

## Revijalni članak

ULOGA ANESTEZIJE U LEČENJU  
MALIGNITETA: POZIV NA AKCIJU ZA  
SRPSKE ANESTEZIOLOGESuzana Bojic<sup>1,2</sup>, Daniela Ionescu<sup>3,4</sup><sup>1</sup>Odeljenje za anesteziologiju i intenzivnu negu, Kliničko-bolnički centar „Dr Dragiša Mišović – Dedinje“, Beograd, Srbija<sup>2</sup>Medicinski fakultet, Univerzitet u Beogradu, Beograd, Srbija<sup>3</sup>Odeljenje za anesteziju i intenzivnu negu 1, Univerzitet medicine i farmacije „Iuliu Hațieganu“, Kluž-Napoka, Rumunija<sup>4</sup>Istraživačka grupa za onko-anesteziju, ESAIC

## Review article

ANAESTHESIA AND CANCER  
OUTCOMES: A CALL TO ACTION FOR  
SERBIAN ANAESTHESIOLOGISTSuzana Bojic<sup>1,2</sup>, Daniela Ionescu<sup>3,4</sup><sup>1</sup>Department of Anaesthesiology and Intensive Care, Clinical Hospital Center “Dr. Dragisa Misovic – Dedinje”, Belgrade, Serbia<sup>2</sup>Faculty of Medicine, University of Belgrade, Belgrade, Serbia<sup>3</sup>Department of Anaesthesia and Intensive Care 1, Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania<sup>4</sup>Onco-Anaesthesia Research Group, ESAIC

Prema podacima Instituta za javno zdravlje Srbije „Dr Milan Jovanović Batut“, svake godine se u Srbiji registruje preko 42.000 novih slučajeva maligniteta sa tendencijom rasta. Ovaj zabrinjavajući trend je postao izvor značajne kontroverze i zabrinutost i stručne i opšte javnosti. Još alarmantnija je činjenica da se stopa smrtnosti od malignih bolesti povećava, sa više od 21.000 smrtnih slučajeva godišnje povezanih sa ovom patologijom. (1) Ovi podaci su u skladu sa situacijom u drugim istočnoevropskim zemljama, koje imaju veće stope smrtnosti od maligniteta u poređenju sa zapadnim i severnim delom Evrope. (2)

Velika većina srpskih anesteziologa, kako na sekundarnom tako i na tercijarnom nivou zdravstvene zaštite, svakodnevno učestvuje u hirurškom lečenju pacijenata obolelih od raka. Tradicionalno, glavni fokus anesteziologije u onkohirurgiji je bio obezbeđivanje perioperativnog monitoringa, bezbednosti pacijenata i terapije bola. Međutim, sve veći broj dokaza ukazuje na to da izbor anestezio-loške tehnike može uticati i na dugoročne ishode lečenja malignih bolesti, uključujući ukupno preživljavanje i pojavu lokalnih recidiva.

Očigledna dilema u onkoanesteziji je izbor između standardne inhalacione anestezije (IA) i totalne intravenske anestezije (TIVA). Pored toga, postoji i dilema o izboru između opšte anestezije kao samostalne tehnike i kombinacije opšte i regionalne anestezije/analgezije.

Prve studije na velikim kohortama pacijenata ukazivale su na značajnu prednost TIVA bazirane na propofolu u odnosu na IA, u pogledu dugoročnog preživljavanja pacijenata koji su podvrgnuti hirurškim zahvatima u okviru lečenja maligniteta. (3) Ovaj obećavajući trend je ubrzo doveo do

According to the Institute of Public Health of Serbia “Dr. Milan Jovanovic Batut”, over 42,000 new cancer cases are registered annually in Serbia, with a consistent increase in incidence over the years. This alarming trend has sparked considerable controversy and public concern. Even more worrisome is the rising mortality rate, with over 21,000 cancer-related deaths each year. (1) These staggering data are congruous with the situation in other Eastern European nations, which face higher cancer mortality rates than those in Western and Northern Europe. (2)

The vast majority of Serbian anaesthesiologists, at both secondary and tertiary hospital levels, are involved daily in the surgical treatment of cancer. Traditionally, the primary focus of anaesthesiology in cancer surgery has been on ensuring perioperative monitoring, patient safety and pain management. However, a growing body of evidence suggests that the choice of anaesthesia technique may also influence long-term cancer outcomes, including overall survival and tumour recurrence.

An obvious clinical dilemma in cancer surgery is choosing between standard Inhalation Anaesthesia (IA) and Total Intravenous Anaesthesia (TIVA). Additionally, whenever possible, there is also the decision between general anaesthesia alone versus a combination of general and regional anaesthesia/analgesia.

Early studies on large patient cohorts suggested a significant advantage of propofol-based TIVA over IA in terms of long-term survival of patients undergoing cancer surgery. (3) This led to numerous randomized controlled trials (RCTs) and observational longitudinal studies addressing this issue, resulting in growing evidence that the

brojnih randomizovanih kontrolisanih (RCT) i opservacionih longitudinalnih studija koje su se bavile ovom problematikom a koje su donele sve više dokaza da je korišćenje TIVA bazirane na propofolu povezano sa manjom rizikom od metastaza i recidiva karcinoma, verovatno zbog disbalansa citokina (4), kao i imunološkog (5) i angiogenog (6) efekta IA. Međutim, ubrzo je ustanovljeno da ovi nalazi zahtevaju precizniju interpretaciju koja u obzir uzima i vrstu tumora i stadijum bolesti. (7-9) Na primer, razlike u ukupnom preživljavanju i preživljavanju bez recidiva su daleko manje ubedljive kod kolorektalnog karcinoma (10) i glioblastoma (11), ali su jasno prisutne kod hepatocelularnog karcinoma (12) i nemikrocelularnog karcinoma pluća (13). U pokušaju da se dodatno ispita ovaj problem kod specifičnih tipova tumora u različitim stadijumima bolesti, predloženi su protokoli za velika međunarodna RCT ispitivanja. (14)

U toku poslednjih desetak godina vrlo intenzivno su ispitivani i potencijalni zaštitni efekti regionalnih tehnika na ishode lečenja malignih bolesti. Pretpostavlja se da anestetici mogu uticati na ishode lečenja raka putem direktnih efekata na maligne ćelije ili mikrosredinu tumora, kao i indirektno, modulisanjem imunološkog ili stresnog odgovora organizma. (15, 16) Međutim, uprkos ovim inicijalnim nalazima (17), dalje analize sve većeg broja kliničkih studija nisu pokazale značajnu korist u smislu preživljavanja ili recidiva tumora kod pacijenata koji su primili regionalnu anesteziju u poređenju sa onima koji su primili opštu anesteziju. (18-20)

S obzirom na relativno slabu zastupljenost regionalne anestezije u našoj zemlji (21), možda trenutno veći značaj ima pitanje izbora anestetika, kao i sve veći interes za opioid-free ili opioid-sparing anesteziju. Anestetici kao što su ketamin, tiopental, isparljivi anestetici, fentanil i morfin mogu smanjiti aktivnost imunih ćelija, koje su ključne u uklanjanju malignih ćelija, dok propofol, remifentanil i tramadol ne pokazuju ovaj nepovoljni efekat. (15, 22, 23) Dalje kontroverze postoje u vezi sa upotrebom opioida u perioperativnom periodu. Iako studije na životinjama jasno ukazuju da opioidi imaju značajan imunosupresivni efekat, kliničke studije još nisu potvrdile značaj ovog efekta kod ljudi. (24-27) Pored toga, istraživanja su pokazala da efekti opioid na ishode lečenja karcinoma zavise od vrste i doze opioida, kao i od tipa maligniteta. (28-31)

propofol-based TIVA is associated with a lower risk of metastasis and cancer recurrence, potentially due to a cytokine imbalance (4), as well as immunosuppressive (5) and angiogenic (6) effect of IA. However, it is recognised that these findings require a more nuanced interpretation that accounts for the influence of specific cancer types and stage on long-term survival outcomes (7-9). For instance, the differences in overall survival and recurrence-free survival are far less convincing in colorectal cancer (10) and glioblastoma (11), but clearly present in hepatocellular (12) and non-small cell lung carcinoma (13). In an attempt to further address this issue in specific cancer types and stages, protocols for large international RCTs have been proposed. (14)

The potential protective effects of regional techniques on cancer outcomes have also been extensively investigated over the past decade. Anaesthetic agents are hypothesized to influence cancer outcomes through direct effects on cancer cells or the tumour microenvironment, as well as indirect effects by modulating the body's immune response or stress response. (15, 16) Despite these initial findings (17), aggregate analyses of now available clinical data have shown no significant benefit in terms of survival or cancer recurrence in patients receiving regional anaesthesia compared to those receiving general anaesthesia. (18-20)

Given the underrepresentation of regional anaesthesia in our regional settings (21), a more pressing question might be the choice of anaesthetic agents as well as the emerging interest in opioid-sparing or opioid-free anaesthesia. Anaesthetics such as ketamine, thiopental, volatile anaesthetics, fentanyl, and morphine might reduce the activity of immune cells, critical in targeting cancer cells, whereas propofol, remifentanyl, and tramadol do not exhibit this adverse effect. (15, 22, 23) Further controversies exist regarding the use of opioids in perioperative period. While animal studies clearly suggest that opioids have a significant immunosuppressive effect, human trials have yet to confirm the clinical significance of this effect. (24-27) Moreover, studies have shown different effects depending on the opioid type and dose as well as the type of cancer. (28-31)

The potential protective effect of intravenous (IV) lidocaine on long-term cancer outcomes has

U poslednjih nekoliko godina veliku pažnju je privukao potencijalni zaštitni efekat intravenskog (IV) lidokaina na dugoročne ishode lečenja maligniteta. Srpski anesteziolozi su upoznati sa njegovom primenom kao delom protokola za brzi oporavak nakon hirurgije (ERAS). (32) Međutim, studije na životinjama su pokazale da lidokain inhibira rast tumora kroz više mehanizama, uključujući blokadu natrijumskih kanala, epigenetske modifikacije, promociju apoptoze i promene u tumorskoj mikrosredini. (33-35) Takođe, IV lidokain inhibira ekspresiju biomarkera povezanih sa metastazama i recidivom tumora u hirurgiji raka dojke, bez obzira na to koja je tehnika opšte anestezije korišćena. (36, 37) Klinički značaj ovih nalaza za sada je kontroverzan, jer upotreba intraoperativnog lidokaina nije dovela do klinički značajnih poboljšanja u ukupnom preživljavanju ili preživljavanju bez bolesti kod pacijenata podvrgnutih pankreatektomiji zbog raka pankreasa. (38) Potrebna su dalja ispitivanja da bi se utvrdilo da li IV lidokain može ponuditi klinički relevantan zaštitni efekat na dugoročne ishode kod pacijenata koji se podvrgavaju kurativnim resekcijama tumora. (23)

Na osnovu dosadašnjih saznanja, možemo da tvrdimo da trenutno nema dovoljno kliničkih podataka koji bi sugerisali promenu u kliničkoj praksi. Zato su nam potrebna dodatna istraživanja koja bi se bavila preciznom evaluacijom efekata svake od navedenih anestezioloških tehnika, kao i drugih faktora na koje anesteziolozi mogu da utiču kao što su ishrana, protokoli za brzi oporavak i povratak na neposrednu oralnu toleranciju (RIOT), na ishode lečenja u onkohirurgiji.

Iako je onkoanestezija trenutno jako uzbudljivo polje u medicini, još uvek smo daleko od donošenja konačnih zaključaka o kliničkom značaju tehnika anestezije na ishode lečenja malignih bolesti. Dalja saznanja na ovom polju verovatno vode ka preciznoj medicini, koja će uzimati u obzir različite tipova maligniteta i populacije pacijenata, fokusirajući se na personalizovan pristup. Aktuelna i buduća ispitivanja zato imaju za cilj da identifikuju koji pacijenti mogu imati najviše koristi od određenih tehnika anestezije razmatranjem individualnih karakteristika pacijenta, biologije tumora i specifičnih anestezioloških tehnika,

Mi, srpski anesteziolozi, zato moramo biti proaktivni u prihvatanju ovog novog poglavlja u razvoju naše specijalnosti. Neophodno je da integrišemo nove naučne nalaze u svakodnevnu kliničku

gained significant attention in the past few years. Serbian anaesthesiologists are familiar with its use as a part of Early Recovery After Surgery (ERAS) protocols. (32) However, animal studies have shown that lidocaine inhibits tumour growth through multiple mechanisms, including sodium channel blockade, epigenetic modifications, apoptosis promotion, and altering the tumour microenvironment. (33-35) Also, IV lidocaine inhibits the expression of biomarkers associated with metastasis and tumour recurrence in breast cancer surgery, regardless of the general anaesthetic technique used. (36, 37) The clinical significance of these findings is, so far, controversial, since the use of intraoperative lidocaine did not show improvements in overall or disease-free survival in patients undergoing pancreatectomy for pancreatic cancer. (38) Further studies are needed to determine if IV lidocaine could offer a clinically relevant protective effect on long-term cancer outcomes in patients undergoing curative cancer resections. (23)

At the moment, there are not enough clinical data to suggest a change in clinical practice, but further studies are needed for a more precise evaluation of the effects of each of the above-mentioned techniques, as well as other anesthetic factors such as nutrition, rapid recovery protocols, and Return of Immediate Oral Tolerance (RIOT), on the outcomes of cancer patients undergoing surgery.

While the topic of oncoanaesthesia is well-established in laboratory research, we are still far from reaching definitive conclusions on the clinical importance of anaesthesia techniques on cancer outcomes. This journey likely leads us toward precision medicine, which leverages the variability in findings across different cancer types and patient populations by focusing on personalized approaches. By considering individual patient factors, tumour biology, and specific anaesthetic agents, ongoing trials and studies aim to identify which patients might benefit the most from particular anaesthesia techniques.

As Serbian anaesthesiologists, we must remain vigilant and proactive in embracing this new frontier in our field. It is imperative that we integrate novel findings into our practice to ensure better patient outcomes. By doing so, we can significantly contribute to improving cancer treatment and



praksu kako bismo optimizirali ishode lečenja naših pacijenata. Na taj način možemo značajno doprineti poboljšanju svih aspektata hirurškog lečenja malignih bolesti čija je ekspanzija u našoj zemlji postaje kritična.

## References

1. Malignant Tumours in Republic of Serbia 2019: Institute of Public Health of Serbia "Dr. Milan Jovanovic Batut"; 2024 [cited 2024]. Available from: <chrome-extension://efaidnbmn-nibpcapjcgclcfndmkaj/https://www.batut.org.rs/download/publikacije/maligniTumoriURpubliciSrbiji2019.pdf>.
2. System E-ECI. Cancer Factsheets in EU-27 countries - 2022: European Commission; 2024 [Available from: [https://ecis.jrc.ec.europa.eu/factsheets\\_2022.php](https://ecis.jrc.ec.europa.eu/factsheets_2022.php)].
3. Wigmore TJ, Mohammed K, Jhanji S. Long-term Survival for Patients Undergoing Volatile versus IV Anesthesia for Cancer Surgery: A Retrospective Analysis. *Anesthesiology*. 2016;124(1):69-79.
4. Li R, Mukherjee MB, Jin Z, Liu H, Lin K, Liu Q, et al. The Potential Effect of General Anesthetics in Cancer Surgery: Meta-Analysis of Postoperative Metastasis and Inflammatory Cytokines. *Cancers (Basel)*. 2023;15(10).
5. Kadantseva K, Subbotin V, Akchulpanov R, Berikashvili L, Yadgarov M, Zhukova L, et al. The impact of inhalation versus total intravenous anesthesia on the immune status in patients undergoing breast cancer surgery: a double-blind randomized clinical trial (TeMP). *Front Oncol*. 2024;14:1401910.
6. Yan T, Zhang GH, Wang BN, Sun L, Zheng H. Effects of propofol/remifentanyl-based total intravenous anesthesia versus sevoflurane-based inhalational anesthesia on the release of VEGF-C and TGF- $\beta$  and prognosis after breast cancer surgery: a prospective, randomized and controlled study. *BMC Anesthesiol*. 2018;18(1):131.
7. Dubowitz J, Riedel B, Blaas C, Hiller J, Braat S. On the horns of a dilemma: choosing total intravenous anaesthesia or volatile anaesthesia for cancer surgery, an enduring controversy. *Br J Anaesth*. 2024;132(1):5-9.
8. Ramirez MF, Gan TJ. Total intravenous anesthesia versus inhalation anesthesia: how do outcomes compare? *Curr Opin Anaesthesiol*. 2023;36(4):399-406.
9. Doleman B, Lund JN, Williams JP. Survival Advantage with Total Intravenous Anesthesia in Cancer Surgery: Is This Confounded by Cancer Type and Stage? *Anesthesiology*. 2016;125(2):417.
10. Xia S, Zhu Y, Wu W, Li Y, Yu L. Effect of different anaesthetic techniques on the prognosis of patients with colorectal cancer after resection: a systematic review and meta-analysis. *Front Oncol*. 2024;14:1397197.
11. Schmoch T, Jungk C, Bruckner T, Haag S, Zweckberger K, von Deimling A, et al. The anesthetist's choice of inhalational vs. intravenous anesthetics has no impact on survival of glioblastoma patients. *Neurosurg Rev*. 2021;44(5):2707-15.
12. Meng XY, Zhang XP, Sun Z, Wang HQ, Yu WF. Distant survival for patients undergoing surgery using volatile survival rates, addressing the pressing healthcare challenges facing our nation. Let us commit to advancing our knowledge and applying evidence-based practices to enhance the quality of care for our patients.
13. Seo KH, Hong JH, Moon MH, Hwang W, Lee SW, Chon JY, et al. Effect of total intravenous versus inhalation anesthesia on long-term oncological outcomes in patients undergoing curative resection for early-stage non-small cell lung cancer: a retrospective cohort study. *Korean J Anesthesiol*. 2023;76(4):336-47.
14. Kim J, Yoon S, Song IK, Lee K, Hwang W, Kim H, et al. Recurrence-free survival after curative resection of non-small cell lung cancer between inhalational gas anesthesia and propofol-based total intravenous anesthesia: a multicenter, randomized, clinical trial (GAS TIVA trial): protocol description. *Perioper Med (Lond)*. 2024;13(1):79.
15. Vrbanović Mijatović V, Gatin L, Tonković D, Bandić Pavlović D, Smuđ Orehovec S, Miklič Bubić M, et al. THE EFFECT OF REGIONAL VS. GENERAL ANESTHESIA ON THE IMMUNE RESPONSE IN BREAST CANCER SURGERY: A NARRATIVE REVIEW OF THE LITERATURE. *Acta clinica Croatica*. 2022;61(Suppl 2):115-20.
16. Alam A, Rampes S, Patel S, Hana Z, Ma D. Anesthetics or anesthetic techniques and cancer surgical outcomes: a possible link. *Korean J Anesthesiol*. 2021;74(3):191-203.
17. Cata JP, Sessler DI. Lost in Translation: Failure of Preclinical Studies to Accurately Predict the Effect of Regional Analgesia on Cancer Recurrence. *Anesthesiology*. 2024;140(3):361-74.
18. Ang E, Ng KT, Lee ZX, Ti LK, Chaw SH, Wang CY. Effect of regional anaesthesia only versus general anaesthesia on cancer recurrence rate: A systematic review and meta-analysis with trial sequential analysis. *J Clin Anesth*. 2020;67:110023.
19. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, et al. Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial. *Lancet*. 2019;394(10211):1807-15.
20. Rahmani LS, Abdelaatti A, Wall TP, Buggy DJ. Anaesthesia and cancer recurrence: the influence of perioperative anaesthetic technique on cancer recurrence after surgery. *Curr Opin Anaesthesiol*. 2023;36(3):361-8.
21. Bojic S, Ladjevic N, Palibrk I, Soldatovic I, Likic-Ladjevic I, Meissner W, et al. Cost-effectiveness of the Perioperative Pain Management Bundle a registry-based study. *Front Public Health*. 2023;11:1157484.
22. Luan T, Li Y, Sun L, Xu S, Wang H, Wang J, et al. Systemic immune effects of anesthetics and their intracellular targets in tumors. *Frontiers in medicine*. 2022;9:810189.
23. Alexa AL, Sargarovschi S, Ionescu D. Neutrophils and Anesthetic Drugs: Implications in Onco-Anesthesia. *International journal of molecular sciences*. 2024;25(7).
24. Thomas TE, Bowers K, Gomez D, Morgan O, Borowsky PA, Dutta R, et al. The association between perioperative

ve opioids and breast cancer recurrence: a narrative review of the literature. *Transl Breast Cancer Res.* 2023;4:12.

25. Ahn HJ. Anesthesia and cancer recurrence: a narrative review. *Anesth Pain Med (Seoul).* 2024;19(2):94-108.

26. Ramirez MF, Strang A, Roland G, Lasala J, Owusu-Agyemang P. Perioperative Pain Management and Cancer Outcomes: A Narrative Review. *J Pain Res.* 2023;16:4181-9.

27. Murphy L, Shaker J, Buggy DJ. Anaesthetic Techniques and Strategies: Do They Influence Oncological Outcomes? *Curr Oncol.* 2023;30(6):5309-21.

28. Cata JP, Keerty V, Keerty D, Feng L, Norman PH, Gottumukkala V, 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(4):900-8.

29. Du KN, Feng L, Newhouse A, Mehta J, Lasala J, Mena GE, 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(1):210-6.

30. Cronin-Fenton D. Opioids and breast cancer recurrence. *Curr Opin Support Palliat Care.* 2019;13(2):88-93.

31. Zhang Y, Chen Q, Chen X, Zhang M, Li P, Huang Z, et al. The Effect of Intraoperative Fentanyl Consumption on Prognosis of Colorectal Liver Metastasis treated by Simultaneous Resection: A Propensity Score Matching Analysis. *J Cancer.* 2022;13(11):3189-98.

32. ERAS Guidelines: ERAS Society; 2024 [Available from: <https://erassociety.org/guidelines/>].

33. Karnina R, Arif SK, Hatta M, Bukhari A. Molecular Mechanisms of Lidocaine. *Annals of Medicine and Surgery.* 2021;69.

34. Wall TP, Crowley PD, Sherwin A, Foley A, Buggy DJ. Effects of Lidocaine and SRC Inhibition on Metastasis in a Murine Model of Breast Cancer Surgery. *Cancers.* 2019;11(10):1414.

35. Zhou D, Wang L, Cui Q, Ifthikhar R, Xia Y, Xu P. Repositioning Lidocaine as an Anticancer Drug: The Role Beyond Anesthesia. *Frontiers in Cell and Developmental Biology.* 2020;8.

36. Zhang W, Liu J, Li X, Bai Z, Sun Y, Chen X. Lidocaine effects on neutrophil extracellular trapping and angiogenesis biomarkers in postoperative breast cancer patients with different anesthesia methods: a prospective, randomized trial. *BMC Anesthesiol.* 2024;24(1):162.

37. Galoş EV, Tat TE, Popa R, Efrimescu CI, Finnerty D, Buggy DJ, et al. Neutrophil extracellular trapping and angiogenesis biomarkers after intravenous or inhalation anaesthesia with or without intravenous lidocaine for breast cancer surgery: a prospective, randomised trial. *Br J Anaesth.* 2020;125(5):712-21.

38. Zhang H, Qu M, Guo K, Wang Y, Gu J, Wu H, et al. Intraoperative lidocaine infusion in patients undergoing pancreatotomy for pancreatic cancer: a mechanistic, multicentre randomised clinical trial. *Br J Anaesth.* 2022;129(2):244-53.

Rad primljen: 02.10.2024. Rad prihvaćen: 10.10.2024.