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Review

Does surgery unfavourably perturb the "natural history" of early breast cancer by accelerating the appearance of distant metastases?

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Abstract

This historical perspective on breast cancer tells us how and why certain therapeutic eras have reached ascendancy and then declined. Therapeutic revolutions occur after a crisis develops when there is a general recognition that clinical interventions are not producing positive results predicted by the prevailing paradigm. The attitude of pre-modern surgeons was influenced by the very real possibility of doing more harm than good by operating upon women with breast cancer. Up until Halsted, the general consensus was clearly that, unless forced by the circumstances, surgical resection should be avoided for disease much more advanced than very early stage tumours (the cacoethesis of Celsus). Twentieth century progress in antisepsis, anaesthesia, and surgery changed this point of view. The first three quarters of that century saw more and more aggressive operations performed while the last quarter century reversed this trend, with reduction of the size of breast cancer operations based largely on the teachings of Fisher. A new crisis is upon us now in that trials of early detection have resulted in unexpected disadvantages to certain subgroups and there is previously unreported structure in early hazard of relapse, clinical data that suggests the act of surgery might accelerate the appearance of distant metastases. The explanation we propose that agrees with these results, as well as physicians of antiquity, is that surgery can induce angiogenesis and proliferation of distant dormant micrometastases, especially in young patients with positive nodes.

Keywords: Surgery; Breast cancer; Metastases; Natural history

1. Introduction

In this paper, we concentrate on the natural history of breast cancer and the punctuated evolution of *conceptual models* to explain its behaviour [1–3]. From antiquity until the 18th century the subject of breast cancer was dominated by the philosophy of Aristotle and the therapeutic dogma of Galen that thought of breast cancer as an imbalance of the vital humours. The therapeutic consequence of this belief was purgation and bleeding to rid the body of a putative excess of *melancholia*. Despite this, tumour removal was a not exceptional therapeutic option (Galen himself excised "small" tumours and recommended excision through surrounding healthy tissue). However, a common belief was that a few favourable results, if any, could seldom be achieved by removal of small easily resectable lumps, while surgery was to be considered detrimental *quoad vitam* and *quoad valetudinem* for more advanced cases.

Celsus (30 BC–38 AD) established the first staging system of cancer. "First there is the cacoetheses, then

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carcinoma without ulceration, then the fungating ulcer... None of these can be removed but the cacoetheses; the rest are irritated by every method of cure. The more violent the operations the more angry they grow. Some use caustics, some burning irons, others remove the growth with the scalpel. After excision, even though a cicatrix is formed, it recurs, bringing with it the cause of death, whereas at the same time, most people, by using no violent methods to attempt the extirpation of the disease but only applying mild medications to soothe it, protract their lives, notwithstanding the disorder, to an extreme old age.'' This was relative of course to the life-expectancy in those times.

A first important change occurred in the 18th century, and was prepared by the crisis of the Galen system following new anatomy findings (Vesalius, Harvey) and the introduction of the microscopical inspection (Leeuwenhoek, Malpighi). Henry LeDran (1684–1770), a French surgeon, first challenged the dominance of the Galenic model. He stressed that cancer was a local lesion in the early stages and spread via lymphatics. LeDran observed that cure was much less likely when lymph nodes were involved. This breaking of anatomical boundaries signalled a stage unfavourable for intervention.

Velpeau (1856), a Frenchman, advocated bleeding, leeches, purgatives and emetics. He retained the Galenic ideas and used various drugs to destroy the humours. Velpeau is considered by some to be the first medical oncologist, Galenic though he was. He wrote: ''To destroy a cancerous tumor by surgical means is usually an easy matter and but little dangerous in itself; but the question arises, whether such a procedure affords a chance of radically curing the patient. This proposition remains undecided.'' He further states: ''The disease always returns after removal, and operation only accelerates its growth and fatal termination.''

James Syme (1799–1870), a Scotsman, condemned the practice of palliative procedures including purging; bleeding, the application of ointments, and limited surgery in the treatment of cancer. He stated: ''The only proceeding that deserves at all to be considered a remedy for cancer is removal of the morbid structure.'' This was a rather audacious statement considering that all of this was done without the availability of microscopic anatomy. Further, all surgery was performed without antisepsis or anaesthesia. Nitrous oxide was described in 1842 and ether was first demonstrated in 1846.

Schleiden (1838), a German, was among the first to appreciate the significance of the cell as a unit in plant structure, and Virchow, another German, considered to be the father of pathology, advanced the concept that any normal cell can become a cancer cell as a result of irritation. These concepts bolstered by microscopic examination of excised tissues led to a fuller understanding of the infiltrative and invasive nature of this disease.

Sir James Paget (1814–1899) first observed that proper seed and soil are necessary for cancer to grow and subsequently spread. He also had great respect for the limitations of surgical separation of seed from soil. Paget stated: ''We have to ask ourselves whether it is probable that the operation will add to the length or comfort of life enough to justify incurring the risk of its own consequences.'' Despite the lack of anaesthesia or asepsis, he had an operative mortality rate of only 10% in 235 cases of breast cancer. However, he believed the disease to be hopeless and stated: ''In deciding for or against removal of the cancerous breast, in any single case, we may, I think, dismiss all hope that the operation will be a final remedy for the disease. I would not say that such a thing is impossible; but it is so highly improbable that a hope of its occurring in any single case cannot be reasonably entertained.''

This pessimistic attitude was also voiced by Robert Liston (1794–1847): ''No one can now be found so rash or so cruel as to attempt the removal of the glands thus affected whether primary or secondary.''

In this pessimistic atmosphere, less rather than more surgery was considered by some to be prudent. Velpeau favoured thorough excision in preference to complete amputation. He stated: ''If the disease requires, the pectoralis muscle should not arrest us. The smallest shade of the disease must be taken away, if we are determined not to lose any chance of success. However, should there appear to be any necessity of interfering with the bones or resecting the ribs we must not deceive ourselves. The return of the disease is then inevitable and it would have been better not to have undertaken the operation at all.''

Hayes Agnew (1818–1892), of the United States, resorted to surgery solely for its moral effect. He believed that surgery actually shortened the life of the patient. He was most pessimistic and stated: ''I do not despair of carcinoma being cured somewhere in the future, but this blessed achievement will, I believe, never be wrought by the knife of the surgeon.''

A treatise by Gross of Philadelphia published in 1880 [4] provides a clear insight into the understanding of the disease in the era immediately before the developments in anaesthesia and antisepsis which allowed surgeons to attempt a radical cure of breast cancer. He describes a series of 616 cases, 70% of whom had skin infiltration on presentation which had ulcerated through in 25% of the patients. About 64% had extensive involvement of axillary nodes and 27% had obvious supraclavicular nodal involvement. Accepting that the meagre benefits of surgery seldom outweighed the risks in those days, he judged it ethical to follow the natural course of 97 cases who received nothing other than ''constitutional support''.

Gross' observations were useful for understanding the natural history of advanced local breast cancer. He describes how skin infiltration appeared an average 14

months after a tumour is first detected, ulceration appears on average 6 months after that, fixation to the chest wall after a further 2 months and invasion of the other breast if the patient lived on average 32 months after the lump first appeared. The average time for the appearance of enlarged axillary nodes was 15 months in those few cases that presented with an "empty" axilla to start with. About 25% of all these untreated cases exhibited obvious distant metastases within a year and 25% after 3 years with only 5% surviving more than 5 years.

Since then a number of different series of untreated breast cancer have been reported. For example Greenwood in 1926 [5] described a 6-year follow-up of 651 cases of untreated breast cancer with only 60 remaining alive at the end of this period. Daland in 1927 reported a series of 100 patients who were considered inoperable, unfit for surgery or who had refused the offer of surgery. The average duration of life was 40 months for the whole group, 43 months for those deemed operable at diagnosis and 29 months for those deemed inoperable [2].

The study that has attracted the most attention over the years was that of Julian Bloom published in 1968 [6]. His data came from the records of 250 women dying of breast cancer in the Middlesex Hospital Cancer ward between 1905 and 1933. Of this group, 95% died of breast cancer, but it should be noted that almost all of them presented with locally advanced or overt metastatic disease. The survival rates from the alleged onset of symptoms were 18% at 5 years, 0.8% at 15 years (remarkably, one person lived 16 years) with a mean survival of approximately two and a half years. The reasons given for withholding treatment are also worthy of note: old age or infirmity 35%, disease too advanced 30%, treatment refused 20% and early death the remainder. Together, these observations lead to the conclusion that uncontrolled breast cancer is lethal with most patients dying within a couple of years, but with many living with the disease for some years longer.

It would of course be inconceivable to suggest we study an untreated group today and the closest approximation we can find comes from a report of the Ontario cancer clinics between 1938 and 1956, just preceding the jump in breast cancer incidence in the developed world [7]. Close on 10 000 cases were analysed accounting for 40% of all new cases arising in the province of Ontario during this period. Amongst this group were 145 well-documented cases who received no treatment of any kind. Although, yet again 100 of these cases were untreated because of late stage of presentation or poor general condition, the rest were unable or unwilling to attend for treatment. A careful note was made of the date the patient first became aware of the lump from which point survival rates were computed. The 5-year survival from first recorded symptom was 35%, with a median survival of 47 months. The most surprising figure was a near 70% 5-year survival for the small group presenting with localised disease.

This then raises the inevitable question, is carcinoma of the breast inevitably a fatal disease if neglected? This question is almost impossible to answer with confidence although hinted at by anecdotal evidence. However, the best documented in the literature was reported by Steckler and Martin in 1973 [8]. They described a 38-year-old woman with histologically proven cancer who refused surgery and was then followed up for 20 years before consenting. We will never know how many of the cases we see in our daily practice carry such a favourable natural history.

2. The influence of surgery on the natural history of breast cancer

From the popularisation of the classical radical mastectomy at the very end of the 19th century [9] until about 1975 almost all patients with breast cancer, of a technically operable stage, were treated with modifications of the radical mastectomy. To those without commitment to a prior hypothesis, this allowed for new insights about the nature of the malignant process. Before considering this matter, it is worth revisiting the conceptual model that allowed the radical operation to reign supreme for 75 years.

In about 1840, Virchow described a revolutionary model of the disease building on the development of microscopy and post-mortem examinations of the cadavers of breast cancer victims [10]. He suggested that the disease started as a single focus within the breast, expanding with time and then migrating along lymphatic channels to the lymph glands in the axilla. These glands were said to act as a first-line of defence filtering out the cancer cells. Once these filters became saturated the glands themselves acted as a nidus for tertiary spread to a second- and then third-line of defence like the curtain walls around a medieval citadel. Ultimately when all defences were exhausted, the disease spread along tissue planes to the skeleton and vital organs.

So convincing were these arguments and so charismatic their chief proponent, the Halsted operation was adopted as default therapy all round the world. At this perspective we are entitled to ask to what extent did the radical operation add to the curability of the disease and what can we learn about the nature of the beast by its behaviour following such mutilating surgery? We can also add a third question concerning human nature and our unwillingness to see facts "which almost slap us in the face" ("It is now, as it was then, as it may ever be, conceptions from the past blind us to facts which almost slap us in the face" – WS Halsted 1908) [11,12].

Unfortunately, only 23% of patients treated by Halsted survived 10 years [11]. The natural response to this

failure 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', but included in the super radical operations that followed or in the extended fields of radiation after surgery.

Retrospective studies indicated that more radical operations improved survival [13]. However, in randomised trials that followed later, no benefit could be demonstrated [14,15]. Thus, 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 dying of the disease over 10 years when they were treated by radical surgery alone [16] and with no evidence of "cure" if patients were followed up for 25 years [17]. In this latter seminal study by Brinkley and Haybittle, a group of over 700 breast cancer patients, treated by radical surgery alone and followed up for 25 years, steadily continued to demonstrate an excess mortality compared with an age-matched population.

3. The biological revolution of the late 20th century

Thinking began to change with Fisher. Prompted by the failures of radical operations to cure patients of breast cancer, Fisher proposed a revolutionary hypothesis that rejected the mechanistic models of the past [18]. He postulated that cancer spreads via the blood stream even before its clinical detection, with the outcome determined by the biology of tumour–host interactions. Based on this concept of 'biological predeterminism', he predicted the following:

(A) The extent of local treatment would not affect survival; and (B) systemic treatment of even seemingly localised tumours would be beneficial and might even offer a chance of cure.

Several pioneers in the field set up randomised clinical trials to test these hypotheses culminating in a series of world overviews [19]. Although the "Fisherian" doctrine is now taken as 'proven', we must accept that the proof is more in principle rather than in cure. The benefits from systemic therapy are modest, with a relative risk reduction in breast cancer mortality of approximately 25% overall, which translates to approximately 10% in absolute terms. As regards the extent of local treatment, many randomised trials have tested less versus more surgery with or without adjuvant radiotherapy.

A recent world overview of these trials [20] concluded that more radical local treatment, surgery or adjuvant radiotherapy does not have any influence on the appearance of distant disease and overall survival with one caveat (*vide infra*). This is in spite of the increase in local recurrence rates with less radical local treatment, i.e., although radical surgery or postoperative radiotherapy had a substantial effect on reducing local recurrence rates, it did not improve overall or distant disease-free survival.

The one exception to the theory of predeterminism might be the "success" of the trials of mammographic screening [21]. From this it might be concluded that 25% of breast cancer deaths in women aged 50–69 years could be avoided if caught "early" at a sub-clinical stage. Forgetting the arguments about the scientific reliability of these studies [22], this still only accounts for approximately 12% of incident cases, i.e., failing those cases in women under 50 years or over 70 years.

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 approximately 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 randomised-controlled trials evaluated the benefit of postoperative radiotherapy after mastectomy for tumours with a poor prognosis. The radiotherapy techniques in these two studies minimised 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% [23] and 10% [24].

3.1. 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 [25]. 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 of the early trials being contradicted by negative or equivocal results of others. However, the overview analysis confirmed that adjuvant systemic therapy can in fact be beneficial [19]. 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 that anticipated from the experimental models.

The next step taken by medical oncologists was very similar in attitude to that taken by surgeons only a few decades ago, if a little does not work then try a lot! This approach was bolstered by the excellent rate of long-term cure achieved in haematological malignancies. In addition, tumour cell lines showed a log-linear dose response when exposed to alkylating agents [26,27].

Needless to say the high-dose chemotherapy with bone marrow rescue was a failure and the least said about this sorry episode in the history of breast cancer

the better, yet there may be lessons to learn from the failure of this approach.

3.2. 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. Thus, there are small or even occult tumours that have several involved lymph nodes, while many large tumours are found not to have metastasised to the axilla. 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 metastases is 0%, 3% and 7% in stages I, II and III of the primary tumour, respectively [28]. 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. (Approximately 5% for stage I and 25% for stage III.)

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 or accelerated only after the primary tumour has been disturbed or removed. This conclusion may logically derive from a consideration of the pessimistic experiences of ancient surgeons we presented in previous sections. It also is the result of very modern day science using computer simulations to analyse an unexpected bimodal hazard rate of relapse for patients treated only with surgical excision of primary breast tumours. Hazards are calculated by dividing the number of events in a particular time-frame by the number of patients at risk of having those events at the start of the period. This is an important way of looking at data because it emphasises when adverse events occur rather than just the cumulative result. Since no one lives forever, including breast cancer patients, when the increased risk for recurrence and death occur is more important than the overall risk. We show in Fig. 1 relapse data from the Milan series.

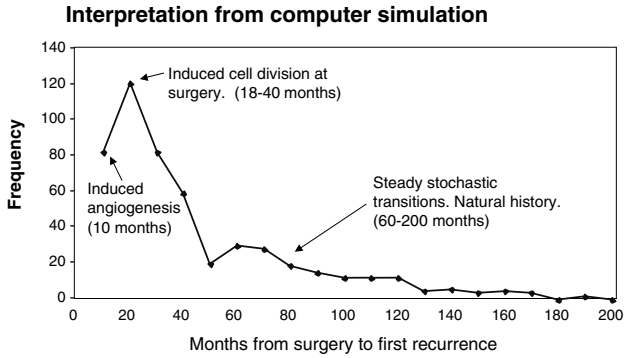

Fig. 1. These are relapse data from 1173 otherwise untreated early stage breast cancer patients with 16–20 year follow-up. There is a sharp peak at 18 months, a nadir at 50 months and a broad peak at 60 months with a long tail extending to 15–20 years. Patients with larger tumours more frequently relapse in the first peak while those with smaller tumours relapse equally in both peaks. Similar patterns to the Milan data can be identified in some but not all disease-free survival [52] and hazard of relapse [53] databases for untreated patients. Based on a computer simulation, breast cancer growth often includes periods of temporary dormancy. The second peak is the natural history of the disease. These relapses result from steady stochastic transitions from single cells (dormancy half-life of 1 year) progressing to an avascular micrometastasis (dormancy half-life of 2 years) to a growing lesion that eventually becomes detected as a relapse. The first peak is too sharp to be the result of steady stochastic transitions. Some breaking of dormancy had to occur at surgery to explain the first peak.

Naumov and colleagues [29] has observed dormant, but viable, single cells in a breast cancer animal model and Klauber-DeMore [30] has observed small dormant micrometastases and growing larger micrometastases in human breast cancer. Folkman and colleagues [31] have reported many examples of dormant micrometastases in animal models. Within the dormant micrometastases there is balance between growth and apoptosis. There are known factors that inhibit angiogenesis and other factors that stimulate angiogenesis. To maintain a dormant state, inhibiting factors dominate locally. If stimulating factors are increased or inhibiting factors are reduced, the dormant condition can no longer be maintained.

It is well documented in the Lewis-lung model that removal of the primary tumour will reduce angiogenesis inhibitors and it is known that after surgery a sharp spike in angiogenesis stimulators and growth factors occurs to aid in wound healing. Thus, it is not surprising that tumour angiogenesis and proliferation result after surgery to remove a primary tumour. Therefore, a likely trigger for 'kick-starting' the growth of micro-metastases, could be the act of surgery itself.

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 remains the same.

These phenomena suggest a non-linear dynamic model for breast cancer, which, like a chaotic system, is exquisitely sensitive to events around the time of diagnosis. It suggests that surgery could be responsible for accelerating the clinical appearance of metastatic disease. However, a randomised 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 randomised trials of mammographic screening [32].

Thus, with this new perspective we come back to discussing the trials of mammographic screening. In these trials, surgery is delayed in the control group by approximately 18–24 months (lead-time) so that 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 under the age of 50 years, there is an early *excess* mortality in the third year. In women 50 years and above, there is no year with a significant excess mortality. Since the time between relapse and death in breast cancer is approximately 2 years, it is reasonable to conclude that the timing surgical-stimulated proliferative wake up and angiogenesis triggering for premenopausal node-positive patients could account for the excess mortality in the 3rd year of the trials.

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.

4. A new model to explain the natural history of breast cancer

Taking all of this data into account we would like to develop a new model to explain the natural history of the disease which in addition to explaining the success of the Fisherian model of "biological predeterminism" also explains the clinical observations from antiquity or that fail to fit neatly into the contemporary early detection paradigm.

The conclusion that more surgery is better is similar to the conclusion that earlier detection/earlier therapy is better. However, this linear thinking has not served as well. The reaction of Halsted's disciples was simply to assume that surgery had to encompass a greater field. The reaction of the mammographic screening community has been identical calling for earlier and more frequent examinations. Neither radical surgery nor earlier screening-induced surgery are free of harm. This linear thinking has done more harm than good. This is because the host–cancer–surgery interaction is not linear.

First of all cancer should be seen as a process, not a morphological entity [33]. 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 [34]. 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 relatively 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 such as the response to wounding. In addition, pathological and autopsy studies have suggested that most of the occult tumours in breast (and prostate cancers) may never reach clinical significance [35,36].

Demicheli and colleagues [37] have also argued that a continuous growth model of breast cancer fails to explain 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 are 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.

The new model [38,39] is based on the concept of tumour dormancy/latency, both in the preclinical phase within the breast and later with the micrometastases that seed in the early phase of the natural history of the disease, once the primary focus has developed its microvasculature. The latter remain dormant until some signal, perhaps the act of surgery or other adverse life-event stimulates them into fast growth.

Single viable cells may remain dormant for some time and may be induced to proliferate by environmental factors. Groups of cells without angiogenic potential can grow, but remain small (up to 10^5 or 10^6 cells). The metastatic focus may grow quickly if (i) a subset of these cells switch to an angiogenic phenotype and/or (ii) the inhibition of angiogenesis is removed. The model suggests that the metastatic development of unperturbed breast cancer is a sequential evolution from a non-proliferative to a proliferative state and from a non-angio-

genic to an angiogenic state, with stochastic transitions from one state to the next.

This model may explain the early peak of hazard function for local and distant recurrences in resected cancer patients by combining with the natural metastatic development of unperturbed disease surgery-driven proliferative wake up induced through growth stimulating factor(s) [40] (''the Fisher effect'') with the angiogenic signal following surgery (''the Folkman effect''). It also correlates well with the findings of a modest benefit after adjuvant systemic chemotherapy.

We can now add a new mathematical model to the biological model described above [41]. Breast cancer is like a complex organism existing in a state of dynamic equilibrium within 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 non-linear dynamics or chaos theory. This model is the first attempt to apply the new mathematics of complexity to make predictions about the factors influencing the natural history of breast cancer, that might one day provide a therapeutic window.

Central to the understanding of this model is the pioneering work of Folkman on tumour angiogenesis [42]. As we know, solid tumours cannot grow beyond 10^6 cells or approximately 1–2 mm in diameter in the absence of a blood supply [43,44]. 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 [45].

In addition to the importance of the microvasculature, we can also visualise these microscopic foci as existing in a 'soup' of cytokines, endocrine polypeptides and steroids, with cells interacting with each other and with the surrounding stroma, interpreting competing signals directing the cancer cells in the direction of proliferation or 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 require a thorough understanding of epigenetic phenomena.

What we now have is a new model of the disease that owes its genesis in part to the interpretation of the results of natural history databases or clinical trials by way of hazard rate plots rather than Kaplan–Meier curves. We can now see a new signal appearing against background noise, that challenges the assumption of linear dynamics in favour of non-linear mathematics or chaos theory [46]. This ''signal'' is the early peak of hazard for relapse that follows surgery within 48 months, whereas the stretched flatter curve thereafter might be the ''echo'' of the natural history of breast cancer left unperturbed by surgical interference.

If that is true then the act of wounding the patient creates a favourable environment for the sudden transfer of a micrometastasis from a latent to an active phase.

We must refocus on the host–cancer balance. We believe that careful reconsideration of both the therapeutic and deleterious effects of the wounding associated with breast cancer resection is in order. Breast cancer and the women who bear it comprise a complex system. The dynamics of the system are not linear. The entry into this complex system by any potentially therapeutic intervention could have very different outcomes depending upon the conditions of the complex dynamic host–cancer relationship at the ''time'' of the intervention. For example, timing of surgery within the menstrual cycle is very probably an important factor regulating surgery-induced angiogenesis for premenopausal node-positive patients [47,48].

The therapeutic consequences of the new models are almost self-evident. The intervention that suggests itself would be anti-angiogenic, 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 or chemotherapy might be a result of their anti-angiogenic potential rather cytostatic/cytocidal effects [49].

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 anti-angiogenic strategy at the first rise might prove successful [50].

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 disease in equilibrium until nature takes its cull in old age [51,52].

Conflict of interest statement

None declared.

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