Editorial

Impact of opioids on postoperative prognosis in lung cancer

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Opioids are widely used worldwide in the treatment of lung cancer. The possible influence of opioids on cancer prognosis has been reported. Zhu *et al.* assessed the association between anesthetic factors and the prognosis of patients with non-small cell lung cancer (NSCLC) after surgery (1). They concluded that perioperative fentanyl equivalents >28.2 μg/kg was associated with prolonged survival. Nonetheless, no consensus exists on opioid use and postoperative prognosis in lung cancer. This article discusses the relationship between opioid use and prognosis in primary lung cancer surgery. Long-term administration of opioids is often necessary not only in the perioperative period but also for prolonged postoperative pain. Therefore, clinicians should use opioids appropriately in the perioperative period, with an understanding of their potential pharmacologic effects on cancer.

Chemical actions in promoting cancer growth and metastasis

The following effects of opioids have been reported: (I) co-activates epidermal growth factor receptors and increases phosphorylation of mitogen-activated protein kinase/extracellular signal-regulated kinase; (II) activates the survival signal PKB/Akt and inhibits apoptosis; (III) increases cyclin D1, thereby promoting cell cycle progression (2). In addition, opioids may promote cancer invasion and metastatic functions. μ-agonists promote epithelial-mesenchymal transition of circulating tumor cells (CTCs) and cancer growth by activating vascular endothelial growth factor (3,4). Consequently, they can promote the metastatic process of CTCs.

The association between cancer growth and immune function is one of the most focused topics today. Reports have been published on opioids and immune suppression. Morphine and fentanyl inhibit natural killer (NK) cell activity, but buprenorphine does not, while tramadol increases this activity (2). Lin *et al.* assessed 69 lung cancer patients randomly assigned to either the naloxone group (n=35) or the non-naloxone group (n=34) for postoperative analgesia during the first 48 h after the operation (5). An infusion of 0.05 μg/kg/h naloxone for patients undergoing sufentanil-controlled analgesia for postoperative pain was used. In the naloxone group, the level of opioid growth factor, which enhances the immune function, increased significantly at 24 h ($P<0.01$), the NK cells and $CD4^+/CD8^+$ T-cell ratio increased 48 h after the operation ($P<0.05$ and $P<0.01$, respectively). The use of naloxone could statistically reduce postoperative pain intensity, request for rescue analgesics, and opioid-related side effects.

These reports indicate that the mechanism by which opioids promote cancer growth is multifaceted, with both direct and indirect effects. In actual clinical practice, opioid use, dosage, and duration of use vary depending

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on the patients. Subsequently, we discuss the relationship between opioid use in real-world clinical practice and actual prognosis. Previous reports have divided perioperative opioid use into several time periods and examined their relationship to prognosis.

Opioids use and prognosis

Cata *et al.* analyzed the effect of intraoperative opioid dose on prognosis in 901 stage I–IIIA NCSCL patients (6). An open thoracotomy (78.9%) and a lobectomy (77.3%) were the most common surgical procedures. The fentanyl equivalents conversion factors for 1 μg fentanyl were as follows: sufentanil 0.1 μg, remifentanil 1 μg, and hydromorphone 10 μg. The median intraoperative fentanyl equivalents dosage was 10.15 lg/kg. In stage I patients, the intraoperative low dose of fentanyl equivalents showed a trend toward better recurrence-free survival (RFS) after the multivariate analysis [hazard ratio (HR) 1.127, 95% confidence interval (CI): 0.99–1.12, P=0.053]. However, no statistical significance was found on RFS for stage II or III patients. Alternatively, opioid consumption was a risk factor for decreased overall survival (OS) for stage I patients (HR 1.15, 95% CI: 1.01–1.32, P=0.036), whereas no association was noted for stage II (HR 0.94, 95% CI: 0.76–1.16, P=0.586) or III patients (HR 0.98, 95% CI: 0.83–1.15, P=0.862). Interestingly, the results indicate that the prognostic effect of intraoperative opioids on prognosis in cancers other than stage I may not be as strong as other prognostic factors. On the other hand, intraoperative opioids may increase the relatively poor prognostic effect in early-stage lung cancer. However, details regarding the use of postoperative opioids in this study model are not available, and further validation is warranted.

Wang *et al.* retrospectively evaluated the impact of postoperative opioids on OS and disease-free survival (DFS) in 984 NSCLC patients with stage I–III (7). The opioids included morphine, pethidine, fentanyl, codeine, and dihydrocodeine. Postoperative opioid usage was associated with shorter OS (HR 1.514, 95% CI: 1.197–1.916, P=0.001) and shorter DFS (HR 1.415, 95% CI: 1.123–1.781, P=0.003) in the multivariate Cox regression model. Similarly, Maher *et al.* showed postoperative opioids could reduce DFS in 99 NSCLC patients with stage I and IIA (8). While these previous reports indicate that postoperative opioids may be a prognostic risk factor after lung cancer surgery, the following authors reported studies that do not support this. Oh *et al.* retrospectively analyzed the association between postoperative opioid use and long-term oncologic outcomes in 871 patients with NSCLC of stage I–IIIA (9). They divided seven-day opioid use into four quartiles. Finally, in the multivariate regression analysis, the amount of opioid usage did not affect the risk of recurrence or death of lung cancer (P=0.520, and P=0.659, respectively). Unfortunately, reliable and reproducible results on opioids and postoperative prognosis of lung cancer have not yet been obtained with respect to postoperative opioid use. Moreover, these studies focusing solely on postoperative opioid use have not considered intraoperative opioids.

Zhu *et al.* assessed the association between anesthetic factors and the postoperative outcomes of patients with NSCLC (1). This study included stage I-IV. The fentanyl equivalents conversion is sufentanil 0.1 μg, remifentanil 1 μg, or 110 μg morphine for 1 μg fentanyl. They found that perioperative fentanyl equivalents >28.2 μg/kg was associated with prolonged survival (HR 0.779, 95% CI: 0.619–0.980, P=0.033) but not with RFS (HR 0.926, 95% CI: 0.741–1.158, P=0.502). This paper differs from previous reports, showing that opioids are associated with improved OS. There may be a bias in this study that healthier patients were more likely to receive opioids. Moreover, due to the diversity of the stages under study, a stage-specific sub-analysis is expected in the future. Together with other reports, this report supports the consensus that opioid use does not improve cancer recurrence. Moreover, they also suggested that perioperative fentanyl equivalents >28.2 μg/kg were associated with an increased postoperative complication (P<0.05). In this study, the majority of patients were complicated by prolonged postoperative air leaks (61.1%; 359 of 588 patients). Prolonged air leaks are clearly a surgical complication. If opioids are actively associated with delayed healing of air leaks, their use must be actively discouraged during pulmonary resections, given their complication rate. Therefore, further analysis of the association between opioid use and postoperative complications is needed.

Nelson *et al.* analyzed 2,884 patients who received a lobectomy for stage I NSCLC from the Surveillance, Epidemiology and End Results-Medicare database using propensity-matched analysis (2). They assessed OS and persistent opioid use, defined as any opioid prescription filled 3 to 6 months after surgery. Those who used the lowest quartile of opioids showed similar OS as no opioid use (HR 1.27, 95% CI: 0.93–1.72). However, the second, third, and highest quartiles of opioid use were associated

with decreased OS (HR 1.53, 95% CI: 1.14–2.03, HR 1.39, 95% CI: 1.04–1.86, and HR 2.50, 95% CI: 1.95–3.21, respectively). However, they stated that this retrospective analysis cannot determine whether opioids are mediators or bystanders.

In summary, the overall prognostic impact of opioid use at low doses and stage ≥III (or stage ≥II) is insignificant. Alternatively, the effect of opioids on cancer prognosis may not be as strong as other prognostic factors. On the other hand, opioids may increase the relatively poor prognostic effect in early-stage lung cancer, and further research is needed. Potential micrometastases and CTCs are suspected of recurrence in patients undergoing radical resection. The pharmacological effects of opioids on cancer progression are still controversial. Opioids are essential drugs in the perioperative period, and research on cancer prognosis remains challenging. A well-considered prospective study is expected in the future.

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Footnote

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