CHALLENGES IN

Breast Cancer
CHALLENGES IN

Breast Cancer

EDITED BY

Ian S. Fentiman MD, FRCS
Professor of Surgical Oncology
Guy’s Hospital
London

Blackwell Science
Contents

List of contributors, vii

Preface, x

Part 1: Biology
1 J.S. VAIDYA AND M. BAUM: The enigma of breast cancer metastasis, 3
2 D.Y. WANG: The uncertain role of steroid hormones in determining breast cancer risk, 18
3 P. BOYLE: Does alcohol consumption increase the risk of breast cancer? 35
5 F. LALLOO, D.G.R. EVANS AND A. HOWELL: Familial breast cancer clinics—good value or waste of resources? 56

Part 2: Diagnosis
6 R.M. RAINSUBY: Why do we need breast surgery specialists? 75
7 I.O. ELLIS, S.E. PINDER, A.H.S. LEE AND C.W. ELSTON: The role of cytology and needle core biopsy in nonoperative diagnosis of breast cancer, 92

Part 3: Initial Treatment Problems
8 M.J. SILVERSTEIN: Ductal carcinoma in situ of the breast—can we tailor treatment to pathological findings? 107
vi CONTENTS

9 I.S. FENTIMAN: Should breast surgery be performed in the luteal phase for premenopausal patients? 129

10 A. RECHT: Early breast cancer—when can radiotherapy be omitted? 139

11 R.E. MANSEL AND R.A. DAOUD: Early breast cancer—how should the extent of axillary surgery be determined? 155

12 I.E. SMITH AND R.H. DE BOER: Primary chemotherapy in operable breast cancer—is mastectomy a redundant operation? 169

13 M.S. AAPRO: Breast cancer in the elderly: is it safe to be less aggressive in treatment? 186

14 W.J.L. JACK AND U. CHETTY: Follow-up of breast cancer patients, 196

Part 4: Systemic Therapy

15 F. CHOMY, L. MAURIAC AND J-M. DILHUYDY: Timing of adjuvant chemotherapy in women undergoing breast-conserving surgery, 205

16 R.D. RUBENS: Taxoids—cost and benefit in the treatment of advanced breast cancer, 213

17 C. SAUNDERS: Is it safe to give HRT to women who have been diagnosed with breast cancer? 221

18 V.C. JORDAN: Is there a better first-line endocrine adjuvant treatment than tamoxifen? The path of Professor Paul Ehrlich revisited, 234

19 R.D. RUBENS: What is the preferred second-line endocrine treatment in metastatic breast cancer? 253

Index, 261
List of contributors

EDITOR

I.S. Fentiman MD, FRCS, Professor of Surgical Oncology, Guy’s Hospital, London
SE1 9RT, UK

CONTRIBUTORS

M.S. Aapro MD, Director, Institut Multidisciplinaire d’Oncologie, Clinique de
Genolier, Route du Muids 1, CH-1245 Genolier, Switzerland

M. Baum ChM, FRCS, FRCR, Professor of Surgery, Department of Surgery, Royal Free
and University College Medical School, University College London, 67–73 Riding
House Street, London W1P 7LD, UK

N.F. Boyd MD, FRCPC, Head, Division of Epidemiology and Statistics, Ontario
Cancer Institute, 610 University Avenue, Toronto, Ontario, Canada M5G 2M9

P. Boyle, Division of Epidemiology and Biostatistics, European Institute of Oncology,
Via Ripamonti 435, 20141 Milan, Italy

J.W. Byng PhD, Post-Doctoral Fellow, Imaging Research, Sunnybrook Health Science
Centre, Toronto, Ontario, Canada

U. Chetty FRCS, FRCR, Director, Edinburgh Breast Unit, Western General Hospital,
Edinburgh EH4 2XU, UK

F. Chomy MD, Medical Oncologist, Department of Medicine, Institut Bergonié, 180
rue de Saint-Genès, 33076 Bordeaux, France

R.A. Daoud RAMC, MBBCh (Cairo), FRCS(Eng, Glas), Specialist Registrar, Breast
Unit, University Hospital of Wales, Cardiff, UK

R.H. de Boer MBBS, FRACP, Research Fellow, Section of Medicine, Institute of Cancer
Research and the Breast Unit, Royal Marsden Hospital, Fulham Road, London SW3
6JJ, UK
viii  LIST OF CONTRIBUTORS

J-M. Dilhuydy MD, Radiotherapist, Department of Radiotherapy, Institut Bergonié, 180 rue de Saint-Genès, 33076 Bordeaux, France

I.O. Ellis MB, BS, FRCPath, Department of Histopathology, Nottingham City Hospital NHS Trust, Hucknall Road, Nottingham NG5 1PB, UK

C.W. Elston MD, FRCPath, Department of Histopathology, Nottingham City Hospital NHS Trust, Hucknall Road, Nottingham NG5 1PB, UK

D.G.R. Evans MD, FRCP, Consultant in Clinical Genetics, Department of Clinical Genetics, St Mary’s Hospital, Hathersage Rd, Manchester M13 0JH, UK

C. Greenberg BASc, Research Associate, Division of Epidemiology and Statistics, Ontario Cancer Institute, 610 University Avenue, Toronto, Ontario, Canada M5G 2M9

A. Howell MD, FRCP, Professor of Medical Oncology, Christie Hospital, Withinslow Road, Withington, Manchester M20 4BX, UK

W.J.L. Jack BSc, MB ChB, DMRT, Senior Clinical Research Fellow, Department of Clinical Oncology and Edinburgh Breast Unit, Western General Hospital, Edinburgh EH4 2XU, UK

V.C. Jordan PhD, DSc, FRSC, Professor of Cancer Pharmacology; Director, Lynn Sage Breast Cancer Research Program, The Robert H. Lurie Comprehensive Cancer Center, Northwestern University Medical School, Olson Pavilion, 825 East Chicago Avenue, Chicago, Illinois 60611, USA

F. Lalloo MD, MRCP, SpR in Clinical Genetics, Department of Clinical Genetics, St Mary’s Hospital, Hathersage Rd, Manchester M13 0JH

A.H.S. Lee MB, BChir, MRCPath, Department of Histopathology, Nottingham City Hospital NHS Trust, Hucknall Road, Nottingham NG5 1PB, UK

G.A. Lockwood MMATH, Research Associate, Division of Epidemiology and Statistics, Ontario Cancer Institute, 610 University Avenue, Toronto, Ontario, Canada M5G 2M9

R.E. Mansel MBMS (London), FRCS (Eng), Professor of Surgery, University Hospital of Wales, Cardiff, UK

L.J. Martin MSc, Research Associate, Division of Epidemiology and Statistics, Ontario Cancer Institute, 610 University Avenue, Toronto, Ontario, Canada M5G 2M9

L. Mauriac MD, Medical Oncologist, Department of Medicine, Institut Bergonié, 180 rue de Saint-Genès, 33076 Bordeaux, France
S.E. Pinder MB, ChB, MRCPath, Department of Histopathology, Nottingham City Hospital NHS Trust, Hucknall Road, Nottingham NG5 1PB, UK

R.M. Rainsbury BSc, MS, FRCS, Director of Breast Unit, Department of Surgery, Royal Hampshire County Hospital, Winchester SO22 5DG, UK; Breast Tutor, Raven Department of Education, Royal College of Surgeons of England, London WC2A 3PN, UK

A. Recht MD, Director of Clinical Investigations, Joint Center for Radiation Therapy; Associate Professor, Department of Radiation Oncology, Harvard Medical School; and Senior Radiation Oncologist, Beth Israel Deaconess Medical Center; Boston, Massachusetts, USA

R.D. Rubens MD, FRCP, Professor of Clinical Oncology, Guy’s Hospital, London, UK

C. Saunders MB BS, FRCS, Senior Lecturer, Department of Surgery, Royal Free and University College Medical School, University College London, 67–73 Riding House Street, London W1P 7LD, UK

M.J. Silverstein MD, Professor of Surgery, The University of Southern California School of Medicine; Director, Harold E. and Henrietta C. Lee Breast Center, USC/Norris Comprehensive Cancer Center, Los Angeles, California 90033-0800, USA

I.E. Smith MD, FRCP, FRCPE, Head of Section of Medicine, Institute of Cancer Research and the Breast Unit, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK

D.L. Tritchler DSc, Senior Scientist, Division of Epidemiology and Statistics, Ontario Cancer Institute, 610 University Avenue, Toronto, Ontario, Canada M5G 2M9

J.S. Vaidya FRCS, MS, DNB, Honorary Lecturer, Department of Surgery, Royal Free and University College Medical School, University College London, 67–73 Riding House Street, London W1P 7LD, UK

D.Y. Wang BSc, MSc, PhD, Honorary Principal Research Fellow, Endocrinology & Metabolic Medicine, Imperial College School of Medicine, St Mary’s Hospital, Praed Street, London W2 1NY, UK

M.J. Yaffe PhD, Senior Scientist, Imaging Research, Sunnybrook Health Science Centre, Toronto, Ontario, Canada
Having been offered the chance to edit this book, I was very pleased to be able to ask colleagues from around the world to deal critically with a challenge within their field of expertise and provide personal but reasoned answers. The almost invariable enthusiasm of their responses was most heartening and I hope that this is apparent in the diverse chapters dealing with basic biology, epidemiology, treatment and follow-up.

In such a book, there will inevitably be important areas which have not been covered, for which no apology will be made. Possibly, future editions will address new challenges. The disparate opinions expressed are indicative of the excitement of research in breast cancer, together with the variety of interpretations possible with such an extensive body of data. If the book succeeds in provoking thought and stimulating new studies, it will have been worthwhile.

Ian Fentiman
April 1999
Part 1: Biology
The changing models of breast cancer and its spread

Throughout the history of medicine mankind has demonstrated extraordinary feats of imagination in elaborating hypothetical models to explain the nature of disease. These models then suggest therapeutic strategies to influence the natural history of these processes. Until the early seventeenth century in western medicine, and to this very day in classical Chinese medicine, these models have been largely metaphysical [1]. However, some of these systems, especially the Indian system of medicine, Ayurveda, were based on the principle of a dynamic balance between three principles: combustion/energy production/anabolism (Pitta), transport/communication (Vata) and excretion/catabolism (Kapha). Disease was supposed to be a manifestation of the disturbance of this balance and the doctor’s duty was to maintain and restore this balance [2]. In the last century or so models of disease progressed from the mechanical to the biological and more recently to the mathematical. The change of allegiance from one model to another has been likened to a Kuhnian revolution or a paradigm shift [3]. The two most famous changes in the history of medicine were the overthrowing of the Gallenic doctrine by William Harvey’s description of the circulation of the blood and the replacement of the miasma theory of infection by the bacterial theory of infection. The latter ultimately led to the success of antimicrobial therapy.

Breast cancer, an enigmatic disease with an unpredictable natural history, has been a ‘fertile soil’ for the development of hypothetical models each with their therapeutic consequence. Until the discovery of the cellular nature of cancer, the disease was managed according to Gallenic principles, the disease being visualized as an excess of melancholia (black bile) that coagulated within the breast [4]. Ridding the body of this excess of black bile involved venesection, purgation, cupping, leaching, enemas and bizarre diets (many ‘alternative’ treatments of breast cancer to this day are in fact a form of neo-gallenism).

In the mid-nineteenth century the humoral theory of breast cancer was overturned by a mechanistic model. This model described the disease as a
phenomenon arising locally within the breast and then spreading centrifugally along lymphatics to be arrested in the first echelon of lymph nodes, which acted as a barrier to onward spread by their innate filtering capacity. A second echelon of lymph nodes existed like the ‘casement walls of a medieval town protecting the citadel at its centre’. The therapeutic consequences of such a belief was the development of the Halsted radical mastectomy, almost exactly 100 years ago [5].

William Halsted operated at a time when the triumph of mechanistic principles was at its peak. The common man had begun enjoying the fruits of the Industrial Revolution. However, at the more fundamental level, it was at this time that the limits of the Newtonian laws of nature in the physical sciences were being realized by Einstein and Hiensenburgh. Biological and medical sciences, on the other hand, were still considered too different from the physical sciences to be affected by these changes. Naturally, Halsted’s ‘complete operation’ was based on straightforward and logical concepts about tumour biology: that the tumour spreads centrifugally in the breast to the surrounding lymphatics and lymph nodes and thence to the rest of the body. His classical operation included en bloc dissection of the breast and surrounding tissue including the lymphatic drainage sites [6]:

The suspected tissues should be removed in one piece (1) lest the wound become infected by the division of tissue invaded by the disease or by lymphatic vessels containing cancer cells, and (2) because shreds or pieces of cancerous tissue might readily be overlooked in a piecemeal extirpation.

His surgical expertise was remarkable, ‘... the operation, as we perform it, is literally an almost bloodless one ...’ and for the first time, breast cancer seemed curable. His recurrence rates (6% local + 14% regional) at 3 years of follow-up were very low, compared to the other series at that time (56–82%). Clearly he believed that ‘we are encouraged to hope for a much brighter, if not very bright, future for operations for cancer of the breast’ and titled his paper ‘The Results of Operations for the Cure of Cancer of the Breast’. Halsted’s pioneering work in breast cancer served as a model for many other solid cancers and his principles are still successful in cancers such as squamous carcinomas of the head and neck, the commando operation, and cervix, Wertheim’s operation.

Unfortunately, only 23% of patients treated by Halsted survived 10 years [7]. The first attempted solution to this was even more radical surgery. Internal mammary lymph nodes that received about 25% of the lymphatic drainage of the breast were not removed in the ‘complete operation’. Nonrandomized studies indicated that more radical operations improved survival [8]. However, in randomized trials, no benefit could be demonstrated [9,10]. Even when the tumour seemed to have been completely ‘removed with its roots’,
the patients still developed distant metastases and succumbed: 30% of node-negative and 75% of node-positive patients eventually succumbed to breast cancer when they were treated by radical surgery alone [11].

Prompted by the failures of radical operations to cure patients of breast cancer, Fisher and Gebhardt [12] postulated that cancer spreads via the blood stream even before its clinical detection and possibly during tumour manipulation during surgery, with the outcome determined by the biology of tumour–host interactions. Based on this concept of ‘biological predeterminism’, they postulated that (i) the extent of local treatment would not affect survival; and (ii) systemic treatment of even seemingly localized tumours would be beneficial and may offer a chance of cure. Several pioneers in the field set up randomized clinical trials to test these hypotheses. Although this revolutionary hypothesis is now taken as ‘proved’, we must realize that the proof is more to the letter than in the spirit. The benefits from systemic therapy are modest—a relative risk reduction of about 25% which is about 8–10% in absolute terms. As regards the extent of local treatment, several randomized trials have tested less versus more surgery and the effect of adjuvant radiotherapy.

A recent world overview of these trials [13] concluded that more radical local treatment, surgery or adjuvant radiotherapy does not have any influence on the appearance of distant disease and overall survival. This is in spite of the increase in local recurrence rates with less radical local treatment, i.e. although postoperative radiotherapy had a substantial effect on reducing local recurrence rates, it did not improve overall survival or distant disease-free survival. At the same time, the collateral support for the hypothesis comes from the fact that the ‘early’ detection of cancer by screening has improved mortality, but only in those above 50 years of age and by only 25%.

All the above can be taken as powerful corroboration of Fisher’s theory that metastases of any importance have already occurred before the clinical or radiological detection of at least 75% of breast cancers.

**Phenomena that challenge the existing models**

**Local treatment**

Even in the world overview there is one finding that was not completely in keeping with Fisher’s doctrine of biological predeterminism. Radiotherapy does actually reduce the breast cancer-specific deaths by about 3%—only to be counterbalanced by the increased mortality from late cardiac complications in those patients with cancer in the left breast because of radiation damage to the heart. More recently, two randomized-controlled trials evaluated the value of postoperative radiotherapy after mastectomy for tumours with a
poor prognosis. The radiotherapy techniques in these two studies minimized the dose to the heart. Not surprisingly, there was a reduction in local recurrence rates, but there was also an improvement in the overall 10-year survival rates—9% [14] and 10% [15]. The most likely explanation for this large difference in survival rates could be a statistical quirk. Let us assume that radiotherapy does impart a small survival benefit. When several trials are conducted, the different magnitudes of effects seen are expected to follow a normal distribution. A sufficiently large trial would be highly likely to detect this small difference, whereas a small trial will rarely yield a positive result because of type II error. The effect in a small trial will need to be larger than the real effect (just by chance) for it to be detected at all, consequently small trials that are positive will usually be those which reveal a larger than real effect. This would also explain the initial Guy’s trials of conservative surgery, which found that radical surgery imparted a survival benefit from 56% to 63% \((P = 0.02)\) in the first series and from 44% to 57% in the second (clinically) node-negative series \((P = 0.04)\) [16].

Whatever the explanations for the magnitude of effect in these trials, it is clear that more extensive local treatment is not completely ineffective in improving survival. This could mean that local recurrence is a source of tertiary spread, although the metastases arising from the primary tumour at the point of diagnosis exert most of the prognostic influence.

**Clonality**

It is known from extensive whole-organ analysis that about 63% of patients with breast cancer harbour other occult cancers scattered in their breast [17,18]. The origin of these tumours is intriguing. In a study of 30 breast specimens, Noguchi and colleagues [19] found that three breasts harboured additional cancers. They analysed the clonality of each focus of the three multiple breast tumours by the method based on restriction fragment length polymorphism of the X-chromosome-linked phosphoglycerokinase (PGK) gene and on random inactivation of the gene. They found that the same allele of the PGK gene was inactivated consistently at each focus in every patient. They concluded that the multiple breast carcinomas are a result of intramammary spread from the primary tumour.

In 1995, Symmans and colleagues, studied DNA ploidy (image analysis), proliferation index (proliferating cell nuclear antigen-1 immunostaining) and expression of Her-2/neu oncoprotein in 36 primary tumour samples and 82 corresponding metastases and found some different results [20].

Quite unexpectedly, in all samples the primary tumour was multiclonal (usually biclonal) by DNA ploidy analysis. However, in 30 out of 34 of metastatic DNA clones the corresponding clone was identified in a primary tumour.
sample representing 25% or more of the tumour cell population. A majority DNA clone (≥ tumour cell population) existed in 60% (21 of 36) of primary tumour samples and in 70% (60 of 82) of metastases. In approximately 50% of metastases (37 of 82) an unexpected majority clone was identified (not a majority in any primary tumour sample). However, in 80% of majority metastatic clones (46 of 60) that clone was a significant primary tumour clone. Proliferation index was quite variable in primary tumour samples and in corresponding metastases. Overexpression of Her-2/neu oncoprotein in the primary tumour of seven of 10 patients also was identified in all corresponding metastases in five of seven patients and in some metastases in two of seven patients. The metastases in three Her-2/neu-negative patients were all negative. Symmans and colleagues concluded that:

1. DNA clones are stable after metastasis.
2. Clonal majorities in metastases reflect clones identified in primary tumours.
3. Different metastatic clones from an individual tumour can establish clonal majorities.
4. Neither diploid nor aneuploid cells have a metastatic advantage in breast cancer.
5. Proliferation indices are heterogeneous.
6. Overexpression of Her-2/neu is usually consistent between primary tumours and corresponding metastases.

In essence, the second study contradicts the Japanese study and suggests that the additional microscopic cancers in breast are probably not metastases from the primary tumour. Because 50% of metastases do not arise from a majority clone, clonality analysis may not be the best way to trace the origin of a tumour. Furthermore, the minority clone may be the one that metastasizes and determines prognosis, but its effect is averaged out because of various proportions of clones of differing characteristics. If the biology of metastases is not reflected by the ‘average’ biology of primary tumour, then where does that leave us with the so-called ‘rational’ selection of adjuvant systemic therapy based on the response to primary (neoadjuvant) chemotherapy?

**Adjuvant systemic therapy has only a modest effect on survival**

The development of adjuvant systemic therapeutic regimens was based on the kinetics of tumour growth and its response to chemotherapy in animal models [21]. However, the early clinical trials predicted a large benefit and were consequently underpowered to detect the modest ‘real’ benefit. Consequently, there was considerable confusion, with the positive results of some trials being contradicted by negative or equivocal results of others. The overview analysis, however, confirmed that adjuvant systemic therapy can in fact be beneficial [22]. It is the magnitude of benefit that is disappointingly
modest—an absolute benefit of a maximum of 12% in high-risk premenopausal individuals and of 2% in equivalent-risk postmenopausal individuals is much smaller than anticipated from the experimental models.

History repeats itself!

The next step taken by medical oncologists was very similar to that taken by surgeons only a few decades ago: making the therapy more aggressive. This approach was prompted by the excellent results—long-term cures—achieved in haematological malignancies. In addition, tumour cell lines showed a log-linear dose response when exposed to alkylating agents [23,24].

Peters and colleagues [25] published the first study of high-dose adjuvant chemotherapy with bone marrow rescue and found an event-free survival of 72% (95% confidence intervals 56–82%) at 2.5 years. They compared these results to three concurrent or historical trials in which the event-free survival for similarly selected patients was between 38 and 52%. Results of two randomized trials have been declared since then. The Dutch trial [26] randomized 97 women with extensive axillary lymph nodes into conventional chemotherapy or high-dose chemotherapy with peripheral stem cell support. At 4 years, there was no significant difference in survival between the two arms. The second randomized trial of 78 patients from the M.D. Anderson Cancer Center also did not show a survival difference: the 4-year overall survival rates were 68% in the standard arm versus 60% in the high-dose chemotherapy arm. Peters’ study had a 12% treatment-related mortality. There was no mortality in the latest Dutch study and details of morbidity are not reported. However, a study of CNS toxicity after high-dose chemotherapy from the same centre revealed that cognitive impairment was found in 32% of the patients so treated, compared with 17% of the patients treated with standard-dose chemotherapy and 9% of the control patients [27]. In comparison with the control patients, those receiving high-dose chemotherapy appeared to have an 8.2 times higher risk of cognitive impairment (odds ratio; 95% confidence interval (CI) = 1.8–37.7). This risk of impairment was 3.5-times higher (95% CI = 1.0–12.8) when compared with the patients who received standard-dose chemotherapy.

Both the randomized trials were not powered to detect small differences, but it is clear that the benefit of such an aggressive therapy is not going to be that big. We will know exactly how big from the larger multicentre studies, which are currently recruiting. One trial, started in 1994, and in which 10 Dutch centres are collaborating, has recruited 370 patients in its first 43 months [28]. It will continue until 880 patients are randomized and will provide a 90% power to detect a 10% survival advantage. The Intergroup trial had already recruited 900 patients by May 1997 [29]. In Europe, the Anglo-Celtic
and International Breast Cancer Trialists’ Group (IBCTG) trials are also comparing the value of conventional adjuvant chemotherapy with high-dose chemotherapy with peripheral blood stem cell rescue. All these trials should be able to report results by the end of the millenium. Whatever the results of these trials, it must be remembered that the benefit is not going to be large. In essence, to achieve a possible improvement in survival from 70% to 77%, a woman would need to take the one in three risk of cognitive impairment!

**When does a primary tumour seed its secondaries?**

If we believe that once a primary tumour gains access to the vasculature it starts seeding metastases in a linear or exponential manner, it should be expected that because a larger tumour has been in the body for a longer time, and therefore has had access to the vasculature for longer than smaller tumours, a much higher percentage of patients with larger tumours should present with metastases. This is true to some extent with regard to lymphatic metastases, i.e. there is a correlation of number of involved lymph nodes with the size of the primary tumour. However, this relationship is far from linear: there is considerable scattering around the straight/exponential line. Thus there are many small or occult tumours that have several involved lymph nodes, while many large tumours are found not to have metastasized to lymph nodes. This discrepancy becomes even more apparent when we consider distant metastases. It would be expected that the proportion of patients presenting with distant metastases would be higher for those with larger tumours as opposed to those with smaller tumours. Nevertheless, in real life a patient presenting with a primary tumour along with distant metastases is uncommon, however large the tumour. In fact, the percentages of patients that present with symptomatic metastasis is 0%, 3% and 7% in stages I, II and III of the primary tumour, respectively [30]. However, when you look at the incidence of metastases in these same groups 18 months after their primary diagnosis and therapy, there is a clear correlation of primary tumour size with the proportion of patients experiencing distant relapse. How can this be explained without challenging the linear model of breast cancer spread?

One explanation would be that although the number of metastases that are seeded by the primary tumour would be linearly related to the tumour size and biological aggressiveness, the clinical appearance of metastases is triggered only after the primary tumour has been disturbed or removed. The tumour dormancy hypothesis suggests that the micrometastases can remain dormant for long periods of time with a potential to grow in response to some trigger. Judah Folkman [31] has demonstrated that the critical balance of factors stimulating and inhibiting angiogenesis is very important in maintaining the
balance between proliferation and apoptosis. When this balance is disturbed, the metastases can grow, or of course completely disappear. One possible trigger for ‘kick-starting’ the growth of micrometastases could be the act of surgery itself. This is based on the finding that many tumours secrete anti-angiogenic factors that circulate in the body and inhibit angiogenesis in the metastases: an almost sinister evolutionary concept—as if the primary tumour keeps the micrometastases at bay so that this will keep its host alive. Another way to look at it is to consider the timing of recurrence and metastasis after primary therapy. This reveals a striking pattern that is usually expressed in terms of ‘hazards’. Hazards are calculated by dividing the number of events in a particular time frame, say 6 months, by the number of patients at risk of having those events at the start of the period. In all clinical trials it is found that the hazards for metastasis and death rise sharply at 2–3 years after the primary diagnosis and then fall to rise to a second peak at about 7–9 years [32]. It is extraordinary that this is true for any stage of the disease. The first peak occurs at the same time, whether the tumour was at stage I or stage III. It is only the amplitude of the peak that changes with stage, the later the stage the higher is the peak, but the timing of the signal is the same.

These phenomena suggest a nonlinear dynamic model for breast cancer, which, like a chaotic system, is exquisitely sensitive to events around the time of diagnosis. It might even suggest that surgery could be responsible for accelerating the clinical appearance of metastatic disease. However, a randomized trial of surgery versus no surgery to prove this would no doubt be judged unethical in the absence of systemic therapy. Nevertheless, such a model is fortuitously available in the setting of randomized trials of mammographic screening [33]. In such trials, surgery is delayed in the control group by about 18–24 months (lead-time). So, the first few years offer the comparison between no surgery in the control arm versus surgery in the screened arm. Later years offer the comparison between late surgery in the control arm versus early surgery in the screened arm. In a meta-analysis of screening trials for breast cancer, it was found that in women < 50 years, there is an early excess mortality for the first 6 years. In women above 50 there was an ultimate reduction in mortality in spite of a small excess in the first year. This indeed suggests that timing of surgery may be critical and opens up another window for therapeutic research.

Clearly a new model for breast cancer is needed that takes into account the fine dynamic balance between the tumour and the host, including various autocrine and paracrine factors which influence proliferation, apoptosis and angiogenesis (Fig. 1.1). The mathematics of complex systems or chaos could underpin the theory of this new model, and computing with neural networks could put it into practical use by better integrating all the myriad facts about prognostic factors and effects of treatment into meaningful guidelines.
New models

Recently, there have been some attempts to construct new models for the natural history of breast cancer. They all approach the problem differently, but they do share several concepts.

Schipper and colleagues [34] proposed a regulatory model for cancer. Their model has five principles and three corollaries.

Principles

1. Cancer is a process, not a morphological entity. Individual cancers, while likely to originate from single cells, are constantly adapting to the local environment.

   There is no single substance or metabolic defect that is unique to cancer. Clonality, previously considered a hallmark of cancer, is neither always demonstrated in malignancy nor restricted to it [35]. Clonality has been most convincingly demonstrated in haematological malignancies, mostly of lymphoid origin.

2. The cancer cell is largely normal, both genetically and functionally. The malignant properties are the result of a small number of genetic and/or environmental changes that have a profound effect on certain aspects of its behaviour. The three main processes of cancer, growth, invasion and metastasis, have their equivalents in normal tissues. Most cancers are diagnosed by virtue of their morphological or histochemical similarity to the tissue of origin. At the genetic level, with the exception of deletions, all necessary information is preserved, and the defective portion of DNA is small. The key processes of malignancy are genetically controlled by the under- or over-expression of normal genes and their products that normally serve essential cellular functions.

Fig. 1.1 A diagrammatic representation of the fine balance of factors acting on a metastatic focus based on the model by Judah Folkman (1995). (Taken from Baum & Benson [47], with permission of Springer-Verlag.)
The process is characterized by regulatory balance, rather than autonomy. The view that cancers are fully autonomous has changed. For example, in lymphomas, solid tumours of childhood, hormone-sensitive breast or prostate cancers, chronic myelogenous leukaemia, spontaneous cycling to the point of complete remission is not uncommon. In addition, pathological and autopsy studies have suggested that most of the occult tumours in breast and prostate cancers may never reach clinical significance [18,36,37]. It would appear that these occult tumours do have access to blood supply—then why does their presence not affect longevity? What is the regulatory fault special to the clinically apparent tumour that allows it to seed metastases?

The imbalance is potentially reversible.

Most of the faulty genetic pathways in a malignant process are potentially reversible and are actually present in a reversible form in the normal organism. An example of exploiting this potential is the differentiating treatment of acute promyelocytic leukaemia with all-trans-retinoic-acid. Another example is germ cell tumours differentiating into mature teratoma after treatment with cis-platinum-based chemotherapy. Complete remission of Mediterranean and MALT lymphomas by antibiotics demonstrates functional reversibility. The biology of Helicobacter pylori-induced lymphoma demonstrates both the induction of ‘malignancy’ by microbiologically induced T cell stimulation of vulnerable B cells, and its spontaneous reversal by removing the stimulus.

Killing strategies may be counterproductive, because they impair host response and drive the already defective regulatory process towards further aberrancy. This point has already been discussed in the preceding section.

Corollaries

1. Host response is critical, and determines long-term outcome.
2. Cancer growth rates are variable, depending on the regulatory balance.
3. Functional cure does not require a complete response.

Demicheli and colleagues [38] have also argued that a continuous growth model of breast cancer fails to corroborate the clinical data. The continuous growth model yielded tumour sizes too large to be missed at the preceding negative physical examinations, and required growth rates significantly lower than those consistent with clinical data. As mentioned before, the continuous growth model also fails to explain the biphasic recurrence pattern seen when hazards of recurrence are plotted for every year after diagnosis. Their new model is mainly based on the hypothesis of tumour dormancy and that the micrometastases do exist from the early part of the natural history of breast cancer, but remain dormant until some unknown signal stimulates...
them into fast growth. Indeed this fast growth is possible in those foci that have the angiogenic potential—present in 4–10% of primary tumour cells. The tumour cells that lodge within seeded tissues and become organized as single cells or nests containing a few cells are designated to be in the first biological state S1. Groups of cells without the angiogenic potential can grow but remain small (up to $10^5$ or $10^6$ cells), and are said to be in the biological state S2. The metastatic focus may grow quickly if (i) the subset of cells in S2 switches to an angiogenic phenotype and/or (ii) the inhibition of angiogenesis is removed. When cells get into the angiogenic phase they are designated to be in the biological state S3. The model suggests that the metastatic development of unperturbed breast cancer is a sequential evolution from S1 to S2 to S3, with stochastic transitions from one state to the next. The transition of S1 to S2 is called the Fisher effect and S2 to S3 is called the Folkman effect. This ‘orderly’ process may be perturbed by surgery or, for that matter, even chemotherapy, which increase significantly the transition probability of S1 to S2 and S2 to S3. Indeed tumour removal could stimulate S1 cells to proliferate, probably via the conversion of noncycling G0 cells and/or by removing the angiogenic inhibition that detains S2 cells in the avascular phase. This model claims to explain the early peak of hazard function for local and distant recurrences in resected cancer patients by the Fisher and Folkman effects joining to the regular metastatic development of unperturbed disease. It also correlates well with the finding of modest benefit after adjuvant chemotherapy that is limited to early events and does not increase with prolongation of duration of chemotherapy. The proposed existence of continuous transition from the S1 to S2 to S3 states, even after the completion of adjuvant systemic therapy, explains the continual response of a recurrence to the same drug (chemotherapy or hormonal therapy) that was used for adjuvant therapy. Most importantly, the model predicts that metastatic breast cancer may in fact be curable if the S3 fraction could be reduced significantly. Data supporting this comes from a study from the M.D. Anderson Cancer Center, in which those with complete response had few late failures. The median pretreatment disease-free interval was 19 months for all 1581 patients and 18 months for patients in complete remission for more than 5 years.

We have developed an alternative model of breast cancer angiogenesis [39]. It is based on the mathematics of nonlinear dynamics and suggests that breast cancer is like a complex organism existing in a state of dynamic equilibrium with the host, the equilibrium being very precarious and close to a chaotic boundary. Furthermore, the mathematics to describe the natural history of these organisms invokes nonlinear dynamics or chaos theory. Our model is the first attempt to apply the new mathematics of complexity to make predictions about the factors influencing angiogenesis that might one day provide a therapeutic window.
Central to the understanding of this model has been the pioneering work of Folkman on tumour angiogenesis [40]. As we know, solid tumours cannot grow beyond $10^6$ cells or about 1–2 mm in diameter in the absence of a blood supply [41]. The initial prevascular phase of growth is followed by a vascular phase in which tumour-induced angiogenesis is the rate-limiting step for further growth and provides malignant cells direct access to the circulation [42]. The poor prognostic indication of extensive angiogenesis quantified by microvessel density in histological sections is well recognized in a wide variety of cancers, including breast cancer [43,44]. The relationship between angiogenesis and tumour cells has been summarized by Folkman’s endothelial cell–tumour cell compartment theory [31]. In the tumour cell compartment, cells may stimulate endothelial cell proliferation by the production of tumour angiogenic factors such as beta fibroblast-derived growth factor (FGF) and vascular endothelial growth factor (VEGF). However, endothelial cells may themselves stimulate the growth of tumour cells, by producing factors such as platelet-derived growth factor (PDGF), heparin-like growth factor and interleukin-6 (IL-6). It has also been proposed that the primary tumour secretes antiangiogenic factors, and therefore removal of the primary tumour might trigger the outgrowth of occult foci into clinically apparent secondary disease. In addition to the importance of the microvasculature, we have also been able to visualize these microscopic foci as existing in a ‘soup’ of cytokines and endocrine polypeptides and steroids, with cells interacting with each other and with the surrounding stroma, with competing signals directing the cancer cells in the direction of proliferation or apoptosis. It is possible to visualize subclinical cancer as a complex structure, with its future determined by the balance of angiogenic and antiangiogenic factors, as well as factors that stimulate or inhibit epithelial proliferation and stimulate or inhibit apoptosis. Such complexity cannot be modelled by linear dynamics, or even a full understanding of the complete catalogue of genetic mutations at the cellular level, because the critical events of multiple cell-to-cell interaction requires a thorough understanding of epigenetic phenomena.

We have tried to model this complex system using the new mathematics of nonlinear dynamics. Our model, like other ‘chaotic systems’, produces beautiful fractal-like images which can be shown to be exquisitely sensitive to initial conditions (e.g. different concentrations or different gradients of the three biological variables). The three-dimensional vasculature of a tumour as simulated by these formulas is very similar to the vasculature of a breast tumour visualized using three-dimensional computerized tomography (CT) reconstruction. It is important to realize that today we have the technology to visualize the vascular architecture of breast tumours in vivo, using contrast-enhanced Doppler ultrasonography and magnetic resonance imaging (MRI). The contrast enhancement in MRI relies on tumour vascularity and vascular permeability,
as demonstrated by histopathological correlation studies [45], and hence may have greater clinical significance. The complex simulations are obtained using only three variables—the angiogenic agents being secreted by the tumour, the matrix factors and the chemotactic and haptotactic response of the endothelial cells to these stimuli. There is therefore ample scope for the addition of further complexity to the model, by incorporating more variables. Various scenarios of vascular architecture can be simulated using differing variables and adding variables like the effect of chemotherapy on tumour and endothelial cells. This type of approach may enable a more accurate means of monitoring the response to treatment. The integration of data derived from various imaging modalities, such as MRI, with histopathological tumour assessment in such a nonlinear model, might better approximate to the natural history of cancer.

The therapeutic consequences of the new models are almost self evident. The therapeutic intervention that suggests itself would be antiangiogenic, and the timing of the intervention would be preoperative, so that at the time of surgery the system is primed to protect against sudden flooding with angiogenic signals. Indeed, some of the success attributed to adjuvant tamoxifen may be a result of its antiangiogenic potential rather than its antioestrogenic function [46].

Assuming we can protect the subject from the first peak of metastatic outgrowth, we will then have to monitor her with extreme vigilance. By the time the metastases are clinically apparent it is perhaps too late, therefore monitoring the patient with tumour markers and reintroducing an antiangiogenic strategy at the first rise in tumour markers might prove successful. Better still, using modern molecular biological techniques to detect variations in the antiangiogenic milieu may provide an even greater lead-time than the use of conventional tumour markers such as CEA and CA15. In the meantime we can continue to add additional layers of complexity to the simulations of our mathematical model, to help develop alternative strategies for biological interventions to maintain the status quo. Unlike the hamster lymphoma models of the past, the new model feeds on complexity and becomes closer and closer to simulating nature in all its awesome beauty.

References

References of particular interest have been highlighted as:
* of special interest

5 Halsted WS. The results of operations for the cure of cancer of the breast performed at the Johns Hopkins


THE ENIGMA OF BREAST CANCER METASTASIS


*29 Hurd DD, Peters WP. Randomized, comparative study of high-dose (with autologous bone marrow support) versus low-dose cyclophosphamide, cisplatin and Carmustine as consolidation to adjuvant cyclophosphamide, doxorubicin, and fluorouracil for patients with operable stage II or III breast cancer involving 10 or more axillary lymph nodes (CLGB Protocol 9802). Cancer Leukemia Group B. J Natl Cancer Inst Monogr 1995; 19: 41–4.


