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

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ABSTRACT

Background

Opioids are commonly used for the treatment of pain, and during and after general anesthesia. Since preclinical studies underlined the potential immunosuppressive activity of these drugs, it was postulated that the perioperative administration of opioids could influence cancer outcomes after surgery. Nevertheless, clinical data have been extrapolated mainly from retrospective analyses. The precise link between perioperative opioids use and cancer recurrence/metastasis or cancer-related mortality/morbidity remains unresolved**.**

Methods and analysis

This scoping review is planned following 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, Conference Proceedings Citation Index (via Web of Science), and Open Grey. 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 August 2021. Two reviewers will independently screen titles and abstracts, followed by a full-text screening of potentially relevant articles with standardized 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 opioids use and cancer outcomes in patients undergoing surgery. The proposed approach will be useful to identify and analyze the knowledge gap in the field and serving as a prerequisite for future research.

Scoping review registration

Open Science Framework https://osf.io/vfhw6/ DOI 10.17605/OSF.IO/VFHW6

Keywords: Opioids, Cancer Surgery, Cancer Outcomes, Postoperative Analgesia, Opioid-free Anesthesia

Article Summary

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 anesthetic and no-anesthetic 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 a large number of redundant references.

Background

Opioids are a class of drugs used for the treatment of pain, and to control analgesia during and after general anesthesia. From the end of the last century, several preclinical investigations were conducted on the potential immunosuppressive activity of opioids. The impact of these agents on both the innate and adaptive immune systems was enphatized.[1] 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, in individuals with a history of opioid abuse, the effects of morphine on the immune system were studied.[2] Furthermore, an association between opioid use and higher risk of infections was found in patients treated for chronic non cancer pain.[3] Nevertheless, to date, the evidence is not strong enough to establish a clear link between chronic opioid use and immunosuppression.[4] Moreover, doubts raised about impact of opioid administration given for a limited period such as the surgical phase and a short postoperative period on immunity. Interestingly, intraoperative opioids can increase expression of opioid receptor in cancer tissues without influencing the expression of immune cell markers.[5]

In the context of the intraoperative phase, anesthesia strategies focused on low-dose opioid use or opioid-avoiding paths (i.e., opioid-free anesthesia, OFA) are rapidly growing, even in cancer surgery.[6] The motivations underlying this phenomenon are multiple. Synthetic short-acting opioids, for instance, can increase postoperative pain through opioid-induced hyperalgesia mechanisms. Again, the use of opioids during and after surgery can lead to a delay in patient mobilization, a slowing of intestinal peristalsis, and an increase in postoperative nausea and vomiting (PONV). Finally, the concern of a potential postoperative opioids over prescriptions is another serious reason that tends to direct the anesthetic choices towards an opioid-free approach. The OFA strategy is based on the concept of multimodal anesthesia which combines different drugs and/or techniques.[7] In the whole perioperative setting, regional anesthesia techniques are pivotal components of this multimodal pain management. These methods could influence the long-term outcome of cancer surgery, mostly by attenuating the immunosuppression effects due to surgery.[8]

In the setting of cancer patients, in addition to the effects on the early postoperative, a debate is underway on possible opioid-induced long-term sequelae. To date, most of the scientific evidence in favor of this thesis comes from preclinical studies while clinical data have been extrapolated mainly from retrospective analyses.[9] For instance, a retrospective study on patients who underwent prostatectomy for cancer showed that patients treated through epidural analgesia had a significant reduction in cancer recurrence compared to those managed with opioids.[10] On the other hand, a recent controlled investigation demonstrated that regional anesthesia-analgesia approaches did not reduce breast cancer recurrence compared with standard opioid-based anesthesia.[11] 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.[12] Thus, the precise link between perioperative opioids and cancer recurrence or metastasis, as well as survival remains unresolved.

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 has immediate effects such as the reduction of PONV, rapid mobilization, and reduced inhibition of peristalsis. A potential improvement of the oncological outcomes is also investigated.

Methods and analysis

Protocol design

The protocol was registered prospectively with the Open Science Framework in June 2021.[13] It has been planned, according the JBI Scoping Review Methodology Group,[14] following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR).[15]

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 multimodal 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, centered on opioids administration and cancer recurrence or metastasis after surgery (Table 1).

Table 1. Eligibility criteria

	Inclusion	Exclusion
Study design	Primary studies of any design	Systematic reviews, meta-analysis, narrative reviews, letter to 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 treatment of pain/anesthesia	n/a
Comparator	Methods of opioid-free anesthesia	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

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 anesthesia management. The Comparator will be any method of opioid-free anesthesia regional anesthesia-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.[16] 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, Conference Proceedings Citation Index (via Web of Science) and Open Grey. The search strategy will be limited to articles published in English language and to human studies.

Table 2. Scoping Review Search Strategy Ovid Medline Search Strategy (June 7, 2021)

Searches		**Results**
1.	cancer.mp.	1870659
2.	oncolog*.mp.	187417
3.	1 or 2	1949974
4.	exp managment/ or exp treatment/	4747134
5.	pain.mp.	762846
6.	opioid.mp.	118491
7.	4 and 5 and 6	23127
8.	monitor*.mp.	1031816
9.	7 and 8	1436
10.	3 and 9	242

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 minimize 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, anesthesia method, type and dose of the opioid(s), type of multimodal analgesia (regional techniques, drugs), and outcomes including type of recurrence or metastasis, 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 a table (Table 3) and exhaustively discussed in 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, 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 odds ratios 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. [17]

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	1. Total number, setting, inclusion and exclusion criteria 2. Participant characteristics at baseline: for each study, average age (years, mean and standard deviation [SD]), sex (%), country, diagnosis (cancer type, stage), treatment(s), comorbidities
Interventions/exposures and comparators	1. Total number of intervention/exposure [opioid(s) type, doses, opioid administration and surgery (pre-, intra-, postoperatively), time of treatment], and comparison [No opioid use] groups and number of participants in each group 2. For each intervention/exposure and comparison group: intervention/exposure/comparison, duration of intervention/exposure, who and how assessed, and results of assessment
Outcomes	Type of recurrence or metastasis; time elapsed since surgery; overall survival
Results	For each quantitative outcome: sample size, number of missing participants, reasons for loss to follow up, summary data for each group (2 × 2 table for dichotomous data, means and SDs for continuous data), estimate of effect for the difference between groups (or change in baseline and final scores for single-arm studies), confidence intervals, and *p* value

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.[18] 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 tumor. To this regard, in a retrospective analysis, Cata et al.[19] found that intraoperative opioid was associated with reduced overall survival for patients with early-stage non-small cell lung cancer compared to those affected by 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 to identify and analyze 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 a large number of 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 anesthetic and no-anesthetic agents. These limitations could lead to serious inconsistency and/or risk of bias, downgrading the outcomes.

Data statement

The datasets generated during the current study and the analytical methods (including preprocessing and eventually the analysis code) will be available from the corresponding author on reasonable request.

Ethics and dissemination

Ethics Approval and Consent to participate

This paper does not require ethics approval.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data dissemination

The results of this scoping review will be disseminated on the authors' web sites. Additional dissemination will occur through presentations at conferences, such as courses and science education conferences, regionally and nationally, and through articles published in peer-reviewed journals. Workshops with health care professionals involved in the management of cancer pain, oncology, and cancer surgery will be planned.

Author contributions

This study was mainly written by MC, and MF. FB, and CAF collected the data. FC and CAF supervised the writing of the paper. AC, MA, and FP critically revised the paper. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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ABSTRACT

Background

During and after general anesthesia, 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 standardized data extraction. Any disagreement for the inclusion between the two reviewers will be discussed with a third reviewer.

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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 analyze the knowledge gap in the field and serve as a prerequisite for future research.

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Background

Opioids are a class of drugs used to control analgesia during and after general anesthesia. 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.[1] 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, in individuals with a history of opioid abuse, the effects of morphine on the immune system were studied.[2] Furthermore, an association between opioid use and a higher risk of infections was found in patients treated for chronic non-cancer pain.[3] Nevertheless, to date, the evidence is not strong enough to establish a clear link between chronic opioid use and immunosuppression.[4]

The role of opioids in cancer development, progression, and metastasis is an open issue.[5] Chronic 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 tumor 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 favor of this thesis comes from preclinical studies[6] while clinical data have been mainly extrapolated from retrospective analyses.[7,8] 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.[9] Interestingly, the expression of MORs in some tumors (e.g., 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.[7] Notably, intraoperative opioids can increase the expression of opioid receptors in cancer tissues without influencing the expression of immune cell markers.[10]

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 to those managed with systemic opioids.[11] On the other hand, a recent controlled investigation demonstrated that regional anesthesia-analgesia approaches did not reduce breast cancer recurrence compared with standard opioid-based anesthesia.[12] Moreover, a retrospective study found that higher intraoperative opioid doses were significantly associated with better recurrence-free survival (p=0.028), but not with increased overall survival.[6] 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.[13] Indeed, conducting studies on the subject is extremely complex. The analysis of the results must be interpreted considering the combination of anesthetic and no-anesthetic agents used. In brief, the potential impact of perioperative opioid administration and oncological outcomes has several confounders. Perioperative interventions such as fluid therapy and anesthetic techniques must be carefully addressed.[14,15]

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

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.[18] It has been planned, according to the JBI Scoping Review Methodology Group,[19] following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR).[20]

Patient and public involvement

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

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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 multimodal 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, centered on opioids administration and cancer recurrence or metastasis after surgery (Table 1).

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/anesthesia	n/a
Comparator	Methods of opioid-free anesthesia	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

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 anesthesia management. The Comparator will be any method of opioid-free anesthesia regional anesthesia-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.[21] 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 supplementary file the full search strategies utilized for all databases).

Table 2. Scoping Review Search Strategy Ovid Medline Search Strategy (January 2, 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

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 minimize 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, anesthesia 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 a table

(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 odds ratios 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.[22]

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	1. Total number, setting, inclusion and exclusion criteria 2. Participant characteristics at baseline: for each study, average age (years, mean and standard deviation [SD]), sex (%), country, diagnosis (cancer type, stage), treatment(s), comorbidities
Interventions/exposures and comparators	1. Total number of intervention/exposure [opioid(s) type, doses, opioid administration and surgery (pre-, intra-, postoperatively), time of treatment], and comparison [No opioid use] groups and number of participants in each group 2. For each intervention/exposure and comparison group: intervention/exposure/comparison, duration of intervention/exposure, who and how assessed, and results of the assessment
Outcomes	Type of recurrence or metastasis; time elapsed since surgery; overall survival
Potential confounders	For example, fluid therapy, and anesthetic 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

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.[23] 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 tumor. In this regard, in a retrospective analysis, Cata et al.[24] found that intraoperative

opioid was associated with reduced overall survival for patients with early-stage non-small cell lung cancer compared to 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 analyze 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 anesthetic and no-anesthetic agents. These limitations could lead to serious inconsistency and/or risk of bias, downgrading the outcomes.

Data statement

The datasets generated during the current study and the analytical methods (including preprocessing and eventually the analysis code) will be available from the corresponding author on reasonable request.

Ethics and dissemination

Ethics Approval and Consent to participate

This paper does not require ethics approval.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data dissemination

The results of this scoping review will be disseminated on the authors' websites. Additional dissemination will occur through presentations at conferences, such as courses and science education conferences, regionally and nationally, and through articles published in peer-reviewed journals. Workshops with health care professionals involved in the management of cancer pain, oncology, and cancer surgery will be planned.

Author contributions

This study was mainly written by MC, and MF. FB, and CAF collected the data. FC and CAF supervised the writing of the paper. AC, MA, and FP critically revised the paper. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Search strategy

PubMed
(((Cancer OR oncolog*) AND surgery) AND opioid) AND (monitor* OR follow-up)

Embase
('cancer'/exp OR cancer OR oncolog*) AND ('surgery'/exp OR surgery) AND 'opioid'/exp AND (monitor* OR 'follow up'/exp OR 'follow up')

Google Scholar via Publish or Perish (macOS GUI Edition) in Keywords:
(((Cancer OR oncolog*) AND surgery) AND opioid) AND (monitor* OR follow-up)

Conference Proceedings Citation Index- Science (CPCI-S) --1990-present via Web of Science:
((Cancer OR oncolog*) AND surgery) AND opioid

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	Page 1 Lines: 1-2
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	Page 2 Lines: 37-61
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Page 3 Lines 83-124
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Pag 4 Lines:141-147
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	Pag 4 Line: 134
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Pag 4 Lines: 150-159
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Page 5 Lines: 170-174
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Page 5 Lines 175-177
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Page 5 Lines 178-181
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5 Lines: 183-190
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Pag 6 Lines: 199-204
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Page 6 Lines: 206-207
Synthesis of results	13	Describe the methods of handling and summarizing the	Pag 7

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
		data that were charted.	Lines: 196-202
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Not appropriate
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Not appropriate
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Not appropriate
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Not appropriate
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Not appropriate
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Not appropriate
Limitations	20	Discuss the limitations of the scoping review process.	Pag 7 Lines: 213-235
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	Not appropriate
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Pag 7 Lines: 250-252

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.