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Postoperative acute pain challenges in patients with cancer

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It is expected that the number of surgical procedures to diagnose, treat, and palliate cancers will increase in the near future. While many of those interventions can be performed with minimally invasive techniques, others require surgical large incisions and in some instances, they involve multiple areas of the body (i.e., tumor resections with flap reconstructions). Pain after major oncological procedures can be severe and many times difficult to treat as patients can present to the operating room with several conditions including preoperative pain (i.e., rapidly growing tumors and painful neuropathies), opioid tolerance, and contraindications to nonopioid analgesics or regional anesthesia. Inadequately treated postoperative pain is associated with activation of the sympathetic system, postoperative complications, large perioperative opioid use, and an increased risk of developing postoperative persistent pain. Furthermore, it has been theorized that poorly treated pain is associated with cancer recurrence and a reduced survival. Lastly, recent research questions the oncological safety of robotic surgery in gynecological procedures and indicates the need of open surgeries, which will be associated with an increased risk in moderate-to-severe postoperative pain. In conclusion, the management of acute postoperative pain in patients with cancer can be challenging.

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Introduction

In 2018, an estimated 1,735,350 patients were diagnosed with cancer in the United States (www.cancer.org) [1]. Many of them needed or will need surgery to diagnose, treat, or palliate their disease [2]. Additionally, with the aging population, every year thousands of cancer survivors will undergo surgical procedures for tumor re-staging or reconstructive surgeries. These numbers indicate that a large number of patients might have suffered or will suffer from significant acute postoperative pain, which in many instances was aggravated by factors such as patients' expectations, treatment-related complications, long incisions or extensive surgical trauma, drug shortages, medication allergies, chronic pain and tolerance to potent analgesics such as opioids [3,4].

Notably, poorly managed postoperative pain is associated with poor clinical outcomes including cardiopulmonary complications, delayed mobilization, prolonged hospitalization, and sleep disturbances [5,6]. Inadequately treated acute postoperative pain is also associated with psychological stress, elevation of inflammatory cytokines and activation of the sympathetic system. In experimental studies elevated concentrations of catecholamines and inflammation during surgery facilitate the seeding of circulating cancer cells in distant organs and the growth of dormant tumors and micrometastasis (also known as the minimal residual disease) [7,8]. Therefore, it has been theorized that treating pain adequately is critical for the long-term survival of patients with cancer [9].

Opioids, regional anesthesia, local anesthetics, non-steroidal anti-inflammatory drugs (NSAIDs) and low-doses of ketamine are frequently used to provide intra- and postoperative analgesia in patients undergoing oncologic surgery. While the efficacy of these pharmacological interventions might be limited in some patients, recent experimental studies also indicate that they can modulate several mechanisms related to the tumor growth and the metastasis process and thus, facilitate or impair cancer spread [7]. Based on those premises, it has been speculated that anesthesiologists could influence oncological outcomes by providing different anesthesia or analgesia techniques [10].

Inadequate analgesia after major cancer surgery also has other complications including the development of postoperative persistent pain and prolonged opioid use, which may increase patient suffering. In the present review, we will summarize the challenges related to the management of acute postoperative pain in patients with cancer. We will also synthesize the evidence on how analgesics might impact tumor growth and dissemination after surgery. Lastly, we will provide evidence on how poorly managed acute pain in oncologic patients can impact the development of persistent pain and opioid use.

Challenges in acute pain management after cancer surgery

The management of acute postoperative pain in patients with cancer can be challenging. For instance, a recent study demonstrated that immediately after patients underwent gastric cancer surgery, the surgeon requested 7 to 16 rescue doses of fentanyl in the postoperative anesthesia care unit [11]. As described below, the challenge associated with inadequate analgesia after major oncologic surgery is multifactorial (Fig. 1) and associated with short- and long-term concerns related to outcomes in patients with cancer (Fig. 2).

Preoperative pain

Patients with cancer can present to the operating room with acute and chronic pain syndromes. Buchakjian et al. reported that 60% of the patients with head and neck cancers complained of pain at the time of treatment [12]. In addition, pain before initiation of anticancer therapies is associated with reduced survival [9]. In patients with cancer, preoperative painful conditions may have different origins such as pathological bone fractures, osteonecrosis, expanding tumors or acute or chronic toxicities such as radiation-induced mucositis or dermatitis. The presence of these conditions makes the perioperative care of subjects with cancer very challenging as patients might be refractory to analgesics or complicate basic things such as positioning on the operative table or hospital beds.

In patients with cancer, neuropathic pain can originate from tumor invasion into nerves and plexus or treatment-related (chemotherapy or radiation) neuropathies. Seretny et al. conducted a meta-analysis that included 4179 patients who received chemotherapy. The authors found that after the

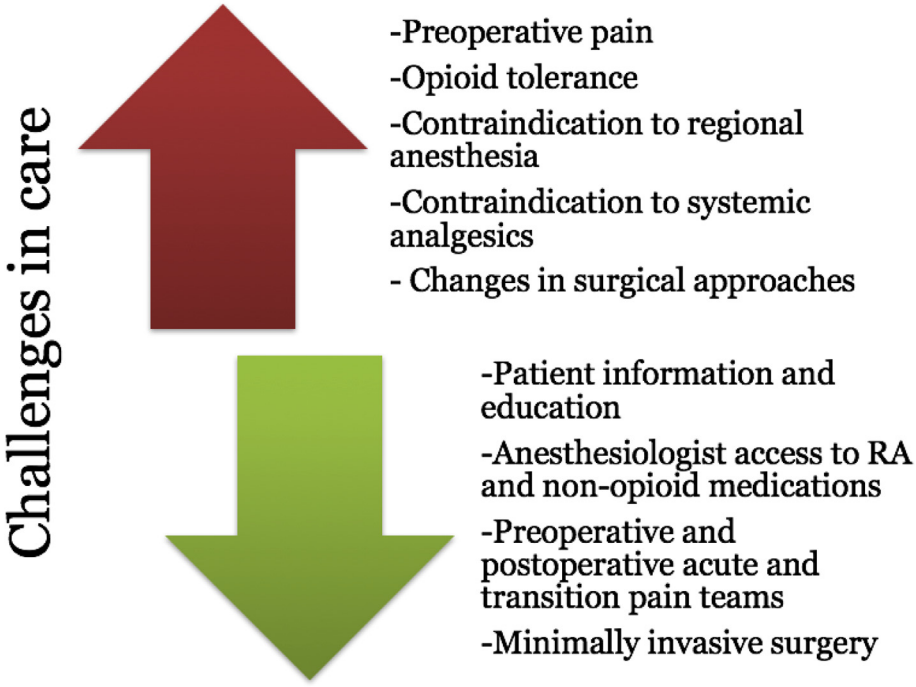

Fig. 1. Factors associated with adequate and inadequate acute postoperative pain.

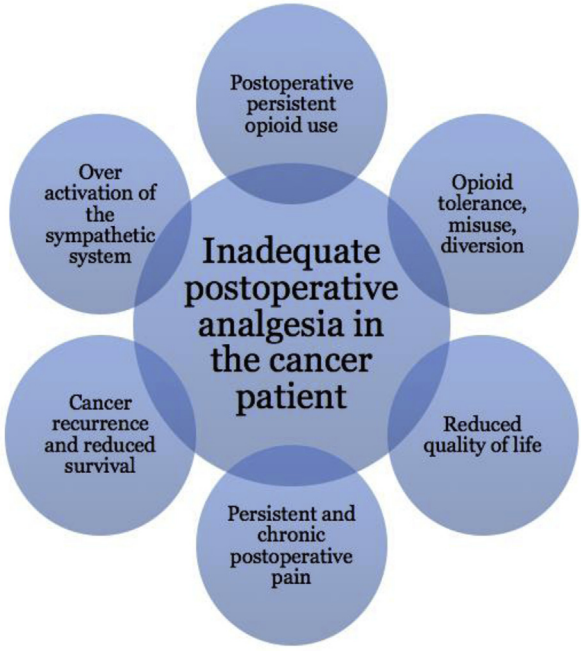

Fig. 2. Consequences of inadequate postoperative analgesia.

first, third, and sixth months of therapy, the incidence of chemotherapy-induced neuropathy was 68.1%, 60%, and 30%, respectively [13]. Patients with solid tumors typically undergo surgery 4–8 weeks after chemotherapy administration. The presence of sensory disturbances from chemotherapy-induced neuropathy (i.e., numbness, tingling and pain) at the time of surgery can make the postoperative care of patients challenging as well, because such disturbances can worsen surgical pain and do not typically respond to traditional opioid and nonopioid analgesics.

In summary, the adequate treatment of acute surgical pain in patients with cancer is complex due to the presence of preoperative pain syndromes.

Postoperative persistent pain in patients with cancer

The development of postoperative persistent and chronic pain is a devastating consequence of surgery in patients with cancer [14]. It can occur in 30–50% of the patients after thoracotomy, limb amputations or rectal surgery and even in higher rates after mastectomies [15–17]. Inadequately treated surgical pain can lead to postoperative persistent pain [18]. Habib et al. reported that the risk of persistent pain after breast cancer surgery was five times higher in patients suffering moderate or severe acute postoperative pain [19]. Other risks factors for the development of postoperative persistent pain include young age, female gender, history of anxiety or depression, preoperative pain, and inadequate resolution [18–21].

Because of its high frequency and its impact on the quality of life of patients, multiple investigations have been conducted to identify strategies to reduce postoperative persistent pain. But unfortunately, a recent large meta-analysis concluded that there is low-to-moderate evidence to recommend specific anesthesia techniques to modify the risk of postoperative persistent and chronic pain in patients undergoing thoracotomies or breast cancer surgery [22]. These results indicate the complexity and challenges that the prevention of postoperative persistent pain presents to researchers and clinicians.

Challenges with regional analgesia

Regional analgesia is an effective strategy to treat acute postoperative pain after most oncological procedures. In fact, regional analgesia is recommended as a key component of multimodal analgesia techniques for large oncological procedures. However, not every subject with cancer is a candidate to received regional anesthesia because of patients' preference, providers' misinformation, need for anticoagulation, febrile neutropenia and thrombocytopenia (Table 1).

The incidence of cancer-associated thrombosis (CAT) and thrombocytopenia in oncologic patients range from 4% to 90% and for both conditions. Both conditions depend on the type of cancer (hematological malignancies > solid cancers) and the anticancer treatments (i.e., chemotherapy regimen or surgery) administered [23]. The recommended treatment for CAT is low-molecular-weight heparin monotherapy [24]. In patents with critical thrombocytopenia, platelet transfusions might be indicated. Strict adherence to the current guidelines of the American Society of Regional Anesthesia has demonstrated that regional anesthesia techniques can be safely performed in patients undergoing major oncological procedures [25]. In those patients in whom regional anesthesia techniques cannot be offered, the administration of systemic nonopioids analgesics (i.e., intravenous lidocaine, paracetamol, ketamine, or NSAIDs) and along with the judicious administration of opioids play a major role in the management of their acute postoperative pain.

Table 1
Challenges in the implementation of effective multimodal analgesia strategies in the treatment of postoperative acute pain in oncologic patients.

Patient-related factors	Non patient-related factors
• Preoperative painful conditions (i.e., chemotherapy-induced painful neuropathy) • Patient comorbidities (i.e., renal failure) • Absolute or relative contraindications to RA (i.e., thrombocytopenia) • Patient's preference • Allergy to medications • Chronic opioid use • Extensive surgical insult (i.e., thoracoabdominal incisions)	• Providers' misinformation • Providers' lack of training • Lack of infrastructure • Drug shortages

Regional analgesia has opioid- and general-anesthetic sparing effects and modulates the inflammatory and immune response to surgery [26]. These effects have led investigators to hypothesize that the use of regional anesthesia could have a significant beneficial impact on the survival of patients with cancer by reducing the risk of cancer recurrence [27]. However, a recent consensus from the American and European Society for Regional Anesthesia concluded that there is no strong evidence to indicate regional analgesia or intravenous anesthetics with the goal of reduce cancer recurrence [10].

Persistent postoperative opioid use in the patient with cancer

Although with questionable efficacy, opioids are still the most common pharmacological intervention used to ameliorate the postsurgical pain associated with cancer surgery [28,29]. Because of the devastating consequences associated with opioid-related adverse effects, several scientific societies recommend a reduction in the perioperative prescription of these analgesics. Furthermore, the implementation of strategies designed to minimize the use of opioids perioperatively is associated with beneficial effects in short-term outcomes. For instance, a reduction in 72% in opioid use after the implementation of an opioid-sparing strategy in women with oncological malignancies was associated with less fatigue and length of hospitalization [30]. However, in a similar patient population, nearly half of the patients still required opioids postoperatively and nearly a third of them were taking > 30 mg of morphine equivalents daily before hospital discharge. This is also evidence of the challenge and limitations in the implementation of multimodal-sparing techniques in oncologic patients [31].

New persistent postsurgical opioid use defined as the use of opioids between 90 and 180 days after surgery is a common postoperative complication in cancer patients, and its rate ranged from 4.5% to 58.9% [32,33]. Persistent postoperative opioid consumption can lead to tolerance, misuse, low levels of quality of life, and opioid diversion [34,35]. Risk factors associated with new persistent postoperative opioid use are preoperative pain or neuropathies, opioid consumption before surgery, inadequate analgesia after surgery, the dose of opioids administered perioperatively, and the administration of adjuvant therapies [32,36–38]. Shah et al. reported that patients with chemotherapy-induced peripheral neuropathies were twice as likely to receive opioids 5 years after treatment compared to those without the neuropathy [32,39]. McDermott et al. concluded that >100 mg of morphine equivalent before treatment initiation was independently associated with long-term use [40]. A similar association was reported in a large population-based study that included 36,177 patients [41]. In that study, a perioperative opioid consumption of $\geq$300 mg oral morphine equivalents after major and minor surgeries was associated with a 14% increase in the risk of new persistent opioid use [41]. These studies are evidence of the need to minimize opioid use in patients undergoing oncologic surgery to reduce the risk of new persistent opioid use.

Tolerance and opioid-induced hyperalgesia (OIH) are associated with the administration of high dosages of opioids, and both can contribute to prolonged opioid use [42–46]. In patients with cancer, the incidence of OIH can be as high as 15%, and in some patients, it can be confused with disease progression due to increased hyperalgesia requiring escalating dosages of opioids [47]. It is currently unclear whether acute OIH can be linked to new persistent opioid use after surgery. But it can be theorized that patients developing this adverse event might have a higher risk of developing prolonged opioid consumption after surgery [41]. The treatment of OIH is based on the rational use of opioid rotation, non-opioids analgesics, interventional pain management technique, and behavioral management. However, in the postoperative setting, patients with OIH typically are poorly responders to those measures and complain of widespread pain on top of exaggerated acute incisional pain. Furthermore, the overlap in symptomatology between OIH and acute tolerance makes it challenging to differentiate one from the other. Whereas OIH requires a reduction in opioid consumption to improve patient comfort, acute tolerance requires escalating doses of opioids to overcome tolerance—an approach that may worsen the symptoms of OIH.

Although not widely reported, there is growing evidence to suggest that patients with cancer may misuse opioids [48,49]. This may prove to be an additional challenge in the postoperative period, where opioid misuse may be difficult to differentiate from inadequately treated pain, OIH, or acute tolerance.

Lastly, it is worth remembering that patients with history of opioid addiction and newly diagnosed cancer can be vulnerable to overdosing after a period of abstinence because they are unprotected from their opioid tolerance [50].

Altogether, the current evidence indicates the need of adequately treating acute pain at the time of surgery to avoid both persistent postoperative pain and opioid use. A critical understanding about opioid prescribing pattern immediately after surgery would help to minimize opioid prescription after major oncologic surgery.

Opioids and oncological outcomes

Opioids bind to the classical opioid receptors (the mu-, delta-, and kappa-opioid receptors) and other receptors (i.e., bradykinin receptors and opioid receptor growth factor). In the nervous system, opioids receptors are located in neurons and glial cells. In peripheral tissues, they can be found in cancer cells, cancer stem cells, and other cells present in the tumor microenvironment (i.e., lymphocytes, macrophages, and endothelial cells).

The *in vitro* effects of opioids on cancer cells range from triggering apoptosis (cell death) to promote mutagenesis, cell proliferation, migration, and invasion [51–54]. This wide variety of effects is explained by activation of different signaling pathways in cancer cell lines, variations in the drug affinity for opioid receptors, duration of treatment, and dose-dependent effects [55]. In the tumor microenvironment, opioids acting on lymphocytes, macrophages, and endothelial cells can trigger immune suppression, inflammation, and angiogenesis respectively, which in turn can also promote tumor growth and dissemination [56,57].

In vivo experimental studies demonstrate that opioids can facilitate tumor spread in different xenograft mice models including those for lung, breast, and bladder cancers; however, this protumoral effects were recently disputed [55,57]. Retrospective studies in humans indicate that the expression of the mu-opioid receptor is associated with cancer progression and reduced survival in lung, gastric, and prostate cancer patients [9,58–62]. Moreover, in humans, high doses of opioids are an independent risk factor for metastasis and shorter survival in lung, prostate, and aerodigestive cancers but not for adenocarcinoma of the esophagus, breast, and colorectal cancers [9,58–65]. Contrarily, Du et al. showed that high dosages of opioids were associated with longer survival in patients with esophageal squamous carcinoma [65].

Altogether, there is no grade 1 evidence to recommend avoiding opioids in patients with cancer; however, judicious use of these analgesics should be considered in patients with lung, prostate, and aerodigestive cancers.

Nonopioid analgesics in the context of cancer surgery

Non-steroidal anti-inflammatory drugs, acetaminophen, dexmedetomidine, intravenous lidocaine, and gabapentinoids are recommended to relieve postoperative acute pain and to reduce opioid use in the context of multimodal analgesia for cancer surgery [66,67]. But unfortunately not all patients with cancer are candidates to receive these drugs due to the presence of adverse events such kidney injury, gastro-intestinal bleeding, and nonunion fracture [68–71].

Furthermore, it is worth considering that patients with cancer who might have received radiation or chemotherapy can experience cognitive disturbances referred to as “chemo-brain” or “brain fog” [72]. Experimental and clinical studies suggest that neuroinflammation and impaired glucose metabolism as mechanism for “chemo-brain” [72]. Deficits in memory, attention, processing speed, and executive function are frequently observed in subjects with “chemo-brain” and might be exaggerated by surgery or predispose to postoperative cognitive dysfunction [72]. Therefore, careful attention should be paid if the perioperative administration of opioids, gabapentinoids, and ketamine is planned as these medications can cause excessive sedation and dizziness [71,73,74]. Contrarily, the intravenous administration of lidocaine causes less sedation and dizziness while providing adequate analgesia and perhaps preventing postoperative persistent pain as it occurs after breast cancer surgery [75,76].

The impact that nonopioid analgesics have on cancer progression is an area of extensive research. In vitro and animal experiments indicate that NSAIDs and local anesthetics including lidocaine have predominantly anticancer effects. Briefly, lidocaine not only sensitizes cancer cells to the cytotoxic effect of chemotherapy agents but also stimulates the function and count of lymphocytes such as

natural killer cells [77–79]. Contrarily, dexmedetomidine stimulates the proliferation of cancer cells and promote cancer spread in animals [80–82].

In humans, the perioperative use of NSAIDs and cyclooxygenase 2 inhibitors have been associated with improved survival in patients with breast and lung cancer [83–85]. In a recent randomized controlled trial, Haldar et al. demonstrated that the perioperative administration of etodolac and propranolol reduced serum levels of interleukin-6, tumor necrosis factor-related apoptosis inducing ligand, C-reactive protein and interferon-γ and the expression of Ki-67 in breast cancer specimens [86]. One of the potential limitations of NSAIDs in patients undergoing gastrointestinal cancer surgery is the risk of anastomotic leaks. Although the findings are controversial, it can be concluded that the risk is increased after the use of celecoxib or diclofenac, mainly when these drugs are given early after surgery or in high dosages [70]. While the intraoperative use of dexmedetomidine is associated with worse oncologic outcomes after lung cancer surgery, the same association was not found in children who underwent hyperthermic chemotherapy surgery [87].

Summarizing, nonopioid analgesics play a major role in the treatment of patients with acute postoperative pain after oncologic surgery. The efficacy of these agents to improve oncological outcomes warrants further research.

Future challenges

Significant advances have been made in surgical techniques with the goal of minimizing tissue trauma and surgical stress. Minimally invasive techniques are usually associated with a significant reduction in catecholamines, inflammation, and lower postoperative pain scores than their open counterparts [88–90]. However, not every cancer patient is a candidate for minimally invasive interventions due to anatomical difficulties, patients' comorbid conditions, or tumor size.

Furthermore, the recently published LACC trial questions the oncological safety of minimally invasive procedures [91]. This randomized controlled trial demonstrated that women with cervical cancer had significant worse survival if their tumor was resected robotically compared to that when resected by open surgery [91]. After this publication, large tertiary centers in the United States and Europe are re-considering the use of robotic surgery in the treatment of gynecological malignancies [92]. Changing the surgical approach will have substantial implications for anesthesiologists in postoperative pain management. Patients might have a higher risk of experiencing inadequately treated acute pain and developing postoperative persistent pain syndromes. Thus, anesthesiologists will need to find new pharmacological and nonpharmacological strategies to provide adequate analgesia while minimizing their side effects.

Over the last decade significant advances were made in the field of onco-immunology. The development of immune checkpoint inhibitors, chimeric antigen receptor T cells (CAR-T), and virus-based therapies have brought new hopes to patients with cancer. However, these therapies have a reported rate of adverse events that ranges from 15% to 90% [93]. Neurological complications such as peripheral sensory neuropathy and encephalopathy are particularly important. However, there is limited evidence on the safety of anesthetics and analgesics in patients with these conditions. In our institution, the use of regional anesthesia in patients with peripheral sensory neuropathies due to immune checkpoint inhibitors and CAR-T therapies is generally avoided. Systemic opioids- and non-opioids analgesics are given according to clinical judgment and after discussion with surgeons and oncologists.

Conclusions

The management of acute postoperative pain in patients with cancer can be challenging. A clear understanding of patients' comorbid conditions, history of chronic pain, and analgesic use is critical to develop multidisciplinary strategies to minimize the impact of acute pain on short- and long-term outcomes. Adequate postoperative analgesia might contribute to reduce both postoperative persistent pain and opioid use. To date, there is consensus from experts to suggest that there is no evidence to indicate the use of a particular anesthesia or analgesia with the goal of improving survival [10].

Conflicts of interest

None.

Practice points

- Multimodal analgesia is recommended to provide adequate postoperative analgesia in patients with cancer.
- Preoperative pain is associated with postoperative persistent pain and opioid use.
- Opioids remain as the strongest analgesic available. Careful use is indicated to avoid opioid-related adverse events.
- Patients with anticancer therapies related central nervous system adverse events might be more vulnerable to the effects of anesthetics and analgesics.

Research agenda

- Future research is warranted to elucidate the impact of analgesics on oncological outcomes.
- The impact of multimodal analgesia techniques on the "chemo" brain deserves further research.
- The consequences of regional anesthesia in patients with chemotherapy-induced neuropathies need to be carefully studied.

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References

[1] American Cancer Society. Overview: breast Cancer. Survival rates for breast cancer. https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-survival-rates.html Last accessed May 2019
[2] Meara JG, Leather AJM, Hagander L, et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. The Lancet 2015;386:569–624.
[3] Hsia IK-H, Dexter F, Logvinov I, et al. Survey of the national drug shortage effect on anesthesia and patient safety. Anesth Analgesia 2015;121:502–6.
[4] Modena B, White AA, Woessner KM. Aspirin and nonsteroidal antiinflammatory drugs hypersensitivity and management. Immunol Allergy Clin North America 2017;37:727–49.
[5] Peters CL, Shirley B, Erickson J. The effect of a new multimodal perioperative anesthetic regimen on postoperative pain, side effects, rehabilitation, and length of hospital stay after total joint arthroplasty. J Arthroplast 2006;21:132–8.
[6] Caumo W, Broenstrub JC, Fialho L, et al. Risk factors for postoperative anxiety in children. Acta Anaesthesiol Scand 2000;44:782–9.
[7] Cata JP, Bauer M, Sokari T, et al. Effects of surgery, general anesthesia, and perioperative epidural analgesia on the immune function of patients with non-small cell lung cancer. J Clin Anesth 2013;25:255–62.
[8] Lee JW, Shahzad MM, Lin YG, et al. Surgical stress promotes tumor growth in ovarian carcinoma. Clin Cancer Res 2009;15:2695–702.
[9] Zylla D, Kuskowski MA, Gupta K, et al. Association of opioid requirement and cancer pain with survival in advanced non-small cell lung cancer. Br J Anaesth 2014;(S1):ii109–16.
[10] Missair A, Cata JP, Votta-Velis G, et al. Impact of perioperative pain management on cancer recurrence: an ASRA/ESRA special article. Reg Anesth Pain Med 2019;44:13–28.
[11] Hong S, Kim H, Park J. Analgesic effectiveness of rectus sheath block during open gastrectomy. Medicine 2019;98.
[12] Buchakjian MR, Davis AB, Sciegienka SJ, et al. Longitudinal perioperative pain assessment in head and neck cancer surgery. Ann Otology, Rhinology Laryngol 2017;126:646–53.
[13] Seretny M, Currie GL, Sena ES, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. Pain 2014;155:2461–70.
[14] Boland EG, Ahmedzai SH. Persistent pain in cancer survivors. Curr Opin Support Palliat Care 2017;11:181–90.
*[15] Peuckmann V, Ekholm O, Rasmussen NK, et al. Chronic pain and other sequelae in long-term breast cancer survivors: nationwide survey in Denmark. Eur J Pain 2009;13:478–85.
[16] Feddern ML, Jensen TS, Laurberg S. Chronic pain in the pelvic area or lower extremities after rectal cancer treatment and its impact on quality of life: a population-based cross-sectional study. Pain 2015;156:1765–71.
[17] van Helmond N, Timmerman H, van Dasselaar NT, et al. High body mass index is a potential risk factor for persistent postoperative pain after breast cancer treatment. Pain Physician 2017;20:E661. e71.

*[18] Yang MMH, Hartley RL, Leung AA, et al. Preoperative predictors of poor acute postoperative pain control: a systematic review and meta-analysis. BMJ open 2019;9:e025091.
[19] Habib AS, Kertai MD, Cooter M, et al. Risk factors for severe acute pain and persistent pain after surgery for breast cancer: a prospective observational study. Reg Anesth Pain Med 2019;44:192–9.
[20] Sherman KA, Winch CJ, Koukoulis A, et al. The effect of monitoring 'processing style' on post-surgical neuropathic pain in women with breast cancer. Eur J Pain 2015;19:585–92.
[21] Hah JM, Cramer E, Hilmoe H, et al. Factors associated with acute pain estimation, postoperative pain resolution, opioid cessation, and recovery. JAMA Netw Open 2019;2.
[22] Weinstein EJ, Levene JL, Cohen MS, et al. Local anaesthetics and regional anaesthesia versus conventional analgesia for preventing persistent postoperative pain in adults and children. Cochrane Database Syst Rev 2018;6:Cd007105.
[23] Castaman G, Pieri L. Management of thrombocytopenia in cancer. Thromb Res 2018;164(Suppl 1):S89–93.
[24] Lyman GH, Bohlke K, Khorana AA, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: american society of clinical oncology clinical practice guideline update 2014. J Clin Oncol 2015;33:654–6.
[25] Su J, Soliz JM, Popat KU, et al. Complications of postoperative epidural analgesia for oncologic surgery: a review of 18,895 cases. Clin J Pain 2019;35(7):589–93.
[26] Vicente D, Patino M, Marcus R, et al. Impact of epidural analgesia on the systemic biomarker response after hepatic resection. Oncotarget 2018;10.
[27] Sessler DI, Ben-Eliyahu S, Mascha EJ, et al. Can regional analgesia reduce the risk of recurrence after breast cancer? Methodology of a multicenter randomized trial. Contemp Clin trials 2008;29:517–26.
[28] Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol 2012;13:e58–68.
*[29] Lee JS, Hu HM, Edelman AL, et al. New persistent opioid use among patients with cancer after curative-intent surgery. J Clin Oncol 2017. JCO2017741363.
*[30] Meyer LA, Lasala J, Iniesta MD, et al. Effect of an enhanced recovery after surgery program on opioid use and patient-reported outcomes. Obstet Gynecol 2018;132:281–90.
[31] Hillman RT, Sanchez-Migallon A, Meyer LA, et al. Patient characteristics and opioid use prior to discharge after open gynecologic surgery in an enhanced recovery after surgery (ERAS) program. Gynecol Oncol 2019;53(3):604–9.
[32] Saraswathula A, Chen MM, Mudumbai SC, et al. Persistent postoperative opioid use in older head and neck cancer patients. Otolaryngology-Head Neck Surg (Tokyo) 2018;160(3):380–7.
[33] Lee JS-J, Hu HM, Edelman AL, et al. New persistent opioid use among patients with cancer after curative-intent surgery. J Clin Oncol 2017;35:4042–9.
[34] Henry M, Alias A, Frenkiel S, et al. Contribution of psychiatric diagnoses to extent of opioid prescription in the first year post-head and neck cancer diagnosis: a longitudinal study. Psycho Oncol 2019;28:107–15.
[35] Kharasch ED, Brunt LM. Perioperative opioids and public health. Anesthesiology 2016;124:960–5.
[36] Silver N, Dourado J, Hitchcock K, et al. Chronic opioid use in patients undergoing treatment for oropharyngeal cancer. The Laryngoscope 2019;129(9):2087–93.
[37] Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945–52.
[38] Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937–44.
[39] Shah A, Hoffman EM, Mauermann ML, et al. Incidence and disease burden of chemotherapy-induced peripheral neuropathy in a population-based cohort. J Neurol Neurosurg Psychiatry 2018;89:636–41.
[40] McDermott JD, Eguchi M, Stokes WA, et al. Short- and long-term opioid use in patients with oral and oropharynx cancer. Otolaryngol Head Neck Surg 2018;160(3):409–19.
*[41] Brummett CM, Waljee JF, Goesling J, et al. New persistent opioid use after minor and major surgical procedures in US adults. JAMA Surg 2017:e170504.
[42] Chia YY, Liu K, Wang JJ, et al. Intraoperative high dose fentanyl induces postoperative fentanyl tolerance. Can J Anaesth 1999;46:872–7.
[43] Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. Clin J Pain 2008;24:479–96.
*[44] Joseph EK, Reichling DB, Levine JD. Shared mechanisms for opioid tolerance and a transition to chronic pain. J Neurosci 2010;30:4660–6.
[45] Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: a preliminary prospective study. J Pain 2006;7:43–8.
[46] Lyons PJ, Rivosecchi RM, Nery JP, et al. Fentanyl-induced hyperalgesia in acute pain management. J Pain Palliat Care Pharmacother 2015;29:153–60.
[47] Lim KH, Nguyen NN, Qian Y, et al. Frequency, outcomes, and associated factors for opioid-induced neurotoxicity in patients with advanced cancer receiving opioids in inpatient palliative care. J Palliat Med 2018 [Epub ahead of print].
[48] Arthur JA, Haider A, Edwards T, et al. Aberrant opioid use and urine drug testing in outpatient palliative care. J Palliat Med 2016;19:778–82.
*[49] Yennurajalingam S, Edwards T, Arthur JA, et al. Predicting the risk for aberrant opioid use behavior in patients receiving outpatient supportive care consultation at a comprehensive cancer center. Cancer 2018;124:3942–9.
[50] Volkow ND, McLellan AT. Opioid abuse in chronic pain–misconceptions and mitigation strategies. N Engl J Med 2016;374:1253–63.
[51] Lennon FE, Moss J, Singleton PA. The mu-opioid receptor in cancer progression: is there a direct effect? Anesthesiology 2012;116:940–5.
[52] Lennon FE, Mirzapoiazova T, Mambetsariev B, et al. The Mu opioid receptor promotes opioid and growth factor-induced proliferation, migration and Epithelial Mesenchymal Transition (EMT) in human lung cancer. PLoS One 2014;9:e91577.
[53] Friesen C, Roscher M, Alt A, et al. Methadone, commonly used as maintenance medication for outpatient treatment of opioid dependence, kills leukemia cells and overcomes chemoresistance. Cancer Res 2008;68:6059–64.

[54] Friesen C, Roscher M, Hormann I, et al. Cell death sensitization of leukemia cells by opioid receptor activation. Oncotarget 2013;4:677–90.
[55] Afsharimani B, Doornebal CW, Cabot PJ, et al. Comparison and analysis of the animal models used to study the effect of morphine on tumour growth and metastasis. Br J Pharmacol 2015;172:251–9.
[56] Sacerdote P. Opioids and the immune system. Palliat Med 2006;20(Suppl 1):s9–15.
[57] Gupta K, Kshirsagar S, Chang L, et al. Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. Cancer Res 2002;62:4491–8.
[58] Patino MA, Ramirez RE, Perez CA, et al. The impact of intraoperative opioid use on survival after oral cancer surgery. Oral Oncol 2017;74:1–7.
[59] Cata JP, Keerty V, Keerty D, et al. A retrospective analysis of the effect of intraoperative opioid dose on cancer recurrence after non-small cell lung cancer resection. Cancer Med 2014;3:900–8.
[60] Zylla D, Gourley BL, Vang D, et al. Opioid requirement, opioid receptor expression, and clinical outcomes in patients with advanced prostate cancer. Cancer 2013;119:4103–10.
[61] Oh TK, Jeon JH, Lee JM, et al. Association of high-dose postoperative opioids with recurrence risk in esophageal squamous cell carcinoma: reinterpreting ERAS protocols for long-term oncologic surgery outcomes. Dis esophagus – Off J Int Soc Dis Esophagus / ISDE. 2017;30:1–8.
[62] Yao Y-s, Yao R-y, Zhuang L-k, et al. MOR1 expression in gastric cancer: a biomarker associated with poor outcome. Clin Transl Sci 2015;8:137–42.
[63] Diaz-Cambronero O, Mazzinari G, Cata JP. Perioperative opioids and colorectal cancer recurrence: a systematic review of the literature. Pain Manag 2018;8:353–61.
[64] Boudreau DM, Chen L, Yu O, et al. Risk of second breast cancer events with chronic opioid use in breast cancer survivors. Pharmacoepidemiol Drug Saf 2019;28:740–53.
[65] Du KN, Feng L, Newhouse A, et al. Effects of intraoperative opioid use on recurrence-free and overall survival in patients with esophageal adenocarcinoma and squamous cell carcinoma. Anesth Analg 2018;127:210–6.
*[66] Nelson G, Bakkum-Gamez J, Kalogera E, et al. Guidelines for perioperative care in gynecologic/oncology: enhanced Recovery after Surgery (ERAS) Society recommendations-2019 update. Int J Gynecol Cancer – Off J Int Gynecol Cancer Soc 2019.
[67] Gustafsson UO, Scott MJ, Hubner M, et al. Guidelines for perioperative care in elective colorectal surgery: enhanced recovery after surgery (ERAS((R))) society recommendations: 2018. World J Surg 2019;43:659–95.
[68] Karlsson N, Rutegard M, Angenete E. Postoperative use of non-steroid inflammatory drugs (NSAID) and anastomotic leakage (AL) in rectal cancer surgery. Colorectal Dis 2015;17:70.
[69] Bhangu A, Singh P, Fitzgerald JE, et al. Postoperative nonsteroidal anti-inflammatory drugs and risk of anastomotic leak: meta-analysis of clinical and experimental studies. World J Surg 2014;38:2247–57.
[70] Cata JP, Guerra CE, Chang GJ, et al. Non-steroidal anti-inflammatory drugs in the oncological surgical population: beneficial or harmful? A systematic review of the literature. Br J Anaesth 2017;119:750–64.
*[71] Rajappa GC, Vig S, Bevanaguddaiah Y, et al. Efficacy of pregabalin as premedication for post-operative analgesia in vaginal hysterectomy. Anesthesiol Pain Med 2016;6:e34591.
[72] Kovalchuk A, Kolb B. Chemo brain: from discerning mechanisms to lifting the brain fog-An aging connection. Cell Cycle 2017;16:1345–9.
[73] Ture H, Sayin M, Karlikaya G, et al. The analgesic effect of gabapentin as a prophylactic anticonvulsant drug on post-craniotomy pain: a prospective randomized study. Anesth Analg 2009;109:1625–31.
[74] Nazemroaya B, Majedi MA, Shetabi H, et al. Comparison of propofol and ketamine combination (ketofol) and propofol and fentanyl combination (fenofol) on quality of sedation and analgesia in the lumpectomy: a randomized clinical trial. Adv Biomed Res 2018;7:134.
[75] Kim JE, Choi JB, Koo BN, et al. Efficacy of intravenous lidocaine during endoscopic submucosal dissection for gastric neoplasm: a randomized, double-blind, controlled study. Medicine (Baltim) 2016;95:e3593.
[76] Terkawi AS, Sharma S, Durieux ME, et al. Perioperative lidocaine infusion reduces the incidence of post-mastectomy chronic pain: a double-blind, placebo-controlled randomized trial. Pain Physician 2015;18:E139–46.
[77] Ramirez MF, Tran P, Cata JP. The effect of clinically therapeutic plasma concentrations of lidocaine on natural killer cell cytotoxicity. Reg Anesth Pain Med 2015;40:43–8.
[78] Cata JP, Ramirez MF, Velasquez JF, et al. Lidocaine stimulates the function of natural killer cells in different experimental settings. Anticancer Res 2017;37:4727–32.
[79] Xing W, Chen D-T, Pan J-H, et al. Lidocaine induces apoptosis and suppresses tumor growth in human hepatocellular carcinoma cells in vitro and in a xenograft model in vivo. Anesthesiology 2017;126:868–81.
[80] Lavon H, Matzner P, Benbenishty A, et al. Dexmedetomidine promotes metastasis in rodent models of breast, lung, and colon cancers. Br J Anaesth 2018;120:188–96.
[81] Su X, Fan Y, Yang L, et al. Dexmedetomidine expands monocytic myeloid-derived suppressor cells and promotes tumour metastasis after lung cancer surgery. J Translational Med 2018;16.
[82] Wang C, Datoo T, Zhao H, et al. Midazolam and dexmedetomidine affect neuroglioma and lung carcinoma cell biology in vitro and in vivo. Anesthesiology 2018;129:1000–14.
[83] Lee BM, Rodríguez A, Mena G, et al. Platelet-to-Lymphocyte ratio and use of NSAIDs during the perioperative period as prognostic indicators in patients with NSCLC undergoing surgery. Cancer Control 2016;23:284–94.
[84] Forget P, Bentin C, Machiels JP, et al. Intraoperative use of ketorolac or diclofenac is associated with improved disease-free survival and overall survival in conservative breast cancer surgery. Br J Anaesth 2014;113(Suppl 1):i82–7.
[85] Forget P, Machiels JP, Coulie PG, et al. Neutrophil:lymphocyte ratio and intraoperative use of ketorolac or diclofenac are prognostic factors in different cohorts of patients undergoing breast, lung, and kidney cancer surgery. Ann Surg Oncol 2013;20(Suppl 3):S650–60.
[86] Haldar R, Shaashua L, Lavon H, et al. Perioperative inhibition of beta-adrenergic and COX2 signaling in a clinical trial in breast cancer patients improves tumor Ki-67 expression, serum cytokine levels, and PBMCs transcriptome. Brain Behav Immun 2018;73:294–309.

[87] Cata JP, Singh V, Lee BM, et al. Intraoperative use of dexmedetomidine is associated with decreased overall survival after lung cancer surgery. J Anaesthesiol Clin Pharmacol 2017;33:317–23.
[88] Kvarnstrom A, Swartling T, Kurlberg G, et al. Pro-inflammatory cytokine release in rectal surgery: comparison between laparoscopic and open surgical techniques. Arch Immunol Ther Exp (Warsz) 2013;61:407–11.
[89] Krikri A, Alexopoulos V, Zoumakis E, et al. Laparoscopic vs. open abdominal surgery in male pigs: marked differences in cortisol and catecholamine response depending on the size of surgical incision. Hormones (Basel) 2013;12:283–91.
[90] Ilic D, Evans SM, Allan CA, et al. Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer. Cochrane Database Syst Rev 2017;9:CD009625.
*[91] Ramirez PT, Frumovitz M, Pareja R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. New Engl J Med 2018;379:1895–904.
[92] Sheetz KH, Dimick JB. Is it time for safeguards in the adoption of robotic surgery? JAMA 2019;321(20):1971–2.
[93] Perrinjaquet C, Desbaillets N, Hottinger AF. Neurotoxicity associated with cancer immunotherapy: immune checkpoint inhibitors and chimeric antigen receptor T-cell therapy. Curr Opin Neurol 2019;32:500–10.