Atlas of Tumor Pathology

Tumors of the Mammary Gland

by
Paul Peter Rosen, M.D.
and
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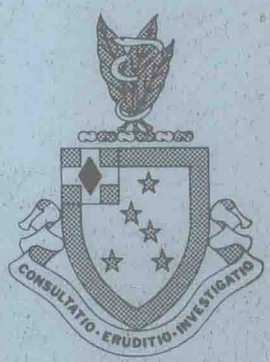

AFIP

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ATLAS OF TUMOR PATHOLOGY

Third Series
Fascicle 7

TUMORS OF THE MAMMARY GLAND

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ATLAS OF TUMOR PATHOLOGY

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EDITORS' NOTE

The Atlas of Tumor Pathology has a long and distinguished history. It was first conceived at a Cancer Research Meeting held in St. Louis in September 1947 as an attempt to standardize the nomenclature of neoplastic diseases. The first series was sponsored by the National Academy of Sciences-National Research Council. The organization of this Sisyphean effort was entrusted to the Subcommittee on Oncology of the Committee on Pathology, and Dr. Arthur Purdy Stout was the first editor-in-chief. Many of the illustrations were provided by the Medical Illustration Service of the Armed Forces Institute of Pathology, the type was set by the Government Printing Office, and the final printing was done at the Armed Forces Institute of Pathology (hence the colloquial appellation "AFIP Fascicles"). The American Registry of Pathology purchased the Fascicles from the Government Printing Office and sold them virtually at cost. Over a period of 20 years, approximately 15,000 copies each of nearly 40 Fascicles were produced. The worldwide impact that these publications have had over the years has largely surpassed the original goal. They quickly became among the most influential publications on tumor pathology ever written, primarily because of their overall high quality but also because their low cost made them easily accessible to pathologists and other students of oncology the world over.

Upon completion of the first series, the National Academy of Sciences-National Research Council handed further pursuit of the project over to the newly created Universities Associated for Research and Education in Pathology (UAREP). A second series was started, generously supported by grants from the AFIP, the National Cancer Institute, and the American Cancer Society. Dr. Harlan I. Firminger became the editor-in-chief and was succeeded by Dr. William H. Hartmann. The second series Fascicles were produced as bound volumes instead of loose leaflets. They featured a more comprehensive coverage of the subjects, to the extent that the Fascicles could no longer be regarded as "atlases" but rather as monographs describing and illustrating in detail the tumors and tumor-like conditions of the various organs and systems.

Once the second series was completed, with a success that matched that of the first, UAREP and AFIP decided to embark on a third series. A new editor-in-chief and an associate editor were selected, and a distinguished editorial board was appointed. The mandate for the third series remains the same as for the previous ones, i.e., to oversee the production of an eminently practical publication with surgical pathologists as its primary audience, but also aimed at other workers in oncology. The main purposes of this series are to promote a consistent, unified, and biologically sound nomenclature; to guide the surgical pathologist in the diagnosis of the various tumors and tumor-like lesions; and to provide relevant histogenetic, pathogenetic, and clinicopathologic information on these entities. Just as the second series included data obtained from ultrastructural (and, in the more recent Fascicles, immunohistochemical) examination, the third series will, in addition, incorporate pertinent information obtained with the newer molecular biology techniques. As in the past, a continuous attempt will be made to correlate, whenever possible, the nomenclature used in the Fascicles with that proposed by the World Health Organization's International Histological Classification of Tumors. The format of the third series has been changed in order to incorporate additional items and to ensure a consistency of style throughout. This includes the dropping of the 's possessive in eponymic terms, in accordance with the WHO and the International Nomenclature of Diseases. Close cooperation between the various authors and their respective liaisons from the editorial board will be emphasized to minimize unnecessary repetition and discrepancies in the text and illustrations.

To its everlasting credit, the participation and commitment of the AFIP to this venture is even more substantial and encompassing than in previous series. It now extends to virtually all scientific, technical, and financial aspects of the production.

The task confronting the organizations and individuals involved in the third series is even more daunting than in the preceding efforts because of the ever-increasing complexity of the matter at hand. It is hoped that this combined effort—of which, needless to say, that represented by the authors is first and foremost—will result in a series worthy of its two illustrious predecessors and will be a suitable introduction to the tumor pathology of the twenty-first century.

Juan Rosai, M.D.
Leslie H. Sobin, M.D.

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TUMORS OF THE MAMMARY GLAND

Contents

TUMORS OF THE MAMMARY GLAND

INTRODUCTION

Like the frames of a motion picture film, the Fascicles of the Armed Forces Institute of Pathology constitute chapters in the history of tumor pathology. This third edition of Tumors of the Mammary Gland is built upon the contributions of its predecessors. Its expanded size and scope reflect the explosive growth of information relating to breast disease that has occurred during the past two decades.

The first Fascicle on Tumors of the Breast, written by Fred W. Stewart, was published in 1950 (6). The 114 pages, 68 figures, and 32 references were designed "to describe and illustrate the pathology of cancer of the human breast" and provide a catalog of tumorous conditions of the breast. Descriptions of benign lesions were brief, "except where the latter are of such pattern that less experienced pathologists often confuse them with mammary cancer." The six major categories (Paget disease, carcinoma, malignant variants of fibroadenoma and cystosarcoma phyllodes, miscellaneous sarcomas, lesions simulating tumors, and benign tumors) were further subdivided into approximately 30 specific diagnoses. As a result, the classification of benign and malignant lesions developed by Ewing and Stewart in the preceding decades was established as an international standard. With the exception of a few histochemical tests, such as the mucicarmine and trichrome stains, the authors relied entirely on hematoxylin- and eosin-stained sections.

The clinical evaluation of patients at that time was limited to physical examination, occasionally assisted by transillumination to detect cysts. The only widely accepted diagnostic procedure was surgical biopsy, although needle aspiration biopsy was practiced in a few centers. Radical mastectomy, sometimes supplemented with local irradiation, was the standard treatment for malignant neoplasms. Introductory comments in the first Fascicle, dealing with "precancerous" lesions, classification, and prognosis contained many observations which are as relevant today as they were then.

Stewart's skeptical views on the concept of a "precancerous" state in the breast were indicated by the following comments:

> ...a progressive change into cancer can be found in duct hyperplasias and papillomas, something that to the unbiased observer means only that cancer can develop in an epithelium that possesses more than the average impetus toward proliferative alteration. But unfortunately, in the same breast one may find cancer without any evidence whatever that it has arisen in such an area. One is apt to be overly impressed by seeing the beginnings in a previously abnormal structure and neglect its origin in another area where the prior abnormality is at least not apparent.... The cancer actually develops in what happens to be in the breast. Even the innocuous old hyalinized fibroadenoma exceedingly rarely develops a cancer.
>
> ...Really I do not know what "precancerous" means. Is it something upon which cancer is engrafted more often than upon something else, or than upon areas revealing no abnormality one can detect? ...Sometimes I think the word "precancerous" is the most abused expression in the whole cancer field....

Regarding the classification of breast carcinoma, Stewart offered the following observation:

> Although the exacting histologist may find comfort and may derive prestige from the employment of many names in the diagnosis of cancer of the breast, it is my impression that surgeon, patient and pathologist could get along with very few.

Thus, it was clear that Stewart was a "lumper" rather than a "splitter" in his approach to classification; terminology had to be clinically meaningful and not simply descriptive. This conservative approach has guided the expansion of the Stewart classification in the present volume.

The most important prognostic variables cited by Stewart were the presence or absence of invasion, the extent of invasion (localized or diffuse), the presence or absence of true lymphatic invasion, and the presence or absence (and extent) of axillary lymph node metastases. "All these things exceed in prognostic importance the mere looking at cells and assigning names and grades ...." This view of prognostic factors giving primary importance to stage, has largely withstood the test of time. In retrospect, Stewart may have underestimated the prognostic importance of some histologic subtypes, although they account for a minority of tumors and are themselves also subject to the effect of stage.

Nearly 25 years passed before the second Fascicle on Tumors of the Breast, authored by Robert W. McDivitt, Fred W. Stewart, and John W. Berg was published in 1968 (3). This book consisted of 156 pages with 120 figures and 81 references. The classification was virtually unchanged from the prior edition. Electron microscopy offered a new view of the structure of many lesions but few studies were done on breast pathology and there were no ultrastructural photographs. Cytologic examination of needle aspirates and nipple secretion had become a diagnostic procedure in a few medical centers, but was still not widely employed. The diagnostic armamentarium available to pathologists had not appreciably enlarged in the quarter century between the first and second Fascicles.

There was one important clinical advance, however. Mammography, developed and refined as a clinical tool for the diagnosis of palpable breast lesions, increasingly led to the discovery of nonpalpable lesions, thereby expanding the range of diagnostic problems. As a consequence, the distinction between hyperplasia and in situ carcinoma was a major concern, occupying about one third of the text and illustrations of the second Fascicle.

Having concluded that the first Fascicle had contributed to "...a substantial decline in overdiagnosis of breast cancer" and that "...the level of diagnosis is much improved," the authors stated that "the orientation of the new Fascicle is somewhat different...placing emphasis on 'early' lesions." The importance of detecting early lesions was stressed because "lacking something new on the horizon for the treatment of the patient with breast cancer, improvement in end results would seem to rest on increasingly early pathologic diagnosis." Early was defined as "...cancer that is confined to ducts or lobules, or both, and nowhere is seen to be infiltrative," that is, in situ carcinoma.

McDivitt, Stewart, and Berg drew attention to problems engendered by the effort to diagnose in situ carcinoma:

> This search has resulted in the tendency on the part of pathologists to recognize earlier and earlier changes on which a diagnosis of cancer may be made, a tendency which is both useful and dangerous owing to overenthusiasm. In these breast lesions we have said that "early" means they are cytologically cancerous but still within the area of origin, that is, intraductal or intralobular. How long such a situation may be maintained is unknown, but it is highly probable that it may last for years or even decades.

It is interesting to note that the discussion of early (in situ) carcinoma in the Introduction to the second edition was completely separate from, and preceded, comments on "Precancerous Lesions." The latter section was concerned mainly with "the proliferative cystic disease complex and subsequent breast cancer."

Employing several illustrative examples, the authors suggested that the "precancerous" properties of "cystic disease" might be attributable to the presence of unrecognized in situ carcinoma in the breast. This might occur through failure to diagnose in situ carcinoma in a biopsy sample or because the lesion, present elsewhere in the breast, was not included in the tissue removed. They acknowledged, however, that components of "the cystic proliferative complex" might also prove to be precancerous and concluded that to identify such changes

> ...requires segregation of various significant and insignificant patterns.... Much more study of "borderline" lesions is needed, especially with description at the cytologic level rather than merely diagnosis by outdated cliches which do not analyze. Most of all, we need the test of time and we do not even know how much time.... If we must wait an indeterminate time for behaviour patterns in cancer already present, then how long must we wait to judge the capabilities of a "precancerous" lesion?

Implicit in the foregoing discussion of early, precancerous, and borderline lesions is the concept that they are associated with an increased risk of subsequent carcinoma. However, the authors appreciated the substantial difficulties inherent in such a conclusion:

> One cannot remove a section of breast, find an *in situ* carcinoma, and be certain that the infiltrative cancer found elsewhere in the same breast years later was there in an *in situ* form at the time of the initial excision. The mere fact that disease of this type is extremely apt to be multifocal gives support of course to the belief that it was there and has taken years to evolve.... Of course, one could speculate that the carcinogenic stimulus might reach the breast on more than a single occasion; thus, not all foci of *in situ* carcinoma need have existed simultaneously, or for that matter have developed at the same rate.

The diagnosis and treatment of breast carcinoma is far different today than it was in 1967. No longer is the surgeon confronted largely with palpable lesions, and no longer is the treatment of carcinoma restricted to mastectomy. The increased use of mammography has heightened recognition of nonpalpable neoplasia, and fine-needle aspiration cytology has accelerated the diagnosis of carcinoma. Probably the most significant development is the advent of breast conservation therapy. The pathologist's role has expanded beyond distinguishing between a benign and a malignant lesion. Issues related to the feasibility of breast conservation and the extent of the procedure, including multicentricity of the neoplasm, the type and distribution of intraductal carcinoma, and the presence of neoplasm at the margins of surgical excision, have grown in importance during the last decade.

The present Fascicle addresses clinical issues that are increasingly integral responsibilities of the pathologist. Mammography must be utilized to correlate specimen radiography with biopsy specimens; interpretation of fine-needle aspiration cytologic specimens brings patient and pathologist together; and biopsy of nonpalpable lesions necessitates recognition of earlier manifestations of intraductal epithelial proliferation.

The pathologist has become involved in treatment decisions and assessment of the prognostic implication of various neoplasms. Immunohistochemical procedures have expanded our ability to detect hormonal receptors in lesions too small for biochemical analysis or in cytologic specimens from lesions not readily accessible to surgical biopsy. A diverse menu of studies for the prognostic appraisal of malignant neoplasms can be utilized, including assessment of the proliferative rate of the tumor, oncogene amplification studies, and flow cytometric determination of the ploidy status of the neoplasm. Many of these studies are new, and their utility has yet to be confirmed.

The pathologist must be aware of benign lesions that can simulate carcinoma, and these are described to a greater extent in this Fascicle than in previous editions. Patterns of mammary neoplasia are sharply distinguished to permit better distinction of their prognostic significance. Most important, there is continued and renewed emphasis on the assessment of "borderline" intraductal epithelial proliferative lesions. This was a central focus of both previous Fascicles, and it continues to be the source of greatest consternation in the pathologic assessment of breast biopsies.

Dr. Joseph Colt Bloodgood, a protégé of Halstead early in this century, was one of a small group of American surgeons who appreciated the crucial role of microscopic pathological studies in the diagnosis and treatment of breast diseases. He advocated early detection as a means of reducing breast cancer mortality decades in advance of mammography, by urging that clinical abnormalities be biopsied before they became obviously malignant. In 1916 he commented "...that the relative proportion of benign lesions of the breast is steadily changing and that the percentage of benign lesions is on the increase" (2). In addition to practicing surgery, Bloodgood was a skilled microscopist. His histopathologic examination of clinically inconspicuous proliferative lesions illuminated the interpretive difficulties that could be presented by microscopic pathologic alterations that did not cause palpable tumors. He used the term "borderline" for lesions about which "both the surgeon and pathologist are in doubt" and stated that "...if women come early we shall find that the borderline group is large."

Bloodgood demonstrated the lack of agreement by pathologists in the interpretation of borderline lesions in the following test:

> I have submitted over sixty borderline cases to a number of pathologists, and have found that in not a single one has there been uniform agreement as to whether the lesion was benign or malignant.... This is no reflection on the diagnostic abilities of the pathologists; it is simply evidence that at the present time there are certain lesions of the breast about which we apparently do not agree from the microscopic appearance only.

The problems presented by borderline lesions concerned Bloodgood for many years and in 1932 he pointed to the diagnostic and therapeutic uncertainty as "...one of the most important problems in surgery of the breast — the problem of whether the tumor alone should be removed or the complete operation for cancer performed" (1).

The current variability in the interpretation of such lesions was described by Rosai in 1991 (4). Seventeen slides, each with a specific intraepithelial lesion circled, were reviewed by five pathologists. Although none of the slides was interpreted unanimously, all were in agreement that 8 lesions (47 percent) were not carcinoma, differing on whether the process was hyperplasia or atypical hyperplasia. Four lesions were diagnosed as in situ carcinoma by two or three pathologists. One pathologist reported in situ carcinoma in 9 of the 17 while at the other extreme another pathologist concluded that none of the lesions was carcinoma. These were clearly borderline lesions as defined by Bloodgood, leading Dr. Rosai to conclude "...that we are far from having reached uniform diagnostic criteria in this field."

As noted by Rosai, it is widely thought that there is "...a continuum between hyperplasia and carcinoma in situ and that the risk for the development of invasive carcinoma correlates with the degree of proliferation and atypia." Hence, assigning a diagnosis to lesions in this spectrum is also an exercise in estimating the risk for subsequent carcinoma. Some of the limitations which impair the precision of this process are summarized here.

1. *Sampling error*: The excised tissue lacks the most extreme proliferative changes.
2. *Extrapolation inability*: Failure to develop carcinoma after the excision of a proliferative lesion may be attributed to the excision of the lesion in the biopsy. Histologic changes in the biopsy serve as a marker but there is presently no method for determining if similar pathologic changes remain in the breast or if they will develop later. It is not possible to trace a later neoplastic lesion, such as invasive carcinoma, directly to a prior, excised proliferative lesion.
3. *Confounding variables*: These include length of follow-up, family history of breast carcinoma, or parity. Most women with proliferative lesions, even those with the most atypical changes, do not develop carcinoma even after long follow-up. Several investigators have shown that the relative risk for carcinoma following a diagnosis of atypical hyperplasia is greater among women with a history of carcinoma in first degree relatives. Tools are not available to detect morphologic alterations influenced by positive family history or other confounding factors. As a consequence, the classification of proliferative lesions as atypical, precancerous, or borderline on the basis of follow-up results alone, is at best crude.
4. *Lack of Gold Standard*: This has yet to be achieved to distinguish hyperplasia from in situ carcinoma. Rosai has pointed out that "...none of the special techniques that have been employed to date in an attempt to achieve a sharper and more reproducible separation between the various groups has yet fulfilled this goal."

A comparison of photographs of proliferative lesions clearly demonstrates the range of interpretations now assigned to lesions in the broad categories of hyperplasia and in situ carcinoma. These representations are at best informed judgements. There is presently no laboratory test to serve as an objective "gold standard" marker to indicate that a specific lesion is at the level of carcinoma in the breast. If a marker can be identified to distinguish between hyperplasia and in situ carcinoma, it will most likely be found by studying invasive or classic in situ carcinoma rather than among borderline lesions of ambiguous significance. While a standard would resolve many issues relating to diagnostic criteria, sampling and extrapolation would still pose problems in making therapeutic decisions.

In the management of individual patients, pathologists do not differ from their clinical colleagues appreciably with respect to "inter-observer variability." Recommendations for the

treatment of cancer from surgeons and medical or radiation oncologists may vary substantially. Reaching a therapeutic decision in these circumstances is a judgement based on experience applied specifically to the patient under consideration. A similar process is employed in the pathologic evaluation of borderline proliferative lesions from individual patients.

Interobserver variability in the interpretation of borderline breast lesions has important implications for epidemiologic and clinical studies. The problem is dramatized in the variable interpretation of the cases assembled by Rosai. It is generally agreed that the highest risk of subsequent invasive carcinoma occurs among patients with antecedent in situ lesions, diminishing progressively among those with atypical and simple hyperplastic changes. On the basis of personal criteria, one reviewer in the Rosai study concluded that nine lesions were sufficiently abnormal to be in the highest risk category while another reviewer concluded that four of these nine warranted an intermediate-risk designation, and five were relatively low-risk lesions. While observer variability can be reduced by standardization of diagnostic criteria, it would not enhance our understanding of how the differing diagnostic interpretations relate to risk (5).

With the foregoing limitations in mind, we describe and illustrate in the following pages our criteria for the diagnosis of a broad range of pathologic conditions including proliferative lesions and in situ carcinoma. The diagnoses offered represent our interpretations for which we take full responsibility. Illustrations included in the volume have been carefully studied and accepted by independent reviewers. They do not differ appreciably from images presented in the prior Fascicle written by McDivitt, Stewart, and Berg. Advances made in coming years should help resolve the diagnostic quandary that now attends lesions variously described as atypical, borderline, precancerous, or in situ carcinoma.

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