Trends in Cancer

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Opinion

Tumor Excision as a Metastatic Russian Roulette: Perioperative Interventions to Improve Long-Term Survival of Cancer Patients

Shamgar Ben-Eliyahu[1,*]

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 postoperative metastatic disease and that these processes can be manipulated to improve cancer survival. Specifically, tumor excision facilitates both prometastatic and antimetastatic processes, which, within each domain, are often synergistic and self-propagating. Consequently, minor perioperative dominance of either prometastatic or antimetastatic processes can trigger a 'snowball-like effect' leading to either accelerated progression of minimal residual disease (MRD) or its dormancy/elimination, establishing the 'surgical metastatic roulette'. Thus, the IPP should become a significant antimetastatic therapeutic arena, exploiting feasible approaches including immunotherapies and manipulations/modifications of inflammatory-stress responses, surgical procedures, and hormonal status.

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 postoperative metastatic disease

Primary tumor excision induces both prometastatic and antimetastatic 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 antimetastatic immunity; and (ii) directly facilitate prometastatic and progrowth characteristics in the primary tumor and in minimal residual disease.

Several antimetastatic approaches are feasible and effective during the IPP with minimal adverse effects, including some immunotherapies and antistress-inflammatory approaches, but none has been integrated into the standard clinical routine.

Uncertainty Regarding Postoperative Metastatic Disease

In many cancer patients who have been operated on, 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 postoperative metastatic disease. In this opinion article, I argue that the immediate perioperative period (IPP) contributes significantly to this uncertainty and that specific prometastatic and antimetastatic processes during this period can be manipulated to potentially improve patients' chances of remaining disease free.

Prometastatic Effects of Surgery

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 to weeks after surgery) often increase the risk for the progression of preexisting micrometastases and for the initiation of new metastases through: (i) directly affecting malignant tissue; (ii) suppressing antitumor cell-mediated immunity (CMI) or protecting minimal residual disease (MRD); and (iii) affecting the microenvironment of the tumor/MRD (Figure 1, Key Figure) [1–3]. Mechanisms underlying these deleterious effects have been implicated or speculated on by numerous translational and clinical studies and include: (i) potential excess shedding of tumor cells and increased numbers of circulating tumor cells (CTCs) as a result of the surgical manipulation of the malignant tissue, its blood vessels, and/or adjacent tissue [4,5]; (ii) a drop in antiangiogenic factors (e.g., endostatin, angiostatin) as a result of the removal of the PT [6]; (iii) local and systemic increases in levels of growth factors and proangiogenic factors, physiologically aimed to promote postoperative tissue healing but inadvertently facilitating the growth of MRD [7]; (iv) protection of CTCs from immunocytes lysis by 'platelet cloaking', which also promote the capacity of CTCs to extravasate and establish new organ metastases [1,8];

[1]Sagol School of Neuroscience and School of Psychological Sciences, Tel Aviv University, Tel Aviv, Israel

*Correspondence: shamgar@tauex.tau.ac.il (S. Ben-Eliyahu).

Key Figure

Surgery for the Removal of a Primary Tumor (PT) Induces Both Pro- and Antimetastatic Processes

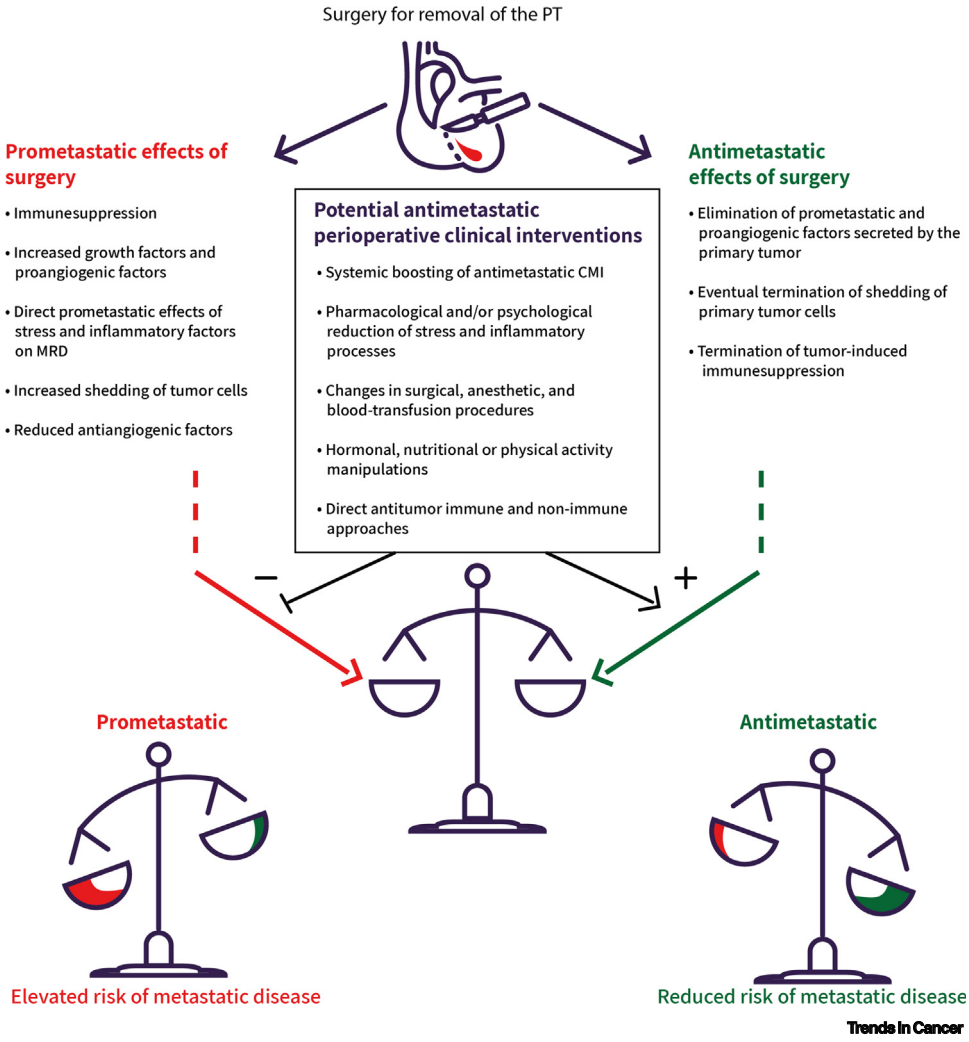

Figure 1. A minor imbalance between these opposing processes during the immediate perioperative period can determine whether minimal residual disease (MRD) will progress toward accelerated growth or reverse toward dormancy/regression. In either case, the effect is often self-propagating, leading to a 'snowball-like effect' that has the power to determine long-term cancer outcomes. Several perioperative interventions can be used during this critical, yet unexploited, window of opportunity to shift the balance toward an antimetastatic balance and potentially save the lives of cancer patients who have been operated on. Abbreviation: CMI, cell-mediated immunity.

and (v) marked suppression of antimetastatic CMI [e.g., cytotoxic T lymphocytes (CTLs), natural killer (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 released 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 mediates many of the abovementioned prometastatic processes and triggers additional processes to do so [2,3,14] (Box 1).

Antimetastatic Effects of Surgery

In addition to having prometastatic effects, the removal of the PT also triggers processes that exert antimetastatic effects. Most healthy adults bear microfoci 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 micromalignancy, 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 micromalignancies 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 the 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 the creation of new metastases. Additionally, the removal of the PT terminates PT secretion of a variety of factors that: (i) suppress antimetastatic immunity; (ii) promote the establishment of metastatic niches [18,19]; and (iii) support the growth of already established micrometastases that are not yet self-sufficient. For example, PGs and interleukin (IL)-8, which are often secreted by PTs, are known to cause systemic suppression of NK cells and of intratumoral antimetastatic 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 prometastatic processes, are antimetastatic to a degree that prevents the postoperative progression of metastatic disease in a substantial portion of cancer patients operated on, despite the postoperative existence of MRD (see Box 2 for mechanisms and examples) (Figure 1).

A snowball Effect

Multifaceted biological processes, such as the progression of metastases, are hard to predict given the known and expected interactions between the many factors that affect them. We assert that both the prometastatic and the antimetastatic processes induced by surgery are often synergistic within each category and/or are self-propagating. For example, epithelial-to-mesenchymal transition (EMT) together with high matrix metalloproteinase (MMP)2/MMP9 levels can lead to an excess release of tumor cells into the circulation that, when combined

Box 1. Catecholamines and Prostaglandins Promote Metastasis: Mechanisms and Prevention

CAs and PGs suppress antimetastatic CMI, directly by deactivating NK and CTL cells and indirectly by reducing levels of pro-CMI T helper (Th)1 cytokines [9]. Additionally, both CAs and PGs directly affect malignant cells, making them more aggressive and improving their metastatic capacity through various mechanisms, including increased tumor cell survival, proliferation, motility, and resistance to anoikis [2,3,52]. CAs and PGs increase tumor release of vascular endothelial growth factor (VEGF), MMP2, MMP9, IL-6, and IL-8, factors that assist the malignant tissue in acquiring new blood vessels, penetrating the extracellular matrix, and proliferation [2,3,52]. CAs and PGs were each shown to induce an EMT in malignant tissue [53,54], another prometastatic process with well-established negative predictive value for DFS in several cancer types [55–59]. Last, CAs and PGs induce a M2-macrophage shift in metastatic foci, which supports metastatic growth [52,60].

Therefore, it would be expected that perioperative inhibition of CA and PG signaling would reduce postoperative metastatic disease. Indeed, a short perioperative use of a β-blocker (propranolol) and a 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 [22–24,61–66]. For example, a single administration of propranolol and etodolac on the day of 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 [65].

Box 2. Mechanism of Antimetastatic 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 CTCs and have the capacity to kill 'resistant' tumor cells [47,61,62,67]. Once immune suppression is eased by the elimination of PT-derived immune-suppressive factors, such as transforming growth factor (TGF)-β and IL-6 [68–71], the lysis of the last remaining CTCs after removal of the PT can markedly reduce the chances of postoperative 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 immunocyte lysis, by lack of blood supply, and/or by lack of growth factors. The elimination of immunosuppressive factors released by the PT and/or induced by stress and surgery [9] may assist tumor-infiltrating lymphocytes (TILs) (e.g., NK cells, CTLs) to eliminate tumor cells in established micrometastases [70–73]. Additionally, proangiogenic, progrowth, and proinvasion factors are abundantly secreted by the PT, including IL-6, IL-8, VEGF, epidermal growth factor (EGF), platelet-derived growth factor aa (PDGFaa), migration inhibitory factor, and SerpinE1 [19,65,66,74]. These factors may be critical for the maintenance and progression of micrometastases [20,75–78], especially at an early stage when these microscopic malignant foci are not yet self-sufficient [66]. Thus, the removal of the PT and the elimination of its secreted factors is expected to halt the progression of micrometastases. We recently found that: (i) the secretome of a human PT supports the growth of its spontaneous metastases in nude mice; and (ii) the removal of the PT causes reliable regression and dormancy of its micrometastases, but not of larger metastases that are apparently self-sufficient [66]. In cancer patients, postoperative regression of metastases is a well-documented phenomenon in several types of cancer, but is a very rare event [79,80]. 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, a postoperative halt of MRD progression or its regression may be markedly more prevalent clinically in unrecognized metastases than is currently assumed.

with immune suppression and growth factors, can markedly increase the chances of the establishment of 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 the 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 antimetastatic immunity will simultaneously recover from immune suppression, some dormant or regressing metastases may be eliminated. Consequently, if the balance between the pro- and antimetastatic processes is significantly leaning toward one direction, beyond a certain threshold it may create a snowball effect leading either to accelerated progression of MRD or to regression/dormancy of MRD (Figure 1).

Is it a Roulette?

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, leukocyte infiltration profile, malignant genomic composition, number of CTCs, etc., there is still uncertainty whether a patient at risk will eventually show disease recurrence. This uncertainty similarly exists in patients who receive neoadjuvant 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 may 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 (Figure 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 development of metastatic disease by tipping the scale toward an antimetastatic dominance.

Immediate Perioperative Interventions Can Significantly Impact Long-Term Cancer Outcomes

Given existing uncertainty in the occurrence of postoperative metastatic disease, the critical empirical question is whether short interventions or events during the critical perioperative period can tilt the balance between pro- and antimetastatic processes, leading to either metastatic dormancy/regression or metastatic progression. I assert that there is ample preclinical 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 CA and PG signaling [22–24], the use of specific anesthetic regimens [25], or perioperative nutrition regimens [26]. For example, in a study where spontaneously metastasizing orthotopic PTs were removed surgically in mice, combined inhibition of CA and PG signaling (i.e., the use of propranolol and etodolac), given only on the day of tumor excision, prevented metastatic disease and doubled the long-term survival rate in two syngeneic tumor models [2,22].

Human Clinical Trials

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

First, 3-day preoperative low-dose IL-2 treatment ending 36 h prior to colorectal resection significantly reduced the 5-year cancer progression rate [27]. Even more impressive, pancreatic cancer patients showed significant improvements in 3-year DFS and overall survival (OS) following this immediate preoperative 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 was evident [27].

Another line of study addresses the controversial claim that levels of female sex hormones during surgery for breast cancer impact long-term cancer outcomes [29–31]. One hypothesis is that high estrogen levels concurrent with low progesterone levels is a perioperative risk factor for metastatic progression [30], potentially because this hormonal pattern promotes greater perioperative immunosuppression [32] and other prometastatic processes. A pivotal RCT conducted in 1000 women with operable breast cancer showed that a single preoperative administration of a synthetic progesterone (hydroxyprogesterone), which disrupts this potentially disadvantageous hormonal pattern, reduced recurrence rates in lymph-node-positive patients (who are at risk for metastatic disease) but not in lymph-node-negative patients, irrespective of tumor hormonal receptor status [33].

Last, recent studies targeted the 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 tumors indicated a significant reduction in EMT status and in the activity of several prometastatic/proinflammatory transcription factors, including GATA-1, GATA-2, early growth response-3 (EGR3), and signal transducer and activator of transcription-3 (STAT-3) [34–36]. Additionally, a change in the tumor-infiltrating white blood cell (WBC) milieu toward an improved immunological response against the malignant tissue was evident [34,36], and reduced levels of the proliferation marker Ki-67 were evident in breast cancer patients [35]. The treatment also reduced serum prometastatic and proinflammatory indices and improved immune-antimetastatic indices [36]. Last, although these studies were not powered to study the long-term cancer outcome, an exploratory analysis of 3-year DFS in colorectal cancer patients indicated a statistically nonsignificant trend for improved DFS from 33.3% in placebo patients to 12.5% in treated patients (intent-to-treat analysis; $P = 0.239$) [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 with placebo [34,36]. In translational studies, this treatment had no adverse effects on wound healing, anastomosis strength, or abdominal wall wounds [37] and improved postoperative long-term survival rates [22].

Overall, these RCTs clearly show that short perioperative interventions that are safe and easy to administer can improve the antimetastatic characteristics of the malignant tissue and/or improve long-term cancer outcomes in patients with various cancer types.

Human Retrospective Studies

Numerous retrospective clinical studies have reported adverse or beneficial long-term cancer outcomes of various immediate perioperative events or modifications of surgical procedures. For example, intraoperative use of the anesthetic agent dexmedetomidine [38], blood transfusion, the occurrence of hypothermia, wound infection [39,40], and 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 with the common use of volatile anesthesia, significantly improved the 5-year OS [43,44]. These studies, although retrospective and statistically controlling only for known risk factors, suggest that immediate perioperative events and processes that are often temporary and appear innocuous (e.g., the intraoperative use of dexmedetomidine or propofol) can have significant long-term cancer consequences.

Perioperative Use of Antimetastatic Interventions and Practical Considerations

Contraindications to surgery are the main reason for not using antimetastatic treatments during the short perioperative timeframe. These include jeopardizing postoperative tissue healing and suppression of immunity, which are common adverse effects of chemo- and radiotherapies [45]. With respect to immune therapies, their common inflammatory-pyrogenic effects: (i) are often indistinguishable from signs of infection, which would usually lead to surgery being postponed; and (ii) may theoretically increase the risk of systemic inflammatory response syndrome (SIRS), which is a postoperative life-threatening complication. Last, some preoperative interventions, such as immunonutritional, physical activity, or psychosocial preparations for surgery, may require surgery to be postponed 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 [45]. 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 the adverse effects of each other. For example, the perioperative use of the immune-stimulating Toll-

like receptor (TLR)9 agonist CpG-C, which is self-limiting in terms of its inflammatory-pyrogenic effects, simultaneous with blockade of inflammatory-stress responses through propranolol and etodolac, was found in translational studies to have synergistic effects without noticeable adverse effects [46].

Overall, our current understanding and empirical evidence indicate that several antimetastatic approaches should be considered and/or tested perioperatively, some without any modification. These include: (i) systemic boosting of antimetastatic CMI through immune-stimulating agents (e.g., CpG-C, low doses IL-2/IL-12) [45,47]; (ii) reduction of stress and inflammatory processes, which could prevent immune suppression and the direct promotion of the effects of CAs and PGs on the progression of MRD [3,34–36,48]; (iii) changes in surgical, anesthetic, and blood-transfusion procedures, which were shown or suggested to improve postoperative survival rates in cancer patients [1,49]; (iv) various perioperative hormonal [33], nutritional [50], physical activity [51], and psychological manipulations [2,3,45]; and (v) various antitumor approaches that may be adjusted to the perioperative period, including immune-checkpoint modification therapies and other antimetastatic approaches.

Concluding Remarks

The short perioperative period is characterized by many prometastatic and antimetastatic processes that can lead either 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 antimetastatic approaches are rarely part of perioperative clinical routine, forfeiting a major potential antimetastatic approach due to our complacency with the uncertainty that stems from perioperative processes. It is time to make the IPP a major focus for antimetastatic interventions by clinically testing feasible existing approaches and by modifying other approaches for use in this timeframe (see Outstanding Questions). 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 than the postoperative 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 speedily growing snowball.

Outstanding Questions

Would a potential perioperative intervention jeopardize or improve tissue healing?

Would perioperative pyrogenic effects of immunotherapy increase or decrease the short-term risks of surgery, including postoperative infections and SIRS?

Could preoperative nutritional and/or physical-exercise interventions reduce the likelihood/severity of the 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 do they contraindicate each other?

Acknowledgments

I am thankful to my students and colleagues for critical discussions of the issues presented herein and for our collaborative empirical work that set the basis for this opinion article.

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