**Onco-Anaesthesiology and palliative medicine: Opportunities and challenges**

Parmanand Jain, Kalpana Balkrishanan, Sukdev Nayak, Nishkarsh Gupta, Shagun Shah

Department of Anaesthesiology, Critical Care and Pain, Tata Memorial Centre and Homi Bhabha National Institute, Mumbai, Maharashtra, 1Department of Anaesthesia, AIIMS, Bhubaneswar, Orissa, 2Department of Onco-Anaesthesiology and Palliative Medicine, AIIMS, New Delhi, 3Department of Anaesthesia and Critical Care, Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India

ABSTRACT

Global cancer burden is on the rise and many more patients present for surgery or other oncological diagnostic or therapeutic interventions requiring anaesthesia. Oncology therapy is unique as it requires a multidisciplinary team of surgical, medical and radiation oncologists apart from palliative medicine (PM) specialists, and anaesthesiologists. Anaesthetic management can affect the outcome of oncology treatment both by ensuring early return to oncology treatment and some anaesthetic techniques being innately associated with recurrence. Hence, the time has come for a separate super-speciality of onco-anaesthesiology to cater to the complex unmet needs of cancer patients. PM is the fourth dimension of oncology care and so mandatory education and training should be included in the undergraduate curriculum.

Key words: Anaesthesiology, curriculum, oncology, palliative medicine, specialisation

INTRODUCTION

As per "Globocan 2018" estimates, there will be 18.1 million new cases and 9.6 million deaths due to cancer in 2018.[1] Cancer is the second most common cause of death in the world and 1 in 6 deaths occur due to cancer.[2] In India, there were 1157294 cases and 784821 cancer-related deaths as per recent Globocan 2018 report.[1] The lifetime risk of developing or dying from cancer is increasing and it is estimated the one in two people born after 1960 have or are at risk of developing some kind of cancer over their lifetime.[3] This is primarily due to increased lifespan, obesity, environmental pollution and increased screening facilities. Moreover, due to improved overall management of cancer more and more patients are surviving cancer and coming for management of secondary malignancy and incidental surgeries.[2]

The oncology treatment is a multidisciplinary and patients often require combination of surgery, chemotherapy and radiation therapy. The complications and disability following oncological surgery may prevent completion of oncology therapy and may reverse the benefits of surgery. Metastasis of tumour is another major problem that affects the overall survival of patients. The battle between the patient’s immunity to fight against malignancy and risk of cancer growth at distant site determines the overall outcome. In this article, we discuss the prospects of an upcoming speciality of onco-anaesthesiology and palliative medicine (PM).

WHY ONCO-ANAESTHESIOLOGY?

Oncological management is multidisciplinary, and patients receive a combination of surgery,

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Jain P, Balkrishanan K, Nayak S, Gupta N, Shah S. Onco-anaesthesiology and palliative medicine: Opportunities and challenges. Indian J Anaesth 2021;65:29-34.
chemotherapeutic agents, radiation therapy and
palliative care depending on the disease and stage.[4,5]

Majority of patients (up to two thirds) may need
anaesthesia for diagnostic or therapeutic management
of the cancer. The onco-anaesthesiologists must be well
versed in the various cancer treatment (chemotherapies,
radiotherapy or newer immunotherapy) modalities that
the patient has received and be aware of complications,
sequelae and adverse effects of each of these modalities so
that they can manage the perioperative phase of the patient
efficiently [Table 1]. Many surgeries like hyperthermic
intraperitoneal heated chemotherapy (HIPEC) and
ischemic limb perfusion (ILP) with chemotherapeutic
agents are unique to oncology setups. In HIPEC surgery,
the heated chemotherapy drugs are delivered directly
into the abdomen after cytoreductive surgery. The
anaesthesiologists must manage fluids optimally, maintain
haemodynamics, manage fluctuations in temperature,
coagulation derangement and electrolyte balance.[6]

There is clear evidence to vouch for the improved
outcome of patients treated in a specialised
oncological centre by an efficient team comprising
the surgeon and anaesthesiologist as a perioperative
physician.[7] As cancer is becoming a public health
problem, anaesthesia for oncology has become a
specialised field with the introduction of onco-
anaesthesiology as a super-specialty.[4,7]

Onco-anaesthesiologists function as perioperative
physicians, resuscitation specialists and are adept
at dealing with difficult airway. They are playing a
leadership role in critical care (surgical, oncology and
now coronavirus disease (COVID) intensive care units)
and managing acute and chronic cancer pain.

Onco-anaesthesiologists have a well-coordinated
perioperative care plan with optimisation of
co-existing diseases, prehabilitation with cardiopulmonary exercise testing, using haematinics
for nutritional optimisation, employing evidence-based
and outcome-driven perioperative care pathways
[Figure 1]. They know the potential impact of the
anaesthetic technique on cancer biology and can deal
with postoperative complications with early rescue.[8,9]

Surgical handling of tissues leads to tumour microemboli
released into circulation and there is evidence that some

| Challenges                        | Reason                                      | Solution                                                   |
|-----------------------------------|---------------------------------------------|------------------------------------------------------------|
| Difficult Airway                  | Secondary to submucous fibrosis-related trismus. Redo head-neck surgery after flap reconstruction | Difficult airway armamentarium to include fiberoptic bronchoscope and C Mac D blade videolaryngoscope Cricothyrotomy/Tracheostomy skills |
| Difficult intravenous access      | Secondary to irritant IV chemotherapeutic agents and multiple surgeries | Peripherally inserted central catheter (PICC) line/Chemo port insertion prior to commencement of chemotherapy. Usual port precautions mandatory while handling |
| Increased requirement of analgesia| Many patients are receiving opioids like morphine to manage their pain leading to opioid receptor conformational changes. | Be aware of the potential problem and manage the analgesia accordingly |
| Nutritional deficiencies and anaemia| Cancer cachexia, dysphagia or poor absorption, chemotherapy drugs | Nutritional counselling, high protein nutrition in preoperative care |
| Immunosuppression and cancer progression| Anaesthetic technique | Regional anaesthesia is considered protective |
|                                    | Anaesthetic drug | Volatile anaesthetics and Morphine associated with cancer recurrence. Total intravenous anaesthesia and regional anaesthesia considered protective. |
|                                    | Surgery, blood transfusion | Blood transfusion based on transfusion trigger. Evidence of decreasing immunity |
| Hypothermia                        |                           | Active peri-operative warming |
| Interaction with chemotherapy drugs| Bleomycin                  | Low inspired oxygen concentration and Goal directed fluid therapy to prevent pulmonary complications |
|                                    | Adriamycin                | Echocardiography (Left Ventricular Ejection Fraction); Cardiac output monitoring |
|                                    | Transtuzumab              | Thyroid function tests to exclude hypothyroidism. LV failure can be precipitated. |
| Radiotherapy                       | Difficult airway          | Videolaryngoscope (Limited neck extension) |
| Depression                         | Cancer is like a death-knell to most patients | Reassurance that cancer is now curable Psychotherapy and counselling |
anaesthetic drugs too impair the immune-mediated inflammatory response. A number of publications point towards effect of the anaesthetic technique in the perioperative period on modulation of malignant cell behaviour and cancer recurrence [Table 1].

Rehabilitation after cancer surgery or therapy is an important aspect that should be discussed with the patient early. There is evidence to support early multidisciplinary rehabilitation of cancer patients improves functional outcomes. So, there is a need to develop the speciality of onco-anaesthesiology for improved care of cancer patients. Training prospects for onco-anaesthesiology are available across cancer centres around the world for many years and such centres are now also available in India [Table 2].

**Ethical issues**

For any major interventions on the patient, the rules of non-maleficence or abiding by the doctrine of primum non nocere (first do no harm), patient’s autonomy, and beneficence (always doing good) are important concepts. In patients undergoing oncological treatment, ethical issues may arise when patients are withdrawn from ongoing treatment due to personal reasons or non-responsive therapy. Also, many patients with advanced malignancy have a ‘do not attempt resuscitation’ order. This may pose an ethical challenge when they come for a palliative procedure.

**ECONOMIC IMPLICATIONS**

Cancer therapy entails tremendous physical, economical and emotional drain. Anaesthesiologist’s duty is to wisely rationalise scarce and expensive medical resources, and at the same time have a moral obligation to proffer drugs/procedures beneficial to patients, disregarding the cost-factor. Should each patient routinely receive the most expensive analgesic/block for postoperative pain relief? Choice of medications and interventions should not be dependent on the insurance policy, personal contacts within the hospital, economic issues or a desire to experiment with new regional blocks.

---

**Table 2: Opportunities for training in Onco-Anaesthesiology and Palliative Medicine**

| Onco-Anaesthesia | Fellowship course (duration in years) |
|------------------|--------------------------------------|
| DM course (duration in years) | Department of Onco-Anaesthesiology and Palliative Medicine, DRBR AIRCH, AIIMS (3 years) | AIIMS Rishikesh |
| | Department of Anaesthesiology, AIIMS Rishikesh (3 years) | Tata Memorial Centre (TMC) Mumbai (Oncoanesthesia & Pain: 2 yrs) |
| | The DM course is expected to be started in other AIIMS as well shortly | Tata Medical Centre (TMC) Kolkata |
| | | Rajiv Gandhi Cancer Institute and Research Centre (RGCI RC) Rohini, Delhi |
| | | Healthcare Global (HCG) Cancer Center Ahmedabad |
| | | Max Hospital Saket New Delhi |
| | | Indo American Cancer Centre Hyderabad |

| Palliative Medicine | Fellowship |
|---------------------|-----------|
| MD | AIIMS (Bhubaneswar) |
| TMH (Mumbai) | National Fellowship in Palliative Medicine at Calicut (one year) |
| AIIMS (New Delhi) | Post-doctoral fellowship in Pain and Palliative care (MNJ, Hyderabad) |
| GCRI (Ahmedabad) | |
PANDEMIC WOES

The COVID-19 pandemic has brought in a change in operating conditions and practice in every speciality across the board be it medical or non-medical. India had an ongoing lockdown for nearly 3 months from end March till 30th of June and guidelines were put in place, wherein elective surgeries were postponed.[13] Oncologists across the world have come up with guidelines on the management of cancer patients during this pandemic.[14-16] Oncological surgery are considered time-sensitive in nature and therefore semi-emergent surgeries continued during the pandemic.[16,17] Anaesthesiologists by the nature of their work have been at the forefront of airway management, oxygen therapy, ventilation support, haemodynamic management, sedation and analgesia during the pandemic. The onco-anaesthesiologist thus had to face the pandemic and various aerosol generating procedures associated with anaesthesia head-on not only in the intensive care but also for elective oncological surgeries too. This has also been made possible by the clear guidelines laid down to manage patients during the pandemic by the onco-anaesthesia society.[18]

For the first time in history, an anaesthesiologist was featured on the cover of TIME magazine. An achievement indeed, but this only comes with associated hardships. The anaesthesiologist had to delve into physics of air circulation in the operation theatre and try to ensure aerosol clearance between cases during the pandemic.

Cancer patients being more vulnerable to COVID-19, (by virtue of their older age group, immunosuppressed state) cancer hospitals have been converted to virtual fortresses by installing multi-level barriers.[19] Head and neck procedures were challenging. The standard precautions including the use of videolaryngoscopes, Personal Protective Equipment (PPE) and aerosol boxes for intubation have become standard practise as per guidelines.[20]

Perception and practice in the medical fraternity

The World Health Organisation (WHO) predicts 22 million new cancer diagnoses per year globally by 2030 and demand for anaesthesia is bound to increase spirally for diagnosis and treatment.[21] Many new cancer centres are being commissioned in major metros across India to face this requirement. It is increasingly recognised that onco-anaesthesiologists have the opportunity to positively influence oncological outcomes of patients with potential for disease modification.[22] Onco-anaesthesiologists can help cancer care by impeccable perioperative care to ensure patients return early to intended oncological treatment (RIOT)[23] and are at a point where they have the opportunity to minimise the biological perturbation of the surgical stress response and to tailor anaesthetic techniques to minimise activation of cancer progression pathways.[24]

A career in Palliative Medicine (PM)

PM is considered the fourth dimension of oncology after medical, surgical and radiation. Today, with the integration of PM from the time of diagnosis of cancer, there are many avenues for a PM physician to flourish.[22] World Health Organisation (WHO) has recognised palliative care as an integral part of the comprehensive services required for the non-communicable disease and approved the framework on integrated people-centred services at the 69th World Health Assembly in 2016.[23] There is a need for maturity and professionalism before taking up PM as a profession.

When PM started, anaesthesiologists were involved because many common aspects like coordination with several different medical specialities, pain, sedation, critical care, physical and social therapy, are in the domain of anaesthesiology.[24] The major limitation of anaesthesiology has been the absence of recognition among the patients and specialists.[25] The additional role of onco-anaesthesiologists as a palliative care physician helps them interact with the patient at various time points during oncology treatment and provides gratification as well.[25] It is obligatory for the physician to not only respect the medical, and legal but also the professional responsibilities. The service rather than profit orientation, collegial discipline and clemency for relieving the suffering is the priority.[26] This bolsters credence of PM amongst other professionals and laymen. The physicians here display this virtue more readily than their brethren because of the daily encounter with continued upheaval of suffering and mortality.[27]

National Medical Commission, the new ‘Avatar’ (form) of erstwhile Medical Council of India (MCI), emphasises on undergraduate (UG) and postgraduate (PG) curriculum in PM in India. Courses in PM are already available [Table 2] and are in pipeline in many other centres to meet the growing demand.
Research opportunity

Many retrospective studies and in vitro studies published in recent years have hypothesised the association between anaesthetic agents like propofol and sevoflurane on immunomodulation. Tumour necrosis factor-alpha is associated with the lidocaine-induced protection of cancer recurrence.[30] Propofol has an inhibitory effect on cancer progression through its association with matrix metalloproteases.[31]

However, most of the evidence on the effect of anaesthesia on cancer recurrence is limited to animal studies. Multiple RCTs (NCT00418457, NCT03034096, NCT02786329, NCT03109990, NCT03172988, NCT02840227) are in progress, being done on lung cancer, breast cancer and colorectal cancer surgeries comparing varying techniques of anaesthesia and disease-free survival and their results are expected in near future. Overall survival as well as recurrence free survival as reported by a retrospective study in hepatocellular cancer patients receiving inhalational anaesthesia versus TIVA is higher for the TIVA group (17.7% vs 12.6%; 15.4% vs 11.7%).[32] Improved recurrence-free survival has also been reported in the TIVA group vs inhalational anaesthesia group in another retrospective Korean study (Hazard Ratio 0.48).[33]

A retrospective Danish study on 8694 colorectal cancer patients published in 2020 reported a weak association between cancer recurrence and inhalation anaesthetic exposure (Hazard Ratio = 1.12).[34] Propofol/remifentanil based TIVA has been shown to inhibit vascular endothelial growth factor (VEGF-C) release after breast cancer surgery when compared with sevoflurane based inhalational anaesthesia in a recent prospective randomised trial. VEGF-C is known to promote tumour growth and metastasis. The 2-year recurrence free survival rates for breast cancer were 78% and 95% in the sevoflurane and TIVA groups, respectively.[35] Another multicentric prospective RCT published in Lancet in 2019 found no difference in mortality between propofol-paravertebral block and morphine sevoflurane groups in 2118 breast cancer patients.[36]

Prospective studies to find the association of anaesthesia with cancer recurrence is the need of the hour and would be an exciting area of study for budding researchers. Some other topics of research in the field of onco-anaesthesiology include the feasibility of opioid-free anaesthesia, techniques to modulate perioperative inflammatory markers, strategies to reduce the time to RIOT, optimum prehabilitation techniques, and integration of palliative care with oncology treatment. Chronic pain is a common problem in patients with malignancy and opioids are the mainstay of management. Opioids have their side-effects and development of targeted opioid drugs for Mu receptor heterodimers is an opportunity for research in times to come.[37]

Indian Council of Medical Research and Indian Cancer Research Consortium are providing increased funding opportunities in onco-anaesthesiology and PM. This would be an additional incentive for those with a keen research interest.

FUTURE PERSPECTIVE

As the incidence of cancer is rising so is the number of exclusive cancer hospitals and demand for trained onco-anaesthesiologists. National cancer institute has been developed at Jhajjar (Haryana) as a nodal institution to provide comprehensive cancer care and opportunities for translational research. Several corporate hospitals have dedicated oncology blocks with very lucrative remuneration packages. Seven comprehensive cancer centers are likely to be commissioned by August 2021 in Assam (4), Chandrapur (1), Tirupati (1) and Ranchi (1) by Tata Trust. (communications Professor KS Sharma, Tata Trust Cancer Care). PM too has made inroads in many corporate hospitals and with the increasing incidence of non-communicable diseases in our country, PM maybe the next sought-after speciality.

CONCLUSION

The perioperative care of oncology patients is complex. Tailoring the anaesthesia technique to individual patient is the need of the hour to reduce inflammatory-immune response, facilitate return to intended oncology therapy, enhance perioperative care and improve long-term outcomes in oncology. Hence, the time has come for a separate super-speciality of onco-anaesthesiology.
Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018. GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.

2. Ahmad A, Ormiston-Smith N, Sasieni P. Trends in the lifetime risk of developing cancer in Great Britain: Comparison of risk for those born from 1930 to 1960. Br J Cancer 2015;112:943-7.

3. Lifetime risk of cancer | Cancer Research UK. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/risk/lifetime-risk. [Last accessed on 2020 Dec 31].

4. Sullivan R, Aaltonen OL, Anderson BO, Audioso R, Antier F, Aggarwal A, et al. Global cancer surgery: Delivering safe, affordable, and timely cancer surgery. Lancet Oncol 2015;16:1193-224.

5. Wigmore T, Gottumukkala V, Riedel B. Making the case for the subspeciality of onco-anesthesia. Int Anaesthesiol Clin 2016;54:19-28.

6. Gupta N, Kumar V, Garg R, Bhatti SJ, Mishra S, Bhatnagar S. Anesthetic implications in hyperthermic intraperitoneal chemotherapy. J Anaesthesiol Clin Pharmacol 2019;35:3-11.

7. Gruen RL, Pitt V, Green S, Parkhill A, Campbell D, Jolley D. The effect of provider case volume on cancer mortality: Systematic review and meta-analysis. CA Cancer J Clin 2009;59:192-211.

8. Kim R. Anesthetic technique for cancer surgery: Harm or benefit for cancer recurrence? Eur J Surg Oncol 2018;44:557-8.

9. Cata JP, Guerra C, Soto G, Ramirez MF. Anesthesia options and the recurrence of cancer: What we know so far? Local Reg Anesth 2020;13:57-72.

10. Pu JB, Raj VS, Guo Y. A guide to inpatient cancer rehabilitation: Focusing on patient selection and evidence-based outcomes. PM R 2017;9 (8S2):S124-34.

11. Thota RS, Garg R, Ramkiran S, Divatia JV. Onco-anaesthesiology as an emerging sub-speciality domain: Need of the hour! Indian J Anaesth 2020;64:69-71.

12. Lyman GH. Economics of cancer care. J Oncol Pract 2007;3:113-4.

13. 2020. M govt. in. Guidelines on the Measures to Be Taken by Territory Government and State/Union Territory Authorities for Containment of COVID-19 Epidemic in the Country. Available from: https://www.mohfw.gov.in/pdf/Annexure_ for Containment of COVID-19 Epidemic in the Country.pdf. [Last accessed on 2020 Nov 12].

14. Curigliano G, Banerjee S, Cervantes A, Garassini MC, Carrido P, Girard N, et al. Managing cancer patients during the COVID-19 pandemic: An ESMO multidisciplinary expert consensus. Ann Oncol 2020;31:1320-35.

15. Hwang ES, Balch CM, Balch GC, Feldman SM, Golshan M, Grobmyer SR, et al. Surgical oncologists and the COVID-19 pandemic: Guiding cancer patients effectively through turbulence and change. Ann Surg Oncol 2020;27:2680-13.

16. Gupta A, Nath S, Trikha A. Anesthesia practice in Covid-19 era: Unprecedented problems call for extraordinary solutions. J Anaesthesiol Clin Pharmacol 2020;36(Suppl 1):575-7.

17. Meoletta L, Pierobon ES, Capovilla G, Costantini M, Salvador R, Merigliano S, et al. International guidelines and recommendations for surgery during Covid-19 pandemic: A systematic review. Int J Surg 2020;79:180-8.

18. Solanki S, Thota R, Garg R, Pingle AA, Goswami J, Ranganath N, et al. Society of onco-anesthesia and perioperative care (SOAPC) advisory regarding perioperative management of onco-surgeries during COVID-19 pandemic. Indian J Anaesth 2020;64:97-102.

19. Shah SB, Chawla R. Cancer in corona times. Saudi J Anaesth 2020;14:504-9.

20. Malhotra N, Bajwa SJS, Joshi M, Mehdiratta L, Trikha A. COVID operation theatre- advisory and position statement of Indian society of anaesthesiologists (ISA National). Indian J Anaesth 2020;64:355-62.

21. Aloia TA, Zimmitti G, Conrad C, Gottumukkala V, Kopetz S, Vauthney JN. Return to intended oncologic treatment (RIOT): A novel metric for evaluating the quality of oncological therapy for malignancy. J Surg Oncol 2014;110:107-14.

22. Aggarwal R, Epstein AS. The role of palliative care in oncology. Semin Intervent Radiol 2017;34:307-12.

23. Chestnun O, Kiemy MP. Planning and Implementing PC Services: A Guide for Programme Managers. Geneva: WHO; 2016. ISBN 978 92 4 156541 7.

24. Fine PG. The evolving and important role of anaesthesiology in palliative care. Anesth Analg 2005;100:183-8.

25. Kettler D, Nauck F. Palliative care and involvement of anaesthesiology: Current discussions. Curr Opin Anaesthesiol 2010;23:173-6.

26. Stuart C. Professionalism in the PM physician: How ought it best be cultivated? MedEdPublish 2018; 7:55. doi: 10.15694/ mep.2018.000123.1.

27. Graham J, Ramirez AJ, Cull A, Finlay I, Hoy A, Richards MA. Job stress and satisfaction among palliative physicians. Palliat Med 1996;10:185-94.

28. World health assembly. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R19-en.pdf. [Last accessed on 2020 Oct 31].

29. NHM, National Programme for Palliative care (NPPC); National Health Mission. Available from: https://nhm.gov.in/index1.php?lang=1&level=2&sublinkid=1047&lid=609. [Last accessed on 2020 Oct 31].

30. Piegerer T, Schlaper M, Dull RO, Schwartz DE, Boragoe A, Minshall RD, et al. Clinically relevant concentrations of lidocaine and ropivacaine inhibit TNF-α-induced invasion of lung adenocarcinoma cells in vitro by blocking the activation of Akt and focal adhesion kinase. Br J Anaesth 2015;115:784-91.

31. Ni Y, Lu J, Zhou HM. Propofol suppresses proliferation, migration and invasion of gastric cancer cells via regulating miR-29/MMP-2 axis. Eur Rev Med Pharmacol Sci 2019;23:8606-15.

32. Meng XY, Zhang XP, Sun Z, Wang HQ, Yu WF. Distant survival for patients undergoing surgery using volatile versus IV anesthesia for hepatocellular carcinoma with portal vein tumor thrombus: A retrospective study. BMC Anesthesiol 2020;20:233.

33. Lee JH, Kang SH, Kim Y, Kim HA, Kim BS. Effects of propofol-based total intravenous anesthesia on recurrence and overall survival in patients after modified radical mastectomy: A retrospective study. Korean J Anesthesiol 2016;69:120-32.

34. Hasselager RP, Hållas J, Gøgenur I. Inhalation or total intravenous anesthesia and recurrence after colorectal cancer surgery: A propensity score matched Danish registry-based study. Br J Anaesth 2020;S0007-0912 (20) 30940-5. doi: 10.1016/j.bja.2020.11.019.

35. Yan T, Zhang GH, Wang BN, Sun L, Zheng H. Effects of propofol/remifentanil-based total intravenous anesthesia versus sevoflurane-based inhalation anesthesia on the release of VEGF-C and TGF-β and prognosis after breast cancer surgery: A prospective, randomized and controlled study. BMC Anesthesiol 2018;18:131.

36. Sesslner DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, et al.; Breast Cancer Recurrence Collaboration. Recurrence of breast cancer after regional or general anaesthesia: A randomised controlled trial. Lancet 2019;394:1807-15.

37. Zhang L, Zhang JT, Hang L, Liu T. Mu opioid receptor heterodimers emerge as novel therapeutic targets: Recent progress and future perspective. Front Pharmacol 2020;11:1078.