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Association of increased postoperative opioid administration with non-small-cell lung cancer recurrence: a retrospective analysis

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Editor's key points

- Immune suppression by perioperative opioids has been implicated in cancer recurrence after surgical resection.
- A single-centre retrospective analysis was conducted on patients undergoing video-assisted thoracoscopic surgery lobectomy for non-small-cell lung cancer.
- Patients with cancer recurrence at 5 yr after resection received greater total opioid dose in the first 96 h postoperative period.
- This association requires confirmation in a large prospective study.

Background. Evidence suggests that opioid-sparing anaesthetic techniques might be associated with increased cancer-free postoperative survival. This could be related to suppression of natural killer cells by opioid analgesics in the perioperative period. This retrospective analysis tested the hypothesis that greater opioid use in the postoperative period is associated with a higher incidence of recurrences after surgery for lung cancer.

Methods. The medical records of 99 consecutive patients who underwent video-assisted thoracoscopic surgery with lobectomy for Stage I or IIa biopsy-proven non-small-cell lung cancer (NSCLC) were reviewed. Perioperative information including patient characteristics, laboratory data, and surgical, anaesthetic, nursing, and pharmacy reports were collected. Doses of opioids administered intra-operatively and for the first 96 h after operation were converted into equianalgesic doses of oral morphine using a standard conversion table. Data were then compared with the National Cancer Registry's incidence of disease-free survival for 5 yr.

Results. A total of 99 patients with similar characteristics were included in the final analysis, 73 of whom were NSCLC recurrence-free at 5 yr and 26 had NSCLC recurrence within 5 yr. Total opioid dose during the 96 h postoperative period was 124 (101) mg of morphine equivalents in the cancer-free group and 232 mg (355) mg in the recurrence group ($P=0.02$).

Conclusions. This retrospective analysis suggests an association between increased doses of opioids during the initial 96 h postoperative period with a higher recurrence rate of NSCLC within 5 yr.

Keywords: analgesics, opioid; carcinoma, non-small-cell lung; killer cells, natural; pain, postoperative; recurrence

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Lung cancer is the most common type of cancer worldwide, with non-small-cell lung cancer (NSCLC) accounting for ~80% of diagnosed lung cancer cases.[1] Survival for Stage I and IIa lung cancer is 43–60 and 18–34 months, respectively. After 5 yr, a patient is classified as free of the original tumour and subsequently found masses classified as new primary tumours, not metastasis or recurrence.[2] Evidence suggests that the most efficacious initial treatment for Stage I and Stage IIa NSCLC regardless of histologic subtype is surgical resection of the tumour as opposed to chemotherapy or radiation therapy.[3]

Although surgical resection of Stage I and IIa NSCLC is the first line of treatment,[3] physical manipulation and other surgical manoeuvres involving the primary tumour are among factors that could cause dissemination of malignant cells into the blood and lymphatic system, thereby allowing metastasis. Natural killer (NK) cells are lymphocytic components of the innate immune system with a crucial role in surveillance for and destruction of metastatic embolic cells.[4 5] In murine models, inhibition of NK cells is associated with increased incidence of pulmonary metastatic disease while increased NK cell activity has been found to suppress development of pulmonary metastasis.[6 7]

In retrospective studies, the use of opioid-sparing pain control measures in the operative period [e.g. regional (paravertebral) anaesthesia, epidural analgesia] has been associated with a decreased risk of cancer recurrence.[8–10] Administration of fentanyl before laparotomy in animal models

was found to decrease NK cell activity, which did not return to baseline values for several days.[11] An opioid-induced dose-dependent qualitative decrease in NK cell function and activity has also been observed in human volunteers.[12]

We hypothesized that patients with recurrence of Stage I or IIa NSCLC at 5 yr after video-assisted thoracoscopic surgery (VATS) lobectomy procedures received larger doses of opioids during the initial 96 h postoperative period than those without recurrence.

Methods

After obtaining approval from the Cedars-Sinai Hospital IRB, a retrospective analysis was performed on 444 consecutive patients who underwent minimally invasive unilateral VATS with a single surgeon between July 2006 and April 2008. Exclusion criteria included not being between the ages of 18 and 80 yr, having a prior diagnosis of any cancer, having received chemotherapy or radiation treatment at any time before surgery or during the 5 yr after operation, having a tumour that was found on final pathology not to be Stage I or IIa NSCLC, or requiring additional surgery beyond single unilateral VATS. Data were collected from both hospital records and the National Cancer Registry (NCR). The main outcome was the incidence of recurrence of NSCLC of the same initial histological subtype at 5 yr after operation, which was obtained through clinic notes and the NCR (if the patient was followed at an outside clinic).

Patient characteristics including age, gender, BMI, preoperative data including ASA status, liver and kidney function tests, use of preoperative opioids, pack-years of cigarette smoking, and co-morbidities and intra-operative data including tumour stage and intra-operative opioid and non-opioid analgesics administered were recorded. Postoperative pain was evaluated using an 11-point numeric rating scale (NRS-11), with 0=no pain and 10=most severe pain imaginable. The NST-11 score was averaged over the 2 h post-anaesthetic care unit (PACU) stay and for each subsequent 24 h interval for 96 h after surgery. Postoperative opioids for pain management were ordered according to the individual patient's pain needs. The timing, type and dose of opioid, and the NRS score were recorded in the medical record. No patient required opioid reversal drugs during their hospitalization. The total amount of opioid was converted into the equianalgesic dose of oral morphine using a standardized conversion ratio (Table 1).[13 37 38] Controversy exists regarding the accuracy of equianalgesic conversion calculations, especially concerning longer-acting opioids (e.g. oxycodone, transdermal fentanyl).[14 15] The amount of paracetamol patients received after operation was also recorded. Other non-steroidal anti-inflammtory drugs (NSAIDs) were avoided during the initial 96 h postoperative period. All patients completed the 5 yr clinical follow-up period. Furthermore, all patients were instructed to stop smoking at the time of their initial diagnosis before VATS lobectomy.

Intra-operatively, patients were under the care of a surgical team of residents, fellows, and a single supervising board certified thoracic surgeon (R.M.). Surgery was conducted utilizing a standardized general anaesthetic technique and one-lung-ventilation was performed in the lateral position. A 1 cm incision was made at the eighth intercostal space at the mid-axillary line for placement of the thoracoscope. A 2 cm incision was also made at the sixth intercostal space at the mid-clavicular line and a 5 cm incision at the mid-axillary line. Masses were identified by palpation and removed with laparoscopic staple devices. After all masses were excised, they were sent for formal pathologic analysis. At the discretion of the attending anaesthesiologist, ketorolac i.v. was administered after removal of the lung mass but before skin closure to allow adequate onset time and minimize the risk of bleeding. Before skin closures, all patients received intercostal nerve blocks with 0.5% bupivacaine with epinephrine at the intercostal spaces corresponding to the surgical incisions through a 25-gauge needle under direct thoracoscopic view. The volume of bupivacaine administered was recorded in the operative report. No additional regional anaesthesia or epidural pain management techniques were used during the intra- or postoperative periods. After tracheal extubation, all patients remained in the PACU for 2 h during which administration of pain medications was at the discretion of the attending anaesthesiologist and nursing staff. Subsequently, all patients were cared for on a non-intensive surgical care unit for the remainder of their 96 h hospitalization.

Patients were classified into NSCLC recurrence and cancer-free survival groups. All data were coded in an Excel file (Microsoft, Redmond, WA, USA) and imported into the SPSS statistical software package (IBM Corp., Armonk, NY, USA) for analysis. Differences in categorical variables were analysed using χ^2 test and *t*-tests were used for continuous variables. Associations with a *P*-value <0.05 were considered statistically significant. Multivariable logistic regression models were performed to examine potential predictors of cancer recurrence at 5 yr. Variables with *P*-values <0.1, factors that have a known clinical

Table 1 Equianalgesic opioid conversion table. All equianalgesic doses are given relative to the equivalent dose of 10 mg of oral morphine.[13 37 38]

Opioid	Administration route	Dose equivalent to 10 mg oral morphine (mg)
Morphine	Oral	10
Morphine	I.V.	3.3
Hydromorphone	Oral	2
Hydromorphone	I.V.	0.5
Fentanyl	I.V.	0.03
Hydrocodone	Oral	10
Oxycodone	Oral	7
Codeine	Oral	80
Tramadol	Oral	40
Propoxyphene	Oral	44
Meperidine	Oral	100
Methadone	I.V.	1.0