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Review

Anesthesia and colorectal cancer – The perioperative period as a window of opportunity?

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Abstract

Gastrointestinal malignancies largely contribute to cancer related deaths in the United States, with colorectal cancer representing the 3rd place of the ten leading entities of mortality due to cancer for both females and males. The majority of patients with GI tumors has to undergo surgery (either as a curative or palliative intervention) and are therefore also in need for a proper general and/or regional anesthesia. Recent findings have suggested that the type of anesthesia administered might have an impact on cancer recurrence and metastasis and thus this new field in the anesthesia world has become a largely studied topic. This review highlights current concepts and summarizes the evidence for an impact of the type of anesthesia on patient outcome after cancer surgery, suggesting the perioperative period might be a "window of opportunity" which should not be missed.

Keywords: Anesthesia; Anesthetics; Colorectal neoplasms; Neoplastic cells; Circulating; Epithelial–mesenchymal transition

Introduction

Surgery is still one of the key components for the therapy of most solid tumors, including colorectal cancer.[1] Different therapy modalities, including (neo-) adjuvant chemotherapy,[2] and new surgical techniques and tools have been developed over the last years in order to improve patients' outcome after cancer surgery.[3] Also, based on several retrospective and experimental reports in recent years the impact of the type of anesthesia administered to patients undergoing cancer surgery on outcome, metastasis and survival has gained a lot of attention.[4,5] The perioperative period is the (rather short) time where the anesthesiologist is taking care of the cancer patient, but this period might also determine patient's outcome due to processes leading to the formation of new (distant) metastatic sites[5] or recurrence. This pathogenic sequence of tumor cell spread is not only enhanced during (and also by) the surgical removal of the tumor, but might as well be influenced by the anesthesia-related medications administered to the patients intraoperatively. With this review, we will highlight these concepts and assess the current evidence for an impact of anesthesia on cancer recurrence and metastasis in colorectal cancer and other malignant diseases.

Circulating tumor cells

Even if patients undergo a complete resection of their primary tumor, there is still a possible risk of recurrence due to undetected micrometastasis.[6] Circulating tumor cells (CTCs) are malignant cells shed from the primary tumor into the circulatory or lymphatic system, thus maybe contributing to metastasis,[7] a concept which has already been reviewed by Glodblatt and Nadel in 1963.[8] Different methods for CTC detection have been developed since then.[9] It could also be shown that the number of CTCs,

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which can be found in the patient's circulation largely depends on the tumor entity, stage and phenotype as well as on the time point, when the blood is drawn (e.g. pre- versus post-operative or pre-versus during chemotherapy).[7,10,11] However, the exact mechanisms leading to the generation of CTCs are not completely understood.[12] Circulating tumor cells are not only released into the circulation in higher numbers during the perioperative period, e.g. in patients with pancreatic adenocarcinoma,[13] there have also been some reports that the number of CTCs generally found in the blood of the patient at given time points might be correlated with overall outcome and survival: Hiraiwa et al. examined the prognostic value of CTC detection in 130 patients with either esophageal, gastric or colorectal cancer.[14] The authors found a clear correlation between the presence of 2 or more CTCs in 7.5 ml blood and an advanced stage of the disease in all entities. Additionally a significant decrease in overall survival in patients with metastatic gastric or esophageal, but not with metastatic colorectal cancer was observed.[14] A meta-analysis evaluating 13 eligible studies for the prognostic value of CTC detection in patients with colorectal cancer undergoing chemotherapy revealed a potential correlation between the detection of CTCs and a worsened prognosis in these patients.[15]

A systematic review evaluating the results of 14 studies with patients undergoing cancer surgery for colorectal tumors found that the presence of CTCs 24 h postoperatively was an independent prognostic factor for cancer recurrence or metastasis, respectively.[16] Therefore detection of CTCs (maybe in combination with determination of circulating nucleic acids) in the perioperative phase in patients undergoing tumor resection of colorectal cancer might be a useful tool to monitor the progress of the disease, assess the accuracy of the surgical removal of the tumor and maybe also determine a possible need for adjuvant chemotherapy.[17]

Interestingly, already in 1968 Turnbull and colleagues could demonstrate a better survival rate and less metastasis for patients undergoing resection of a colorectal tumor using the so-called "no-touch isolation technique" and concluded this might be due to less hematogenous dissemination of tumor cells during (and after) surgery.[18]

Most of the validated CTC detection methods are based on the recognition of the epithelial surface marker epithelial cell adhesion molecule EpCAM,[11] although there are also other options available, such as the detection of circulating nucleic acids[17] or marker genes using polymerase chain reaction[19] or filtration-based methods.[20,21] EpCAM is a type I transmembrane protein, which is expressed by most epithelial cells and has been reported to be overexpressed in several malignant tumors originating from epithelial cells as well.[22] However, in certain types of cancers, e.g. in esophageal cancer, the expression of EpCAM during the process of metastasis seems to have a dynamic component: it could be shown that esophageal carcinoma cells expressing high levels of EpCAM could be correlated with proliferation, and cells with low levels of EpCAM were associated with migration, invasion and metastasis *in vitro* and *in vivo*.[23] This "context-dependent adaption"[23] of EpCAM expression could also be an explanation, why some CTCs might not be detected by EpCAM-based CTC detection methods.[24]

Several studies also aimed at determining a cutoff-value for the number of CTCs detected in the patient's circulation as a prognostic decision point. For colorectal cancer, a CTC count of $\geq$3/7.5 ml blood has been postulated.[25] However, the statistical method used for the identification of the threshold value has been criticized immensely[26] and despite the increasing number of papers published on the subject, the overall importance and clinical relevance of CTCs detected in the blood of patients with cancer remains controversial and thus the detection of CTCs has not led to any changes in therapeutic decisions or regimens so far.[27]

Epithelial–mesenchymal transition

The process of epithelial–mesenchymal transition (EMT), which is characterized in epithelial cells by a loss in, e.g., E-cadherin, a transmembranous glycoprotein, and an antipodal increase in, e.g., vimentin, an intermediate filament expressed by mesenchymal cells,[28] could be one (of many) factor(s) contributing to the generation of CTCs, mostly by increasing the migratory and invasive potential of the tumor cells.[12] And although the exact importance of this process for the generation of CTCs and new metastatic sites has yet to be determined,[12] this review aims to give a short overview about the processes involved due to possible interactions of certain types of anesthetics with these signaling/transition events.

During EMT the epithelial tumor cells further lose their apical-basal polarity as well as most of their cell–cell (adherens and tight) junctions[29] and become increasingly able to migrate along a matrix consisting of mostly fibronectin and type I collagen produced by the malignant cells themselves.[30] The cells' invasive potential therefore increases dramatically and even the extracellular matrix and the basal lamina (type IV collagen and laminin[29]) are no obstacle for the mesenchymal cells any more, as these structures are degraded by matrix-metalloproteinases (MMPs) released by the tumor cells as well.[31,32] Epithelial–mesenchymal transition can be initiated by a variety of stimuli and signaling pathways (mostly intracellular kinase signaling cascades), e.g. induced by cytokines like transforming growth factor β (TGFβ), bone morphogenetic protein (BMP), epidermal growth factor (EGF), fibroblast growth factor (FGF) or platelet-derived growth factor (PDGF).[29,33–35] Interestingly, EpCAM seems to be an important mediator of TGFβ-induced EMT, at least in breast cancer cells.[22]

The extravasation of CTCs is thought to be similar to the process of transendothelial migration of leukocytes,[36] and