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The Perioperative Period is an Underutilized Window of Therapeutic Opportunity in Patients With Colorectal Cancer

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Objective: In this review, we address the underlying mechanisms by which surgery augments metastases outgrowth and how these insights can be used to develop perioperative therapeutic strategies for prevention of tumor recurrence.

Summary Background Data: Surgical removal of the primary tumor provides the best chance of long-term disease-free survival for patients with colorectal cancer (CRC). Unfortunately, a significant part of CRC patients will develop metastases, even after successful resection of the primary tumor. Paradoxically, it is now becoming clear that surgery itself contributes to development of both local recurrences and distant metastases.

Methods: Data for this review were identified by searches of PubMed and references from relevant articles using the search terms "surgery," "CRC," and "metastases."

Results: Surgical trauma and concomitant wound-healing processes induce local and systemic changes, including impairment of tissue integrity and production of inflammatory mediators and angiogenic factors. This can lead to immune suppression and enhanced growth or adhesion of tumor cells, all of which increase the chance of exfoliated tumor cells developing into secondary malignancies.

Conclusions: Because surgery remains the appropriate and necessary means of treatment for most CRC patients, new adjuvant therapeutic strategies that prevent tumor recurrence after surgery need to be explored since the perioperative therapeutic window of opportunity offers promising means of improving patient outcome but is unfortunately underutilized.

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Colorectal cancer (CRC) is one of the most prevalent solid organ cancers in both men and women in developed countries. Approximately 1 million cases are recorded every year worldwide, and over half a million patients die of this disease yearly.[1] Currently, surgical removal of the primary colorectal carcinoma is the preferred treatment.[1] Unfortunately, postsurgical development of metastases is a frequent complication, which is accompanied by high morbidity and mortality. Approximately 25% to 33% of all patients already have metastatic disease upon diagnosis of CRC. However, another 25% to 30% of patients who do not have visible evidence of metastases at the time of diagnosis and who are therefore eligible for surgery with curative intent, will develop metastases within 5 years.[2,3]

The notion that surgical removal of CRC may enhance the risk of tumor recurrence was already acknowledged by the ancient Greeks, who cautioned against disturbing tumors. This was reiterated by Paget and Halsted in the beginning of the 20th century.[4,5] The theory that surgery enhances the risk of tumor growth reemerged in the 60s when it was realized that the long-term benefits of tumor removal were modest in comparison with nonoperated historical controls. However, it was discovered that addition of chemotherapy to surgery resulted in improvements in survival. Unfortunately, in the last 40 years, these promising results were largely ignored. However, presently new insights in mechanisms of surgery-enhanced tumor growth and successful use of perioperative adjuvant therapies have led to renewed interest in this concept.

It is believed that metastasis of CRC often occurs through the portal circulation, which generally leads to the development of liver metastases, although occasionally, lung, bone, or brain metastases are observed. Alternatively, secondary malignancies can develop by spread through the lymphatic system or via intraperitoneal dissemination. To metastasize, tumor cells must undergo a complex cascade of events (extensively reviewed by Bird et al).[3] Tumor cells need to detach from the tumor and invade into the blood circulation or lymphatic system. For this to happen, tumor cells must decrease expression of specific adhesion molecules, such as cadherins and catenins.[6] Additionally, production and secretion of proteolytic enzymes like metalloproteinases is essential for degradation of the basement membrane and subsequent intravasation.[7] Tumor cells must then withstand both mechanical forces and immunologic defense systems, which eliminate most of disseminated tumor cells. A wide range of adhesion molecules including intercellular adhesion molecule, vascular cell adhesion molecule, and selectins on both tumor cells and target organs mediate subsequent arrest, which must take place rapidly as disseminated tumor cells have limited life span.[3] Thus, classic metastasis is a complex and inefficient process because of the multiplicity of events that are required. However, we recently proposed an alternative route of metastasis that is initiated after surgery and which short-cuts several of these steps (see in the following paragraphs).[8] This review summarizes the growing body of evidence that supports the concept of surgery-induced metastases (Fig. 1) and focuses on the different mechanisms underlying this phenomenon (Fig. 2). Additionally, the therapeutic window of opportunity in the perioperative period during CRC resection will be addressed.

Surgery-Induced CRC Metastases Development

It was demonstrated in animal models that sites of injury are a preferential locus for tumor outgrowth, and it was previously shown that surgical trauma enhances loco-regional metastases.[9] Severity of trauma was furthermore shown to correlate with the amount of tumor load, as laparoscopy (causing minor trauma) induced less loco-regional tumor load compared with laparotomy.[10] Interestingly, the influence of surgery on tumor development is not confined to local peritoneal sites. Several reports describe that surgical trauma results in systemic alterations that accelerate tumor development.[11,12] For example, it was demonstrated that thoracotomy enhances tumor development in the peritoneal cavity.[13] Moreover, we recently established a new model in rats by placing a catheter in the portal vein, which allowed investigation of liver

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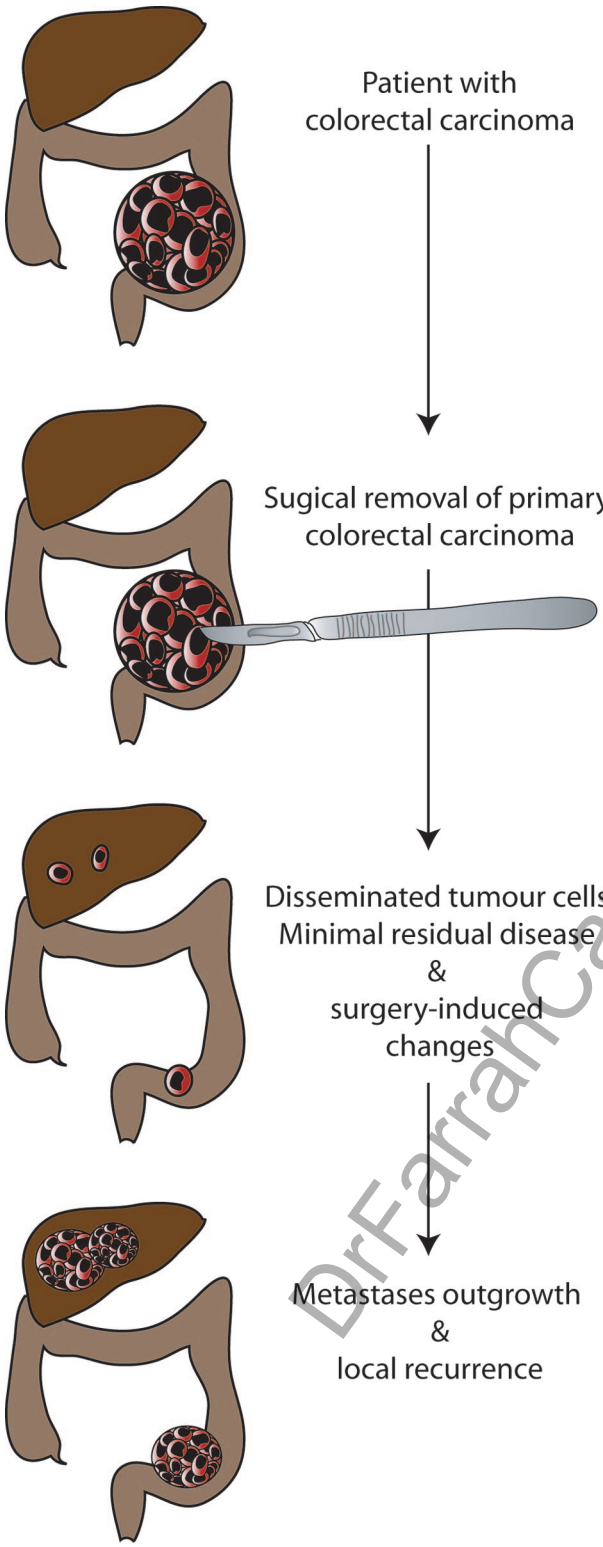

FIGURE 1. Surgery-induced metastases formation. In the majority of patients, the primary colorectal carcinoma is surgically removed. During the operation, tumor cells are spilled and enter the peritoneal cavity and circulation. Additionally, the operation induces a local and systemic stress response, which can accelerate metastases development.

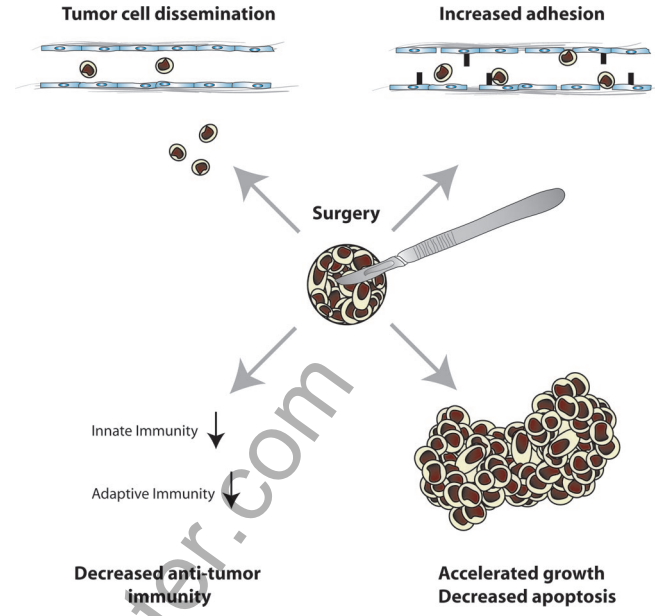

FIGURE 2. Overview of mechanisms by which surgery accelerates tumor recurrence. Surgical trauma can augment metastases formation in several ways. First, manipulation of the tumor results in spillage of tumor cells, which can be found in the peritoneal cavity and circulation shortly after resection. Additionally, the operation induces damage to the vasculature and peritoneal lining. Several adhesion molecules are up-regulated and vessel integrity is compromised. This way, spilled tumor cell can readily adhere in the peritoneal cavity and in the liver sinusoids. Surgery-induced immunosuppression may furthermore facilitate metastases outgrowth as spilled tumor cells are less efficiently eradicated. Finally, systemically released mediators, including angiogenic and growth factors, may stimulate growth or impede apoptosis of tumor cells.

metastases outgrowth in the absence or presence of surgery. Using this model, we showed that intraperitoneal surgery increased liver metastases outgrowth.[14] Thus, surgery induces both local and systemic changes that facilitate metastases development.

Unfortunately, since clinical research investigating the effects of surgical resection on local and systemic metastases development has limitations, this topic is still subject of debate and not yet generally accepted despite the overwhelming evidence from experimental studies. Clearly, omitting surgery in patients with CRC in an objective randomized clinical trial is unacceptable, and as such, we can only rely on anecdotal clinical evidence to evaluate this phenomenon. For example, an accepted historical database of patients with breast cancer that did not have surgery showed 1 peak in the hazard ratio for death around the fourth and fifth year.[15] However, 2 peaks, namely one around 3 to 4 years after surgery, and one 8 years after surgery were observed in patients who underwent mastectomy.[16] This finding strongly supports that surgery alters the natural course of the disease by elongating life expectancy in the greater part of the patient population, but also by simultaneously shortening survival in a smaller subset of patients. Thus, both experimental and clinical evidence support that surgery, although greatly reducing tumor mass and potentially curative, paradoxically can also augment metastases development.

Surgery-Induced Tumor Cell Dissemination

Cancer tissue is particularly noncohesive and tumor cells are often found in the tumor vasculature. Tumor excision almost always disrupts the neoplasm or its associating blood vessels, which can lead to dissemination of tumor cells in the circulation or in the peritoneal cavity.[17,18] However, circulating tumor cells can also already be detected in the majority of CRC patients before surgery.[19] Additionally, various reports suggest that handling of the tumor during resection can result in spilling of tumor cells, as increased numbers of free floating tumor cells have been observed in the peritoneum, circulation, and liver.[20,21] Several clinical studies, which analyzed perioperatively and postoperatively obtained blood, showed that tumor cell presence was a strong predictor of CRC recurrence.[19,22]

These studies not only indicate that examination of disseminated tumor cells in blood after surgery may serve as a prognostic tool, but also provide evidence that surgical resection results in an increase of exfoliated tumor cells, which can develop into metastases. However, implantation of circulating tumor cells is a highly inefficient process because most circulating tumor cells are rapidly removed by the immune system. As such, shedding of tumor cells during surgery cannot fully explain the high recurrence rate. Surgery inevitably leads to trauma, which initiates a stress response that encompasses a wide range of endocrinologic, immunologic, and hematologic effects. It is now clear that the systemic inflammatory response after surgery also contributes to successful tumor development via several mechanisms.

Defective Antitumor Immunity

First, surgery is associated with a transient suppression of immunologic functions, starting within hours after surgery and lasting over 7 days.[23] Directly after surgery, the acute phase response is initiated to counteract microbial invasion, to clear the body of debris and to induce repair of injured tissues. Immunologically, the postsurgical acute phase response is associated with increased secretion of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α.[24,25] Although release of these pro-inflammatory cytokines could potentially favor antitumor cytotoxicity, subsequent release of anti-inflammatory mediators, including transforming growth factor (TGF)-β, IL-10, and IL-1 receptor antagonist, prevails and induces a general systemic immunosuppression.[26] Additionally, rapid postsurgical release of corticosteroids, which are potent anti-inflammatory mediators that impede cell-mediated immunity, hampers antitumor immune function.[27] Operative procedures that contribute to immunosuppression include administration of anesthetic agents and opioids, extent of surgery, blood transfusions, pain, and psychologic stress. It was reported that the degree of these factors correlates with severity of the immunosuppression.[28,29]

Several components of the innate immune system, including macrophages and natural killer (NK) cells, protect against metastases development by eliminating disseminated tumor cells.[30–32] However, experimental and clinical data indicate that tumoricidal activity of NK cells is reduced immediately after surgery.[33] It was demonstrated that mice undergoing either laparotomy or laparoscopy showed accelerated growth of tumors located in the flank, which was accompanied by diminished NK cytotoxicity. Additionally, animals that underwent laparotomy had a more prominent immunosuppression, which was accompanied by increased tumor growth, compared with animals that underwent laparoscopy. This indicates that the extent of injury determines the magnitude and duration of NK cell suppression.[34] The importance of macrophages in eliminating tumor cells was illustrated in experiments in which peritoneal macrophages or Kupffer cells were depleted before tumor cell administration.[30,32] In peritoneal macrophage-depleted animals, abdominal metastases outgrowth was dramatically enhanced compared with tumor growth in control animals. Similarly, Kupffer cells depletion resulted in drastic enhancement of liver metastases.[31] Thus, surgery-induced impairment of macrophage function might increase chances of exfoliated tumor cells to grow out into metastases. Next to impediment of innate immune cell function, surgery was shown to affect adaptive immune reactions as well. Surgery-induced impairment of T helper 1 cell functions in humans has been demonstrated, including diminished proliferation and production of interferon (IFN)-γ, TNF-α, and IL-2.[35] Impairment of T helper 1 responses, which are associated with cellular immunity and proliferation of cytotoxic T cells, might hamper antitumor cytotoxicity as well.

Enhanced Tumor Growth

Second, increased growth of malignancies by enhanced proliferation rate of tumor cells has been reported to underlie rapid tumor recurrence after CRC resection. It has been described that both local recurrent tumors and distant metastases show reduced apoptosis and increased proliferation compared with the primary tumor after resection.[36,37] Changes in apoptotic and cell cycle events, but also alterations in surface antigen and adhesion molecule expression, can result from alterations of the tumor cell's intracellular machinery. Surgery-induced changes in gene expression and subsequent protein expression could therefore affect tumor growth directly. Indeed, alterations in proliferation after surgery has been linked to changes in the phosphoinositide-3 kinase (Pi3k) pathway in tumor cells. Secondary and recurrent tumors showed higher expression of Pi3k compared with the primary tumors.[37,38] Additionally, targeting of this pathway with Pi3k inhibitors resulted in attenuation of increased tumor progression.[37,38]

Surgery is furthermore associated with transient plasma-compositional changes, and it was demonstrated that postoperative plasma stimulated tumor cell growth in vitro.[39] For instance, mediators such as IL-6, TNF-α, and TGF-β, which are released after surgery have been shown to accelerate tumor cell proliferation.[40] Insulin-like growth factor binding protein 3 (IGF-BP3) was reduced in blood plasma after surgery.[41] This decrease is attributed to cleavage by surgery-induced up-regulation of plasma MMP-9 levels, hereby rendering IGF-BP3 inactive.[42] As IGF-BP3 can directly induce tumor cell apoptosis and reduce tumor cell proliferation indirectly by binding insulin-like growth factor, reduction of blood plasma levels might contribute to enhanced tumor growth.[43,44] Thus, these mediators may account for increased tumor recurrence after removal of primary CRC.

After surgery, the angiogenic balance of pro- and antiangiogenic factors is shifted in favor of angiogenesis to facilitate wound healing. Especially levels of vascular endothelial growth factor (VEGF) are persistently elevated.[45,46] This may not only benefit tumor recurrence and the formation of metastatic disease, but also result in activation of dormant micrometastases.[47] Additionally, it has been suggested that primary tumors can secrete antiantigenic mediators in the circulation. These mediators suppress angiogenesis in distant micrometastases, which restricts metastases development. However, resection of the primary tumor removes the source of antiangiogenic mediators, and growth of distant micrometastases is no longer inhibited.[36]

Increased Tumor Cell Adhesion

Third, pro-inflammatory cytokines such as IL-1β, TGF-β, and TNF-α, which are released shortly after surgery, stimulated adhesion of tumor cells to mesothelial and endothelial monolayers in vitro.[48,49] Moreover, it was demonstrated that in vivo tumor cell adhesion was increased after intraperitoneal administration of

TNF-α and IL-1.[50,51] Additionally, incubation of mesothelial cells with reactive oxygen species (ROS) resulted in increased expression of adhesion molecules like intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 and increased tumor cell adherence to mesothelial cells.[52] The acute phase reaction that occurs shortly after surgical trauma is associated with influx of large numbers of polymorphonuclear neutrophils, which are potent producers of ROS. As such, ROS production by polymorphonuclear neutrophils following surgery may contribute to tumor cell arrest.

We previously demonstrated that abdominal trauma resulted in a rapid impairment of the mesothelial monolayer in the peritoneal cavity. After surgery, mesothelial cells bulged, retracted and detached, resulting in exposure of underlying extracellular matrix (ECM) components, to which tumor cells preferentially interacted. Blocking integrin subunits on tumor cells, which are the main ligands for ECM, prevented adhesion, hereby strongly supporting interaction of tumor cells with exposed ECM.[53] Surgical trauma also resulted in impaired integrity of liver vasculature, as indicated by reduced expression of tight junction molecules and increased von Willebrand factor deposition. Moreover, intraperitoneal surgery resulted in increased tumor cell adhesion and outgrowth of liver metastases, which was completely reverted when tumor cell-ECM interactions were inhibited by blocking α2 integrins.[54]

As such, we propose a novel model of surgery-induced metastasis (Table 1). During surgery, manipulation of the primary tumor results in tumor cell shedding, which overcomes the need of complex cellular changes, such as loss of E-cadherin and β-catenin expression. Additionally, in classic metastasis malignant cells have to express specific adhesion molecules for arrest and subsequent outgrowth. By contrast, surgery induces both increased expression of adhesion molecules and exposure of subendothelial ECM in the vasculature, which facilitates tumor cell arrest in target organs through commonly expressed adhesion molecules on malignant cells (eg, integrins). Thus, surgery creates permissive circumstances for tumor cells to adhere in target organs and thereby increase chances of metastases development.

THERAPEUTIC OPTIONS

Optimizing Surgical Procedures (Limiting Trauma)

It was demonstrated that patients have decreased local recurrence incidence and improved disease-free survival when they are operated by experienced surgeons in a hospital with a high incidence of CRC resections.[55] Similarly, the use of more sophisticated techniques for tumor resection has resulted in better patient outcome.[56] By contrast, necessity of blood transfusions in the perioperative period, presumably reflecting severe surgical trauma, was not only associated with enhanced postoperative immunosuppression, operative mortality, complications, and length of hospital stay, but also with increased tumor recurrence.[29,57] These data support the relation between the extend of surgical trauma and the risk of developing tumor recurrence, and suggests that reducing tissue damage will lead to better patient prognosis. Laparoscopic resection of colorectal carcinomas is now increasingly performed since faster recovery and shorter duration of hospital stay can be achieved. Additionally, surgery-induced alterations of immune responses are less pronounced after laparoscopic procedures, reflected by diminished and faster normalization of cytokine production and unimpaired immune cell function.[25,58] Moreover, many compositional changes in blood plasma after open surgery, including levels of MMP-9, VEGF, IL-6, TNF-α, and IGF-BP3 that have been shown to enhance in vitro tumor growth, are not present after laparoscopic surgery.[39,42,45,59,60] Thus, there is considerable experimental and human data supporting that laparoscopic surgery results in reduced risk of tumor recurrence and metastases formation compared with open surgery. Lacy et al showed improved survival and fewer recurrences in patients undergoing laparoscopic surgery, compared with open surgery.[61–63] Furthermore, a meta-analysis from 2006 including 10 randomized clinical trials showed a trend of improved survival and fewer recurrences after laparoscopic resection of CRC.[64] Thus, although consensus is not agreed upon as of yet, laparoscopic surgery for CRC potentially favors patient outcome over open surgery.

Unfortunately, even though tissue damage may be reduced by developing better surgical techniques, every operation for intra-abdominal cancer is inevitably accompanied by peritoneal trauma, which cannot be avoided altogether. Understanding surgery-induced tumor development may however open up new possibilities for perioperative adjuvant therapies, which will benefit patient survival.

Immunotherapy

Because surgery was shown to induce immunosuppression, the perioperative period represents an advantageous moment for immunomodulation. Studies have been performed that investigated efficacy of perioperative administration of immunostimulatory mediators like IL-2, granulocyte macrophage-colony stimulating factor (GM-CSF), and IFNs.[65,66] In general, these clinical studies showed that surgery-associated immunosuppression was reduced by immunomodulation, as immune cell numbers and antitumor cytotoxicity were restored and production of inflammatory mediators normalized.[65–67] Animal studies furthermore supported that immunomodulation, such as administration of GM-CSF and IL-2 or TNF-α after laparotomy reduces surgery-associated tumor development.[50,68] However, no data addressing tumor recurrence and survival is yet available from randomized clinical trials. Additionally, histamine

TABLE 1. Characteristics of Classical and Surgery-Induced Metastasis and Potential Therapeutic Options to Minimize the Latter Phenomenon

	Classical Metastases Development	Surgery-Induced Metastases Development	Therapeutic Options
Detachment	Loss of cell-cell contact	Manipulation of primary tumor	Minimizing surgical trauma
	Loss of cell-stroma contact		
Adhesion	Upregulation of adhesion molecules on tumor cell surface	Surgery-induced upregulation of adhesion molecules in target organs	Blockade of adhesion (anti-integrin antibodies, RGD peptides)
		Adhesion to surgery-induced exposed ECM	Prevention of endothelial activation/ retraction
Immune escape	MHC downregulation	Surgery-induced immunosuppression	Immunomodulation (GM-CSF, IFN, IL-2)
	Anti inflammatory cytokine production		Antibody therapy
Growth	Production of growth factors and angiogenic mediators by tumor	Surgery-induced release of angiogenic and growth factors	Chemotherapy Radiotherapy Anti-angiogenic therapy (anti-VEGF)

H2 receptor antagonists (H2RA), like cimetidine, have been reported to improve antitumor immunity in the perioperative setting by increasing numbers of tumor-infiltrating and peripheral lymphocytes.[69,70] Several clinical trials showed a beneficial effect of H2RA on survival.[71,72] As other studies were unable to show a beneficial effect, no consensus has been reached yet regarding the efficacy of H2RA in CRC. It is, however, now becoming clear that specific subsets of CRC patients, such as patients without complications in the perioperative period and patients with tumors expressing high levels of sialyl Lewis antigens X and A, do benefit from H2RA treatment.[73,74] Thus, further research should aim to unravel the underlying mechanisms by which H2RA work, to identify eligible candidates for this treatment.

An alternative promising approach consists of using tumor vaccines, which might confer active specific cell-mediated antitumor immunity. The efficacy of tumor vaccines has been studied extensively and results so far are promising.[75] The most encouraging results were noted in trials including over 1300 patients in which tumor vaccination was performed after resection. These trials demonstrated significantly reduced recurrence rates and improved survival, suggesting that a low tumor burden after resection favors efficacy of this strategy.[76,77] As such, the perioperative period may represent an even more advantageous moment for induction of antitumor immunity. Additionally, an adequate adaptive immune reaction against the tumor in the perioperative period might overcome surgery-induced immunosuppression.

Several authors demonstrated an important tumor growth-enhancing role for lipopolysaccharide (LPS) in postoperative period. Following several surgical procedures for resection of CRC levels of LPS are increased as a result of bacterial translocation from the gastrointestinal tract into the systemic circulation. LPS can enhance metastatic capacity and induce apoptosis resistance of tumor cells.[78,79] As such, therapies that target LPS could favor patient outcome. Another possible intervention in this context is perioperative administration of probiotics, which are reported to positively alter the immune system and prevent overgrowth of bacteria in the gut.[80] The latter minimizes the risk of bacterial translocation and subsequent spread of LPS during surgical resection of CRC. Although there is no consensus regarding perioperative use of probiotics, it has been reported that administration of probiotics in the perioperative period reduces the risk of infections and possibly contributes to prevention of tumor recurrence after surgery.[81,82]

An alternative and very promising approach to stimulate antitumor immune responses constitutes the use of monoclonal antibodies (mAb) that have been developed to specifically target proteins that are (over-) expressed on tumor cells. The Fc tails of mAb can be recognized by immune cells, which are then able to kill the target tumor cell more effectively via antibody dependent cellular cytotoxicity. Postoperative treatment of rats with mAbs directed against CC531s colon carcinoma cells was able to prevent surgery-induced development of liver metastases (own unpublished data). In humans, most carcinomas of the colon, rectum, pancreas, and stomach express Ep-CAM.[83] A phase II clinical trial, in which anti-Ep-CAM mAb Edrecolomab was administered late postoperatively, showed a 32% reduction of tumor-related mortality. Furthermore, mAb-treated patients developed significantly fewer distant metastases, suggesting that Edrecolomab efficiently acts on isolated disseminated tumor cells or micrometastases.[84] Additional phase III trials have, however, yielded contradictory results and more data from trials are awaited to draw definite conclusions.[85] Until now, anti-EpCAM antibodies have only been tested in the late-postoperative period, which might not be the most advantageous moment for intervention. By starting intervention during or directly after resection, the therapeutic window might be more efficiently used.

Inhibition of Growth

The value of perioperative chemotherapy for improvement of patient prognosis by decreasing incidence of recurrent disease has been evaluated in several large clinical trials. Already in the late 70s, Nissen-Meyer et al showed that a 6-day course of chemotherapy immediately after mastectomy reduced tumor recurrence and patient death. Interestingly, the same chemotherapy course given 3 weeks after mastectomy did not show any beneficial effect.[86] In analogy, more recent trials showed that local recurrence of breast carcinoma was reduced by perioperative adjuvant chemotherapy.[87] Furthermore, perioperative chemotherapy reduced gastro-esophageal and rectal cancer recurrence and improved patient survival.[88,89] Patients suffering from CRC also benefited from perioperative chemotherapy. Both Sadahiro et al and Xu et al showed that perioperative hepatic infusion of chemotherapy after resection of CRC decreased liver metastases incidence.[90,91] The notion that perioperative but not late postoperative chemotherapy (eg, 3 weeks after surgery) is able to reduce tumor recurrence strongly argues for meticulous use of the therapeutic window of opportunities of surgical resection of cancer. As chemotherapeutics have the potential to impair wound/anastomose healing, surgeons have been reluctant to give these therapies in the perioperative period. In the abovementioned studies, however, perioperative administration of chemotherapeutics did not result in added morbidity.[88–91] This is strengthened by experimental data, in which healing intestinal anastomoses was unaffected by early postoperative chemotherapy.[92]

Because tumors need neovascularization to grow beyond 1 to 2 mm^3, angiogenesis is increasingly being targeted in the treatment of CRC metastases.[93] Although Wu et al demonstrated that perioperative GM-CSF administration was associated with enhanced VEGF plasma levels,[94] GM-CSF administration has also been shown to reduce the angiogenesis-promoting effects associated with CRC resection by increased soluble VEGF receptor 1 plasma levels. Because sVEGF receptor 1 can bind and inactivate VEGF, perioperative GM-CSF therapy could hamper tumor growth.[95] Additionally, inhibition of angiogenesis by administration of anti-VEGF mAb (bevacizumab) to conventional chemotherapeutic strategies has shown significant increase in patient responses and overall survival. Patient outcome may be improved even more when anti-VEGF mAb are administered in the perioperative setting.[96] However, perioperative use of angiogenesis inhibitors potentially affects surgical morbidity, and has been associated with a higher incidence of wound complications and gastrointestinal perforation.[97,98] Thus, caution must be taken regarding perioperative anti-VEGF therapy and further research is needed to assess the risks in more detail.

Blocking Tumor Cell Adhesion

Experimental studies showed that blocking of adhesion molecules by administration of mAb directed against carcinoembryonic antigen (CEA) can decrease metastases formation.[99] CEA is specifically expressed by a large number of CRC and can mediate tumor cell binding to endothelium. Anti-CEA mAb are effective in reducing tumor cell adhesion in vitro and diminishing metastases outgrowth in mice.[99] Although promising, interference with tumor cell adhesion to prevent metastases formation has not been explored in the perioperative clinical setting. We have shown that directly following abdominal surgery, ECM is exposed in the peritoneal cavity, which facilitated tumor cell binding. Moreover, impaired integrity of liver vasculature after surgery stimulated ECM-mediated tumor cell binding and metastases development. Blocking integrin molecules on tumor cells could prevent surgery-induced tumor cell adhesion and metastases outgrowth, both in the peritoneal cavity and in the liver.[53,100] Thus, blocking integrins on tumor cells, either by mAb or by Arg-Gly-Asp containing peptides (RGD peptides), which

are synthetic peptides that bind to several integrin subunits, potentially prevent recurrent malignant disease.[101] As such, integrins may represent promising new therapeutic targets.

FUTURE DIRECTIONS

Detailed knowledge of the changes that occur after surgery is pivotal for development of new therapeutic strategies to prevent tumor recurrence. For instance, immunomodulation therapies should be further explored. Additionally, efforts should be made to identify the mediators that induce up-regulation of adhesion molecules and impairment of vessel integrity. Subsequently, blocking of these mediators in the perioperative period by mAb could prevent tumor cell arrest and thereby inhibit metastases development. The direct effect of surgical stress on tumors could be studied with genomic and proteomic analysis. For example by laser capturing the different tumor components (eg, tumor cells, immune infiltrate) that have been exposed to surgical stress could yield new insights in etiology and therapy for surgery-induced tumor recurrence.

CONCLUSION

Accumulating evidence is emerging that supports that surgical resection of CRC adversely affects the development of local recurrence and systemic metastases. However, the small remnant of malignant tissue after surgery renders successful perioperative therapy feasible. Some treatment modalities for CRC, like chemotherapy and antiangiogenic therapy, are increasingly being tested in the perioperative period, with promising results. Potential interference with wound healing needs to be taken into account. Yet, current insights in surgery-induced metastases formation allow development of new treatment modalities that specifically target the prevention of secondary growth and subsequently decrease morbidity and mortality. As such, we feel that the window of opportunity around surgical resection for CRC is not yet fully exploited and efforts should be made to initiate new clinical trials that explore the ample opportunities of perioperative adjuvant therapies.

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