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Tumor excision as a metastatic Russian roulette: Perioperative interventions to improve long-term survival of cancer patients

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Abstract

Uncertainty regarding the development of postoperative metastatic disease is highly prevalent. Here we assert that numerous processes that occur during the immediate perioperative period (IPP) markedly affect the probability of post-operative metastatic disease, and that these processes can be manipulated to improve cancer survival. Specifically, tumor excision facilitates both pro-metastatic and anti-metastatic processes, which, within each domain, are often synergistic and self-propagating. Consequently, minor perioperative dominance of either pro-metastatic or anti-metastatic processes can trigger a “snowball-like effect”, leading to either accelerated progression of minimal residual disease (MRD), or to its dormancy/elimination, establishing the “surgical metastatic roulette”. Thus, the IPP should become a significant anti-metastatic therapeutic arena, exploiting feasible approaches including immunotherapies and manipulations/modifications of inflammatory-stress responses, surgical procedures, and hormonal status.

Keywords

perioperative; cancer; metastases; surgery; beta-adrenergic blocker; COX2 inhibitor

Uncertainty regarding post-operative metastatic disease

In many operated cancer patients, despite all known prognostic factors and the specific treatments used, there is a high level of uncertainty regarding whether a patient at risk will develop post-operative metastatic disease. In this Opinion article I argue that the immediate perioperative period (IPP) significantly contribute to this uncertainty, and that specific pro-metastatic and anti-metastatic processes during this period can be manipulated to potentially improve patients’ chances of remaining disease-free.

For most solid cancers, surgery for the removal of the primary tumor (PT) is an essential life-saving procedure. Unfortunately, various aspects of surgery and of the IPP (defined as days before to days-weeks after surgery) often increase the risk for progression of

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preexisting micrometastases and for the initiation of new metastases through (i) directly affecting malignant tissue, (ii) suppressing anti-tumor CMI or protecting MRD, and through (iii) affecting the microenvironment of tumor/MRD (also see Fig 1, Key Figure) [1–3]. Mechanisms underlying these deleterious effects have been implicated or speculated upon by numerous translational and clinical studies and include: (i) potential excess shedding of tumor cell and increased number of circulating tumor cells (CTC) as a result of the surgical manipulation of the malignant tissue, its blood vessels, and/or adjacent tissue [4, 5]; (ii) a drop in anti-angiogenic factors (e.g., endostatin & angiostatin) as a result of the removal of the PT [6]; (iii) local and systemic increase in levels of growth factors and pro-angiogenic factors, physiologically aimed to promote post-operative tissue healing, but inadvertently facilitate growth of minimal residual disease (MRD) [7]; (iv) protection of CTC from immunocytes lysis by “platelet cloaking”, which also promote CTC capacity to extravasate and establish new organ metastases [1, 8]; and (v) marked suppression of anti-metastatic cell-mediated immunity (CMI) (e.g., CTL & NK cells) caused by tissue damage, anesthetic and analgesic agents, hypothermia, blood transfusion, and other perioperative events [2, 9–11]. It is also acknowledged that inflammation, a hallmark of cancer, and adrenergic-stress responses, which collectively are mediated by the release prostaglandins (PGs, e.g. PGE2) and catecholamines (CAs, i.e., epinephrine and norepinephrine), are prominent factors driving cancer progression through their direct and indirect effects on malignant tissue [2, 3, 12, 13]. Both PGs and CAs are abundantly released during the perioperative period [3], and excess release of these factors synergistically mediate many of the abovementioned prometastatic processes, and triggers additional process to do so [2, 3, 14] (see Box 1).

In addition to having pro-metastatic effects, the removal of the PT also triggers processes that exert anti-metastatic effects. Most healthy adults bear micro foci of malignant tissue, which are apparently not progressing or slowly progressing (e.g., in the prostate, breast, or thyroid)[15]. A single malignant cell is believed to initiate each micro-malignancy, but at some undefined time point the malignant mass halts its exponential growth, probably due to limiting interactions with its microenvironment (including immune cells) [16]. Thus the progression of micro-malignancies can naturally be limited or terminated by the host. Here we suggest that the removal of the PT (rather than the surgical procedure) may present an opportunity to halt progression of MRD and to prevent the initiation of new metastatic foci. Specifically, removal of the PT eventually stops or reduces the shedding and spread of tumor cells [17], which are necessary for creating new metastases. Additionally, the removal of the PT terminates PT secretion of a variety of factors that (i) suppress anti-metastatic immunity, (ii) promote the establishments of metastatic niches [18, 19], and (iii) support the growth of already established micrometastases that are not yet self-sufficient. For example, PGs and IL-8, which are often secreted by PTs, are known to cause systemic suppression of NK cells and of intra-tumoral anti-metastatic immune activity [9], as well as to directly support the growth of malignant foci[20]. It is our belief that the cumulative effects of removing the PT, which terminates these pro-metastatic processes, are anti-metastatic to a degree that prevents postoperative progression of metastatic disease in a substantial portion of operated cancer patients, despite postoperative existence of MRD (see Box 2 for mechanisms and examples) (also see Fig 1).

Multifaceted biological processes, such as progression of metastases, are hard to predict, given known and expected interactions between the many factors that affect them. We assert that both the pro-metastatic and the anti-metastatic processes induced by surgery are often synergistic within each category, and/or are self-propagating. For example, EMT together with high MMP2/MMP9 levels, can lead to excess release of tumor cells into the circulation, that, when combined with immune suppression and growth factors, can markedly increase the chances of establishing new metastatic foci. Existing metastatic foci become more effective in inducing local immune suppression and angiogenic signals due to increasing numbers of secreting malignant cells and facilitation of such secretion by high CA levels. Conversely, elimination of PT-secreted growth factors may cause regression in existing micrometastases, which will then become even less self-sufficient and will further regress or remain dormant. If anti-metastatic immunity will simultaneously recover from immune-suppression, some dormant or regressing metastases may actually be eliminated. Consequently, if the balance between the pro- and anti-metastatic processes is significantly leaning towards one direction, beyond a certain threshold, it may create a snowball effect, either leading to accelerated progression of MRD, or to regression/dormancy of MRD (Fig 1).

Clinically, it would be advantageous to know whether a patient currently identified as at-risk for metastatic disease would benefit from perioperative interventions, as any potential intervention entails medical risks or financial costs. Currently, however, despite the use of multiple biomarkers, including tumor stage, grade, receptor status, proliferation markers, lymph node status, leukocytes infiltration profile, malignant genomic composition, number of CTC, etc., there is still uncertainty whether a patient at-risk will eventually show disease recurrence. This uncertainty similarly exists in patients who receive neo-adjuvant and/or adjuvant therapy. This state resembles a roulette whose outcome is practically unpredictable, although completely based on multiple physical properties of the roulette play. One may even consider it a Russian roulette, as the outcome may depend on processes activated by tumor excision, and eventually be life or death. I propose that a significant level of this uncertainty is explained by the numerous perioperative processes described above, leading to either progression or regression/dormancy of MRD following PT removal (Fig 1). These multiple processes are not assessed nor manipulated clinically, and their combined integrative impact is hard to consider. It therefore seems unlikely that one could successfully predict whether these factors collectively cause a self-propagating process that promotes metastatic progression, or that causes metastatic regression.

Most importantly, I believe that addressing even some of the unattended perioperative factors described above would suffice to markedly reduce the risk of developing metastatic disease by tipping the scale toward an anti-metastatic dominance.

Immediate perioperative interventions can significantly impact long-term cancer outcomes

Given existing uncertainty in the occurrence of post-operative metastatic disease, the critical empirical question is whether short interventions or events during the critical perioperative

period can tilt the balance between pro- and anti-metastatic processes, leading to either metastatic dormancy/regression or to metastatic progression. I assert that there are ample pre-clinical and clinical evidence supporting this claim.

Translational studies

Animal studies employing models of spontaneous metastasis, where survival and/or metastatic growth were assessed following the excision of a metastasizing PT, directly indicated beneficial effects of short perioperative interventions, including immune-stimulation [21], blockade of CAs and PGs signaling [22–24], or the use of specific anesthetic regiments [25] or perioperative nutrition regimens [26]. For example, in a study where a spontaneously metastasizing orthotopic PTs were removed surgically in mice, the combined inhibition of CAs & PGs signaling (i.e., the use of propranolol and etodolac), given only on the day of tumor excision, prevented metastatic disease and doubled long-term survival rate in two syngeneic tumor models [2, 22].

Human clinical trials

More convincing are evidences from human studies, and specifically randomized clinical trials (RCT). As exemplified below, few short perioperative interventions or randomized modifications in surgical procedures were shown to improve long-term cancer outcomes or biomarkers of DFS. Unfortunately, none of these approaches has been integrated into standard clinical routine.

First, a 3-day pre-operative low-dose IL-2 treatment, ending 36h prior to colorectal resection, significantly reduced 5-year cancer progression rate [27]. Even more impressive, pancreatic cancer patients showed significant improvements in 3-year DFS and OS following this immediate pre-operative treatment [28]. Although low fever was evident in nearly all treated patients, no interference with the surgical treatment and no increase in short- or long-term complications were evident [27].

Another line of studies addresses the controversial claim that levels of female sex hormone during surgery for breast cancer impact long-term cancer outcomes [29–31]. One hypothesis is that high estrogen levels concurrently with low progesterone levels is a perioperative risk factor for metastatic progression [30], potentially because this hormonal pattern promotes a greater perioperative immunosuppression [32] and other pro-metastatic processes. A pivotal RCT conducted in 1,000 women with operable breast cancer showed that a single pre-operative administration of a synthetic progesterone (hydroxyprogesterone), which disrupts this potentially disadvantageous hormonal pattern, reduced recurrence rates in lymph-node-positive patients (which are at risk for metastatic disease), but not in lymph-node-negative patients, irrespective of tumor hormonal receptor status [33].

Last, recent studies targeted excess perioperative release of CAs and PGs in two biomarker RCTs [34–36]. Breast and colorectal cancer patients received 11–20 days of treatment with a β-adrenergic antagonist and a COX-2 inhibitor (propranolol and etodolac), or were treated with placebo, beginning 5 days prior to tumor excision. Molecular analyses of the excised tumor indicated a significant reduction in EMT status and in the activity of several pro-metastatic/pro-inflammatory transcription factors, including GATA-1, GATA-2, EGR3

(early-growth-response-3), and STAT-3 (signal transducer and activator of transcription-3) [34–36]. Additionally, a change in tumor infiltrating WBC milieu towards an improved immunological response against the malignant tissue was evident [34, 36], and reduced levels of the proliferation marker Ki67 was evident in breast cancer patients [35]. The treatment also reduced serum prometastatic and pro-inflammatory indices and improved immune-anti-metastatic indices [36]. Last, although these studies were not powered to study long-term cancer outcome, an exploratory analysis of 3-year DFS in colorectal cancer patients indicated a statistically non-significant trend for improved DFS from 33.3% in placebo patients to 12.5% in treated patients (intent-to-treat analysis, p =.239) [34], suggesting the long-term safety of the treatment and its potential efficacy. The treatment was well tolerated in both trials, with adverse event rates comparable to placebo [34, 36]. In translational studies, this treatment had no adverse effects on wound healing, anastomosis strength, and abdominal wall wounds [37], and improved post-operative long-term survival rates [22]. Overall, these RCTs clearly show that short perioperative interventions that are safe and easy to administer can improve anti-metastatic characteristics of the malignant tissue and/or improve long-term cancer outcomes in patients bearing various cancer types.

Human retrospective studies

Numerous retrospective clinical studies reported adverse or beneficial long-term cancer outcomes of various immediate perioperative events or of modifications in surgical procedures. For example, the intraoperative use of the anesthetic agent dexmedetomidine [38], blood transfusion, the occurrence of hypothermia, wound infection [39, 40], or anastomotic leak [41, 42], were all shown to be associated with decreased OS in cancer patients, even when all known risk factors were matched to control patients [1, 2]. Conversely, the use of propofol anesthesia, compared to the common use of volatile anesthesia, significantly improved 5-year OS rate [43, 44]. These studies, although retrospective and only statistically controlling for known risk factors, suggest that immediate perioperative events and processes that are often temporary and seems innocuous (e.g., the intraoperative use of dexmedetomidine or propofol) can have significant long-term cancer consequences.

Perioperative use of anti-metastatic interventions and practical considerations

Contraindications to surgery are the main reason for not using anti-metastatic treatments during the short perioperative timeframe. These include jeopardizing post-operative tissue healing and suppressing immunity, which are common adverse effects of chemo- and radio-therapies [45]. With respect to immune-therapies, their common inflammatory-pyrogenic effects are (i) often indistinguishable from signs of infections, which would usually lead to postponing surgery, and (ii) may theoretically increase the risk for SIRS (systemic inflammatory response syndrome), which is a post-operative life-threatening complication. Last, some pre-operative interventions, such as immuno-nutritional, physical-activity, or psychosocial preparations for surgery, may require postponing surgery for a few days or a few weeks, potentially increasing the risk of metastatic disease. However, various existing interventions can be used perioperatively with minimal risks that are manageable, and

other interventions may be adjusted to enable their perioperative use [46]. Interventions that require a brief postponement of surgery should be considered against potential benefits. Combination of interventions may be most effective, given their independent-complementary nature or synergistic effects, and given that they could prevent adverse effects of each other. For example, the perioperative use of the immune-stimulating TLR9 agonist, CpG-C, which is self-limiting in terms of its inflammatory-pyrogenic effects, simultaneously with blockade of inflammatory-stress responses through propranolol and etodolac, was found in translational studies to have synergistic effects without noticeable adverse effects [47].

Overall, our current understanding and empirical evidence indicate that several anti-metastatic approaches should be considered and/or tested perioperatively, some without any modification. These include: (i) Systemic boosting of anti-metastatic CMI through immune-stimulating agents (e.g., CpG-C or low doses IL-2/IL-12) [46, 48]; (ii) Reduction of stress and inflammatory processes, which could prevent immune suppression and the direct promoting effects of CAs and PGs on progression of MRD [3, 34–36, 49]; (iii) Changes in surgical, anesthetic, and blood-transfusion procedures, which were shown or suggested to improve postoperative survival rates in cancer patients [1, 50]; (iv) Various perioperative hormonal [33], nutritional [51], physical activity [52], and psychological manipulations [2, 3, 46]; and (v) Various anti-tumor approaches that may be adjusted to the perioperative period, including immune-checkpoint modification therapies and other anti-metastatic approaches.

Concluding remarks

The short perioperative period is characterized by many pro-metastatic and anti-metastatic processes that can either lead to accelerated progression of MRD or to its dormancy and regression. Thus, relatively minor interventions during this sensitive and largely unexploited period may have large impacts on long-term cancer outcomes. Empirical clinical evidence supports this claim, yet currently anti-metastatic approaches are rarely part of perioperative clinical routine, forfeiting a major potential anti-metastatic approach due to our complacency with uncertainty that stem from perioperative processes. It is time to make the immediate perioperative period a major focus for anti-metastatic interventions by clinically testing feasible existing approaches, and by modifying other approaches for use in this timeframe (see Outstanding Questions box). Exploiting this short window of opportunity may improve the odds of the surgical metastatic roulette for the benefit of cancer patients. Perioperative intervention may also be less aversive compared to the post-operative use of standard adjuvant therapies or experimental immune therapies, which, unfortunately, need to target metastases at their more advanced and resistant phase, aiming to arrest a speeding growing snowball.

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Box 1 –

Catecholamines and prostaglandins promote metastasis: Mechanisms and prevention

Catecholamines (CAs) and prostaglandins (PGs) suppress anti-metastatic CMI, directly by deactivating NK and CTL cells, and indirectly by reducing levels of pro-CMI Th1 cytokines [9]. Additionally, both CAs and PGs directly affect malignant cells, making them more aggressive and improving their metastasizing capacity through various mechanisms, including increase tumor cell survival, proliferation, motility, and resistance to anoikis[2, 3, 53]. CAs and PGs increase tumor release of VEGF, MMP2, MMP9, IL-6 and IL-8, factors which assist the malignant tissue in acquiring new blood vessels, penetrating the extracellular matrix, and proliferating [2, 3, 53]. CAs and PGs were each shown to induce an epithelial-to-mesenchymal transition (EMT) in malignant tissue [54, 55], another pro-metastatic process with well-established negative predictive value for disease-free-survival in several cancer types [56–60]. Last, CAs and PGs induce a M2macrophage shift within metastatic foci, which support metastatic growth [53, 61].

Therefore, it would be expected that perioperative inhibition of CAs and PGs signaling would reduce post-operative metastatic disease. Indeed, a short perioperative use of a β-blocker (propranolol) and COX2 inhibitor (etodolac) was shown to counteract many deleterious effects of surgery, and to reduce metastasis and long-term cancer mortality in several animal models [22–24, 62–67]. For example, a single administration of propranolol and etodolac on the day of tumor excision of a spontaneously metastasizing human PT in nude mice, prevented a post-operative eruption of metastatic foci, keeping them in a dormant/non-progressing state [66].

Box 2 –

Mechanism of anti-metastatic effects of tumor removal

Many single tumor cells are susceptible to lysis by CTLs, macrophages, or NK cells, especially by specialized hepatic and pulmonary marginating-NK cells that are strategically located to lyse circulating tumor cells and have the capacity to kill "resistant" tumor cells [48, 62, 63, 68]. Once immune suppression is eased by elimination of PT-derived immune-suppressive factors, such as TGFβ and IL-6 [69–72], the lysis of those last remaining CTC after removal of the PT can markedly reduce the chances of post-operative initiation of new metastatic foci.

Additionally, pre-existing growing micrometastases may regress to a dormant state or may be eradicated following a drop in PT-secreted factors. Growth of micrometastases is restricted by immunocytes' lysis, by lack of blood supply, and/or by lack of growth factors. The elimination of immuno-suppressive factors released by the PT, and/or induced by stress and surgery [9], may assist tumor-infiltrating-lymphocytes (TILs) (e.g., NK cells and CTLs) to eliminate tumor cells in established micrometastases[71–74]. Additionally, pro-angiogenic, pro-growth, and pro-invasion factors are abundantly secreted by the PT, including IL-6, IL-8, VEGF, EGF, PDGFaa, MIF, and SerpinE1 [19, 66, 67, 75]. These factors may be critical for maintenance and progression of micrometastases [20, 76–79], especially at an early stage when these microscopic malignant foci are not yet self-sufficient [67]. Thus, the removal of the PT and the elimination of its secreted factors is expected to halt the progression of micrometastases. Indeed, we recently found that (i) the secretome of a human PT supports the growth of its spontaneous metastases in nude mice, and that (ii) the removal of the PT causes reliable regression and dormancy of its micrometastases, but not of larger metastases that are apparently self-sufficient [67]. In cancer patients, post-operative regression of metastases is a well-documented phenomenon in several types of cancer, but is a very rare event [80, 81]. However, in patients this phenomenon can be potentially recognized only regarding detectable (large) metastases, which often contain 10^6-10^9 cells, unlike in the aforementioned animal studies that employ labeled tumor cells and imaging techniques recognizing micrometastases containing as few as 10^2-10^3 tumor cells. Thus, postoperative halt of MRD progression or their regression may be markedly more prevalent clinically in unrecognized metastases than is currently assumed.

Outstanding Questions Box:

- Would a potential perioperative intervention jeopardize or improve tissue healing?
- Would perioperative pyrogenic effects of immunotherapy increase or decrease shortterm risks of surgery, including postoperative infections and systemic inflammatory response syndrome (SIRS)?
- Could pre-operative nutritional and/or physical-exercise interventions reduce the likelihood/severity of deleterious effects of surgery, including immune suppression and excessive stress-inflammatory responses?
- If several perioperative approaches are found feasible, should they be used simultaneously or sequentially, and do specific approaches act synergistically or are contra-indicated to each other?

Highlights:

- The immediate perioperative period (IPP), although spanning only a few days before and after surgery, has a disproportionately large impact on the probability of the occurrence of post-operative metastatic disease
- Primary tumor excision induces both pro-metastatic and anti-metastatic processes, which, within each category, can act synergistically and in a self-propagating manner (snowball-like effect)
- Excess perioperative release of inflammatory and stress factors (and specifically prostaglandins and catecholamines) often (i) suppress anti-metastatic immunity, and (ii) directly facilitate pro-metastatic and progrowth characteristics in the primary tumor and in minimal residual disease
- Several anti-metastatic approaches are feasible and effective during the IPP, with minimal adverse effects, including some immunotherapies and anti-stress-inflammatory approaches, but none has been integrated into standard clinical routine

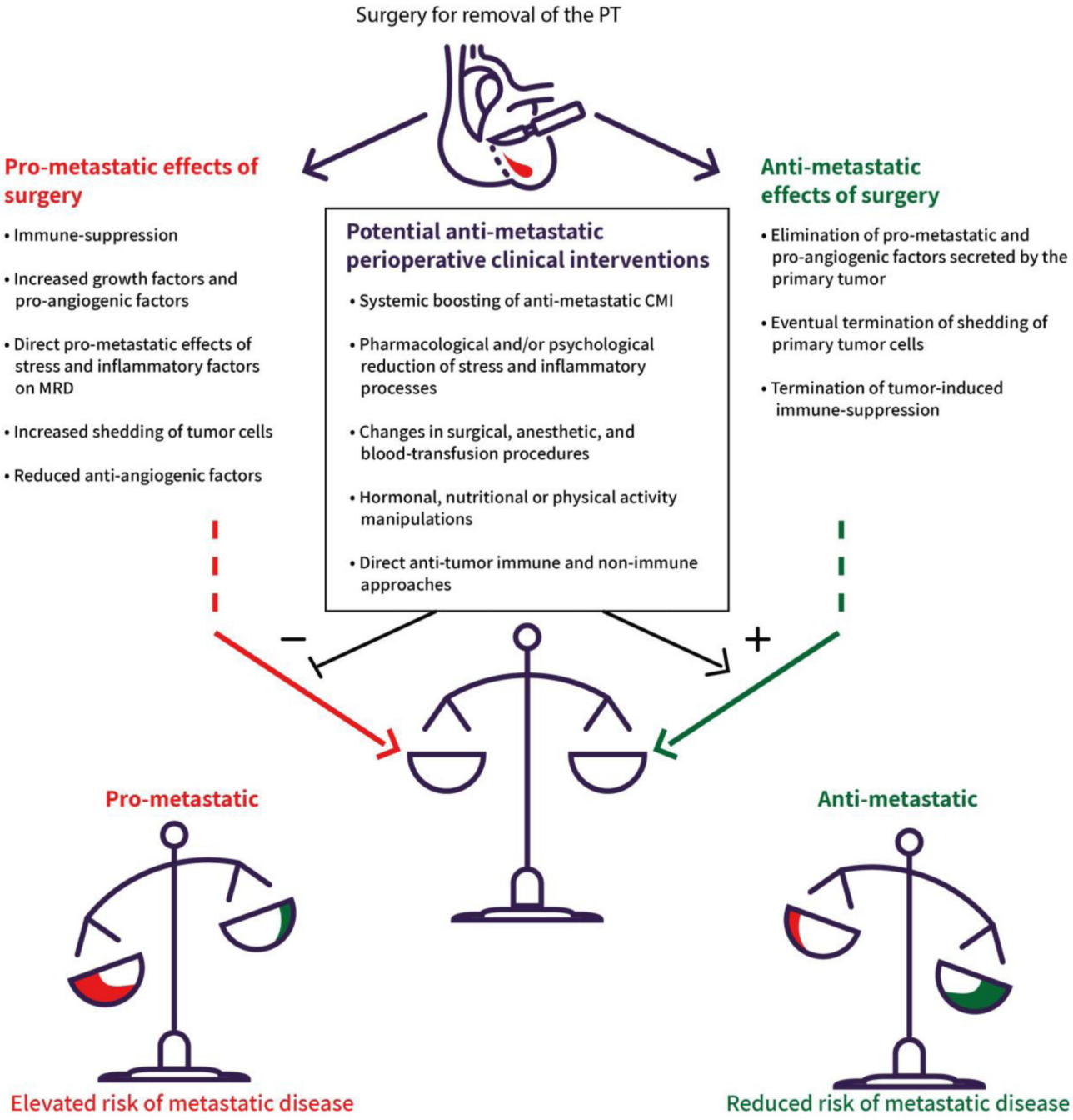

Figure 1, Key Figure. Surgery for the removal of a primary tumor (PT) induces both pro- and anti-metastatic processes.

A minor imbalance between these opposing processes during the immediate perioperative period can determine whether minimal residual disease (MRD) will progress toward accelerated growth, or revers toward dormancy/regression. In either case, the effect is often self-propagating, leading to a “snowball-like effect” that has the power to determine long-term cancer outcomes. Several perioperative interventions can be used during this critical,

yet un-exploited, window of opportunity to shift the balance toward an anti-metastatic balance and potentially save the lives of operated cancer patients.