Breast Cancer Management

The Experience of the Combined Breast Clinic, St George's Hospital / The Royal Marsden Hospital

Edited by

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Preface

Over a period of fifteen years a group of us, working together at the Royal Marsden Hospital, Surrey, have developed a combined approach to the management of cancer of the breast. Each in his own speciality has had something to offer; all have not always appreciated the advances in fields other than their own.

In writing this book we have all tried to paint our own individualistic impressions based on our own experience. We have done this in an effort to help each other and perhaps help our colleagues who have found this a perplexing and saddening field of medical and surgical endeavour.

In outlining our experience, we recognize that our views may be controversial: similarly, we realize that only a part of the subject can be covered in a book such as this. However, we hope to have adequately described diagnostic methods, both for primary and metastatic disease. We have devoted a large part of the book to therapy: surgical, radiotherapeutic, hormonal and chemotherapeutic methods are all adequately covered, and we have attempted to introduce some investigative approaches that may prove valuable in years to come.

We are convinced of the importance of the techniques of early diagnosis which depend so much on the skill of the diagnostician. We appreciate that there are few such as Peter Trott and John Williams, prepared to study the cytology and radiology of breast cancer with such care. Chemotherapy, whether adjuvant or for advanced disease, has been in the news for a decade. Charles Coombes, Ian Smith and Trevor Powles have many sobering thoughts on the role of this form of therapy which require careful evaluation. The factor of greatest importance seems to be the selection of patients who might benefit from such treatment.

Hormone therapy, now reasserting its rightful place in the manage-

ment of breast cancer, is certainly rationalized by the use of the steroid receptor measurements. Hopefully, such measurements, together with new forms of endocrine therapy, may enable real progress to be made.

Surgery has advanced but little. Most agree that radical surgery, though important in concept, has failed to improve survival. Such surgery has been overshadowed by cosmesis, but cosmetic surgery, with or without the use of implants, is still a matter of grave controversy. One factor that has emerged has been the psychological discomfort suffered by women following surgery. A specialist nurse can provide great comfort for these patients.

Radiotherapy, under the meticulous care of Hubert Ford, has in our opinion justified its position both in preventing local recurrence following surgery and in palliating patients with advanced disease. Our own results speak for themselves. Yet the technique in use would still appear to be evolving and urgently requires further study.

However, these studies have led to exciting new developments in tumour biology that may soon have application in detection and therapy. We hope that over the next decade, scientists will provide us with some more suitable tools to combat this disease.

Of one thing we are totally convinced: this is not a disease for the occasional practitioner or amateur. It is time that conditions such as this were treated wholely in combined units comprising surgeon, radiotherapist and physician with the support of pathologists, radiologists and clinical scientist ever present. There have been advances in this disease, but only by united efforts.

This book should stimulate controversy; if not it has failed in one of its primary concepts. The conclusions are our own personal views based on the facts available to us.

January 1981 Jean-Claude Gazet

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1. Diagnosis of Primary Breast Cancer

P. A. TROTT and J. M. THOMAS

I. INTRODUCTION

In recent years there has been a radical change in the attitude towards the diagnosis of primary breast cancer. This is partly a result of the general willingness of patients nowadays to participate in the discussion of their illness and to be consulted on the methods of treatment once a diagnosis has been made and partly the result of improvements in the diagnostician's armamentarium. Formerly, clinical examination in outpatients in which a lump suspected of being cancer was palpated, was followed by urgent admission for excision biopsy and diagnosis by rapid histopathological "frozen" section while the patient remained anaesthetized. If cancer was diagnosed the operation was continued and radical or simple mastectomy usually with axillary dissection performed. Thus from the patient's point of view a period of extreme anxiety existed between the time of outpatient examination and recovery from the operation when she was uncertain whether she would have the small scar from the excision of a lump or the mutilation of mastectomy. From the clinician's point of view the preoperative staging of the extent of the cancer was dependent solely on physical examination which had a variable accuracy depending on the experience of the examiner.

The Royal Marsden Hospital and other centres with special interest in breast cancer have now abandoned total reliance on diagnosis at the time of operation as a result of the introduction of better-quality mammography and needle aspiration cytology. This has been called

the sequential approach to the diagnosis of breast cancer, the object being to differentiate between cancer and benign disease.

II. MAMMOGRAPHY (OR XEROMAMMOGRAPHY)

Important differences in the images of benign and malignant breast tumours are described and have recently been reviewed by Starer (1975). The images of benign and malignant tumours may differ in density, shape, the nature of the tumour border versus surrounding tissues, the presence and pattern of calcification, and finally the relative size of the image compared to that of the palpable tumour. Nevertheless, there are difficulties in image interpretation resulting in false-negative and false-positive interpretations. Burns (1978) reported the incidence of false-negative interpretation as 5% in a group of patients subsequently proven to have breast cancer. Among this 5% of patients, diagnosis was consequently delayed in 7% for a mean interval of 45 weeks. More alarmingly, Lesnick (1977) has reported an incidence of false-negative interpretation of 63% in patients with breast cancer with delay in treatment in half of these. In our own series (Thomas *et al.*, 1978) the incidence of false-negative interpretations is 19% and that of false-positive interpretations 14%. Therefore, in those patients with breast cancer and a "normal" mammogram, the patient and clinician may be wrongly reassured by the false-negative interpretation resulting in delay in diagnosis. A false-positive interpretation, on the other hand, may be less dangerous because although admission to hospital may be accelerated and although the patient may be unnecessarily investigated for metastatic disease, the nature of the error will be recognized at the time of excision and frozen-section histopathology and before any ablative surgery is performed. Therefore, useful as mammography may be in the detection of non-palpable carcinoma of the breast, a palpable mass is still an indication for urgent biopsy irrespective of its mammographic interpretation.

Not only are patients and clinicians frequently misinformed about the benefits of mammography, they are often unaware of its risks. It is known that the female breast is sensitive to radiation carcinogenesis and that it is more susceptible even than bone marrow, lung or thyroid gland (Gregg, 1977; Bailar, 1978). It was therefore reasonable to express concern about the wisdom of exposing large

numbers of young women to even small doses of irradiation on a routine and recurring basis (Bailar and Simon, 1977). A small risk of radiation carcinogenesis may be acceptable if mammography is responsible for detecting breast cancer in a large number of patients, but even the smallest risk is unacceptable if the examination does not contribute substantially to the control of breast cancer mortality in young women. Therefore it has been suggested that routine mammographic screening should not be performed on women under 50 years of age (Breslow *et al.*, 1977).

The main application of mammography should therefore be seen as a screening method for the detection of non-palpable breast cancer in asymptomatic women over the age of 50 years (Strax, 1973). Detection of suspicious but non-palpable lesions will result in localization problems for the surgeon and this can be overcome by pre-biopsy mammographic needle localization (McLelland, 1978). To confirm that this method of pre-biopsy localization has been accurate, it is essential to X-ray the biopsy specimen to confirm the presence of microcalcification seen on the original mammogram.

It has recently been suggested that mammographic parenchymal patterns may indicate whether or not a patient is at risk of developing breast cancer (Wolfe, 1967, 1969, 1976). Patients with mainly fatty breasts and an unexaggerated ductal pattern are at least risk whereas a prominent ductal pattern appears to have a definite relationship to the development of breast cancer. Further evaluation of this observation may define a group of women who are at greater risk and who should be very closly observed.

III. ASPIRATION CYTOLOGY

A. Needle Aspiration

The fundamental difference between needle biopsy and needle aspiration is the thickness of the bore of the needle. The biopsy needle, of which the "Trucut" variety made by Travenol is perhaps the best known, is 14 gauge in internal diameter and the needle has a cutting edge which cuts out a thread of tissue which is processed and embedded

in paraffin wax and sections cut for histopathological diagnosis. The biopsy procedure in our experience is very traumatic for the patient and requires local anaesthetic as well as a "nick" of the skin with a scalpel blade. Unless the tumour is large and easily felt, accurate biopsy is difficult when local anaesthetic has infiltrated the skin which distorts the feel of the underlying breast. In addition it can be a very forceful procedure for the patient and often results in profuse haemorrhage requiring plaster.

Needle aspiration, however, is certainly less distressing for the patient and, with practice, equally effective for tumour diagnosis. The purpose of the technique is to aspirate a blob of tumour juice that can be smeared on to a slide and stained. The recommended procedure in this hospital is to use a 10 ml syringe and a 21 guage (green top) or 22 guage (blue top) hypodermic needle which has a dividing and not a cutting edge. The tumour is fixed between the left index finger and thumb in a right-handed person and the needle inserted into the centre of the tissue, having first drawn about 2 ml of air into the syringe barrel. The texture of the tumour can be assessed during needling and if the tumour is a cyst fluid will be drawn up into the syringe when the plunger is withdrawn.

When needling solid tumours it is important to put the needle tip into the middle of the tumour and then aspirate with much force (usually a negative pressure of 6-8 ml in the syringe barrel) while moving the tip of the needle about, sampling different areas of the tumour. It is most important at this stage to allow the pressures to equal out before withdrawing the needle through the skin, otherwise the carefully aspirated material will be forced into the syringe by the rapid intake of air and will be inaccessible within the barrel of the syringe. The small volume of air drawn into the syringe before needling is now used to expirate the material sucked out of the tumour on to glass slides. Despite precautions, aspirated material sometimes sticks to the inside of the syringe and rinsing the syringe out in a 1 IU/ml concentration of heparin in normal saline to leave a "wet" surface inside the syringe, a technique recommended by Duguid *et al.* (1979), will prevent this. The blob of tissue on the slide is smeared immediately in a similar way to a blood film or marrow aspirate and the cells air dried and stained with a Romanowsky stain such as May Grunwald Giemsa, or wet fixed in spirit and stained with the Papanicolaou modification of the haematoxylin and eosin stain familiar

to histopathologists. Ideally both staining techniques should be used as the different appearances complement each other but it is important to remember that the smear earmarked for wet fixing should be thicker than the one left to dry and it should be fixed immediately either with a spray or total immersion in spirit.

B. Cell Appearances

The appearances of the cells range from infrequent clusters and single small cells that are found in fibrotic benign mammary dysplastic lesions to numerous loosely cohesive large cells with pleomorphic nuclei and irregular chromatin patterns seen in carcinomas (see Figs 1 and 2). Between these extremes are a variety of appearances in which the diagnostic criteria may be difficult to apply. In benign disease a variety of cell types can be identified including foam cells that indicate a cystic component, apocrine cells and small bare oval nuclei usually not more than 12 μm in maximum diameter that often cling together in pairs (Fig. 3). These are probably myoepithelial cell nuclei because they are easily differentiated from the large cuboidal cells with quite a lot of cytoplasm that are found in clusters. The identification of these myoepithelial cells and cuboidal cells indicates an epithelial double cell layer (Fig. 4) and therefore benignity. Fibroadenomas produce very cellular aspirates and the identification of myoepithelial cell pairs between the clusters of larger cells that may appear hyperplastic and even contain mitotic figures, is the clue to the correct diagnosis. The misinterpretation of cells from fibroadenomas which mimic carcinomas is a trap that can snare the unwary. The aspirates from some carcinomas contain small cells that are often less than 15 μm in diameter. These are commonly seen in postmenopausal women and may correspond to infiltrating lobular carcinoma diagnosed by the histopathologist although not all cases will show this appearance on histopathological examination. These cases are easily overlooked unless the cytopathologist is aware of the possibility of the diagnosis because the cell nuclei are small and are unobtrusive even on high power microscopy. Two observations are crucial for this diagnosis: first, the way the cells have separated from each other when spread on the slide and, secondly, the absence of the tell tale pairs of myoepithelial cell nuclei. The diagnosis is supported at low power microscopy when the loose patterns without cell clusters are recognized.

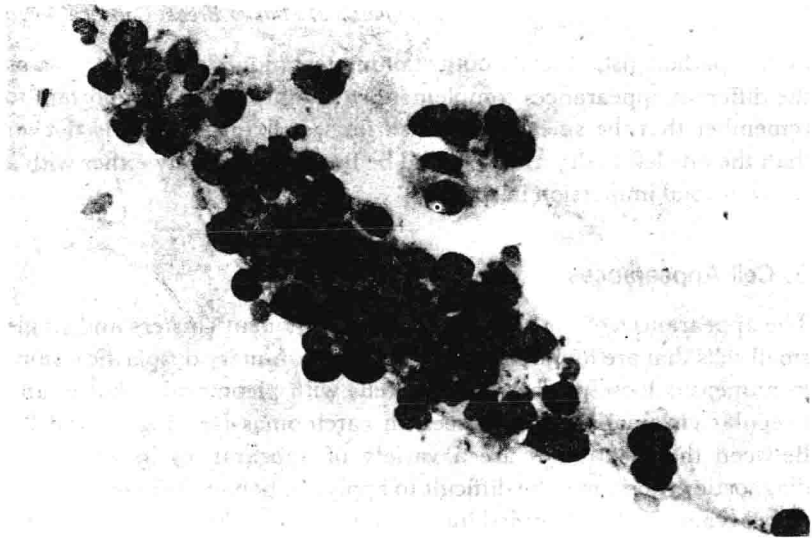

Fig. 1 Cluster of benign duct epithelial cells in which the even appearance of the nuclei and small size can be seen.

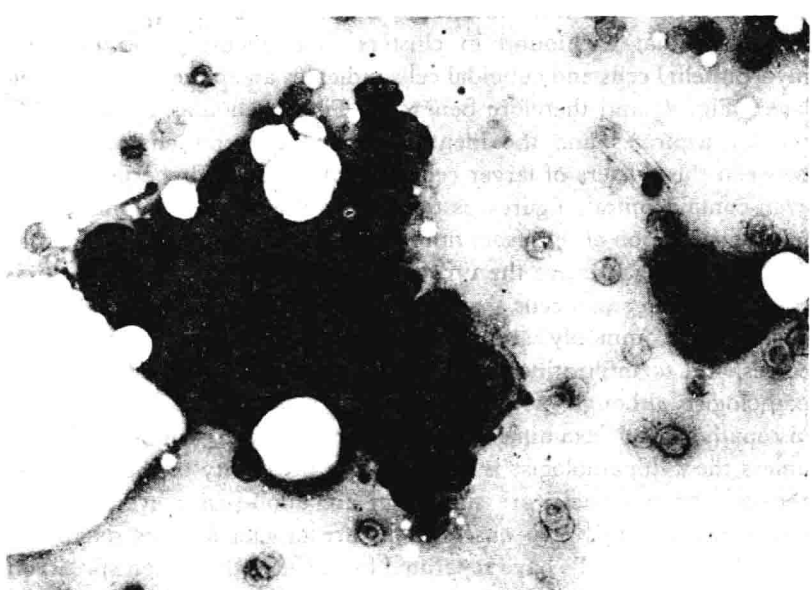

Fig. 2 Group of carcinoma cells photographed at the same magnification as Fig. 1. The marked increase in size of the nucleus and the variation in appearance and staining consistency indicates carcinoma.

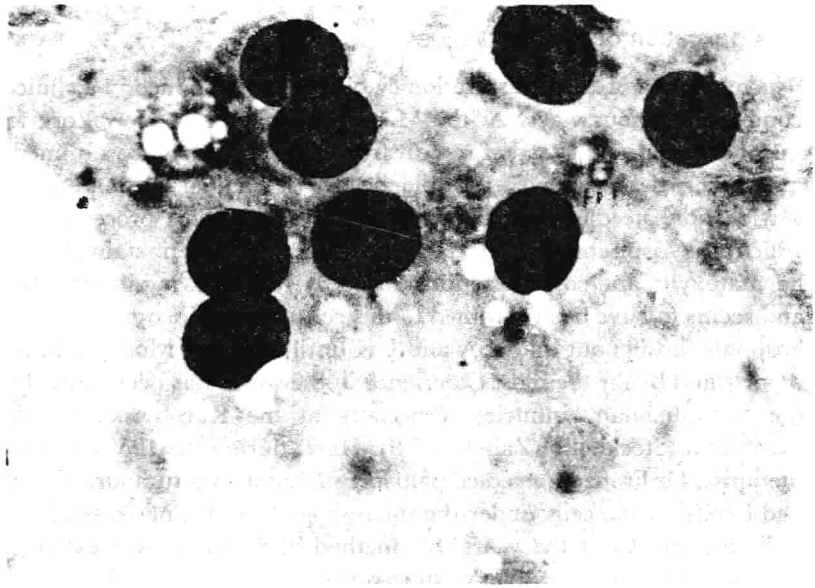

Fig. 3 Myoepithelial cell nuclei photographed at high magnification (compare size of nuclei with red blood cells). The nuclei tend to group in pairs.

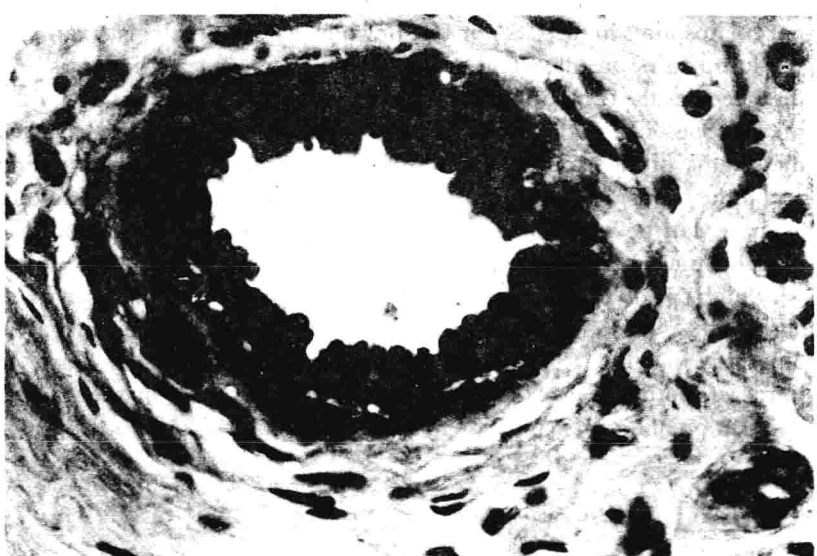

Fig. 4 Histological sections of a small duct showing a double layer of epithelial cells. The myoepithelium is the deeper layer and is evidence of benign disease.

C. Application of the Technique

The technique of needle aspiration cytology can be applied in a clinical context in various ways. At the Memorial Hospital in New York for instance it is used instead of rapid "frozen" section diagnosis immediately before definitive surgery while the patient is under the anaesthetic; a wide bore needle is used (Rosen *et al.*, 1972). This procedure, in which the aspirated material is air dried and then stained with haematoxylin and eosin, was introduced by James Ewing in the 1920s and seems to have been confined to this centre and not copied by other hospitals throughout the USA and UK until recently. Most published reports and by far the most experience in the world has been gained in the Scandinavian countries, especially at the Karolynska Cancer Institute in Stockholm (Zaijek, 1979). Here, during the 1950s a radiotherapist, Dr Franzen, needled palpable subcutaneous tumours himself and looked at the cells under the microscope from his patients having radiotherapy. Over the years this method of diagnosis was extended and expanded and a cytology clinic was established which had a full-time staff of pathologists, technicians and nurses and to which patients were referred by clinicians including general practitioners. In this way a hospital department has developed in Scandinavia having no counterpart in hospitals in the USA or UK in which a cytopathologist examines the lump to be needled and so makes his own clinical diagnosis and then needles the tumour and examines the aspirated material under the microscope. The pathologists in these centres are better able to assess the quality of the aspirate as a result of their own clinical examination and if they consider the aspirated material is not representative another aspirate can be performed. The needle aspiration technique and the microscopic criteria of malignancy have been refined so that there is a very high specificity, i.e. no falsely positive reports and a sensitivity of about 90%, although since 1974 Zaijek has given a falsely negative diagnosis in only 1·8% of 226 carcinomas. The Fondation Curie in Paris is another centre that also has great experience in the clinical application of breast aspiration cytology (Zajdela *et al.*, 1975).

IV. ROYAL MARSDEN EXPERIENCE

Three studies have been carried out at the Royal Marsden Hospital in recent years to assess the various procedures used in primary diagnosis.