Opioids and cancer recurrence

Rohit Juneja

Purpose of review
With the majority of deaths from cancer because of their metastases, strategies to reduce this from occurring are at the forefront of treatment. It has been hypothesized that morphine may result in an increase in cancer metastases, following many in-vitro and animal studies, but the evidence from human retrospective data is inconclusive. This article will explore the possible mechanisms by which opioids can impact on the natural history of the cancer cell and whether they are likely to be harmful in individuals with cancer.

Recent findings
Although there have been trials demonstrating benefits with regional anaesthesia techniques (opioid sparing) in the surgical population, it is not clear whether the source of the benefit arises directly from the avoidance of opioids or an added benefit afforded by regional anaesthesia. Research has shown that in particular cancer cell types, morphine may actually be beneficial and that the μ-opioid receptor (MOR) plays a role in cancer disease. With the crystal structure of the MOR having recently been elucidated, this may offer new opportunities for treatments aimed at reducing cancer metastasis.

Summary
The role opioids play in the development of cancer metastasis and recurrence is far from clear and appears to differ depending on the cancer cell type in question. Prospective randomized controlled trials are currently underway in humans to help clarify the situation further and there results are awaited with anticipation. The negative impact of pain on the immune system is well documented and it appears that appropriate analgesia is paramount in minimizing this. Opioids still constitute a central role in the management of moderate-to-severe cancer pain.

Keywords
cancer, immunomodulation, metastasis, morphine

INTRODUCTION

With 32.6 million people living with cancer worldwide [1] and pain being reported in up to 64% of those patients with advanced disease [2], the need for strong analgesia to reduce suffering and distress is great. Strong opioids are recommended for the treatment of moderate-to-severe cancer as part of the World Health Organization (WHO) Cancer Pain Ladder with morphine being the prototypical strong opioid. Over the past 30 years, there has been a growing body of evidence associating opioid use with a potential increase in cancer recurrence. This may have caused some to question the role of opioids in modern analgesic therapy; however, much of the available evidence is in conflict with itself and the answers are far from clear.

The perioperative period presents an opportunity for cancer cells to metastasize because of a combination of diminished host immune responses as a consequence of the surgical stress response [3–5] and anaesthetic pharmacology [6], dissemination of cancer cells secondary to tumour handling [7] and the negative immunomodulatory effects of pain [8]. This proportionally small time period in the patient's cancer treatment journey presents a disproportionately large risk in the potential for cancer recurrence and as such is a focus of much investigation in the field of opioids and cancer recurrence research. For this reason, many of the works referenced in this article will focus on this scenario.

MECHANISMS OF METASTASIS

Morphine is considered to be the archetypal exogenous opioid and β-endorphin, the endogenous ligand for the μ opioid receptor (MOR) [9]. Both are known

The Royal Marsden Hospital NHS Foundation Trust, London, UK

Correspondence to Dr Rohit Juneja, MBBS, BSc (Hons), FRCA, Consultant Anaesthetist, The Royal Marsden Hospital NHS Foundation Trust, Fulham Road, London SW3 6JJ, UK. Tel: +44 207 808 2727; e-mail: rohit.juneja@rmh.nhs.uk

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KEY POINTS

- Pain itself is immunosuppressive.
- There is a large amount of research data from in-vitro, animal and human studies but no consensus exists on the benefit or harm posed by opioids on cancer recurrence.
- Prospective randomized controlled trials in cancer surgery are underway and the utilisation of prognostic biomarkers may help to selectively recruit patients who are deemed at greater risk/benefit from opioid use.
- The MOR mediates multiple effects beyond analgesia and the complex interplay between the MOR and other biochemical messenger systems involved in tumour growth are continually being discovered.
- Cancer pain is still undertreated and opioids remain the mainstay of treatment.

to result in analgesia but concerns have been raised that they may also play a role in cancer progression and recurrence [10].

In 1889, Paget [11] observed that the distribution pattern of secondary growths was not random and that certain tumour cells (the 'seed') had a propensity for a favoured environmental milieu (the 'soil') and it is suggested that opioids may induce changes, which allow the 'soil' to become more fertile. Immunosurveillance was introduced as a concept in the late 1950s by Burnet and Thomas and describes the ability of the host's immune system to recognize foreign cancer cells and destroy them [12]. An evolution of this hypothesis, called immunoediting, defines three phases of 'elimination', 'equilibrium' and 'escape' [13▪▪], of which 'elimination' is analogous to immunosurveillance. A minority of tumour cell variants survive this phase, but do not form frank metastases, as they are kept under control by the adaptive immune system.

This delicate balancing act of 'equilibrium' continues until something tips the scales in favour of tumour progression to allow 'escape' and established growth (Fig. 1) [14]. Schatten and Kramer [15] observed in 1957 that dissemination of tumour cells alone was not enough to explain the development of metastases and that 'proper conditions' had to exist to allow the survival and growth of these emboli. This 'metastatic inefficiency' [16] was noted by Fidler, as less than 0.01% of tumour cells in circulation are eventually successful in establishing secondary growths [17].

A Darwinian process of natural selection allows poorly immunogenic tumours, which evade the host's immune system, to be selected for further cell growth, but in the context of opioids/pain and cancer progression, it is the resulting immunosuppression from various cytokines such as vascular endothelial growth factor (VEGF), interleukin-6, interleukin-10, prostaglandin E_2 (PGE_2), activation of MOR and β-adrenergic activation of transcription factor STAT3 [18], which heralds the start of the 'escape' phase. This has led some to propose the use of perioperative β-blockade [19▪▪,20▪] and cyclooxygenase-2 (COX-2) inhibition to reduce long-term cancer recurrence following surgery [21,22].

The important role of the immune system and the universality of tumour cells' ability to evade the host's defences has been supported by the addition of 'Evading Immune Destruction' to the existing Hallmarks of Cancer by Hanahan and Weinberg in 2011 [23].

Cell-mediated immunity (CMI) is the first line of defence in the fight against disease progression and metastasis [24]. Central to CMI are natural killer (NK) cells, cytotoxic T-cells, dendritic cells and macrophages [13▪▪]. NK cells possess a 'natural' ability to identify foreign targets in a non-major histocompatibility complex-dependent manner (they do not require prior exposure and sensitisation to eradicate tumour cells) and measures of NK cell cytotoxicity (NKCC) are often employed in studies investigating cancer recurrence because of their importance in CMI and the host's defences [25].

With respect to the major components of the immune system, opioids have been associated with the inhibition of macrophages and NKCC [26], neutrophil migration [27] and impaired cytokine production [28].

When the effects of 3-μg/kg fentanyl were assessed on healthy human volunteers, it was noted that there was a rapid and significant rise in measures of NKCC and numbers of CD8+ cytotoxic T-cells when measured *ex vivo* [29]. The dose administered appears to affect outcome too, as small (1–5 μg/kg) and large (75–100 μg/kg) doses of fentanyl given to patients undergoing surgery resulted in longer suppression of NKCC in the large fentanyl dose group [30].

The differences in duration of administration of opioids between studies have also been shown to affect levels of NKCC with 'chronic' (greater than 4 days) dosing resulting in recovery of NKCC [31], drawing parallels with the observations of Dublin *et al.* [32]. This was an epidemiologic study conducted in an immunocompetent geriatric population, which concluded that the use of opioids was associated with an increased risk of pneumonia [odds ratio (OR) = 1.38; 95% confidence interval (CI): 1.08–1.76], but this effect was more noticeable in those patients who used opioids, which the

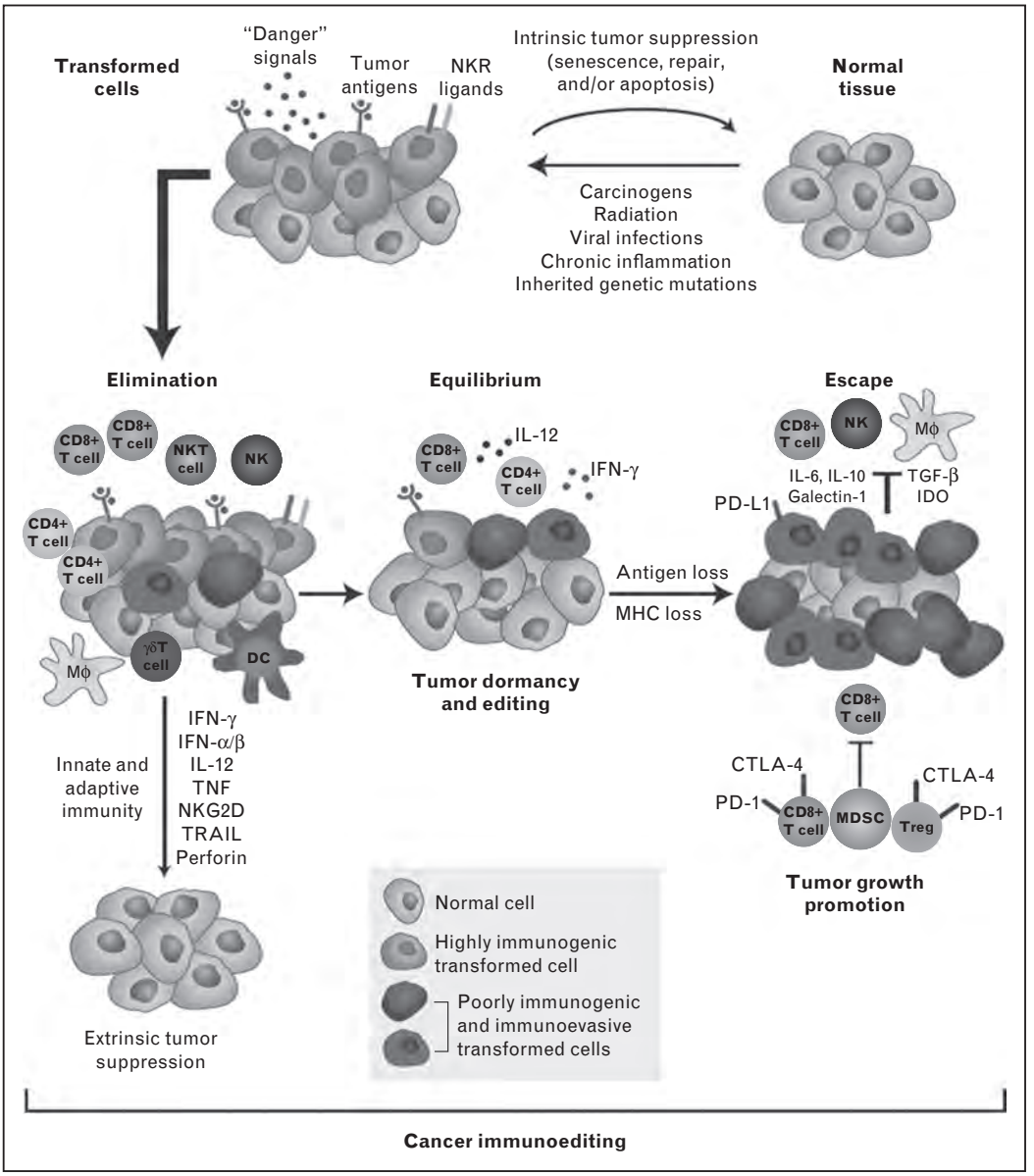

FIGURE 1. The cancer immunoediting concept. Cancer immunoediting is an extrinsic tumor suppressor mechanism that engages only after cellular transformation has occurred and intrinsic tumor suppressor mechanisms have failed. In its most complex form, cancer immunoediting consists of three sequential phases: elimination, equilibrium and escape. In the elimination phase, innate and adaptive immunity work together to destroy developing tumours long before they become clinically apparent. Many of the immune molecules and cells that participate in the elimination phase have been identified, but more work is needed to determine their exact sequence of action. If this phase goes to completion, then the host remains free of cancer, and elimination thus represents the full extent of the process. If, however, a rare cancer cell variant is not destroyed in the elimination phase, it may then enter the equilibrium phase, in which its outgrowth is prevented by immunologic mechanisms. T cells, interleukin-12, and interferon-γ are required to maintain tumour cells in a state of functional dormancy, whereas natural killer cells and molecules that participate in the recognition or effector function of cells of innate immunity are not required; this indicates that equilibrium is a function of adaptive immunity only. Editing of tumour immunogenicity occurs in the equilibrium phase. Equilibrium may also represent an end stage of the cancer immunoediting process and may restrain outgrowth of occult cancers for the lifetime of the host. However, as a consequence of constant immune selection pressure placed on genetically unstable tumor cells held in equilibrium, tumor cell variants may emerge that are no longer recognized by adaptive immunity (antigen loss variants or tumours cells that develop defects in antigen processing or presentation), become insensitive to immune effector mechanisms or induce an immunosuppressive state within the tumour microenvironment. These tumor cells may then enter the escape phase, in which their outgrowth is no longer blocked by immunity. These tumor cells emerge to cause clinically apparent disease [14].

investigators deemed 'immunosuppressive' such as morphine, codeine, fentanyl and methadone (OR = 1.88; 95% CI: 1.26–1.79) [32]. Of relevance, these patients did not have cancer and no documentation of pain scores or the original indication for opioid prescription was made. However, no difference in the incidence of pneumonia was noted in those patients who were chronic morphine users.

In another group of chronic opioid users, those with chronic pain diagnoses, a study into the effects of various opioids (mostly morphine) on NKCC failed to demonstrate any immunosuppressive effects when compared with a control arm. In fact, they did demonstrate significantly increased levels of interleukin-2-induced NKCC cells in the treatment group [33]. The scientific principles underpinning this phenomenon are as yet undetermined but could be similar to those involved in the development of opioid tolerance.

Animal investigations comparing chronic fentanyl administration with that of buprenorphine noted reductions in NKCC in the fentanyl group but not the buprenorphine group. However, these changes were not sustained and NK function returned to normal after 72 h [34]. When compared with morphine and fentanyl in a rodent model of surgical stress, only buprenorphine was able to reverse the immunosuppressive effects of surgery and reduce the level of MADB106 lung metastases [35].

Although it is not a classical opioid, tramadol is recommended as part of Step Two treatment in the WHO Analgesic Ladder [36]. As well as its actions at the MOR, it also possesses noradrenergic and serotonergic activity, which may result in a favourable immunostimulatory profile. When administered to patients undergoing surgery for uterine carcinoma, tramadol was noted to be equianalgesic when compared with morphine, but actually resulted in a significant increase in NKCC [37]. In a subsequent study in rats using the NK-sensitive MADB106 tumour model, tramadol was able to prevent surgically induced immunosuppression and the associated reduction in NKCC, unlike morphine. This resulted in significantly fewer lung metastases following surgery [38].

Assessment of the immune status of patients entering into future trials present an interesting strategy to ascertain those individuals who would truly benefit either from the avoidance of opioids or the addition of regional anaesthesia. Measures include the neutrophil:lymphocyte ratio (NLR), which correlates with low-grade systemic inflammation and has been suggested as a prognostic biomarker for various cancer types. A high NLR has been associated with larger tumours but also provides a reflection of the individual's immune response to the tumour and any associated NK suppression and PGE_2 or VEGF upregulation prior to surgery [39▪▪]. These patients in particular may benefit from non-steroidal anti-inflammatory drugs (NSAIDs) such as ketorolac or diclofenac [20▪]. The importance of the patient's immune phenotype has been noted in various cancer cell types in different organs [40] and may help to identify susceptible individuals in whom specific treatments, which augment the immune system, would be of benefit.

Outside of the contentious debate surrounding opioids and their effects on cancer recurrence, the majority of other studies investigating perioperative factors such as pain [31], temperature [41], blood transfusion [42] and regional anaesthesia [43] have pointed to the immunomodulatory impacts of these interventions as the primary source of benefit/harm.

The endocrine and immunomodulatory effects of the surgical stress response are well established [5] and raised levels of plasma glucocorticoids can result in suppression of cellular immunity [44]. It is possible that some of the benefits seen from regional anaesthesia may be because of better analgesia along with attenuation of this stress response rather than the avoidance of 'harmful' opioids.

'Evading Immune Destruction' [23] on its own is not sufficient for the survival of cancer cells. When a cancer cell begins its uncontrolled cellular division, angiogenesis must occur to establish a local blood supply if it is to exceed 2 mm in size [17] (Fig. 2) [45].

Tumours release VEGF in an autocrine and paracrine manner to establish a new capillary and lymphatic network as well as PGE_2 which inhibits NKCC [46▪▪]. This is one of many strategies which the tumour employs to help it evade the host's defences. The observations that morphine [47] can increase levels of VEGF and angiogenesis in an animal model and that this effect can be inhibited by the administration of the peripheral MOR antagonist methylnaltrexone (MNTX) [48] has added to the discussion regarding opioids' association with cancer recurrence in humans. However, there is also experimental evidence demonstrating the opposite phenomenon of morphine-induced tumour apoptosis and reduced cellular proliferation when morphine is administered to mice with Michigan Cancer Foundation-7 (MCF-7) breast tumours [49] and gastric cancer cell growth [50] *in vitro*.

Differences between the outcomes of these two studies are thought to be secondary to the differing analgesic regimens employed – a higher analgesic dose administered systemically [49] versus a sub-analgesic dose applied locally [47]. It would seem

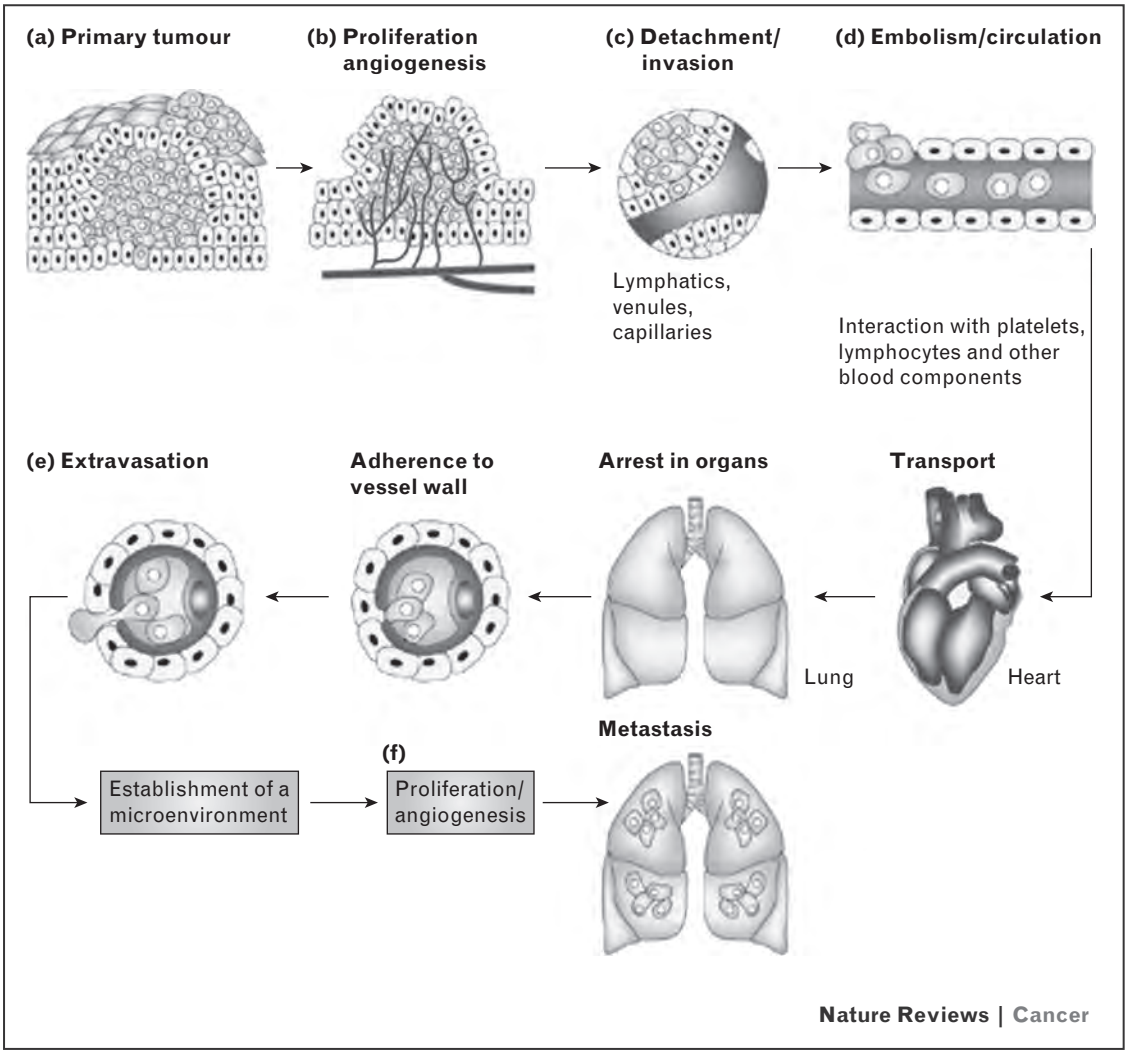

FIGURE 2. (a) Cellular transformation and tumour growth. Growth of neoplastic cells must be progressive, with nutrients for the expanding tumour mass initially supplied by simple diffusion. (b) Extensive vascularization must occur if a tumour mass is to exceed 1–2 mm in diameter. The synthesis and secretion of angiogenic factors establish a capillary network from the surrounding host tissue. (c) Local invasion of the host stroma by some tumour cells occurs by several parallel mechanisms. Thin-walled venules, such as lymphatic channels, offer very little resistance to penetration by tumour cells and provide the most common route for tumour-cell entry into the circulation. (d) Detachment and embolization of single tumour cells or aggregates occurs next, most circulating tumour cells being rapidly destroyed. After the tumour cells have survived the circulation, they become trapped in the capillary beds of distant organs by adhering either to capillary endothelial cells or to subendothelial basement membrane that might be exposed. (e) Extravasation occurs next – probably by mechanisms similar to those that operate during invasion. (f) Proliferation within the organ parenchyma completes the metastatic process. To continue growing, the micrometastasis must develop a vascular network and evade destruction by host defences. The cells can then invade blood vessels, enter the circulation and produce additional metastases [45].

that some opioids have both immunosuppressive and angiogenic effects, which would support tumour cell survival and proliferation under certain conditions. Suppression of tumour angiogenesis with morphine has also been demonstrated in a murine model of LLC and this effect was reversed with the administration of naltrexone and in MOR knockout mice *in vitro* [51].

Matrix metalloproteinases (MMPs), such as MMP-2, 3 and 9, are proteolytic enzymes, which degrade type IV collagen in the basement membrane [52] thus facilitating invasion and metastasis and morphine has been demonstrated to both increase [53] and, more recently, decrease [54▪▪] levels of MMP-9.

THE μ-OPIOID RECEPTOR

The importance of the MOR in cancer evolution has been illustrated in a study of OPRM1 (the gene

which encodes the MOR) knockout mice and Lewis Lung Carcinoma (LLC) [55]. This cancer type was chosen, as it was noted that there was a 5–10-fold increase in MOR expression in human nonsmall cell lung cancer cell lines and in-vitro application of morphine resulted in increased cellular proliferation, which was antagonized by the peripheral MOR antagonist MNTX. Intravenous injection of LLC into MOR knockout mice significantly reduced the formation of primary and metastatic tumours and this was verified with MNTX administration too.

A single-nucleotide polymorphism (SNP) in the MOR gene (*OPRM1*) at A118G is associated with a reduced analgesic response and increased survival in breast cancer [hazard ratio (HR) = 0.32; 95% CI: 0.22–0.49, $P = 0.006$)] when there are more than one copy of the G allele at this position [56▪▪]. This association between opioid receptor genotype and cancer incidence has also been documented in oesophageal cancer, with the G allele at position 118 conferring a lower risk of incidence [57].

Apart from the effects demonstrated by the A118G SNP, other genetic polymorphisms have failed to demonstrate much impact on the pain phenotype, although this is possibly because each SNP is studied in isolation and it may only be when multiple haplotypes are studied that an effect will be evident [58,59].

An in-vitro study of chronic morphine treatment in a human epidermal growth factor receptor 2 (HER2)-positive human breast cancer cell line demonstrated a significant reduction in Heregulin-induced cellular growth and increase in cellular apoptosis. Morphine interacts with fully functioning MORs present on the cancer cells and these effects were reversed with naloxone [60▪▪]. What was most revealing in this study, and may shed some light on the discrepant results witnessed over the years in this field of research, was that these beneficial effects of morphine only manifested themselves when the natural in-vivo environment was replicated by the addition of the HER3 agonist Heregulin. This highlights the importance of interpreting the results of studies performed *in vitro* wherein the complex signalling mechanisms, which naturally exist in the in-vivo tumour microenvironment, are not in operation.

Morphine's actions on peripheral MORs expressed on both cells of the immune system [61▪] and certain cancer cells [55] has led to the interest in peripheral MOR antagonists such as naloxone, naltrexone and methylnaltrexone, which are structurally similar to the oestrogen, 17β-oestradiol (E2), which binds to the oestrogen receptor present in approximately 80% of human breast cancers. Oestrogen receptor binding of E2 promotes both breast cancer cell survival and angiogenesis and these effects can be inhibited by the administration of naloxone in a murine model of MCF-7 breast cancer [62].

The interpretation of data from animal studies must be interpreted with caution, for example morphine metabolism is significantly different in rodents compared with humans, as the main metabolite is the inactive morphine-3-glucoronide (M3G) in rodents compared with highly analgesic morphine-6-glucoronide (M6G) in humans [63].

Triple-negative breast cancer (lacking the presence of HER-2, oestrogen or progesterone receptors) has few treatment options and twice the mortality of other breast cancers, yet opioid growth factor (OGF, an enkephalin) [64] and its receptor (OGFr) are present in these cancers, offering a therapeutic avenue to be explored. Intermittent low-dose naltrexone treatment in a cell culture model of MDA-MB-231 triple-negative breast cancer stimulated the production of endogenous OGF, which results in inhibition of DNA synthesis and a 35% reduction in cell numbers [65]. Alvimopan, another peripherally acting MOR antagonist, is licensed for the prevention of postoperative ileus following gastrointestinal surgery. The combination of alvimopan and a COX-2 inhibitor in a rodent study was noted to inhibit the immunosuppressive action of morphine [66] and further study into its utility in cancer surgery is warranted.

There are many inconsistencies in the findings between these studies, depending on the measure being assessed and the species studied [67], to draw any reliable and translatable conclusions when dealing with real patients with pain and cancer.

HUMAN RETROSPECTIVE DATA

Several retrospective studies in humans have suggested that employing regional anaesthesia techniques, either by epidural, paravertebral or intrathecal routes, at the time of surgical resection may reduce the incidence of cancer recurrence for breast [68], prostate [69,70], rectal [71], oesophageal [72▪], ovarian [73] and colon cancer [74]. However, there is also a significant body of evidence from human retrospective studies, failing to demonstrate any significant reduction in cancer recurrence rates in surgical resection of major abdominal [75,76], prostate [77▪,78], colorectal cancer [79▪▪,80▪,81].

A meta-analysis by Chen and Miao [82▪] investigating the impact of epidural anaesthesia on cancer survival in humans failed to support an association between their use and recurrence-free survival, although there was a small association with

epidurals and overall survival in colorectal cancer surgery (HR = 0.65; 95% CI: 0.43–0.99, $P = 0.045$).

A retrospective study of 113 patients with stage IV prostate cancer revealed an association between increased opioid requirement and shorter overall survival and progression free-survival, and increased MOR expression was also noted to be associated with worse overall survival [83▪]. However, on multivariate analysis, there was also an association with advancing age and higher Gleason score with worse overall survival and it is likely that more aggressive disease is associated with more pain and as a consequence of this, higher opioid requirements.

The terminology involved in the outcome measures also varies greatly between studies and can have an impact on the 'positive' or 'negative' effects of opioids and regional anaesthesia. A retrospective study of 148 patients addressed all of these measures and reported no significant differences in biochemical recurrence-free, local and distant recurrence-free, cancer-specific survival and overall survival [77▪].

A retrospective analysis of over 3000 patients undergoing radical prostatectomy demonstrated a statistically significant increased risk of systemic progression and all-cause mortality (but not prostate cancer mortality) in those patients who did not have regional anaesthesia. A potential problem with large retrospective analyses such as this is that they span a long period of time (15 years in this case) during which anaesthetic, surgical, diagnostic and treatment regimens are likely to have changed, although the authors of this study mention that they did match patients for the year in which surgery was performed [84▪].

Hiller *et al.* recently published data on a cohort of patients who underwent gastro-oesophageal cancer surgery from a single institution and operated on by a single surgeon. In this study, they retrospectively identified 140 patients, of which 97 had a successful epidural, which required no opioid supplementation, and noted that an effective epidural afforded patients with a reduced risk of cancer recurrence within 2 years following oesophagectomy (HR = 0.34; 95% CI: 0.16–0.75, $P = 0.005$) and an overall survival benefit (HR = 0.42; 95% CI: 0.21–0.83, $P < 0.0001$) [72▪]. They commented that a limitation of the study was the heterogeneity of the disease groups and that future studies would require 152 patients in each arm to detect a 25% difference. Although they were unable to demonstrate an overall benefit on cancer recurrence in gastro-oesophageal surgery, the results of this study yielded new information on the patients likely to most benefit from an epidural intervention, namely, those with oesophageal cancer and lymphovascular space infiltration, a history of smoking, a higher tumour stage and requiring postoperative radiotherapy.

Although retrospective analyses are unlikely to result in any changes in practice, they are still an extremely important area of research. Through multivariate analysis, it is possible to identify patterns of association, which may point to a higher-risk subcategory of patient from within the total cohort. This knowledge is helpful in generating hypotheses and focussing the efforts of future prospective studies on the correct individuals thus avoiding the unnecessary inclusion of patients who are unlikely to show any benefit.

Tsui *et al.* [78] 2010 did not show an improvement in cancer recurrence following radical prostatectomy with epidural analgesia, although this retrospective analysis was performed on a subgroup of patients enrolled in a previous trial investigating the association of epidural placement and reduced transfusion in radical prostatectomy patients [85].

Similarly, Myles *et al.* [76] found no difference in recurrence-free survival with the use of epidural for major abdominal cancer resection. However, this study was powered to detect an ambitious 33% difference in recurrence-free survival and unsurprisingly failed to demonstrate one. They were a heterogeneous group of abdominal cancers rather than a specific cancer type and the retrospective analysis was also performed on a subgroup of patients previously enrolled in another trial [86].

An example of a possible risk stratification strategy followed a systematic review into prognostic biomarkers for oesophageal carcinoma, which revealed an increased HR for VEGF and cyclin D1 in squamous cell carcinoma and COX-2 and HER-2 in adenocarcinoma [87▪▪]. Further work into prognostic biomarkers for various types of cancer may help to elucidate the specific individuals who would benefit most from regional anaesthesia or alternatives to opioid analgesia.

Prospective trials investigating cancer recurrence following surgery (or initiation of opioid therapy) are time-consuming, as the recruitment periods can be very long if the inclusion criteria are suitably focussed. Even longer are the follow-up periods, which run into many years. There are currently three multicentre prospective randomized control trials in progress, investigating the effects of regional anaesthesia in patients undergoing surgery for breast, lung and colon carcinoma (ClinicalTrials.gov Identifiers NCT00418457, NCT011799308 and NCT00684229) and these are scheduled for completion in 2015, 2018 and 2022, respectively [88▪▪].

The big question is what are these studies demonstrating – a benefit from regional anaesthesia or harm from systemic opioids?

OPIOIDS OR PAIN: WHICH IS THE TRUE CULPRIT?

Pain is a prevalent feature in patients with cancer, ranging from 33% following curative treatment to 64% in those with advanced or metastatic disease [2] and up to two-thirds of patients requiring strong opioids for analgesia [89]. In treating moderate-to-severe cancer pain, strong opioids are still the foundation of therapy and this is supported by the European Society for Medical Oncology (ESMO) [90], the WHO [36], European Association for Palliative Care (EAPC) [91] and the International Association for Hospice and Palliative Care (IAHPC) [92].

Studies that have demonstrated the immunosuppressive effects of morphine include those in which morphine is being investigated in isolation and not in the context of pain such as those documenting the reduction in NK activity with morphine administered to healthy volunteers [93]. Pain is known to result in the release of endogenous opioids such as β-endorphin. Page *et al.* [94] when investigating the effects of morphine in a rodent pain model demonstrated the immunosuppressive effects of pain and the recovery in CMI with the addition of appropriate analgesia such as morphine, especially if administered preoperatively. These effects were also replicated when examining the effects of fentanyl in a rodent pain model of MADB106 mammary adenocarcinoma, further supporting the hypothesis that appropriate management of perioperative pain is crucial in preventing the pro-metastatic immunosuppressive changes induced by surgery [8]. In 2002, Sasamura *et al.* demonstrated that morphine could suppress tumour growth and lung metastasis in rats inoculated with B16-BL6 melanoma as a consequence of the analgesia it provided. The importance of analgesia was confirmed in this rat model by demonstrating reduced tumour proliferation and metastasis following neurectomy of the sciatic nerve [95].

Is it the quality of analgesia afforded by an effective epidural, along with the beneficial humoral effects in abrogating the stress response and sympatholysis, which ensures they are 'superior' to opioids in the surgical population?

What is less controversial are the physiological benefits of regional anaesthesia, namely, good analgesia, ablation of afferent pain signals, sympatholysis, reduction in opioid requirements, decreased surgical stress response and activation of the hypothalmic–pituitary–adrenal axis with a concomitant reduction in immunosuppressive cortisol release, and decreased impairment of NKCC.

To state that 'regional anaesthetic techniques should be used in preference to opioids because of these potential benefits' is a more accurate and responsible assertion currently, than 'opioids should be avoided due to the increased risk of cancer recurrence'. The current body of evidence in humans from retrospective studies demonstrates small benefits from epidurals, which are not consistently reproduced between authors and many of the studies demonstrating deleterious effects of morphine were either performed *in vitro* or in animal models, and in scenarios that do not replicate pain. Pain in humans is an emotional experience and the complex conscious and cognitive aspects of this cannot be reliably replicated in animal models [96].

COMBATTING 'OPIOPHOBIA'

Opiophobia [97] still exists in the field of cancer pain management [98] and with the under treatment of cancer pain reported in 43% of patients [99], huge improvements must be made to reduce the impact of this physical and emotional burden. The prevalence of long-term pain syndromes is only likely to increase in the future, thanks to the ever-increasing survival rates of most cancers [100].

Such is the growing concern for practitioners surrounding opioids and their potential side effects, that in order to bring some balance to the debate, the IAHPC released a position statement putting all the evidence into perspective and requesting that opioids continued to be used for the relief of cancer pain, in appropriately effective (high) doses [101▪].

The converse of this situation was described recently in a population-based cohort study in Canada where it was established that more than 3% of non-cancer postoperative patients were still being prescribed opioid medication more than 90 days after discharge from hospital [102]. Opioids should only be prescribed where warranted and this limitation should be endorsed to avoid the potential side-effects of addiction and immunosuppression seen in subjects who are not suffering with pain.

When introducing alternatives to opioid analgesia, an assessment of the risks, which will be introduced as a result of any new intervention, has to be considered. For example, NSAIDs and COX-2 inhibitors are not a panacea for overall or disease-free survival and concerns exist regarding the cardiovascular and thrombotic morbidity following their use [103]. The epidural 'magic bullet' also has shortcomings including the technicalities of inserting and safely managing epidurals, along with the not so insignificant failure rate [104]. In addition, a recent retrospective study in the United States analyzing over 4000 patients (with and without cancer) who underwent laparoscopic colorectal surgery with epidural analgesia noted that use of epidurals was associated with a statistically significant longer hospital

stay, higher cost and greater incidence of urinary tract infection [105].

Despite the conflicting evidence regarding the use of opioids and their impact on cancer recurrence, the use of opioids for the treatment of pain in palliative care will continue, as supported by guidance from the WHO [36], IAHPC [92], EAPC [91], and ESMO [90] in addition to this, the treatment of breakthrough pain with rapidly acting transmucosal fentanyl formulations [106,107] have also been recommended [91].

Quite simply, patients with advanced cancer want to 'live normally' and continue to perform their 'everyday tasks' [108]; therefore, improved access to strong opioids is mandatory for the treatment of moderate-to-severe pain [109].

It may be that specific tumour types, which have been shown to possess particular receptors, will have a higher propensity to be 'opioid reactive', either in a positive or negative manner, and appropriate analgesic regimens can be personalized to that patient to afford them the best chance of long-term survival, while ensuring their basic human rights of analgesia and freedom from suffering are met. With the crystal structure of the MOR having recently been elucidated [110▪], there is excitement regarding the future development of new opioid analgesic drugs with better side-effect profiles and these may also impact on the natural history of certain cancers.

CONCLUSION

Until the results of robust prospective randomized trials in humans are scrutinized, there should be no change in clinical practice and even then, any changes made should be to those specific conditions under which the studies were conducted. With the first of these (NCT00418457) due to complete in 2015 it will be interesting to see whether and how the results differ from their retrospective counterparts. Many of these studies are investigating the effects of acute morphine administration in the relatively short perioperative period, and as we have seen from other studies, the effects of acute and chronic opioid administration on the immune system are very different. In the interim, there is no clear evidence to support a change in our current practice and we should endeavour to improve our provision of analgesia rather than curb the use of opioids.

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Conflicts of interest

No conflict of interests or external funding declared.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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