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Anaesthesia for Cancer Surgery

Key Points

- Surgery, and the resultant stress response, may paradoxically create conditions which favour invasion and spread of malignancy.
- Numerous perioperative factors have been implicated in affecting both the cancer directly and the patent's anti-cancer immune response.
- The best evidence currently available indicates that both volatile anaesthetics and opioids might have an unfavourable effect on cancer recurrence. However, there is no Level 1 evidence to support this and therefore no Grade A recommendations can be made.
- Propofol, NSAIDs and local anaesthetics are some of the anaesthetic options which may prove to offer patients a better chance of disease-free survival.
- Close diabetes control and rational blood management are among the elements of perioperative care which require meticulous attention in cancer surgery.

MCQ

True or False:

1)

a) Propofol may have anti-tumor effects

b) Propofol may have pro-tumor effects

c) TIVA increases cancer free survival after surgery

d) Inhalational anaesthesia may increase overall mortality after cancer surgery

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2)

a) Opioids may inhibit natural killer cell function

b) NSAIDS may inhibit tumor cell ability to proliferate

c) Local anaesthetic agents promote metastatic spread via their action on voltage-gated sodium channels on tumor cell membranes

d) The use of regional anaesthesia reduces survival following cancer surgery

3)

a) Neoadjuvant chemotherapy increases cardiorespiratory reserve as determined objectively by CPET

b) Perioperative blood transfusion reduces the chance of postoperative infection following cancer surgery by increasing oxygen delivery to non-cancerous tissue

c) Patients undergoing surgery for colonic cancer should not be transfused unless their Hb falls below 60g/L due to risk of cancer recurrence

d) Chronic hyperglycaemia is associated with a reduction in cancer-free survival

Answers: 1. TTFT 2. TTFF 3. FFFT

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Introduction

Surgical resection remains central to the management of many cancers. Nonetheless, even the most vigilant surgical technique may leave residual malignancy and promote tumour cell shedding into the blood and lymphatics. The propensity of these residual cells to thrive is determined by a complex interplay between the intrinsic ability of the cells to proliferate and invade, the microenvironment serving those cells and the patient's ability to mount an anti-cancer response. While the intrinsic make-up of residual cells is not modifiable, there is growing interest in the ability of anaesthetic drugs to directly affect the cancer.

Postoperatively, the ability of the patient to mount a meaningful defence against malignant invasion is dependent on a well-functioning immune system. Unfortunately, a multitude of perioperative factors, including the surgical stress response, pain, anaesthetic drugs, blood transfusions and preoperative functional status may all work to hinder an optimal host response. Therefore, in many respects, surgery might be considered to create optimal conditions for malignancy to thrive. By appreciating the relevance of these factors, and the levels of evidence supporting them, it may be possible to facilitate a perioperative course that optimises future good health and cancer remission.

Choice of anaesthetic

While there is growing interest in the relationship between anaesthetic agents and cancer recurrence, much of the available evidence is based on either pre-clinical research (with inherent limited transferability to real world outcomes) or retrospective analyses (which may lack the statistical robustness to convincingly alter clinical practice). Below is a narrative describing some of the key areas of existing and ongoing research.

Inhalational agents

There has been concern over the use of volatile anaesthetic agents for cancer surgery due to their proposed potential to tip the balance in favour of tumour recurrence. The serum of patients managed with a sevoflurane-based anaesthetic demonstrates reduced natural killer (NK) cell activity (1). NK cells being one of the most essential components of the immunosurveillance responsible for identification and destruction of residual cancer cells. In addition, *in vitro* studies have implicated isoflurane, sevoflurane and desflurane in augmenting cancer cell mechanisms important in invasion and metastasis, specifically

through the distortion of gene expression (2) and also through the promotion of angiogenesis (3).

Counter to these findings, there is experimental laboratory data to indicate that sevoflurane may attenuate the spread of some lung cancers (4) and down-regulate gene expression important in proliferation (5). The suggestion that the effect of volatiles might be specific to the type of cancer has been further demonstrated by Kvolik and colleagues who showed experimentally that sevoflurane may be capable of inducing apoptosis in colon cancer lineages but may reduce apoptosis in laryngeal carcinoma (6).

With reference to alternative inhalational agents, there is a evidence that an anti-cancer affect might be added to the list of the many desirable properties of xenon. Ash and colleagues demonstrated that when compared to sevoflurane, xenon inhibited migration of both oestrogen receptor positive and negative breast adenocarcinoma, while it also suppressed the release of pro-angiogenic factors (7). The more commonly used agent, nitrous oxide, has also come under scrutiny, as its inhibition of methionine synthase is known to suppress immune function (8). Nonetheless, an RCT specifically investigating the effect of nitrous oxide on colorectal cancer recurrence indicated no increased risk (9), although it should be noted that this study was only powered to detect a 56% difference in risk.

Propofol

The potential benefit of propofol is that it appears to have direct anti-cancer effects while having a negligible effect on the immune system. *In vitro* and animal modelling has demonstrated the ability of propofol to both inhibit metastatic spread and induce apoptosis across multiple variants of cancer (10). Animal modelling has also indicated that while numerous anaesthetic agents may promote metastatic spread and suppress NK activity, propofol does not (11).

Inhalational anaesthesia vs. TIVA

Experimental data comparing volatiles with total intravenous anaesthesia (TIVA) has produced results which largely favour the use of TIVA (12, 13). Similar conclusions have been drawn from recent retrospective studies. A propensity matched analysis of over 11,000 patients undergoing elective cancer surgery at the Royal Marsden Hospital suggested a significant benefit in TIVA (14). A more recent systematic review similarly showed inhalational anaesthesia may increase overall mortality after cancer surgery, and

may reduce recurrence-free survival after cancer surgery (15). There is a growing amount of research and evidence in this area, much of which points to a survival advantage after cancer surgery from TIVA. At present, however, we must await findings from robust RCTs.

Opioids

Good analgesia is essential to reducing the stress response to surgery and facilitating recovery. The typical analgesic plan for major surgery is often opioid-centred, however, there is mounting evidence of a link between opioids and cancer recurrence.

Opioid receptors have been located on multiple immunologically active cells including NK, macrophages and lymphocytes (16) and have also been identified on cancers of the pancreas, thyroid, breast, colon, lung and endometrium (17). *In vivo o*pioids have demonstrated the potential to inhibit cellular immunity and natural killer cell function in humans (18) and also directly promote angiogenesis and tumour cell growth in mice (19). Furthermore, retrospective studies have indicated an association between increased intraoperative (20) and post-operative (21) opioid delivery and cancer recurrence. However, the availability of level 1 evidence to corroborate these findings is thin and and some animal models even suggest that perioperative opioids may have a beneficial effect (22). Indeed, an RCT -albeit underpowered and single centre- comparing opioid vs opioid-free postoperative analgesia in colon cancer surgery (23) noted no difference in post-operative NK activity, inflammatory response or short term (1-year) cancer recurrence.

As a consequence of these mixed findings, for now at least, expert opinion does not advise against opioid use (22). However, on balance, a multimodal approach to analgesia which limits opioid consumption might be beneficial, not just in reducing cancer recurrence, but also to limit the other deleterious effects of opioids.

Nonsteroidal anti-inflammatory drugs

One of the proposed mechanisms by which surgery enhances cancer spread is through augmentation of inflammatory processes (24). Long term use of NSAIDS, and specifically, COX-2 inhibitors, has been implicated in cancer prevention (24) and there is also emerging evidence of a benefit in perioperative use. It appears that NSAIDs have a direct effect on the tumour microenvironment and more specifically the proteolytic profile responsible for successful proliferation (25) and angiogenesis (26). Again, clinical validation remains wanting, although a retrospective analysis by Forget and colleagues, looking at 720 breast

cancer patients, noted intraoperative administration of diclofenac or ketorolac was demonstrably associated with disease-free survival (27).

Ketamine

Ketamine has been consistently shown to downregulate NK cell activity *in vitro* and in animal modelling (11, 28). However, pre-incisional ketamine at a dose of 0.5mg/kg appears to prevent suppression of NK cell function (29), presumably because the enhanced analgesia results in an attenuated stress response. Meanwhile, the direct effect on cancer cells has yet to be conclusively elucidated. For example, separate animal studies on the same variant of breast cancer have contrastingly concluded that ketamine may both promote (11) and inhibit (30) metastatic spread.

Dexamethasone

The use of dexamethasone, principally as an antiemetic, is widespread in anaesthesia. As a glucocorticoid, its anti-inflammatory properties may be beneficial, however, its immunosuppressive action has the potential to blunt the patient's anti-cancer response. Current available evidence is conflicting. A retrospective analysis of 260 patients with ovarian cancer did not demonstrate an association between perioperative dexamethasone use and cancer recurrence (31). However, a small RCT of 43 patients undergoing surgery for colon cancer indicated a statistically significant increase in recurrence in patients receiving dexamethasone compared to placebo. It should be noted that cancer recurrence was a secondary outcome and that the authors themselves lament the small sample as inadequate to assess for a genuine association. Therefore, at present there is no conclusive evidence that perioperative dexamethasone affects cancer recurrence.

Local anaesthetic agents

Voltage-gated sodium channels are found in abundance on cancer cell membranes and have been implicated in the pathway of successful metastatic invasion (32). Through interaction with these receptors, amide local anaesthetics have the potential to cause neoplastic apoptosis, degradation of gene expression and inhibition of metastasis. While much of the evidence is based on *in vitro* studies (33, 34, 35), animal modelling has indicated that ropivacaine, bupivacaine and lignocaine may induce apoptosis at clinically relevant concentrations (35, 36). Furthermore, an intravenous lignocaine infusion may have indirect benefits both as an anti-inflammatory and as an opioid-sparing agent (37).

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Regional

There are numerous potential mechanisms by which regional anaesthesia may be beneficial in cancer surgery:

1. Attenuation of the surgical stress response and reduction in inflammation
2. Reduction in both volatile and opioid requirement
3. Anti-cancer effects of local anaesthetic agents

Despite a number of biological plausible mechanisms, the clinical evidence is mixed. The authors of a 2014 Cochrane Review (38) on the topic reported that the low quality of available evidence meant meaningful conclusions could not be surmised. A systematic review and meta-analysis comprising results from nearly 55,000 patients suggested that intra-operative regional anaesthesia was associated with improved survival, however, there was no difference with respect to cancer recurrence (39). The analysis was comprised of largely retrospective analyses, again reflecting the paucity of level 1 evidence.

With respect to specific cancers, a large multi-centre randomised trial of over 1000 patients is underway comparing anaesthetic technique in breast cancer surgery (40). The primary outcome for this study is cancer recurrence, and the techniques compared are propofol sedation/anaesthesia combined with regional (paravertebral or epidural analgesia) vs. volatile anaesthesia and morphine analgesia. 1311 participants have been recruited with completion of data collection expected in March 2019.

Anaesthesia for colorectal cancers is another area which has received significant attention. Both RCTs (41) and retrospective analyses (39, 42) have indicated a survival benefit from the use of thoracic epidural anaesthesia (TEA). However, the largest RCT to-date -of 446 patients- concluded no difference in 5-year survival or recurrence rates (43). Meanwhile, a retrospective analysis in the UK of 457 laparoscopic colorectal resections (44) demonstrated no survival benefit from neuraxial anaesthesia but did indicate TEA increased hospital length of stay by 2 days. Further trials are ongoing.

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Other perioperative considerations

Neoadjuvant chemotherapy:

Neoadjuvant chemotherapy (NAC) is a specialised oncological treatment that, when followed by surgery, improves survival for a number of forms of cancer (45).

Of interest, and of perioperative importance, is evidence that NAC may decrease cardiorespiratory reserve as determined objectively by cardiopulmonary exercise testing. This is true both immediately after NAC and also at the point of surgery (46, 47, 48). If there is a decline in cardiorespiratory reserve, then it follows that a patient may be at higher risk of postoperative complications (46). A study by Jack et al suggested the possibility that in some patients the harms of NAC may outweigh the benefits. They found a significant overall reduction in physical fitness in their cohort of oncology patients. In those who had received NAC this poor fitness was associated with inferior postoperative survival. In those who had not received NAC, the poor fitness was not associated with a difference in survival (45). To balance this, West et al demonstrated that, after NAC, a structured prehabilitation programme returned their subjects preoperative fitness to baseline levels, suggesting that the negative effects of NAC may be mitigated (49).

As with all areas of medicine, there is always a balance of risk to be weighed in individual cases. Appreciating the detrimental effects of NAC on physiological reserve and, therefore, fitness for surgery, may help the multidisciplinary team plan and optimise the patient's perioperative course.

Blood transfusion

Cancer patients are often anaemic on diagnosis and transfusions are frequently required perioperatively to treat blood loss. Anaemia may be related to the cancer itself (secondary to chronic disease, malnutrition or occult blood loss) or secondary to chemotherapy. Preoperative anaemia is associated with reduced survival in patients with cancer (50) and therefore diligence to treatment is essential.

It has long been recognised that perioperative red blood cell transfusion may have adverse effects on outcomes in cancer surgery, including recurrence and time to recurrence (51). There is evidence that blood transfusion leads to higher rates of 30-day operative mortality, major complications, total number of complications, and prolonged length of stay (52). There are no RCTs as yet, and they may prove to be very difficult to undertake, however, there are meta-analyses based on retrospective studies (53, 54) that support an association

with adverse outcomes, particularly in colorectal cancer. This is supported by the arguments from biological plausibility regarding the immunosuppressive effects of transfusion and the potential for recurrence and infection (54). Avoidance of transfusion also circumvents the associated generic hazards and preserves precious blood products.

Hyperglycaemia

The coexistence of diabetes, stress response to illness and the use of steroid therapy are all potential reasons why cancer patients may experience extended periods of hyperglycaemia. Cancer cells are highly metabolically active and require a ready supply of glucose to aid growth and invasion. It therefore stands to reason that a persistent hyperglycaemic state might negatively impact survival. Indeed, a recent meta-analysis comprising data from nearly 10,000 patients indicated a significant association between hyperglycaemia and adverse overall survival and disease-free survival, both in patients with and without diabetes (55).

Summary

The difficulty attaining high quality evidence assessing the suitability of specific anaesthetic techniques in this field is largely the result of the methodological complexities required for such trials. It is also perhaps a reflection that the major factors influencing survival and recurrence are related to the cancer itself, the surgery and the genetic makeup of the patient. Indeed, expert consensus published by the BJA in 2015 concluded "*While the concept that anaesthetic or analgesic technique might affect cancer outcomes is intriguing, there is currently insufficient evidence to support any change in clinical practice*" (22).

Nonetheless, the idea that an anti-cancer ERAS-esque protocol might be developed is obviously appealing. Such a protocol might include preoptimisation with iron infusions, tight glucose control and prehabilitation, and an anaesthetic technique comprised of TIVA, regional anaesthesia, NSAIDS and a sparring of opioids. Unfortunately, without strong evidence widespread uptake is improbable. Furthermore, throughout this article there have been indications that specific anaesthetic agents may have pro- or anti-cancer affects depending on the cancer variant. A perioperative management programme and selection of anaesthetic technique based on particular cancer genomics, while perhaps the ultimate goal, is surely unlikely in the near future. In the interim, well powered RCTs remain the most important step in clarification of the optimal anaesthesia for cancer surgery.

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