Editorial

Can a single intraoperative dose of non-steroidal anti-inflammatory drugs reduce cancer recurrence?

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We read with great interest the article by Mao *et al.* entitled "Intraoperative use of single dose of nonsteroidal anti-inflammatory drugs was not associated with cancer recurrence and mortality after bladder cancer surgery: a retrospective study". Their study addressed an interesting topic in perioperative oncology medicine that is the association between the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and cancer-related outcomes after bladder cancer surgery. The authors performed a single center, retrospective study to investigate the association between a single intraoperative dose of parecoxib and mortality, recurrence-free survival and overall survival. They included 185 patients and concluded that the intraoperative administration of 40 mg of parecoxib was not associated with a decreased in overall mortality or a benefit in recurrence-free or overall survivals.

According to the American Institute for Cancer Research, bladder cancer is the most common malignancy of the urinary system (1). In 2018, approximately 500,000 new cases of bladder cancer were diagnosed worldwide, thus making it the 10th most common malignancy overall (2). The mortality rate is still high with only 70% of patients with localized disease alive 5-year after initial treatment. In those with metastatic disease to lymph nodes or distant organs the 5-year survival rates are 35% and 5%, respectively. These worrisome statistics along with the financial burden on the society has encouraged scientists to better understand the biology of bladder cancer.

A number of laboratory studies have examined the relationship between NSAIDs use and cancer risk. NSAIDs are thought to protect against carcinogenesis and tumor progression by inhibiting cyclooxygenase (COX) (3). COX converts arachidonic acid to prostaglandins (PGs) and the PGs overexpression is key during the early steps in a variety of oncogenic events (4). Furthermore, NSAIDs can block tumor cell proliferation, migration and invasion, inhibit tumor angiogenesis (throughout the reduction of VEGF expression), and promote programmed cell death (5-7). Thus, it has been speculated that NSAIDs could reduce the pro-tumoral effects associated with surgery including inflammation and angiogenesis (8).

When examining the literature, one can erroneously conclude that the results from Mao *et al.* are opposing to the findings reported in a meta-analysis conducted by Zhang *et al.* and a pooled analysis by Daugherty *et al.* Zhang's meta-analysis included seventeen studies (8 cohort and 9 cases-control studies) involving a total of 1,008,800 participants, including 10,618 bladder cancer cases. The study involved 3 categories of analgesic: acetaminophen, aspirin and non-aspirin NSAIDs. Six studies were used for analysis of non-aspirin NSAIDs with a total of 761,687 participants. The study period was variable (2–20 years). They reported that non-aspirin NSAIDs use was significantly associated with reduced risk of bladder

cancer among case-control studies but not cohort studies. In addition, the study found that non-aspirin NSAIDs use was associated with a 43% reduction in bladder cancer among smokers but not among current smokers. Unfortunately, there was significant heterogeneity among studies (9). Daugherty *et al.* also investigated the association of NSAIDs and bladder cancer in 3 large prospective studies (NIH-AARP Diet and Health Study; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; and U.S. Radiologic Technologist Study). The analysis included 508,842 patients with 2,489 incident cases of bladder cancer. They observed a reduction of bladder cancer risk for patients who reported regular use (>2 times/weeks) of non-aspirin NSAIDs compared with those who reported no use. The association was found for non-smokers only. No significant heterogeneity was observed (10). The most obvious difference between these studies and Mao's work is that the formers were focused on the so-called "chemo-preventive" effects of NSAIDs, which are typically observed after their prolonged. In other terms, the beneficial effects of NSAIDs in bladder cancer might be seen after prolonged exposure and not after a single administration, as it occurred in Mao's work (parecoxib 40 mg).

However, as we mentioned previously, a group of investigators have suggested that the single administration of NSAIDs can offer protective effects against growth of the postoperative minimal residual disease (8). Forget *et al.* conducted a retrospective analysis of 720 cancer patients undergoing conservative breast cancer surgery. In that study a single dose of either ketorolac 30 mg or diclofenac 75 mg was associated with an improved disease-free survival and an improved overall survival (11). Similar results were also found and reported by the same group of researchers after prostate and lung cancers surgery (12). Differences in tumor sensitivity to different NSAIDs could explain the discrepancies in outcomes between studies. For instance, urogenital tumor cells are particularly sensitive to ibuprophen-induced expression of P75NTR tumor suppressor gene (5). Other NSAIDs including indomethacin, sulindac, ketoprophen and piroxicam that have shown anti-tumor effects; however, there are not *in vitro* or *in vivo* studies that demonstrate an anti-tumoral effect of the parecoxib on tumor cells. Thus, one could speculate that the protective effect might vary according to NSAID class (13-15). Last, the current studies on the effect of NSAIDs on cancer recurrence after surgery are mostly retrospective. These studies have limitations in particular, significant bias and confounding. Unable to control for possible confounders such as concomitant drugs administrations, quality of surgical resection and blood transfusions are always a source of misinterpretation of the data.

In our opinion, it remains unclear whether NSAIDs are associated with reduced recurrence or longer overall survival after cancer surgery. It is unlikely that a single dose of any NSAID will prolong survival after oncological procedures. However, a prolonged perioperative treatment (before and after surgery) with NSAIDs may overcome the impact of surgery on cancer spread. Only well designed randomized controlled trials will help to determine the clinical benefits of these drugs.

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Footnote

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