Editorial

Can the use of perioperative epidural impact survival outcome in women with advanced ovarian cancer?

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The surgical stress response following major surgery is characterized by a physiologic cascade of immunologic and endocrine alterations and an activation of the sympathetic nervous system with release of catecholamines like dopamine, norepinephrine, and epinephrine (1). The stress response is activated by afferent neuronal impulses from the site of tissue injury. The resultant sympathoadrenal response increases secretion of cortisol from the adrenal cortex, which in turn elevates the level of blood glucose via an increased hepatic glycogenolysis, gluconeogenesis, and a decreased peripheral metabolism of glucose. The surgical tissue injury furthermore induces a release of cytokines like interleukin-1, tumor necrosis factor-α and interleukin-6 from leucocytes and fibroblasts which mediates the inflammatory cascade and induces angioneogenesis (2). The surgical stress response is a complex physiologic mechanism, which enables the organism to encounter vast tissue damage. Clinical studies, however, have demonstrated that the release of cytokines and catecholamines induced by the stress response as well as the use of systemic opioids and general anesthesia can inhibit the cell-mediated immunity (CMI) which plays a key role in the recognition of foreign antibodies (3,4). In cancer surgery, this immunosuppressive consequence is problematic seeing that the reduced CMI also affects the recognition of tumor cells thereby promoting micrometastasis (5).

An emerging theory have hypothesized that the use of epidural analgesia could decrease the neuroendocrine and cytokine mediated surgical stress response. Additionally, the use of epidural analgesia could decrease the need for systemic opioids and general anesthesia thereby reducing the negative effect on the CMI (3). Theoretically, the use of epidural analgesia would thereby reduce the level of micrometastasis, thus resulting in improved survival outcome following cancer surgery.

Several retrospective studies and a few randomized controlled trials have investigated this proposed theory over the past decade in numerous cancer diseases [e.g., colorectal cancer (6), breast cancer (7), malignant melanoma (8), prostate cancer (9), urinary bladder cancer (10) and ovarian cancer (11,12)]—mainly with contradictory results. This was further evaluated in a meta-analysis published in 2017 of 28 studies concerning the effect of epidural in various cancer diseases. The meta-analysis concluded that epidural analgesia had no benefit in overall survival (OS), recurrence-free survival, or biochemical recurrence-free survival in cancer patients (3).

Recently, the effect of perioperative epidural in patients undergoing primary debulking surgery for advanced ovarian cancer was addressed in a retrospective cohort study published by Tseng et al. (13). The cohort consisted of 648 patients with FIGO stage IIIB to IV epithelial ovarian cancer who underwent primary debulking surgery from 2005 to 2013 at Memorial Sloan Kettering Cancer Center in New York, USA. Roughly, two thirds of the patients received a perioperative epidural, while one third did not. The decision to place an epidural or not was made by the attending surgeon and anesthesiologist in respect of the

patient's preference. The epidural catheters were all placed preoperatively while infusion started either intraoperatively or immediately postoperatively. Adjuvant chemotherapy was given either as intravenous infusion or in combination with intraperitoneal chemotherapy. Postoperative imaging assessed recurrence and progression and the outcome measures were progression free survival (PFS) and OS. The epidural group had a significantly higher FIGO stage distribution, higher rate of carcinomatosis, and bulky upper abdominal disease compared to the non-epidural group. Complete gross resection was achieved more frequently in the epidural group compared to the non-epidural group (48% *vs.* 31%). The results showed a significantly higher risk of recurrence, progression, and death in the non-epidural compared to the epidural group with a PFS of 13.9 *vs.* 20.8 months (P=0.021) and an OS of 41.9 *vs.* 62.4 months (P<0.001), respectively. The authors suggest this considerable difference in PFS and OS to be the effect of the diminished surgical stress response in patients who received an epidural.

Retrospective studies are prone to a high risk of bias. If unexpected results emerge one must consider potential confounding. During the past two decades several studies and a Cochrane review have confirmed that complete resection of any intraabdominal gross disease (R0) is the most important prognostic factor for survival in women with advanced ovarian cancer (14-18). Further, both the number of residual nodules and the volume of disease have been shown to impact on survival (19).

In the study of Tseng *et al.* information on complete gross resection and presence of peritoneal carcinomatosis was obtained retrospectively from medical chart review (13). Complete gross resection was defined as cytoreduction leaving tumor nodules measuring 1–10 mm, which is usually defined as R1. Both factors constitute significant confounders. The inaccuracy by retrospective scrutiny of the medical charts for the surgeon's specification of residual disease cannot be disregarded. Further, it remains unknown whether a single or hundreds of small nodules <10 mm were left and how the patients with different degrees of residual disease were distributed between the two groups. Other inherent confounders could be mentioned: Imbalance between groups regarding the choice of epidural or not, lack of standardized set up related to start and discontinuation of the epidural during the intra- and postoperative phase, different chemotherapy regimens used e.g., only some patients had intraperitoneal chemotherapy while other had intravenous chemotherapy only and this was not balanced between groups.

However, another confounder may be even more important and is likely to jeopardize the internal validity of the study. Recently, in a second paper, the authors discussed the importance of surgeon's expertise and time related factors with institutional improvement over time in the complete cytoreduction rate (20). In the present study (13), the epidural group had significantly worse baseline disease distribution in critical locations but obtained better surgical outcome than the non-epidural group. This is counterintuitive and draws the reader's attention. A problematic imbalance between surgeons' competences and experience within primary debulking surgery in advanced ovarian cancer could explain the findings. The authors therefore include the surgeon as a cluster effect in the Cox proportional Hazard model to account for potential influence of variances in surgeons' competences. However, considering the indisputable less favorable baseline disease distribution in the epidural group, the results of the survival analyses between epidural groups are still surprising. The close correlation between surgeons' competences and the rate of R0/R1 after primary debulking surgery in ovarian cancer and the well-known correlation between R0/R1 and survival is likely to introduce multicollinearity in the regression analyses. Hence, despite an attempt to adjust for the differences between groups, the imbalance severely compromises the internal and external validity of the study. Further, multicollinearity is likely to be present and influence the response variable. Hence, it is questioned whether epidural use in the present setting represents a true independent variable as suggested. Surgeons' competences may play a greater role than accounted for and it could be questioned whether the suggested study design is suitable to evaluate the question of whether perioperative epidural impact survival outcome in women with advanced ovarian cancer.

Having said that the results of the study are interesting and warrant further studies. The mechanisms responsible for the formation of micrometastasis and the complex immunologic aspects of the surgical stress response are yet to be fully understood. Until then, large randomized controlled trials are needed to form an unambiguous conclusion when it comes to the effect of a perioperative epidural on survival outcome in solid tumor cancers.

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