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Oncologic Impact of Surgery in the Early Postoperative Period

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Surgical intervention represents a deliberate form of tissue injury producing the acute phase response. The response to injury is also associated with a period of relative immune suppression and the magnitude of the response is proportional to the degree of surgical trauma. The proinflammatory cascade of events produced by the response to injury coupled with a impairment of postoperative cell-mediated immune function may provide a stimulus for the progression of neoplastic disease. There is strong evidence from animal studies that all types of abdominal surgical procedures are associated with increased rates of systemic tumor establishment and growth postoperatively. In preclinical models, minimally invasive techniques have been shown to ameliorate the effects of surgically induced tumor progression. This pattern of tumor behavior was noted following sham operations and after bowel resections. The precise mechanism of these changes remains unclear; however, both an increased rate of tumor cell proliferation and a decreased apoptosis have been noted after open surgery. There is also evidence that the cell-mediated immunosuppression that has been documented to occur after surgery accounts for some of the differences in tumor growth after open versus laparoscopic surgery. Systemic plasma factors elaborated following laparotomy have also been associated with increased tumor cell proliferation in vitro, suggesting that it may prove possible to pharmacologically protect patients from the deleterious side effects of surgery on postoperative tumor proliferation.
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Surgical intervention represents a deliberate form of tissue injury producing the acute phase response. Local reaction at the site of injury includes activation of the coagulation cascade and platelets, capillary leak, and the accumulation of leukocytes and inflammatory mediators including interleukin-6, interleukin-1, and tumor necrosis factor alpha. The neuroendocrine systemic response to injury involves the secretion of catecholamines, aldosterone, antidiuretic hormone, adrenocorticotropin hormone, thyroid stimulating hormone, and glucagon, resulting in a catabolic state characterized by gluconeogenesis, and accelerated protein metabolism causing a negative nitrogen balance, insulin resistance, and sodium and water retention.[1,2] The response to injury is also associated with a period of relative immune suppression[3-7] and the magnitude of the response is proportional to the degree of surgical trauma.[8]

The proinflammatory cascade of events produced by the response to injury coupled with a impairment of postoperative cell-mediated immune function may provide a stimulus for the progression of neoplastic disease. The response to injury and the process of tissue repair involves the release of multiple factors that promote tumor growth. Hofer and coworkers observed a significant increase in the growth of subcutaneously injected B16 melanoma cells when they were coinjected with wound fluid or isolated transforming growth factor beta (TGF-β) and fibroblast growth factor (bFGF).[9] Wound drainage fluid and postoperative serum samples from humans have been shown to stimulate the growth of breast cancer cells in vitro.[10]

Surgical Trauma Is Associated with Increased Tumor Establishment, Growth, and Metastasis

Multiple authors have observed increased tumor establishment, growth, and metastasis in animal models after abdominal surgery or trauma. A series of murine studies performed by Fisher and coworkers in the 1950s demonstrated that surgical trauma and tissue injury accelerated tumor growth.[11-13] During the

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same time period, Lewis and Cole observed an increased rate of lung metastases after amputation of the tumor-bearing hindlimbs of rodents.[14] More recently, Eggermont and colleagues reported a significant increase in intraperitoneal tumor growth when mice were subjected to laparotomy 4 days after tumor cell inoculation as compared to mice that did not undergo surgery. The authors further demonstrated that the stimulatory effects of surgery on tumor growth abated 14 days after the injury occurred.[15] These findings were corroborated by Zeamari and coworkers who demonstrated that stimulatory effects of laparotomy on peritoneal tumor growth abated after postoperative day 10.[16] Ratajczak and coworkers injected mouse mammary carcinoma cells into the dorsal skin of mice. The authors observed that sham laparotomy significantly increased the rate of tumor establishment when a threshold dose of tumor cells was injected and that there was a significant increase in the mass of tumors when a large dose of tumor cells was inoculated, again demonstrating that the trauma associated with a midline laparotomy provides a stimulant to the biology of tumor cells in rodents.[17]

Goshima and coworkers observed that surgical stress induced by laparotomy significantly increased the number of pulmonary metastases after intravenous injection of mammary tumor cells in rats.[18] Kodama hypothesized that the metastatic process facilitated by major abdominal surgery was a function of the stress response and demonstrated an increased rate of pulmonary metastases in mice that were treated with glucocorticoids.[19]

Tumor Establishment, Growth, and Metastasis Are Reduced Following Laparosopy versus Laparotomy

With the advent of laparoscopy for the treatment of malignant disease, multiple authors have tested the hypothesis that the stimulatory effects of surgical trauma on tumor biology can be reduced by using minimally invasive techniques. The sentinel report compared the growth of mouse mammary carcinoma injected as a single cell suspension into the dorsal skin of mice who were then subjected to either laparotomy, carbon dioxide pneumoperitoneum, or anesthesia alone. When a threshold dose of tumor cells was inoculated, the author found a significant increase in the incidence of tumor establishment after laparotomy compared with pneumoperitoneum. There was no difference between the pneumoperitoneum and anesthesia control groups when the animals were followed out to 30 days. When a large dose of tumor cells was inoculated into the dorsal skin, the author observed a significant stepwise increase in tumor mass 12 days after surgery from the anesthesia control group to the carbon dioxide pneumoperitoneum group to the sham laparotomy group. These results suggested that the stimulatory effect of surgery on tumor biology could be reduced by a reduction in surgical stress using minimally invasive techniques.[20] These findings were later corroborated by Southall and coworkers who, using the same experimental model, found a significant reduction in tumor growth after pneumoperitoneum versus laparotomy for colon adenocarcinoma (CT26) and melanoma (B16), demonstrating that the observed effect was not tumor line specific.[21] An independent investigation by DaCosta and coworkers also found a significant increase in B16 melanoma tumor growth following laparotomy versus carbon dioxide pneumoperitoneum in mice.[22]

Potential differences in tumor behavior after laparoscopy and conventional open surgery are maximized when sham procedures are performed. The addition of an intraabdominal procedure adds operative trauma and may eliminate the observed differences in tumor behavior after laparotomy and carbon dioxide pneumoperitoneum alone. Three studies were conducted to evaluate the impact of adding a bowel resection to the experimental model. Using a mouse model of laparoscopic cecal resection, the author found a significant reduction in the establishment and growth of intradermally inoculated mouse mammary carcinoma cells after laparoscopic versus open bowel resection in mice.[23]

Bouvy and coworkers, using a rat small bowel resection model that involved a hand-sutured bowel anastomosis, demonstrated significantly slower tumor growth after laparoscopic resection than after open bowel resection. In this model 8 mg of colon tumor (CC531) was implanted beneath the renal capsule of all animals undergoing operative interventions. Two weeks later the tumors were excised and weighed. The open group tumors were found to be significantly larger than the laparoscopic group lesions.[24]

Gutt and coworkers developed a rat model of colon resection. In this model, rats received a transanal injection of a one million colon adenocarcinoma cells (CC 531) using an 8-cm probe. Rats then underwent a standardized colonic resection either through an open laparotomy incision or under carbon dioxide pneumoperitoneum. The investigators observed a significant reduction in tumor burden on postoperative day 24 in the rats that underwent the colon resection using carbon dioxide pneumoperitoneum for exposure.[25]

Thus, despite the addition of an intraabdominal procedure, tumors grew more quickly and were more easily established after open versus laparoscopic surgery in three different small animal models.

A decreased rate of pulmonary and hepatic metastases has also been observed after minimally invasive surgery. DaCosta and coworkers established flank tumors in mice by injecting single-cell suspensions of B16 melanoma cells. Tumors were excised when they reached a volume of 1500 mm^3, at which point the animals were randomly assigned to halothane anesthesia alone, carbon dioxide pneumoperitoneum, or midline laparotomy. Two weeks later the mice were killed and the number of metastatic nodules in the lungs was counted. The investigators found a significant stepwise increase in the number of metastases from anesthesia control to laparoscopy to laparotomy.[26]

The author developed a mouse model of liver metastasis by injecting a single-cell suspension of colon adenocarcinoma cells (CT26) directly into the portal vein. Mice reliably develop liver nodules by postinjection day 21. Using this model, the investigator found significantly decreased tumor burden after a minimally invasive approach to tumor cell

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