MALAYSIAN SOCIETY OF ANAESTHESIOLOGISTS YEARBOOK 2023/2024

KESELAMATAN DALAM BIUS

MALAYSIAN SOCIETY OF ANAESTHESIOLOGISTS

Yearbook 2023/2024

Cancer and Anaesthesia

ISSN 2462-1307
9 772462 130007

MALAYSIAN SOCIETY OF ANAESTHESIOLOGISTS

Yearbook 2023/2024

Published by
Malaysian Society of Anaesthesiologists
Unit 3.3, Level 3
Medical Academies Malaysia Building
No. 5, Jalan Kepimpinan P8H
Presint 8, 62250 Putrajaya, Malaysia
Tel: (603) 8996 0700
Email : secretariat@msa.net.my

Pusat Kebangsaan ISBN/ISSN Malaysia
ISSN 2462-1307

CONTENTS

Foreword

Cancer remains a leading cause of death worldwide, with 8.8 million deaths reported by the WHO in 2018. Anaesthesia plays a crucial role in cancer care, with 80% of patients requiring it for treatment or palliation. In adults, it is essential for surgeries on common cancers like breast, bowel, and prostate, while in children, anaesthesia supports diagnostic and therapeutic procedures such as CT scans, radiotherapy, and surgeries. Anaesthesiologists also manage cancer pain and provide palliative care, alleviating both physical and emotional suffering.

In 2023, the World Federation of Societies of Anaesthesiologists (WFSA) chose Anaesthesia and Cancer Care as its inaugural Annual Theme, underscoring the vital role anaesthesia plays in cancer management. This theme is especially relevant post-COVID-19, as the pandemic strained healthcare systems and delayed cancer care, emphasizing the need to refocus on timely treatment.

The Malaysian Society of Anaesthesiologists (MSA) dedicated its 2023/24 Year Book to "Cancer & Anaesthesia," aiming to raise awareness of anaesthesia's impact on cancer patient outcomes and advocate for stronger anaesthesia services in cancer care. Advancements such as regional anaesthesia, understanding anaesthetic drug effects on cancer progression, and improved blood transfusion practices highlight the evolving relationship between anaesthesia and oncology. With cancer treatments becoming more complex, ensuring that anaesthesiologists are equipped with the latest knowledge and skills is crucial, especially in sensitive cases like paediatric cancers and specialized surgeries. This initiative can greatly contribute to improving patient outcomes and experiences.

MSA hopes the 2023/24 Year Book will serve as a valuable resource for anaesthesiology and critical care specialists involve in the care of cancer patients. The Society extends its sincere gratitude to the authors, led by editors Dr Adlin Dasima Abdul Kadir and Dr Mardhiah Sarah Harnani Mansor of Universiti Teknologi MARA, for their dedication in producing an excellent yearbook.

Dato' Dr Yong Chow Yen
President
Malaysian Society of Anaesthesiologists

Preface

It is part of the year again for Malaysian Society of Anaesthesiologists (MSA) to come up with its MSA Year Book. We would like to express our utmost gratitude to the MSA for entrusting us as first timer in editing this most awaited and invaluable publication of the society for the Year of 2023/2024. We would like to thank all the authors for their effort in producing such exciting and beneficial articles. Not to forget to all the reviewers as well for spending their time giving their insightful reviews and constructive comments for the articles.

We were given the task to handle the book with the theme of 'Cancer and Anaesthesia'. At first it was quite challenging and we were a bit stunt and so called quite clueless with the theme as it was not something which was popular to be discussed in the past and yet despite increasing number of cancer patients requiring anaesthesia for certain surgeries or to help in alleviating chronic cancer pain, anaesthesia for cancer patients is not openly discussed and the relation between anaesthesia and cancer are always not fully understood. Besides that, it is quite difficult to look for any established guidelines as references for us when it comes to cancer patients.

After trying to sort out the major subheadings of this theme, we at last managed to arrange it to eight chapters in total starting with general perspective of anaesthesia and cancer, followed by shared experiences by our colleagues in cancer centre. We subsequently brought the readers to go through the perioperative anaesthetic concerns for cancer patients with cardiac diseases for non-cardiac surgery. Approaches of anaesthesia for children with cancer followed through and subsequently we moved on in trying to explore patient blood management for cancer surgery. Moving on from perioperative setting, we sailed through on regional anaesthesia for palliative surgery and also nerve blockades as the treatment options for painful bone metastases. Not to forget, our final chapter covered the big topic of critical care in oncology.

Once again thank you so much for this great opportunity and enjoy reading!

Dr Adlin Dasima Abdul Kadir
Dr Mardhiah Sarah Harnani Mansor
Editors
MSA Yearbook 2023/2024

Acknowledgements - Reviewers

This Yearbook would not have been possible without the contributions from the following reviewers:

Dr Nik Rowina Nik Mohammed
Lecturer & Anaesthesiologist,
Department of Anaesthesiology & Intensive Care
Faculty of Medicine & Health Sciences
Universiti Putra Malaysia
Selangor
Malaysia

Dr Collins Chong Chi Hun
Lecturer & Anaesthesiologist,
Department of Anaesthesiology & Intensive Care
Faculty of Medicine & Health Sciences
Universiti Putra Malaysia
Selangor
Malaysia

Dr Isqandar Adnan
Senior Lecturer and Consultant Anaesthesiologist
Department of Anaesthesiology & Intensive Care
Faculty of Medicine
Universiti Teknologi MARA
Selangor
Malaysia

Dr Ivy Sim Chui Geok
Lecturer and Anaesthesiologist,
Department of Anaesthesiology & Intensive Care,
Faculty of Medicine,
Universiti Teknologi MARA
Selangor
Malaysia

Cancer in Anaesthesia Perspective

Abdul Majid Ghazali, Khairul Anam Mansor
Department of Anaesthesiology and Critical Care, Kulliyyah of Medicine, International Islamic University Malaysia, Pahang, Malaysia

Cancer represents a significant global health burden. In 2020, an estimated 19.3 million new cancer cases were reported worldwide, accompanied by nearly 10 million cancer-related deaths. Projections indicate that the incidence of cancer could rise to 28.4 million cases by 2040.[1] Surgical resection is widely regarded as the primary treatment modality for solid malignant tumours. However, post-surgical cancer recurrence and metastasis remain the leading causes of cancer related mortality.[2] Emerging evidence suggests that anaesthetic agents used during surgical ptrocedures may disrupt the delicate balance between tumour aggressiveness and the body's immune surveillance, thereby contributing to cancer recurrence and metastasis. Consequently, it is imperative to identify the optimal anaesthetic agents for patients undergoing oncologic surgery.[3]

Although surgery is typically performed with the intention of curing cancer, tumour resection can paradoxically increase the risk of metastasis. Tumour cells may enter the bloodstream perioperatively, leading to dissemination and subsequent metastasis in distant organs. Despite achieving clear surgical margins, minimal residual disease can persist and proliferate. Additionally, localized spread can occur within body cavities, and tumour emboli can disseminate through the lymphatic system.[4]

Metastasis occurs when cancer cells evade immune surveillance, proliferate, and invade distant tissues. The perioperative period creates a physiological environment that favours tumour growth, with both direct and indirect effects on tumour cell survival. Several factors during surgery contribute to a state of relative immunosuppression, including the stress response to surgery, the inflammatory response, and the pharmacological effects of anaesthetics, opioids, and other perioperative medications. Additionally, hypothermia and blood transfusions can impair immune function, further facilitating tumour cell survival and dissemination.[5]

- Physiological Stress Response: The stress response to surgery induces immunosuppression through the release of mediators such as catecholamines, prostaglandins, and growth factors. These mediators can activate pathways that enhance the metastatic potential of cancer cells, particularly involving β2-adrenergic receptors and cyclooxygenase-2 (COX-2) enzymes.[6]

- Inflammatory Response: Tissue trauma during surgery releases cytokines, including interleukin-6 (IL-6) and prostaglandin E2 (PGE2), which can suppress the activity of natural killer (NK) cells. NK cells are essential during the perioperative period for identifying and eliminating circulating tumour cells.[7]

Addressing tissue hypoxia is crucial for the growth of solid tumours, and cancer cells have developed several adaptive pathways to survive under hypoxic conditions. Hypoxia upregulates the expression of hypoxia-inducible factor 1-alpha (HIF1A), a key regulator that promotes angiogenesis, cell proliferation, and metastasis. HIF1A stimulates the expression of vascular endothelial growth factor (VEGF), which in turn promotes angiogenesis, tumour growth, and the remodelling of lymphatic pathways, thereby facilitating metastasis. Elevated levels of HIF1A are associated with poorer outcomes in various solid tumours.[8]

ANALGESICS

Animal studies have demonstrated that morphine significantly facilitates established tumor progression. This is achieved through several mechanisms, including enhancing tumor angiogenesis, activating mast cells, promoting peri-tumoral lymphomagenesis, and increasing levels of cytokines and substance P.[9] These effects are likely mediated by the μ-opioid receptor. Additionally, several studies have shown that morphine can decrease the levels of natural killer (NK) cells in the bloodstream[10] and inhibit their ability to destroy target cells in vitro.[11] However, the specific impact of morphine alone is challenging to determine due to the concurrent administration of other medications, such as propofol, in clinical settings.

Studies examining the impact of opioids administered during or after surgery on cancer recurrence have yielded inconsistent findings. Historically, experimental and observational research suggested that opioid use during cancer resection surgery was associated with unfavorable oncologic outcomes. For instance, studies have shown that the administration of methylnaltrexone, a μ-opioid receptor (MOR) antagonist, enhances patient survival.[12] However, a systematic review in the clinical setting of breast cancer found no clear beneficial impact of opioid avoidance.[13] This review indicated that protumor receptors were either not expressed or suppressed, while antitumor receptors were upregulated. Similarly, studies on patients with colorectal cancer[14] and non-small cell lung cancer[15] found no evidence linking opioid use to a higher likelihood of recurrence. Currently, there is no valid reason to alter the prescription of opioids during the perioperative period with the intention of impacting cancer recurrence.

The potential benefit of NSAIDs arises from their ability to inhibit cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2), thereby reducing the production of prostaglandins such as PGE2. PGE2 significantly influences angiogenesis in cancer and the inhibition of apoptosis.[16] Multiple retrospective studies suggest that the use of NSAIDs, such as ketorolac, during cancer surgery may reduce the likelihood of cancer recurrence and improve overall survival.[17,18] Additionally, prolonged use of aspirin and other NSAIDs is associated with decreased mortality from colorectal and potentially other types of cancer.[19] However, there is currently no evidence from large randomized controlled trials to support the use of celecoxib in reducing cancer recurrence.[20]

LOCAL ANAESTHETICS

Laboratory experiments have shown that intravenous lignocaine may have beneficial effects in preventing cancer recurrence by decreasing levels of inflammatory markers such as IL-1, TNF-alpha, and IL-8.[21] However, clinical data supporting this claim is limited. In a mouse model of breast cancer, lignocaine administration resulted in decreased viability and motility of cancer cells, as well as improved survival.[22] Several retrospective clinical studies have reported favorable outcomes with intravenous lignocaine administration.[23,24] Nonetheless, the conclusions from these studies are constrained by their retrospective design and the presence of various surgical variables. Additionally, administering lignocaine directly into the peritumor site has shown potential advantages in improving survival.[25]

A randomized controlled trial (RCT) conducted in breast cancer patients compared the use of paravertebral block and propofol against sevoflurane and opioid. The study did not observe any decrease in breast cancer recurrence or improvement in survival rates.[26] Currently, there is a lack of compelling data from human studies suggesting that local anesthesia impacts cancer surgery outcomes in terms of cancer development.

OTHER DRUGS

The available evidence on cancer recurrence is both scarce and contradictory. Breast cancer patients exhibit elevated expressions of alpha-adrenoreceptors,[27] suggesting that manipulating these receptors may impact cancer recurrence. Retrospective research on lung cancer patients who received intraoperative dexmedetomidine demonstrated an enhanced survival rate with a similar recurrence rate.[28] However, another study found that intraoperative clonidine resulted in an equal survival rate.[29]

Laboratory studies have shown that the combination of beta blockers with NSAIDs can help maintain the activity of natural killer (NK) cells.[30] However, clinical research has yielded inconclusive results regarding cancer recurrence. One meta-analysis revealed no significant alterations in the rate of recurrence,[31] while another meta-analysis, which included smaller studies conducted on breast cancer patients, reported a decreased risk of mortality.[32]

Glucocorticoids possess both anti-inflammatory and immune-modulating properties, which can potentially decrease the efficacy of cancer cell killing. Dexamethasone is commonly administered to patients undergoing anaesthesia and chemotherapy as an antiemetic and adjuvant analgesic. Various clinical investigations have yielded contradictory findings, ranging from no significant difference[33] in outcomes to extended post-surgery survival.[34] Currently, there is insufficient evidence to warrant altering existing clinical practices.

Both hypoxia and hyperoxia have been implicated in the mechanisms of angiogenesis during tumour growth. The PROXI trial involved 1,386 patients who underwent elective or emergency laparotomy. These patients were randomly assigned to receive either 80% or 30% oxygen during surgery and for 2 hours postoperatively. Although no significant difference in the rate of cancer recurrence was observed, the group exposed to 80% oxygen had a shorter duration of cancer-free survival.[35]

SUMMARY

The available evidence is inadequate to support any alteration in current anaesthesia practices for cancer surgery. This includes both the avoidance of specific agents and the recommendation of certain agents to reduce the risk of cancer recurrence. The primary constraint lies in the inability to assess the specific impact of individual pharmaceuticals in clinical trials, as patients typically receive a mixture of drugs from several categories. Although laboratory research has shown promise, clinical investigations have not yielded consistent results due to their greater complexity and heterogeneity. Further clinical trials are required to investigate the potential direct effects of anaesthetics, opioids, steroids, and other substances, while considering existing limitations. It is also crucial to understand that surgical techniques could impact the likelihood of cancer recurrence. Additional non-pharmacological factors, such as hypothermia, blood transfusion, hyperglycaemia, stress, and pain control, can impact the recurrence rate by inducing a state of relative immunosuppression.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians.* 2021 May;**71**(3):209-49

2. Murphy O, Forget P, Ma D, Buggy DJ. Tumour excisional surgery, anaesthetic-analgesic techniques, and oncologic outcomes: a narrative review. British journal of anaesthesia. 2023 Sep 9

3. Wall T, Sherwin A, Ma D, Buggy DJ. Influence of perioperative anaesthetic and analgesic interventions on oncological outcomes: a narrative review. *British journal of anaesthesia.* 2019 Aug 1;**123**(2):135-50

4. Engilbertsson H, Aaltonen KE, Björnsson S, Kristmundsson T, Patschan O, Rydén L, Gudjonsson S. Transurethral bladder tumor resection can cause seeding of cancer cells into the bloodstream. *The Journal of urology.* 2015 Jan 1;**193**(1):53-7

5. Wall T, Sherwin A, Ma D, Buggy DJ. Influence of perioperative anaesthetic and analgesic interventions on oncological outcomes: a narrative review. *British journal of anaesthesia.* 2019 Aug 1;**123**(2):135-50

6. Murphy O, Forget P, Ma D, Buggy DJ. Tumour excisional surgery, anaesthetic-analgesic techniques, and oncologic outcomes: a narrative review. British journal of anaesthesia. 2023 Sep 9

7. Alazawi W, Pirmadjid N, Lahiri R, Bhattacharya S. Inflammatory and immune responses to surgery and their clinical impact. *Annals of surgery.* 2016 Jul 1;**264**(1):73-80

8. Pérez-Sayáns M, Somoza-Martín JM, Barros-Angueira F, Diz PG, JM GR, García-García A. Beta-adrenergic receptors in cancer: therapeutic implications. *Oncology research.* 2010 Jan 1;**19**(1):45-54

9. Nguyen J, Luk K, Vang D, Soto W, Vincent L, Robiner S, Saavedra R, Li Y, Gupta P, Gupta K. Morphine stimulates cancer progression and mast cell activation and impairs survival in transgenic mice with breast cancer. *British journal of anaesthesia.* 2014 Jul 1;**113**(suppl_1):i4-13

10. Cui JH, Jiang WW, Liao YJ, Wang QH, Xu M, Li Y. Effects of oxycodone on immune function in patients undergoing radical resection of rectal cancer under general anesthesia. *Medicine.* 2017 Aug 1;**96**(31):e7519

11. Boland JW, Pockley AG. Influence of opioids on immune function in patients with cancer pain: from bench to bedside. *British journal of pharmacology.* 2018 Jul;**175**(14):2726-36

12. Janku F, Johnson LK, Karp DD, Atkins JT, Singleton PA, Moss J. Treatment with methylnaltrexone is associated with increased survival in patients with advanced cancer. *Annals of Oncology.* 2016 Nov 1;**27**(11):2032-8

13. Lucia M, Luca T, Federica DP, Cecilia G, Chiara M, Laura DM, Carlo DR, Grazia PM. Opioids and breast cancer recurrence: a systematic review. *Cancers.* 2021 Nov 1;**13**(21):5499

14. Diaz-Cambronero O, Mazzinari G, Cata JP. Perioperative opioids and colorectal cancer recurrence: a systematic review of the literature. *Pain management.* 2018 Sep 1;**8**(5):353-61

15. Oh TK, Jeon JH, Lee JM, Kim MS, Kim JH, Cho H, Kim SE, Eom W. Investigation of opioid use and long-term oncologic outcomes for non-small cell lung cancer patients treated with surgery. *PLoS One.* 2017 Jul 21;**12**(7):e0181672

16. Brogi E, Forfori F. Anesthesia and cancer recurrence: An overview. *Journal of Anesthesia, Analgesia and Critical Care.* 2022 Jul 20;**2**(1):33

17. Luyckx M, Verougstraete C, Jouret M, Sawadogo K, Waterkeyn M, Grandjean F, Van Gossum JP, Dubois N, Malvaux V, Verreth L, Grandjean P. Intraoperative Ketorolac and Outcomes after Ovarian Cancer Surgery. *Journal of Clinical Medicine.* 2024 Mar 7;**13**(6):1546

18. Forget P, Vandenhende J, Berliere M, Machiels JP, Nussbaum B, Legrand C, De Kock M. Do intraoperative analgesics influence breast cancer recurrence after mastectomy? A retrospective analysis. *Anesthesia & Analgesia.* 2010 Jun 1;**110**(6):1630-5

19. Chan AT, Arber N, Burn J, Chia WK, Elwood P, Hull MA, Logan RF, Rothwell PM, Schrör K, Baron JA. Aspirin in the chemoprevention of colorectal neoplasia: an overview. *Cancer prevention research.* 2012 Feb 1;**5**(2):164-78

20. Coombes RC, Tovey H, Kilburn L, Mansi J, Palmieri C, Bartlett J, Hicks J, Makris A, Evans A, Loibl S, Denkert C. Effect of celecoxib vs placebo as adjuvant therapy on disease-free survival among patients with breast cancer: the REACT randomized clinical trial. *JAMA oncology.* 2021 Sep 1;**7**(9):1291-301

21. Chamaraux-Tran TN, Mathelin C, Aprahamian M, Joshi GP, Tomasetto C, Diemunsch P, Akladios C. Antitumor effects of lidocaine on human breast cancer cells: an in vitro and in vivo experimental trial. *Anticancer research.* 2018 Jan 1;**38**(1):95-105

22. Johnson MZ, Crowley PD, Foley AG, Xue C, Connolly C, Gallagher HC, Buggy DJ. Effect of perioperative lidocaine on metastasis after sevoflurane or ketamine-xylazine anaesthesia for breast tumour resection in a murine model. *British Journal of Anaesthesia.* 2018 Jul 1;**121**(1):76-85

23. Cazenave L, Faucher M, Tourret M, Marques M, Tezier M, Mokart D. Intravenous lidocaine and cancer outcomes after radical cystectomy. *European Journal of Anaesthesiology / EJA.* 2022 Apr 1;**39**(4):396-9

24. Zhang H, Yang L, Zhu X, Zhu M, Sun Z, Cata JP, Chen W, Miao C. Association between intraoperative intravenous lidocaine infusion and survival in patients undergoing pancreatectomy for pancreatic cancer: a retrospective study. *British journal of anaesthesia.* 2020 Aug 1;**125**(2):141-8

25. Badwe RA, Parmar V, Nair N, Joshi S, Hawaldar R, Pawar S, Kadayaprath G, Borthakur BB, Rao Thammineedi S, Pandya S, Balasubramanian S. Effect of peritumoral infiltration of local anesthetic before surgery on survival in early breast cancer. *Journal of Clinical Oncology.* 2023 Jun 20;**41**(18):3318-28

26. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, Mayers DB, Meyer-Treschan TA, Grady M, Tan EY, Ayad S. Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial. *The lancet.* 2019 Nov 16;**394**(10211):1807-15

27. Powe DG, Voss MJ, Habashy HO, Zänker KS, Green AR, Ellis IO, Entschladen F. Alpha-and beta-adrenergic receptor (AR) protein expression is associated with poor clinical outcome in breast cancer: an immunohistochemical study. *Breast cancer research and treatment.* 2011 Nov 1;**30**:457-63

28. Cata JP, Singh V, Lee BM, Villarreal J, Mehran JR, Yu J, Gottumukkala V, Lavon H, Ben-Eliyahu S. Intraoperative use of dexmedetomidine is associated with decreased overall survival after lung cancer surgery. *Journal of Anaesthesiology Clinical Pharmacology.* 2017 Jul 1;**33**(3):317-23

29. Forget P, Berlière M, Poncelet A, De Kock M. Effect of clonidine on oncological outcomes after breast and lung cancer surgery. *British Journal of Anaesthesia.* 2018 Jul 1;**121**(1):103-4

30. Glasner A, Avraham R, Rosenne E, Benish M, Zmora O, Shemer S, Meiboom H, Ben-Eliyahu S. Improving survival rates in two models of spontaneous postoperative metastasis in mice by combined administration of a β-adrenergic antagonist and a cyclooxygenase-2 inhibitor. *The Journal of Immunology.* 2010 Mar 1;**184**(5):2449-57

31. Yap A, Lopez-Olivo MA, Dubowitz J, Pratt G, Hiller J, Gottumukkala V, Sloan E, Riedel B, Schier R. Effect of beta-blockers on cancer recurrence and survival: a meta-analysis of epidemiological and perioperative studies. *British journal of anaesthesia.* 2018 Jul 1;**121**(1):45-57

32. Childers WK, Hollenbeak CS, Cheriyath P. β-blockers reduce breast cancer recurrence and breast cancer death: a meta-analysis. *Clinical breast cancer.* 2015 Dec 1;**15**(6):426-31

33. Merk BA, Havrilesky LJ, Ehrisman JA, Broadwater G, Habib AS. Impact of postoperative nausea and vomiting prophylaxis with dexamethasone on the risk of recurrence of endometrial cancer. *Current medical research and opinion.* 2016 Mar 3;**32**(3):453-8

34. Huang WW, Zhu WZ, Mu DL, Ji XQ, Nie XL, Li XY, Wang DX, Ma D. Perioperative management may improve long-term survival in patients after lung cancer surgery: a retrospective cohort study. *Anesthesia & Analgesia.* 2018 May 1;**126**(5):1666-74

35. Meyhoff CS, Jorgensen LN, Wetterslev J, Siersma VD, Rasmussen LS, PROXI Trial Group. Risk of new or recurrent cancer after a high perioperative inspiratory oxygen fraction during abdominal surgery. *British Journal of Anaesthesia.* 2014 Jul 1;**113**(suppl_1):I 74-81

A Day in Institut Kanser Negara

Nor Syafiza Mohamad Shariff, Nor Azlin Dahalan, Nabila Azizan
Department of Anaesthesia and Intensive Care, Institut Kanser Negara, Putrajaya, Malaysia

It was a typical weekday morning with heavy traffic as usual. Everyone was rushing to their destinations: work, school, hospital follow-ups, etc. As I turned my car onto Jalan P7D, the modern and aesthetically pleasing building of Institut Kanser Negara (IKN) came into view. Operating since 2014, this institute is the first in Malaysia dedicated to the management of adult cancer patients. Over the years, its services have expanded significantly.

The usual crowd of staff, patients, and relatives hurriedly crossed the road from the public car park to the main building. I observed a buggy car operated by an NGO, assisting patients and relatives in need from the parking lot to the main building. A shuttle had just stopped at the main lobby, transporting patients and staff from Putrajaya Sentral to IKN or to the adjacent Putrajaya Hospital. I parked my car in the staff parking area and proceeded to the general operating theatre on level 5.

Two elective operating theatres (OT) were scheduled for the day. In OT 1, my assigned theatre, the Upper Gastrointestinal Surgical team had listed a major case. In OT 2, the Gynaecology Oncology team had listed four cases: the first was a hysteroscopy for post-menopausal bleeding, the second was a large loop excision of the transformation zone for cervical intraepithelial neoplasia, the third was a diagnostic laparoscopy, staging, and biopsy for an ovarian tumour, and the fourth was a radical hysterectomy for endometrial carcinoma.

Two medical officers were assigned to OT 1 with me today. They had prepared all necessary medications and checked all required equipment for the operation. The medical assistant on duty, along with the anaesthetic nurse, was busy preparing essential instruments to ensure the procedure ran smoothly.

The routine check as per the Safe Surgery Save Life (SSSL) protocol was conducted at the airlock when the patient arrived at the OT. Vital signs were checked, and the patient was then wheeled into the operating theatre. Mr NNR, a 53-year-old gentleman, was diagnosed 5 months ago with Siewert II GOJ (gastroesophageal junction) adenocarcinoma of the oesophagus. He was scheduled to undergo a right thoracotomy, subtotal oesophagectomy with gastric pull-up.

Mr NNR was reviewed in the anaesthetic clinic 2 weeks prior to the operation. He had underlying hypertension, managed with regular medication and follow-up. His blood pressure was well controlled before the operation. He ceased smoking after his cancer diagnosis, having been an active smoker for over 30 years. He initially experienced progressive dysphagia for about 6 months before seeking medical advice. A comprehensive history, physical examination, and necessary routine and specific investigations were conducted to determine the correct diagnosis and plan appropriate management. He underwent neoadjuvant chemotherapy due to the advanced stage of his disease. Post-chemotherapy, a CT scan evaluation showed positive responses. He was subsequently scheduled for surgery with curative intent.

From an anaesthetic perspective, this major operation involves significant lung and heart functions. A thorough history and physical examination were conducted. Considering the nature of the operation, additional investigations, including routine blood tests, chest x-ray, electrocardiography, echocardiogram, and lung function test, were performed. A baseline arterial blood gas was obtained. All investigations were within acceptable ranges, and his airway assessment was unremarkable.

The patient had lost approximately 35% of his body weight since the initial presentation of symptoms, resulting in a body mass index of only 17kg/m . His functional status remained acceptable, classified as NYHA 2 and METs >4. The surgical team initiated a prehabilitation program to optimize his condition and promote a better surgical outcome. The Enhanced Recovery After Surgery (ERAS) protocol was implemented, requiring him to follow specific regimes. He attended gym sessions specialized by physiotherapists under ERAS, learning breathing exercises and proper incentive spirometry techniques. All progress was recorded in the ERAS form to monitor his improvement. His nutritional status was optimized according to the protocol.

On the day of the operation, necessary monitoring was applied as the patient entered the operating theatre. One medical officer scrubbed in for the insertion of the thoracic epidural catheter. The patient was positioned sitting, the area cleaned and draped. Sign-in as per the SSSL protocol was completed. The intervertebral space was identified, targeting the T7-T8 level. The procedure was smooth, with the medical officer successfully identifying the space on the first attempt. A 4cm catheter was inserted into the epidural space, a test dose was administered, and the catheter was anchored. The patient was then positioned supine for induction. A warming blanket was applied due to the cold temperature in the IKN OT. Rapid sequence induction with cricoid pressure was performed due to the high risk of aspiration in such patients. Forty seconds after the injection of Suxamethonium, tracheal intubation was attempted using a C-MAC video laryngoscope. An endotracheal tube (ETT) size 8.0mm was used, anchored at 21cm after confirmation by auscultation.

Another medical officer scrubbed in for central venous line insertion. Given the surgical plan for a right thoracotomy, the line was inserted into the right internal jugular vein. While waiting, I inserted a large-bore cannula and arterial line in the left upper limb. The arterial line was connected to the FloTrac system from Edwards Lifescience, a minimally invasive system providing reliable haemodynamic monitoring. As an anaesthetist, balanced fluid administration is crucial for a positive outcome. Adequate fluid is necessary to maintain optimal perfusion while avoiding excessive fluid that could cause mucosal oedema and compromise surgical anastomosis.

Central venous cannulation was performed under aseptic technique with ultrasonographic guidance to minimize the risk of arterial puncture and other injuries. The surgical medical officer then inserted a continuous bladder drainage catheter for hourly urine output monitoring intraoperatively. The OT assistant (Pembantu Perawatan Kesihatan) applied bilateral pneumatic cuff compression to minimize the risk of deep vein thrombosis. All personnel involved in the case assisted in positioning the patient in the left lateral position, optimizing the surgical field and minimizing position-related complications.

The next step involved inserting an endobronchial blocker to occlude the right lung for one-lung ventilation during the thoracotomy. The anaesthetic medical assistant prepared the flexible fibreoptic endoscope and a new endobronchial blocker size 9Fr. The procedure was conducted under aseptic technique and was uneventful.

"Time out" was called at 9:30 am, and surgery commenced. The patient's status was monitored using standard monitoring, FloTrac, and arterial blood gas analysis. After ensuring the patient was stable and the right lung had collapsed properly, I took a short coffee break. A colleague who was on call the previous night brought some nasi lemak for us in the OT. While enjoying our breakfast, she shared details about a case referred to her last night.

The patient was a 65-year-old gentleman diagnosed with locally advanced nasopharyngeal carcinoma, currently undergoing concurrent chemoradiotherapy under the Oncology team. He was initially counselled for a tracheostomy prior to commencing treatment but declined. As the treatment progressed, local oedema became increasingly prominent, resulting in acute upper airway obstruction. An immediate referral to the anaesthesia and ENT (Ear, Nose & Throat) teams from Hospital Putrajaya was made. Both teams responded promptly. For both teams, the medical officers are in-house on-call, while specialists are passive on-call. An immediate decision was made for an emergency tracheostomy, and the patient and his family consented this time. The on-call OT staff were alerted and arrived as soon as possible, as IKN OT operates during office hours.

After assessing the patient's condition and a quick review of the latest CT scan, the plan was for awake C-Mac intubation by the anaesthesia team, with a fallback to tracheostomy under local anaesthesia if unsuccessful. Upon arrival in the OT, all monitoring devices were attached to the patient, and various sizes of ETT and micro laryngoscopy tubes (MLT) were prepared. The patient was asked to gargle 20ml of 1% Lignocaine in batches of 4ml. IV Glycopyrrolate was administered. He was then positioned supine to the best extent he could tolerate. The team proceeded with preoxygenation. Target controlled infusion (TCI) Remifentanil was started and titrated to effect, aiming for the patient to feel calm and comfortable enough to tolerate laryngoscopy while maintaining his airway.

The TCI Remifentanil was gradually increased to 1, then 2, then 3 ng/ml while continuously monitoring the patient's response. When the TCI Remifentanil dose reached 5 ng/ml, the team deemed the patient ready for the manoeuvre. Awake laryngoscopy using a D-blade C-Mac was attempted, achieving a POGO (percentage of glottic opening) score of 80%. The team successfully secured the airway with an MLT size 6.0mm. The ENT team then proceeded with the tracheostomy. Post-procedure, the residual muscle relaxant was reversed with Sugammadex, and the patient was awakened. The patient tolerated well oxygen via the tracheostomy mask and was transferred to the primary ward for acute care. All these nerve-wrecking events occurred at 2 in the morning.

I then returned to my OT. So far, everything was proceeding according to plan. Pain control was adequate with boluses of an epidural cocktail solution of Ropivacaine and fentanyl. The adjacent OT had already started their third case. The brachytherapy OT on level 1 was performing the last case for the insertion of a brachytherapy applicator under spinal anaesthesia. They had listed five cases for the day. The OT would then be used by the surgical team for chemo port insertion under local anaesthesia; three cases were listed. Our remote team had already started the cryoablation of lung metastasis under general anaesthesia at 10 am in the radiology suite.

There were two cases in the ICU this morning. A 52-year-old lady underwent debulking of a tumour and ileal conduit for recurrent ovarian high-grade serous carcinoma yesterday. The Urology team from Serdang Hospital was also involved in this case. Postoperatively, she was sent to the ICU for stabilization and weaning, having lost almost 5 litres of blood during the operation, requiring transfusion of packed cells and a cycle of DIVC. She was extubated this morning and, if stable, could be transferred out later in the evening. She was started on Patient Controlled Analgesia (PCA) Morphine for pain relief under the Acute Pain Service (APS). The other patient was a 76-year-old gentleman post-oesophagectomy 2 weeks ago, referred to us after six days in the ward with surgical-related complications. He was stable but we were having difficulty weaning him off the ventilator. He was planned for a tracheostomy in a day or two.

My phone beeped, signalling a new message. The on-call anaesthetist had updated something in the WhatsApp group. We use this medium as one of the ways to share relevant information or discuss cases among us. All five of us are usually stationed in different places, so this is a practical way of communicating. I read the message. She sent a summary of a case referred to the ICU team: a 40-year-old lady with advanced-stage breast cancer, currently undergoing palliative chemotherapy. She experienced worsening dyspnoea since last night and was unable to maintain saturation despite increasing oxygen requirements. We discussed the case; everyone provided opinions and suggestions for the best course of action. We concluded to put this patient on HFNC in the ward to reduce her work of breathing and make her more comfortable. A suggestion for a palliative referral was made to optimize pain control and prepare the patient and family for end-of-life care.

The thoracotomy was completed at 12:45 pm. We then expanded the lung and, with the help of everyone in the OT, positioned the patient for the next surgical stage. Surgery resumed. I went to the adjacent OT to assist the team with inducing the fourth case. They were having difficulty establishing intravenous access. Finally, we managed to secure adequate intravenous access after almost an hour of trying. I returned to my OT. The surgeon requested Indocyanine green administration to establish the area of the stomach with good perfusion for resection as the conduit. At this moment, the arterial line waveform was fluctuating with slightly low blood pressure compared to the trend since the beginning of the operation. The stroke volume variation (SVV) reading was 17%. I decided to administer a fluid bolus of 100ml Gelafusine over 10 minutes. The FloTrac system provides continuous hemodynamic assessment. After completing the fluid bolus, the SVV value decreased to 10%, indicating fluid responsiveness. His mean arterial pressure returned to the initial baseline.

As expected, this complex case did not conclude by 5 pm. The patient was transferred to the ICU for stabilization and weaning. For such cases, the patient is kept ventilated overnight. The decision for weaning and extubation will depend on the patient's hemodynamics, investigations, and other critical parameters. The on-call anaesthetist took over the case until completion. She was running a bit late as she was assisting a medical officer with inserting a cannula for an oncology patient referred to us for difficult line insertion.

After handing over, I gathered my belongings, contemplating tomorrow's oral and maxillofacial surgery case. A 45-year-old lady with squamous cell carcinoma of the tongue is planned for tumour excision, neck exploration, and flap. The team in charge planned for awake fibre optic intubation due to the large tumour occupying the oral cavity and limited mouth opening. The ENT team will then proceed with the tracheostomy. All medical personnel involved had been informed of the preparations needed for tomorrow. The estimated surgical time is 12 hours. It is going to be a long day for me as I am on call the next day.

On the way down to the car park, I decided to stop at everyone's favourite department in IKN, the Coffee Department. Nothing beats a great cup of coffee to help me unwind after a long day.

Cancer Patients with Cardiac Disease for Non-Cardiac Surgery: Perioperative Anaesthetic Concerns

Vimal Varma A/L Spor Madiman, Isqandar Adnan, Mardhiah Sarah Harnani Mansor
Department of Anaesthesiology & Intensive Care, Faculty of Medicine, Universiti Teknologi MARA, Selangor, Malaysia

The perioperative management of cancer patients with concurrent cardiac disease undergoing non-cardiac surgery presents a unique set of challenges. These patients require a meticulous and comprehensive preoperative assessment to evaluate their overall health status, including nutritional status, symptom control, and particularly their cardiac function. The interplay between cancer treatments, such as chemotherapy and radiation, and cardiac health further complicates the perioperative period. These are the outlines for the critical considerations and strategies for managing these patients, emphasizing the importance of evaluating physiologic fitness, monitoring for perioperative cardiac complications, and understanding the impact of anaesthesia and immunosuppression on patient outcomes.

GENERAL EVALUATION

Patients with cancer require a comprehensive preoperative assessment. Patients with recent cardiac issues are at higher risk during surgery.[1] This assessment should cover several key areas:

Nutritional Status:

- **Importance:** Adequate nutrition is vital for healing and recovery. Malnutrition can impair immune function, wound healing, and overall recovery.

- **Assessment:** Evaluate the patient's weight, body mass index (BMI), and dietary intake. Look for signs of malnutrition, such as unintentional weight loss, muscle wasting, and deficiencies in essential nutrients.

- **Interventions:** If malnutrition is identified, consider nutritional support, such as dietary counselling, supplements, or even enteral or parenteral nutrition if necessary.

Symptom Control:

- **Pain Management:** Effective pain control is crucial for patient comfort and recovery. Assess the patient's pain levels and current pain management strategies.

- **Other Symptoms:** Evaluate other symptoms that may affect the patient's overall health and surgical outcome, such as fatigue, nausea, vomiting, and respiratory issues.

- **Interventions:** Optimize symptom control through medications, physical therapy, and other supportive measures.

General Medical Issues:

- **Comorbidities:** Identify and manage any other medical conditions the patient may have, such as diabetes, hypertension, or chronic obstructive pulmonary disease (COPD).

- **Medications:** Review the patient's current medications, including over-the-counter drugs and supplements, to identify potential interactions or contraindications with anaesthesia and surgery.

Cardiac Status Assessment:

Given the increased risk of cardiac complications in cancer patients, a thorough evaluation of their cardiac health is essential:

- **Functional Capacity:**
  - **Importance:** Functional capacity is a strong predictor of perioperative risk. It reflects the

patient's ability to perform daily activities and their overall cardiovascular fitness.

- **Assessment:** Use tools like the Duke Activity Status Index (DASI) or the New York Heart Association (NYHA) classification to evaluate functional capacity. Consider stress testing or cardiopulmonary exercise testing if needed.

- **Recent Cardiac Events:**
  - **Importance:** Recent cardiac events, such as myocardial infarction (heart attack) or unstable angina, significantly increase the risk of perioperative complications.

  - **Assessment:** Obtain a detailed cardiac history, including any recent hospitalizations, interventions (like stenting or bypass surgery), and current symptoms.

  - **Interventions:** If recent cardiac events are identified, consult with a cardiologist to optimize the patient's cardiac status before surgery. This may involve medication adjustments, further diagnostic testing, or delaying surgery if possible.

- **Overall Cardiovascular Health:**
  - **Importance:** A comprehensive understanding of the patient's cardiovascular health helps in risk stratification and perioperative planning.

  - **Assessment:** Perform a physical examination, electrocardiogram (ECG), and echocardiogram to evaluate heart function. Consider additional tests like coronary angiography if indicated.

  - **Interventions:** Address any identified cardiovascular issues, such as heart failure, arrhythmias, or valvular disease, in collaboration with a cardiologist.

Understanding Cancer's Natural History and Prior Treatments:

Cancer and its treatments can have significant effects on the patient's overall health and surgical risk:

- **Natural History of Cancer:**
  - **Importance:** Understanding the stage and progression of the cancer helps in planning the timing and extent of surgery.

  - **Assessment:** Review the patient's oncology records, including imaging studies, biopsy results, and tumour markers.

- **Prior Treatments:**
  - **Chemotherapy:** Some chemotherapeutic agents can cause cardiotoxicity, leading to heart failure or other cardiac issues. Assess the patient's chemotherapy history and any related cardiac side effects.

  - **Radiation Therapy:** Radiation to the chest can cause long-term damage to the heart and lungs. Evaluate the extent and timing of radiation therapy and its potential impact on cardiac function.

  - **Interventions:** Collaborate with the oncology team to understand the implications of prior treatments and to plan perioperative care accordingly.

PHYSIOLOGIC FITNESS

Recognize that cancer patients may be deconditioned due to various factors. Consider enrolling them in a prehabilitation program upon diagnosis. Functional status matters more than chronological age when making treatment decisions.

Deconditioning Factors:

Cancer patients with cardiac conditions may experience additional challenges due to:

- **Cardiac Disease:** Conditions like heart failure, coronary artery disease, or arrhythmias can further limit physical activity and endurance.

- **Combined Treatments:** Both cancer treatments and cardiac medications can have side effects that exacerbate fatigue, weakness, and other symptoms.

Prehabilitation Programmes:

- **Definition:** Prehabilitation for these patients involves a multidisciplinary approach to prepare them for cancer treatment while managing their cardiac condition.
- **Components:** These programs include tailored exercise regimens, nutritional support, psychological counselling, and close monitoring of cardiac health.
- **Benefits:** Improved physical fitness and mental resilience can lead to better treatment outcomes, reduced complications, and faster recovery.

Functional Status vs Chronological Age:

- **Functional Status**: This remains a critical factor in treatment decisions. For cardiac patients, this includes assessing their cardiovascular fitness and ability to tolerate physical activity.
- **Importance:** Functional status is a better predictor of treatment tolerance and outcomes than age alone.
- **Assessment:** Healthcare providers use physical exams, patient history, cardiac function tests (like echocardiograms or stress tests), and sometimes specific cancer-related assessments.

Why It Matters?

- **Personalized Treatment:** By focusing on functional status and cardiac health, healthcare providers can tailor treatments to each patient's unique needs and capabilities.
- **Improved Outcomes:** Patients who are physically fit and mentally prepared, even with cardiac conditions, often experience fewer complications and better overall outcomes.

Additional Considerations for Cardiac Patients

- **Cardiac Monitoring:** Regular monitoring of heart function during cancer treatment is essential to manage any potential cardiac side effects.
- **Medication Management**: Coordination between oncologists and cardiologists is crucial to ensure that treatments for cancer and cardiac conditions do not adversely interact.
- **Lifestyle Modifications:** Encouraging heart-healthy lifestyle changes, such as a balanced diet, regular physical activity, and stress management, can support overall health and treatment success.

PERIOPERATIVE CARDIAC COMPLICATIONS

Surgery and anaesthesia can increase the risk of cardiac events due to stress responses (sympathetic stimulation, cortisol release, hypercoagulability, and inflammation). Advanced hemodynamic monitoring is recommended in additional to routine monitoring peri-operatively.

Myocardial Ischemia:

Perioperative myocardial ischemia can occur due to the increased oxygen demand and reduced oxygen supply to the heart muscle during surgery. This imbalance can lead to:

- **Infarction:** Death of heart muscle tissue due to prolonged lack of oxygen.
- **Heart Failure:** The heart's inability to pump blood effectively.
- **Arrhythmias:** Irregular heartbeats that can disrupt normal cardiac function.
- **Myocardial Injury:** Damage to the heart muscle, which can be detected by elevated cardiac biomarkers like troponin.

Mechanisms:

- **Sympathetic Stimulation:** Surgery and anesthesia can trigger a stress response, increasing heart rate and blood pressure, which raises myocardial oxygen demand.
- **Inflammation:** Surgical trauma can cause systemic inflammation, leading to endothelial dysfunction and a pro-thrombotic state.
- **Hypercoagulability:** Increased blood clotting tendency can lead to coronary artery occlusion.

Management:

- **Aggressive Medical Therapy:** Includes the use of beta-blockers, statins, and antiplatelet agents to manage ischemia and prevent complications.
- **Coronary Revascularization:** Procedures like angioplasty or bypass surgery may be considered postoperatively, especially in patients with significant coronary artery disease.[2]

Chemotherapy-Related Cardiotoxicity

Certain chemotherapeutic agents can cause direct damage to the heart, leading to cardiotoxicity. This can manifest as:

- **Cardiomyopathy:** Disease of the heart muscle that can lead to heart failure.
- **Arrhythmias:** Irregular heartbeats.
- **Pericarditis:** Inflammation of the pericardium (the sac surrounding the heart).

Common Culprits:

- **Busulfan, Cisplatin, Cyclophosphamide, Doxorubicin, and 5-Fluorouracil:** These drugs can cause oxidative stress, mitochondrial damage, and apoptosis (cell death) in cardiac cells.

Mechanisms:

- **Oxidative Stress:** Chemotherapeutic agents can generate reactive oxygen species (ROS), leading to oxidative damage of cardiac cells.
- **Mitochondrial Dysfunction:** Damage to mitochondria impairs energy production, crucial for heart muscle function.
- **Apoptosis:** Programmed cell death of cardiac cells can weaken the heart muscle.

Management:

- **Preoperative Evaluation:** Assess cardiac and respiratory function to identify patients at risk.
- **Monitoring:** Continuous monitoring of cardiac function during and after chemotherapy.
- **Cardioprotective Agents:** Use of drugs like dexrazoxane to mitigate cardiotoxic effects.[3]

TIMING AND PURPOSE OF SURGERY

Cancer surgery is usually not elective, and time for medical optimization may be limited. When a cancer patient with cardiac problems needs non-cardiac surgery, the situation becomes more complex.

Timing and Urgency

- **Cancer Surgery:** Often urgent and not elective, meaning there's limited time for extensive preoperative optimization.
- **Cardiac Concerns:** These need to be balanced with the urgency of the cancer surgery. Delaying cancer treatment to optimize cardiac health might not always be feasible.

Preoperative Assessment

- **Cardiac Evaluation:** A thorough cardiac assessment is crucial. This might include stress tests, echocardiograms, or consultations with a cardiologist.

- **Risk Stratification:** Assessing the risk of cardiac complications during and after surgery helps in planning. Tools like the Revised Cardiac Risk Index (RCRI) can be useful.

Coordination of Care

- **Multidisciplinary Approach:** Internists play a key role in coordinating care among surgeons, oncologists, cardiologists, and other specialists.

- **Communication:** Clear communication between all team members ensures that the patient's overall health is considered in surgical planning.

Intraoperative and Postoperative Management

- **Monitoring:** Close cardiac monitoring during surgery is essential. Anaesthesiologists need to be aware of the patient's cardiac status and potential risks.

- **Postoperative Care:** Intensive monitoring and management of cardiac function post-surgery can help in early detection and treatment of complications.

Patient-Centred Approach

- **Informed Decision-Making:** Patients and their families should be involved in discussions about risks and benefits, helping them make informed decisions about their care.

- **Quality of Life:** Consideration of the patient's quality of life and personal preferences is crucial in planning and executing treatment.

IMPACT OF ANAESTHESIA

Anaesthetics and analgesics used during the perioperative period can modulate the immune system, inflammation, and angiogenesis.

Preclinical and retrospective studies suggest that anaesthetic agents and interventions have complex effects on cancer recurrence and long-term outcomes.[4] Anaesthetic management, techniques, and body temperature control matter during the perioperative period.[5]

Immune System Modulation:

- **Volatile Anesthetics:** Agents like sevoflurane and isoflurane can suppress immune function, potentially affecting cancer recurrence.[6] They may inhibit natural killer (NK) cell activity, which is crucial for targeting cancer cells.

- **Intravenous Anaesthetics:** Propofol is known for its less immunosuppressive properties compared to volatile anesthetics. It may even have anti-inflammatory effects, making it a preferable choice in some cancer surgeries.[7]

- **Local Anesthetics:** Lidocaine and other local anesthetics can enhance NK cell activity and reduce the inflammatory response, which might be beneficial in reducing cancer recurrence.[6]

Analgesics:

- **Opioids:** While effective for pain management, opioids can suppress immune function. Alternatives like regional anesthesia or non-opioid analgesics (e.g., NSAIDs) may be considered to minimize this effect.[7]

- **Cardiotoxicity from Cancer Treatments:**
  - **Chemotherapy:** Agents like doxorubicin and cyclophosphamide are known for their cardiotoxic effects, which can lead to conditions such as cardiomyopathy or arrhythmias.[7] Preoperative cardiac evaluation is essential to assess the extent of any damage.

  - **Radiation Therapy:** Radiation can cause fibrosis and damage to the heart and surrounding vessels, increasing the risk of ischemic heart disease and other cardiac complications.[7]

- **Anaesthetic Management:**
  - **Cardioprotective Strategies:** Using beta-blockers, optimizing fluid management, and avoiding agents that significantly depress

myocardial function are crucial. For instance, etomidate may be preferred over propofol in patients with severe cardiac dysfunction due to its minimal cardiovascular effects.[3]

- **Regional Anesthesia:** Techniques like epidural or spinal anesthesia can reduce the stress response and provide excellent pain control, which is beneficial for both cardiac and cancer patients.[3]

Long-Term Outcomes:

- **Cancer Recurrence:**
  - **Anaesthetic Choices:** The choice of anesthetic agents and techniques can influence long-term cancer outcomes. Retrospective studies suggest that regional anesthesia and certain intravenous agents may be associated with lower rates of cancer recurrence.[9]

  - **Inflammation and Angiogenesis:** Anesthetic agents can modulate inflammation and angiogenesis, which are critical in cancer progression and metastasis.[7]

IMMUNOSUPPRESSION

When managing anaesthesia for patients with both cancer and cardiac disease, several scientific considerations are crucial, particularly regarding immunosuppression and the perioperative surgical stress response and anaesthesia-related factors contribute to relative immunosuppression perioperatively. Understanding these implications is essential for optimal care.[8]

Surgical Stress Response:

- **Inflammatory Response:** Surgery triggers an inflammatory response, releasing cytokines and stress hormones like cortisol and catecholamines. This response can suppress the immune system, making patients more susceptible to infections and potentially impacting cancer recurrence.[10]

- **Neuroendocrine Response:** The hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) are activated during surgery, leading to increased levels of stress hormones that further contribute to immunosuppression.[11]

Anaesthesia-Related Factors:

- **Anesthetic Agents:** Different anesthetic agents have varying effects on the immune system. For instance, volatile anesthetics like sevoflurane and isoflurane may suppress immune function more than intravenous agents like propofo.[12] Local anesthetics such as lidocaine can enhance natural killer (NK) cell activity, which is beneficial for immune surveillance.[11]

- **Opioids:** While opioids are effective for pain management, they can also suppress immune function. Alternatives like regional anesthesia or non-opioid analgesics may be preferable in some cases.[11]

CONCLUSION

In conclusion, the perioperative care of cancer patients with cardiac disease necessitates a multidisciplinary approach to optimize outcomes. Thorough preoperative evaluation, including assessment of cardiac status and physiologic fitness, is essential. Advanced hemodynamic monitoring and aggressive management of perioperative cardiac complications are crucial to mitigate risks. Additionally, understanding the cardiotoxic effects of certain chemotherapeutic agents and the complex interactions between anaesthesia, immune function, and cancer recurrence is vital. By addressing these factors, healthcare providers can improve the safety and efficacy of non-cardiac surgeries in this vulnerable patient population. **Remember, each patient's situation is unique, influenced by their specific cancer type and cardiac condition. It's essential to work closely with a multidisciplinary team to customize anaesthesia management for optimal care.**

References

1. Hensley, N.B., Hogue, C.W. (2024) Anesthesia for noncardiac surgery in patients with ischemic heart disease. Retrieved July 31, 2024, from https://www.uptodate.com/contents/anesthesia-for-noncardiac-surgery-in-patients-with-ischemic-heart-disease

2. Smilowitz, N. R., & Berger, J. S. (2020). Perioperative cardiovascular risk assessment and management for noncardiac surgery: a review. Jama, 324(3), 279-290

3. Smilowitz, N. R., Gupta, N., Ramakrishna, H., Guo, Y., Berger, J. S., & Bangalore, S. (2017). Perioperative major adverse cardiovascular and cerebrovascular events associated with noncardiac surgery. JAMA cardiology, 2(2), 181-187

4. Irvine, D. (2022). Anesthesia Pain and Safety Considerations in Cancer Patients. APSF Initiative on Medical Technology Education, 59

5. Chan, B. C., & Yim, R. L. (2023). Perioperative cardiac complications. Anaesthesia & Intensive Care Medicine, 24(6), 315-321.

6. Xia, S. H., Zhou, D., Ge, F., Sun, M., Chen, X., Zhang, H., & Miao, C. (2023). Influence of perioperative anesthesia on cancer recurrence: from basic science to clinical practice. Current Oncology Reports, 25(2), 63-81

7. AAo, A. Statement on ASA Physical Status Classification System

8. Manzullo E. F., Sahai S.K., Weed H. G. (2024) Preoperative evaluation and management of patients with cancer. Retrieved March 04, 2024, from https://www.uptodate.com/contents/preoperative-evaluation-and-management-of-patients-with-cancer

9. Burt, C. C., Littwin, S. M., Adebayo, J., Mallavaram, N. A., & Thys, D. M. (2021). Regional anesthesia and cardiovascular disease

10. Bezu, L., Akçal Öksüz, D., Bell, M., Buggy, D., Diaz-Cambronero, O., Enlund, M., ... & EuroPeriscope Group. (2024). Perioperative Immunosuppressive Factors during Cancer Surgery: An Updated Review. Cancers, 16(13), 2304

11. Kim, R. (2018). Effects of surgery and anesthetic choice on immunosuppression and cancer recurrence. Journal of translational medicine, 16, 1-13

Enhancing Patient Blood Management in Colorectal Surgery: Insights from UiTM's Experience

Mardhiah Sarah Harnani Mansor, Isqandar Adnan, Adlin Dasima Abdul Kadir, Zawiah Kassim, Asmah Azizeh
Department Anaesthesiology & Intensive Care, Faculty of Medicine, Universiti Teknologi MARA, Selangor, Malaysia

CASE REPORT

A 66-year-old woman was diagnosed with mid-rectal cancer (T3bN2bM0) and was scheduled for elective laparoscopic low anterior resection with covering ileostomy. She initially presented with per rectal bleeding. The initial investigations were done to confirm the diagnosis.

Colonoscopy findings were rectal polyp 5cm FAV (HPE: HGD), 6mm ascending colon polyp (cold snare polypectomy HPE: hyperplastic polyp), 3mm polyps (snare polypectomy & discarded). Serial CEA showed an increment in the value. CT TAP imaging reported as mid rectal tumour at anterior wall 1.5 x 3cm (9cm FAV), few mesorectal nodes, small segment VII liver lesion (0.5 x 0.7cm).

She was seen in anaesthetic clinic for preoperative assessment 2 weeks prior to the date of surgery. Her weight was 74kg with height 157cm and BMI 30kg/m^2. She was anaemic with haemoglobin 10.3g/dL and haematocrit (Hct) 31.7. She was then referred to Patient Blood Management Clinic for intravenous (IV) iron therapy and received IV iron as per hospital policy at the daycare unit.

Her serum iron profile indicated iron deficiency anaemia, as evidenced by a normal serum iron level (14.4 µmol/L), normal total iron-binding capacity (50.7 µmol/L), and normal unsaturated iron-binding capacity (36.3 µmol/L), alongside an elevated ferritin level (452.3 µg/L). She received 2 doses of intravenous iron therapy in 1 week apart. Her preoperative Hb increased to 12.1g/dL with Hct of 37.2. She received 2 doses of intravenous iron therapy 1 week apart. Her preoperative Hb increased to 12.1g/dL with Hct of 37.2. The operation was uneventful, and she did not require an allogenic blood transfusion pre, intra and post operatively.

IRON DEFICIENCY ANAEMIA IN COLORECTAL CANCER PATIENT

Iron deficiency anaemia (IDA) is a prevalent complication in patients with colorectal cancer (CRC), resulting from various mechanisms associated with malignancy and its treatment. Understanding these mechanisms is crucial for the effective management of IDA in CRC patients, as addressing iron deficiency can improve overall patient outcomes and quality of life.

- Chronic Blood Loss: One of the primary aetiologies of IDA in CRC patients is chronic gastrointestinal bleeding. Tumours located in the colon or rectum can induce continuous, often occult, blood loss, leading to progressive depletion of iron stores.[1]
- Inflammation: Chronic inflammation, a common feature in cancer, can significantly alter iron metabolism. Inflammatory cytokines promote the sequestration of iron within macrophages and other cells, thereby reducing its bioavailability for erythropoiesis (the production of red blood cells).[2]
- Nutritional Deficiencies: Patients with CRC frequently experience reduced dietary intake due to anorexia or malabsorption, which further exacerbates iron deficiency.[2]
- Chemotherapy and Radiation: Oncological treatments such as chemotherapy and radiation therapy can exacerbate anaemia by suppressing bone marrow function, where red blood cells are produced.[3]

Iron deficiency anaemia (IDA) in colorectal cancer (CRC) patients can result in significant clinical symptoms such as fatigue, weakness, pallor, and dyspnoea (shortness of breath). These symptoms can severely impact the quality of life and complicate cancer treatment1. IDA is diagnosed through blood tests that measure haemoglobin, haematocrit, serum ferritin, and transferrin saturation levels. In CRC patients, it is crucial to regularly monitor these parameters to detect anaemia early.[1]

Treatment of iron deficiency anaemia (IDA) in colorectal cancer (CRC) involves addressing the underlying cause of iron deficiency. This may include:

- Iron Supplementation: Oral or intravenous iron supplements can be used to replenish iron stores. Intravenous iron is often preferred in cancer patients due to its better efficacy and tolerance.[4]

- Erythropoiesis-Stimulating Agents (ESAs): These agents can be used to stimulate red blood cell production, particularly in patients undergoing chemotherapy.[3]

- Blood Transfusions: In severe cases, blood transfusions may be necessary to quickly restore haemoglobin levels.[1]

ANAEMIA AND SURGICAL OUTCOME

Anaemia is a prevalent condition that significantly impacts surgical outcomes. It is characterized by a reduced number of red blood cells or haemoglobin, leading to decreased oxygen delivery to tissues. This condition can arise from various causes, including chronic diseases, nutritional deficiencies, and acute blood loss. Understanding the relationship between anaemia and surgical outcomes is crucial for optimizing patient care.

Impact of Anaemia on Surgical Outcomes

- ***Increased Perioperative Risk:*** Anaemia is associated with higher perioperative morbidity and mortality. Patients with anaemia undergoing surgery are at an increased risk of complications such as infections, delayed wound healing, and prolonged hospital stays.[5]

- ***Cardiovascular Complications:*** Anaemic patients are more susceptible to cardiovascular complications during and after surgery. The reduced oxygen-carrying capacity of the blood can lead to myocardial ischemia, arrhythmias, and heart failure.[6]

- ***Increased Need for Blood Transfusions:*** Anaemia often necessitates perioperative blood transfusions, which carry their own risks, including transfusion reactions, infections, and immunomodulation.[7] Transfusions can also increase the length of hospital stays and healthcare costs.

- ***Delayed Recovery:*** Anaemia can slow postoperative recovery, leading to longer durations of mechanical ventilation, extended intensive care unit (ICU) stays, and delayed mobilization.[5] This can negatively affect the overall quality of life and functional outcomes.

Mechanisms Contributing to Poor Outcomes

- ***Reduced Oxygen Delivery:*** Anaemia leads to decreased oxygen delivery to tissues, which can impair wound healing and increase the risk of surgical site infections.[5]

- ***Inflammatory Response:*** Anaemia can exacerbate the inflammatory response to surgery, contributing to complications such as sepsis and multi-organ dysfunction.[5]

- ***Hemodynamic Instability:*** The body's compensatory mechanisms for anaemia, such as increased cardiac output and redistribution of blood flow, can lead to hemodynamic instability during surgery.[5]

Management Strategies

- ***Preoperative Optimization:*** Identifying and treating anaemia before surgery is crucial. This may involve iron supplementation, erythropoiesis-stimulating agents (ESAs), and addressing underlying causes such as nutritional deficiencies or chronic diseases.

- ***Intraoperative Management:*** Minimizing blood loss during surgery through meticulous surgical techniques and the use of haemostatic agents can reduce the need for transfusions. Intraoperative blood salvage and autologous blood transfusion techniques can also be beneficial.

- ***Postoperative Care:*** Close monitoring and management of anaemia in the postoperative period are essential. This includes regular assessment of haemoglobin levels, continued iron supplementation, and addressing any ongoing sources of blood loss.

PREOPERATIVE IRON THERAPY FOR CANCER PATIENT

Intravenous (IV) iron therapy has emerged as a crucial treatment for managing anaemia in cancer patients. Anaemia is a common complication in cancer, often exacerbated by the disease itself and its treatments, such as chemotherapy and radiation. Here's an overview of the role and benefits of IV iron therapy in this context.

Advantages of Intravenous Iron Therapy

- ***Enhanced Hematopoietic Response:*** Studies have shown that IV iron, such as iron dextran or ferric gluconate, significantly improves hematopoietic response rates in cancer patients receiving chemotherapy.[8] This is particularly beneficial when combined with erythropoiesis-stimulating agents (ESAs), enhancing their efficacy.

- ***Rapid Repletion of Iron Stores:*** IV iron bypasses the gastrointestinal tract, allowing for quicker and more efficient replenishment of iron stores compared to oral iron supplements.[8]

- ***Improved Quality of Life:*** By effectively treating anaemia, IV iron therapy can alleviate symptoms such as fatigue and weakness, thereby improving the overall quality of life and performance status of cancer patients.[9]

Clinical Evidence and Safety

- ***Efficacy:*** Clinical trials have demonstrated that IV iron therapy can significantly increase haemoglobin levels and reduce the need for blood transfusions in anaemic cancer patients.[8]

- ***Safety:*** Modern IV iron formulations have a favourable safety profile, with adverse events being relatively rare. The risk of severe allergic reactions is low, making it a safe option for most patients.[6]

Practical Considerations

- ***Assessment of Iron Status:*** Before initiating IV iron therapy, it is essential to assess the patient's iron status through laboratory tests, including serum ferritin and transferrin saturation.[6]

- ***Dosage and Administration:*** The dosage of IV iron should be tailored to the individual patient's needs, considering factors such as the severity of anaemia and the patient's overall health status.[9]

Types of IV Iron Therapy

Several types of IV iron formulations are available for treating iron deficiency anaemia in cancer patients:

- ***Iron Dextran:*** Often used due to its cost-effectiveness and ability to correct iron deficiency with a single infusion.[10]

- ***Ferric Gluconate:*** Administered in multiple smaller doses, making it suitable for patients who may not tolerate large single doses.[10]

- ***Iron Sucrose:*** Similar to ferric gluconate, it is given in multiple smaller doses.[10]

- ***Ferric Carboxymaltose:*** Can be administered in one or two infusions, depending on the severity of the deficiency.[10]

- ***Ferumoxytol:*** Known for its rapid administration and fewer infusion reactions.[11]

Reasons for Choosing One Type Over Another

The choice of IV iron therapy depends on several factors:

- ***Patient Tolerance:*** Some patients may experience fewer side effects with certain formulations.
- ***Severity of Deficiency:*** Ferric carboxymaltose and iron dextran are often chosen for severe deficiencies due to their ability to deliver larger doses in fewer sessions.[10]
- ***Speed of Response Needed:*** Ferric carboxymaltose and ferumoxytol provide rapid iron repletion.[11]
- ***Previous Reactions:*** Patients with a history of reactions to one type of IV iron may be switched to another.[6]

Clinical Evidence

Clinical studies have shown that IV iron therapy can significantly improve haemoglobin levels in cancer patients:

- ***Haemoglobin Improvement:*** Studies report an increase in haemoglobin levels by approximately 1-2 g/dL within 4-6 weeks of treatment.[12]
- ***Duration:*** The time to achieve these improvements varies, but most patients see significant changes within a few weeks.[12]

Side Effects

While IV iron therapy is generally well-tolerated, it can have side effects:

- ***Common Side Effects:*** Include nausea, headaches, dizziness, and swelling at the injection site.[13]
- ***Less Common Side Effects:*** Some patients may experience low blood pressure, fainting, or allergic reactions.[14]

This comprehensive approach ensures that cancer patients receive the most appropriate and effective iron therapy tailored to their specific needs and conditions.

PBM IN UiTM

Patient Blood Management (PBM) is a multidisciplinary approach aimed at optimizing the care of patients who might need a blood transfusion. The goal is to improve patient outcomes by minimizing unnecessary blood transfusions and enhancing the patient's own blood health.

Key Principles of PBM:

- ***Optimizing Haemoglobin Levels:***
  - Ensure patients have adequate iron stores and treat any underlying anaemia before surgery or other procedures.
  - Use medications or supplements to boost red blood cell production if necessary.
- ***Minimizing Blood Loss:***
  - Employ surgical techniques and technologies that reduce blood loss.
  - Use medications that help control bleeding.
  - Implement strategies like controlled hypotension and normothermia during surgery.
- ***Enhancing Anaemia Tolerance:***
  - Optimize the patient's physiological tolerance to anaemia.
  - Use restrictive transfusion thresholds to avoid unnecessary transfusions.
  - Monitor and manage the patient's hemodynamic status closely.

Benefits of PBM:

- Reduced risk of transfusion-related complications.
- Improved patient outcomes and recovery times.
- Lower healthcare costs due to fewer transfusions and related complications.

At UiTM, we initiated Patient Blood Management (PBM) during the COVID-19 pandemic due to a shortage of blood supply for cardiac surgeries, particularly coronary artery bypass grafting (CABG). A comparative cross-sectional study was conducted on two groups of patients who underwent cardiac surgery requiring cardiopulmonary bypass (CPB) at Pusat Perubatan UiTM (PPUiTM) before and after the implementation of Preoperative Autologous Blood Donation (PABD) and Intraoperative Interventions (IIT) during the Movement Control Order (MCO) in 2020. The early data concluded that both PABD and IIT significantly reduced perioperative allogeneic blood transfusion rates in cardiac surgeries requiring CPB.

CONCLUSION

Anaemia is a significant risk factor for adverse surgical outcomes. Addressing anaemia in the surgical setting is crucial for enhancing recovery and overall patient health. Iron deficiency anaemia (IDA) is particularly prevalent and problematic among colorectal cancer patients. Effective management of anaemia through preoperative optimization, meticulous intraoperative techniques, and vigilant postoperative care can significantly improve patient outcomes and reduce complications. Understanding the mechanisms, clinical implications, and management strategies of anaemia is essential for improving patient outcomes and quality of life. Regular monitoring and timely intervention can help mitigate the adverse effects of IDA in this patient population. Intravenous (IV) iron therapy is a valuable tool in managing anaemia in cancer patients. It offers rapid and effective repletion of iron stores, enhances the response to erythropoiesis-stimulating agents (ESAs), and improves quality of life. With a good safety profile and proven efficacy, IV iron therapy should be considered a standard component of supportive care in oncology.

References

1. Dixon, S. (2023, March 06). Anemia and Colon Cancer. Verywellhealth. https://www.verywellhealth.com/anemia-can-signal-colon-cancer-3974312
2. Bhurosy, T., Jishan, A., Boland, P. M., Lee, Y. H., & Heckman, C. J. (2022). Underdiagnosis of iron deficiency anaemia among patients with colorectal cancer: an examination of electronic medical records. BMC cancer, 22(1), 435
3. Cirino E. (2023, May 23). Understanding the Connection Between Anemia and Cancer.Healthline.https://www.healthline.com/health/cancer/anemia-cancer
4. Ng, O. (2016). Iron, microbiota and colorectal cancer. Wiener Medizinische Wochenschrift, 166, 431-436
5. Hare, G. M., & Mazer, C. D. (2021). Anemia: perioperative risk and treatment opportunity. Anesthesiology, 135(3), 520-530
6. Gilreath, J. A., & Rodgers, G. M. (2020). How I treat cancer-associated anaemia. Blood, The Journal of the American Society of Hematology, 136(7), 801-813
7. O'Carroll, D. (2024, January 18) Anemia Surgery: What should you know. Healthline. https://www.healthline.com/health/anemia/surgery-overview
8. Henry, D. H. (2006). The role of intravenous iron in cancer-related anaemia. Oncology (Williston Park, NY), 20(8 Suppl 6), 21-24
9. Lebrun, F., Klastersky, J., Levacq, D., Wissam, Y., & Paesmans, M. (2017). Intravenous iron therapy for anemic cancer patients: a review of recently published clinical studies. Supportive Care in Cancer, 25, 2313-2319
10. Yates, A. (2022, June 16) IV Treatment For Iron Deficiency Anaemia. Verywellhealth https://www.verywellhealth.com/iv-iron-for-treatment-of-iron-deficiency-anemia-4124271
11. Saljhougian, M. (2010). Parenteral Irons: indications and comparison. US Pharm, 35(11), 22-24
12. Lim, J., Auerbach, M., MacLean, B., Al-Sharea, A., & Richards, T. (2023). Intravenous iron therapy to treat anemia in oncology: A mapping review of randomized controlled trials. Current Oncology, 30(9), 7836-7851
13. Cirino, E. (2024, Jan 24) What to Expect from an Iron Infusion. Healthline. https://www.healthline.com/health/iron-infusion
14. Cleveland Clinic (2023, August 30) Iron Infusion https://my.clevelandclinic.org/health/treatments/14571-intravenous-iron-supplementation

Anaesthesia for Children with Cancer

Rufinah Teo[1]**, Maryam Budiman**[2]
[1]Department of Anaesthesiology & Intensive Care, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
[2]Department of Anaesthesiology & Intensive Care, Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Childhood cancer, although rare, can manifest at any age with a diverse range of signs and symptoms. Over the past few decades, significant advancements in treatment have led to improved survival rates and outcomes. According to data from the Malaysian Childhood Cancer Registry (2012-2016), the incidence of childhood cancer has increased, with a higher prevalence among males and the highest incidence occurring in the 0-4 years age group. Lymphoma, germ cell, gonadal and bone tumours are more commonly diagnosed in adolescence.

As cancer therapies have advanced, the demand for anaesthesia services has concurrently risen. Anaesthesiologists frequently encounter paediatric cancer patients in their practice, often presenting complex and high-risk challenges. The anaesthetic considerations for these children can be broadly categorized into cancer-related and treatment-related issues, each requiring careful assessment and management.

CANCER-RELATED PROBLEMS

Haemodynamic Profile

Children with cancer rarely present with major cardiovascular issues. However, they may experience haemodynamic compromise due to underlying sepsis or anatomical anomalies. A thorough cardiovascular assessment is strongly recommended for children presenting with sepsis and for those with a mediastinal mass.

Respiratory Issues

Primary lung tumours and metastases are rare in children and could present with respiratory symptoms. However, respiratory problems can occur in various types of cancer, often due to indirect causes such as pleural effusions, pneumonia, pulmonary embolism, airway obstruction from a mediastinal mass, or chylous effusion resulting from lymphatic obstruction. Consequently, a thorough respiratory assessment is essential in the management of paediatric cancer cases.

Mediastinal Mass

Children with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) are most commonly associated with mediastinal involvement at presentation. Less frequently, those with acute lymphoblastic lymphoma, neuroblastoma, or germ cell tumours may also present with a mediastinal mass. Given the proximity of these masses to the heart, airways, and great vessels, it is crucial to assess the child both clinically and radiologically for potential obstruction of these vital structures. Symptoms that may necessitate further evaluation include postural cough, postural dyspnea, stridor, wheezing, Horner's syndrome, facial swelling, dilated upper body veins, and superior vena cava syndrome.

Intracranial tumours

Intracranial tumours in children are mostly primary brain tumours, with a small percentage being metastatic lesions. These tumours pose the risk of increased intracranial pressure due to the obstruction of cerebrospinal fluid flow, tumour mass effect, cerebral oedema, and intracranial bleeding. Symptoms of raised intracranial pressure, such as vomiting, headache, and loss of consciousness, are strong indicators of this problem. However, these symptoms can be challenging to detect in younger children, who may instead present with nonspecific signs like refusal to eat or drink, inconsolable crying, restlessness, and agitation. Such presentations warrant urgent assessment.

Seizures can be a significant issue for children with intracranial tumours. It is important to assess the type and severity of seizures, seizure control, and adherence to medication regimens in these patients.

Renal System

Primary kidney tumours, such as Wilms tumour and renal cell carcinoma, as well as non-renal tumours like neuroblastoma, can lead to urinary tract obstruction and cellular damage, though acute renal failure is rare.

Electrolyte imbalances may arise in any type of cancer and could be the consequence of significant gastrointestinal symptoms and dehydration.

Haematological System

Cancer patients are at an increased risk of developing hypercoagulability and thrombosis. This procoagulant state can lead to bleeding complications due to cytokine release, vascular wall anomalies, and deficiencies in blood proteins (e.g. tissue factor, thrombin) and coagulation factors. Additionally, cancer patients are at risk of a prothrombotic state, which increases the likelihood of deep vein thrombosis and pulmonary thromboembolism - the latter being the second leading cause of death in cancer patients. This prothrombotic state is characterized by elevated fibrinogen, fibrin degradation products, and coagulation factors.

Bone marrow suppression in cancer patients can result from tumour infiltration, as seen in conditions like acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL). This suppression often leads to thrombocytopenia, neutropenia, and anaemia. Solid and musculoskeletal tumours such as neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, and osteosarcoma can have marrow infiltration and bleeding within the tumour, leading to anaemia. Severe thrombocytopenia can cause spontaneous bleeding, while severe neutropenia increases the risk of infections. Additionally, chronic severe anaemia can lead to complications such as cardiac failure, neurological disorders, and failure to thrive. Therefore, clinical assessment, haematology, and coagulation testing are essential for managing cancer patients with symptoms or those undergoing interventions.

Liver Impairment

Liver tumours, including hepatoblastoma, germ cell tumours, and hepatocellular carcinoma, are rare in children and typically cause only mild liver enzyme derangements. However, liver impairment and liver failure can occur in children with any type of cancer, particularly in the context of sepsis or other types of shock.

CANCER-TREATMENT PROBLEMS

Cancer treatment is typically tailored based on the cellular diagnosis, type, and stage of the disease, and often requires a multimodal approach. This approach commonly involves a combination of adjuvant or neoadjuvant chemotherapy, radiation therapy, and surgery. In recent years, targeted immunotherapy has gained popularity, particularly for certain cancer types. Regardless of the specific treatment modality, these therapies carry significant risks, especially when patients require anaesthesia. Managing these risks is crucial to ensure safe and effective anaesthetic care for paediatric cancer patients.

Chemotherapy

Chemotherapy regimens often use a combination of at least two cytotoxic drugs, designed to kill rapidly dividing cells by various mechanisms. Some like leukaemia and NHL require intrathecal chemotherapy under anaesthesia. Although chemotherapeutic drugs eliminate cancer cells, they can also destroy normal cells which can cause long-term systemic side effects.

Cardiotoxicity

Chemotherapy-related cardiotoxicity can manifest acutely within a few doses of treatment and is generally reversible. However, chronic toxicity may develop over time, leading to a progressive decline in cardiac function. Among chemotherapeutic agents, anthracyclines, particularly doxorubicin, are the most cardiotoxic, causing myocardial depression, ischemia, hypotension, myocarditis, conduction defects, supraventricular tachycardia, and heart blocks. Risk factors for cardiotoxicity include increasing cumulative doses, the total dose administered during a session, the rate and route of administration, drug combinations, and dosing intervals. Routine echocardiography before and after therapy is recommended and should be included in the pre-operative assessment.

Pulmonary toxicity

Pulmonary complications from chemotherapy can occur early or, more commonly, later in the treatment course. Up to 10% of patients receiving bleomycin develop bleomycin-induced pneumonitis (BIP), a condition exacerbated by the administration of high inspired oxygen concentrations (FiO_2) due to its oxidant-mediated pathways. Intraoperatively, patients receiving bleomycin should be managed with a safe and lower FiO_2 to minimize the risk of pulmonary complications.

Haematological toxicity

Myelosuppression is the most common dose-limiting side effect of cancer therapy, leading to anaemia, neutropenia, and thrombocytopenia. Not all anaemic patients require a routine blood transfusion, as transfusion-related adverse effects pose serious risks, particularly in immunosuppressed and immunodeficient patients. One significant complication is transfusion-associated graft-versus-host disease (TA-GvHD), which can affect immunocompetent individuals who receive HLA-matched components or blood from a close relative with a similar HLA haplotype.

TA-GvHD results from engrafted donor lymphocytes in immunosuppressed patients whose immune systems cannot eliminate the foreign cells. In immunosuppressed recipients of homozygous HLA-matched blood, donor lymphocytes are not recognized as foreign, allowing them to engraft and proliferate, ultimately attacking host tissues. This often fatal condition presents with symptoms like dermatitis, high fever, hepatitis, and pan-marrow suppression within four to 30 days post-transfusion, with death typically occurring within the first month after symptom onset.

Preventing TA-GvHD involves gamma irradiation of blood products to prevent lymphocyte proliferation. Irradiation does not compromise red blood cell viability, and irradiated products are generally viable for up to 14 days post-irradiation. Absolute indications for irradiated cellular products are limited to patients with HL. Patients with acute leukaemia, NHL, or solid organ tumours generally do not require irradiated blood products.

Children undergoing chemotherapy are highly susceptible to infection and immunosuppression. Neutropenia, defined as a neutrophil count of less than 1.5×10^9/L, is common in ALL and AML, where normal bone marrow is replaced by immature, dysregulated cells. Neutropenia often necessitates the cessation or dose limitation of therapy. Children with neoplasia account for 12.8% and 17.4% of severe sepsis cases among those aged one to nine and 10 to 19, respectively, with an associated mortality rate nearing 16%.

Thrombocytopenia is another frequent consequence of myelosuppression, often leading to clinically significant bleeding, and is a common cause of premature death in children with leukaemia. For children scheduled for procedures, a platelet count of more than 50×10^9/L is recommended.

Tumour lysis syndrome

Tumour lysis syndrome results from the massive release of intracellular contents following tumour destruction at the onset of chemotherapy. Predisposing factors include leukaemia and high-grade lymphomas. This syndrome leads to hyperkalaemia, hypocalcaemia, hyperphosphataemia, and hyperuricaemia, which can cause arrhythmias, seizures, and death. A diagnostic indicator of tumour lysis syndrome in children is a lactate dehydrogenase (LDH) level > 1000 U/L. Preventive measures include hyperhydration, urinary alkalinisation, and supportive care.

Radiotherapy

Radiation therapy uses high-energy radiation beams to shrink tumours and disrupt the DNA of cancer cells, leading to apoptosis. However, this treatment also affects surrounding normal tissues. Radiotherapy can be administered externally or internally and can involve either proton or photon beams. The radiation is targeted at specific areas of the body with a carefully measured dose, typically delivered in a series of sessions over days or weeks. Proton beam therapy is more precise and requires a lower radiation dose compared to photon beam therapy.

Table 1: Differences Between Photon and Proton Therapy

Photon	Proton
Uses ionizing photon (X-rays)	Uses positively charged particle (hydrogen)
Produced with a linear accelerator	Produced with accelerators known as cyclotrons and synchrotrons
Beam loses energy but does not stop, so a dose is delivered behind the target	Beam stops at specific depth based on the energy, so there is no exit dose
Machine can be housed in a standard hospital building	Machine must be placed in a specifically designed self-contained building

Airway and mucositis

High-dose radiotherapy targeting the neck and oral cavity presents significant airway risks for the anaesthesiologist. The radiation can lead to desquamation in both dry and moist areas, causing fibrosis and stiffness of the soft tissues. This may result in limited mouth opening, restricted neck extension, mucosal fibrosis, subglottic oedema, and stenosis. Additionally, hypoplasia of the jaw and xerostomia are potential complications.

Mucositis, characterized by ulcerative, erythematous, and extremely painful lesions, is another concern. It often leads to subglottic oedema and airway bleeding due to tissue friability. Mucositis typically appears 7-10 days after the initiation of chemotherapy and can persist for 1-2 weeks, further complicating airway management during anaesthesia.

ANAESTHESIA MANAGEMENT FOR PAEDIATRIC ONCOLOGY CASES

Anaesthesia Consideration for Oncology Surgery

The involvement of anaesthesiologists in paediatric cancer therapy is crucial to ensuring that treatment is targeted, effective, and safe, while also minimizing distress and trauma for the child. In addition to providing comfort and analgesia, anaesthesiologists often play a key role in managing long-term intravenous access, which is essential for administering drugs and chemotherapy, hydration, and blood sampling. Vascular access may be established by surgeons, interventional radiologists, or, in some centres, by anaesthesiologists. Close attention to the patient's coagulation status and platelet count is vital to prevent haematoma and bleeding during these procedures.

While the fundamental principles of anaesthesia do not differ significantly from standard practice, certain considerations specific to paediatric oncology must be taken into account. For example, echocardiography is critical in assessing cardiac function, particularly if cardiomyopathy is suspected due to the use of doxorubicin. When managing patients on bleomycin, a lower FiO_2 should be maintained intraoperatively to prevent oxidative injury from BIP.

The routine use of dexamethasone for postoperative nausea and vomiting must be approached with caution in children with acute leukaemia or large lymphomas, as it may precipitate tumour lysis syndrome. The presence of pancytopenia increases the risk of perioperative haemorrhage, and alternatives to blood transfusion, such as desmopressin and antifibrinolytic agents, should be considered during surgery. Recent evidence suggests that intraoperative cell salvage, when combined with leucodepletion filters, can be safely utilized in oncological surgery.

Given that 70% of children with cancer experience significant pain during their treatment, effective pain management is essential. Severe pain often necessitates the use of short or long-term opioids, administered either by the patient or by nursing staff. A multimodal approach to analgesia, including regional anaesthesia techniques, can be beneficial, but caution is required due to the increased risk of haematoma in this patient population.

Anaesthesia Consideration for Paediatric Radiology and Radiotherapy

Diagnostic and interventional radiology procedures, as well as radiotherapy, often necessitate the involvement of an anaesthesiologist to facilitate the procedures, primarily through monitored anaesthesia care (MAC) or general anaesthesia (GA). Key concerns include the challenges associated with non-operating room anaesthesia, special unit layouts with restricted access to patients, radiation safety considerations, special precautions related to specific procedures, and the management of the delicate paediatric cancer population.

Considerations for Non-operating Room Anaesthesia (NORA)

The anaesthesia team should include paediatric-trained anaesthesia providers and anaesthetic assistants experienced in conducting paediatric NORA. Familiarity with the area, procedures, and equipment is essential to ensure safe anaesthesia management. Anaesthesia equipment must be sufficient to handle both routine anaesthesia care and potential crises that may arise. Specifically for MRI, the GA machine, airway devices, infusion and TCI pumps, and monitoring devices must be MRI-compatible.

The unique layout of radiology units, where patients are isolated in scanning or treatment rooms to prevent radiation hazards to others, presents challenges in efficiently monitoring and accessing patients. To address this, a second concurrent monitoring unit should be set up in the control room, allowing anaesthesiologist and staff to monitor the patient closely while the scanning or procedure is in progress. Effective planning and communication between the anaesthesia and radiology teams are crucial for anticipating potential issues and managing any acute medical and anaesthesia problems that may arise.

Figure 1: General anaesthesia set up for Non-operating Room Anaesthesia

Figure 2: Second monitoring unit in MRI control room

Anaesthesia Techniques for Radiology and Radiotherapy Procedures

CT scans, MRI, and external-beam radiotherapy are non-painful procedures; however, due to the need for cooperation and immobility, anaesthesia is often required for children. The type of anaesthesia varies from MAC to GA, depending on the child's age, level of cooperation, and the type and duration of the procedure. For most interventional radiology procedures, GA is required.

Monitored anaesthesia care can be achieved using intravenous anaesthetic agents, with oxygen delivered via nasal cannula or face mask. For GA, supraglottic airway devices are mainly used, and tracheal intubation is rarely necessary. Commonly used GA drugs include inhalational agents like sevoflurane, and intravenous agents such as propofol, ketamine, and midazolam. Target-controlled infusion (TCI) of propofol is recommended for precise dosing. Analgesia can be provided with boluses of fentanyl or TCI remifentanil.

Since the patient is positioned away from the GA machine to accommodate the large scanning or radiotherapy equipment, extended-length anaesthesia circuits, oxygen tubings, intravenous giving sets, and infusion tubings are necessary. These should be securely fastened at key points and tested to ensure stability during any movement of the patient's bed required for the procedure.

In external-beam radiotherapy, a mould such as a rigid mask covering the patient's head or a cast covering the body is used to ensure the accuracy of the radiotherapy beams targeting the cancer site. However, this mould can present challenges. For example, a head mould may prevent optimal positioning of the airway device and impede rapid access to the airway during an emergency. In addition, a body cast could restrict chest movement during breathing or ventilation, and it may also lead to pressure sores. To address these concerns, the mould should be carefully prepared during the radiotherapy simulation to ensure that it fits well with the airway device that will be used and that it does not obstruct chest movement.

Management of the Delicate Paediatric Cancer Population

It is important to note that radiotherapy is not an elective procedure but a critical component of the patient's cancer treatment. If the patient contracts an infection or there is a need to postpone the procedure, a thorough assessment should be conducted, followed by a joint discussion and decision-making process between the anaesthesiologist and the paediatric oncologist.

Taking a detailed drug history and reviewing the drug chart are crucial, as these children are often prescribed analgesics, antiemetics, and occasionally anxiolytics. It is essential to prevent double dosing of the same medication and to avoid administering drugs from the same class to minimize the risk of complications.

Pre-operative laboratory tests, such as full blood count and renal profile, are typically required before procedures but are not usually necessary for a single CT or MRI scan. In paediatric oncology patients, lower normal levels should be accepted. For a series of radiotherapy sessions, conducting blood tests at weekly or two-weekly intervals is generally acceptable, following a discussion between the anaesthesiologist and the paediatric oncologist.

Patients are at a higher risk of gastric aspiration due to their underlying comorbidities, stress, chemotherapy-induced factors, or opioid use. Ensuring proper fasting periods is mandatory to reduce this risk.

Difficult intravenous access is a common challenge in paediatric oncology cases. Ultrasound-guided cannulation can be helpful in these situations. Long-term intravenous access may be necessary for patients undergoing a series of daily treatments, such as a 3 to 6-week course of external-beam radiotherapy. Infection control practices are essential when using long-term intravenous lines to prevent complications.

The airway management of paediatric oncology patients can be challenging, particularly in those with mucositis secondary to chemotherapy or due to frequent airway instrumentation during a series of radiotherapy treatments. These patients are more prone to airway oedema, airway bleeding, and laryngospasm. Management should be tailored to each individual case, with anticipation of potential complications. Consideration to use supraglottic airway devices should be in place to minimize airway manipulation and reduce the risk of complications.

Hypothermia is a potential risk for children undergoing procedures in the radiotherapy unit and radiology department, as patient exposure is often required for the procedure itself, and to prevent deflection of the radiotherapy beam. To maintain normothermia, steps such as using mattresses and blankets, and wrapping the limbs should be implemented.

Anaesthesiologists may encounter paediatric patients and their parents or carers once or multiple times during radiotherapy sessions. As such, they are responsible for addressing the psychological well-being of both the patient and the parents. Coping with cancer and its treatment is challenging for the child, regardless of age, as well as for the parents. Anaesthesia delivery should be child-centred and aim to minimize trauma. The presence of parents and the use of distraction tools are often necessary for younger children. For older children, understanding and respecting their requests and needs can help foster a better bond between the anaesthesiologist and the patient.

References

1. Ministry of Health. *Incidence of childhood cancer in Malaysia 2007-2016.* 2016;**1**:1-27
2. Universiti Kebangsaan Malaysia Medical Centre. *Guidelines on blood and blood components transfusion.* 2014;**1**:1-3
3. M. Sara & O. Lauren. Anaesthesia for paediatric radiotherapy. *Anaesthesia Tutorial of The Week.* 2020;ATOTW **423**:1-7
4. Z. Kostense & J. de Ruiter. Anaesthesia for children with cancer. *BJA Education.* 2024;**24**(7):231-237
5. S. Barnaby & M. Kylie. Anaesthetic considerations for paediatric oncology. *Anaesthesia Tutorial of The Week.* 2013;ATOTW **280**:1-8
6. O. Louise & J.B. Liam. Anaesthetic management of the child with haematological malignancy. *Continuing Education in Anaesthesia, Critical Care & Pain.* 2013;**13**(5):158-164
7. C. Sims, D. Weber & C. Johnson. A Guide to Pediatric Anesthesia. *Springer.* 2020;**2**:745-746

Regional Anaesthesia for Palliative Surgery

Fauziah Ahmad[1], Afifah Samsudin[1], Nor Haliza Zainol Abidin[2], Siti Aznida Ab Karim[1], Nurafza Ahmad Hisham[2]
[1]Department Anaesthesiology & Intensive Care, Faculty of Medicine, Universiti Teknologi MARA, Selangor, Malaysia
[2]Department Anaesthesiology & Intensive Care, Hospital Al-Sultan Abdullah, Universiti Teknologi MARA, Selangor, Malaysia

'In caring for those approaching the end of life, we must strive to be the gentle hands that bring comfort and serenity with every touch, ensuring their final chapters are filled with dignity and peace'

INTRODUCTION

The global incidence and mortality rates of advanced diseases have been rising over the decades, influenced by factors such as the ageing population, lifestyle changes, and genetic predispositions.[1] In Malaysia, cancer remains a significant health concern, being the fourth leading cause of death.[2] The number of cases increased from 10.5% in 2021 to 12.6% in 2022, with 168,822 new cancer cases documented between 2017 and 2021.[2,3] Advancements in healthcare have led to more patients surviving advanced diseases.[1]

Palliative surgery has become more common as a means to improve the quality of life and comfort in patients with advanced, life-limiting conditions. Unlike curative surgery, palliative surgery focuses on alleviating pain, managing symptoms, addressing complications arising from advanced diseases and improving the patient's overall well-being.[4] Its effectiveness relies heavily on a multidisciplinary approach involving surgeons, anaesthesiologists, and other healthcare professionals.

Administering general anaesthesia (GA) in these cases can be particularly challenging due to their complex health profiles, which often include multiple comorbidities, advanced disease and compromised physiological reserves.[5,6] These factors make them more susceptible to anaesthesia-related complications, including cardiovascular and respiratory depression, postoperative cognitive dysfunction (POCD) and delirium. GA can exacerbate physiological stress, further compromising the quality of life in this vulnerable population.[5]

Given these complexities, regional anaesthesia (RA) has emerged as a valuable tool in palliative surgery, providing effective pain management and minimising the side effects of GA. Emerging evidence also suggests that RA potentially prolong survival in some instances.[6,11] However, further research is needed to validate these findings. RA techniques, from peripheral nerve blocks to neuraxial analgesia, are widely used in various surgical procedures, including primary tumour resections and other palliative interventions.[6]

This article explores the benefits, considerations, case reports, ongoing research and future of RA in palliative surgery.

BENEFITS OF REGIONAL ANAESTHESIA

Regional anaesthesia can be used as an adjunct to GA to ensure optimal intraoperative and postoperative pain relief or as a viable option as the sole anaesthetic, particularly for patients who may not respond well to GA. It can also be used for postoperative analgesia.

- **Improved pain control and comfort:** RA offers superior pain relief compared to systemic analgesics. Techniques such as nerve blocks and epidurals can extend prolonged pain relief, significantly enhancing patient comfort during and after surgery.[7,8] It may also help prevent persistent postsurgical pain (PPP) and address the problem of inadequate pain relief due to opioid tolerance in cancer and advanced disease patients.[6]

- **Reduced systemic effects:** By targeting specific body areas, RA reduces the need for GA, thus decreasing the risk of cardiovascular and respiratory depression. This makes RA a safer alternative, particularly beneficial for high-risk patients with comorbidities, as it minimises physiological stress and lowers the risk of postoperative complications.[7,8] For example, several case reports have highlighted the effectiveness of RA as sole anaesthesia in patients with compromised cardiopulmonary function. In these cases, the use of regional techniques helped to maintain hemodynamic stability both during surgery and in the postoperative period.[9,10]

- **Reduction of opioid use:** RA can significantly reduce opioid consumption, minimising opioid-related side effects such as nausea, vomiting and constipation.[7]

- **Lower risk of cognitive complications:** Unlike GA, RA significantly reduces the risk of postoperative cognitive dysfunction (POCD) and delirium, which is particularly beneficial in palliative care, where maintaining cognitive function is essential.[8]

- **Enhanced recovery:** RA effectively controls pain, facilitating early mobilisation and rehabilitation, leading to faster recovery times and shorter hospital stays, which is particularly beneficial for those with limited life expectancy.[8]

- **Improved quality of life:** Effective pain management with RA improves mobility, mood and overall satisfaction. It has been associated with improved long-term survival and reduced cancer recurrence, although further research is needed to confirm these findings.[4]

ANAESTHETIC CONSIDERATIONS IN PALLIATIVE SURGERY

Regional anaesthesia offers significant benefits for palliative surgery patients. Managing these patients, who often present with multiple comorbidities and compromised physiological reserves, requires a strategic approach to patient selection and anaesthetic planning. In many cases, RA can serve as the primary anaesthetic technique, providing adequate pain control while reducing the risks associated with GA, especially in high-risk patients. For specific surgeries such as limb amputations, mastectomy and even certain abdominal procedures, RA can be used as sole anaesthesia, supplemented with mild sedation. This approach is particularly beneficial for patients who are unable to tolerate GA due to advanced cardiopulmonary disease or frailty.[9] For example, thoracic paravertebral and brachial plexus blocks have been successfully used as the sole anaesthetics in high-risk patients undergoing mastectomy or upper limbs surgeries, offering effective pain control and stable perioperative outcomes.[9,10]

Patient Assessment

Health Status Evaluation

A comprehensive evaluation of the patient's overall health status is essential when considering RA for palliative surgery. This assessment should include a detailed examination of their cardiovascular, pulmonary, renal, hepatic functions and nutritional status, as these aspects are often compromised in patients with advanced disease. Understanding the patient’s health status helps determine the patient’s ability to tolerate the physiological effects of RA and surgery and identify potential potential complications.[7]

Given the complexities associated with palliative care patients, selecting suitable patients for RA may be challenging. Patients with severe comorbidities, coagulopathies, severe infections, or compromised neurological status are at an increased risk for complications such as bleeding, infection, or worsening of existing conditions.[5,7,8] In such cases, preoperative optimisation and correction of reversible abnormalities are essential to enhance patient outcomes and reduce risks associated with surgery.

Despite these challenges, RA remains a viable and often safer alternative to GA in many palliative patients. In cases such as limb amputations for advanced cancer or thoracotomy for pleurodesis, RA alone, combined with mild sedation, can provide adequate anaesthesia, reducing the need for GA and its associated risks. This technique not only reduces systemic complications but also improves patient recovery, allowing faster mobilisation and shorter hospital stays.[10]

Surgical Considerations

Understanding the specific surgical procedure, including type, location, extent, and duration, is essential to determine suitable RA techniques. Major abdominal or thoracic surgeries might require techniques like epidural anaesthesia, while peripheral nerve blocks may be suitable for limb surgery or minor procedures.[6,7] In cases involving high-risk patients, the use of RA not only provides adequate pain relief but also minimises the physiological stress and potential complications associated with GA, making it a preferred option in selected palliative surgeries.

Tables 1 and 2 provide an overview of various clinical indications, palliative surgery, and examples of RA techniques that can be utilised.

Table 1: Common clinical indications and palliative surgery

Clinical Indication	Palliative Surgery
Pain relief	Debulking surgery
	Fixation of pathological fracture
	Relief of obstruction / compression
Malignant effusion	Pleurodesis
	Pericardial Window
Relief of obstruction	Gastrojejunostomy
	Biliary stenting
	Choledoco-enterostomy
	Nephrostomy / ureteric stenting
	Colostomy or ileostomy creation
	Fistula management surgery
Haemorrhage control	Embolisation of bleeding tumours
	Pelvic exenteration
	Gastrointestinal bleeding control (e.g. sclerotherapy, laser coagulation)
Functional improvement	Thoracocentesis
	Chest tube insertion
	Surgical stabilisation for bone metastases (e.g. internal fixation)
Fungating mass in the breast	Simple / toilet mastectomy
Amputation	Limb amputation

Source of information:
Garg, R., & Bhatnagar, S. (Eds.). (2021). *Textbook of onco-anesthesiology*. Singapore: Springer Singapore.

Table 2: Common regional anaesthesia techniques, their role, and use in palliative surgery

Regional Anaesthesia Technique	Role	Use in Palliative Surgery
Epidural Anaesthesia	Surgical Anaesthesia, Analgesia, Adjunct to GA	Suitable for major abdominal, thoracic, pelvic, and lower limb surgeries, including colon resection, thoracotomy, and pelvic tumour debulking.
Spinal Anaesthesia	Surgical Anaesthesia, Analgesia	Suitable for lower abdominal, pelvic, or lower limb procedures such as stoma creation, ureteric stenting or lower limb amputation where GA may be high risk.
Paravertebral Block	Surgical Anaesthesia, Analgesia, Adjunct to GA	Ideal for unilateral thoracic or abdominal surgeries, including mastectomy or VATS, reducing opioid requirements.
Brachial Plexus Block (e.g., Interscalene, Supraclavicular)	Surgical Anaesthesia, Analgesia, Adjunct to GA	Effective for upper limb procedures, including amputations or fracture fixation in patients with metastatic disease.
Lumbar Plexus Block (e.g., Psoas Compartment Block)	Surgical Anaesthesia, Analgesia, Adjunct to GA	Useful in lower limb procedures, such as hip fracture repair or amputation, in frail or high-risk palliative patients.
Fascia iliaca Block	Analgesia	Helpful for hip pain or fractures.
Popliteal Sciatic Nerve Block	Surgical Anaesthesia, Analgesia, Adjunct to GA	Suitable for palliative surgeries involving the foot or ankle, such as foot amputation or ulcer debridement.
Transversus Abdominis Plane (TAP) Block	Analgesia, Adjunct to GA	Effective for managing postoperative pain in lower abdominal and pelvic surgeries, such as Tenckhoff insertion, open hernia repair, gastrostomy, or stoma creation.
Erector Spinae Plane Block	Analgesia, Adjunct to GA	Provides broad pain control for thoracic and abdominal surgeries such as colorectal surgery, VATS, rib fractures.
Pectoral Nerve Blocks (PECS I and II)	Analgesia, Adjunct to GA	Provides analgesia for thoracic wall pain and palliative breast surgeries such as mastectomy for fungating tumours or axillary clearance.
Saphenous Nerve Block (Adductor Canal Block)	Analgesia	It offers pain control for knee-related procedures such as arthroplasty or knee replacement surgery without significantly affecting motor function.
Intrathecal Opioids (e.g., Morphine, Fentanyl)	Analgesia, Adjunct to GA	Provide long-lasting analgesia without continuous infusions in major lower abdominal, pelvic, and lower limb surgeries, such as pelvic exenteration or colon resection.
Celiac Plexus Block	Analgesia	Can be used to relieve severe abdominal or visceral pain, particularly in patients with advanced pancreatic or abdominal cancers, particularly when opioids fail to control visceral pain in palliative care settings.

VATS: video-assisted thoracoscopy;
Sources of information:

- Hutton, M., Brull, R., & Macfarlane, A. J. R. (2018). Regional anaesthesia and outcomes. *BJA Education*, 18(2), 52-56.
- Barash, P. G., Cullen, B. F., & Stoelting, R. K. (Eds.). (2017). *Clinical Anesthesia* (9th ed.). Wolters Kluwer.
- Albrecht, E., & Chin, K. (2020). Advances in regional anaesthesia and acute pain management: a narrative review. *Anaesthesia*, 75, e101-e110.

Several case reports emphasised the use of RA as the sole anaesthetic technique in palliative surgery. For example, in a case report by Kulkarni et al., a thoracic paravertebral block was performed on a 92-year-old patient with cardiopulmonary dysfunction who underwent radical mastectomy. The procedure effectively provided adequate anaesthesia while maintaining cardiopulmonary stability.[9] This highlights the advantages of RA as sole anaesthesia in palliative surgery, as this approach can reduce stress on the cardiovascular and respiratory systems compared to GA.

Another case report by Mumin et al. highlights the use of RA in a patient with end-stage metastatic osteosarcoma who required a right above-the-elbow amputation. The patient's anaesthetic management was particularly challenging due to a large mediastinal mass that severely compromised the patient's pulmonary reserve. To address these challenges, intraoperative and postoperative care were successfully managed using an interscalene block as sole anaesthesia.[10] This case showcases how RA can offer a safer approach in complex scenarios.

Anatomical and Technical Challenges

Anatomical variation and the anaesthesiologist's skill can significantly impact RA success. Tumour invasion, oedema, scarring, and prior surgeries or radiotherapy can alter nerve block landmarks, making structure identification challenging. For example, in patients with previous neck or thoracic radiotherapy, fibrosis and distortion of the brachial plexus can complicate nerve block placement.[13] However, ultrasound guidance significantly enhances the accuracy of these blocks, allowing for real-time visualisation of anatomical structures and facilitating precise needle placement. Preprocedural neuraxial scanning before epidural anaesthesia also helps identify challenging anatomical structures, especially in obese or oedematous patients.[15,16]

Patient Comfort and Sedation

Patients undergoing the RA procedure or surgery may experience anxiety, discomfort, and difficulty maintaining the required position.[7,17] These factors can make the procedures more challenging and increase the risk of complications. To address this, mild sedation with dexmedetomidine or ketamine can be administered. Positioning support, such as pillows and blankets, can help maintain the necessary positioning for the procedure.

Duration of Regional Anaesthesia

Regional anaesthesia's main limitation is its short duration, typically lasting no longer than 16 hours with a single injection technique.[14] However, this limitation can be addressed through several strategies, including pharmacological adjuncts, sustained-release local anaesthetics and continuous catheter techniques (Table 3). Continuous peripheral nerve catheter techniques provide prolonged analgesia post-surgery, offering control over the duration and intensity of the block. Moreover, sustained-release local anaesthetics, such as liposomal bupivacaine, are being explored for their potential to extend analgesia duration with a single injection, although further evidence is needed to support widespread use.[14]

Table 3: Strategies to prolong the duration of regional anaesthesia

Method	Advantages	Limitations
Local Anaesthetic Adjuncts (e.g. adrenaline, dexmedetomidine, dexamethasone)	Easy to administer	Off-label use when administered perineurally, except for adrenaline.
Sustained-Released Local Anaesthetic (e.g. liposomal bupivacaine)	Easy to administer	Approved only for specific blocks (e.g. interscalene brachial plexus block, TAP block and surgical infiltration). Lack of solid evidence supporting its benefits. It is more expensive than plain bupivacaine.
Continuous Catheter Technique	Allows continuation of analgesia in the postoperative period. Flexibility and control of duration and intensity of analgesia.	It is more technically demanding to perform than single-injection blocks. Resource- and labour-intensive needs organised follow-up, such as an Acute Pain Service, until catheter removal.

TAP: Transversus abdominis plane.
Adapted from Albrecht, E., & Chin, K. J. (2020). Advances in regional anaesthesia and acute pain management: A narrative review. *Anaesthesia*, 75(S1), e101-e110. https://doi.org/10.1111/anae.14868

Chemotherapy Agents

Chemotherapy can influence the safety and effectiveness of RA due to its effect on various organs. Bone marrow suppression from chemotherapy may cause anaemia and thrombocytopenia, increasing the risk of periprocedural bleeding. Specific chemotherapy agents, like methotrexate, vincristine, and cisplatin, are associated with neurotoxicity and autonomic dysfunction, such as peripheral neuropathy and orthostatic hypotension.[7,20] Assessing baseline neurological status and exercising vigilance during procedures is essential.

Multidisciplinary Collaboration

A multidisciplinary team approach is essential in palliative surgery to ensure holistic and patient-centred care. Effective collaboration and coordinated efforts between surgeons, anaesthesiologists, palliative care specialists and rehabilitation therapists are vital in creating tailored care plans that address symptom control and functional recovery.[4,21] Regular team meetings facilitate real-time adjustments of care plans based on patient progress, helping minimise complications and optimise outcomes. For example, palliative surgery for bone metastases often requires close coordination between anaesthesiologists, palliative care specialists, and physiotherapists to ensure optimal postoperative mobility and pain control.

Anaesthesiologists play a crucial role in managing pain and anaesthesia, working with the palliative care team to develop individualised pain management plans.[5,6] Their expertise in selecting appropriate RA techniques ensures optimal pain control while minimising the risks associated with GA.[6,22] The palliative care team focuses on enhancing the quality of life by managing symptoms, providing emotional support, and assisting with decision-making. Their involvement extends beyond medical management to address patients' and their families' emotional and psychosocial needs, especially during challenging times.[18]

Surgeons perform necessary surgical interventions to alleviate symptoms and improve the patient's quality of life, while physiotherapists, occupational therapists, and speech therapists contribute by helping patients maintain or improve their physical and functional abilities through rehabilitation.[22]

This collaborative, team-based approach ensures that care is tailored to meet the evolving needs of each patient, providing evidence-based, patient-centred care. Guided by established practices and guidelines, this promotes comprehensive care for palliative surgery patients.

Ethical Considerations

Decision-making and Informed Consent

In palliative surgery, decision-making for surgical and invasive procedures is inherently complex, as it is crucial to align medical care with ethical principles and patient values, considering patients' limited life expectancy and poor performance status. Therefore, this decision-making process is best managed using a multidisciplinary approach and should always be made with the patient's best interest in mind.[21]

The patient, their caregiver or legal guardian and the managing healthcare team should engage in thorough discussions to evaluate symptom severity, care goals, and the potential benefits of palliative surgery on the patient's quality of life.[4] Transparent and empathetic communication about the surgery's purpose, risks, benefits, and alternatives, including non-surgical options, ensures a comprehensive understanding among all involved parties. Consent from a legal guardian is necessary for patients with diminished decision-making capacity.[22,23]

Patient Autonomy and Advance Directives

Patient autonomy allows individuals to make decisions about their medical care, including refusing treatments based on their values. Advanced directives, such as do not attempt resuscitation (DNAR) orders are crucial in respecting patient autonomy, even if they are unable to communicate them during a medical emergency.[23] Detailed discussions with patients and families are essential to ensure these directives are respected perioperatively.

Patients with advanced disease are at higher risk of anaesthesia-induced complications, such as cardiovascular instability, increasing the complexity of care to minimise the risk of cardiac arrest. Managing perioperative care for patients with DNAR orders presents significant challenges, particularly in balancing the need for anaesthesia while respecting these directives.

To navigate these challenges, the American Society of Anesthesiologists (ASA) recommends three options for managing DNAR orders perioperatively:

1. **Full Resuscitation:** Suspend DNAR throughout the perioperative period.

2. **Limited Resuscitation Based on Specific Procedures:** Limit resuscitation to agreed-upon procedures.

3. **Limited Resuscitation Based on Specific Goals and Values:** Tailor resuscitation to the patient's goals and values.[23]

Before making this important decision, the patient, their caregiver or legal guardian, and the healthcare team must thoroughly discuss this matter, guided by the hospital or local policy.

EXAMPLES OF CASE REPORTS

The following case examples of successful management of patients undergoing palliative surgery under RA in our institution:

Case 1: Paravertebral Block for a Patient with Significant Comorbidities Undergoing Mastectomy[24]

Patient Profile: A 76-year-old woman with invasive breast cancer and long-standing severe restrictive lung disease with severe pulmonary hypertension.

Procedure: She underwent a right mastectomy using a thoracic paravertebral block (TPVB) for anaesthesia supplemented with IVI dexmedetomidine (Figure 1).

Outcome: Additional pain relief was provided using boluses of IV ketamine intraoperatively, resulting in adequate pain control and stable haemodynamics. Analgesia was continued via TPVB catheter infusion in the postoperative period, resulting in reduced opioid usage and improved recovery. She was discharged on the fourth day after the surgery and showed no signs of recurrence during follow-up.

Case 2: Brachial Plexus Block for a Patient with Metastatic Cancer Undergoing External Plating of Pathological Fracture of the Humerus

Patient Profile: A 75-year-old male with advanced lung adenocarcinoma, a pathological fracture of the left humerus, and multiple metastases to the lung, liver, bone, and adrenal glands. The patient also had a large lung mass obliterating the left bronchus.

Procedure: He underwent external plating of the left humerus with combined supraclavicular and infraclavicular brachial plexus block for anaesthesia (Figure 2).

Outcome: Effective pain control with stable haemodynamics intraoperatively. The patient regained full sensation and movement in his left hand by the third postoperative day. Discharged three weeks later and continued with chemo-radiotherapy. He survived for six months with palliative therapy and family support despite a predicted median survival rate of less than two months.

Figure 1: Right paravertebral block and catheter insertion (left); Intraoperative sedation with IVI dexmedetomidine (right)

Figure 2: Combined left supraclavicular and infraclavicular brachial plexus block and infraclavicular catheter insertion

ADVANCEMENTS IN REGIONAL ANAESTHESIA TECHNIQUES

Research and clinical trials continuously refine RA techniques, unveiling more of its use in palliative surgery. Recent advancements include:

- **Fascial plane blocks:** These blocks provide widespread analgesia with a single injection, which is beneficial in palliative care settings where patients may have widespread pain.[6]
- **Sustained-release local anaesthetics:** Formulations like liposomal bupivacaine offer extended pain relief from a single injection, reducing additional medication needs and potentially enhancing patient comfort.[14,19]
- **Continuous peripheral nerve block techniques:** These techniques provide prolonged post-surgery pain relief, improving patient comfort and recovery while decreasing reliance on other medications like opioids or non-steroidal anti-inflammatory drugs (NSAIDs).[14]
- **Ultrasound technology:** Ultrasonography advancements have revolutionised RA by improving accuracy and reducing complications. This is particularly important in palliative care, where patients often have anatomical distortion and multiple comorbidities.[16]
- **Machine learning and image-recognition technologies:** Incorporating artificial intelligence (AI) in ultrasound technology could enhance image quality for ultrasound-guided RA and improve the accuracy and safety of RA techniques.[25]
- **Neuromodulation techniques:** The use of electrical currents or magnetic fields to modulate nerve activity is being explored for managing chronic and refractory pain, a common issue in palliative care.[18]

FUTURE PROSPECTS OF REGIONAL ANAESTHESIA IN PALLIATIVE SURGERY

The future of regional anaesthesia in palliative surgery is advancing with the integration of emerging technologies, particularly artificial intelligence (AI) and machine learning (ML).[25,26] These technologies are expected to enhance the precision, safety, and efficacy of ultrasound-guided RA techniques. AI-enhanced ultrasound systems are already being used in clinical practice, allowing anaesthesiologists with varying experience levels to perform nerve blocks with greater accuracy by helping them identify important anatomical structures and landmarks more easily.[26] This integration has the potential to significantly reduce procedural complications while improving patient outcomes, particularly in complex or high-risk cases.

Technology-based learning, including virtual (VR) and augmented reality (AR), holds great promise for enhancing the training of healthcare professionals, particularly anaesthesiologists. These technologies provide realistic simulations for practising and refining skills in a risk-free environment, leading to improved accuracy, ease of performance, and reduced procedural duration for novice providers.[25-27] This is especially pertinent in palliative care, where the focus is on enhancing comfort and quality of life with minimal risk.

Training tools such as AI-driven simulation platforms can analyse trainees' performance during ultrasound-guided RA procedures, providing real-time feedback and helping them improve their proficiency in a controlled environment.[26] ML algorithms can predict areas where trainees might struggle and adjust the training accordingly, creating a more personalised learning environment.[26,27] By incorporating AI and ML into RA training, anaesthesiologists can gain more confidence and competence in using advanced RA techniques, ultimately improving patient care, especially in high-risk palliative settings.[26,27]

ONGOING RESEARCH

Numerous studies and case reports have illustrated the efficacy and advantages of RA in palliative surgery patients. There is increasing evidence suggesting that RA may exert effects beyond pain management, potentially influencing tumour progression and metastasis. While this area of investigation is still developing, the ability of RA to modulate stress responses and inflammation could have significant implications for cancer prognosis.[28]

Furthermore, RA has demonstrated a potential impact on cancer-related outcomes, thus influencing cancer recurrence rates by decreasing the necessity for systemic opioids and modulating the immune response. It is hypothesised that one mechanism by which RA reduces cancer recurrence is through anti-inflammatory effects and reduction of surgical stress response. Studies also found that RA inhibits tumour recurrence by blocking sodium channels of cancer cells and improves immune function.[29,30]

In a recent meta-analysis investigating the effect of RA on cancer recurrence and metastases, it is concluded that RA, used alone or adjunctively with GA, is associated with a lower risk of cancer recurrence, particularly in patients with prostate cancer. However, no significant effects were observed on local recurrence or distant metastasis.[11]

Local anaesthetics given during RA may protect against tumour growth and metastasis. They appear to act via several mechanisms, including induction of apoptosis, prevention of cell proliferation, and gene expression modulation.[31] Additionally, in vivo studies suggest intravenous lidocaine can reduce tumour size and metastatic load in mouse cancer models.[32]

There are also studies which suggest that opioids may promote tumour growth by causing immunosuppression and enhancing cancer metastasis.[33] Therefore, employing regional anaesthesia, which can minimise or eliminate the need for opioids, may help mitigate this effect.

Nonetheless, systematic reviews looking at the association between survival and cancer recurrence generally found that current evidence is insufficient to draw concrete conclusions regarding the benefit of RA. A recent large systematic review, which included more than 54,000 patients, found that perioperative RA is associated with improved survival but not reduced cancer recurrence.[31] While the potential benefits of RA in cancer care are an exciting area of research, the current evidence does not yet support definitive conclusions regarding its impact on survival and cancer recurrence. These mixed results might vary depending on the type of cancer, surgical procedure, and individual patient factors.[28,31]

Even when comparing GA to RA amongst cancer patients undergoing surgery, systematic reviews reveal that overall survival and recurrence-free survival in late-stage cancers were similar.[31] Ongoing research and future studies will be critical in clarifying these relationships and guiding clinical practice. For now, RA is primarily valued for its role in effective pain management and improving the quality of life for cancer patients, with its potential oncological benefits remaining an area of active investigation.

CONCLUSION

Regional anaesthesia plays a crucial role in palliative surgical care for patients with advanced disease, enhancing patient comfort and quality of life. Its benefits, multidisciplinary approach, and ongoing advancements make it an invaluable tool in palliative care. Integrating RA in palliative surgery demonstrates a patient-centred approach that ensures comprehensive and compassionate care throughout the patient's palliative journey. Ongoing research into the potential oncological benefits of RA and its continuous advancement will also be pivotal in shaping the future of palliative care.

References

1. World Health Organization. (2022). World health statistics 2022: Monitoring health for the SDGs, sustainable development goals. Retrieved from: https://www.who.int/publications/i/item/9789240074323

2. Department of Statistics Malaysia. (2023). Statistics on causes of death, Malaysia, 2023. Department of Statistics Malaysia. Retrieved from: https://www.dosm.gov.my/uploads/release-content/file_20231030100000.pdf

3. National Cancer Registry Department, Institut Kanser Negara. (2023). Summary of Malaysia National Cancer Registry Report 2017-2021. Ministry of Health Malaysia. https://nci.moh.gov.my/images/pdf_folder/SUMMARY-OF-MALAYSIA-NATIONAL-CANCER-REGISTRY-REPORT-2017-2021.pdf

4. Lilley, E. J., Farber, O. N., & Cooper, Z. (2024). Palliative surgery: state of the science and future directions. British Journal of Surgery, 111(3), znae068

5. Sawyer, R. J., & McCartney, C. J. L. (2001). Anaesthetic considerations in the management of the patient with advanced malignancy. Current Anaesthesia & Critical Care, 12(6), 302-308

6. Hutton, M., Brull, R., & Macfarlane, A. J. R. (2018). Regional anaesthesia and outcomes. BJA Education, 18(2), 52-56

7. Barash, P. G., Cullen, B. F., & Stoelting, R. K. (Eds.). (2017). Clinical Anesthesia (9th ed.). Wolters Kluwer

8. Miller, R. D., Eriksson, L. I., Fleisher, L. A., Wiener-Kronish, J. P., Young, W. L., & Cohen, N. H. (Eds.). (2020). Miller's Anesthesia (9th ed.). Elsevier

9. Kulkarni, K., Dubey, P., & Ray, M. S. (2017). Management of radical mastectomy under sole thoracic paravertebral block in a 92 years old patient with cardiopulmonary dysfunction. ARC J Anesthesiol, 2, 1-3

10. Hakim, M., Burrier, C., Bhalla, T., Raman, V. T., Martin, D. P, Dairo.O & Tobias, J. D. (2015). Regional anesthesia for an upper extremity amputation for palliative care in a patient with end-stage osteosarcoma complicated by a large anterior mediastinal mass. Journal of Pain Research, 641-645

11. Xie, S., Li, L., Meng, F., & Wang, H. (2024). Regional anesthesia might reduce recurrence and metastasis rates in adult patients with cancers after surgery: a meta-analysis. BMC anesthesiology, 24(1), 19

12. Allman, K., Wilson, I., & O'Donnell, A. (Eds.). (2016). Oxford handbook of anaesthesia. Oxford University Press

13. Bowen, B. C., Verma, A., Brandon, A. H., & Fiedler, J. A. (1996). Radiation-induced brachial plexopathy: MR and clinical findings. American Journal of Neuroradiology, 17(10), 1932-1936

14. Albrecht, E., & Chin, K. (2020). Advances in regional anaesthesia and acute pain management: a narrative review. Anaesthesia, 75, e101-e110

15. Karmakar M.K., & Jinn Chin K (2017). Spinal sonography and applications of ultrasound for central neuraxial blocks. Hadzic A(Ed.), Hadzic's Textbook of Regional Anesthesia and Acute Pain Management, 2e. McGraw-Hill Education

16. Kamdar, B. B., & Hao, D. (2024) Ultrasound guidance for neuraxial anaesthesia technique. UpToDate. https://www.uptodate.com/contents/ultrasound-guidance-for-neuraxial-anesthesia-techniques

17. Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018. (2018). Anesthesiology, 128(3), 437-479

18. Cherny, N. I., Fallon, M. T., Kaasa, S., Portenoy, R. K., & Currow, D. C. (2021). Oxford Textbook of Palliative Medicine (6th ed.). Oxford University Press

19. Ranganath YS, Seering MS, Marian AA. Curb your enthusiasm: local anesthetic adjuvants for peripheral nerve blocks. ASRA News 2020;45. https://doi.org/10.52211/asra110120.071

20. Allan, N., Siller, C., & Breen, A. (2012). Anaesthetic implications of chemotherapy. Continuing Education in Anaesthesia, Critical Care & Pain, 12(2), 52-56

21. Soon, J. J., Juan, D. W., Ong, W. S., Bek, S., Neo, P. S., Salazar, E., ... & Wong, J. S. (2023). Implementation of a multidisciplinary team and quality of goals of care discussions in palliative surgical oncology patients. Annals of Surgical Oncology, 30(13), 8054-8060

22. Garg, R., & Bhatnagar, S. (Eds.). (2021). Textbook of onco-anesthesiology. Singapore: Springer Singapore

23. American Society of Anesthesiologists. (2023). Statement on ethical guidelines for the anesthesia care of patients with do-not-resuscitate orders. https://www.asahq.org/standards-and-practice-parameters/statement-on-ethical-guidelines-for-the-anesthesia-care-of-patients-with-do-not-resuscitate-orders

24. Ahmad, F., Zainol Abidin, N.H. (2023). Thoracic Paravertebral Block for Mastectomy: A Promising Alternative as Sole Anaesthesia for High-Risk Patients. Malaysian Journal of Anaesthesiology, 2(2, Suppl), S1-2. https://doi.org/10.35119/myja.v2i2(Suppl)

25. Viderman, D., Dossov, M., Seitenov, S., & Lee, M. H. (2022). Artificial intelligence in ultrasound-guided regional anesthesia: A scoping review. Frontiers in Medicine, 9, 994805

26. Mika, S., Gola, W., Gil-Mika, M., Wilk, M., & Misiołek, H. (2024). Artificial Intelligence-Supported Ultrasonography in Anesthesiology: Evaluation of a Patient in the Operating Theatre. Journal of Personalized Medicine, 14(3), 310

27. Mokhtar, M.N., Samsudin, A., Azizeh, A., Ken, W.C., Varma, V., Khalid, I., Tan, K.W., Lim, A., Budiman, M., Hor, C.K., Abdul Shokri, A.F., Xuan, K.P., Izaham, A. (2023). Novice Regional Anaesthesia Practitioners Simulated Training: Which is better - Augmented reality or Tissue Simulation Model? Malaysian Journal of Anaesthesiology, 2(2, Suppl), S1-2. https://doi.org/10.35119/myja.v2i2(Suppl)

28. Sun, Y., Li, T., & Gan, T. J. (2015). The effects of perioperative regional anesthesia and analgesia on cancer recurrence and survival after oncology surgery: a systematic review and meta-analysis. Regional Anesthesia & Pain Medicine, 40(5), 589-598

29. Djamgoz, M. B., Fraser, S. P., & Brackenbury, W. J. (2019). In vivo evidence for voltage-gated sodium channel expression in carcinomas and potentiation of metastasis. Cancers, 11(11), 1675

30. Wang, L., Liang, S., Chen, H., Xu, Y., & Wang, Y. (2019). The effects of epidural anaesthesia and analgesia on T lymphocytes differentiation markers and cytokines in patients after gastric cancer resection. BMC anesthesiology, 19, 1-7

31. Zhang, Y. L., Pei, L. J., Sun, C., Zhao, M. Y., Che, L., & Huang, Y. G. (2021). Regional anesthesia and cancer recurrence in patients with late-stage cancer: a systematic review and meta-analysis. Chinese Medical Journal, 134(20), 2403-2411

32. Xing, W., Chen, D. T., Pan, J. H., Chen, Y. H., Yan, Y., Li, Q., ... & Zeng, W. A. (2017). Lidocaine induces apoptosis and suppresses tumor growth in human hepatocellular carcinoma cells in vitro and in a xenograft model in vivo. Anesthesiology, 126(5), 868-881

33. MacFater, W. S., Xia, W., Barazanchi, A., Su'a, B., Svirskis, D., & Hill, A. G. (2018). Intravenous local anaesthetic compared with intraperitoneal local anaesthetic in abdominal surgery: a systematic review. World Journal of Surgery, 42, 3112-3119

Painful Bone Metastases and Common Sonographic Nerve Blockade

Kamaruddin Ibrahim
Department of Anaesthesiology & Intensive Care, School of Medical Sciences Health, Universiti Sains Malaysia, Kuala Lumpur, Malaysia

INTRODUCTION

Malignancy refers to the presence of cancer cells that can grow locally or spread distally and invade surrounding tissues including nerves. It is common for bony metastases to produce severe pain.

Nerve blocks are often part of a comprehensive pain management strategy alongside other treatments such as analgesics, radiation therapy, and surgery. Integrating nerve blocks into the overall cancer treatment plan requires coordination among oncologists, pain specialists, and other healthcare providers.

Nerve blocks are often used as a method of pain relief in cancer patients, especially when the cancer or its treatment causes significant pain. These blocks can target specific nerves or nerve plexuses to alleviate pain effectively.

Nerve blocks can also be used diagnostically to determine the source of pain in cancer patients. By temporarily blocking nerve signals, we can identify which nerves are transmitting pain signals from the cancerous tissue. Once we identify the responsible nerve, we can plan to damage the nerve by using a neurolytic agent.

Upon referral by the primary team, we must know the exact or probable diagnosis and explain how the malignant tissue induces pain. Involvement of nerve injury will cause neuropathic pain. Clinical assessment for diagnosis of neuropathic pain can be guided by using the painDETECT tool, a neuropathic pain screening tool.

The tumour's location or distal metastases can be precisely deciphered by imaging modalities like CT, MRI, or bone scan.

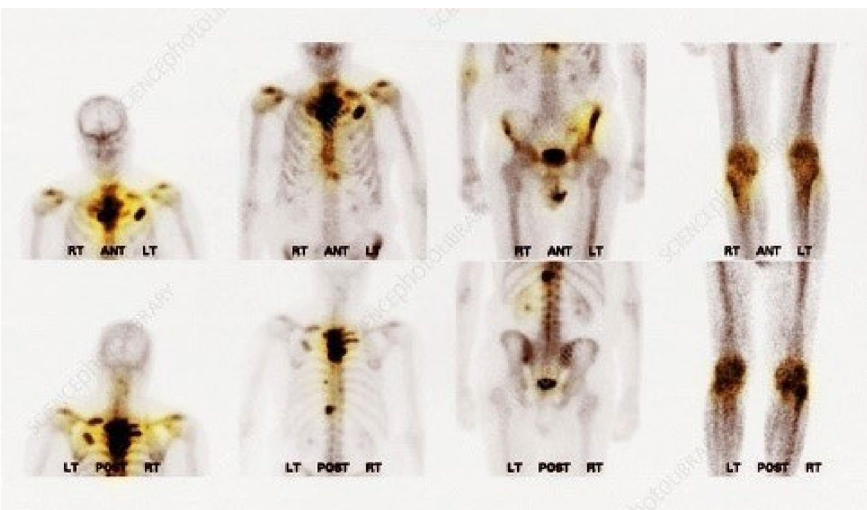

Figure 1: Bone scan showing multiple metastases

PAINFUL RIB METASTASES

Rib metastases can cause localized pain or radiculopathy due to the involvement of intercostal nerves around the ribs. Nerve blocks can be used to target these specific nerves, which are responsible for transmitting pain signals from the ribs.

Several types of nerve blocks can be considered, depending on the location and extent of the rib metastases.

Intercostal Nerve Blocks: These are commonly used for pain relief in cases of rib metastases. It involves injecting a local anesthetic with or without a steroid near the affected nerve to provide temporary. Longer-lasting pain relief is achieved by using alcohol for neurolysis.

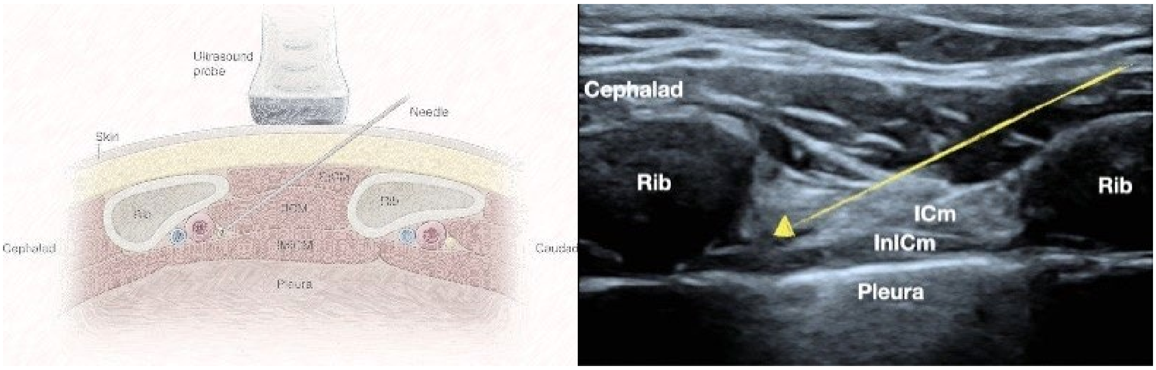

Figure 2: The intercostal nerve lies in the intercostal groove inferior to the intercostal artery. Sonographic guidance with needle tip visualization during injection ensures maximum safety in avoiding pleural puncture

Paravertebral Nerve Blocks: These blocks target the nerve root as they exit the thoracic vertebrae. It can be effective for pain that radiates from the spine to the affected metastatic ribs. The injection can be anterior or posterior to the superior costo-transverse ligament (SCTL) using local anaesthetic with or without steroids. Its advantage is that a single injection can block several levels of ribs or intercostal nerves.

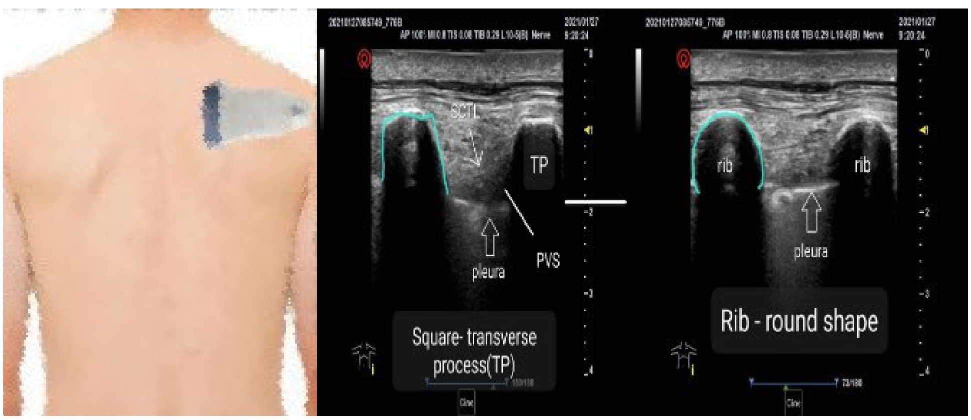

Figure 3: Probe held sagittal on the thoracic spinous process and then moved laterally to visualise the transverse process. Note the difference in the shape of the transverse process (TP), square and rib, round. Identify superior Costo-transverse ligament SCTL

Erector Spinae Plane Blocks: In some cases, identification of TP/SCTL is difficult, especially in obese patients.

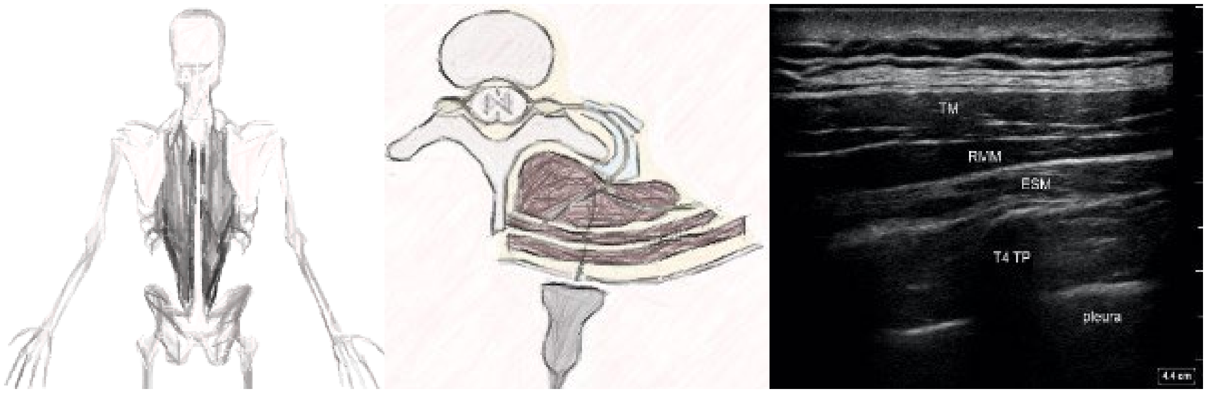

Figure 4: Thoracic erector spinae muscle (ESM) is a boundary to this block. The plane lies between ESM and TP. Touching TP with the tip of the needle ensures its block location and prevents a more anterior needle placement

PAINFUL SCAPULA METASTASES

Intercostal Nerve Blocks: These blocks target the intercostal nerves supplying the shoulder joint. Technically difficult to perform on T1 and T2.

Interscalene Blocks: The brachial plexus is a network of nerves that supply the shoulder and upper arm. Blocks targeting this area can help alleviate pain in the scapula region. However, neurolysis is not possible in this area.

Suprascapular Nerve Block: The suprascapular nerve innervates the shoulder joint and parts of the scapula. Blocking this nerve can provide localized pain relief due to scapula metastases. Radiofrequency neurolysis is possible in this nerve.

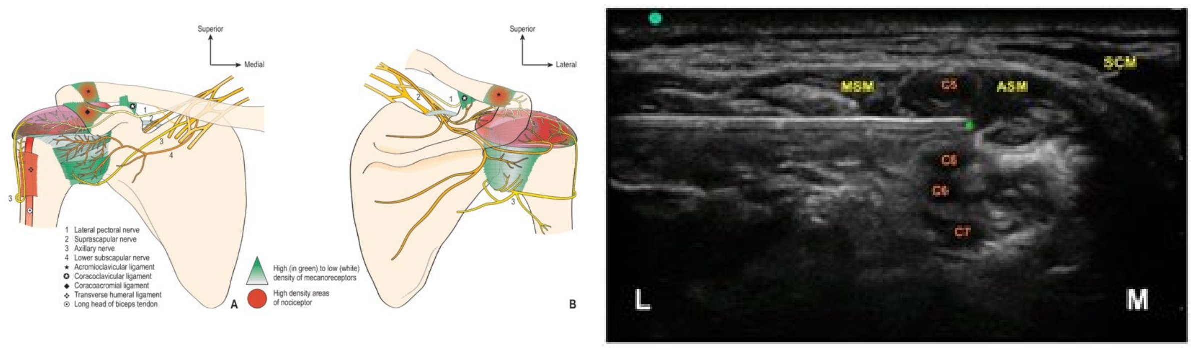

Figure 5: Innervation of shoulder originating from nerve root of brachial plexus. Interscalene block is a superficial structure and can be easily blocked after identifying the scalenus muscle

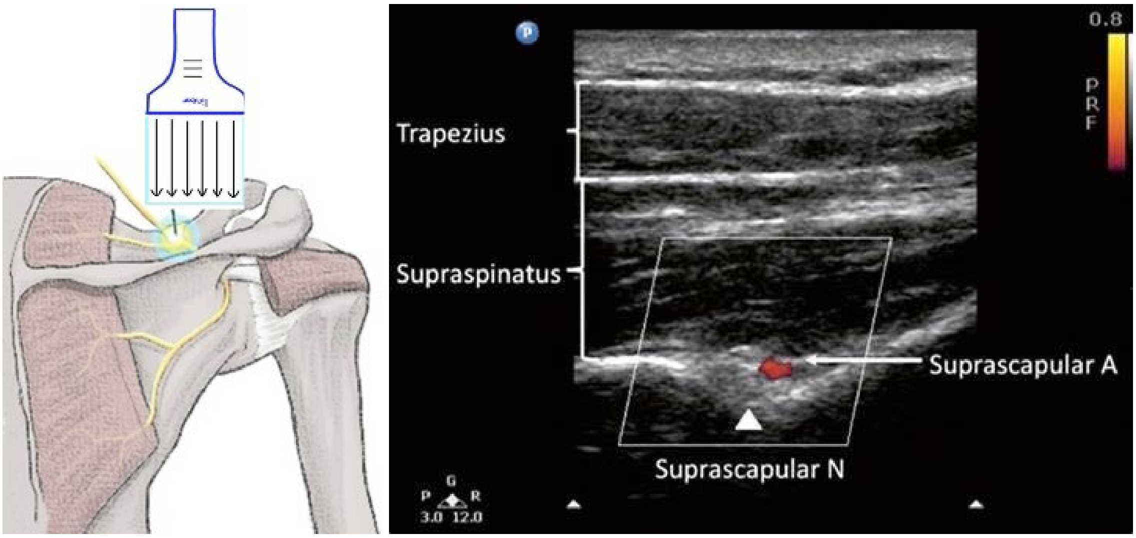

Figure 6: Suprascapular nerve exiting through the scapular notch. The scapular notch is an area of loss of bony sonography and the presence of a pulsatile artery indicating a neurovascular bundle

PELVIC BONE PAIN

Fascia iliaca blocks are a valuable regional analgesia technique for managing pain from pelvic metastases, particularly in the anterior hip and thigh regions. They offer targeted pain relief and can significantly improve the quality of life for patients experiencing pain related to metastatic disease in this area.

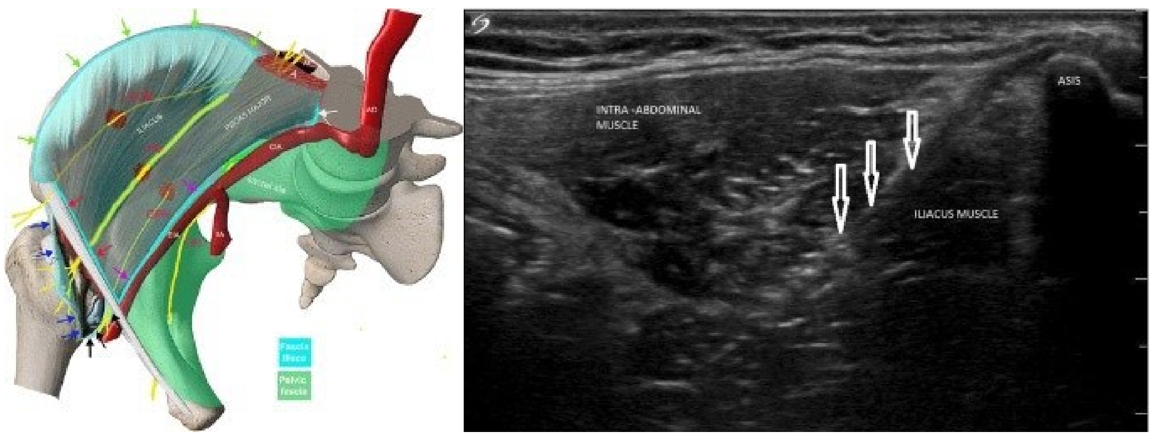

Figure 7: Identify the iliacus muscle and abdominal muscle in the area of the antero-superior iliac spine. Carefully identify an artery and avoid puncturing it

MUST READ NOTE

Sonographic interventions might cause temporary analgesic effects only. Even with neurolytic nerve damage, we cannot accurately quantify the extent of metastases or cancer tissue lesions. This intervention must be combined with analgesics guided by the WHO analgesics ladder.

Antinociceptive and antineuropathic agents still play a vital role in ensuring the adequacy of daily analgesia. Non-pharmacological treatment of cancer pain as part of the concept of total pain must be implemented as well. Patients and their families should be well informed and explained regarding the stage of the malignancy and its current treatment. Psychological and spiritual support is compulsory in ensuring that their motivation in living is optimal to prevent immunosuppression that might lead to infection.

POSSIBLE COMPLICATIONS

Peripheral nerve block may cause infection, bleeding, nerve damage, and in rare cases, worsening of the underlying cancer (if the block inadvertently affects tumour growth or spread). Therefore, these procedures should be performed by experienced clinicians who weigh the risks and benefits for each patient individually.

CONCLUSION

In summary, while nerve blocks can be valuable for managing pain in cancer patients, they require careful consideration and expertise due to the complexities involved with malignancy and its treatment. The goal is to alleviate suffering while minimizing risks and optimizing the patient's quality of life.

References

1. Wallace, E. et al. (2014). Pain in Bone Metastases: Types and Mechanisms. In: Vassiliou, V., Chow, E., Kardamakis, D. (eds) Bone Metastases. Cancer Metastasis - Biology and Treatment, vol 21. Springer, Dordrecht. https://doi.org/10.1007/978-94-007-7569-5_3

2. Mercadante S. Alcoholization of Intercostal Nerves for Incident Pain Due to Rib Metastases. *J Pain Symptom Manage.* 2023 Sep;**66**(3):e427-e429. doi: 10.1016/j.jpainsymman.2023.06.018. Epub 2023 Jun 19. PMID: 37343899

3. Baxter CS, Singh A, Ajib FA, et al. Intercostal Nerve Block. [Updated 2023 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482273/

4. Krediet AC, Moayeri N, van Geffen GJ, Bruhn J, Renes S, Bigeleisen PE, Groen GJ. Different Approaches to Ultrasound-guided Thoracic Paravertebral Block: An Illustrated Review. *Anesthesiology.* 2015 Aug;**123**(2):459-74. doi: 10.1097/ALN.0000000000000747. PMID: 26083767

5. Chin KJ, El-Boghdadly K. Mechanisms of action of the erector spinae plane (ESP) block: a narrative review. *Can J Anaesth.* 2021 Mar;**68**(3):387-408. English. doi: 10.1007/s12630-020-01875-2. Epub 2021 Jan 6. PMID: 33403545

6. Ameta N, Ramkiran S, Vivekanand D, Honwad M, Jaiswal A, Gupta MK. Comparison of the efficacy of ultrasound guided pectoralis-II block and intercostal approach to paravertebral block (proximal intercostal block) among patients undergoing conservative breast surgery: A randomised control study. *J Anaesthesiol Clin Pharmacol.* 2023 Jul-Sep;**39**(3):488-496. doi: 10.4103/joacp.joacp_411_21. Epub 2023 Aug 16. PMID: 38025564; PMCID: PMC10661648

7. Kang R, Ko JS. Recent updates on interscalene brachial plexus block for shoulder surgery. *Anesth Pain Med (Seoul).* 2023 Jan;**18**(1):5-10. doi: 10.17085/apm.22254. Epub 2023 Jan 10. PMID: 36746896; PMCID: PMC9902626

8. White L, Reardon D, Davis K, Velli G, Bright M. Anterior suprascapular nerve block versus interscalene brachial plexus block for arthroscopic shoulder surgery: a systematic review and meta-analysis of randomized controlled trials. *J Anesth.* 2022 Feb;**36**(1):17-25. doi: 10.1007/s00540-021-03000-z. Epub 2021 Sep 17. PMID: 34533639

9. Zhang XY, Ma JB. The efficacy of fascia iliaca compartment block for pain control after total hip arthroplasty: a meta-analysis. *J Orthop Surg Res.* 2019 Jan 25;**14**(1):33. doi: 10.1186/s13018-018-1053-1. PMID: 30683117; PMCID: PMC6347785

10. Mestdagh F, Steyaert A, Lavand'homme P. Cancer Pain Management: A Narrative Review of Current Concepts, Strategies, and Techniques. *Curr Oncol.* 2023 Jul 18;**30**(7):6838-6858. doi: 10.3390/curroncol30070500. PMID: 37504360; PMCID: PMC10378332

Critical Care in Oncology: Addressing the Unique Needs of Cancer Patients

Cheah Saw Kian[1], Syarifah Noor Nazihah Sayed Masri[2]
[1]Department of Anaesthesiology & Intensive Care, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
[2]Department of Anaesthesiology & Intensive Care, Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

INTRODUCTION

Cancer patients are frequently admitted to the intensive care unit (ICU) at various stages of their treatment, whether during chemotherapy, disease progression, or when complications such as neutropenic sepsis and life-threatening organ dysfunction arise.

Infections pose a significant risk, often leading to severe illness or even death, due to factors such as low immunoglobulin levels, neutropenia, frequent hospital visits, and the use of indwelling medical devices like central venous lines and chemoports. While intensive care has traditionally focused on rapid resuscitation and short-term survival, it is equally crucial to address the underlying causes of infections and provide comprehensive care to improve long-term outcomes for cancer patients.

This chapter explores the primary reasons for ICU admission and the key elements of intensive care management for cancer patients, with a special emphasis on integrating palliative care and addressing the challenges within the overall management approach.

PRIMARY REASONS FOR ICU ADMISSION

Neutropenic Sepsis

Neutropenic sepsis is defined as a single temperature measurement 38.5°C, or a sustained temperature ≥38°C for more than 1 hour in a patient with a decreased absolute neutrophil count (ANC) of <0.5 x 109/L. It often results from chemotherapy and bone marrow suppression, with a high incidence during and post-treatment phase.

Common gram-negative bacteria involved such as Escherichia coli, Klebsiella species, and Pseudomonas aeruginosa frequently show antibiotic resistance due to extended-spectrum beta-lactamase (ESBL) production. Additionally, Gram-positive cocci such as coagulase-negative staphylococci and Staphylococcus aureus, are also common. Fungal infections, namely the Candida albicans and non-albicans species, are also part of the microbial spectrum but are less common than bacterial infections.

Treatment usually involves broad-spectrum antibiotics like cefepime, piperacillin-tazobactam, and carbapenems, which cover both Gram-positive and Gram-negative bacteria. Prompt initiation of the right antibiotics is crucial for improving survival in neutropenic sepsis.

Complications of Cancer Therapy

While systemic therapy and radiotherapy can be highly beneficial for cancer patients, they also carry risks of serious complications. Most complications can be managed on an outpatient basis or with hospital care. However, some patients may experience severe issues requiring intensive care, such as acute respiratory failure, radiation injury and drug-induced lung injury, acute kidney injury (AKI), and tumour lysis syndrome (TLS). These complications must be addressed quickly to prevent further deterioration.

- ***Acute Respiratory Failure***
  Acute respiratory failure is a common and serious complication in cancer patients, often leading to ICU admissions. In patients requiring mechanical ventilation, the mortality rate is 50% or higher. The causes of respiratory failure

include bacterial pneumonia, opportunistic pulmonary infections, and non-infectious conditions like pneumonitis.

Table 1 lists the most common causes of acute respiratory failure in cancer patients.

Table 1: Causes of acute respiratory failure in the cancer patient

Airway disorders	Parenchymal disorders	Cardiac disease	Vascular disorders	Chest wall and pleural disease	CNS disorders	Infections
Obstruction	ARDS and ARDS Mimics	Pericardial effusion	Thromboembolic disease	Obesity	Intracranial Malignancy	Viral
Bronchitis	Radiation injury	Congestive heart failure	Alveolar hemorrhage	Pleural effusion	Medications	Bacterial
COPD	Chemotherapy reactions	Coronary artery disease	Tumor emboli	Malignant	Metabolic encephalopathy	Fungal
Extrinsic compression	Pulmonary edema		Veno-occlusive disease	Hemothorax	Iatrogenic injury	Opportunistic pathogens
Tumor invasion	TACO/TRALI		Pulmonary hypertension	Pneumothorax	Paraneoplastic syndrome	
	Aspiration			Lung entrapment		
	Organizing pneumonia			Chest wall invasion		
	BOOP			Pathologic fractures		
	Malignant infiltration					
	Lymphangitic spread					
	Leukostasis					
	Peri-engraftment syndrome					
	Idiopathic pneumonia syndrome					

(Sears SP, Carr G, Bime C. Acute and Chronic Respiratory Failure in Cancer Patients. Oncologic Critical Care. 2019 Jul 9:445-75).
**The table was granted permission by the authors and publisher.*

- ***Radiation Injury and Drug-Induced Lung Injury***
  Radiotherapy is an essential treatment for many cancers, known for being generally well-tolerated with relatively mild side effects. However, the lungs are particularly sensitive to radiation, and up to 30% of patients may experience lung-related complications such as radiation pneumonitis and radiation fibrosis. Radiation pneumonitis usually occurs within six months of chest radiotherapy and radiation fibrosis tends to develop six months to a year after radiation therapy is completed. While corticosteroids can effectively treat radiation pneumonitis, they are less effective for radiation fibrosis.

Drug-induced lung injuries are often challenging to diagnose and are typically identified by excluding other causes. Many cancer medications can cause pulmonary toxicity and are listed in Table 2.

Treatment for acute respiratory failure in cancer patients generally aligns with standard approaches for non-cancer patients, including oxygen therapy, mechanical ventilation, corticosteroids, and antibiotics as needed.

The initial supportive treatment for respiratory failure in the cancer patient is illustrated in Figure 1.

Table 2: Pulmonary complications associated with common chemotherapeutic drugs

Drug	Associated pulmonary complication
Bleomycin	ARDS, eosinophilic pneumonia, organizing pneumonia, pulmonary fibrosis, acute interstitial pneumonia, pneumothorax, pulmonary veno-occlusive disease, NSIP
5-FU	Pulmonary fibrosis, ARDS, pulmonary edema
Bevacizumab	ARDS, DAH, bronchospasm, pulmonary arterial hypertension
Bortezomib	Organizing pneumonia, ARDS, DAH, pulmonary arterial hypertension, infection
Carfilzomib	DAH, pulmonary arterial hypertension
Carmustine	Pulmonary fibrosis, ARDS, pleural effusion, pneumothorax, radiation recall pneumonitis, pleuroparenchymal fibroelastosis (PPFE)
Cyclophosphamide	Organizing pneumonia, pulmonary fibrosis, PPFE, ARDS, DAH, bronchospasm, pleural effusion, pulmonary veno-occlusive disease
Doxorubicin	Organizing pneumonia, pulmonary fibrosis, ARDS, radiation recall pneumonitis
Etoposide	ARDS, DAH, bronchospasm, angioedema
Fludarabine	Eosinophilic pneumonia (acute and chronic), organizing pneumonia, lung nodues, ARDS, DAH, pleuritic
Gemcitabine	Eosinophilic pneumonia, pulmonary fibrosis, radiation recall pneumonitis, AIP or ARDS, pulmonary edema, bronchospasm, pleural effusion, pleuritis
Ifosfamide	Pulmonary fibrosis, radiation recall pneumonitis, pulmonary edema, hypoxia
Melphalan	Pulmonary fibrosis, ARDS, bronchospasm, organizing pneumonia, NSIP, UIP
Methotrexate	Organizing pneumonia, pulmonary fibrosis, lung nodules, ARDS, AIP, DAH, bronchospasm, eosinophilic pleural effusion, pulmonary embolism, angioedema
Paclitaxel	ARDS and AIP, radiation recall pneumonitis
Pemetrexed	Organizing pneumonia, ARDS and AIP, DAH, pleuritis, capillary leak
Rituximab	Organizing pneumonia, pulmonary fibrosis, ARDS, pulmonary edema, hemoptysis, cough, asthma attack
Thalidomide	Eosinophilic pneumonia, organizing pneumonia, pulmonary embolism, pulmonary arterial hypertension
Vincristine	Cellular NSIP, laryngospasm
Nivolumab	Eosinophilic pneumonia, AIP, organizing pneumonia, shrinking lung, ARDS, pleural effusion

Sears SP, Carr G, Bime C. Acute and Chronic Respiratory Failure in Cancer Patients. Oncologic Critical Care. 2019 Jul 9:445-75).

**ARDS=Acute respiratory distress syndrome, NSIP=Non-specific interstitial pneumonitis, DAH=Diffuse alveolar hemorrhage, AIP=Acute interstitial pneumonia*

** The table was granted permission by the authors and publisher.*

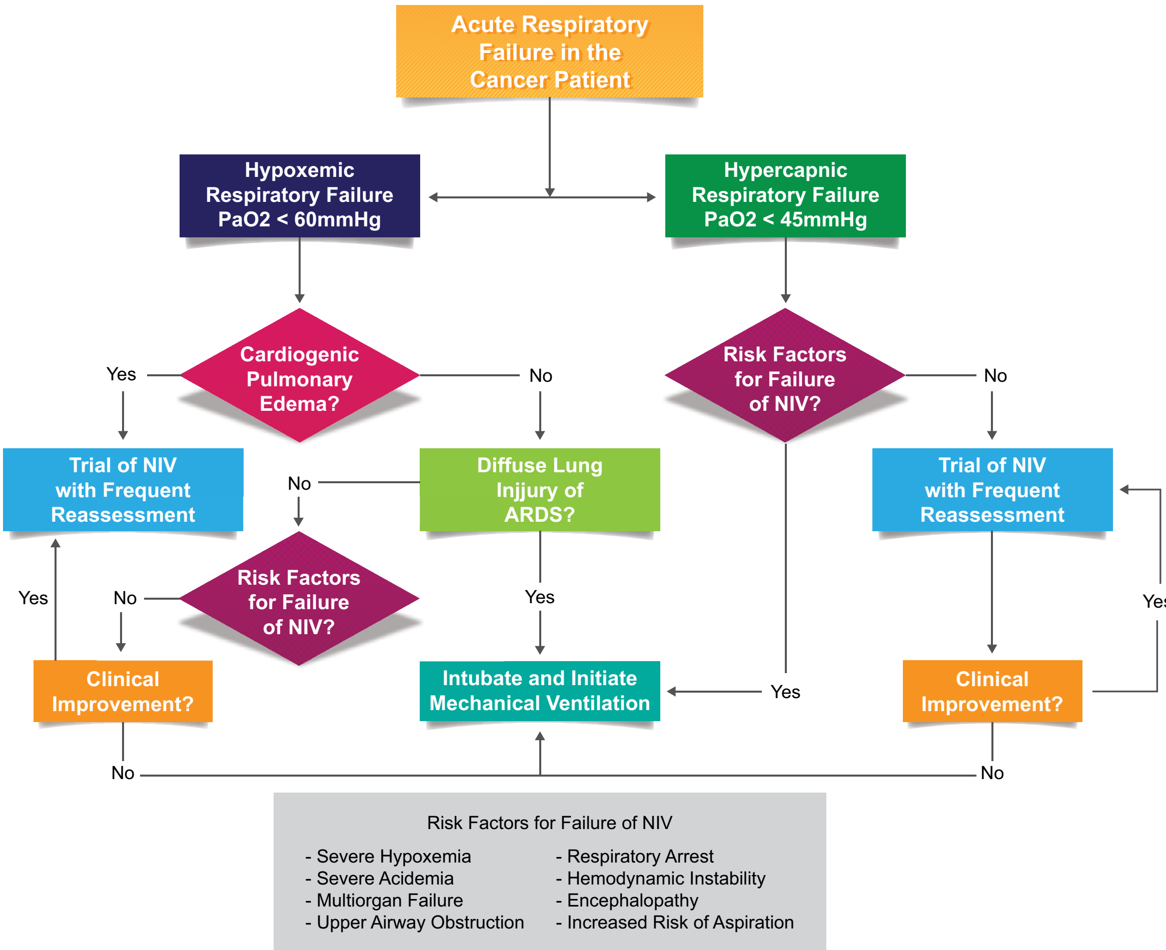

Figure 1: Initial supportive treatment for respiratory failure in the cancer patient

(By Sears SP, Carr G, Bime C. Acute and Chronic Respiratory Failure in Cancer Patients. Oncologic Critical Care. 2019 Jul 9:445–75).
** The figure was granted permission by the authors and publisher.*

- ***Acute Kidney Injury***
  Acute kidney injury is increasingly recognized as a complication in cancer patients. It can occur due to various factors, including pre-renal, renal, and post-renal factors. The presence of cancer adds complexity to AKI, as it can be triggered by cancer itself (through infiltration or paraneoplastic syndromes), cancer-related metabolic disturbances (such as hypercalcemia or tumor lysis syndrome), or treatments like chemotherapy, immune checkpoint inhibitors, and stem-cell transplants. The risk of developing AKI in cancer patients is estimated to be between 17% and 27% within five years of diagnosis.

- ***Tumor Lysis Syndrome***
  Tumor lysis syndrome is the most common oncologic emergency. It occurs either spontaneously or after starting chemotherapy and is marked by a combination of

metabolic disturbances such as hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia, which can lead to organ damage. Tumors at high risk for developing TLS include advanced Burkitt lymphoma, leukemia, B-cell lymphoma, and myeloid leukemia. The Cairo-Bishop classification shown in Table 3 provides specific criteria and grading for diagnosing and managing TLS.

The mainstay of treatment is supportive. This includes ensuring adequate hydration, correcting electrolyte imbalances, managing uric acid levels with allopurinol or rasburicase, and starting early renal replacement therapy if needed.

Table 3: Cairo Bishop classification

CAIRO-BISHOP GRADING OF CLINICAL TUMOR LYSIS SYNDROME						
Grade	0	1	2	3	4	5
Laboratory TLS	Absent	Present	Present	Present	Present	Present
Creatinine	<1.5 Times ULN	1.5 Times ULN	1.5 to 3.0 Times ULN	>3.0 to 6.0 Times ULN	>6.0 Times ULN	Death
Cardiac arrythmias	None	Intervention not needed	Nonurgent Medical Intervention Indicated	Symptomatic Despite Medications, Controlled with a Device (e.g., Defibrillator)	Life-Threatening and Associated with congestive heart failure Syncope, Shock	Death
Seizures	None	Not applicable	One Brief Generalized Seizure; Seizure(s) Well controlled by Anticonvulsants; Infrequent Focal Motor Seizures not Interfering with Activities of Daily Living	Seizure with Altered Consciousness; Poorly Controlled Seizure Disorder with Breakthrough Generalized Seizures Despite Medical Management	Intractable Seizure, Status Epilepticus	Death

INTEGRATING PALLIATIVE CARE INTO ICU MANAGEMENT

Integrating palliative care into ICU management is essential for managing symptoms and providing support to both patients and their families. For critically ill cancer patients, making decisions about care goals, including whether to continue aggressive treatments, is crucial. In some cases, continuing life-sustaining therapy may be futile, underscoring the importance of palliative care.

There are two primary models for delivering palliative care in the ICU: the integrated model and the consultative model. In the integrated model, the ICU team provides palliative care by regularly assessing the patient's symptoms, palliative care needs, and prognosis, and also discussing the treatment plan with the family. This approach shifts the ICU culture by incorporating palliative care alongside standard ICU treatments.

In the consultative model, a specialized palliative care team takes charge of the patient's palliative care, reducing the workload on the ICU team and easing potential conflicts with the patient's family. The palliative care team also ensures continuity of care after the patient is discharged from the ICU.

Challenges in ICU for Managing Cancer Patients

Managing cancer patients in the ICU presents several challenges that require specialized knowledge and a multidisciplinary approach. Here are some of the key challenges:

- ***Improving Survival or Prolonging the Dying Process?***
  There is limited data on the long-term outcomes of cancer patients in the ICU, making it difficult to determine whether ICU care truly extends survival with a good quality of life or simply postpones an inevitable death. Even after receiving ICU care, patients with poor functional status may still be unable to undergo the necessary treatments for their cancer.

- ***Assessing Quality of Life Outcomes***
  Research on the quality of life for cancer patients who survive ICU care is limited. Many survivors face ongoing challenges such as pain, discomfort, anxiety, sleep disturbances, and depression. They often experience dependence and restricted mobility, which can place a significant burden on their families. Therefore, it is important to evaluate the mental, physical, and overall quality of life outcomes for all ICU survivors.

- ***Addressing Family Needs and Communication***
  The impact of ICU care on the families of survivors is a significant concern. Caregivers often experience high levels of stress, making it crucial to identify their needs and develop effective communication strategies to provide them with the necessary support.

- ***Reevaluating ICU Admission Policies***
  Careful consideration is needed when deciding whether to admit cancer patients to the ICU, weighing the benefits and potential drawbacks. The decision to admit patients for palliative or terminal care is particularly contentious, as expanding admission criteria could lead to conflicts among clinicians and strain already limited resources.

- ***Improving the Transition from Curative to Palliative Care***
  Determining the appropriate time for end-of-life decision-making is challenging, particularly for end-stage cancer patients. The shift from curative to palliative care can be difficult, especially for younger patients or those with recurrent, resistant infections. Family expectations can further complicate this process. It is essential to document the patient's wishes regarding resuscitation and end-of-life care at the time of ICU admission.

CONCLUSION

The number of cancer patients requiring ICU care, whether for intensive treatment or palliative support, is on the rise. Timely recognition, early ICU admission, and close collaboration between intensivists and oncologists are crucial for improving survival rates among critically ill cancer patients.

ACKNOWLEDGEMENT

The authors acknowledged that the tables and figures in this publication are reproduced under a

References

1. Antonia Koutsoukou. Admission of critically ill patients with cancer to the ICU: many uncertainties remain. *ESMO Open.* 2017 Oct 12;**2**(4):e000105.

2. Frank Daniel Martos-Benítez, Caridad de Dios Soler-Morejón, Karla Ximena Lara-Ponce, Versis Orama-Requejo, Dailé Burgos-Aragüez, Hilev Larrondo-Muguercia, Rahim W Lespoir. Critically ill patients with cancer: A clinical perspective. *World J Clin Oncol* 2020 October 24;**11**(10):809-835

3. Elie Azoulay, Marcio Soares, Michael Darmon, Dominique Benoit, Stephen Pastores, Bekele Afessa. Intensive care of the cancer patient: recent achievements and remaining challenges. *Ann Intensive Care.* 2011 Mar 23;**1**(1):5. doi: 10.1186/2110-5820-1-5

4. May Hua, Hannah Wunsch. Integrating palliative care in the ICU. *Curr Opin Crit Care.* 2014 Dec;**20**(6):673-80. doi: 10.1097

5. Sears SP, Carr G, Bime C. Acute and Chronic Respiratory Failure in Cancer Patients. Oncologic Critical Care. 2019 Jul 9:445-75. doi: 10.1007/978-3-319-74588-6_43. PMCID: PMC7123817

6. Sipsas NV, Bodey GP, Kontoyiannis DP. Perspectives for the management of febrile neutropenic patients with cancer in the 21st century. *Cancer.* 2005;**103**(6):1103-13

7. Meraz-Munoz A, Langote A, K DJ, Izzedine H, Gudsoorkar P. Acute Kidney Injury in the Patient with Cancer. Diagnostics (Basel). 2021;11(4)

8. Jairam V, Lee V, Park HS, Thomas CR, Jr., Melnick ER, Gross CP, et al. Treatment-Related Complications of Systemic Therapy and Radiotherapy. *JAMA Oncol.* 2019;**5**(7):1028-35