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Review

Surgery-induced tumor growth in (metastatic) colorectal cancer

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ABSTRACT

Metastatic colorectal cancer (mCRC) is a devastating disease causing 700.000 deaths annually worldwide. Metastases most frequently develop in the liver. Partial hepatectomy has dramatically improved clinical outcome and is the only curative treatment option for eligible patients with mCRC. Pre-clinical studies have shown that surgical procedures can have tumor-promoting local 'side-effects' such as hypoxia and inflammation, thereby altering the behaviour of residual tumor cells. In addition, systemically released factors following (colon or liver) surgery can act as a wakeup-call for dormant tumor cells in distant organs and/or help establish a pre-metastatic niche. Tumor handling during resection may also increase the number of circulating tumor cells. Despite the overwhelming amount of pre-clinical data demonstrating the pro-tumorigenic side effects of surgery, clinical evidence is scarce. Indications for hepatic surgery are rapidly increasing due to a rise in the incidence of mCRC and a trend towards more aggressive surgical treatment. Therefore, it is increasingly important to understand the principles of surgery-induced tumor growth, in order to devise perioperative or adjuvant strategies to further enhance long-term tumor control. In the current study we review the evidence for surgery-stimulated tumor growth and suggest strategies to assess the clinical relevance of such findings.

Contents

Abbreviations: bFGF, basic fibroblast growth factor; CSC, cancer stem cell; CT, computed tomography; EMT, epithelial to mesenchymal transition; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; HIF, hypoxia inducible factor; HIPEC, hyperthermic intraperitoneal chemotherapy; IL-11, interleukin-11; CRC, metastatic colorectal cancer; MHC, major histocompatibility complex; MRI, magnetic resonance imaging; NK cell, Natural Killer cell; PET, positron emission tomography; PVE, portal vein embolization; RFA, radiofrequent ablation; SDF-1, stromal derived factor 1; TAE, transcatheter arterial embolization; TARE, transcatheter arterial radioembolization; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

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1. Introduction

Surgery has been a treatment modality for tumors in the abdomen since the early 19th century. The concept of metastatic spread was introduced in 1829 by Récamier [1]. A few years later, in 1835, John Hunter advocated the surgical removal of primary tumors and metastases whenever possible. It took another 43 years before the first colon tumor was surgically removed by von Volkmann in 1878 [2], and more than a century before the first liver metastasis was surgically removed by Lortat-Jacob in 1952 [3].

The fields of cancer surgery and basic cancer research have evolved in parallel. Virchow noted around 1860 that all cells, including malignant cells, arise from other cells and observed a close correlation between inflammation and cancer. Around the same time tumor cells were found in the bloodstream of cancer patients at autopsy and were recognized to be potential seeds for metastases. In 1899 Paget hypothesized that such cells may need a specialized environment in order to grow out and that this would make some organs more metastasis-prone than others. Strikingly, these topics are still very relevant today and are actively being researched worldwide.

Surgery became a curative treatment modality for cancer patients and has improved survival dramatically improved over the years. In addition, a large number of chemotherapeutic- and targeted anti-cancer drugs have become available, which in some cases, have had spectacular effects on (progression-free) survival. In metastatic colorectal cancer (mCRC), systemic combination therapy has increased median overall survival from 5 to 6 months (best-supportive care) to approximately 2 years with the most effective regimens [4]. However, in the vast majority of cases, systemic treatment alone is not curative and surgery, whenever possible, remains the only chance for cure.

Despite the overwhelming impact of oncological surgery on patient survival, it was noted already in the early twentieth century that surgical manipulation might also promote tumor outgrowth and metastasis formation [5,6]. Liver surgery has been particularly linked to accelerated outgrowth of microscopic tumor deposits residing in the liver remnant (see Supplemental Table 1 for an overview of translational experiments regarding surgery-induced tumor growth confined to the liver). However, the concept of surgery-induced tumor growth is largely built on results from preclinical studies; clinical data to support this are scarce. With the increasing incidence of mCRC and a trend towards more aggressive surgical treatment it is becoming more important than ever to understand the principles and clinical relevance of surgery-induced tumor growth.

In this review we discuss our current understanding of how surgical resection of primary tumors and liver metastases might accelerate tumor growth in patients with mCRC based on the available (preclinical and clinical) data. For the scope of the article, we focus on the direct effects of surgery itself on tumor growth and leave other known or presumed factors, such as anaesthetics, medication, and comorbidities, undiscussed. We ascertain a gap between preclinical and clinical data and describe how new modalities and strategies might bridge this gap.

2. Pre-clinical evidence

2.1. Local and systemic changes by surgery

2.1.1. Surgery and circulating tumor cells

A report from 1914 described that chemically damaged peritoneum harboured metastases from subcutaneously injected tumor cells while non damaged peritoneum did not [7]. Also, massage of subcutaneous tumors resulted in increased circulation of tumor cells and metastasis formation in the majority of the cell lines studied [8], despite the fact that the vast majority of these cells dies during dissemination and only a fraction of surviving cells has the capacity to form metastases. In short, surgical handling promotes cancer cell shedding via manipulation of the tumor, and surgical trauma acts as a preferred site for metastases formation.

2.1.2. Hypoxia

Surgery, by definition, creates tissue damage and disruption of the (micro)vascular system. This leads to hypoxia, which is essential for initiating wound repair through a cascade of interconnected processes including inflammation, angiogenesis, vasculogenesis, fibroplasia and re-epithelialization. In tumors, hypoxia is common and chronic and can be aggravated by external factors such as surgery. Interestingly, the local effects of surgery-induced tumor growth are found within the surgery-induced hypoxic tissues, potentially containing residual tumor cells [9,10]. Exposure of these