


# BMJ Open Could the perioperative use of opioids influence cancer outcomes after surgery? A scoping review protocol

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## ABSTRACT

**Background** During and after general anaesthesia, opioids are commonly used for pain treatment. Since preclinical studies underlined the potential immunosuppressive activity of these drugs, it was postulated that their perioperative administration could influence cancer outcomes after surgery. Nevertheless, clinical data have been extrapolated mainly from retrospective analyses. Consequently, the precise link between perioperative opioid use and cancer recurrence/metastasis or cancer-related mortality/morbidity is still an unsolved issue.

**Methods and analysis** This scoping review is planned to follow the Joanna Briggs Institute recommendations. The authors will conduct a literature review through the PRISMA statement using PubMed and EMBASE databases; the Grey literature will be explored using Google Scholar and Conference Proceedings Citation Index (via Web of Science). The search strategy will be limited to articles published in the English language and to human studies. The database searches are planned from the inception to January 2022. Two reviewers will independently screen titles and abstracts, followed by a full-text screening of potentially relevant articles with standardised data extraction. Any disagreement for the inclusion between the two reviewers will be discussed with a third reviewer.

**Ethics and dissemination** The review aims to map the available literature, focusing on a possible association between perioperative opioid use and cancer outcomes in patients undergoing surgery. The proposed approach will be useful to identify and analyse the knowledge gap in the field and serve as a prerequisite for future research.

**Scoping review registration** Open Science Framework <https://osf.io/vfhw6/> DOI 10.17605/OSF.IO/VFHW6

## BACKGROUND

Opioids are a class of drugs used to control analgesia during and after general anaesthesia. From the end of the last century, several preclinical investigations were conducted on their potential immunosuppressive activity. The impact of these agents on both the innate and adaptive immune systems was underlined.<sup>1</sup> Since many factors such as the type of opioid, the dose, the timing of administration and the animal strain used can influence the data; these findings are not conclusive. Later,

## Strengths and limitations of this study

- A strategy that limits or eliminates the use of opioids during and after surgery could induce immediate effects on perioperative outcomes and a potential improvement of the oncological course.
- The analysis of the results must be interpreted considering that clinical trials of the perioperative opioid-induced effects on cancer are difficult to conduct due to a combination of anaesthetic and non-anaesthetic agents used.
- Because of the inclusion of publications written only in the English language, the search may exclude relevant articles in other languages.
- The broad search strategy might be associated with less accuracy on the aim of the review that may result in many redundant references.

in individuals with a history of opioid abuse, the effects of morphine on the immune system were studied.<sup>2</sup> Furthermore, an association between opioid use and a higher risk of infections was found in patients treated for chronic non-cancer pain.<sup>3</sup> Nevertheless, to date, the evidence is not strong enough to establish a clear link between chronic opioid use and immunosuppression.<sup>4</sup>

The role of opioids in cancer development, progression and metastasis is an open issue.<sup>5</sup> Long-term or short-term use of these drugs could have different effects on these phenomena, and it could be assumed that prolonged use plays a more important role in tumour progression and development. Nevertheless, doubts were also raised about the impact of opioid administration given for a limited period, such as the surgical phase and the immediate postoperative period, on immunity. Thus, in the setting of cancer patients undergoing surgery, there is a debate about possible opioid-induced long-term oncological sequelae. To date, however, most of the scientific evidence in favour of this thesis comes from preclinical studies<sup>6</sup> while clinical data have been mainly extrapolated

**Table 1** Eligibility criteria

	Inclusion	Exclusion
Study design	Primary studies of any design	Systematic reviews, meta-analysis, narrative reviews, letters to the editor, case reports, case series, animal studies, in vitro investigations, studies on human volunteers
Population	Patients who underwent surgery for cancer disease	n/a
Intervention/exposure	Administration of opioids for the treatment of pain/anaesthesia	n/a
Comparator	Methods of opioid-free anaesthesia	No opioids should be administered in the whole perioperative
Outcomes	Disease-free survival and/or overall survival	Those other than the chosen outcomes
Language	English	Those other than in English
Publication status	Published in peer review journals, full-length articles	Published in not peer-review journals, unpublished works as a full-text, abstract, conference meetings
Others	All study dates, length of follow-up, setting	n/a

from retrospective analyses.<sup>7,8</sup> For example, since preclinical investigations demonstrated that the mu-opioid receptor (MOR) is often expressed in cancer tissues, patients requiring increased intraoperative opioid doses could show worse outcomes, especially if they express high MOR levels.<sup>9</sup> Interestingly, the expression of MORs in some tumours (eg, pancreatic ductal adenocarcinoma) and not in others could explain how, in some studies, the higher intraoperative opioid administration could be associated with better oncological outcomes.<sup>7</sup> Notably, intraoperative opioids can increase the expression of opioid receptors in cancer tissues without influencing the expression of immune cell markers.<sup>10</sup>

About clinical data, a retrospective study on patients who underwent prostatectomy for cancer showed that the use of epidural analgesia involved a significant reduction in cancer recurrence compared with those managed with systemic opioids.<sup>11</sup> On the other hand, a recent controlled investigation demonstrated that regional

anaesthesia-analgesia approaches did not reduce breast cancer recurrence compared with standard opioid-based anaesthesia.<sup>12</sup> Moreover, a retrospective study found that higher intraoperative opioid doses were significantly associated with better recurrence-free survival (p value = 0.028), but not with increased overall survival.<sup>6</sup> Recently, a systematic review that included 13 studies on perioperative opioids and colorectal cancer recurrence found no conclusive results. Furthermore, the authors decided to not perform the meta-analysis because of the low quality of the primary studies.<sup>13</sup> Indeed, conducting studies on the subject is extremely complex. The analysis of the results must be interpreted considering the combination of anaesthetic and no-anaesthetic agents used. In brief, the potential impact of perioperative opioid administration and oncological outcomes has several confounders. Perioperative interventions such as fluid therapy and anaesthetic techniques must be carefully addressed.<sup>14,15</sup>

On these premises, the precise link between perioperative opioids and cancer recurrence or metastasis, as well as survival, is still an unsolved problem.<sup>16,17</sup>

### Implications

This scoping review may clarify doubts on an extremely important topic. The task is to understand, in a cancer patient, if an approach that limits or eliminates the use of opioids during and after surgery could influence cancer outcomes.

## METHODS AND ANALYSIS

### Protocol design

The protocol was registered prospectively with the Open Science Framework in June 2021.<sup>18</sup> It has been planned, according to the JBI Scoping Review Methodology Group,<sup>19</sup> following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR).<sup>20</sup>

**Table 2** Scoping review search strategy Ovid Medline search strategy (2 January 2022)

Searches	Results
1. cancer.mp.	1953928
2. oncolog*.mp.	198380
3. 1 or 2	2037054
4. surgery.mp.	2848733
5. 3 and 4	317280
6. opioid.mp.	123308
7. 5 and 6	1111
8. monitor*.mp.	1073758
9. Follow-Up Studies/	678247
10. 8 or 9	1724632
11. 7 and 10	101

**Table 3** Planned variables to be extracted in the scoping review

General study details	Study ID number, lead author, title, journal, year of publication, type of publication, information source
Study characteristics	Study design, study duration, pilot/feasibility study (y/n), number of study arms, covariates (definition and measurement methods)
Participants	<ol style="list-style-type: none"> <li>1. Total number, setting, inclusion and exclusion criteria</li> <li>2. Participant characteristics at baseline: for each study, average age (years, mean and SD), sex (%), country, diagnosis (cancer type, stage), treatment(s), comorbidities</li> </ol>
Interventions/exposures and comparators	<ol style="list-style-type: none"> <li>1. Total number of intervention/exposure (opioid(s) type, doses, opioid administration and surgery (preoperatively, intraoperatively, postoperatively), time of treatment), and comparison (No opioid use) groups and number of participants in each group</li> <li>2. For each intervention/exposure and comparison group: intervention/exposure/comparison, duration of intervention/exposure, who and how assessed and results of the assessment</li> </ol>
Outcomes	Type of recurrence or metastasis; time elapsed since surgery; overall survival
Potential confounders	For example, fluid therapy, and anaesthetic techniques
Results	For each quantitative outcome: sample size, number of missing participants, reasons for loss to follow-up, summary data for each group (a 2 × 2 table for dichotomous data, means and SDs for continuous data), the estimate of effect for the difference between groups (or change in baseline and final scores for single-arm studies), confidence intervals, and p value

### Patient and public involvement

Patients and public were not involved in the preparation of this protocol.

### Research questions

This review is planned to answer the following research question:

Could the perioperative use of opioids influence cancer outcomes after surgery?

The research sub-questions include:

1. Is it possible to find possible differences according to the type of opioid used?
2. Is there a correlation between chronic opioid use and variation in outcomes in cancer patients?
3. Are there any differences related to the type of multi-modal analgesia applied?

### Eligibility criteria

Primary studies of any design will be included. No restrictions on publication year will be adopted. We will exclude unpublished works as a full-text, abstract, conference meetings, studies published in not peer-review journals, uncontrolled studies as case series or case reports, reviews and studies published not in English.

Manuscripts will be excluded if they do not match the assumed framework of the study, centred on opioids administration and cancer recurrence or metastasis after surgery (table 1).

### Search strategy

The search strategy will be defined following the PICO strategy. The Population will be patients who underwent surgery for cancer disease, and the Intervention will be the administration of opioids alone or in combination with other drugs used for both treatment of pain perioperatively and anaesthesia management. The Comparator will be any method of opioid-free anaesthesia regional

anaesthesia-analgesia approaches for the perioperative management of pain. The Outcomes will be the time of disease-free survival, and the overall survival. The search strings follow the evidence-based guideline for Peer Review of Electronic Search Strategies (PRESS) for systematic reviews, health technology assessments and other evidence syntheses developed by McGowan and colleagues.<sup>21</sup> A proposed search string for Medline, via Ovid, is detailed in table 2; the search strategies for the other databases will be comparable in structure with similar search terms and synonyms.

A consequent search using keywords and index terms will be performed using several computer-assisted databases, including PubMed, EMBASE and for the grey literature: Google Scholar and Conference Proceedings Citation Index (via Web of Science). The search strategy will be limited to articles published in the English language and to human studies (in online supplemental file the full search strategies used for all databases).

### Study selection

Articles will be selected by the authors by evaluating titles and abstracts to identify potentially eligible studies; subsequently, the full text of eligible studies will be reviewed by the authors to exclude irrelevant studies or methodologies that are not usable for future analysis.

### Data charting

The reviewers will record key information from included articles in a Microsoft Excel data extraction form. Two reviewers (FB and CAF) will independently extract data to minimise errors. Each study will be extracted with the following information: title, year of publication, first author, the country where the study was conducted, type of study, lying cancer disease for which the surgery was required, anaesthesia method, type, and dose of the

opioid(s), type of multimodal analgesia (regional techniques, drugs), and outcomes including the type of recurrence or metastasis, the time elapsed since surgery, and overall survival.

### Data synthesis

The number of studies identified and selected at each stage of the scoping review and the reasons for exclusion will be presented in the PRISMA flow diagram. Results will be recapitulated in [table 3](#) and exhaustively discussed in a narrative way to address the research questions. Results will be assembled conceptually in terms of general study details, study characteristics, participants, interventions/exposures/comparators, instruments used in goal setting, outcomes, potential confounders and results. This review will illustrate summaries of these categories, including quantitative measurements of associations (mean differences for scores by validated questionnaires, risk ratios or ORs for dichotomous outcomes), if applicable. Additional groups may be identified during the extraction of results. Authors of papers will be contacted to request missing or additional data for clarification, where required. We will report the results of critical appraisal in narrative form and in one or more tables.

### Risk of bias

As this is a scoping review, there will be no risk of bias assessment. This is consistent with relevant guidance.<sup>22</sup>

### Strengths and limitations of this study

This scoping review aims to describe the link between perioperative opioids and cancer recurrence or metastasis. The subject is particularly complex. The main issue is to establish what is the weight of the intervention in the determinism of outcomes. The outcomes considered, indeed, may be dependent on multiple factors such as type of opioid and dose. For both variables, literature data are conflicting.<sup>23</sup> Moreover, it will be important to accurately extract data on the disease (stage, grading). For example, in prostate cancer, a Gleason 4 + 3 = 7 will have a higher probability of developing recurrence or metastasis than a Gleason 3 + 4 = 7. The effect of opioids may vary depending on the stage of the tumour. In this regard, in a retrospective analysis, Cata *et al*<sup>24</sup> found that intraoperative opioid was associated with reduced overall survival for patients with early-stage non-small cell lung cancer compared with those affected by the more advanced disease.

Another important challenge regards the potential immunosuppressive effects among patients receiving, preoperatively, opioids for the management of chronic cancer pain. Our goal is that the proposed approach will allow us to identify and analyse the knowledge gap in the field and, in turn, will serve as a prerequisite for future research including systematic review and clinical studies.

Although we will follow an accurate method for this scoping review, several limitations are anticipated. Because of the inclusion of publications written only in

the English language, the search may exclude relevant articles in other languages. Furthermore, our broad search strategy might be associated with less accuracy on the aim of the review that may result in many redundant references. Third, the analysis of the results must be interpreted considering that clinical trials of the perioperative opioid-induced effects on cancer are difficult to conduct, as during the perioperative care, patients require a combination of anaesthetic and no-anaesthetic agents. These limitations could lead to serious inconsistency and/or risk of bias, downgrading the outcomes.

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