ROSAI AND ACKERMAN'S Surgical Pathology

Juan Rosai MD

Chairman, Department of Pathology
National Cancer Institute
Milan, Italy

Professor, Department of Pathology
Weill Medical College of
Cornell University
New York, New York, USA

NINTH EDITION

VOLUME 2

MOSBY
An affiliate of Elsevier Inc.

First edition 1953
Second edition 1959
Third edition 1964
Fourth edition 1968
Fifth edition 1974
Sixth edition 1981
Seventh edition 1989
Eighth edition 1996

ISBN: 0323013422

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging in Publication Data
A catalog record for this book is available from the Library of Congress

Notice
Medical knowledge is constantly changing. Standard safety precautions must be followed, but as new research and clinical experience broaden our knowledge, changes in treatment and drug therapy may become necessary or appropriate. Readers are advised to check the most current product information provided by the manufacturer of each drug to be administered to verify the recommended dose, the method and duration of administration, and contraindications. It is the responsibility of the practitioner, relying on experience and knowledge of the patient, to determine dosages and the best treatment for each individual patient. Neither the Publisher nor the authors assume any liability for any injury and/or damage to persons or property arising from this publication.
The Publisher

ELSEVIER your source for books, journals and multimedia in the health sciences
www.elsevierhealth.com

Printed in China

The publisher's policy is to use paper manufactured from sustainable forests

tumors, of course, should be distinguished from the cases in which two separate neoplasms of different microscopic appearances are present in the same breast. They should also be distinguished from so-called tubulolobular carcinoma, which has a reasonably distinct morphologic appearance (see page 1817).

Undetermined (unclassified) carcinoma

This category includes all cases of invasive carcinoma in which features of ductal or lobular type are not definite enough to place it into either category. Azzopardi[812] states that 3% to 4% of the invasive breast carcinomas belong to this category.

Microinvasive breast carcinoma

Once the concept of "microinvasive carcinoma" was entrenched in the gynecological literature, especially in connection with cervical squamous cell carcinoma, it was only natural that it would be proposed at other sites, including the breast, and the time has arrived. Alas, its application at this site is not as straightforward, one of the reasons being that the mammary epithelium is not separated from the stroma by a sharp, straight line as it is in the cervix.[818] Be that as it may, the proposal has been made to designate as microinvasive carcinoma any CIS of the breast showing one or more areas of stromal invasion not surpassing 1 mm in thickness.[815] Theoretically, it is applicable to both ductal and lobular lesions, but the term seems to be used more often to the former. It may be single or multiple, the mean number of foci being two.[817] Immunohistochemical evaluation with myoepithelial and basement membrane markers is useful for a confirmation of the diagnosis.[815,819] Problems related to the definition criteria and clinical significance of this finding remain and need to be addressed.[814,818] On the whole, it would seem that patients with microinvasive carcinoma are at risk for nodal metastases[820] but that their survival rate is better than for patients with T1 invasive carcinoma.[816] Apparently, the risk for metastases is greater if the invasive component is in the form of cell clusters than in the form of a few isolated tumor cells.[813]

Hormone receptors

A crucial development in the evaluation of breast carcinoma has been the realization that the presence of hormone (estrogen and progesterone) receptors in the tumor tissue correlates well with response to hormone therapy and chemotherapy.[823,833] Traditionally, these hormone receptors were measured by the dextran-coated charcoal and sucrose gradient assay, but this has been replaced in nearly all centers by the immunohistochemical method, on the grounds that it offers several important advantages (it does not require fresh tissue, it can be done with minute amounts of tumor, etc.), and that the correlation between the two methods is very good[824,832,835,842,844] (Fig. 20.98). Several attempts have been made to semiquantitate this method by standardizing the technical procedure and reporting and by using the appropriate controls—a need that has been strongly emphasized.[821,838] Regarding the latter, Battifora's team has proposed a very innovative procedure for a control, which they refer to as the Quicgel method.[839] Although the idea is ingenious indeed (as we have been accustomed to expect from this group), it may be a little too complex to be widely adopted.

The two parameters evaluated in immunohistochemical preparations of hormone receptors are the number of tumor cell nuclei stained and the intensity of the reaction. The first is expressed as a percentage of the entire tumor cell nuclei population, and the second is graded as negative, weak, moderate, and strong. The two parameters are sometimes combined into a scoring system, of which three major versions exist.[832,837] Although several sophisticated image analysis programs have been devised for this purpose,[822] in most laboratories these estimations are done visually.

Hormone receptors can also be evaluated in paraffin-embedded breast tissue by the in situ hybridization technique and by PCR.[829,831]

Not much correlation exists between the cytoarchitectural type of breast carcinoma and presence of hormone receptor protein[840]; specifically, no statistically significant difference has been found between ductal-type and lobular-type tumors. However, most series have shown that most medullary carcinomas and intraductal carcinomas of the comedocarcinoma type are negative, whereas mucinous carcinomas have the highest rates of positivity.[836,841] In DCIS, a predominance of large cells is the best morphologic predictor of estrogen receptor-negative status.[827]

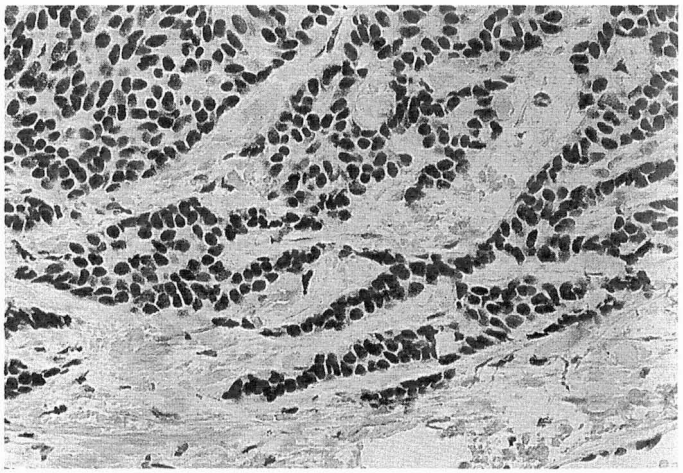

Fig. 20.98 Immunocytochemical stain for estrogen receptors in invasive breast carcinoma. The strong nuclear positivity in tumor cells is shown against a negative cytoplasmic and stromal background.

Generally, estrogen receptor concentrations are lower (and androgen receptor concentrations are greater) in tumors of premenopausal women than in those of postmenopausal women.[834,841] Fisher et al.[830] found the presence of estrogen receptors to be significantly associated with high nuclear and low histologic grades, absence of tumor necrosis, presence of marked tumor elastosis, and older patients' age groups. Hormone receptor positivity also correlates with bcl-2 immunoreactivity[861] and absence of *p53* mutations,[828] and it correlates inversely with the presence of epidermal growth factor receptors.[843]

It should be pointed out that most breast carcinoma cells also have receptors for androgens, and that these may be found in the absence of estrogen and progesterone receptors.[825] As a matter of fact, they seem to be more common in estrogen receptor-negative tumors.[820a]

HER2/*neu*

HER2/*neu* (c-*erb*B-2) is an oncogene that encodes a transmembrane glycoprotein with tyrosine kinase activity known as p185, which belongs to the family of epidermal growth factor receptors.[848,853] Its overexpression can be measured by immunohistochemistry or FISH (or its chromogenic equivalent),[854] and a good correlation exists between these methods[847,850,852] (Fig. 20.99). A heated controversy has been generated in recent years regarding the relative merits of the two methods, fueled by the availability of trastuzumab (Herceptin) as a therapeutic agent. Most workers in the field have concluded that the best approach from the point of view of cost effectiveness is to start with the immunohistochemical procedure, which is graded according to the scheme in Table 20.2.

If the results are either 3+ or 0, the determination can safely stop there, since the correlation with gene overexpression or lack of it, respectively, as measured by FISH, is nearly 100%. If the immunotest gives instead a result of 1+ or 2+, the performance of FISH is recommended.

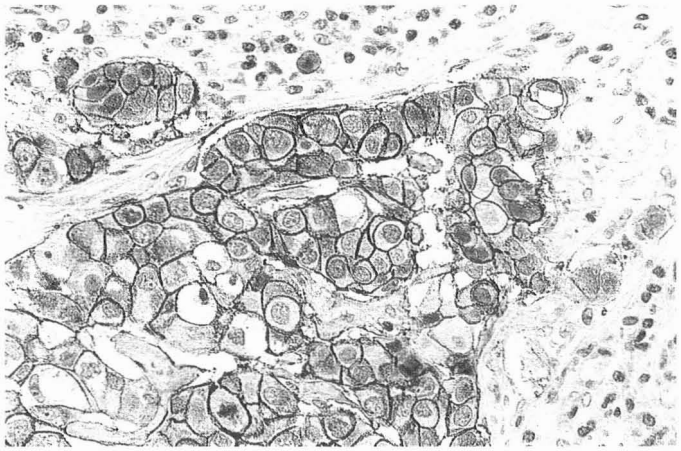

Fig. 20.99 Strong (3+) membrane immunoreactivity for HER2/*neu* in high-grade breast carcinoma.

Overexpression of HER2/*neu* by either technique is a very good predictor of response to Herceptin, but not a very good predictor of response to chemotherapy or overall survival (see p. 1826).

In terms of relationship with tumor types, HER2/*neu* overexpression is found in nearly all cases of high-grade (comedo-type) DCIS, in 20% to 30% of invasive ductal carcinomas, and in a smaller percentage of invasive lobular carcinomas.[845,846,849,851]

Spread and metastases

Breast carcinoma spreads by direct invasion, by the lymphatic route, and by the blood vessel route.[888] Some of these metastases are already present at the time of diagnosis, and others become manifest clinically months, years, or decades after the initial therapy.[857]

Table 20.2 Grading of the immunohistochemical staining for HER2/*neu* overexpression

Staining pattern	Score	HER2/*neu* protein overexpression assessment
No staining is observed or membrane staining is observed in less than 10% of the tumor cells	0	Negative
A faint/barely perceptible membrane staining is detected in more than 10% of the tumor cells. The cells are only stained in part of their membrane	1+	Negative
A weak to moderate complete membrane staining is observed in more than 10% of the tumor cells	2+	Weakly positive
A strong complete membrane staining is observed in more than 10% of the tumor cells	3+	Strongly positive