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TO STUDY EFFECT OF REGIONAL ANESTHESIA ON PREVENTION OF RECURRENCE OF COLORECTAL CARCINOMA

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Abstract:
Colorectal cancer is a prevalent condition, with an approximate annual global incidence of 1.8 million cases. Given the projected rise in its occurrence, this disease is increasingly posing a significant global health concern. Surgical intervention continues to be the principal therapeutic modality for the management of colorectal cancer. However, the occurrence of cancer recurrence after surgery is prevalent, constituting the leading cause of mortality among those afflicted with this ailment. Paradoxically, the physiological stress induced by curative surgery has the potential to create a conducive microenvironment for the progression of cancer, affecting both the immunological and neuro-humoral systems. The perioperative period holds significant importance in the progression of metastasis and cancer reoccurrence. To gain a comprehensive understanding of the impact of perioperative regional anesthesia on metastasis and tumors recurrence, it is crucial to consider the perioperative window within its appropriate context. Typically, individuals diagnosed with solid tumors can be effectively treated with surgical interventions, either with or without the inclusion of pre and post-surgical adjuvant therapies such as radiation treatment, chemotherapy, or hormone therapy. The outcomes obtained from the assessment of the utilization of RA in colorectal tumors exhibit a heterogeneous pattern. The benefits of regional anesthesia are influenced by several key criteria, namely the stage and type of colorectal cancer, the patient's age, the timing of epidural administration, and the American Society of Anesthesiology physical state classification. Research has demonstrated that RA does not provide any significant advantages in terms of overall survival, recurrence-free survival, and biochemical recurrence-free survival.

Introduction:

Colorectal cancer is a prevalent condition, with an approximate annual global incidence of 1.8 million cases [1]. Given the projected rise in its occurrence, this disease is increasingly posing a significant global health concern [2,3]. Surgical intervention continues to be the principal therapeutic modality for the management of colorectal cancer. However, the occurrence of cancer recurrence after surgery is prevalent, constituting the leading cause of mortality among those afflicted with this ailment [4,5]. Paradoxically, the physiological stress induced by curative surgery has the potential to create a conducive microenvironment for the progression of cancer, affecting both the immunological and neuro-humoral systems [6,7] The stimulation of the hypothalamic pituitary-adrenal axis and systemic inflammation has been found to facilitate wound healing [8]. However, it has been observed that this process also hampers the immune system's ability to detect and remove tumors cells [9]. Therefore, by reducing the disruptive effects of surgery on physiological homeostasis, it may be possible to decrease the likelihood of circulating tumors cells spreading and dormant micro-metastases becoming active [10,11]. The utilization of epidural analgesia has been demonstrated to effectively decrease the need for opioids during surgery and alleviate postoperative pain in abdominal procedures. Epidural analgesia administered at the mid-thoracic level is effective in providing pain relief to the abdomen. This is achieved through the inhibition of afferent transmission of pain signals to the brain, resulting in a decrease in the activation of the sympathetic nervous system within the cerebral region. Additionally, thoracic epidural analgesia functions by impeding sympathetic tone through the obstruction of efferent fibers originating from the brain and extending to the sympathetic trunk [7]. As a consequence, there is a decrease in postoperative discomfort and a lessened neuro-humoral reaction to the surgical procedure [12,13]. Hence, the mitigation of physiologic stress generated by surgery may potentially lead to a decrease in the production of metastases [9,14,15]. There have been suggestions in the literature that opioids [9] and inhalational anesthesia [16] might have the potential to facilitate the spread of metastases, and thus minimizing the dosage of these medications could potentially decrease the likelihood of cancer recurrence. Given the potential mitigating effects of epidural analgesia on the surgical stress response, our hypothesis posits that the utilization of epidural analgesia is associated with a reduced risk of cancer recurrence subsequent to colon cancer surgery. Our objective was to evaluate the correlation between the utilization of localized analgesia and the occurrence of colorectal cancer recurrence in patients who underwent surgery for colorectal cancer. This analysis was conducted using data obtained from Danish registries that contain prospectively gathered information.

Colorectal Carcinoma and Immune System

The innate immune response is an unspecific immune defense mechanism that is inherently present from birth. The innate immune response has a diverse array of consequences, encompassing rapidity, efficacy, and robustness. The innate immune system exhibits a non-discriminatory response to the introduction of foreign antigens into the body, serving as a protective mechanism for their removal. The activation of the innate immune system occurs when pathogen-associated molecular patterns are recognized by pattern recognition receptors. This detection leads to the production of several cytokines, including interleukins and tumors necrosis factor. The activation of pattern recognition receptors plays a crucial role in modulating the immunological microenvironment of tumors and the development of tumors. Pattern recognition receptors are extensively expressed in diverse innate immune cells within the host, including dendritic cells, mononuclear macrophage NK cells, among others. Subsequently, a cascade of immunological responses is triggered. Toll-like receptors have garnered significant interest among a range of pattern recognition receptors due to their involvement in carcinogenesis via the recognition of inflammation induced by pathogen-associated molecular patterns. The Nod-like receptors have garnered considerable interest due to their involvement in the formation of inflammasomes. These inflammasomes have been demonstrated to play a crucial role in immune response regulation and the suppression of carcinogenesis [17,18]. In 2004, Rakoff-Nahoum and colleagues conducted a

study examining the susceptibility to colitis induced by dextran sulphate sodium and the involvement of receptor-interacting protein 2 in mice lacking Toll-like receptor 4, Toll-like receptor 2 and myeloid differentiation factor. In comparison to mice of the wild-type phenotype, the authors have established that the MyD88-dependent axis confers favorable effects. MyD88 serves as a crucial intermediary molecule within the Toll-like receptor signaling pathway, exerting a significant influence on the transmission of upstream signals and the progression of various diseases. Consequently, it serves as a crucial mediator for numerous molecular cascade processes. Moreover, interleukin-17 serves as an initial catalyst for T-cell-mediated inflammatory reactions and has the ability to enhance the inflammatory response through the facilitation of proinflammatory cytokine secretion. Interleukin-17 serves as the primary mediator of T-helper interleukin-17-producing cells.Th17 cells have the ability to produce interleukin-6 and tumors necrosis factor-alpha, among other cytokines [19]. One study has since shown that the beginning of tumors in IL-17 mutant mice involves the participation of IL-17. Currently, the primary therapeutic intervention for colorectal cancer is surgical intervention. Hence, the treatment of anesthesia assumes a crucial role in determining the prognosis of colorectal cancer during the perioperative phase [20].

Colorectal Surgery and regional Anesthesia:

The perioperative period holds significant importance in the progression of metastasis and cancer reoccurrence. To gain a comprehensive understanding of the impact of perioperative regional anesthesia on metastasis and tumor recurrence, it is crucial to consider the perioperative window within its appropriate context. Typically, individuals diagnosed with solid tumors can be effectively treated with surgical interventions, either with or without the inclusion of pre and post-surgical adjuvant therapies such as radiation treatment, chemotherapy, or hormone therapy. Surgery serves a dual purpose in the medical field, as it not only plays a crucial role in the processes of diagnosis and staging, but it also possesses the potential to provide curative outcomes. Paradoxically, the perioperative phase is characterized by a state of vulnerability, wherein the host immune system, weakened by surgical stress and the pharmacologic effects of cancer-fighting drugs, may inadequately eliminate minimal residual disease [21,22]. The primary cause of mortality in cancer patients is attributed to complications arising from cancer metastasis, which can occur through direct extension, lymphatic dissemination, or hematogenous dissemination. The ability of a tumor to undergo metastasis is influenced by both its inherent characteristics and its interaction with the host organism. While metastasis does not occur randomly, there is significant biological diversity in cancer initially and metastatic tumors, which presents significant challenges in comprehending and managing cancer [23]. Moreover, the outcomes for the majority of tumors exhibit dissimilarities. As an illustration, the five-year survival rate for breast cancer is greater than 80%, while for colon cancer it is roughly 70%. whereas the corresponding percentage for lung cancer is roughly 15%. Likewise, the variability of median growth rates is observed among all tumors. The presence of heterogeneity within this context gives rise to a vast and complex area of study that might pose significant challenges in terms of comprehensibility and navigation.

Effect of regional anesthesia on recurrence of colorectal cancer:

The outcomes obtained from the assessment of the utilization of RA in colorectal tumors exhibit a heterogeneous pattern. The benefits of regional anesthesia are influenced by several key criteria, namely the stage and type of colorectal cancer, the patient's age, the timing of epidural administration, and the American Society of Anesthesiology physical state classification [24,25,26,27]. The study conducted by Gupta et al. revealed that those diagnosed with rectal cancer experienced enhanced overall survival rates. However, this advantageous outcome was not observed among patients diagnosed with colon cancer [26]. Moreover, Christopherson et al conducted a small randomized controlled trial which revealed enhanced overall survival among patients diagnosed with colorectal cancer without metastases who had epidurals, with the improvement lasting for duration of up to 1.46 years post-surgery [25]. The study conducted by Cummings et al. in the Surveillance, Epidemiology, and End Results investigation focused on a

cohort of 49,655 individuals who underwent surgical intervention for colon cancer. The researchers discovered that there was no discernible disparity in recurrence-free survival between patients who received epidural analgesia and those who underwent general anesthesia. However, a notable advantage in terms of overall survival was observed among those who received epidural analgesia. The group receiving RA treatment demonstrated a higher overall survival rate over a period of 5 years, with 61% compared to 55% in the control group. Nevertheless, the researchers discovered no discernible disparity in disease recurrence over a span of four years [28]. Holler et al conducted a study which revealed a notable disparity in the 5-year overall survival rates between patients classified as ASA class III-IV who underwent regional anesthesia versus general anesthesia. Nevertheless, this disparity was not observed among patients classified as ASA class I and II [27]. Several other researches have indicated that there is no discernible advantage associated with RA. In a randomized controlled trial comprising a total of 446 patients, Myles et al. observed that the utilization of epidural block during abdominal surgery for colon cancer did not exhibit any significant correlation with enhanced cancer-free survival or a reduced 5-year mortality rate [29]. The limited study's sample size posed a challenge in detecting nuanced distinctions among the groups; yet, significant disparities could still be identified. Gottschalk et al arrived at comparable findings. Nevertheless, a reduced likelihood of recurrence was observed in the cohort receiving epidural treatment among individuals aged 65 years and older [24]. Day et al. conducted a study with a cohort of 424 patients and observed that there was no discernible disparity in overall survival rates between individuals receiving RA and GA. Moreover, it was observed that patients in the epidural group had a lengthier duration of hospitalization, with an average stay of 5 days, in contrast to the two groups: the spinal analgesia group and the patient-controlled analgesia group where the average stay was 3 days [30]. In a retrospective study conducted by Binczak et al, a cohort of 132 patients was examined over a 17-year period to evaluate the impact of bupivacaine thoracic epidural analgesia versus fentanyl and morphine on recurrence-free survival. The results of the study indicated that there was no statistically significant difference observed between the two treatment approaches in terms of recurrence-free life. Nevertheless, the extended duration of the follow-up period may have mitigated the potential influence of the anesthesia approach [31]. Although Heinrich et al. did not observe any direct advantages of regional anesthesia in the treatment of esophageal cancer; their study revealed that the decreased utilization of opioids resulting from RA was associated with several positive outcomes. These included a reduction in the number of days spent in the intensive care unit and on mechanical ventilation, as well as a decreased risk of re-intubation, fewer days requiring antibiotics, and a lower likelihood of perioperative anemia. In spite of the aforementioned advantages, a multivariate Cox analysis revealed no discernible disparity in terms of cancer recurrence, tumor metastasis, or overall survival when considering the utilization of epidural analgesia [32]. Only one study was identified that indicated a potentially poorer outcome associated with the use of RA compared to GA. Lai et al conducted a retrospective study to assess the utilization of GA against epidural anesthesia in patients having radiofrequency ablation for the treatment of hepatocellular cancer. The analysis conducted by the researchers indicated that the utilization of radiofrequency ablation under general anesthesia for the treatment of hepatocellular carcinoma is linked to a decreased likelihood of cancer recurrence. However, the authors did not observe any impact of the anesthetic approach on the overall survival of patients. Nevertheless, this study distinguishes itself from previous research by focusing on hepatocellular carcinoma, a distinct pathophysiological condition apart from colorectal cancer [33].

In their study, Day et al. conducted a retrospective analysis on a cohort of 424 patients. These patients were selected from a database, and all had undergone laparoscopic resection for colorectal cancer. The utilization of regional analgesia in the context of individuals undergoing laparoscopic resection for colorectal cancer did not yield any observed advantage in terms of OS or disease-free survival. There was no observed survival benefit associated with localized analgesia, even after excluding patients with extra nodal metastases from the analyses [34]. Myles et al. conducted a retrospective analysis on patients included in the MASTER trial who underwent surgical resection with the potential for curative treatment of their malignancy. The researchers reached the

conclusion that the utilization of epidural block during abdominal surgery for cancer does not exhibit any correlation with enhanced cancer-free survival [35]. The MASTER experiment was a prospective randomized controlled trial that aimed to compare the efficacy of combined epidural and general anesthesia with GA plus systemic opioid analgesia in patients undergoing major abdominal surgery. Among the 503 patients included in the study, the majority of whom were diagnosed with colon cancer, the researchers found that there was no significant difference in recurrence-free survival between the group that had epidural treatment and the control group. The hazard ratio was calculated to be 0.95, with a 95% confidence range ranging from 0.76 to 1.17. The p-value associated with this comparison was 0.61 [36]. In a similar vein, Binzack et al. [37] conducted a retrospective analysis on individuals who had been previously enrolled in a prospective randomized controlled trial. The experimental group was administered general anesthesia along with thoracic epidural analgesia with bupivacaine, while the control group received GA with fentanyl followed by continuous subcutaneous morphine. After a period of 5 years, the rate of recurrence-free survival was found to be 43% in the experimental group and 24% in the control group. However, it should be noted that the observed difference in RFS between the two groups did not approach statistical significance. Similarly, the difference in overall survival between the EP and SC groups also did not reach statistical significance, with p-values of 0.10 and 0.16, respectively. The statistical research revealed that the kind of analgesia did not have a significant predictive effect on the recurrence-free survival when considering several variables. The sole study that indicated a more unfavorable outcome associated with epidural anesthesia was a retrospective analysis conducted on patients receiving radiofrequency ablation of hepatocellular carcinoma, comparing the use of general anesthesia vs epidural anesthesia [38]. The results of the multivariate analysis revealed no significant association between the utilization of opioids during both intraoperative and postoperative periods and adverse outcomes. The authors postulated that the use of general anesthesia may have facilitated longer and more frequent treatment sessions, hence potentially contributing to the observed improved outcome.

Limitation:

This study is subject to several limitations, with the foremost being the inclusion of a substantial number of retrospective studies. Although certain studies incorporated multiple parameters to ensure patient matching in the study arms, it is possible that certain factors remain unaddressed. In research examining advanced stage malignancies, the initial death rate is observed to be significantly elevated. Hence, the task of defining overall survival and quantifying recurrence free survival in these cohorts can provide challenges. Individuals diagnosed with advanced-stage cancer may face a considerable probability of succumbing to diseases that are not directly caused by the cancer itself, hence posing challenges in accurately assessing the benefits of survival. In research investigations that employ recurrence as the principal measure, diverse criteria are frequently employed to establish the definition of recurrence. There are numerous varieties of recurrence that occur, and the task of comparing these various patterns can provide a significant challenge. Certain forms of recurrence are not correlated with the overall survival rate, hence reducing its prognostic significance. Moreover, numerous studies assess patients within a limited timeframe that may not allow for the attainment of substantial findings. Many research had insufficient statistical power to make robust results. Certain research conducted on specific demographics, hence posing potential challenges in extrapolating these findings to the broader population. Ultimately, certain research involved the administration of multimodal analgesia to patients, thereby becoming the assessment of individual analgesia strategies notably arduous.

Conclusion:

Research has demonstrated that RA does not provide any significant advantages in terms of overall survival, recurrence-free survival, and biochemical recurrence-free survival. However, a multitude of independent research has demonstrated certain advantages, but the findings have been subject to debate. Several mechanisms have been suggested to elucidate this advantageous phenomenon;

however, none of them have been substantiated. Therefore, further investigation is required to thoroughly assess the involvement of RA in a prospective and randomized manner. Numerous clinical trials are currently being conducted globally to assess the effects of regional anesthesia. Regional anesthesia possesses the capacity to revolutionize the approach to cancer pain management, hence exerting a substantial influence on morbidity and mortality rates.

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