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## **STATE OF THE SCIENCE:**

### **OPIOIDS AND SURVIVAL IN CANCER PAIN MANAGEMENT**

Dr Jason W Boland<sup>a,\*</sup>, Professor Michael I Bennett<sup>b</sup>

<sup>a</sup> Wolfson Palliative Care Research Centre, Hull York Medical School, University of Hull,  
Hull, HU6 7RX, UK

<sup>b</sup>Academic Unit of Palliative Care, University of Leeds, LS2 9LJ

**\*Corresponding author:** Dr Jason Boland, Senior Clinical Lecturer and Honorary  
Consultant in Palliative Medicine.

Address: Hull York Medical School, University of Hull, Hull, HU6 7RX, UK.

Tel: +44 1482 463482; fax: +44 1482 464705.

E-mail address: Jason.Boland@hyms.ac.uk

URL: <https://www.hyms.ac.uk/about/people/jason-boland>

## **1. INTRODUCTION**

Opioids are commonly used for cancer-related pain in advanced disease and about 75% of people have a good response. However, under-treatment is common, and opioids often started only weeks before death. Undertreated pain might decrease survival in some although prospective studies to delineate how pain and opioids affect cancer progression and survival in various malignancies are absent<sup>1</sup>. One systematic review found that most (11/17) studies in advanced prostate cancer showed pain to be an independent prognostic factor for shorter survival<sup>1</sup>. However, five studies defined pain by analgesic use, making it difficult to determine if pain or opioid use was more important. In breast, colorectal, or lung cancer evidence was insufficient to definitively determine if pain independently influences survival<sup>1</sup>. In a secondary data analysis, recurrent ovarian cancer pain was an independent marker for shorter overall survival<sup>2</sup>. In this study, survival was shorter in those with pain and without pain medication compared with those on sufficient pain medication<sup>2</sup>.

## **2. LONG TERM OPIOID ADVERSE EFFECTS**

Clinicians and patients are understandably concerned respectively about prescribing and taking opioids. These concerns include side-effects, addiction and the perception that opioid-use indicates the end of life. There is sometimes concern opioids might shorten survival, even towards the end of their life.

Opioids might potentially affect survival by various mechanisms. These include acute effects on respiration and cardiac rhythm<sup>3,4</sup> (Figure 1) and chronic influences on cancer cell growth and immunity. These can vary by opioid and use duration<sup>3</sup>. Some data

suggests opioids influence immune function in cancer but this has not been correlated to survival<sup>5</sup>.

### **3. OPIOIDS AND INITIAL CANCER SURGERY**

There have been many, mostly retrospective studies, assessing the effect of opioids on survival in cancer surgery. The data are mixed. A systematic review found no conclusive evidence to support any practice which avoided opioids to reduce colorectal cancer recurrence<sup>6</sup>. Furthermore, a recent RCT showed no difference in breast cancer recurrence (after potentially curative surgery) with regional anaesthesia-analgesia by paravertebral blocks and propofol compared to general anaesthesia with sevoflurane and opioids<sup>7</sup>. However, studies in different cancer types and stages vary. For example, persistent opioid use (3 to 6 months after surgery) was independently associated with worse survival after lobectomy for stage I non-small cell lung cancer<sup>8</sup>. Further RCTs are needed to advance the influence of opioids in cancer surgical management.

### **4. OPIOIDS AND CANCER PAIN MANAGEMENT**

In people with a longer life expectancy (months to years), a systematic review found a potential association between opioid use and decreased survival, but no high-quality study specifically assessed this and causality cannot be determined<sup>4</sup>. There are many confounding factors: those with more aggressive tumours might have more pain requiring opioids and/or such tumours intrinsically associated with more pain.

Subsequently, a secondary multi variable analysis in advanced, incurable cancer during palliative care showed opioid-use was associated with decreased survival<sup>9</sup>. When

adjusted for C-reactive protein data, the independent relationship between survival and opioid-use weakened suggesting more aggressive painful disease also influenced survival<sup>9</sup>. A prospective cohort study of incurable non-small cell lung cancer showed median overall survival was 242 days in an opioid group and 627 days in the no-opioid group. Opioid-use was an independent predictor of shorter OS<sup>10</sup>.

## **5. EVIDENCE FROM END OF LIFE CARE**

At the end of life (people with days or weeks left to live) results are mixed; some show none, others increases or decreases<sup>4</sup> in survival. There is no consistent data which supports an association between opioids and prognosis, although based on very low quality data<sup>4</sup>. These studies are mostly retrospective comparing survival between opioids v no systemic opioids, or high v low-dose opioids. However, the low-dose group cut off in these studies were 200-300mg oral morphine equivalent per day; even this “low-dose” comparator group were often on high opioid doses. This potentially makes these studies less sensitive to detect an opioid effect. They also generally had a follow-up of days to short weeks, some just measured use in the last days of life. They were usually hospice-based studies with a heterogeneous population. There was no consistent body of data suggesting appropriately titrated opioids in the last days or weeks of life shorten survival. As there was no truly matched comparison to evaluate causality, only associations between opioids and survival exist.

## 6. PRACTICAL GUIDANCE FOR CLINICIANS (BOX)

- Opioids should continue to be used in advanced cancer for cancer-related pain.
- In cancer surgery there is no conclusive evidence of an effect of opioids on survival
- In cancer survivors with a longer-life expectancy, until we get better quality data (which account for confounding factors) opioids can be used with caution.
- At the end of life, there is no justification for stopping or reducing appropriately titrated opioids for survival reasons.

## **7. SUMMARY**

Opioids are essential for cancer-related pain associated with progressive disease.

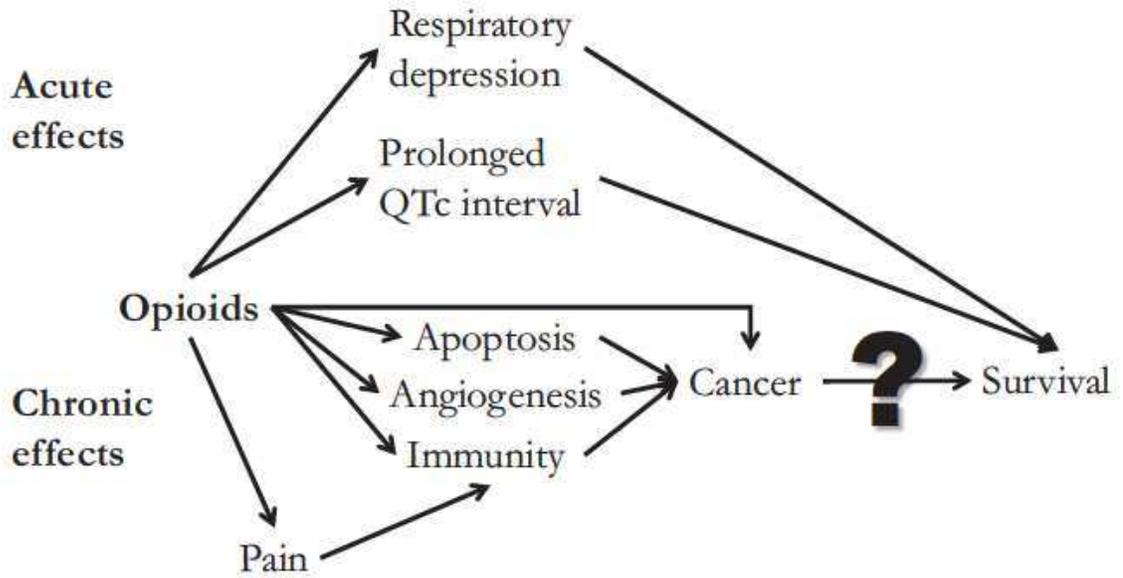
Some have reported an association between greater pain and shorter survival highlighting the need to manage pain well. Currently there is no conclusive evidence of an opioid effect on survival during cancer surgery. There might be an association between chronic opioid use and decreased survival but there are many confounding factors. People with more aggressive tumours might have more pain requiring opioids.

There does not seem to be a detrimental effect of appropriately used opioids on survival at the end of life, although no high-quality study has assessed this.



Figure 1: Potential opioid mechanisms which might impact cancer survival.

Reproduced from <sup>4</sup>



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