Review

Is Surgical Trauma Prometastatic?

FERDY J. LEJEUNE

Professor Emeritus of Oncology, University Hospital of Lausanne, Lausanne University, Lausanne, Switzerland

Abstract. *A review of the literature is made on animal models showing that surgical trauma can facilitate the metastatic spread of experimental tumours. Whilst clinical evidence is often lacking, except controversial results for blood transfusion, several rodent models provided proof that operative stress, peritoneal trauma and hepatectomy create conditions which facilitate cancer metastasis. Moreover, it seems that mechanisms through which the metastatic process can be enhanced include inflammation, angiogenesis, secretion of growth factors and immunosuppression. Animal models do have limitations and the clinical translation is difficult. However, these models suggest that molecular mediators induced by surgical trauma can enhance metastasis. These molecules, already identified in surgical patients, could be inhibited with already available drugs. Appropriate controlled clinical studies covering the perioperative period should be designed.*

There are some experimental observations suggesting that cancer surgery may facilitate the metastatic process. Searching in the literature for conditions where this potential risk could be measured, operative stress, peritoneal trauma and surgical resection of tumours offer the possibility to experimentally assess this problem. Except for blood transfusion associated with surgery, no strong clinical evidence was found, but rodent models provided a clear proof of concept. Clinical translation is difficult and it is a hard problem to overcome because surgery is rarely unavoidable in cancer and most oncologists and surgeons pay little attention to the pathophysiological response to surgical trauma.

This review is based on a literature search in Pubmed and Google. The following key words were used for the search: surgery and tumour metastasis facilitation; operative stress and

metastasis; immunosuppression and metastasis; peritoneal/ peritoneum trauma and metastasis; hepatectomy and metastasis process; blood transfusion and metastasis; mechanisms of metastatic process; inflammation and metastasis; angiogenesis and metastasis; inhibitors of metastatic process; angiogenesis inhibitors; growth factors inhibitors.

Only articles from peer reviewed journals were considered. Case reports were excluded.

Blood Transfusion

There has been controversy for many years on the role of blood transfusion in the facilitation of the metastatic process. Numerous clinical studies were conducted regarding colorectal cancer surgery. A large meta-analysis published in 1998 (1), showed that out of 32 studies covering 11,071 patients, 19 included multivariate analysis and, among them, 11 suggested a negative impact on survival. Only nine studies were prospective, as pointed out elsewhere in a 2005 review article (2).

However, some well-conducted controlled studies suggest that blood transfusion can facilitate metastasis. Perioperative blood transfusions were found to reduce long-term survival following surgery for colorectal cancer(3). The cut-off point was transfusion of two or more units of blood which was an independent risk (hasard ratio, HR=2.7). Some authors suspected that allotransfusion could produce some sort of immunodepression. This led to a randomized trial in colorectal cancer (4) on autologous compared with allogeneic blood transfusions: no difference in disease free interval (DFI) was found, but there was an increase of local recurrence after allotransfusion and no difference in the occurrence of distant metastases was observed. The authors concluded that these results suggest that not the blood transfusions themselves but rather the circumstances necessitating them are the real predictors of metastasis. One hundred and seventeen patients who underwent curative resection of colorectal cancer were evaluated for risk factors. (5). Multivariate analysis revealed several independent risk factors for shorter survival: i) blood transfusion; ii) T stage and N stage; iii) perioperative peak of IL-6 followed by triggering of hepatocyte growth factor (HGF) and vascular cell adhesion molecule 1 (VCAM-1). This study

Correspondence to: Professor Ferdy J. Lejeune, Chemin du Levant 98, CH-1005, Lausanne, Switzerland. E-mail: ferdinand.lejeune@ unil.ch

is important because, for the first time, it shown that patients submitted to surgery can develop different cytokine and growth factor responses which might be harmful. Indeed, the role of these factors in the metastatic process has been identified in some animal models. However, for obvious reasons, no experimental data on tumour bearing animal transfusions are available.

Operative Stress

Facilitation of tumour metastasis to the lung by operative stress was demonstrated in the rat in a classical paper (6). Female rats grafted with spontaneously metastasible-transplanted tumours subjected to operative stress experienced increased lung metastases which were reduced by adrenalectomy. In the same way, hydrocortisone increased lung metastases dose-dependently. This kind of demonstration became the paradigm of immunosuppression resulting in tumour enhancement. Indeed, more recently, perioperative immunosuppression was evidenced in cancer patients. The surgically mediated decrease in natural killer (NK) cell activity was pinpointed as the major contributing factor associated with an increase in metastasis. Not only do commonly used anaesthetic and opioid agents inhibit NK activity, but also surgery itself results in a 3- to 4-fold increase in retention of metastasis in experimental models (7).

Peritoneal Trauma

Peritoneal trauma in visceral surgery can facilitate metastasis (8). A correlation ($p<0.018$) was found between the amount of peritoneal trauma (surgical compared with wiper) and the degree of tumour take at damaged peritoneal surface. Moreover, tumour take at remote peritoneal sites was also correlated to trauma intensity ($p<0.005$), suggesting the existence of a mediator. Tumour growth promoting effects could be passively transferred with lavage fluid to naïve recipients. The authors did not identify the involved factors but inflammatory mediators are likely to be the effectors, as demonstrated by tumour obtainment in experimental granulation tissue (9). There was a clear correlation of tumour formation with the amount of growth factors induced in the granulation tissue which did vary with time: vascular endothelium growth factor (VEGF), transforming growth factor beta (TGFbeta) and lysophosphatidic acid (LPA).

It is frequently claimed that laparoscopic surgery is preferable to laparotomy. It was of interest to evaluate the two methods in terms of effect on cancer metastasis. The facilitation of peritoneal dissemination of a tumour was studied in a rabbit model (10). Inoculation of tumour cells was performed during laparotomy or laparoscopy, or by intraperitoneal (i.p.) injection as control. Whilst inoculation of a small number of tumour cells did not lead to any difference, inoculation of a large number of tumour cells induced a mean of 14 peritoneal metastases after laparotomy, 9.9 after laparoscopy (non significant, NS trend) and 3.3 in the control.

The results of these studies strongly suggest that peritoneal trauma, even limited, can facilitate tumour spread in the peritoneal cavity and that it is mediated by the up-regulation of growth factors.

Laparoscopic surgery induces alterations in the peritoneal integrity and causes local acidosis, probably due to peritoneal hypoxia. Deleterious effects on the immune system and inflammation, together with inhibition of peritoneal plasmin lead to conditions enhancing tumour metastases (11).

However, clinical evidence is still lacking. A large clinical trial comparing open surgery with laparoscopic colectomy for colorectal cancer did not identify an increased risk of peritoneal recurrence associated with the laparoscopic approach (12).

Hepatectomy

Removing a part of an organ can also facilitate metastasis in animal models. Partial hepatectomy has been used by several authors as a model because it creates conditions facilitating both liver and lung metastasis. Facilitation of tumour growth within the rat liver was demonstrated following intraportal injection of syngeneic tumour cells(13). After two third partial hepatectomy, tumour cells grew at the excision scar if hepatectomy had been carried out less than 2 days before and if it had been performed 4-7 days before, tumours grew within the regenerating lobe. Animals with intact liver had few tumours. Heparin-binding epidermal growth factor-like –a member of theepidermal growth factor (EGF) family-peaked at day 2 after hepatectomy. Lung metastasis was evaluated during liver regeneration after hepatic resection in rats (14). Partial hepatectomy followed by intravenous injection of carcinoma cells, resulted, 14 days later, in increased number of lung colonies and shorter survival. The number of metastases correlated with the extent of hepatectomy. Similarly, colon carcinoma cells injected intravenously produced increased number of lung nodules only when this was synchronous to partial hepatectomy (15).

Hepatic radiofrequency ablation is associated with increased expression of matrix metalloproteinase 2 (MMP-2) and MMP-9 in macrophages in the transition zone surrounding the coagulated hepatic parenchyma, contributing to an environment beneficial for tumour invasion (16).

Mechanisms Involved in Metastasis Facilitation

Taken together, all these effects of various surgical procedures, clearly support the concept already proposed as early as in 1978, of oncotaxis (17): inflammation causes
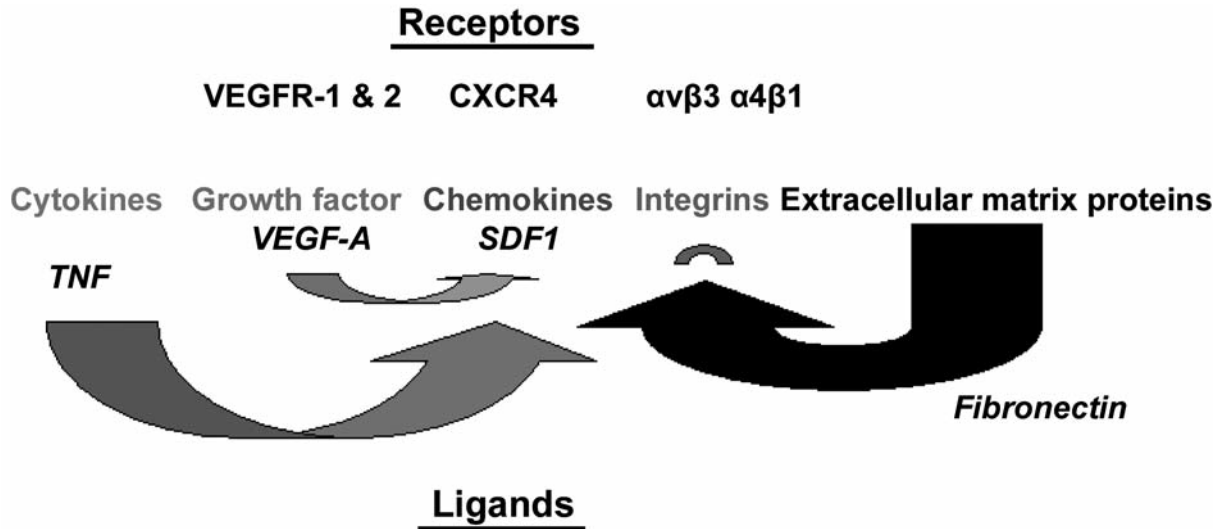
Receptors

VEGFR-1 & 2   CXCR4   αvβ3 α4β1

Cytokines   Growth factor   Chemokines   Integrins   **Extracellular matrix proteins**

VEGF-A   SDF1

TNF

Fibronectin

Ligands

Figure 1. *Ligands and receptors involved in inflammation and angiogenesis facilitating metastasis (see text).*

attraction and transcapillary tumour cell migration into tissues, hence leading to metastasis.

There are three mechanisms which are involved in organ selectivity of metastasis (18): i) tumour cells leave blood and lymphatics in the same way but multiply only in organs with growth factors; ii) tumour cells are stopped by adhesion molecules in vessels of certain organs; iii) Organ specific molecules exert a chemo attraction resulting in organ invasion. These mechanisms can work either together or sequentially in different orders (19).

The major factors which enhance tumour invasion and metastasis are closely related to angiogenesis (20). Tumour necrosis factor (TNF) released by activated macrophages and by some tumour cells induces the cytokine cascade, including the expression of IL-6, IL-8 as well as of chemokines, especially stromal derived factor 1(SDF1)/ chemokine (C-X-C motif) ligand 12 (CXCL12). This triggers the production of growth factors such as VEGF-A, the main angiogenic factor and other factors such as EGF and hepatocyte growth factor (HGF). In parallel, activated cyclo-oxigenase 2 (COX2) leads to the production of prostaglandins. Activated fibroblasts secrete several extracellular matrix (ECM) proteins (*i.e.* vitronectin, collagen), which are the ligands of some integrins, especially alphaVbeta 3 and alphaVbeta5 that are essential for tumour angiogenesis (21). This concept is illustrated in Figure 1.

There are compelling data which show the role of TNF and VEGF-A in the metastatic process. Endogeneous TNF promotes growth and metastasis. This was demonstrated experimentally in ovarian cancer as well as in the clinic

(22). The anti-TNF monoclonal infliximab was able to reduce the number of peritoneal and distant metastases from ovary cancer (23) and colorectal and pancreas cancer xenografts were inhibited (24). In the clinic, infliximab produced stable disease in ovarian cancer (22) and in renal cancer (25).

VEGF-A is not only responsible for inducing angiogenesis upon triggering by hypoxia inducible factor (HIF), as the tumour milieu contains hypoxic regions, but a new concept recently emerged, the concept of the "premetastatic niche" (26). Bone marrow precursor cells that express VEGR-1 (in contrast to endothelial cells that express VEGFR-2) are recruited by VEGF-A to colonize target organs where tumour cells will be recruited in turn after a lag time (27). In other words, bone marrow derived cells prepare the niche or nest where tumour cells will later seed and develop.

The induction of VEGF can vary according to the treatment procedure. Complete excision of breast and colorectal cancer resulted in long lasting reduction of soluble VEGF-A levels in plasma. In contrast, in the case of regional tumours, which cannot be removed, regional therapy by isolated limb perfusion with TNF and chemotherapy induced tumour necrosis, but this was followed by increased levels of soluble VEGF-A (28). A proposed explanation was that isolated limb perfusion with TNF and alkylating agent, produced an intense in situ tumour necrosis responsible for up-regulating the expression of HIF, the major inducer of VEGF. It seems, therefore, that excision of tumours produces less angiogenic agent as compared to isolated limb perfusion thus resulting in tumour necrosis.

Candidate Drugs or Therapies which Could Be Used for Inhibiting Metastasis after Surgical Trauma

All experimental evidence found for a negative influence of surgical interventions on cancer outcomes came only from mouse, rat and rabbit models. Although the clinical translation is difficult, molecular mediators of metastasis have been identified. Inhibitors of these factors already exist or are in development (29). Candidate agents might include: Cox2 inhibitors (30), antibody to VEGF (bevacizumab, Avastin) (31), small molecules inhibitors of VEGF-R1 (32), integrins inhibitors (33), and antibodies to TNF (34) or inhibitors of EGFR (35). Most of these agents are currently in use or at least in clinical trials for metastatic disease. The clinical benefit was not so high when these agents were compared with classical treatments (36). No clinical data are available on the effect of these agents on the metastatic process.

Neoadjuvant chemotherapy might improve outcome of hepatic resection. However this can be at the expense of specific toxicities: irinotecan can increase liver failure, prolonged oxaliplatin therapy can produce sinusoidal obstruction. Bevacizumab more than 5 weeks before hepatectomy was claimed to be beneficial (37).

Recurrence of liver metastases of colorectal cancer could be due to ineffient local immunity. In experimental models, low dose radiotherapy of the liver kills some tumour cells, improves dendritic cells (DC) presentation and T cell migration by endothelium activation. A new protocol aims at evaluating this concept by giving a single radiotherapy session to the liver from 0.5 to 5 Gy before resection of liver metastases from colorectal cancer (38).

Dexamethasone reduced recurrence and metastasis in a pancreatic carcinoma xenograft system (39). Moreover, 2.5 mg/kg dexamethasone given before DC vaccine rendered the latter efficent while it had no effect without dexamethasone because of the immune impairement due to the inflammatory response (40).

A recent review on endoscopic peritoneal surgery points out the interest in evaluating the effect of anti-inflammatory and anti-adhesion drugs for preventing peritoneal recurrence from colorectal cancer after surgery (41). Hyperthermic peritoneal perfusion could reduce peritoneal recurrences of ovarian cancer (42).

Considering the complexity of the patient response to oncological surgery and the possible influence of blood transfusion, this short review can only generate a hypothesis arising from animal models: oncological surgery might create conditions facilitating tumour dissemination.

A clinical proof of concept is badly needed. The strategy would be completely different from the classical adjuvant or neoadjuvant treatment: the aim is not to treat metastatic disease but rather to prevent the consequences of inflammatory and growth factor response to surgical trauma. Therefore, theoretically, the therapy should be administered in the perioperative period.

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