review

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# The effects of surgery on tumor growth: a century of investigations

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A few clinical investigations suggest that while primary breast cancer surgical removal favorably modifies the natural history for some patients, it may also hasten the metastatic development for others. The concepts underlying this disease paradigm, i.e. tumor homeostasis, tumor dormancy and surgery-driven enhancement of metastasis development, have a long history that is reviewed. The review reveals the context in which these concepts were conceived and structured to explain experimental data and shows that they are not so new and far fetched. The idea that surgical cancer resection has both beneficial and adverse effects upon cancer spread and growth that result from the modulation of tumor dormancy by the resection should be considered a potentially fruitful working hypothesis.
**Key words:** breast cancer, metastasis development, surgery effects, tumor dormancy, tumor homeostasis



## introduction

The surgical extirpation of primary breast cancer has been regarded with different attitudes through the centuries [1]. The opinions of premodern surgeons were influenced by both the tremendous technical problems and the common belief that surgery was detrimental *quoad vitam* and *quoad valetudinem* in almost all cases but those with small and easily resectable lumps, such as those called *cacoethes* by Celsus. This pessimistic attitude remained quite widely accepted until the middle of 19th century, when, on the basis of the arguments suggested by Virchow, the Halsted operation was adopted as default therapy worldwide. Twentieth-century progress in antisepsis, anesthesia and surgery fueled aggressive surgical treatments and operations even more extensive than the radical mastectomy were explored. In spite of all these surgical efforts and patient suffering, however, 30% of resected node-negative and 75% of node-positive patients still developed distant metastases and succumbed [2].

The failure of more and more aggressive operations to cure patients led to a reversion of this trend, and the last quarter century has witnessed a progressive reduction of the extent of surgery. The hypothesis proposed by Fisher [3], who assumed that cancer spreads even before its clinical detection and predicted that the extent of local treatment would not affect survival, supported the abandonment of the most aggressive surgical approaches.

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Further, clinical investigations and mathematical modeling suggested that surgical resection might not always be beneficial [4, 5] as, while it favorably modifies the natural history for some patients, it may also hasten the metastatic development for others by triggering tumor growth. Supporters of this disease development model did not deny the usefulness of primary tumor surgical removal. Nevertheless, they suggested that oncologists should be aware of the biological consequences of surgical treatments.

This 'new' biological model of breast cancer has not favorably impressed many oncologists and has been heavily criticized [6]. The concepts underlying the model, i.e. tumor homeostasis, tumor dormancy and surgery-driven enhancement of metastasis development, seem difficult for many to accept. It is worthy, therefore, to carefully review the venerable history of investigations and speculations revealing the context in which these concepts were conceived and structured to explain experimental data (Table 1). It will become clear that these ideas are not so new or 'far fetched'.

## a century ago: phenomena recognized

The early observations about the effects that tumours may have at distant sites in animal models were published around a century ago. Ehrlich and Apolant [7] in experiments of double inoculations of rat sarcomas observed a retarded growth of a subsequently injected tumor in comparison with the previous (primary) tumor. They hypothesized that a competition for essential host-derived nutrients was required for tumor proliferation ('athrepsia' hypothesis). Bashford et al.

[8] termed this phenomenon 'concomitant immunity' assuming that the inhibition resulted from host immune reaction due to the previous tumor.

A few years later, Marie and Clunet [9] found that implanted tumors, which if allowed to develop naturally rarely resulted in spontaneous metastases, frequently produced metastases if the primary implant was incompletely excised. The results were again explained on the basis of the athrepsia hypothesis. This finding was further detailed by Tyzzer [10], who reported that for a high-metastasizing mouse tumor, incomplete primary tumor excision resulted in larger metastases than those of the control mice not undergoing tumor resection. Again, athrepsia was considered a possible reason of this observation.

Therefore, the capacity of tumor surgical resection to enhance cancer growth at metastatic sites was clearly identified almost a century ago, though the proposed mechanisms were incorrect and incomplete. Of note, at that time, other basic findings about neoplasms were acknowledged and 'modern' hypotheses had already been devised. The first report on circulating tumor cells (CTCs) had been published in 1869 by Ashworth [11], the concept that their presence does not necessarily cause metastasis had been proposed in 1897 by Goldmann [12] and the 'seed and soil' hypothesis suggested by Paget [13] for the metastasis process is dated 1889.

## half a century ago: general traits outlined

Further conceptual developments were offered during the fourth and fifth decades of the past century. In particular, Hadfield [14] published a lecture with the notable title 'The dormant cancer cell', where he adopted the word 'dormant' to describe malignant cells which although remaining alive in the tissues for relatively long periods, show no evidence of multiplication during the time, yet retain all their former and vigorous capacity of multiply.

Studies on animal models supported these views. The Fisher brothers published a series of reports on the effect of partial hepatectomy, sham hepatectomy and observation on the development of hepatic metastases [15–18]. Also, studies with parabiotic pairs of animals were carried out. These authors studied the dynamics of metastasis appearance by sequential weekly laparotomies and found that the incidence of animals demonstrating hepatic metastases (20%) did not rise over the observation time (2–20 weeks). However, if such animals were subjected to repeated laparotomies with partial hepatectomy, sham hepatectomy, liver manipulation and chemical hepatic injury, the incidence progressively increased to virtually 100%. The authors stated that 'it would seem that … tumor cells remained in the liver in a viable but dormant state until triggered into growth by some factor or factors still to be elucidated'. By liver injury, 'dormant' or 'latent' tumor cells may be stimulated to become overt metastases in almost 100% of animals, suggesting that cancer cells might be converted from the state of 'peaceful coexistence' with the host to one of active growth should 'conditions' be appropriate. All these findings were later validated [19].

Other significant points were clearly highlighted by Schatten [20, 21], who carried out studies on murine sarcoma and melanoma (Table 2), and by other investigators [22–25], who proved a positive correlation between the final size attained by the primary tumor in a given time and the number of lung metastases. Beyond the liver, several other tissues were proven to be susceptible to tumor cell seeding following injury [26, 27]. In addition, it was found that susceptibility to cancer wore off over time as the injured organ healed. Also, it was proposed that partial hepatectomy in rats carrying hepatomas promoted hepatoma growth as a result of injury-related growth factors releasing [23, 25].

The effect of primary tumor surgical removal drew increasing attention of researchers. Systematic studies on the number and size of spontaneous metastases [28–30] showed that the control tumor-bearing animals exhibited more metastases per mouse and a greater percentage of mice with metastasis than did the corresponding animals undergoing tumor removal. The resected animals displayed fewer metastatic foci in their lungs that, however, were larger than the corresponding untouched animals. It was concluded that the removal of the primary tumor decreased the number of metastases essentially stopping the shedding of new tumor cells and 'in some way' allowed those metastases that did develop to grow to a larger size.

**Table 1.** Main steps of the research history on tumor homeostasis tumor dormancy and surgery-driven enhancement of metastasis development

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| 1905–1910 | Homeostatic phenomena identified. The athrepsia hypothesis. The immunologic hypothesis. |
| 1955–1960 | Tumor dormancy and growth-stimulating effects from surgery proposed. |
| 1975–1985 | Immunologic hypothesis rejected. Growth-stimulating effects from surgery demonstrated. |
| 1995–2000 | Angiogenesis-based tumor dormancy demonstrated. |
| 2000–2005 | Single-tumor cell dormancy demonstrated. |

**Table 2.** Findings from murine studies reported half a century ago (from Schatten [20, 21])

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| A primary tumor of sufficient size inhibits the development and growth of its distant spontaneous metastases. |
| Pulmonary metastases become established and grow before the primary tumor becomes large. |
| Removal of the primary results in the establishment and rapid growth of large numbers of latent metastases the majority of which would have been dormant or would have succumbed if the primary tumor had not been removed. |
| The growth-stimulating effects on metastases postoperatively are due to removal of primary. |

## the 1970s and 1980s: further traits detailed

The next 20 years marked an increasing effort to determine the details of the relationship between tumors in different sites, the surgery-driven effects and the tumor dormancy, which it became clear were intimately connected.

### relationships between tumors in different sites

The relationship between tumor behavior in different sites was investigated in a quite original way by DeWys [31], who measured the growth kinetics of the primary transplanted tumor, of its lung and kidney metastases and simulated metastases. The growth pattern at each location was compatible with a Gompertzian description with similar degree of slowing of the growth rate of metastases, even though the metastatic foci remained microscopic in size. The simulated metastases approached an asymptote at much smaller tumor size. Following removal of the primary, however, the slowing of tumor growth of both lung metastases and simulated metastases was significantly reduced or abrogated depending on the time the initial tumor had been present. The author concluded that any explanation of these phenomena should account for both retardation increasing with increase in tumor mass and retardation manifesting its effect systemically.

The concomitant immunity hypothesis previously suggested by Bashford et al. [8] began to show its limits when it failed to adequately explain several findings:

- Tumor-bearing animals may be refractory to reinoculation of a dose of identical tumor cells 100 000 times higher than that dose required to produce primary tumors, while removal of the tumor rapidly results in the appearance of metastatic deposits [32].
- In animals developing multiple tumors, the more tumors per mouse the slower the average growth rate of the earliest tumor [33].
- The survival time for animals undergoing double transplant (s.c. and i.p.) of a lethal tumor is prolonged in comparison with animals receiving the same tumor at a single site, proving the naivety of the assumption that if one transplant kills, two will kill sooner [34].
- The tumor growth at the s.c. injection site may be depressed in mice that received artificial metastases in addition to an s.c. implant, proving that metastases can inhibit s.c. tumor growth without themselves being affected [35].

The immunologic hypothesis received the *coup de grâce* when concomitant immunity was demonstrated in immune-suppressed animals. Gorelik et al. [36, 37] observed similar results in immunologically competent and immunologically compromised nude mice as well as in mice with functions of macrophages and natural killer cells suppressed. It was concluded that resistance of mice bearing immunogenic and nonimmunogenic tumors is mediated by different mechanisms. The resistance to a second tumor challenge in mice bearing nonimmunogenic tumor is due mainly to nonimmunological mechanisms. The findings of Gorelik and his suggestions were confirmed by further studies [38–41] and the term concomitant immunity was appropriately changed to 'concomitant resistance'.

At the end of this phase of cumulative investigations, Prehn [42] recognized that a number of prior observations supported the idea that a tumor is an integrated, organ-like entity rather than a collection of independent atypical cells. In particular, he pointed out that the only significant difference between organ growth, organ regrowth after partial resection and tumor growth is the resetting of the plateau size upward in tumors. He explicitly stated that concomitant resistance is an asymmetrical nonimmunologic phenomenon where the inhibited tumor is always the smaller tumor and the larger tumor, paradoxically, continues to grow. Also, he proposed the existence, in sera, of circulating tumor-inhibiting ligands and, locally, slowly diffusible growth-facilitating ligands with different site-related balance: the facilitating factor would be dominant in the larger primary tumor while the inhibiting factor would be dominant in the smaller metastases.

### primary tumor surgical removal

The studies of Simpson-Herren et al. [43] on Lewis lung carcinoma investigated the effects of surgery on the host–tumor system by analyzing both tumor cell population kinetics and host survival time. Early surgical excision of the primary s.c. tumor provided some long- term ''cures'' and an increase in life span over the untreated controls. Later excision was, however, noncurative and resulted in an increase in the proliferation and growth rate of the lung metastases. This surgery-induced stimulation of the lung nodules was accompanied by a small but consistent decrease in median life span. Artificial metastases were inhibited by the presence of a second s.c. implant and the median life span of the doubly implanted mice exceeded that of mice bearing i.v. implants only. The authors concluded that in mice bearing widely metastasized Lewis lung carcinoma, surgery alone may have a detrimental effect on life expectancy.

Further, an incidental but important observation was reported. In three different mouse systems in mice that had an open biopsy before the primary was resected, a small but significant increase in pulmonary metastasis was found presumably as a result of that biopsy [44].

A few years later, Gunduz et al. [45–47] reported a series of investigations on growth parameters of double tumor implants. Following removal of one of the tumors, changes were observed within 24 h in the proliferation kinetics of the residual focus. There was a transient increase in labeling index and primer-dependent DNA polymerase index, subsequent increase in tumor growth rate and a measurable increase in the size of the remaining tumor. A variety of serum transfer experiments between animals provided evidence for the presence of a serum growth factor that might be responsible for the phenomenon. The findings thoroughly refute the idea that removal of a primary tumor is a local phenomenon with no other biological consequences. Most of these results were investigated and confirmed by others [48–52] and dormancy was explicitly named as being an important contributor to these phenomena [48].

## more recent times: looking for the mechanisms

As the era of breast cancer conservation surgery emerged, the mechanisms of local recurrence following primary tumor removal were center staged and the effect of surgical trauma was actively investigated, mainly by studying experimental metastases or direct tumor cell implants in healing wounds.

It was proven that surgical trauma of normal tissue promotes implantation and/or growth of CTCs [53–57] and that extent of trauma influences the metastatic success rate of these CTCs [53]. It was confirmed that the ability of malignant tissue to respond to surgical wounding of normal tissue is not tumor cell type or even species specific and that the effect is temporary, diminishing as the wounds heal [53–55]. Neoangiogenesis elicited by mechanisms of wound healing seems to be crucial to tumor growth [57] and wound fluids are both directly mitogenic to tumor cells [58] and angiogenic to avascular microscopic tumors [57]. Among the many mediators in wound healing, transforming growth factor beta and basic fibroblast growth factor proved to prominently increase tumor growth at an extent nearly similar to wound fluid [58].

Basic aspects of the relationship between primary tumor and its metastases were made even clearer by the work of Folkman [59–61]. The experimental designs included evaluation of DNA synthesis, apoptosis, corneal micropocket assay for angiogenesis and newer technologies apt to purify biological molecules. The metastatic pattern in mice with an intact primary tumor was described as the presence of microscopic perivascular cuffs or thin colonies of tumor cells on pleural surfaces. After removal of the primary tumor, large highly neovascularized growing metastases were observed. DNA synthesis was similar in both situations; apoptosis was, however, significantly diminished in the growing metastases. It was demonstrated that when the primary tumor is present, metastatic growth is suppressed by circulating angiogenesis inhibitors (angiostatin and endostatin). The proposed mechanism is conceptually similar to that proposed by Prehn [42]. Primary tumors secrete inducers of angiogenesis and also generate inhibitors of angiogenesis. In the microenvironment of the large primary tumor, the inducers are apparently sufficient to overcome the effects of the inhibitors because the new vessels essential for progressive tumor growth are present. However, when inducers and inhibitors are shed from the tumor bed into the circulation, levels of the more labile inducers fall off rapidly, whereas levels of the more stable inhibitors create a systemic antiangiogenic environment that prevents small nests of metastatic cells from inducing neovascularization. As a result, these incipient tumors remain small and dormant. Upon removal of the primary tumor, inhibitor levels fall and the previously dormant metastases expand vigorously. The central role of angiogenesis in explaining some features of the metastatic process has been confirmed by others [62–66] and the balance of angioactive molecules (enhancers versus inhibitors) has been recognized as crucial for determining if and when the 'angiogenic switch' is thrown [64, 66].

The previously hypothesized single-cell dormancy condition has also been identified and studied, mostly by Chambers and her group [67, 68]. Elegant quantitative investigations by several sophisticated techniques including *in vivo* video microscopy proved that a large proportion of injected tumor cells persists as solitary dormant cells. These cells can be recovered as viable cells long after they have been administered. The mechanism underlying the single-cell dormancy condition has yet to be elucidated, although some data indicate that extracellular signal-regulated kinase and p38 pathways may be involved [69].

## findings from clinical studies

Obviously, most of the above reported experiments carried out in animals cannot be carried out in humans. There is increasing evidence, however, that the helpful for understanding tumor behavior in animal models may be important at the clinical level.

The findings of the early experiments in rats by Ehrlich and Apolant may be replicated also in men as it is strongly supported by investigations of host resistance factors. It has been reported that the autotransplantation of cancer cells (in incurable patients) requires considerable number of cells and that even when 1 million cells in suspension are injected s.c., <50% of the transplants 'take' [70].

Lange et al. [71] reported the detailed clinical histories of eight patients for whom surgical removal of bulky metastases of non-seminomatous germ-cell testicular cancer was followed by a sudden and dramatic exacerbation of the disease. In some cases, a marked rise in the serum levels of alpha-fetoprotein and human chorionic gonadotropin was observed within 2–4 weeks following radical resection. Authors acknowledged that the cause and prevalence of such exacerbations are unknown and concluded that cytoreductive surgery in patients with advanced testicular tumor in some cases may adversely alter the course of the malignancy.

More recently, a randomized study to compare the efficacy of laparoscopy-assisted colectomy (LAC) and open colectomy for treatment of nonmetastatic colon cancer in terms of tumor recurrence and survival [72] proved that the probability of cancer-related survival was significantly higher in the LAC group. Therefore, it seems that a less extensive surgical tissue damage may have favorably influenced the subsequent development of metastatic colon cancer.

The study of biological fluids in patients undergoing surgical procedures has also been revealing. Vascular endothelial growth factor (VEGF) increases postoperatively in sera of patients undergoing surgery for lung [73] and gastric [74] cancer. For breast cancer, wound drainage fluid was found to include epidermal growth factor-like growth factors [75], VEGF [76, 77], endostatin [77] and other unidentified proliferation inducers [75] at levels significantly higher than the corresponding serum levels. The concentration of these substances correlate with the amount of surgical damage associated with tumor resection [75]. In particular, wound drainage fluid and postsurgical serum samples stimulated *in vitro* growth of HER2-overexpressing breast carcinoma cells [75].

Even more direct evidence of surgery-induced changes of metastasis steady state was achieved in a study of the vascular

density in patients with hepatic metastases from colorectal carcinoma undergoing biopsies or resection for synchronous metastases or resection for metachronous metastases [78] (Table 3). The study confirms that phenomena already well established in animals [44, 59–61] may be observed even in humans.

Strong direct support for the tumor dormancy in breast cancer was recently provided by Meng et al. [79], who studied the incidence of CTCs in patients, 7–22 years after mastectomy, who had no evidence of clinical disease. Fifty-nine percent of women displayed CTCs. As, after primary tumor removal, CTC half-life is a few hours, authors concluded that several years after primary tumor removal, clinically silent tumors foci may exist and continuously shed CTCs. Therefore, the balance between tumor replication and cell death appears to be one mechanism underlying tumor dormancy, which determines breast cancer outcome.

Finally, the postresection recurrence dynamics have been investigated in breast cancer [80, 81] and non-small-cell lung cancer [82] patients undergoing potentially curative resection of early-stage disease. The model assuming postsurgery acceleration of disease progression by a burst of growth in previously dormant micrometastases appeared to best fit the clinical data [4, 5, 82].

## further insights into the surgery—tumor–host interactions in breast cancer

Breast cancer displays profound interaction with the woman's biology. The sex hormone dependence of breast cancer has been obvious since Cooper's [83] observation of the waxing and waning of breast cancer growth during the menstrual cycle, Beatson's [84] discovery of remission following oophorectomy and Huggin's [85] later careful confirmation and extension of Beatson's work. Also, breast cancer has a prominent tendency toward heterogeneity and unpredictability and unpredictable and abrupt appearance of metastatic disease years and often decades following the primary breast cancer may occur [80, 86].

Screening for and early resection of breast cancer among premenopausal women result in breast cancer death rate higher than among premenopausal women who are randomized to a control group, the members of which are observed and not invited to screening [87]. This burst of early relapse and death fails to occur among mammographically screened postmenopausal women [88]. This negative 'screening' effect occurred in seven large randomized breast cancer mammographic screening trials, persisted for 6–8 years and resulted in 0.11 early deaths among each thousand mammographically screened premenopausal women.

Computer simulations of premenopausal recurrence pattern [5] indicated that the most likely cause of this burst of early breast cancer relapse is probably the surgical resection of the primary tumor that invariably and almost immediately follows its discovery [89]. The physiologic process at least in part responsible for this synchronization of early premenopausal recurrence is the interruption of metastatic breast cancer dormancy [90]. Angiogenic switch is emerging as one of the most important determinants of tumor dormancy interruption and the subsequent growth of breast cancer metastases [89–91].

Studies on menstrual and estrous cycles suggest that the termination of tumor dormancy might intimately depend upon when in the menstrual cycle the surgical resection of the primary breast cancer is carried out. It was reported that women resected in the follicular phase of the cycle suffer more frequent and earlier metastatic relapse than those resected in the luteal phase of the cycle [92–97]. These data indicate that the state of the host, in this case the sex hormone milieu, at the time of resection, may be a critical determinant of whether the operation cures the woman or the widespread lethal metastases develop.

## concluding remarks

The idea that surgical cancer resection has both beneficial and adverse effects upon cancer spread and growth that result from the modulation of tumor dormancy by the resection has roots in both experimental and clinical literatures that stretch back more than a century. We wonder why this reality has continued to cause denial and consternation among clinicians.

In our opinion, the difficulties arise from a perception of cancer borrowed from the paradigms of bacterial infections (Table 4). In this case, the disease results from invading 'alien enemies' that need to be completely destroyed in order to achieve the cure. In this reductionist framework, it is difficult to understand that the primary tumor may exert influences upon distant metastases resulting in inhibited proliferation and/or enhanced apoptosis, mimicking the organ homeostasis that maintains the ultimate organ mass following the growth process.

Yet, a growing body of evidence from animal and a few advanced *in vitro* models is highlighting the crucial role that tumor stroma plays both in carcinogenesis and in tumor development and clinical behavior [98–104] and support a new image of the disease (Table 5). According to it, some of the most clinically important properties of cancer may better be understood by considering it as an organ-like structure rather

**Table 3.** Phenomena yet established in animals are observable in patients with colorectal carcinoma (from Peeters [78])

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| Both peritumoral and intratumoral vascular densities were elevated in synchronous metastases from patients with the primary tumor removed compared with synchronous metastases from patients with the primary tumor *in situ*. |
| Comparable results were observed in patients with metachronous metastases. |
| An increase in vascular density after resection of the colorectal malignancy was also observed in biopsies taken from the same patient before and after primary tumor resection. |

**Table 4.** Perception of cancer borrowed from the paradigms of bacterial infections

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| Cancer is a pathologic phenomenon occurring at cellular level. It is a genome-driven disease: accumulation of a sufficient number of mutations, amplifications and/or deletions in key genes that are essential for tissue homeostasis result in 'cell transformation'. |
| Tumorigenesis is mainly a cell-autonomous process, in which genetic derangement renders the cells independent of external context. Tumor microenvironment is an idle bystander, sometimes forced to provide factors supporting tumor progression. |
| Cell transformation is an irreversible process. 'Once a cancer cell, always a cancer cell.' Killing all cancer cells is the only way to manage the disease. |

**Table 5.** A new conceptual model of solid tumors

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| Cancer may be viewed as a pathologic phenomenon occurring at tissue level. While normal structures can be disrupted by overexpression of given genes, conversely the tissue architecture may act as dominant tumor suppressor. |
| A dynamic and reciprocal relationship between genetically damaged cells in a tissue and their microenvironment may be conceived. Damaged cells modify their environment, which in turn brings about more pathological behavior from the cells. Ultimately, it is this relationship that precipitates a deleterious change over many years, resulting in cancer. |
| Cell transformation is not always an irreversible process. Ways to manage the disease other than killing all cancer cells, such as maintaining tumor cells in dormant state, may be conceived. |

than as an invading organism. We believe that such a view forces us to adopt a more holistic approach better suited to understand, prevent, diagnose and control cancer. Indeed, such a view is more appropriate for understanding complex systems where some properties of the whole system cannot be inferred by the separate properties of its individual components. If one regards the tumor as an organ-like structure within an organism, it appears much less outlandish that tumor homeostasis, tumor dormancy and surgery-driven enhancement of metastasis development may well occur.

In our opinion, even the most skeptical breast cancer researchers should recognize the plausibility of the new breast cancer paradigm, at least as a potentially fruitful working hypothesis with therapeutic consequences that might fuel the next leap forward.

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