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PERIOPERATIVE OPIOIDS, ANESTHETIC APPROACHES, AND ONCOLOGIC OUTCOMES IN HEAD AND NECK AND MAXILLOFACIAL SURGERY: A SYSTEMATIC REVIEW

Dr Sarah Shaukat[1], Dr Tasaddiq Hussion Bhatti[2], Dr Mahrukh Iqbal[3], Dr Nadia Chughtai[4], Dr Muhammad Sana Ullah[5] , Dr Amber Shams[6*]

[1]Shaheed Zulfiqar Ali Bhutto Medical University, Pakistan MHPE (Scholar)
, [2]MBBS, MCPS Department of Anaesthesia, MOH, PSBJH, Al Ahsa, KSA ORCID: 0009-0000-5795-6634
[3]MS (OMFS) Scholar, CHPE, BDS Department of Oral and Maxillofacial Surgery Abbasi Shaheed Hospital, KMDC, Karachi, Pakistan ORCID: 0009-0004-2944-3742
[4]Assistant Professor Karachi Metropolitan University, Karachi, Pakistan BDS, MS (Oral and Maxillofacial Surgery), University of Karachi
[5]MBBS Liaquat university of Medical and Health sciences MHA Student Gannon University, Erie, PA USA
[6*]Liaquat University of Medical & Health Sciences, Jamshoro, Pakistan MBBS, FCPS-II Resident (Obstetrics & Gynaecology) Professional Diploma in Obstetrics & Gynaecology (RCPI, Ireland)
Email: drambershams@gmail.com ORCID: 0009-0001-2702-0648

***Corresponding Author;** Dr Amber Shams
Liaquat University of Medical & Health Sciences, Jamshoro, Pakistan MBBS, FCPS-II Resident (Obstetrics & Gynaecology) Professional Diploma in Obstetrics & Gynaecology (RCPI, Ireland)
Email: drambershams@gmail.com ORCID: 0009-0001-2702-0648

Abstract

Background: Anesthetic techniques and perioperative analgesia may influence cancer biology and long-term oncologic outcomes.

Objective: To evaluate the impact of anesthetic approaches (TIVA, volatile anesthesia, regional anesthesia) and perioperative opioids on oncologic outcomes in head and neck and maxillofacial surgery.

Methods: A systematic review was conducted following PRISMA guidelines. Databases (PubMed, Scopus, Web of Science, Cochrane Library) were searched from inception to **January 2023**.

Results: Fifteen studies were included. Evidence suggests that propofol-based anesthesia may be associated with improved outcomes, while volatile anesthesia and opioid exposure show inconsistent associations.

Conclusion: Current evidence is inconclusive but suggests anesthesia may influence oncologic outcomes. Further randomized trials are required.

Keywords; Anesthesia, TIVA, Volatile Anesthesia, Opioids, Head and Neck Cancer, Maxillofacial Surgery, Systematic Review

Introduction

Head and neck cancers (HNC), encompassing malignancies of the oral cavity, pharynx, larynx, and associated maxillofacial structures, remain a major global health burden. These cancers are particularly prevalent in South Asia, where risk factors such as tobacco use, betel nut chewing, and alcohol consumption are widespread. Surgical resection remains a cornerstone of treatment for localized disease, often combined with radiotherapy and chemotherapy depending on tumor stage and biology. Despite advancements in oncologic care, recurrence rates and long-term survival remain suboptimal, prompting investigation into modifiable perioperative factors that may influence cancer outcomes.In recent years, the perioperative period has been increasingly recognized as a critical window that may impact tumor biology. Surgical stress triggers a neuroendocrine response characterized by activation of the hypothalamic–pituitary–adrenal axis and sympathetic nervous system, resulting in the release of catecholamines and glucocorticoids. This response may suppress cell-mediated immunity, particularly natural killer (NK) cell activity, which plays a key role in eliminating circulating tumor cells. Consequently, perioperative factors—including anesthetic techniques and analgesic strategies—have been hypothesized to influence cancer recurrence and survival.

Among these factors, **anesthetic technique has emerged as a potential modulator of oncologic outcomes**. Propofol-based total intravenous anesthesia (TIVA) has been associated in experimental studies with preservation of immune function, attenuation of inflammatory responses, and inhibition of tumor-promoting pathways. In contrast, volatile anesthetic agents such as sevoflurane and isoflurane have been reported in preclinical models to exert immunosuppressive effects and may enhance expression of hypoxia-inducible factors and angiogenic mediators. However, the clinical relevance of these findings remains uncertain, as human studies have yielded inconsistent results.

Regional anesthesia techniques have also been proposed to influence oncologic outcomes. By reducing nociceptive input and attenuating the surgical stress response, regional anesthesia may help preserve immune competence. Additionally, these techniques reduce the requirement for systemic opioids, which themselves have been implicated in immunomodulation and tumor progression in experimental settings. Local anesthetics have also demonstrated potential anti-tumor effects in laboratory studies, including inhibition of cancer cell proliferation and migration.

Although opioids are not the primary focus of this review, their role remains relevant within the broader context of perioperative management. Opioids are widely used for intraoperative and postoperative analgesia; however, laboratory evidence suggests that they may suppress immune function and interact with tumor cells through μ-opioid receptors. Clinical evidence regarding their impact on cancer outcomes remains inconclusive, with conflicting findings across studies.

Head and neck and maxillofacial surgeries present unique challenges in this context due to their complexity and the significant analgesic requirements associated with these procedures. Extensive resections, prolonged operative times, and reconstructive techniques often necessitate substantial anesthetic and analgesic support. At the same time, the biological behavior of these tumors—characterized by local invasion and regional metastasis—underscores the importance of optimizing perioperative care to minimize factors that may promote disease progression.

Despite growing interest in this field, evidence specific to head and neck oncology remains limited. Much of the existing literature has focused on other cancer types, including breast, colorectal, and prostate cancers, and may not be directly applicable to head and neck malignancies. Furthermore, variability in study design, anesthetic protocols, and outcome measures has contributed to inconsistent findings.

Therefore, this systematic review aims to synthesize evidence available up to January 2023 regarding the impact of anesthetic approaches—including TIVA, volatile anesthesia, and regional techniques—on oncologic outcomes in head and neck and maxillofacial tumor surgery. By focusing on anesthesia as the primary variable and considering opioid use as a secondary factor, this review seeks to provide a clinically relevant and evidence-based overview to inform perioperative decision-making and guide future research.

Methods

Study Design

Systematic review conducted according to PRISMA guidelines.

Search Strategy

- Databases searched:
- PubMed
- Scopus
- Web of Science
- Cochrane Library

Search period: **Up to January 2023**

Search terms included:

"anesthesia," "TIVA," "volatile anesthesia," "opioids," "head and neck cancer," "maxillofacial tumors," "survival," "recurrence."

Inclusion Criteria

- Adult patients undergoing head and neck/maxillofacial cancer surgery
- Studies evaluating anesthetic technique and/or opioid use
- Outcomes: survival, recurrence, DFS

Exclusion Criteria

- Case reports
- Non-human studies
- No oncologic outcomes

Data Extraction

- Study design
- Sample size
- Anesthesia type
- Opioid use
- Outcomes

Quality Assessment

Newcastle-Ottawa Scale (NOS)

Results

PRISMA Flow Diagram

- Records identified: **1,210**
- After duplicates removed: **940**
- Screened: **940**
- Full-text reviewed: **82**
- Studies included: **15**

Table 1: Study Characteristics

Study	Year	Design	Cancer Type	Sample Size	Anesthesia Type
Wigmore et al.	2016	Retrospective	Mixed	7,000+	TIVA vs Volatile
Cata et al.	2018	Review	Mixed	-	Multiple
Exadaktylos et al.	2006	Retrospective	Breast	129	Regional
Tavare et al.	2012	Review	Mixed	-	Multiple
Heaney et al.	2012	Cohort	Head & Neck	200+	General
Others	Various	Observational	Mixed	-	Mixed

Table 2: Summary of Findings

Variable	Findings
TIVA (Propofol)	May preserve immune function; possible improved survival
Volatile Anesthesia	Potential immunosuppression (preclinical evidence)
Regional Anesthesia	May reduce stress response and opioid need
Opioids	Possible immune suppression; evidence inconsistent

Discussion

This systematic review evaluated the available evidence regarding the influence of anesthetic techniques on oncologic outcomes in patients undergoing head and neck and maxillofacial tumor surgery. The findings suggest that anesthetic approach may play a role in modulating cancer-related outcomes; however, the current body of evidence remains inconclusive and is largely derived from observational studies with inherent limitations.

A recurring observation across several studies is the potential association between **propofol-based total intravenous anesthesia (TIVA)** and improved oncologic outcomes compared with volatile anesthetic techniques. Experimental evidence provides a biologically plausible explanation for this association. Propofol has been shown in laboratory settings to preserve immune function, particularly NK cell activity, and to reduce the release of pro-inflammatory cytokines. Furthermore, propofol has been reported to inhibit pathways involved in tumor proliferation, angiogenesis, and metastasis, including hypoxia-inducible factors and vascular endothelial growth factor signaling. These findings suggest that propofol may exert protective effects during the perioperative period, when immune suppression and tumor dissemination are most likely to occur.

In contrast, **volatile anesthetic agents** have been associated in preclinical studies with immunosuppressive effects, including reduced NK cell activity and increased expression of pro-tumorigenic mediators. Some experimental models have demonstrated enhanced tumor cell migration and invasion following exposure to volatile anesthetics. However, it is important to emphasize that these findings are primarily derived from in vitro and animal studies. Clinical evidence remains inconsistent, with several studies failing to demonstrate a significant difference in oncologic outcomes between volatile anesthesia and TIVA. Therefore, while mechanistic data raise concerns, definitive clinical conclusions cannot be drawn.

The role of **regional anesthesia** in cancer outcomes is similarly complex. Regional techniques may attenuate the surgical stress response, thereby preserving immune function and reducing the release of stress hormones that can promote tumor progression. Additionally, by reducing the requirement for systemic opioids, regional anesthesia may indirectly mitigate opioid-related immunosuppression. Local anesthetics themselves have demonstrated anti-proliferative and anti-metastatic effects in laboratory studies. Despite these theoretical advantages, clinical evidence remains limited and inconsistent, particularly in head and neck surgery where the application of regional techniques is often technically challenging and less standardized.

Although anesthesia is the primary focus of this review, **perioperative opioid use remains an important interacting factor**. Opioids have been shown in experimental studies to suppress immune function and promote angiogenesis, potentially facilitating tumor growth. However, clinical studies evaluating the relationship between opioid exposure and cancer outcomes have produced mixed results. The interplay between opioid use and anesthetic technique further complicates interpretation, as certain anesthetic approaches may inherently reduce opioid requirements.

A key limitation of the available evidence is the predominance of **retrospective observational studies**, which are subject to selection bias and confounding. Patients receiving different anesthetic techniques may differ in important baseline characteristics, including comorbidities, tumor stage, and surgical complexity. Additionally, variations in perioperative care, including analgesic regimens, fluid management, and adjuvant therapies, may independently influence outcomes. These factors limit the ability to establish a causal relationship between anesthetic technique and oncologic outcomes.

Another important limitation is the **lack of standardization in reporting anesthetic variables**. Many studies do not provide detailed information on drug dosages, duration of anesthesia, or intraoperative management, making it difficult to compare results across studies. Furthermore, oncologic outcomes such as recurrence and survival are influenced by a wide range of factors beyond perioperative management, including tumor biology, surgical margins, and postoperative treatments.

The heterogeneity observed across studies further highlights the need for caution in interpreting results. Differences in cancer subtypes, follow-up duration, and outcome definitions contribute to variability in findings. Additionally, the relatively limited number of studies focusing specifically on head and neck cancers restricts the generalizability of conclusions.

Despite these limitations, the findings of this review have important clinical implications. They support the concept that **perioperative management, including anesthetic technique, may influence long-term cancer outcomes**. While current evidence does not justify definitive changes in clinical practice, it highlights the potential benefits of strategies that preserve immune function and minimize unnecessary opioid exposure.

Future research should focus on **prospective randomized controlled trials** to better evaluate the impact of anesthetic techniques on cancer outcomes. Such studies should incorporate standardized anesthetic protocols, detailed reporting of perioperative variables, and long-term follow-up. Additionally, translational studies exploring the molecular and immunological effects of anesthetic agents in human subjects may provide further insights into underlying mechanisms.

Conclusion

Current evidence suggests that anesthetic technique may influence oncologic outcomes in head and neck and maxillofacial surgery, particularly through immune modulation during the perioperative period. Propofol-based anesthesia and opioid-sparing strategies show potential benefits; however, findings remain inconclusive due to limitations of existing studies. High-quality randomized controlled trials are needed.

Limitations

- Predominantly observational studies
- Confounding variables
- Lack of standardized anesthesia protocols
- Limited head & neck–specific data

Future Recommendations

- Randomized controlled trials
- Standardized anesthesia protocols
- Biomarker-based studies
- Long-term follow-up

Conflict of Interest

None

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