The Interpretive Art/Science of Pathology

The Editor interviews:
Robert V.P. Hutter, M.D.
Director of Pathology,
Saint Barnabas Medical Center
Livingston, New Jersey and
Adjunct Professor of Pathology
College of Physicians and Surgeons
Columbia University
New York, New York

Recent controversy surrounding the Breast Cancer Detection Demonstration Projects has raised the issue of whether some previously diagnosed minimal cancers were in fact benign. Perhaps you can begin by defining the term, minimal cancer.

Dr. Hutter: Minimal cancer has been defined for the BCDDP review as non-invasive breast cancer or invasive cancer less than one centimeter in diameter. Others have restricted the invasive component to 0.5 cm.

Editor: Does this definition hold true for cancers other than those in the breast?

Dr. Hutter: The concept of minimal cancer could be applied to other sites. However, the term “minimal cancer” of the breast was introduced by Gallager and Martin at about the time that some investigators were challenging radical mastectomy as the preferred treatment for all breast cancers.

In practice, as noted above, the term applies to small invasive breast cancers, or non-invasive cancers of two types: (1) lobular carcinoma in situ: those that arise in the terminal portion of the ductal system (the ductules) of the lobule; and (2) intraductal carcinoma: those intraductal lesions that arise proximal to the lobule. As the concept evolved it became evident that there are also some histologic types of breast cancer that are biologically less aggressive than conventional lesions, which may therefore be amenable to less than conventional radical mastectomy.
Editor: Why would a lesion appear to be a minimal breast cancer to one pathologist and not to another?

Dr. Hutter: The diagnosis of a small invasive breast cancer is reasonably objective. There could possibly be some controversy in deciding whether or not a lesion is invasive, but not usually whether or not it is cancer.

Differences of opinion are more likely to occur in the diagnosis of non-invasive carcinomas. When there are varied interpretations the first concern is: have all reviewers examined precisely the same evidence? Indeed in the McDivitt Committee pathology review of the Breast Cancer Detection Demonstration Projects, it was initially impossible, because of the constraints of time, to verify whether the tissue slides reviewed were truly representative of the material from which the original diagnosis had been made.

Editor: In other words, this part of the problem is really technical.

Dr. Hutter: Exactly. And the technical problems are further compounded when there is no visible or palpable tumor from which to obtain a sample, but only microscopic evidence. This can perhaps be more fully appreciated when one understands the mechanics of tissue preparation.

Editor: How is a specimen prepared for histologic diagnosis?

Dr. Hutter: Tissue samples, each smaller than the size of a postage stamp and the thickness of a five-cent piece, are placed in small perforated cassettes, which hold and identify them. The cassettes are then passed through a series of solutions that remove the water and fatty substances from the tissue so that it can be permeated with warm liquid paraffin. Once cooled and hardened, each piece of tissue in paraffin is held firmly and sliced with a microtome knife, producing a ribbon of paraffin and tissue, several centimeters long and approximately six microns thick. These pieces of tissue are placed on 1” x 3” glass slides and stained so that the tissue can be studied microscopically.

If the microscopic lesion is very small we may try to determine its greatest extent by examining every third or fifth piece of tissue in the paraffin ribbon as we cut deeper into the tissue. The maximum size of the lesion may be either at the top of the piece of tissue or deeper into it. Now if 20 slides are prepared from these ribbons, the pathologist who examines the first slide may not see exactly the same lesion, or the same extent of the lesion, as the pathologist who looks at the 20th slide.

Editor: Suppose, however, that the material being reviewed is the same. Instead of making 20 cuts from the same paraffin block, one slide is distributed in succession among 20 pathologists.

Dr. Hutter: In this circumstance, any differences are interpretive and not due to technique. Pathologic changes occur on a continuum. Examining a slide is not like looking at a traffic signal that
changes abruptly from green (completely benign) to red (obvious cancer). There is a yellow transitional zone between the green and red that represents the progressive, continuous changes of early and minimal cancer from benign to frankly invasive. At each end of the continuum, the chances of disagreement are slight. It would be unusual for someone with basic training in diagnostic pathology not to recognize benign tissue or infiltrating breast cancer. In fact, studies have shown more than 95 percent concordance among pathologists on the diagnosis of non-minimal breast cancer. The evaluation of "garden variety" lesions can therefore be more objective; certain criteria can be established and reproduced with great precision. On the other hand, the diagnosis of minimal lesions is interpretive and susceptible to a range of subjective variation. The clinical significance of this range of subjective variation is questionable.

**Editor:**

*Are you implying that it is impossible to establish criteria for the histologic diagnosis of these very small cancers?*

**Dr. Hutter:**

No, it is very easy to record the criteria; it may be difficult to attain uniformity in interpretation and application. For example, lobular carcinoma in situ is characterized by cells that are generally much larger than normal lobular cells, and that tend to obliterate the lumens of the ductules in which they arise, although this is not an absolute requirement. It is interesting that in this type of lesion the cells do not show the usual cytologic attributes associated with cancer; the diagnosis depends on the pattern and on disproportionate cell size.

In intraductal carcinoma we see cells with typical cytologic characteristics of carcinoma at any site. Not only are the cells large, but the nuclear enlargement is even more striking. Instead of a 1:4 nuclear-cytoplasmic ratio, it may be 1:2 or 1:1. Whereas the nuclear membrane normally tends to be smooth and round or oval, in cancer it is irregular. The nucleolus is not inconspicuous as in a normal cell, but prominent or multiple. A cancer cell has granular, clumped chromatin, rather than the fine, dusty chromatin normally seen. Cancer cells lose their uniformity, and marked variations in size and shape are common.

So yes, it is extremely easy to tabulate descriptive criteria for the diagnosis of minimal cancer. However, they may be difficult to apply with complete conformity because of the subjective range in interpreting the criteria.

**Editor:**

*Why?*

**Dr. Hutter:**

These histologic changes, as I have mentioned, occur on a continuum. How disproportionate is the cell size? How granular is the chromatin? Is the nucleus really prominent in a neoplastic way or is it regenerative? The answers are arrived at through individual perceptions of observed phenomena.

As an example, I could describe my wife's face and provide you with a list of identifying criteria. Based on these criteria,
and because of my experience, I could accurately identify her in a photograph of a crowd. But, since you have never met her, it is questionable whether you could recognize her in the same photograph, even if you could verbalize my criteria exactly. Variations in physiognomy may also occur on a continuum.

Editor:  

Will differences in pathologic interpretation ever be resolved?

Dr. Hutter:  

I think so, through more frequent exposure and a greater accumulation of personal experience the "yellow zone" will progressively become more narrow. Obviously, if the yellow zone were broader than the green or red, diagnostic pathology would serve no useful purpose and would be abandoned.

It should be remembered that while the concept of early cancer is not new—Dr. James Ewing included illustrations of what we would now call lobular carcinoma in situ and intraductal carcinoma in his 1919 textbook on neoplastic diseases—today we deal with the problem much more frequently than we did in the past.

Editor:  

Because of mammography?

Dr. Hutter:  

Absolutely. In a large series recorded by the SEER Program (Surveillance, Epidemiology and End Results Reporting) sponsored by the National Cancer Institute, only five percent of 8,649 breast cancers were in situ. In the screening program of the Breast Cancer Detection Demonstration Projects of the American Cancer Society and the National Cancer Institute, 27 percent were in situ and 38 percent were minimal.

Editor:  

That's a dramatic increase!

Dr. Hutter:  

It is certainly a far cry from the days when minimal cancer was such a rare finding that the slides were routinely sent off to a consultant. Now, as many pathologists are seeing these lesions in increasing numbers, they feel more confident in interpreting them. And this leads to another aspect of the problem which is: what is the clinical significance of minimal cancer?

Editor:  

Will this information affect the pathologist in his review of the material?

Dr. Hutter:  

I hope so. An awareness of the clinical implications of a pathologic diagnosis makes the difference between a histologic exercise and a medical consultation.

Editor:  

What is a histologic exercise?

Dr. Hutter:  

By a histologic exercise I mean that a pathologist studies a slide with no knowledge of the clinical circumstances of the patient from whom the tissue was removed. He records his interpretation but this information is not released for use in patient management; it may be used for research or other non-
clinical purposes. The pathologist as a consultant is a member of the clinical team who fully integrates all clinical data in formulating his opinion and recommendations.

Editor: Are you saying that the pathologist should not be restricted to simply reviewing the slide?

Dr. Hutter: Yes, he must interpret a slide in the total clinical context. If I am asked to consult on a case that may involve carcinoma in situ, my first reaction is always, "tell me about this patient." And not infrequently, the response from a physician not familiar with our policy is, "I do not want to influence you." We need to be influenced; we are trying to arrive at the most appropriate recommendation for the management of the patient. Consider for example, that the lesion is histologically "borderline" (neither obviously benign nor malignant), but I learn that five years ago the patient had cancer of the opposite breast and is therefore at very high risk. This information modulates the interpretation of what I see histologically, and influences my recommendations.

Editor: Do you recommend a second pathologic opinion in these difficult cases?

Dr. Hutter: My reflex reaction is yes, if the pathologist feels he needs it or if the patient requests it. But there is a point of diminishing returns with "shotgun" consultations. Should one make a clinical decision based on concurrence in three out of five, or five out of seven opinions? The best approach to a pathologic consultation, as in any other consultation in medicine, is to rely on a source in which you have confidence. This is not the most sensational technique, but is more practical than sending out sections to 20 consultants and tabulating the results. However, if ultimately two or three consultant pathologists disagree, you know you are in that "yellow zone." Then the course to pursue is a matter of judgement based on the total clinical setting and not just the interpretation of the histologic slides.

Editor: Thank you, Dr. Hutter.