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Review

Evolution of pain management in lung cancer surgery: from opioid-based to personalized analgesia

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Pain management in lung cancer resection has undergone a paradigm shift from opioid-centric approaches to multimodal analgesia, and more recently, personalized strategies that integrate the principles of precision medicine. Historically, opioids have been the mainstay of perioperative analgesia. However, concerns regarding opioid-related adverse effects, including respiratory depression, immunosuppression, and potential oncologic implications, have driven the adoption of opioid-sparing techniques. Current strategies emphasize multimodal analgesia, combining nonsteroidal antiinflammatory drugs, acetaminophen, regional anesthesia, and adjunctive agents to enhance pain control while minimizing opioid exposure. However, growing evidence suggests that perioperative analgesics may differentially influence tumor biology depending on molecular and genetic factors, necessitating a more tailored approach. This has led to the emergence of precision oncoanesthesia, which aims to integrate tumor-specific genomic insights into perioperative pain management. Although promising, the clinical implementation of precision oncoanesthesia remains in its early stages, with key challenges including the lack of large-scale prospective studies, limited real-time genomic profiling in anesthetic planning, and variability in patient responses to analgesics. Future research should focus on identifying biomarkers that predict individual responses to perioperative analgesia and establishing evidence-based guidelines for precision-based pain management. By evolving beyond traditional opioid reliance and standard analgesic protocols, perioperative pain management in lung cancer surgery can align with emerging precision medicine approaches, ensuring effective pain control and optimized oncologic outcomes.

Keywords: Analgesics, opioid; Lung neoplasms; Pain management; Perioperative care; Precision medicine; Thoracic surgery.

KSCVA

INTRODUCTION

Lung cancer resection is a major surgical procedure associated with significant postoperative pain, necessitating effective analgesic strategies that can profoundly influence patient recovery and long-term outcomes [1]. Opioids have been the cornerstone of anesthesia and analgesia in thoracic surgery, providing potent hemodynamic stability and pain relief. However, increasing awareness of opioid-related adverse effects and the potential for long-term dependence has led to a paradigm shift toward strategies that minimize opioid exposure.

Opioid-free anesthesia (OFA) and opioid-sparing anesthesia (OSA) have emerged as alternative approaches often incorporated within a broader multimodal analgesia (MMA) framework [2]. These strategies integrate non-opioid analgesics with regional anesthesia techniques to achieve adequate pain control while reducing opioid-related complications. Moreover, emerging evidence suggests that opioids may influence tumor biology, potentially affecting cancer recurrence and long-term survival. Consequently, interest in their role in oncological surgery has increased.

This review explores the evolution of pain management strategies in lung cancer surgery, transitioning from opioid-based analgesia to opioid-sparing approaches and MMA. Furthermore, we discuss the emerging concept of precision oncoanesthesia, which integrates tumor biology and patient-specific factors to optimize perioperative analgesia, while potentially influencing cancer prognosis. Finally, we propose future directions for refining personalized pain management strategies in thoracic oncology.

HISTORICAL PERSPECTIVE: THE ERA OF OPIOID-CENTERED ANALGESIA

1. Opioids as the standard for thoracic surgery

Since the 1990s, opioids have been the primary analgesic agents used in thoracic surgery, including lung cancer resection [3]. The World Health Organization analgesic ladder and the 'Pain as the Fifth Vital Sign' initiative emphasized the need for aggressive pain management, leading to the widespread adoption of opioids as first-line analgesics in perioperative care.

Lung cancer resection through open thoracotomy causes significant postoperative pain due to extensive soft tissue trauma from rib retraction and muscle dissection [1]. Although minimally invasive techniques such as video-assisted thoracoscopic surgery (VATS) reduce pain severity, postoperative pain remains a significant concern. Given the intensity of pain associated with these procedures, opioids have become the primary analgesics owing to their potent efficacy, cost-effectiveness, and ease of administration.

In addition to their role in postoperative pain management, opioids have become essential adjuncts to intraoperative anesthesia with the adoption of balanced anesthesia techniques [4]. Their ability to maintain hemodynamic stability, modulate anesthetic depth, and attenuate excessive sympathetic responses is particularly critical in high-risk thoracic surgeries, in which these factors significantly influence perioperative outcomes.

2. Adverse effects and the need for change

Although opioids play a central role in perioperative pain management in lung cancer surgery, their extensive use has been re-evaluated owing to a range of adverse effects that may compromise recovery and long-term outcomes [5,6].

One of the most prevalent concerns associated with opioid use is its detrimental effects on the gastrointestinal function. Postoperative nausea and vomiting (PONV) and paralytic ileus are common complications that can significantly delay recovery. Given the critical role of early oral intake and active pulmonary rehabilitation after lung cancer resection, opioid-related gastrointestinal side effects may lead to inadequate nutrition, systemic deconditioning, delayed mobilization, and prolonged hospitalization.

Respiratory depression is an even more serious concern, particularly in patients with lung cancer and underlying pulmonary impairment. Following lung resection, the pulmonary reserve is compromised, and opioid-induced suppression of the respiratory drive can exacerbate hypoxemia and carbon dioxide retention, increasing the risk of respiratory failure. This risk is particularly pronounced in patients undergoing open thoracotomy, where pain-related splinting and restricted lung expansion predispose them to atelectasis and pneumonia. Moreover, in elderly patients or those with severe pre-existing pulmonary disease, even standard opioid doses can induce profound respiratory depression, necessitating intensive monitoring and, in some cases, ventilatory support.

Beyond the immediate postoperative risks, opioid-induced hyperalgesia has emerged as a significant concern. Paradoxically, prolonged opioid exposure increases pain sensitivity through central sensitization, leading to an increased postoperative opioid requirement and persistent pain. This maladaptive response can complicate postoperative analgesia and perpetuate the escalating cycle of opioid consumption, making opioid-sparing strategies particularly relevant for thoracic surgery.

Perhaps, the most pressing concern is the risk of opioid dependence and misuse [7]. Recent studies have suggested that even short-term perioperative opioid exposure can increase the risk of prolonged opioid use and dependence, particularly in opioid-naïve patients [8,9]. As postoperative pain can persist beyond hospital stay, many patients contin-

ue opioid use after discharge, thereby increasing the likelihood of long-term opioid-related complications.

In response to these challenges, there has been a paradigm shift toward minimizing opioid exposure throughout the perioperative period. Strategies such as OFA and OSA have been introduced to reduce intraoperative opioid use while maintaining hemodynamic stability and effective analgesia [10,11]. Similarly, MMA has emerged as the mainstay of postoperative pain management, integrating regional anesthesia, non-opioid analgesics, and adjunctive agents that target multiple pain pathways. These approaches aim to optimize perioperative pain control while mitigating the risks associated with opioid use.

TRANSITIONING TO OPIOID-SPARING STRATEGIES: THE PRESENT PARADIGM

1. Rise of opioid-free anesthesia and opioid-sparing anesthesia

Increasing awareness of opioid-related adverse effects and the potential for dependence has driven shifts in perioperative management strategies. This has led to the growing adoption of OFA and OSA.

OFA is an anesthetic approach that eliminates intraoperative opioid administration, relying on alternative agents to provide analgesia and maintain anesthetic depth. OFA protocols employ a range of pharmacological adjuncts, each of which targets a different pain pathway [12,13]. Dexmedetomidine, α2-adrenergic agonist, provides sedation and analgesia while attenuating the sympathetic response to surgical stimuli. When administered intravenously, lidocaine exhibits systemic anti-inflammatory and anti-hyperalgesic effects beyond its local anesthetic properties. Magnesium sulfate modulates nociceptive transmission by blocking NMDA receptors, whereas ketamine, another NMDA antagonist, prevents opioid-induced hyperalgesia and enhances postoperative pain control.

Despite their benefits, the complete omission of opioids presents challenges. The analgesic efficacy of OFA alone may be insufficient for highly painful procedures such as lung cancer resection [14]. Additionally, reliance on alternative agents often necessitates higher doses, which increases the risk of adverse effects [15]. Consequently, OFA requires careful patient selection and individualized anesthetic planning.

In contrast, OSA provides a more flexible approach by allowing limited opioid use when necessary while still prioritizing non-opioid analgesics [12,13]. However, OSA has limitations; opioid exposure, although reduced, is not eliminated, and the selection of adjunctive agents must be tailored to the individual patient's response. Both strategies require a patient-centered approach to balance pain control with the potential risks.

Devine et al. [16] first demonstrated the feasibility of OFA in thoracic surgery by incorporating intravenous lidocaine, magnesium, clonidine, and a paravertebral block (PVB) as part of an opioid-free anesthetic protocol. Similarly, Laure et al. [17] reported the feasibility of OFA in VATS by incorporating dexmedetomidine, local anesthetics, magnesium, and ketamine. Clinical investigations of OFA and OSA during thoracic surgery have demonstrated inconsistent outcomes. Some studies have suggested that OFA may be associated with better postoperative outcomes than OSA or conventional opioid-based anesthesia (OBA), including lower postoperative opioid requirements, reduced pain intensity, decreased incidence of PONV, and improved recovery quality [18-21]. However, other studies have reported comparable outcomes among OFA, OSA, or OBA [17,22-25]. This inconsistency may be attributed to variations in study design, range of surgical procedures, differences in pharmacological agents and regional anesthesia techniques, and outcome measures.

A meta-analysis of OFA in thoracic surgery identified potential benefits, such as reduced postoperative opioid consumption, decreased PONV, and enhanced recovery [26]. However, another meta-analysis found no significant differences between OFA and OSA, suggesting that the clinical advantages of OFA may be limited to thoracic surgery [27]. Both reviews noted high inter-study heterogeneity and a lack of robust randomized controlled trials (RCTs), making the comparative efficacy of OFA and OSA in this surgical population inconclusive.

Moreover, an RCT comparing OFA and OSA within the MMA framework demonstrated that overall perioperative opioid-sparing strategies, rather than intraoperative opioid avoidance alone, played a more significant role in enhancing recovery quality [28]. These findings suggest that rather than focusing solely on intraoperative opioid minimization, a comprehensive perioperative pain management approach incorporating the MMA principles may have a meaningful impact on patient recovery.

2. Multimodal analgesia: integrating pharmacologic and regional techniques

Postoperative pain following lung resection is complex, as it arises from both nociceptive and neuropathic mechanisms, making adequate analgesia challenging to achieve with a single agent [29]. The MMA has become an essential perioperative strategy that simultaneously targets multiple pain pathways to optimize pain control and minimize opioid-related complications.

MMA in lung cancer surgery consists of two primary approaches: pharmacological and non-pharmacological [30]. These approaches complement each other, which enhances analgesic efficacy while reducing opioid consumption and minimizing associated complications.

1) Pharmacological approach

Pharmacological strategies for MMA involve the combined use of non-opioid analgesics, each targeting distinct pain pathways to provide effective postoperative pain control. NSAID and acetaminophen modulate inflammatory responses by inhibiting cyclooxygenase (COX) enzymes and reducing prostaglandin synthesis, thereby alleviating nociceptive pain. They serve as the foundation of MMA and are strongly recommended for routine administration during and after surgery to optimize pain control while minimizing opioid consumption. Regular dosing is advised rather than on-demand administration because consistent analgesia improves postoperative recovery and reduces breakthrough pain. Studies have demonstrated that their combined administration significantly reduces opioid requirements and improves postoperative pain scores [31,32].

Gabapentinoids (gabapentin and pregabalin) modulate neuropathic pain pathways and have been shown to lower the risk of developing chronic postoperative pain [33]. Preoperative administration of these agents has been shown to decrease postoperative pain scores and reduce opioid requirements. However, their use in elderly patients or those with cognitive impairment requires caution because they may increase the risk of sedation, dizziness, and delirium.

Other agents such as ketamine, lidocaine, and magnesium have been investigated as adjuncts to MMA. Although these agents are not universally recommended as standard therapies, they may serve as useful adjuncts in selected patients, particularly in opioid-sparing protocols. NMDA receptor antagonists such as ketamine and magnesium are particularly effective in preventing opioid-induced hyperalgesia. Low-dose ketamine has been shown to enhance postoperative pain control even at subanesthetic doses [34], whereas magnesium provides additional muscle relaxation and anti-inflammatory benefits [35]. Lidocaine also demonstrates systemic analgesic and anti-inflammatory properties when administered intravenously. Continuous lidocaine infusion is associated with reduced opioid consumption and improved postoperative pain relief [36].

Opioids should be reserved as a last resort for treating severe pain that is unresponsive to multimodal approaches. Their use should be restricted to the lowest effective dose and the shortest duration necessary to avoid opioid-related adverse effects.

2) Non-pharmacological approach

Regional anesthesia plays a central role in MMA by providing targeted pain relief, while minimizing systemic opioid exposure and its associated side effects. Traditionally, thoracic epidural analgesia (TEA) has been the gold standard for open thoracic procedures because it effectively blocks intercostal nerve transmission and provides profound pain relief [29]. TEA facilitates the preservation of pulmonary function, thereby contributing to improved postoperative outcomes. However, its use in minimally invasive procedures, such as VATS, has declined due to concerns over hypotension, urinary retention, and epidural catheter-related complications. As a result, PVB is now the preferred regional technique for VATS, as it provides analgesia comparable to TEA while demonstrating a superior safety profile [29]. PVB effectively blocks the thoracic spinal nerve roots and offers sufficient postoperative pain control with a lower incidence of hypotension, making it the first-line treatment according to the current guidelines.

Recently, erector spinae plane block (ESPB) and serratus anterior plane block (SAPB) have emerged as viable alternatives to PVB [37]. These methods provide effective analgesia by targeting intercostal nerve pathways through local anesthetic infiltration. Although their analgesic efficacy may be slightly lower than that of PVB, they are technically easier to perform, less demanding in terms of expertise, and have a lower risk of complications. As a result, ESPB and SAPB are now considered viable second-line options, particularly in patients at risk of hemodynamic instability or those for whom PVB is not feasible.

Intercostal nerve block (ICNB) has been recognized as an effective option in minimally invasive procedures, such as single-port VATS, providing superior analgesia to systemic

analgesics [29]. However, its short duration necessitates repeated administration and its overall efficacy remains inferior to that of other regional techniques.

With the increasing adoption of minimally invasive surgical techniques and the advancement of ultrasound-guided peripheral nerve blocks, more precise and less invasive analgesic options have become available, leading to the re-evaluation of traditional approaches such as TEA. The 2022 PROSPECT guidelines recommend regional anesthesia as a fundamental component of postoperative pain management. For thoracoscopic surgery, TEA is less favored, with PVB or ESPB being preferred as the first-line technique and SAPB as the secondary option [38]. Additionally, the 2023 Practice Advisory broadened postoperative recovery assessment beyond opioid consumption by incorporating factors such as hospital length of stay. Based on these criteria, ICNB has been identified as the preferred regional technique for VATS because of its overall recovery [39].

3) Multimodal analgesia in Enhanced Recovery After Surgery (ERAS): optimizing perioperative pain management

The ERAS protocol is a multidisciplinary approach designed to optimize perioperative management, reduce complications, and improve postoperative outcomes [40]. A central component of ERAS is effective pain management with minimal opioid exposure, positioning MMA as a fundamental strategy in thoracic surgery. To achieve this, recent ERAS guidelines have incorporated OFA or OSA into a multimodal approach and have limited opioid use to a minimal rescue role.

Beyond pain control, MMA within the ERAS protocols has been associated with the mitigation of systemic inflammation, which may have implications for cancer progression [41]. Additionally, faster recovery via the ERAS pathway enables earlier initiation of adjuvant therapies, contributing to improved prognosis in various cancers [42,43]. Although the direct impact of opioid minimization within the ERAS on lung cancer recurrence and survival remains inconclusive, emerging evidence suggests that perioperative analgesic choices may influence oncological outcomes, warranting further investigation.

Although MMA has demonstrated benefits, its implementation requires an individualized approach that considers surgical technique, patient comorbidities, and pain sensitivity. Future research should aim to elucidate the effect of different perioperative analgesic strategies on oncological outcomes, particularly in the context of lung cancer surgery, within the ERAS framework.

3. Practical recommendations for perioperative pain management

Table 1 summarizes a phase-specific protocol based on current guidelines [38-40]. It outlines the recommended pharmacological, regional, and non-pharmacological strategies across the perioperative period.

Key elements include preemptive non-opioid analgesia, regional techniques tailored to the surgical approach, and the selective use of non-opioid anesthetic adjuvants. Postoperative management emphasizes scheduled nonopioid analgesics and limits opioid use to minimize dose rescue. This protocol aimed to enhance pain control, minimize opioid-related side effects, and support early recovery.

FUTURE DIRECTIONS: PRECISION ONCOANESTHESIA AND PERSONALIZED PAIN MANAGEMENT

1. Impact of analgesics on cancer recurrence and metastasis

A growing body of evidence suggests that perioperative analgesic strategies influence cancer recurrence and metastasis via various biological pathways [44,45]. Although their precise impact remains debated, numerous preclinical and clinical studies have investigated the role of commonly used analgesics, including opioids, NSAIDs, local anesthetics, and NMDA receptor antagonists, in modulating tumor progression. The perioperative period represents a critical window in oncological outcomes, as surgical stress, inflammation, and immune suppression create an environment that may either suppress or promote residual tumor cell survival and metastatic spread. Understanding how different analgesics interact with these processes is essential for optimizing perioperative pain management while minimizing the potential adverse effects on long-term cancer prognosis.

Opioids have been implicated in cancer progression via multiple mechanisms. Immunosuppression is one of the most frequently cited pathways as opioids can reduce natural killer cell activity, impair cytotoxic T-cell responses, and promote regulatory T-cell expansion, all of which may create an immunosuppressive tumor microenvironment [46,47]. Additionally, opioids can enhance angiogenesis by upregu-

Table 1. Recommended Multimodal Analgesia Protocol for Thoracic Surgery Based on Current Guidelines

Phase	Modality	Recommended strategy	Description
Preoperative	Pharmacologic	Pre-emptive non-opioid analgesics	Acetaminophen 1 g PO/IV ± NSAIDs or COX-2 inhibitors 1–2 h before induction; pregabalin 75–150 mg PO 1–2 h preoperatively (optional; use with caution due to sedation risk)
	Non-pharmacologic	Patient education	Provide verbal and written instructions about pain control plan and recovery expectations
Intraoperative	Regional analgesia	US-guided PVB preferred; alternative techniques selected based on surgical approach	PVB or TEA (with caution) for thoracotomy; PVB, ESPB or SAPB (as alternatives), or ICNB (minimal procedures) for VATS
	Pharmacologic	IV non-opioid adjuvants	Dexmedetomidine: loading 0.5–1 μg/kg over 10 min, then 0.2–0.7 μg/kg/h; lidocaine: loading 1.5 mg/kg over 10 min, then 1–2 mg/kg/h; ketamine bolus 0.25–0.5 mg/kg, then 0.1–0.25 mg/kg/h; magnesium sulfate: 30–50 mg/kg bolus (max 2 g), over 10–15 min
	Non-pharmacologic	Thermal regulation	Maintain normothermia
Postoperative	Pharmacologic	Scheduled non-opioid analgesics	Acetaminophen 1 g every 6 h ± NSAIDs/COX-2 inhibitors for 48–72 h postoperatively if tolerated
	Regional analgesia	Continuation of regional techniques	Continue infusion through catheter if placed; adjust per protocol
	Monitoring	Regular pain assessment and tailored opioid rescue	Use VAS/NRS to assess pain; administer minimal-dose opioids strictly as rescue (e.g., morphine 2–3 mg IV when VAS > 4); reassess every 4–6 h

PO: per os (by mouth), IV: intravenous, NSAIDs: non-steroidal anti-inflammatory drugs, COX-2: cyclooxygenase-2, US: ultrasound, PVB: paravertebral block, ESPB: erector spinae plane block, SAPB: serratus anterior plane block, ICNB: intercostal nerve block, TEA: thoracic epidural analgesia, VATS: video-assisted thoracoscopic surgery, PRN: pro re nata (as needed), VAS: visual analogue scale, NRS: numeric rating scale.

lating vascular endothelial growth factors and increase metastatic potential by modulating the epithelial-mesenchymal transition pathways [48].

In contrast, NSAIDs have been proposed to exert antitumor effects via both COX-dependent and COX-independent mechanisms [49]. They reduce prostaglandin E2 levels by inhibiting COX enzymes, thereby suppressing tumor growth, immune evasion, and angiogenesis. Additionally, some NSAIDs have been shown to modulate Wnt/β-catenin signaling and induce apoptosis in cancer cells through the COX-independent pathways.

Local anesthetics, particularly lidocaine, have also been investigated for their role in modifying tumor biology [50,51]. Lidocaine inhibits voltage-gated sodium channels that have been implicated in cancer cell invasiveness. Additionally, it exhibits anti-inflammatory properties by downregulating NF-κB signaling and reducing pro-inflammatory cytokine release. Some studies have suggested that lidocaine enhances immune surveillance by modulating neutrophil and macrophage activities, further supporting its potential as an antitumor agent.

Other analgesic agents such as ketamine and dexmedetomidine have also been explored for their potential interactions with cancer progression. Ketamine has been proposed to reduce inflammation-induced tumor growth and limit opioid-induced immunosuppression [52,53]. Some experimental models have suggested that ketamine attenuates surgery-induced immune suppression, although its direct impact on cancer cells has not been well established. Similarly, dexmedetomidine has demonstrated immunomodulatory properties; however, its effect on cancer progression remains controversial [54,55]. While some studies have suggested that dexmedetomidine may preserve perioperative immune function by reducing stress-induced catecholamine release, others have raised concerns regarding its potential pro-tumorigenic effects through β-adrenergic receptor activation.

2. Opioids in lung cancer prognosis: preclinical and clinical evidence

Among various cancer types, lung cancer has been a ma-

jor focus of opioid-related research because of its high surgical burden and aggressive nature. Given the widespread use of opioids in thoracic surgery, concerns have emerged regarding their potential influence on tumor progression and survival outcomes [56].

Preclinical studies suggest that opioids, particularly through μ-opioid receptor (MOR) activation, may enhance lung cancer cell proliferation, migration, and resistance to apoptosis [57,58]. MOR-related signaling has been linked to increased expression of hypoxia-inducible factor-1α, matrix metalloproteinases, and PI3K/Akt and ERK/MAPK pathways, all of which contribute to tumor growth and metastasis. These findings have led to investigations of MOR antagonists such as methylnaltrexone as potential strategies to mitigate opioid-induced tumor progression [59].

Despite these preclinical findings, the results of clinical studies remain inconclusive. Some retrospective analyses have associated perioperative opioid use with higher recurrence rates and reduced overall survival [60,61], while others have found no significant effect [62]. The variability in the results may stem from differences in the opioid type, dosage, duration, and patient characteristics [63,64]. Adequate pain control is critical to reduce perioperative stress responses that can contribute to immune suppression and systemic inflammation.

Future research should focus on identifying biomarkers and patient-specific factors that influence opioid sensitivity and tumor response. Integrating pharmacogenomics and individualized analgesic protocols could optimize pain management while minimizing potential negative oncological effects, aligning with the broader concept of precision oncoanesthesia.

3. Precision oncoanesthesia: a paradigm shift in perioperative pain management

As precision oncology continues to revolutionize cancer treatment by integrating genomic and molecular insights into therapy selection, there is growing recognition that these principles should extend beyond oncologic interventions to other aspects of perioperative care. Traditional perioperative pain management has primarily focused on immediate surgical recovery, with little consideration for long-term oncological outcomes. However, recent studies have suggested that anesthetic and analgesic agents may influence tumor biology, potentially affecting tumor recurrence and metastasis. This has led to the emergence of "precision oncoanesthesia," which aims to optimize perioperative pain management by incorporating tumor-specific molecular and genetic insights [65].

Cancer is not a single disease but a heterogeneous group of malignancies with distinct molecular characteristics that influence the response to various therapies. The same principle applies to anesthetic and analgesic agents; different tumor types may respond differently to opioids, NSAIDs, and local anesthetics owing to variations in receptor expression, metabolic pathways, and immune interactions. Similar to precision oncology, which tailors systemic therapies to individual tumors, precision oncoanesthesia applies this concept to perioperative analgesia, selecting agents based on tumor-specific genomic insights to optimize both pain control and oncologic safety.

1) Precision oncology perspectives on analgesics and cancer outcomes

Emerging evidence suggests that perioperative analgesics may not exert uniform effects on cancer progression but rather interact with tumor-specific molecular pathways, leading to variable oncologic outcomes. This concept has been demonstrated in multiple studies, particularly in lung cancer, where the relationship between opioid use and prognosis appears to be influenced by tumor genetics.

A retrospective study of early-stage NSCLC patients undergoing primary tumor resection found that higher intraoperative opioid doses were associated with poorer overall survival [66]. Further molecular analyses revealed that this effect was most pronounced in patients harboring CDKN2A mutations, a genetic alteration frequently linked to aggressive tumor behavior and poor prognosis. This suggests that opioids interact with tumor cell cycle regulatory pathways, potentially promoting disease progression in genetically susceptible tumors.

Notably, opioid administration has been linked to improved recurrence-specific survival in patients with tumors exhibiting mutations in the Wnt or Hippo signaling pathways, which regulate cell adhesion and differentiation in the same study. These findings indicate that the oncologic impact of opioids may not be uniform but rather dependent on the underlying tumor genotype. Similar variability has been observed in colorectal and renal cancers, in which opioids appear to modulate immune regulation and tumor survival in a gene-dependent manner [67,68]. In addition to opioids, NSAIDs such as ketorolac have also been shown to exert tumor-modulating effects, with studies indicating that their

impact on tumor biology varies depending on specific molecular pathways [69].

These findings reinforce a key principle of precision oncology: therapeutic strategies should not be applied uniformly but rather tailored to individual tumor biology. The observed variability in tumor response to analgesics highlights the need for precise oncoanesthesia, which integrates tumor-specific genomic insights into anesthetic planning. By incorporating molecular profiling into perioperative pain management, this approach may help refine analgesic selection, ensuring both optimal pain control and improved oncological outcomes.

2) Challenges and future directions in precision oncoanesthesia implementation

Despite the potential of precision oncoanesthesia, several challenges must be addressed before it can be widely adopted in clinical practice. A major barrier is the limited awareness and integration of tumor biology into anesthetic decision making. While precision medicine is a fundamental aspect of oncology, its application in perioperative care remains underdeveloped. Most anesthetic protocols are standardized across patient populations without considering the tumor-specific characteristics that may influence the response to analgesics. Bridging the gap between anesthesiology and oncology is essential for advancing precise onco-anesthesia as a viable clinical strategy.

Another significant limitation is the practical feasibility of incorporating tumor genomic profiling into perioperative decision making. Although oncologists routinely perform molecular testing for treatment stratification, these analyses are typically conducted weeks or months before surgery and are not designed for rapid intraoperative decision making. Advancements in fast and cost-effective genomic screening technologies are necessary to enable the real-time integration of tumor-specific data into anesthetic planning. Developing streamlined systems that allow anesthesiologists to access and interpret relevant molecular data preoperatively can facilitate personalized perioperative analgesic selection.

Additionally, the current evidence supporting precision oncoanesthesia is largely based on retrospective observational studies, which are limited by confounding factors and lack of prospective validation. Large-scale RCTs are required to establish a definitive link between perioperative analgesia and cancer prognosis. Future research should also focus on identifying biomarkers that predict individual tumor responses to analgesics, allowing for a more tailored approach to pain management.

To make precision oncoanesthesia a clinically viable approach, a structured framework that integrates molecular and genetic profiling into perioperative decision making must be developed. This requires interdisciplinary collaboration among anesthesiologists, oncologists, and molecular biologists to develop standardized evidence-based protocols that ensure consistency in implementation across institutions. Expanding the education and training programs for anesthesiologists in tumor biology and molecular pharmacology will also be critical for bridging this knowledge gap.

As precision oncology continues to shape cancer treatment, precision onco-anesthesia represents a natural extension of this paradigm. By incorporating tumor-specific insights into perioperative management, this approach has the potential to refine pain management strategies, optimize recovery, and enhance oncological outcomes in patients with cancer.

To implement this concept in clinical practice, we propose a stepwise model for personalized perioperative analgesia that incorporates patient-, surgical-, and tumor-specific factors (Fig. 1). This framework may serve as a practical foundation for future clinical applications and research on precision onco-anesthesia.

CONCLUSION

Perioperative pain management in lung cancer surgery has shifted from opioid-centered strategies to multimodal approaches that incorporate both opioid-sparing and opioid-free techniques. Although opioids have traditionally been integral to thoracic surgery analgesia, concerns about their adverse effects have driven the adoption of MMA. Current guidelines advocate for NSAIDs, acetaminophen, regional anesthesia, and adjunctive agents to reduce opioid use while maintaining effective pain control.

The debate over the use of opioids in lung cancer surgery remains unresolved. Although some studies have suggested that opioids may influence tumor progression through immunomodulatory and angiogenic pathways, the clinical evidence is inconsistent. Instead of a binary opioid inclusion approach, personalized analgesic strategies that balance pain relief with potential oncological risks are needed.

The emergence of precision oncoanesthesia has introduced a tumor-informed perspective to perioperative pain management. Future research should focus on identifying biomarkers that predict individual tumor responses to anal-

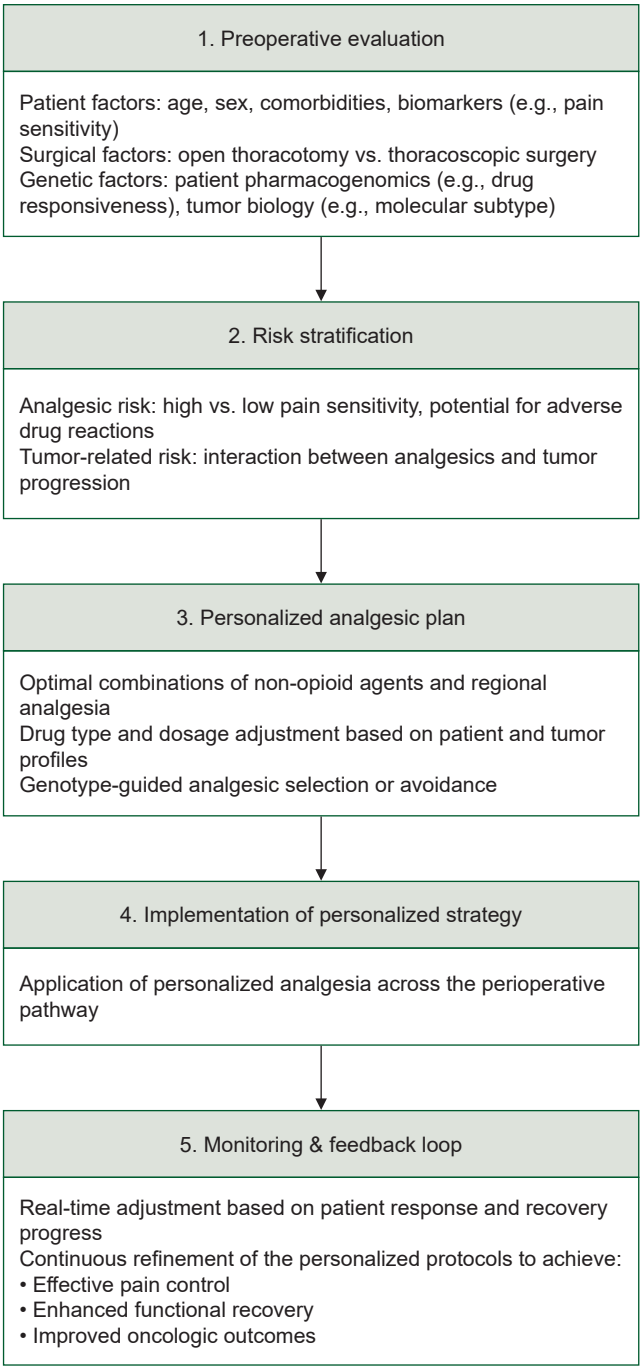

Fig. 1. Proposed model for implementing personalized perioperative analgesia in the context of precision oncoanesthesia. A stepwise framework integrating patient characteristics, surgical factors, and tumor biology into perioperative analgesic planning aimed to support the clinical implementation of precision oncoanesthesia.

gesics, thereby enabling personalized pain management strategies. Thus, perioperative analgesia is anticipated to evolve beyond opioid avoidance toward personalized approaches guided by molecular and tumor-specific information. These strategies are expected to be developed following the principles of precision medicine, to improve both functional recovery and long-term oncological outcomes.

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DATA AVAILABILITY STATEMENT

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