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Association of opioid requirement and cancer pain with survival in advanced non-small cell lung cancer

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Editor's key points

- Clinical and laboratory evidence suggest that pain and opioid use are associated with survival in cancer.
- A retrospective analysis of pain and opioid use was conducted in 209 patients with advanced lung cancer.
- More severe pain and greater opioid use were independently associated with shorter overall survival.
- Prospective studies are required to determine if reducing opioid use without sacrificing analgesia can improve outcomes.

Background. Pain is associated with shorter survival in non-small cell lung cancer (NSCLC). Lung cancer cells express opioid receptors. Opioids promote angiogenesis, tumour growth, and metastases, and shorten survival in animal models.

Methods. We examined retrospectively if long-term opioid requirement, independently of chronic pain, is associated with reduced survival in 209 patients with stage IIIB/IV NSCLC. Opioid doses were converted to average oral morphine equivalents (OME). Patients were stratified by proportion of time they reported severe pain, and required <5 or ≥ 5 mg day^{-1} OME. Effects of pain, opioid requirement, and known prognostic variables on overall survival were analysed.

Results. Severe pain before chemotherapy initiation was associated with shorter survival (hazards ratio 1.39, 95% confidence interval, 1.02–1.87, $P=0.035$). The magnitude of pain and opioid requirement during first 90 days of chemotherapy were predictive of shorter survival: patients with no/mild pain and requiring <5 mg day^{-1} OME had 12 months longer median survival compared with those requiring more opioids, experiencing more pain, or both (18 compared with 4.2–7.7 months, $P\leq 0.002$). Survival differences (16 compared with 5.5–7.8 months, $P<0.001$) were similar when chronic pain and opioid requirement were assessed until death or last follow-up. In multivariable models, opioid requirement and chronic pain remained independent predictors of survival, after adjustment for age, stage, and performance status.

Conclusions. The severity of chronic cancer-related pain or greater opioid requirement is associated with shorter survival in advanced NSCLC, independently of known prognostic factors. While pain adversely influences prognosis, controlling it with opioids does not improve survival. Prospective studies should determine if pain control using equi-analgesic opioid-sparing approaches can improve outcomes.

Keywords: analgesics, opioid; metastasis; morphine; mortality; neoplasm recurrence; pain

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Cancer-related pain is common, negatively impacts quality of life (QOL), and often requires opioid analgesics. Two-thirds of patients with advanced malignancies experience pain, with almost 50% experiencing moderate–severe pain.[1] Opioid medications are the mainstay of treatment of severe, chronic cancer pain.[2 3] Experimental studies and retrospective clinical analyses raise concern that opioids might promote cancer progression and reduce survival.[4–16]

However, pain at diagnosis is itself associated with shorter survival in lung cancer[17 18] and other malignancies.[19–22] Pain may induce cancer progression via tumour innervation[23] and release of tachykinins such as substance P,[24] endogenous opioid peptides that modulate immune function,[25] or cyclo-oxygenase-mediated prostaglandin release.[26 27] Therefore, it is unclear whether reduced survival in patients treated with opioids is due to opioids, pain, or both. Since pain has a direct impact on QOL and perhaps disease outcomes, it is critical to understand the independent contribution of pain and opioids to cancer progression and survival in order to develop strategies to improve cancer outcomes.

Lung cancer is the most common malignancy worldwide,[28] and ranks third highest for pain prevalence among all malignancies.[1] Preclinical data on cellular mechanisms and murine models demonstrate that opioids promote lung cancer progression and metastasis and reduce survival.[5 6 12 14] Opioids directly activate mitogenic signalling via μ-opioid receptors

(MOR), and also by co-activating receptor tyrosine kinases including vascular endothelial growth factor receptor-2 and epidermal growth factor receptor in endothelial[4] and lung cancer cells,[5 6 12 14] respectively, and promote epithelial–mesenchymal transition.[14] MOR expression is increased in human lung cancer specimens compared with normal human lungs,[5 29] and even higher in lung cancers with metastases to lymph nodes.[30] Opioids might therefore be associated with lung cancer progression in patients.

In a retrospective study of patients with advanced prostate cancer receiving androgen-deprivation therapy, we found that greater opioid requirement and higher MOR expression in the tumour are independently associated with shorter progression-free survival and overall survival (OS).[16] Halabi and colleagues[22] confirmed and extended our findings to patients with advanced prostate cancer receiving first-line chemotherapy, reporting that opioid use is an independent prognostic factor for survival. Some prospective studies suggest that systemic exposure to endogenous or pharmacological opioids promotes cancer progression in patients with astrocytomas,[31] pancreatic cancer,[32] and various advanced solid tumours including lung cancer.[33]

However, the above studies did not differentiate between impact of pain and opioid use independently of the other. Previous studies also did not evaluate the effect of chronic (ongoing) pain or long-term quantitative opioid exposure on cancer outcomes. Further, there is marked inter-patient variability in treatment of pain and use of opioids depending upon individual patient pain thresholds and patient and provider preferences.[2 3] Therefore, we objectively determined the effect of chronic cancer-related pain and quantitative systemic opioid use, independent of each other, on survival of patients with advanced non-small cell lung cancer (NSCLC).

Methods

Patients

We retrospectively studied 209 patients diagnosed with stage IIIB or IV NSCLC from 2003 to 2010 at the Minneapolis Veterans Affairs Health Care System (MVAHCS) treated with palliative chemotherapy to determine whether chronic pain, opioid requirement, or both are associated with survival. Patient characteristics, clinical, and pharmacy data were obtained from patient records, the tumour registry, and VA Data Support Services. The study was approved by the institutional Human Subjects Committee.

Opioid requirement

All oral and transdermal outpatient opioid prescriptions dispensed from any VA in the USA from 2002 to 2012 were collected to determine the total opioid quantity dispensed per prescription. All opioids were converted to oral morphine equivalents (OME) using an equi-analgesic conversion table.[16] Average daily opioid requirement was calculated for three distinct treatment intervals: (i) 90 days before chemotherapy initiation, (ii) 90 days after chemotherapy initiation, and (iii) chemotherapy initiation to death or last follow-up.

Pain levels

All pain values recorded from inpatient and outpatient clinical encounters were collected. Pain levels were analysed for the same three treatment intervals used for opioids. Pain severity was categorized in accordance with the Brief Pain Inventory: low (0–3), moderate (4–6), and severe (7–10).[34] For analysis of pain during the 90 days before chemotherapy, we used the patient's maximum reported pain level to maintain consistency and comparability with previous studies which assessed pain before treatment initiation.[17 21]

Pain–opioid groups

For treatment intervals after chemotherapy initiation, both pain and opioid requirement were separated into high and low groups, to better assess for interactions. The categorization of pain levels, opioid requirement, and patient groupings are shown and explained in Table 1. Briefly, pain was stratified by the proportions of time a patient reported severe or moderate–severe pain. Patients requiring $\geq$5 mg day^{-1} OME were considered to have high opioid use. We previously found that this cut-off (5 mg day^{-1} OME) distinguished patients who used either short courses of opioids intermittently or required opioids only occasionally from patients who required ongoing scheduled opioids.[16] Four subgroups were created based on the severity of pain and quantitative opioid requirement (Table 1), reflecting clinical scenarios observed in clinical

Table 1 Categorization of pain level and opioid requirement. Patients were stratified into low pain (LP) or high pain (HP) groups, based on the proportion of time they reported severe, or moderate–severe, pain. Categorization of patients into low opioid (LO) or high opioid (HO) groups was based on an opioid requirement cut-off of 5 mg day^{-1} OME. Four subgroups were created based on pain level and opioid requirement: (i) low pain/low opioid (LPLO: reference group against which the other three groups were compared), (ii) high pain/low opioid (HPLO), (iii) low pain/high opioid (LPHO), and (iv) high pain/high opioid (HPHO). Analyses were performed separately using the severe pain or moderate–severe pain categorizations

	Low pain (LP) group	**High pain (HP) group**
Severe pain (7–10)	<10% of all recordings	≥10% of all recordings
Moderate–severe pain (4–10)	<25% of all recordings	≥25% of all recordings
	Low opioid (LO) group	**High opioid (HO) group**
Average opioid requirement (mg day^{-1} OME)	<5	≥5
Pain	**Opioid requirement** **Low**	**High**
Low	LPLO	LPHO
High	HPLO	HPHO