

## **Opioids do not influence metastasis in experimental animal cancer models.**

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There are no figures or tables.

We read with interest the detailed and much-needed review and meta-analysis of analgesics on cancer metastasis in animal models by Hooijmans et al [4]. This is an area that is of increasing concern for clinicians and patients. When sub-analysed by analgesic groups, they reported a link between non-steroidal anti-inflammatory drugs (NSAIDs) and reduced metastasis, but from the limited data available, opioids did not influence metastasis in animal models. It was also of interest that co-administration of opioids abolished the benefit of reduced metastasis from NSAIDs. Most of the opioid experiments used morphine and, as these are a group of heterogeneous molecules with potentially differing effects [5], there was unfortunately not enough data to discern if there was a difference between opioids,

Opioids, especially morphine, are commonly used in cancer pain management. There are two main scenarios in which opioids are used in patients with cancer: 1) acute administration for surgical resection of cancer and 2) for chronic cancer pain management. The influence of opioids on patients following surgical resection of their cancer is likely to be very different to their influence on individuals being treated for chronic cancer pain due to differing drug regimens (including anaesthetics), the duration of opioid administration, immune cell activation and systemic tumour cell release [3,6].

The non-surgical literature assessing clinical outcomes in patients with cancer prescribed opioids is sparse. A systematic review indicated that morphine (no studies with other opioids were identified) might affect aspects of immune function but did not find any studies measuring the impact of these immunological changes on clinical outcomes [1].

Although we agree that the animal data is useful to guide translational studies, clinicians need adequately powered studies in relevant groups of patients in order to inform clinical practice and optimise the care of patients with cancer. This is particularly pertinent as our own recent systematic review reported a possible association between long-term regular systemic opioid analgesia and shorter survival in adult patients with cancer [2]. However, an important limitation of research in this field is that the relationship between greater analgesic requirements and shorter survival is likely to

be mediated by painful progressive cancer. Pain control is vital and there is no definitive data suggesting that opioids are detrimental, thus based on current evidence opioids should continue to be used for cancer pain management. However, we are still lacking critical data on how to optimally manage pain with opioids in patients with cancer. There is a need for high-quality prospective studies which assess clinical endpoints such as metastasis and survival in patients with cancer on long-term opioids.

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