Surgery, wound healing, and metastasis: Recent insights and clinical implications

Wim Ceelen a,*, Piet Pattyn a, Marc Mareel b

a Department of Surgery, Ghent University Hospital, B-9000 Ghent, Belgium
b Department of Radiotherapy and Experimental Cancer Research, Ghent University Hospital, B-9000 Ghent, Belgium
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Abstract

Background: Surgery-induced acceleration of tumour growth has been observed since several centuries.
Methods: We reviewed recent insights from in vitro data, animal experimentation, and clinical studies on how surgery-induced wound healing or resection of a primary cancer influences the tumour–host ecosystem in patients harbouring minimal residual or metastatic disease.
Results: Most of the growth factors, chemokines, and cytokines orchestrating surgical wound healing promote tumour growth, invasion, or angiogenesis. In addition, resection of a primary tumour may accelerate synchronous metastatic growth. In the clinical setting, indirect evidence supports the relevance of the above findings. Randomized clinical trials are underway comparing resection versus observation in metastatic breast and colon cancer with asymptomatic primary tumours.
Conclusions: In depth knowledge of how surgical intervention alters the tumour–host-metastasis communicating ecosystems could have important implications for clinical decision making in patients with synchronous metastatic disease and for the design and timing of multimodality treatment strategies.
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* Corresponding author at: UZ Gent – 2K12 IC, De Pintelaan 185, B-9000 Ghent, Belgium. Tel.: +32 9332 6251; fax: +32 9332 1503.
E-mail address: Wim.ceelen@ugent.be (W. Ceelen).
1. Introduction

Popular sayings often contain a nucleus of truth. A fitting illustration is the proverbial expression that when a cancer ‘hits the air’ by surgical intervention, rapid demise of the patient usually follows [1,2]. The fact that surgical intervention may promote cancer growth has been suspected since ancient times, but has received little attention from clinicians [3]. Several developments have now led to a renewed interest in this phenomenon. First, recent insights into the biology of metastasis formation and of the tumour–host relationship have added weight to the hypothesis of treatment-induced stimulation of cancer growth and dissemination. The primary tumour, its host, and distant metastasis (DM) are communicating ecosystems, characterized by a multiplicity of host cells, recruited locally and from the bone marrow as well as by the multiplicity of molecular pathways responsible for the communication of the cancer cells with each of the host cells [4,5]. As a consequence, manipulation of one element of this complex system will have consequences on the other elements. Second, in parallel with improvements in systemic antitumour therapies, an increasing number of patients with metastatic disease are candidates for surgery. Therefore, consideration of how removal of a primary or metastatic tumour affects the established communicating ecosystem has attracted increasing attention. Finally, perioperative systemic therapy aiming to eradicate micrometastatic disease is now the standard of care in several solid cancers, and insight into the effects of surgery on the behaviour of micrometastatic disease may allow to define the ideal schedule, timing, and duration of perioperative therapy.

Here, we review the current knowledge on the underlying biological mechanisms, animal studies, and clinical data examining the effects of wound healing and surgery on DM.

2. Results

2.1. Aspects of tumour growth and metastasis

Metastatic cancer cells may leave the primary tumour early during its development. At the time of surgery metastatic cancer cells may be present as clinically visible macrometastases, as micrometastases at the future sites of metastasis or as disseminated tumour cells for example in the blood or in the bone marrow. The latter organ is an important source of host stem cells that contribute to tumour metastasis. Micrometastasis and disseminated tumour cells may be in a state of dormancy and eventually grow and transit to overt metastases at an unpredictable moment. In some cases, metastases become overt in absence of a primary tumour, a situation described as CUP (cancer with unknown primary) [6]. At each moment of its history a metastatic tumour should be considered as a collection of communicating ecosystems each comprising cancer cells and tumour-associated host cells (Fig. 1). Alterations in one of the elements of such communicating ecosystems may change the whole; it is,
therefore, crucial to consider the effect of surgery on all these elements.

2.2. Similarities between wound healing, inflammation, and tumour growth

Hundreds of molecules and their signalling pathways are implicated in tumour growth, invasion and metastasis, regulating the activities of the cancer cells and their communication with the tumour-promoting host cells [5]. Many of these host cells and molecules are also found in healing wounds [7]. Since the histological observation of Rudolf Virchow in the 19th century of leucocytes within a tumour, the link between inflammation and cancer has been firmly established. Tumours have been denoted as ‘wounds that do not heal’ by Harold Dvorak in 1986 [8]. Inflammatory processes, acute and chronic, may play a pivotal role in tumour initiation, transformation, invasion and metastasis [9]. Surgical tissue trauma is rapidly followed by a complex cascade of inflammatory signalling and activation of epithelial, endothelial and inflammatory cells, platelets and fibroblasts. The process of wound healing following tissue injury is traditionally divided into three overlapping stages. The first inflammatory stage is initiated immediately after wounding by blood coagulation and activation of platelets, which release growth and chemotactic factors such as platelet-derived growth factor (PDGF), insulin-like growth factor I (IGF-I), epidermal growth factor (EGF) and transforming growth factor-b (TGF-β). In response to chemotactic factors, lymphocytes and polymorphonuclear leukocytes (PMN) enter the wound within hours, followed by monocytes which subsequently mature into wound macrophages. This is followed from day 3 to 4 onwards by a proliferation stage, characterized by fibroblast proliferation, ECM remodelling, angiogenesis, and simultaneous phagocytosis of debris by macrophages. Proliferation of epidermal cells and formation of granulation tissue are followed by scar formation mediated by keratinocytes and fibroblasts. Recent research has identified several populations of epidermal stem cells that are activated during wound healing and participate in tissue repair [10,11]. Many of the growth factors, chemokines, and cytokines released in the wound healing process may promote tumour progression locally or at a distance (Table 1). In addition, local as well as systemic production of inflammatory mediators is significantly enhanced after ischaemia-reperfusion related increased intestinal permeability and bacterial translocation [12,13].

Recently, microvesicles (shedding microvesicles and exosomes) were described as essential vehicles of crosstalk between cells and with their microenvironment, both in physiological circumstances and during tumour progression [14].

In addition to the wound related effects, physiological consequences of surgery such as tissue hypoxia, caused by hypoperfusion or exposure of the peritoneum to laparoscopic gases, may stimulate tumour angiogenesis through HIF-1α signalling [15]. Also, in patients treated with perioperative chemotherapy or radiotherapy, cell kill by necrosis, a proinflammatory form of cell death, may promote tumour growth by the release of factors such as the high-mobility group box 1 protein (HMGB1) which acts on RAGE (receptor for advanced glycation end products) [16]. These and other molecular alterations explain the pro-invasive and pro-metastatic effect that ionizing radiation may cause [17]. Finally, a growing body of experimental evidence suggests that surgical trauma creates an environment rich in reactive oxygen species (ROS) induced by activated NADPH oxidases and by pro-inflammatory mediators; the resulting redox signalling may promote cancer cell invasion, adhesion, and metastasis [18].

In summary, the microenvironmental signals and homeostatic changes that orchestrate normal wound healing may stimulate local or systemic tumour growth.

3. Tumour metastasis models and dormancy

One of the most important insights in cancer biology gained over the past decades is that, rather than as a foreign body – like extraneous growth, cancer should be seen as a process, interacting with the host organism from the very start. Most solid cancers do not progress, as Halsted proposed, in an orderly and stepwise manner from the primary cancer to locoregional nodes, and thenceforth to distal nodes and eventually to distant organs [19]. Rather, an important body of clinical, molecular, and genetic studies underpins the hypothesis that metastatic spread is, in reality, a very early event in the process of cancer growth [20–22]. Distant metastasis is, however, a very inefficient process, and from the thousands of cells that are shed into the circulation daily only very few will be able to establish an overt metastasis [23]. The observation that metastatic cancer recurrence may occur years to decades after therapy underlies the concept of tumour dormancy, i.e. a state of permanent minimal residual disease which remains asymptomatic [24]. Several mechanisms of tumour dormancy have been described. Cellular dormancy, characterized by G0–G1 arrest, has been associated with activation of the p38 MAPK pathways and inhibition of the ERK1/2 MAPK pathways [25]. Angiogenic dormancy occurs when the pro-angiogenic stimulus is outweighed by anti-angiogenic factors such as thrombospondin, endostatin, angiostatin, and vasculostatin [26]. By mechanisms that are poorly understood, a transient increase in angiogenic factors may tip the balance and initiate tumour angiogenesis; this event has been termed the ‘angiogenic switch’ [27]. A third possible mechanism of tumour dormancy is immunosurveillance, which prevents proliferation of micrometastases by an active immune system [28]. Whatever the underlying mechanism, it has been shown that the dormant state can be reversed by tissue trauma, including surgical wounding [29,30].

A key step in the establishment of metastatic disease is the homing of disseminated tumour cells in the target tissue. As
already clinically noted by Stephen Paget in the nineteenth century, metastatic growth can only be supported in the presence of a favourable microenvironment [31]. It has now been established that this microenvironment is ‘primed’ by the primary tumour as a pre-metastatic niche before the actual arrival of the disseminated tumour cells [32]. Several growth factors and chemokines produced by the primary tumour are implicated in the formation of the pre-metastatic niche by the recruitment of bone marrow derived cells (BMDC) and by remodelling of the extracellular matrix [33]. Kaplan and coworkers demonstrated that VEGF-A and PIGF from the primary tumour recruit VEGFR1+ bone marrow derived cells to the premetastatic niche [34]. Other secreted factors shown to mediate BMDC recruitment to the premetastatic niche include osteopontin and tissue factor [35,36]. An intriguing, yet unanswered, question is how surgical wounding affects the premetastatic niche.

4. Effects of surgery on tumour growth and metastasis

Surgery may stimulate DM in various ways (Fig. 1). First, surgical manipulation of the tumour and its vascular supply may mechanically introduce MCC into the circulation [37]. Second, surgical wounding creates a new ecosystem rich in newly attracted host cells producing pro-metastatic factors. When a complete (R0) resection is performed, surgery induced factors are active only when MCC are present at distant sites; in case of incomplete resection (R1) they may stimulate remnant cancer cells to metastasise. Pro-metastatic factors may act directly on the sites of metastasis, including pre-metastatic niches, or on the bone marrow, harbouring DTCs and pro-metastatic host stem cells, or on the neuroendocrine system. Third, removal of the primary tumour, which may be a source of anti-metastatic factors, may disturb the

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EGF, epidermal growth factor; TGF, transforming growth factor; BMP, bone morphogenetic proteins; PDGF, platelet derived growth factor; VEGF, vascular endothelial growth factor; IGF, insulin like growth factor; EC, endothelial cells; CTGF, connective tissue growth factor; HGF, hepatocyte growth factor; SF, scatter factor; IL, interleukin; TNF, tumour necrosis factor; M-CSF, macrophage colony stimulating factor; GM-CSF, granulocyte monocyte colony stimulating factor; MCP, macrophage chemo-attractant protein; IP, interferon inducible protein; GRO, growth related oncogene; SDF, stromal derived factor; MIP, macrophage inflammatory protein.
balance between pro- and anti-metastatic factors acting on distant metastasis. These mechanisms will now be elaborated further.

4.1. Experimental data

4.1.1. Wound ecosystems stimulate tumour growth

Several authors have described enhanced tumour growth by wound fluid and purified factors. Hofer and coworkers injected B16 melanoma cells in a wounded murine leg and observed a significantly enhanced tumour growth compared with the nonwounded control leg [38]. In addition, they found that injection of wound fluid or a combination of TGF-beta and bFGF increased tumour growth. Similarly, Abramovich and coworkers examined the influence of wound fluid derived from cutaneous injuries in pigs on angiogenesis and growth of C6 glioma spheroids implanted subcutaneously in nude mice [39]. They found that wound fluid significantly accelerated angiogenesis and tumour growth, and identified HB-EGF and PDGF as the dominant mitogens for C6 glioma. Both experimental situations serve as surrogates for primary tumours that are not completely resected (R1).

4.1.2. Surgery stimulates growth of distant tumours

The following observations indicate that surgery causes the release of mediators that are able to stimulate the growth of distant tumours that may be considered as surrogate metastases. One of the first demonstrated the effects of surgery on the growth of dormant micrometastases, as published over five decades ago by the Fisher brothers [40]. Upon intraperitoneal injection of Walker-256 cancer cells in rats, a model for artificial metastasis, no hepatic tumour growth had occurred after five months. If, however, three months after injection animals were subjected to repeat laparotomies at 7-day intervals, all animals developed a tumour, which lead the authors to conclude that perturbation of the host could produce metastasis from dormant cells. In addition, surgery-associated beta adrenergic stress signalling was shown to enhance tumour growth. Lee et al. performed laparotomy or mastectomy 4 days after intraperitoneal injection of ovarian cancer cells in athymic mice [41]. They found that surgery enhanced tumour growth, but this was not seen in animals without the beta-adrenergic receptor or after administration of propranolol. The same authors showed that increased tumour growth and metastasis by neurobehavioral stress are mediated by a FosB-driven increases in IL-8 [42]. Surgery-induced inflammation may also alter the ultrastructure of the target organ, facilitating metastasis. In a recent experimental study, Gül and colleagues found that reactive oxygen species (ROS), produced by macrophages (Kupffer cells) during surgery, disrupts the endothelial lining in the liver by downregulating the expression of tight junction proteins in liver cells and enhances colon cancer cell adhesion as demonstrated in vitro [43]. The relevance of these findings is supported by the comparison of liver biopsies from patients undergoing liver resection due to colorectal metastases before and after surgery, showing downregulation of the tight junction molecule claudin-5. Finally, surgery may mobilize bone marrow derived progenitor cells, which home to sites of future metastasis. This was demonstrated in a mouse melanoma model by Lavotshkin et al., who noted enhancement of circulating bone marrow derived progenitor cell mobilization following tumour resection and, to a lesser extent, after control (sham) surgery [44].

4.1.3. Removal of the primary tumour stimulates metastasis

More relevant for the clinical situation are experiments in which the primary tumour is removed in the presence of metastasis. As early as 1958, Schatten examined how removal of S-91 melanoma and DBA 49 tumours grown in the hind leg of mice affects growth of pulmonary metastasis [45]. They found that removal of the tumour bearing leg, but not of the heterolateral normal leg, resulted in a significantly increased number of pulmonary metastases, indicating that the primary tumour inhibits the growth of its metastases. During the seventies, it was noted in animal models that when simultaneous tumours were inoculated, removal of one tumour resulted in accelerated growth of the remaining one. The underlying mechanisms were unclear, and the phenomenon was attributed to competition for nutrients (athrepsia) and to immunological mechanisms [46].

In 1994, Folkman and coworkers showed that a primary tumour inhibits angiogenesis of metastases by a circulating 38 kDa plasminogen fragment that inhibits endothelial cell proliferation in vitro, and was termed as angiostatin [47]. This molecule, similar to its parent molecule plasminogen, binds to a variety of receptors such as ATP synthase, integrins, and annexin II [48]. The same group later identified a second endogenous angiogenesis inhibitor termed endostatin, a 20 kDa C-terminal fragment of collagen XVIII [49]. Similar results were observed by the Folkman group when the primary tumour was treated with radiation therapy: the mean number of pulmonary surface metastases was five per lung in the control animals versus fifty-three per lung in irradiated animals ($P<0.001$) [50]. Others have observed similar effects of resection of a primary rodent tumour on angiostatin levels and subsequent growth of residual metastases, histologically characterized by increased neoangiogenesis, increased tumour cell proliferation, and decreased apoptosis [51]. This is in line with the data from Sckell et al., using in vivo microscopy in mice cranial windows, showing a positive correlation between the size of a primary prostatic tumour and the extent of angiogenesis inhibition at the distant cranial site [52]. Human bladder cancer cell lines were found to express a range of angiogenesis inhibiting molecules including two active variants of angiostatin, endostatin and thrombospondin-1 [53]. A novel mechanism explaining how primary tumours inhibit the growth of concomitant tumours was recently proposed by Ruggiero et al. [54]. In a murine model, they found that tumour growth was inhibited by ortho and meta isomers of the amino acid tyrosine, an effect
mediated in part by inhibition of the MAPK pathway and inactivation of STAT3, potentially driving tumour cells into a state of dormancy.

In a recent murine breast cancer model, Al-Sahaf et al. showed that after resection of the primary tumour, pulmonary metastases showed increased proliferation as well as upregulation of genes involved in adhesion, invasion, and angiogenesis [55]. The authors do not mention candidate molecules sent by the site of the primary tumour to the metastasis. Additional evidence stems from animal studies examining the effects of adjuvant chemotherapy on the outgrowth of metastatic or residual disease. Fisher et al. implanted mammary tumours in both hind legs of mice, one of which was arbitrarily regarded as a ‘primary’, the other as a surrogate metastasis [56]. They examined how, after removal of one tumour bearing leg, the timing of adjuvant cyclophosphamide affected proliferation and growth of residual tumour cells as well as animal survival. It was found that chemotherapy was maximally effective when administered before or on the day of primary tumour removal, and much less so when administered three or seven days postoperatively.

4.2. Clinical data

Surgical resection is the mainstay of therapy for solid cancer, and cure may be achieved even in patients with microscopic nodal or distant metastatic disease. There is, however, circumstantial evidence pointing to the possibility that in some patients surgery may indeed provoke growth of distant metastasis. In breast cancer, computer stimulation suggested that surgery-induced stimulation of angiogenesis explains the ‘mammography paradox’ for women aged 40–49, viz. the unexplained temporary excess in mortality for the screened population compared to controls [57]. The same phenomenon has been suggested to explain the observation of an early (after 8–10 months) peak of metastatic recurrence following mastectomy alone in premenopausal node positive patients [58]. Similarly, analysis of the event rate of tumour recurrence after surgery for non-small-cell lung cancer proved compatible with the hypothesis of accelerated growth of dormant micrometastatic foci elicited by surgery [59].

Further circumstantial evidence stems from the observation that delaying adjuvant chemotherapy after breast and colorectal cancer resection results in worse overall and disease free survival [60,61]. It should be noted, however, that this observation stems from retrospective analyses and that others did not find any benefit associated with early administration of adjuvant chemotherapy in breast cancer [62]. Several studies have investigated the pro-angiogenic properties of postoperative plasma and wound fluid. Kumara et al. found that plasma VEGF and angiopoietin (Ang)-2 were significantly elevated after minimally invasive colorectal cancer (CRC) resection [63]. Importantly, the peak was noted at day 7–13 postoperatively, and plasma taken at this time window stimulated endothelial cell invasion and migration in vitro. Later, the same group reported that minimally invasive CRC resection is associated with a persistent increase in plasma soluble vascular cell adhesion molecule-1 (sVCAM-1) levels during the first month postoperatively, which may promote endothelial cell chemotaxis and angiogenesis [64]. Other growth factors shown to increase after CRC resection include HGF and the placental growth factor, while the epidermal growth factor was noted to decrease rapidly after surgery [65–67]. In patients with colorectal liver metastasis, it was recently shown that pre-resection portal vein embolization resulted in significant growth of metastatic tumours in both the embolized and the nonembolized liver lobes [68].

Additional evidence consists of the observed relation between the intensity of postoperative inflammatory changes and oncological outcome. Several authors have shown worse long term outcomes in patients who developed anastomotic leakage after colorectal cancer or gastric cancer resection [69–72]. The underlying mechanisms are unclear, but, in colon cancer, may include stimulation of metastatic ability by toll like receptor (TLR) signalling activated by lipopolysaccharide (LPS), a bacterial product known to translocate across the bowel wall during surgery and infectious episodes [73]. On the other hand, it has been suggested that efforts to reduce tissue trauma and the postoperative inflammatory response by minimally invasive techniques may result in superior oncological outcomes. In rectal cancer surgery, the laparoscopic approach resulted in a significantly lower level of IL-6 two hours after surgery compared to the open procedure [74]. Lacy and coworkers, in a small randomized trial comparing open with laparoscopy-assisted colectomy for cancer, found improved cancer-specific survival in the laparoscopically treated patients [75]. A similar conclusion was reached by Law et al. based on a retrospective comparison [76]. It should be noted, however, that several large randomized prospective trials found similar rates of distant metastasis and long term survival between laparoscopic and open resection for colorectal cancer [77].

One of the earliest clinical observations of the potential effects of surgery on the growth of metastasis was reported by Lange et al., who noted a rapid and dramatic disease exacerbation after cytoreductive surgery of bulky testicular cancer metastases [78]. Similarly, local excision of malignant melanoma was observed in some patients to result in rapid local recurrence and locoregional lymph node metastases [79]. Important insights in patients with synchronous colorectal liver metastases were provided by Peeters et al. They observed that after resection of the primary tumour, growth of the metastases was accompanied by an increase in cell proliferation and a significant decrease in the fraction of apoptotic cells on serial biopsies [80]. The same group later showed a significantly increased metabolic activity measured by 18F-FDG-PET in liver metastases after resection of the primary tumour [81]. Others have demonstrated remote effects of surgery on mobilization of bone marrow derived progenitor cells. Grzelak and coworkers noted an increase in circulating CD34+, CD13+, CD14+, and CD33+ hematopoietic
progenitor cells after elective cholecystectomy, which lead the authors to conclude that surgery results in an expansion of the total bone marrow cell number and a subsequent release of these cells into the blood circulation [82]. Similar effects on the bone marrow were reported following cardiac surgery and after major pelvic trauma [83,84].

4.3. Therapeutic implications

Obviously, these data could have important implications for the management of patients with synchronous metastatic disease and an asymptomatic primary. The retrospective clinical studies that have looked at the benefit, if any, of resection of an asymptomatic primary colorectal cancer in the presence of metastatic disease are difficult to interpret due to the inherent selection bias: resection is more likely to be performed in patients with a better performance status or a less extensive disease burden. Nevertheless, a recent Cochrane meta-analysis suggests that resection of the primary does not confer a survival benefit [85]. A prospective randomized trial (CAIRO 4, NCT01606098) is currently opened by the Dutch Colorectal Cancer Group, aiming to demonstrate superiority in terms of overall survival of resection versus nonresection of an asymptomatic primary tumour in stage IV colorectal cancer [86]. A similar trial was recently initiated in Germany (SYNCHRONOUS, ISRCTN30964555) aiming to define the efficacy and safety of primary tumour resection before beginning of systemic chemotherapy in patients with metastatic colon cancer [87]. It should be noted that most patients with asymptomatic primary tumours will never require palliative surgery whilst undergoing systemic treatment, and that the risk of bowel complications from the use of combined chemotherapy with angiogenesis inhibitors in these patients is low [88,89]. The possible biological effects of resection of the primary tumour on metastatic growth are among the arguments supporting the ‘liver first’ strategy, i.e. resection of the liver metastatic disease before surgery of the primary [90,91].

In metastatic breast cancer, several retrospective studies have suggested that resection of the primary tumour actually improves survival [92,93]. However, significant selection bias confounds the interpretation of these studies as evidenced by the fact that in matched analyses no survival benefit remains apparent [94,95]. Several randomized trials have been initiated in order to establish the effect of local therapy on survival in stage IV disease. The SUBMIT trial (NCT01392586), coordinated by the Dutch Breast Cancer Trialists’ Group (BOOG), will compare upfront surgery followed by systemic treatment to systemic treatment alone [96]. The Eastern Cooperative Oncology Group initiated a randomized phase III trial (E2108, NCT01242800) which will compare continuation of systemic therapy versus local therapy in patients who do not progress during upfront systemic treatment. Similar trials were initiated in Japan (JCOG1017), Turkey (MF07-01, NCT00557986) and India (Tata Memorial Hospital, NCT00193778) [97,98]. Preliminary analysis of the latter randomized trial suggested a trend towards worse overall and progression free survival in the patients who underwent surgery [99]. In metastatic renal cell cancer (mRCC), two phase III randomized trials demonstrated that ‘cytoreductive’ radical nephrectomy followed by interferon alfa-2b is superior to interferon alfa-2b alone [100,101]. However, the conclusions of these trials, which predate the availability of effective biological targeted therapy for mRCC, have been questioned on methodological grounds such as baseline imbalance in performance score between both groups, and inadequate sample size [102]. Of note, spontaneous regression of coexisting (mainly pulmonary) metastases has been observed after resection of a primary RCC [103]. This is a rare event, however, and most of these metastatic lesions were not biopsy proven.

In locally advanced solid tumours without clinical metastases, priority should be given to studies that relate the extent of surgery, the extent of postoperative inflammatory changes, and the risk of systemic relapse. The results of such studies could provide a framework for the design of trials aiming to maximize the prognostic impact of (neo) adjuvant regimens.

5. Conclusions

There is a substantial body of evidence indicating that the homeostatic changes induced by surgery associated tissue trauma and wound healing can promote growth, angiogenesis, and metastatic ability of micrometastatic disease. Nevertheless, the exact mechanisms and their clinical relevance in patients remain largely unexplored by the surgical community. In depth knowledge of how surgical intervention alters the tumour-host relationship could have important implications for the design and timing of multimodality treatment strategies. In patients with synchronous metastatic disease, resection of the primary may accelerate growth of the metastatic burden by a variety of mechanisms including loss of circulating angiogenesis inhibitors produced by the primary. Ongoing randomized trials comparing resection versus observation in patients with metastatic breast and colorectal cancer and asymptomatic primaries in situ will help establish the clinical relevance of the proposed mechanism.

Conflict of interest

None of the authors have any conflicts of interest to declare.

Reviewers

Dr Idriss M. Bennani-Baiti, Executive Director, RefGD, The Reference Gene Database, Peter-Jordan Strasse, A-1180 Vienna, Austria.

Dr Marjolein van Egmond, Mol Cell Biology and Immunology, VU University Medical Center, Amsterdam, Netherlands.
Dr Paul Redmond, Chair, Department of Surgery, Cork University Hospital, Ireland.

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