Surgery: A New Candidate to Explain Breast Cancer Paradoxes?

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ABSTRACT

The modern paradigm of breast cancer therapy is to eradicate the disease while minimising unnecessary trauma. Actually, new information is emerging on the possible detrimental effect of surgery in cancer patients as it may stimulate latent metastases into an active state of vascularisation and proliferation. This phenomenon could also explain the lack of efficacy of mammography screening in the premenopausal age when the early balance between benefit from tumour downsizing and harm from surgery-induced metastasis acceleration may in fact result in harm. Since extensive experimental evidence is accumulating on the extreme biological heterogeneity of cancer and on the mechanisms leading to the transition of isolated circulating cancer cells into metastases, conventional chemotherapy must be substituted by new tailored treatments. In particular, the low proliferative rate of single disseminated cells suggest that a better strategy could be to maintain micrometastatic cancer cell in their dormant state, instead of trying to eradicate them from the body. Promising innovative adjuvant treatments directed to new targets involved in the processes of angiogenesis, proliferation, apoptosis and immune response are being tested in the clinical setting and may even provide a chance of cure if applied before the occurrence of overt metastases. With this regard, the short therapeutic window at the time of tumour surgical excision appears the best setting to prove if these new ideas will stand the test of randomised trials.

Keywords: *breast cancer, surgery, metastasis*

THEORIES ON BREAST CANCER NATURAL HISTORY

Breast cancer is an extraordinarily heterogeneous disease whose clinical outcome encompasses a wide spectrum of possibilities from definitive cure to early death. Several theories on the dissemination of breast cancer through the lymphatics have been derived from experimental and clinical observations. The belief that lymph nodes function as a barrier to tumour spread,[1] suggested that the "en bloc" excision of the tumour with its efferent lymphatics (radical mastectomy) could lead to definitive cure (*dissemination*

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theory). Nevertheless, it was subsequently recognised that less aggressive surgery was able to confer a similar survival benefit. A biologic explanation was provided according to which nodal involvement is not due to an orderly contiguous extension, but it is rather a marker of distant disease. Therefore, the outcome of the disease is pre-determined by the extent of micrometastases disseminated via the microvasculature of the tumour very early on in its natural history (*systemic theory*).[2] This theory shifted the attention from the chronology ("early" versus "late") to the biology ("good" versus "bad") of the disease. One important therapeutic consequence was the development of adjuvant systemic therapies using cytotoxic drugs or endocrine agents. As an example of the major impact of this strategy, adjuvant therapy with aromatase inhibitors produces a relative reduction of recurrence rates approaching 50% in breast cancer patients with estrogen receptor positive disease.[3] Nevertheless, it cannot be overlooked that in absolute terms the benefits in disease free and overall survival are considerably lower and that no real major progress has been witnessed over the last 20 years. A more pragmatic approach stems from the clinical observation that many patients are actually cured after adequate loco-regional treatment, although others are not. Breast cancer may thus be considered a spectrum of diseases with increasing inclination towards metastasising as a function of tumour growth and progression (*spectrum theory*) and a nodal metastasis may either be the only site of dissemination or a marker of distant disease.[4]

INCONSISTENCIES OF THE CONTEMPORARY MODEL OF BREAST CANCER GROWTH AND DISSEMINATION

The majority of the models proposed to describe tumour biological behaviour are characterized by continuous growth. The Gompertzian function has been successfully utilized to describe tumour growth in laboratory animals and is usually considered a satisfactory mathematical description of tumour growth in its clinical phase.[5] However, when it is extrapolated to subclinical tumours, the Gompertzian curve does not have an initial exponential region of sufficient duration and the initial doubling time is too short.[6] Refinement of this model have been suggested, such as the exponential–Gompertzian model, where an exponential early growth changes to a Gompertzian growth when tumour size has reached a critical value. Nevertheless, none of these models has proven adequate to explain either the extremely variable temporal pattern of breast cancer relapses or the constant rapid and unfavourable evolution of distant metastases once they occur.

As pointed out by Baum et al,[7] the current understanding of breast cancer natural history has major flaws since it cannot explain a number of inconsistencies and paradoxes. For instance, tumour diameter is not linearly correlated with the number of involved nodes; instead, very large cancers may never metastasise, while extensive axillary nodal disease can derive from occult primaries in the breast. Even more strikingly, although less than 5% of all breast cancers show distant metastases at presentation, recurrences peak after 2-3 years from surgery. Of note, only the amplitude of the peak, but not the timing is influenced by tumour diameter or nodal status. Furthermore, the clinical observation that breast cancer cells can bypass the microvascolature of lungs to metastasise in the liver and bone or that distant metastases are inevitably fatal in a relatively short time even when appearing decades after the primary tumour, have still not received a plausible explanation.

Also the effect of clinical interventions on breast cancer mortality is not consistent with the models mentioned above. Baines et al.[8] reviewed the evidence of a paradoxical effect of screening mammography which cannot be explained by conventional thinking of breast cancer natural history. The utility of screening depends on the hypothesis that breast cancer behaves as a linearly progressive disease, with overt metastases developing only in a fraction of patients which is related to the tumour size at diagnosis. As mammography screening allows smaller tumour detection both in pre and postmenopausal women, it should invariably improve the outcome of the disease. While this seems to be the case in postmenopausal women,[9] the same effect has not been observed in the younger women. Actually, among women of 40-49 years of age the mortality is increased for up to 11 years after the initiation of screening and it is significantly so in the third year (rate ratio = 2.4, 95% CI = 1.1 - 5.4).[10]

THE ACQUISITION OF METASTATIC POTENTIAL: EARLY OR LATE EVENT DURING CANCER LIFETIME?

For many years the multi-step process of carcinogenesis, according to which metastatic cells represent the very last product of a sequence of mutational events allowing their uncontrolled growth, has been a universal and undisputed dogma.[11] This view was substantiated by several clinical evidences such as the correlation between the tumour size and histological grading with the likelihood of metastatic relapse. Also *in vitro* studies and animal models indicated that cells isolated from metastases

were genetically and phenotypically different from cells isolated from their primary tumours.

Nevertheless, animal models from which most of our knowledge on metastatic spread has been traditionally based on, are poorly comparable to the clinical behaviour of human cancers. Examples of such inconsistency are represented by the long latency before a human cancer becomes manifest as well as the cellular heterogeneity present in primary tumours. Furthermore, several clinical observations suggest that cells with metastatic potential may be already present in a very early phase of the natural history of the disease. One of these is represented by the disturbing occurrence of systemic metastases from small and/or well-differentiated primary breast tumours that were completely excised up to four decades before.[12] Another puzzling condition is the development of metastasis in patients with unknown-primary carcinoma. Precise estimates of this syndrome are difficult, but it has been suggested that it may affect around 5 percent of hospital patients.[13] In 30% of patients with unknown-primary carcinoma, primaries are not found at all despite extensive laboratory and radiological investigations, while in the remaining patients the tumour is only identified post mortem, usually as a small, well differentiated lesion. Again, one must hypothesise that metastatic cells may depart from the primary tumour and colonise different organs in a very early clinical stage and that the primary lesion regressed spontaneously or was casually removed (i.e. surgery for a benign condition).[14] More recently, with the diffusion of organ transplantation, a new clinical scenario has emerged: the inadvertent transmission of solid tumours with organ transplants taken from cadaveric donors diagnosed as tumor-free at the time of transplantation. Also this tragic event can only be explained by taking into account the possibility that metastatic cancer cells may reside silently in the body of patients with unknown primary tumours.[15]

The introduction of gene profiling techniques has made it possible to study the expression signature of cancer cells and thus to compare the primary tumour and its metastases. In general, also microarray data appear to challenge the conventional belief that metastases arise from a rare subset of cells within a primary tumour, as the expression signature of a specific primary cancer is remarkably stable when analysed in loco-regional and distant metastatic sites.[16-18] According to this studies, the metastatic potential of a cancer cell is not the result of clonal selection after subsequent mutational events due to genetic instability, but instead it is acquired *ab initio* or very early in the natural history of the tumour.[19] As an example, Ramaswamy et al. identified the presence of a gene-expression signature of adenocarcinoma metastases in some primary tumours that could be used to predict which tumours would become metastatic.[20] Remarkably, it has been shown that specific gene-expression profiles, early established in primary tumour development, may be associated with either lymphatic or haematogenous routes of dissemination.[21] This last results is in agreement with the observation that tumour cells in the regional lymph nodes and in the bone marrow provide independent prognostic information on clinical outcome.[22]

These conclusion and the very conceptual approach of expression profiling studies to unravel the metastatic process have been recently challenged. The main criticism is that microarray studies focus on the formation of overt metastases as the end point of their analysis and do not allow the metastatic process to be scrutinised in detail. Indeed, microarray data derive from the analysis of mixtures of RNA from multiple tumour cells and stromal cells, rather that from a "head to head" comparison of single primary and metastatic cancer cells. It is then unclear whether the metastatic profile is actually derived from the cancer cells themselves or from the surrounding stromal cells included in the expression profiles. In order to circumvent these problems and to precisely dissect the metastatic cascade, several authors have started to compare single tumour cells selected from the primary cancer, from the blood marrow and from established metastases. Microdissection techniques can be used to selectively isolate cancer cells and the development of immuno-cytochemical and molecular assays has actually enabled the detection of even individual disseminated tumour cells.[23]

Using this approach, *in vitro studies* and analyses of animal models have shown that major genetic and phenotypic differences can be found by comparing cells isolated from metastases and from their parental primary tumours. This result is in line with the theory that subpopulations of primary tumour cells acquire their metastatic features during later stages of tumour progression.[24] In brief, most tumours are clonal in origin but they acquire multiple phenotypes with different metastatic potential during their growth as a result of genetic instability. The coordinated expression of multiple genes and also tumour cell interactions with the host microenvironment are required for metastatic competence, rendering this process highly inefficient.[25] Therefore, the ability of disseminated cells to complete subsequent steps in the metastatic cascade is not inherent *a priori,* as would be inferred by the relative infrequency of overt metastases. Conversely, it is likely that many tumours contain subpopulations with an incomplete metastasis signature and that only when a sufficient proportion of cells with the whole set of

"metastasis genes" is represented in the tumour, the development of a metastasis may actually take place.[26,27]

A unifying hypothesis to describe the metastatic cascade in breast cancer patients has been recently proposed by Pantel et al.[28] Very early systemic dissemination is likely to occur as suggested by studies on the molecular biology both of the primary tumour[17] and of single disseminated tumour cells isolated from cancer patients.[29] Metastatic spread might follow two models: during the early stages of tumour growth, cancer cells disseminate from the primary tumour either to the lymph nodes or to the blood. In the first case, tumour cells proliferate and form solid metastases in lymph nodes and at later stages they metastasise to distant sites. As a result, distant metastatic spread is dependent on the presence of lymph-node metastases. In the second model, cancer cells undergo very early haematogenous dissemination to distant sites where they progress to overt metastases and lymphatic dissemination is not required. In both models, the early disseminated cells, either in the lymph-nodes or in the blood/bone marrow, might be considered 'immature' tumour cells, with a limited lifespan, usually not proliferating and biologically heterogeneous. Nevertheless, during their permanence in these tumour reservoirs, some of these cells acquire genetic mutations independent from those of the primary tumour which allow them to proliferate at the distant site. At this stage, tumour cells may re-circulate from the distant metastasis and disseminate to secondary tissues. These cells are very aggressive due to the selective pressure that allowed them to survive; such a pressure may also account for the close genetic similarity of disseminated tumour cells in patients with overt metastases.[29]

CURRENT HYPOTHESES ON THE RELATIONSHIP BETWEEN THE REMOVAL OF PRIMARY TUMOUR AND THE GROWTH OF RESIDUAL CANCER CELLS

Over the last few years there has been increasing interest on the possibility that the removal of the primary tumour and even the very act of surgery may interfere unfavourably with the natural history of the disease. In particular, clinical data, substantiated by *in vivo* experiments, suggest that the primary tumour can exert a suppressive action on systemic micrometastases through the secretion of anti-angiogenic and anti-proliferative soluble mediators. Accordingly, it appears that tumour removal can elicit an angiogenic and proliferative response in these dormant micrometastases and turn them into an active phase that eventually leads to the formation of overt metastases. The clinical and experimental evidence suggesting that tumour removal may adversely impact on residual neoplastic disease has been extensively reviewed by Coffey et al.[30]

Acceleration of residual tumour growth after surgery has been documented for many types of cancer. Most breast surgeons have experienced either local or distant relapses after very short time-intervals from tumour removal or the rapid and unpredictable transition of a localised small in situ lesion conservatively excised into an extensive and aggressive disease. Although this can be considered as anecdoctal evidence, the observation that local recurrences after conservative surgery for primary breast cancer almost invariably occur near or at the site of original tumorectomy is certainly strong evidence involving the act of surgery in the process of cancer relapse. With this regard, a recent review of 10000 breast cancer cases operated conservatively, showed that 71% of local recurrences appeared in the index quadrant (i.e the breast quadrant where the tumour was excised) and just 3.3% of the overall patients experienced a recurrence in another quadrant.[31]

Compelling experimental data supporting a fundamental role of surgery in influencing local relapse in breast cancer patients can be found in two recent provoking papers. At the Milan National Cancer Institute, Tagliabue et al. demonstrated that wound drainage fluid and postsurgical serum samples from breast cancer patients stimulated *in-vitro* growth of HER2-overexpressing breast carcinoma cells. Furthermore, tumour cell proliferation induced by the serum and the wound drainage was directly correlated with the amount of surgical damage, while treatment of HER2-positive tumour cells with an anti-HER-2 monoclonaal antibody (trastuzumab) before adding the growth stimulus abolished drainage-fluid-induced proliferation.[32] Another paper by Chang et al. showed remarkable similarities between cancer progression and wound healing. In this study, based on gene expression profiles of human fibroblasts, the authors identified a stereotyped gene expression program in response to serum exposure related to the process of wound healing. Interestingly, the same gene set is coordinately regulated in many human tumours and is expressed by the tumour cells themselves and/or by tumour-associated fibroblasts. These molecular features are evident at an early clinical stage, persist during treatment, and predict increased risk of metastasis and death in breast and other carcinomas.[33]

By comparing patients that underwent mastectomy with an historical database of untreated patients, at least two papers have suggested that surgery can perturb the pattern of mortality rates for breast cancer. While patients who

undergo surgery show two peaks of mortality at the 3rd-4th year and 8th year after surgery, only the second peack is present in untreated patients.[34,35] With this regard, Retsky et al highlight the importance of taking into consideration the role of menopausal status in determining the pattern of relapse. By studying their breast cancer database of over 1000 patients treated with surgery only, they observed that in premenopausal and node positive patients, 27% of all distant relapses occurred within the first 10 months following surgery. This figure was twice as high as that of any other clinical group. Using computer simulation, they interpreted that these early relapses probably resulted from a disadvantage induced at surgery and also hypothesised that sex hormones could have favoured the angiogenic switch responsible for the metastatic surge among premenopausal women.[36]

The same group provided also evidence that this phenomenon could the explain the paradoxical survival disadvantage produced by mammography screening during the first decade and suggested that for younger women (but not for post-menopausal women), the early balance between benefit from tumour downsizing and harm from surgery-induced metastasis acceleration results in harm.[37] More recently, they also reported that the differential angiogenetic stimulus for distant dormant micrometastases in premenopausal versus postmenopausal women may also play a role in adjuvant chemotherapy effectiveness and account for the long-held notion that chemotherapy is most beneficial for premenopausal patients.[38] By the way, a possible influence of the hormonal milieu at the time of surgery on the prognosis of breast cancer premenopausal patients is also suggested by several studies reporting a worse prognosis for patients operated on during follicular as compared to the luteal phase of the menstrual cycle.[39]

CONCLUSION

Better understanding of tumour biology and the development of a multidisciplinary, integrated therapeutic approach is likely to increase the cure rate and improve the quality of life of breast cancer patients. The modern paradigm of breast cancer therapy is to eradicate the disease while minimising unnecessary trauma. Less mutilating operations are now possible by combining surgical, radiating and medical treatments and they often also result in improved overall survival. Radical mastectomy has been almost entirely abandoned in favour of breast preserving operations provided that patients receive adequate doses of radiotherapy to the breast. Another major revolution is represented by the "sentinel node biopsy" that will likely replace and hopefully increase the prognostic information provided by radical axillary lymphadenectomy in breast cancer patients.

The progressive abandonment of extensive operations for breast cancer is to be particularly welcomed in the light of the new information emerging on the possible detrimental effect of surgery in cancer patients and may also been partly responsible for the recent fall of breast cancer mortality in developed countries. Modern technologies are now available to test the hypotheses that have been suggested some years ago by illuminated clinicians.[40,41] As briefly reviewed in this paper, experimental confirmatory data are accumulating on the possibility that surgery may kick start "latent" metastases of patients with "early" breast cancer into an active state of vascularisation and proliferation. The pattern of hazard curves for relapse suggest that the process resulting in overt clinical metastases may have discontinuous features that cannot be explained by uninterrupted tumour growth. According to the new model proposed, at the time of primary tumour removal the majority of micrometastases reside in a non proliferative condition, but the act of surgery could exert a synchronous micrometastatic wake up responsible for the first early peak of relapses. Several theories have been proposed to explain the biological basis of this phenomenon related to surgery, such as dissemination of tumour cells, escape of immune-mediated cancer cell kill, accelerated residual tumour growth and induction of angiogenesis.[30]

The most important take-home message of this new way of thinking on breast cancer biology is the definitive disillusionment on the possibility to cure the disease by seeking super-radical surgical or cytotoxic interventions. Both early systemic dissemination and the potential unfavourable effects of the surgical act are good reasons to spare nonsense mutilations to breast cancer patients (not to mention the avoidance of emotional and physical side effects). The intellectual courage of the surgeons who pursued this philosophy in contradiction with the halstedian dogma of their times and finally demonstrated its efficacy in clinical trials, will never be underlined and acknowledged enough.[42,43] It is now time for oncologists to do the same by accepting clinical and experimental evidence that the principle of indiscriminate cell-kill by chemotherapy is a path that will take to nowhere. The inter and intra-tumoral extreme heterogeneity of cancer cells speaks against the possibility that a single or even a mixture of cytotoxic drugs may suit for all cases. Furthermore, the "sleepy" attitude of single disseminated cells who early colonise distant organs through the lymphatic or vascular circulation, should discourage everyone from thinking that they can be eradicated with

conventional chemotherapy.

Cancer should no more be regarded as an enemy to be destroyed at all cost, while it seems more rational to consider it as a "host" of the body, struggling itself to survive. The tumour necessitates that the organism in which it resides does not succumb; the data here reviewed suggest that our interventions, by perturbing what Baum calls "dynamic equilibrium",[7] may adversely alter the fine balance between the competing interest of these two living entities. As a consequence, a better strategy could be to maintain micrometastatic cancer cell in their dormant state as long as possible, instead of trying to eradicate them from the body.

Fortunately, deeper insights are now emerging on the physiology of isolated circulating cancer cells and on their transition into metastases.[23] Innovative adjuvant treatments directed to new targets involved in the processes of angiogenesis, proliferation, apoptosis and immune response, hold the promise of stabilising the disease and even provide a chance of cure if applied before the occurrence of overt metastases.[44] The perioperative period seems to offer unique conditions for influencing the likelihood of micrometastatic colonisation and eventually the development of metastatic disease. As suggested more than 25 years ago by Nissen-Meyer et al in a trial showing beneficial effects of perioperative chemotherapy as opposed to postoperative chemotherapy,[45] a short therapeutic window at the time of the tumour surgical excision appears the best setting to prove if these new ideas will stand the test of randomised trials.

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