ANAESTHESIA
&
CANCER OUTCOMES

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Learning Outcomes

- To be able to describe the basic biological processes involved in cancer recurrence
- The outline the theoretical basis of how anaesthetic technique can improve outcomes in oncological surgery
- To understand the current (limited) evidence for anaesthetic technique in improving outcomes in oncological surgery

Oncological Surgery

- Surgery is potentially curative for many solid organ cancers and ~80% of such patients will undergo at least one surgical procedure

- Recurrence following surgery is a major cause of morbidity and mortality burden for patients

- This is influenced by:
  - Stage
  - Grade
  - Ability to achieve clear sample margins
  - Minimisation of tumour handling

Recurrence following Surgery

Complex & incompletely understood. Main subtypes:

- Local recurrence at the tumour resection site due to proliferation of residual cells
- Lymph-node metastasis due to tumour cells released into the lymphatic system before or during the procedure
- Seeding within a body cavity (e.g. peritoneal spread)
- Distant organ metastasis due to seeding by circulating tumour cells (CTCs) released before or during the procedure

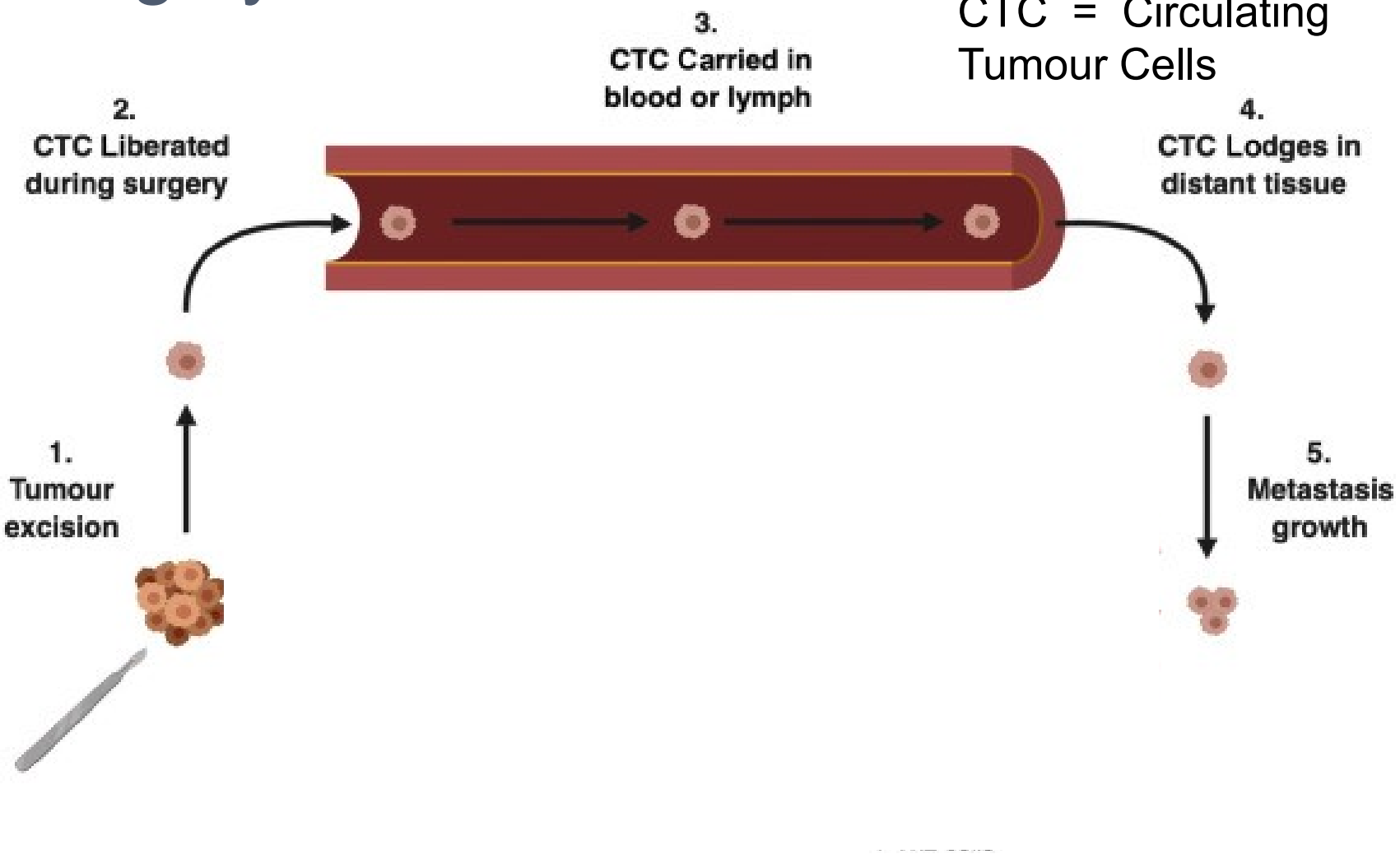
How can anaesthesia affect cancer outcomes ?

Main mechanisms:

- By affecting tumour biology and Immunity
- By modification of the surgical stress response
- By enabling faster recovery from surgery (ERAS) and return to intended oncological treatment (RIOT)

Pathophysiology of Tumour Spread by Surgery

CTC = Circulating Tumour Cells



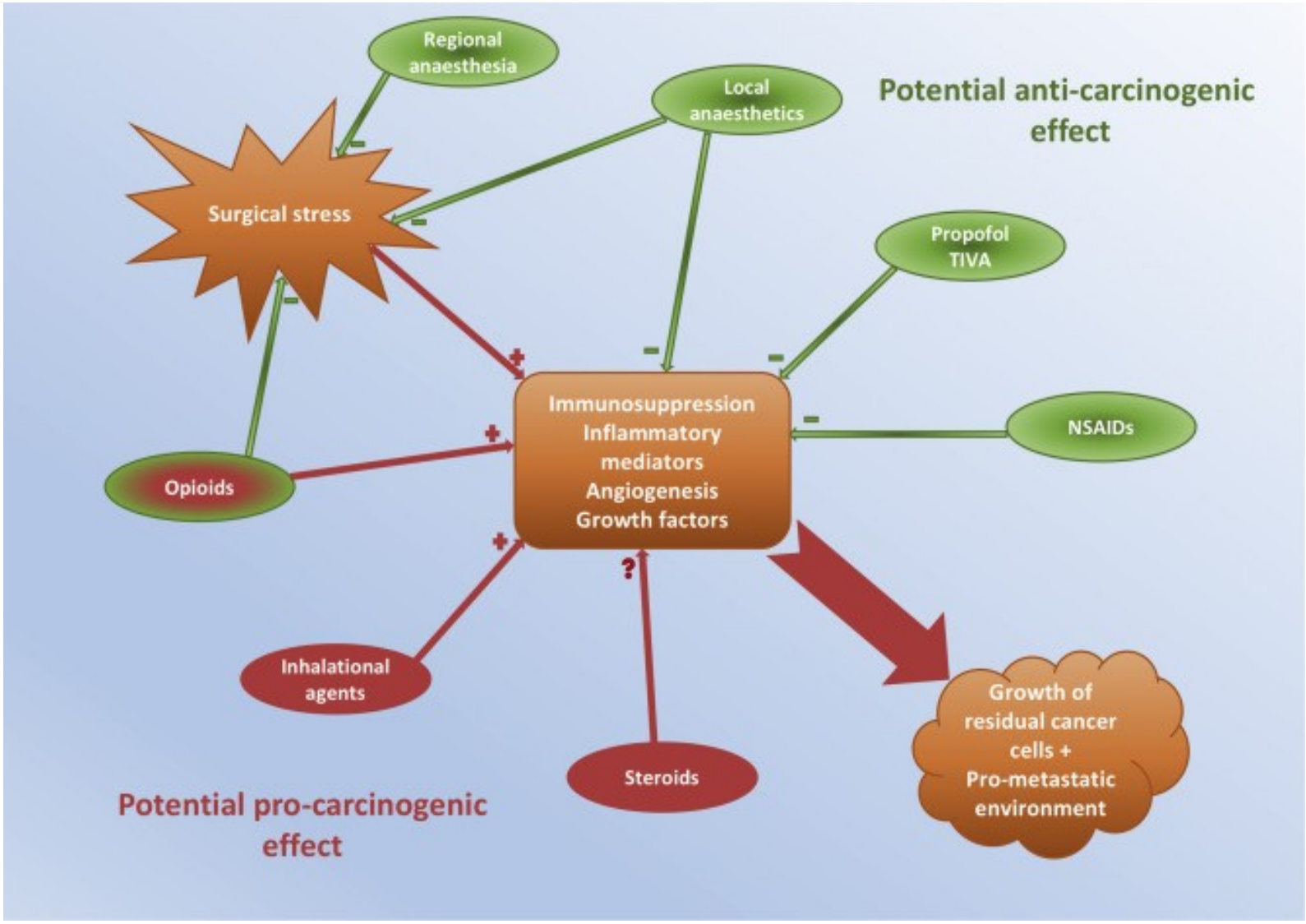
Key Terms

- Stephen Paget's **'Seed and Soil' theory**

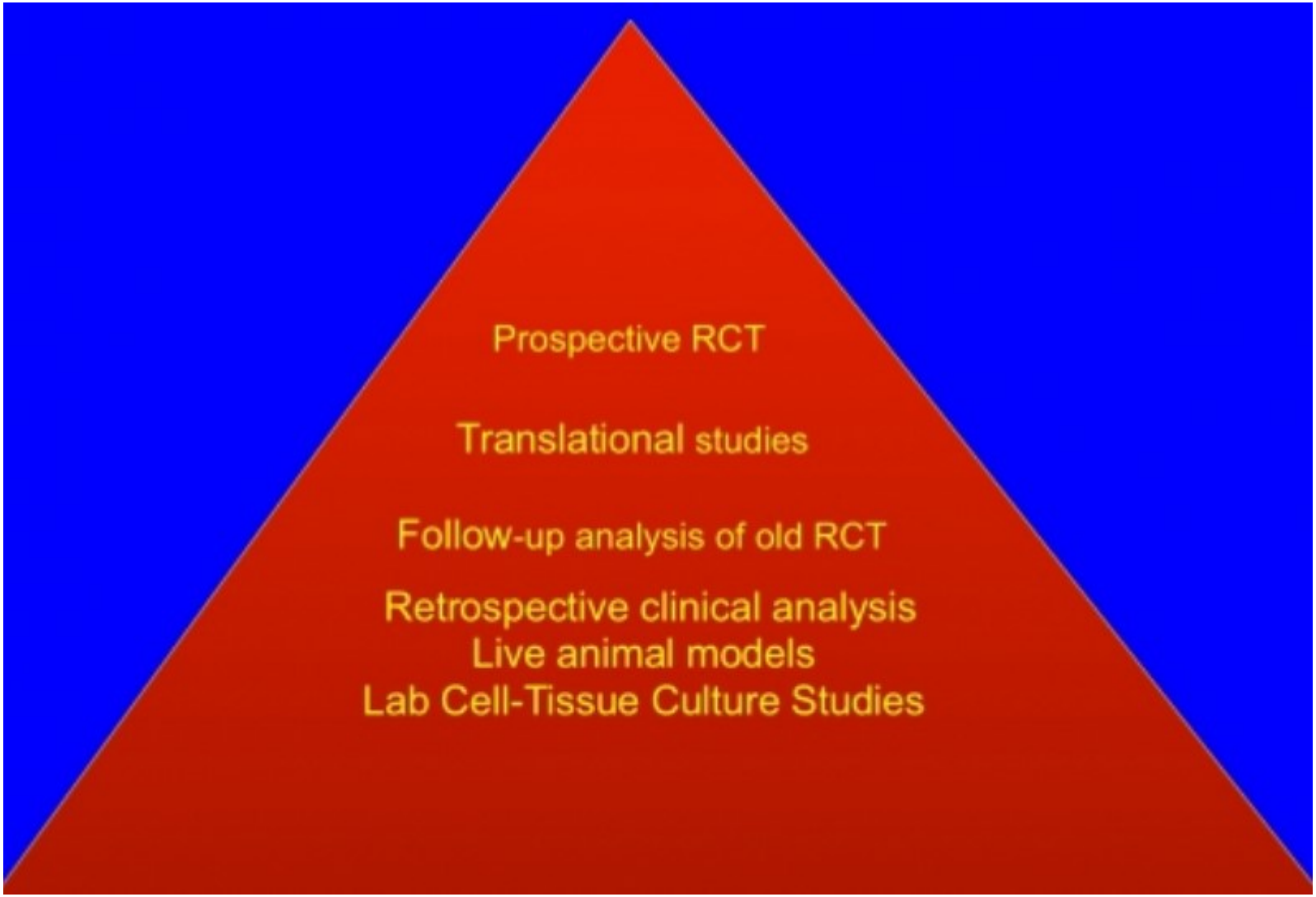
- **Epithelial-to-mesenchymal transition**
  - Epithelial cancer cells develop a mesenchymal phenotype facilitating cellular motility, and thus, metastatic potential

- **Inflammatory Oncotaxis**
  - Distant sites of inflammation, with disrupted endothelial surfaces and bathed in growth factors, may provide favourable sites for seeding by CTCs liberated during surgery

Potential Impact of Anaesthetic Agents



Levels of Evidence



Inhalational Agents

- Decrease Cellular Immunity
  - Reduce NK cells and Cytotoxic Lymphocytes
  - Augments the decrease in the Th1/Th2 ratio commonly seen in the perioperative phase
- Promote tumorigenic growth factors
  - HIFs - hypoxia-inducible factors
  - IGF - Insulin-like growth factor

Propofol

- Has anti-inflammatory properties as well as stimulatory effects on immune function
- Reduction in HIF-1 alpha expression
- Increases apoptosis
- Decreases invasion, migration, and proliferation across multiple cell lines
- Patients given TIVA had better preserved NK function against the breast cancer cells and apoptosis than those given volatiles

Clinical Data: TIVA

Long-term Survival for Patients Undergoing Volatile *versus* IV Anesthesia for Cancer Surgery

A Retrospective Analysis

Timothy J. Wigmore, M.A., F.R.C.A., F.F.I.C.M., F.C.I.C.M., Kabir Mohammed, M.Sc., Shaman Jhanji, Ph.D., M.R.C.P., F.R.C.A., F.F.I.C.M.

- Retrospective series looked at more than 7000 patients anaesthetised for elective unselected cancer surgery in a single cancer centre in the UK.

- After propensity matching, the hazard ratio (HR) for death in the inhalational group compared with the TIVA group median follow-up of 2.6 yr was **1.46** [95% (CI) 1.29-1.66, P<0.001]

Survival at 1 year

87.9% in the inhalational group

vs

94.1% in the TIVA-based group.

Clinical Data: TIVA 2

3 other retrospective trials:

- 1 trial had survival advantage that didn't last after adjustment for confounders (breast and colorectal)
- 1 showed reduction in breast cancer recurrence
- 1 showed improved survival and improved recurrence free survival with TIVA vs inhalational agents in oesophagectomy after multivariable adjustment

RCT Evidence: Sessler et al 2019

- 2132 women enrolled undergoing potentially curative primary breast cancer resections. Compared:

Propofol TIVA + Paravertebral block

vs

Sevoflurane and Opioids

- Primary outcome (ITT) was local or metastatic recurrence (median follow up 36 months) in which no difference found

THE LANCET

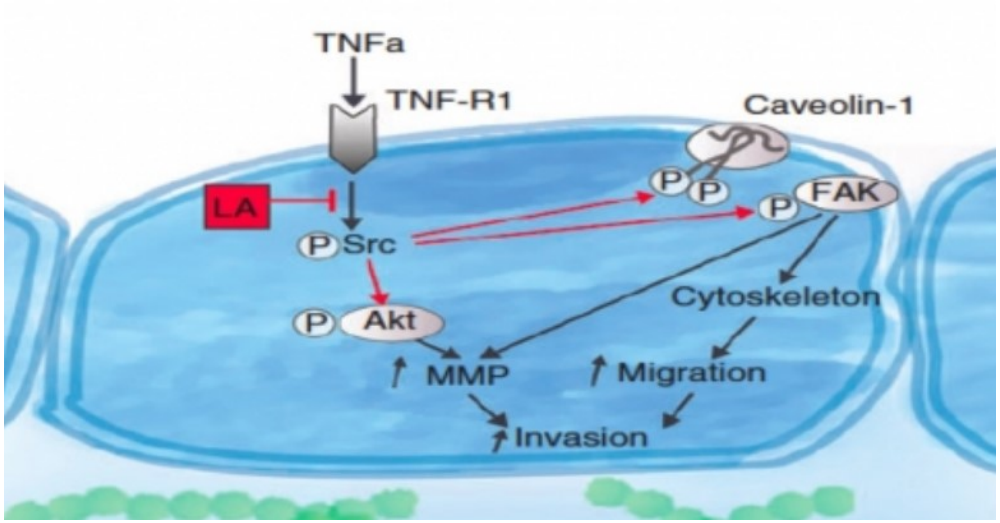
Regional Anaesthesia: Advantages

- Lowers perioperative requirement for high dose systemic opioids avoiding effects on cancer progression
- Neuraxial techniques and the resultant sympathetic blockade have been shown to attenuate the stress response, better maintaining host immunity and minimising the impact that immunosuppression has upon the oncological disease process
- Local anaesthetics may themselves have an immunomodulatory effect

Amide Local Anaesthetics

- Voltage gated channel SCN5A is key regulator of gene transcriptional network that controls colon cancer invasion

- Blocks matrix metalloproteases:



Clinical Data: Regional Anaesthesia

- Meta-analysis examining data from five prospective trials and 13 retrospective studies:
  - Concluded that there was an overall survival benefit with epidural anaesthesia, especially in colorectal surgery
  - However did not find any impact upon cancer recurrence
- RCT (Falk et al BJA 2021):
  - 221 patients undergoing colorectal resection (open and lap)
  - No difference in 5 yr. survival ? underpowered

Clinical Data: Regional Anaesthesia 2

A systematic review looking at PVB in breast cancer was equivocal:

- Due to the number of low quality studies and heterogeneity of biochemical measurements, meta-analysis was not possible
- Concluded that current evidence neither supports nor refutes the oncological benefit of PVB

Perez-Gonzalez O, Cuellar-Guzman LF, Soliz J, Cata JP. Impact of regional anesthesia on recurrence, metastasis, and immune response in breast cancer surgery. Reg Anesth Pain Med 2017; 42: 751e6

Opioids: Bad??

- The mu opioid receptor (MOR) is expressed in a wide range of cancer cells, with significantly increased levels of MOR proteins being found in breast, colon, and lung cancer.

- Agonism of the MOR with morphine has been shown to promote the release of vascular endothelial growth factor, implicating the receptor in tumour angiogenesis and growth.

- Patients with polymorphism of the MOR gene that leads to reduced receptor transcription, not only had a reduced analgesic response to opioids, but also increased breast cancer survival

Opioids Good??

In Murine Models

- Morphine reduced the adhesive and invasive potential of the tumour cells by inhibiting the production of matrix metalloproteinases
- Chronic use of morphine at clinically relevant doses significantly reduced tumour angiogenesis and growth when compared to placebo
- ?? Negative effects a result of intermittent withdrawal state and increase in stress response
- ?? Are differential effects of different opioids including partial agonist with NK cell effects

Clinical Data: Opioids

Evidence is mixed and influenced by setting, dosing, and chronicity:

- Largest epidemiological study to date 34,188 patients:
  - No association between use of opioids and breast cancer recurrence
  - Effect was regardless of opioid type, strength, chronicity of use, or cumulative dose
- Retrospective review 2021:
  - higher intraoperative morphine mg equivalent associated with decreased survival in lung adenocarcinoma

Dexamethasone

- ??Theoretically good as anti-inflammatory effect, *however*
- Inhibits both the innate and cellular immune responses by reducing the number and activity of NK cells and of multiple other T cell subtypes
- Animal models have demonstrated a suppressed anti-tumour immune response after dexamethasone

- In vitro data
  - significantly reduced the invasive potential of pancreatic tumour cells and secretion of pro-inflammatory Cytokines
- In vivo data
  - reduction in both the number and volume of metastatic tumour deposits in mice treated with dexamethasone

Dexamethasone: Clinical

- Retrospective analysis in ovarian ca undergoing chemo:
  - No impact on the disease-free interval or survival time
- Recent retrospective cohort studies of NSCLC and pancreatic cancer patients suggested that perioperative dexamethasone may be associated with improved patient survival
- Retrospective analysis in ovarian ca after primary resection:
  - Failed to demonstrate an association between perioperative dexamethasone use and ovarian cancer recurrence

NSAIDS

COX is essential in production of prostaglandins

Prostaglandins:

- Act via G-protein coupled receptors
- Regulation of the inflammatory response
- Reduce NK cell cytotoxicity

- PGE-2
  - Has been shown to promote cancer mutagenesis, mitogenesis, angiogenesis, and metastasis.

- ?Benefit also in terms of opiate sparing effects

Clinical Data: NSAIDS

- Mostly in studies relating to long term NSAID use prior to diagnosis

Regular NSAID associated with reduced CRC incidence in observational and randomised studies

- 3 Retrospective Reviews:
  - Periop NSAID use improved outcomes in Ca breast
  - Benefit in NSCLC (when combined with dexamethasone)
  - No benefit in prostate or NSCLC (as sole intervention)

Others……

Alpha 2 Agonists

- Alpha 2 adrenoreceptor agonists
- Theoretically good as catecholamines have pro-tumour effects
- Opiate and MAC sparing

However

- Detrimental in cell studies
- Small trial in gastrectomy patients given dexmedetomidine showed improved immune function markers

Beta Blockers

- May ameliorate the effects of surgery-induced SNS activation, and thus, limit the resulting cancer-promoting effects of catecholamines
- Initial meta-analyses of retrospective clinical studies examining clinical outcomes in cancer patients suggested that ß-blocker use improves survival
- More recent meta-analysis concluded that ß-blockers have no evident effect on cancer recurrence, and effects on disease-free survival and overall survival vary with tumour type from beneficial to harmful

Blood Transfusion

Causes:

- Immunosuppression
- Inflammation

Both factors known to adversely affect cancer recurrence risk

- Macrophages consuming iron released from damaged RBCs demonstrate compromised phagocytic activity and shift towards pro-tumour Th2 effector responses

Blood Transfusion: Clinical

- Cochrane meta-analysis of Colorectal cancer patients reported an overall odds ratio for recurrence of 1.42 (95% CI:1.20-1.67)
- Study heterogeneity and insufficient data on surgical technique prevented the definitive establishment of a causal relationship
- ? More aggressive cancer = more transfusions

Future/ Ongoing NCTs

Trial	Cancer Type	Intervention
VAPOR-C: NCT01975064	Colonic Breast	Propofol vs Sevoflurane
GA-CARES: NCT03034096	Surgical Oncology	Propofol vs Volatile
NCT02660411	Surgical Oncology	Propofol vs Sevoflurane
NCT02786329	Colorectal	TIVA + Lidocaine sevo +lidocaine TIVA + placebo Sevo + placebo
NCT03172988,	NSCLC	Dexamethasone Flurbiprofen
NCT02840227	NSCLC	GA with opioid analgesia GA with epidural
NCT03109990	Breast	Saline Dexmedetomidine

Summary

- In vitro and in vivo animal data suggest that anaesthetic agents can influence cancer biology both +ve and -ve
- Safer / beneficial agents may include propofol, amide local anaesthetics and NSAIDS
- Potentially deleterious affects may be induced by volatiles, opioids, and steroids
- To date, there is no RCT evidence to suggest that anaesthetic techniques affect cancer outcomes

References

- M.T. Evans, T. Wigmore and L.J.S. Kelliher. The impact of anaesthetic technique upon outcome in oncological surgery *BJA Education* 19(1): 14-20 (2019)

- T. Wall, A. Sherwin, D. Ma and D. J. Buggy. Influence of perioperative anaesthetic and analgesic interventions on oncological outcomes: a narrative review. *British Journal of Anaesthesia* 123 (2): 135-150 (2019)