Improving oncological outcomes: does perioperative care matter?

Introduction

Cancer continues to pose a significant challenge to healthcare systems worldwide. There are approximately 367,000 new cancer cases diagnosed in the UK annually, with 45% of these patients undergoing surgical resection of their tumour as part of their primary management (1,2). Additionally, a number of cancer patients will require surgery and anaesthesia for non-cancer indications whilst concurrently receiving treatment for their malignancy. It is feasible that undergoing surgery in these circumstances may influence an individual's cancer journey in a variety of ways, from the impact of the perioperative period in terms of physiological stress, to the time spent recovering to baseline function before subsequent return to the intended oncological therapy (RIOT). Therefore, oncologically speaking, designing care pathways that minimise the stress of the perioperative period and optimise short-term recovery could potentially lead to long term benefits. Additionally, achieving such a goal could have benefits for healthcare systems as a whole, improving productivity, lessening the burden of disease and freeing up limited resources to utilise on further patients (3).

Over recent decades, many strategies have been developed to improve the care received during the perioperative phase for cancer patients. These have included numerous advances in surgical and anaesthetic technique, the creation of enhanced recovery after surgery (ERAS) programmes and the evolution of neoadjuvant medical oncology therapies. This editorial, part of a special edition of *Digestive Medicine Research* reviewing the perioperative care of the cancer patient, examines recent advances and strategies in the fields of anaesthesia and surgery particularly relevant in the management of cancer. Additionally we will look at the use of the return to cancer therapy, beyond surgery, as a novel metric that is increasingly used to measure quality improvement in the care pathways of surgical oncology patients.

Advances in surgical technique: minimally invasive surgery and the robotic revolution

It has been estimated that 45 million surgical procedures will be needed for cancer, worldwide by 2030 (4). Despite being a key component of the treatment of many patients, the stress response to surgery, with its pronounced neurohumoral and immunological impact, combined with the ever present risk of residual tumour and circulating micrometastases represents a perfect storm for the generation of metastasis and future recurrence. Consequently, many of the advances in surgical and anaesthetic techniques are aimed at reducing the degree and impact of the stress response. A full review of the impact of the surgical stress response in cancer patients forms part of this special edition of the journal.

The term minimally invasive surgery (MIS) describes the use of surgical methods designed to reduce the magnitude of tissue trauma generated at the point of operation thereby, reducing the consequent inflammatory response generated by the body. Since its first use in 1988 by the gynaecologist Kurt Semm, the laparoscopic approach has been applied to numerous surgical procedures and subspecialties (5). Data has been published which appears to lend itself to the theory that a reduction in magnitude of surgical trauma results in a reduction of inflammatory response. Specifically a reduced proinflammatory response has been found in laparoscopic colorectal surgery compared to open alternatives, with lower levels of Interleukin-6 (IL-6) and C-reactive protein (CRP), in addition to higher natural killer (NK) cell numbers in the laparoscopic group (6). NK cells are thought to play a key role in the immunological defence against micrometastasis. Additionally, data has been published demonstrating a reduction in postoperative complication rates in several surgical subgroups, including laparoscopic liver resection, rectal cancer resection, hernia repair and appendicectomy, compared to open alternatives (7-10).

More recently, the advent of robotically assisted surgery has led to further evolution in MIS. The first use of robotics was described in neurosurgery surgery in 1988, however it's first reported laparoscopic use of was in 1997, facilitating a laparoscopic cholecystectomy (11,12). Despite the expansion of the use of robotics to enable MIS in a wide range of surgical specialties, it's efficacy with respect to longer term outcomes and disease-free survival in cancer surgery remains controversial. Notably a large epidemiological study investigating long-term overall survival after radical hysterectomy demonstrated a significantly higher 4-year mortality rate in those patients who had MIS as opposed to an open surgical approach (13).

Additionally, there is ongoing concern regarding the use of pneumoperitoneum and the potential for dissemination of cancer cells at tumour resection resulting in port site metastasis (14-17).

Despite this conflicting information, it remains clear that both cancer as an entity, and the population of patients afflicted by it are widely heterogenous. Consequently it is unlikely that definitive evidence regarding the precise benefits or limitations of specific surgical techniques will emerge in the near future. However any surgical approach that reduces postoperative complications without evidence of a negatively impacting cancer recurrence warrants further investigation. A more in depth review of the role of robotics in cancer surgery can be found later in this special edition of *Digestive Medicine Research*.

Advances in anaesthetic technique: first do no harm?

It may seem inconceivable that the choice of anaesthetic technique can have a significant impact upon longer term cancer prognosis, given the surgical episode represents such a small part of the patient's overall healthcare journey. Despite this, there has been significant interest in recent years on the potential impact that anaesthetic choice may have upon cancer biology in the perioperative phase and beyond.

As previously described, the surgical episode represents a time of potential dissemination of micrometastases, which, combined with the stress response to surgery, may accelerate potential recurrence and metastatic growth. In addition to the possible direct impact that our perioperative medications and anaesthetic drugs may have upon tumour development, there is recent evidence suggesting that the same medications may bring about epigenetic changes in residual tumour cells (18). Importantly, these changes are known to contribute to various phases of the life of a tumour cell, and can be inherited through cell lines (19).

As with the conclusions made regarding surgical technique, it should be noted that due to the heterogenous nature of the cancer population, although multiple areas of biological plausibility exist, definitive clinical evidence from robust, prospective randomised controlled trials is lacking. Nevertheless, there are multiple areas of ongoing research aiming to answer some of these ongoing clinical dilemmas.

One such dilemma revolves around the choice of agent used for maintenance of anaesthesia, with some data suggesting that a total intravenous anaesthetic (TIVA) based technique may be less deleterious than a volatile anaesthetic alternative. This assertion is largely based upon laboratory data demonstrating the promotion of tumorigenic growth factors such as hypoxia inducible factors (e.g., HIF-1α) and insulin-like growth factor (IGF) by volatile anaesthetics, with no such changes seen with propofol (20). Additionally propofol has been shown to preserve NK cell function, unlike volatile anaesthetic agents, which have been linked to a reduction in both NK cells and cytotoxic T lymphocytes (CTLs), both of which are important in the perioperative immunological defence against circulating micrometastases (21). Importantly, these biologically plausible benefits have yet to be borne out in robust prospective clinical studies.

A thorough review of the current evidence regarding the impact of individual anaesthetic drugs is beyond the scope of this editorial, however the ongoing debate between the use of intravenous and inhalational anaesthesia is discussed in it's own part of this edition of the journal. Additionally an in depth review of the impact of postoperative analgesia is also included. In the absence of clear clinical evidence, a pragmatic approach should be adopted, aiming to provide a high level of care, whilst remaining cognisant of the fact that our choices as perioperative clinicians may have a long-lasting impact, beyond the surgical episode.

The rise of ERAS

The concept of ERAS was first developed in the 1990s, originating from the work led by Henrik Kehlet, a Danish gastrointestinal surgeon (22). Since its inception, the ERAS approach has become increasingly popular, and has been applied to a wide range of surgical specialties and procedures to good effect.

In essence, ERAS does not describe any one particular intervention or treatment. It is wide reaching, and aims to inform patient care across the entire perioperative journey, with the overarching goal being a reduction of the impact a particular surgical procedure has on the patient, thereby facilitating a rapid recovery and return to normal function. This is achieved by regularly examining traditional perioperative practices and modifying them where required, creating a standardised,

Table 1 Summary of key non-procedure-specific elements of the ERAS Guidelines for Oesophagectomy and Gastrectomy. Reproduced with permission from Evans M, Kelliher L. Enhanced recovery for upper gastrointestinal surgery: A Review. Dig Med Res 2019;2.

Gastrectomy	Oesophagectomy
Preoperative Counselling	
Smoking and Alcohol Cessation	
Avoidance of Oral Bowel Preparation	
Avoidance of Prolonged Preoperative Fasting and Carbohydrate Preload	
Avoidance of Long Acting Pre-anaesthetic Anxiolytics	
Antithrombotic Prophylaxis	
Control of Postoperative Nausea and Vomiting	
Postoperative Glycaemic Control	
Multimodal Stimulation of Bowel Movement	
Consider Early Removal of Urinary Catheters	
Anaesthetic Management	Avoidance of Hypothermia
Antimicrobial Prophylaxis and Skin Preparation	Patient Specific Prophylaxis of Atrial Dysrhythmia
Epidural Analgesia	Continuation of Beta Blockade if appropriate
Intravenous Analgesia	Cardiopulmonary Assessment
Neutral Fluid Balance	
Early and Scheduled Mobilisation	

evidence based perioperative pathway in line with current consensus opinion. Consequently the perioperative pathway for the procedure in question will be refined over time, effectively achieving ongoing quality improvement through the accumulation of marginal gains as additional data is published and pre-existing techniques are modified. Therefore ERAS can be seen as a means of combining the advancements surgical technique, anaesthetic practice and the relevant fields of the allied health professionals who make up the wider multidisciplinary team (MDT).

ERAS guidelines may be created on a local level, however since the creation of the ERAS Study Group in 2001, later registered as the ERAS Society in 2010, international consensus opinion has generated ERAS guidelines for over 19 surgical procedures. These guidelines contain both recommendations specific to the surgical procedure being addressed, but also a number of non-specific recommendations which will be common to a host of perioperative pathways. An example of this can be seen in *Table 1*, which summarises the recommendations made for ERAS in the upper gastrointestinal surgical population. This demonstrates the wide reaching nature of the components of ERAS. Risk stratification, preoptimisation and patient blood management form key parts of any ERAS programme, and are addressed in their own review articles as part of this special edition.

Hospital length of stay remains one of the key measures of success for the implementation of an ERAS pathway, with many groups reporting a significantly reduced hospital stay for patients enrolled in ERAS programmes (23). This reduction in length of stay also translates into a reduction in hospital cost per patient. The implementation of ERAS for a colorectal surgical cohort in Alberta, Canada, resulted in a cost saving of between CA$2806 and CA$5898 per patient (24). However, of particular importance to the cancer patient is the fact that ERAS has been shown to reduce the immunological impact of the surgical stress response, as demonstrated by reductions in postoperative Interleukin 6 (IL-6) and C-reactive protein (CRP) levels (25). In fact, ERAS for open liver resection has been shown to significantly improve two year survival, yet have no impact upon five year survival in a post hoc analysis of data collected as part of an RCT investigating ERAS in liver surgery (25). Therefore it is plausible that ERAS may have a beneficial impact upon ongoing cancer prognosis and the development of

recurrence, although again, in such a heterogenous population, across a broad range of surgical specialties, it would be a challenge for even the most rigorous of clinical studies to identify such an association.

Time to RIOT

Although primary tumour resection surgery is a key component of the oncological management for a significant number of patients diagnosed with cancer, the perioperative episode typically only constitutes a small part of the overall patient journey. Advances in non-surgical cancer management has resulted in the adoption of both adjuvant and neoadjuvant chemotherapy and radiotherapy programmes for a wide range of malignancies to good effect (26-29). Importantly these neoadjuvant therapies may in fact render some previously unresectable tumours amenable to surgical management. Additionally, adjuvant therapies are continually being refined to achieve both improved efficacy and reduced toxicity. Nevertheless, they will still rely upon an appropriate convalescence period after the surgical insult.

The concept of using the Return to Intended Oncological Therapy (RIOT) rate as a metric to evaluate the quality of surgery in the oncological population was first described by Aloia *et al.* in 2014 (30). The group demonstrated that 100% of patients undergoing MIS hepatectomy in their sample population returned to their intended oncological therapy (a RIOT Rate of 100%), whereas only 75% of patients in the open hepatectomy cohort had a similar trajectory (a RIOT Rate of 75%). Perhaps even more importantly, when comparing the time interval for RIOT, the MIS cohort were found to have reinitiated their adjunctive therapy nearly 4 weeks earlier than the open surgical approach cohort.

Subsequent research has attempted to identify the key perioperative features which impact RIOT rate. Factors which have been shown to negatively impact RIOT include an open surgical approach, prolonged length of hospital stay (of 5 days or more), the development of any postoperative complication and an increased perioperative disease burden (31,32). Interestingly, the application of ERAS principles effectively aims to address the majority of these factors.

When considering the ethos behind ERAS, an improvement in both the number of patients able to restart their ongoing oncological therapy and the time interval between surgery and this reinitiation is the logical result of the reduction in the physiological impact of surgery that ERAS strives towards. In fact, a prospective investigation of the impact of ERAS in liver surgery has demonstrated not only an increase in the RIOT rate, but also a more rapid RIOT in those patients enrolled on an ERAS programme when compared to a traditional perioperative care pathway (33).

Conclusions and future avenues

This paper highlights the need to strive towards the proliferation of ERAS across additional surgical subspecialties, aiming to reduce the impact of the resultant surgical stress response, thereby improving RIOT. In order to guide this quality improvement, audit and assessment should be both contemporaneous and continuous. We should aim to not only record improvements in traditional metrics such as length of stay and mortality, but we should aim to record changes in both patient reported outcome measures (PROMs) and patient reported experience measures (PREMs). The latter is of particular importance, as improvement in patient experience has been independently linked to an improvement in patient reported outcome measures (34). Despite the inherent challenges faced when examining such a varied population, further investigation into the impact of the aspects of the perioperative pathway described above is warranted.

The ongoing improvement in the quality of perioperative care of the cancer patient will not be driven solely by new techniques and novel therapies It will also be achieved through the accumulation of marginal gains across the entire perioperative journey, and the integration of both ERAS principles and further refinements in surgical and anaesthetic technique. We hope you enjoy this special edition of *Digestive Medicine Research* exploring some of these strategies in the perioperative care of the cancer patient.

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References

1. Cancer Incidence Statistics. Cancer Research UK. Available online: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence#heading-Zero
2. Evans MT, Wigmore T, Kelliher LJS. The impact of anaesthetic technique upon outcome in oncological surgery. BJA Educ 2019;19:14-20.
3. Mayor S, Balch C. Cancer surgery: the key factors that influence outcomes. CancerWorld 2018;(Spring):39-45.
4. Semm K. Die pelviskopische Appendektomie. Dtsch med Wochenschr. 1988;113:3-5.
5. Wichmann MW, Hüttl TP, Winter H, et al. Immunological effects of laparoscopic vs open colorectal surgery. A prospective clinical study. Arch Surg 2005;140:692-7.
6. Fretland ÅA, Dagenborg VJ, Bjørnelv GMW, et al. Laparoscopic Versus Open Resection for Colorectal Liver Metastases. Ann Surg 2018;267:199-207.
7. Biondi A, di Stefano C, Ferrara F, et al. Laparoscopic versus open appendectomy: A retrospective cohort study assessing outcomes and cost-effectiveness. World J Emerg Surg 2016;11:44-9.
8. Al Chalabi H, Larkin J, Mehigan B, et al. A systematic review of laparoscopic versus open abdominal incisional hernia repair, with meta-analysis of randomized controlled trials. Int J Surg 2015;20:65-74.
9. Dai J, Yu Z. Comparison of Clinical Efficacy and Complications Between Laparoscopic Versus Open Surgery for Low Rectal Cancer. Comb Chem High Throughput Screen 2019;22:179-86.
10. Kwoh YS, Hou J, Jonckheere EA, et al. A robot with improved absolute positioning accuracy for CT guided stereotactic brain surgery. IEEE Trans Biomed Eng 1988;35:153-60.
11. Lane T. A short history of robotic surgery. Ann R Coll Surg Engl 2018;100:5-7.
12. Melamed A, Margul DJ, Chen L, et al. Survival after Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer. N Engl J Med 2018;379:1905-14.
13. Berger-Richardson D, Chesney TR, Englesakis M, et al. Trends in port-site metastasis after laparoscopic resection of incidental gallbladder cancer: A systematic review. Surgery 2017;161:618-27.
14. Shigeta K, Kikuchi E, Hagiwara M, et al. Prolonged pneumoperitoneum time is an independent risk factor for intravesical recurrence after laparoscopic radical nephroureterectomy in upper tract urothelial carcinoma. Surg Oncol 2017;26:73-9.

15. Emoto S, Ishigami H, Yamaguchi H, et al. Port-site metastasis after laparoscopic surgery for gastrointestinal cancer. Surg Today 2017;47:280-3.
16. Jakub J, Greene FL. Pneumoperitoneum in Cancer. In: Rosenthal RJ, Friedman RL, Phillips EH, editors. The Pathophysiology of Pneumoperitoneum [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 1998. p. 147-58.
17. Lirk P, Fiegl H, Weber NC, Hollmann MW. Epigenetics in the perioperative period. Br J Pharmacol 2015;172:2748-55.
18. Kanwal R, Gupta S. Epigenetic modifications in cancer. Clin Genet 2012;81:303-11.
19. Behmenburg F, van Caster P, Bunte S, et al. Impact of Anesthetic Regimen on Remote Ischemic Preconditioning in the Rat Heart In Vivo. Anesth Analg 2018;126:1377-80.
20. Wigmore TJ, Mohammed K, Jhanji S. Long-term survival for patients undergoing volatile versus IV anesthesia for cancer surgery: A retrospective analysis. Anesthesiology 2016;124:69-79.
21. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth 1997;78:606-17.
22. Grocott MPW, Martin DS, Mythen MG. Enhanced recovery pathways as a way to reduce surgical morbidity. Curr Opin Crit Care 2012;18:385-92.
23. Nelson G, Kiyang LN, Crumley ET, et al. Implementation of Enhanced Recovery after Surgery (ERAS) Across a Provincial Healthcare System: The ERAS Alberta Colorectal Surgery Experience. World J Surg 2016;40:1092-103.
24. Ding J, Sun B, Song P, et al. The application of enhanced recovery after surgery (ERAS)/fast-track surgery in gastrectomy for gastric cancer: a systematic review and meta-analysis. Oncotarget 2017;8:75699-711.
25. Morrison B, Jones C, Kelliher L, et al. ERAS for open liver resection surgery improves two-year survival but not five-year survival. Clin Nutr ESPEN 2017;19:78.
26. Tajima H, Ohta T, Kitagawa H, et al. Pilot study of neoadjuvant chemotherapy with gemcitabine and oral S-1 for resectable pancreatic cancer. Exp Ther Med 2012;3:787-92.
27. Song WA, Zhou NK, Wang W, et al. Survival Benefit of Neoadjuvant Chemotherapy in Non-small Cell Lung Cancer: An Updated Meta-Analysis of 13 Randomized Control Trials. J Thorac Oncol 2010;5:510-6.
28. FOxTROT Collaborative Group. Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial. Lancet Oncol 2012;13:1152-60.
29. Robova H, Rob L, Halaska MJ, et al. High-dose density neoadjuvant chemotherapy in bulky IB cervical cancer. Gynecol Oncol 2013;128:49-53.
30. Aloia TA, Zimmitti G, Conrad C, et al. Return to intended oncologic treatment (RIOT): A novel metric for evaluating the quality of oncosurgical therapy for malignancy. J Surg Oncol 2014;110:107-14.
31. Lillemoe HA, Marcus RK, Kim BJ, et al. Severe Preoperative Symptoms Delay Readiness to Return to Intended Oncologic Therapy (RIOT) After Liver Resection. Ann Surg Oncol 2019;26:4548-55.
32. Lillemoe HA, Marcus RK, Kim BJ, et al. Detours on the Road to Recovery: What Factors Delay Readiness to Return to Intended Oncologic Therapy (RIOT) After Liver Resection for Malignancy? J Gastrointest Surg 2019;23:2362-71.
33. Day RW, Cleeland CS, Wang XS, et al. Patient-Reported Outcomes Accurately Measure the Value of an Enhanced Recovery Program in Liver Surgery Poster abstract presented at the 123rd Annual Western Surgical Association Meeting, Napa Valley, CA, November 2015. J Am Coll Surg 2015;221:1023-1030.e1.
34. Kingsley C, Patel S. Patient-reported outcome measures and patient-reported experience measures. BJA Educ 2017;17:137-44.

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