issue but did not include sufficient patients with long-term follow-up for definitive conclusions to be drawn. Large studies with long-term clinical correlation are necessary to identify which antibody clones are best able to predict the *in vivo* binding characteristics of the Herceptin-carrying antibody so that decisions regarding Herceptin therapy can be most accurately made based on Her-2/*neu* analysis of tissue specimens.

Lester J. Layfield, M.D.
University of Utah
Salt Lake City, Utah

Neal S. Goldstein, M.D.
William Beaumont Hospital
Royal Oak, Michigan

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