Biomedicine & Pharmacotherapy 87 (2017) 1–7

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Review

Effects of anesthetic and analgesic techniques on cancer metastasis

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ARTICLE INFO

Article history:
Received 6 October 2016
Received in revised form 11 December 2016
Accepted 19 December 2016

Keywords:
Anesthesia
Metastases
Recurrence
Cancer
Analgesic techniques

ABSTRACT

The rate of mortality and morbidity among cancer patients is at an alarming rate and its ratio of incidence is increasing as a result of its effects of metastasis and recurrence in its patients. Several factors including anesthetic agents and analgesia techniques have been identified as causative agents for cancer metastasis. In this mini-review, we will summarize some of the available effects of anesthetic and analgesic techniques on cancer metastasis as derived from experimental cell culture and live animal data and also form clinical studies.

Contents

1. Introduction

The mortality and morbidityrate of cancer continues to increase and thereby making it a difficult challenge in treating and managing cancer patients [1]. Presently the only available treatment for cancer tumour patients is surgical resection to remove the primary tumour; but it comes without a consequence, metastatic recurrence. Several reports have suggested that several perioperative factors can directly stimulate both cancer cells and cell mediated type of immunity and as such leading to spreading of metastatic tumour [2,3] (Table 1).

The mechanism of metastasis is marked by the separation of cells that shows metastatic properties from the primary tumour and its completion is demonstrated by formation of tumour within a close or usually a distant organ [4,5]. It should be noted that the spreading of a tumour depends majorly on the formation of new blood vessels (angiogenesis) and aggressive attack of the immune system of the host. As described by Fidler, single cell undergoing uncontrollable multiple cycles of cell division and mutation results into a tumour cell [6] that are non-responsive to biological cell signaling that mediates and control normal cell division thereby resulting into uncontrollable tumour growth [7]. Wide-ranging angiogenesis processes are developed in other for a tumour to thrive in terms of growth. However the angiogenesis process is stimulated by the release of, vascular endothelial growth factor (VEGF) and prostaglandin E2 from the evolving tumour [8]. After angiogenesis has been established, metastatic cell separates from the tumour's origin and migrate to neighboring cells [9]. It should be noted that a benign carcinoma tumour transform into a malignant tumour at the onset of the invasion of the basement

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http://dx.doi.org/10.1016/j.biopha.2016.12.073
0753-3322/

Table 1
Influence of perioperative factors on cancer recurrence and metastasis.

Surgery	Increases neuroendocrine and cytokine stress response Incapacitate cell-mediated immunity [10] Stimulates tumour growth and metastasis in animal models
Volatile anaesthesia	Suppresses the immune activity of leucocytes [11] Connected with induction of apoptosis in lymphocytes in vitro
Opioids	Suppresses cell-mediated and humoral immunity [12] Promote tumour cell migration [13], proliferation, and cancer gene expression in human cells in vitro Facilitate angiogenesis
Propofol	Decreases cancer cell migration, proliferation, and metastasis in vitro Possible COX inhibitor
Pain	NK cell activity was suppressed as reported in animal studies that pain was ineffectively treated postoperative [14].
NSAIDs/COX inhibitors	PGs inhibit NK cell cytotoxicity and modulate the tumour microenvironment Long-term use associated with reduced incidence of cancer [15]
Hypothermia	Stimulates sympathetic nervous system and glucocorticoid release [16] Increases bleeding and allogeneic blood transfusion Suppresses cell-mediated and humoral immunity [17]
Psychological stress	Animal and clinical evidence of an association between stress, depression, and cancer progression Activates HPA-axis and sympathetic nervous system Contributes to perioperative immunosuppression [18]
Allogeneic blood transfusion	Associated with immunosuppression, increased risk of cancer recurrence, and reduced survival

Table 2
Anesthetic Agents.

Drug	Type	Importance
Halothane	Inhalational, halogenated	Upkeep of anesthesia
Isoflurane	Inhalational, halogenated	Upkeep of anesthesia
Sevoflurane	Inhalational, halogenated	Upkeep of anesthesia
Propofol	Intravenous Induction.	Can also be used as continuous infusion for maintenance.
Thiopentone	Intravenous, barbiturate	Initiation of anesthesia.
Lidocaine	Local (short acting)	Infiltration can be used for simple procedures and postoperative pain relief
Bupivicaine	Local (long acting)	Used in regional techniques (spinal, epidural) for intra- and postoperative analgesia and anesthesia
Xenon	Inhalational, noble gas	Upkeep of anesthesia, not widely used clinically due to expense
Nitrous oxide	Inhalational	Adjunct to general anesthesia, reduces need for other inhalational agents; useful analgesic properties

membrane and also invades the systemic circulation of the host cells via the lymphatic systems.

1.1. Local anesthetics and regional anesthesia

Some researchers have reported in their clinical studies of a connected link that exist between the use of regional anesthesia and decreased cancer metastasis [19]. However with these clinical studies, report has also emerged about the use of regional anesthetic techniques leading to lack of the stress response activation in cancer patients. Piegeler and co-worker reported and proposed that the prevalence of cancer recurrence is as such decreased by local anesthetic agents (Table 2) via anti-inflammatory action and a direct effects on the proliferation and migration of cancer cells [20]. In addition Martinsson reported that lidocaine and ropivacaine have been demonstrated to be effective on cancer cells when cultured in-vitro as an s anti-proliferative agent [21]. Sakaguchi also corroborated the effectiveness of lidocaine in his report, that lidocaine was demonstrated to suppress cancer cell proliferation through direct inhibitory action on some specific growth factor receptor responsible for proliferation and differentiation of epithelial cells and tumours of epithelial cell origin [22].

Table 3
Ongoing research investigating the effects of anesthetic agents on immune cell function and metastasis.

Cancer type	Area of investigation	NCT number	Principal investigator
Breast cancer	TIVA vs inhalational anesthesia	2089178	Koo
Breast cancer	Propofol sedation with local infiltration vs general anesthesia with sevoflurane	00938171	Chang
Breast cancer	Regional plus TIVA vs general anesthesia + opioids	418457	Buggy
Breast cancer	TIVA vs inhalational anesthesia	2005770	Beck Schimmer
Pancreatic Cancer	TIVA vs inhalational anesthesia	2335151	Beck Schimmer
Colon/Rectal/Breast cancer	TIVA vs sevoflurane-maintained anesthesia	01975064	Bergkvist
Malignant melanoma	Regional vs general anesthesia	1588847	Van Aken
Colon cancer	Regional vs general anesthesia	684229	Reytman
Colon cancer	Regional vs general anesthesia	2326727	Kurz
Colon cancer	Perioperative analgesia with morphine PCA vs epidural	2314871	Berta
Colon cancer	Epidural anesthesia vs no epidural anesthesia	2326727	Reytman
Tongue Cancer	TIVA vs combined intravenous-inhalational anesthesia vs inhalational anesthesia	1854021	Zhang
Breast cancer	Peritumoral local anesthesia vs no peritumoral local anesthesia	1916317	Badwe

NCT = ClinicalTrials.gov clinical trial number; PCA = patient-controlled analgesia; TIVA = total intravenous anesthesia.

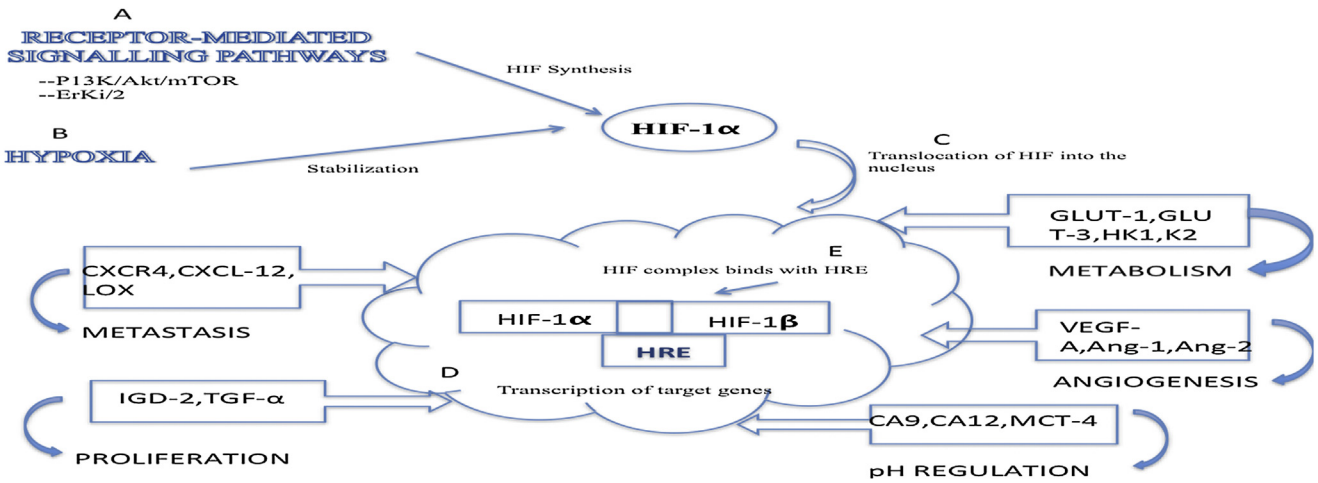

Fig. 1. Mechanisms and implications of HIF-1a upregulation in cancer cells. (A)Receptor mediated signaling pathways, including the PI3K/Akt and the MAP kinase Erk1/2, has been implicated in upregulating neosynthesis of HIF-1a. (B) Hypoxia stabilizes HIF-1a. (C) Accumulation and translocation of HIF-1a into the nucleus. (D) mRNA formation via gene transcription. (E) HIF-1a binds with HIF-b.This figure was reproduced from [46].

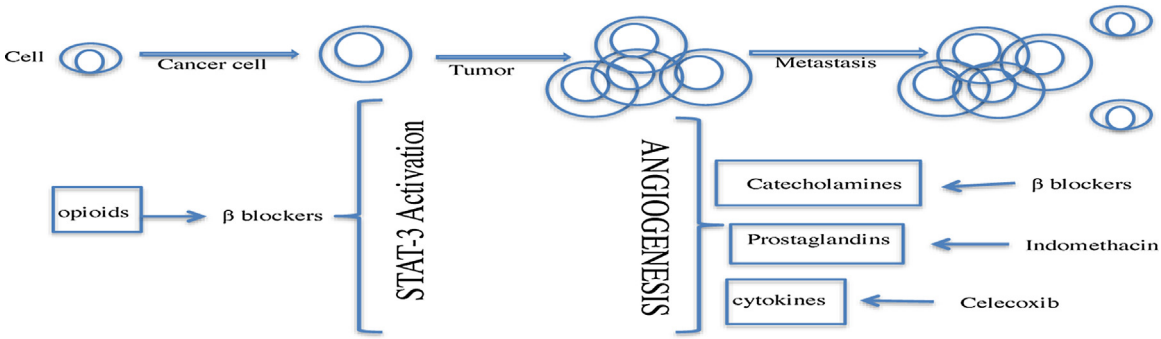

Fig. 2. Perioperative mechanism of immunosuppression. STAT signal transducer of activation and transcription; the words in the boxes are the surgical stress response to which the anesthesiologist administer specific anesthesia drug.

In addition the invasion of metastatic colon cancer cell have been reported to be inhibited by inhibiting voltage- activated Na+ channels by amide local anesthetics [23,24].

Furthermore Navada and colleagues reported that at clinically significant concentrations, methylation process is suppressed in tumour cells by lidocaine and by activating tumour suppressor genes [25], demethylation of DNA in breast cancer cells is stimulated. Lirk and co-worker also reiterated Navadas findings that lidocaine is more potent as a demethylating agent compared to ropivacaine and bupivacaine on breast cancer cellswhen cultured in vitro, he went further to report that lidocaine in combination with 5-aza-2′-deoxycytidine, proves to be a more potent demethylating agent [26]. Conclusively, recent reports mentioned above suggest that in vitro models have been able to demonstrate that amide local anesthetics are effective in suppressing metastatic cancer cells. However it should be noted that no recent report have surfaced as regards in vivo animal model data appraising this hypothesis.

There has been some reported conflicting results as regards the resultant effects of the administration of regional anesthesia in cancer surgery in relation to reduced cancer recurrence with cancer spread. Scavonetto et al. recently carried out a large sample (n = 3284) spaced retrospective analysis of patients who underwent radical retro-pubic prostatectomy for adenocarcinoma [27].

Table 4
HIF regulated genes implicated in Cancer Cell Biology.

Gene	Protein	Function
VEGF	Vascular endothelial growth factor	Stimulates angiogenesis
ANG-1, ANG-2	Angiopoietins 1 and 3	Initiate vessel sprouting in angiogenesis
GLUT-1, GLUT-3	Glucose transporters 1 and 3	Glucose transport across plasma membrane
HK-1, HK-2	Hexokinases 1 and 2	Glycolytic enzymes that shift metabolism toward glycolysis
CA9, CA12	Carbonic anhydrases IX and XII	Catalyses conversion of carbonic acid to protons and bicarbonate
MCT-4	Monocarboxylate transporter 4	Lactate/Hþ symporter; mitigate changes in pH
CXCR-4, CXCL-12	Chemokine receptor 4 and CXC chemokine ligand 12	Migration and homing of metastatic cells to distant sites
LOX, LOXL-2	Lysyl oxidases	Suppress E-cadherin expression; promotes invasion of malignant cells

They reported that when general anesthesia was administered singly, it resulted into an increased risk for systemic progression, increased risk of death and higher rate of mortality when compared with a combined (general + regional anesthesia) administration [28,29]. Buckley and co-workers in a recent research study carried out among female patients with breast cancer (n = 10) reported that the serum of the patient that were administered with propofol-paravertebral anesthesia [30] (See

Table 5
Summary of retrospective clinical evidence of effects of regional anesthesia and cancer recurrence.

Type of study	Surgery	Technique	Reference	Outcome
Retrospective	Mastectomy and axillary clearance for breast cancer	GA + PVAA(n = 50) GA + opioid analgesia(n = 79)	[50]	4-fold decrease in cancer recurrence in PVAA group 2.5–4 yr follow-up
Retrospective	Radical prostatectomy for prostate carcinoma	GA + thoracic epidural analgesia (n = 102) GA + opioid analgesia(n = 123)	[51]	57% reduction in cancer recurrence in epidural group, P1/40.012 Recurrence defines as increase in PSA
Retrospective	Radical prostatectomy for localized prostate carcinoma	GA + thoracic epidural(n = 103) GA + ketorolac + opioid analgesia (n = 158)	[52]	Increase in clinical progression- free survival (P1/40.009) in epidural group No difference in biochemical recurrence-free survival (P1/40.42), cancer-specific survival (P1/40.9), or overall survival (P1/40.9)
Retrospective	Brachytherapy for cervical cancer	Neuraxial anaesthesia (n = 69) GA (n = 63)	[53]	No difference in tumour recurrence (P1/40.526) or survival(P1/40.537)
Retrospective	Open colectomy	GA + epidural group (n = 256) GA + opioid analgesia (n = 253)	[54]	No difference in cancer recurrence except in patients 0.64 yr Follow-up 1.8 yr
Retrospective	Open colectomy	GAGA + epidural groupepidural(n = 562) GA + PCA opioid analgesia (n = 93)	[55]	GA + opioid group had higher mortality rate in rectal cancer (P1/40.049) No difference with colon cancer (P1/40.23)
Retrospective	Laparotomy for ovarian carcinoma	Epidural anaesthesiaGA + epidural groupanalgesia (n = 106) GAGA + epidural groupopioid analgesia (n = 37)	[56]	Epidural group had improved 3 yr and 5 yr survival rates (P1/40.043)
Retrospective	'Debulking' surgery for ovarian cancer	Epidural(n = 55) Opioid analgesia(n = 127)	[57]	Intraoperative epidural analgesia associated with reduced risk of cancer recurrence
Retrospective	Radiofrequency ablation of hepatocellular carcinoma	Epidural or GA hazard ratio for disease-free survival = 3.66, P = 0.001	[58]	GA associated with increased recurrence-free survival No difference in overall survival
Retrospective	Laparoscopic colorectal resection for adenocarcinoma	Epidural (n = 07) Spinal (n = 144) Morphine PCA (n = 173)	[59]	No difference in overall (P1/40.622) or disease-free survival at 5 yr (P1/40.490)
Retrospective	Lymph node dissection for malignant melanoma	Spinal anaesthesia (n = 52) GA–sevoflurane/sufentanil (n = 118) GA-propfol/remifentanil total i.v. anaesthesia (n = 103)	[60]	Non-significant trend towards improved cumulative survival rate in spinal anaesthesia group (P1/40.087)
RCT (follow-up)	Open colectomy for colorectal cancer	GAGA + epidural groupepidural analgesia (n = 85) GAGA + epidural groupopioid analgesia (n = 95)	[61]	Early survival benefit (for up to 1.46 yr) in epidural group (P1/40.012)No benefit if metastatic disease present
RCT (follow-up)	Major abdominal surgery, subgroup analysis of patients with colorectal cancer	GAGA + epidural groupepidural analgesia (n = 49) GAGA + epidural groupopioid analgesia (n = 50)	[33]	No difference in cancer recurrence (P1/40.61)or recurrence-free survival (P1/40.61)Recurrence and mortality rates at 5 yr also similar
RCT (follow-up)	Open colectomy for non-metastatic colorectal cancer	GAGA + epidural groupepidural analgesia (n = 230) GAGA + epidural groupopioid analgesia (n = 216)	[61]	61% 5-yr survival with epidural vs 55% opioid(P,0.001)No difference in cancer recurrence rates(P1/40.28)
RCT (follow-up)	Radical prostatectomy	GAGA + epidural groupepidural analgesia (n = 49) GAGA + epidural groupopioid analgesia (n = 50)	[62]	No difference in disease-free survival (P1/40.44)4.5 yr follow-up
Retrospective population	Open colectomy for non-metastatic colorectal cancer	Epidural analgesia (n = 9670) Opioid pain management n = 32 481	[63]	61% 5-yr survival with epidural vs 55% opioid(P,0.001)No difference in cancer recurrence rates(P1/40.28)

Title	Study design	Primary outcome	Location	Intervention	Estimated completion date
Regional anaesthesia and breast cancer recurrence, NCT00418457	Multi-centre prospective randomized clinical trial, n = 1110	Cancer recurrence rate up to 10 yr	GA + postoperative opioid analgesiaorGA or deep sedation with epidural or paravertebral anaesthesia/analgesia	Mater University Hospital, Ireland; Cleveland Clinic, OH, USA Medical University of Vienna, Austria; University of Dusseldorf, Germany	March 2015 August 2018
The effect of adding intraoperative regional anaesthesia on cancer recurrence in patients undergoing lung cancer resection, NCT011799308	Prospective randomized, double-blind trial, n = 1532	Disease-free survival up to 5 yr	GA + postoperative opioid analgesiaor GA + thoracic epidural analgesia	Cleveland Clinic, OH, USA Mater University Hospital, Ireland	
Regional anaesthesia in colon rectal surgery, NCT00684229	Multi-centre, prospective, randomized, double-blind trial, n = 2500	Cancer recurrence rate up to 5 yr	GA (sevoflurane) + opioid analgesiaor GA + epidural anaesthesia/analgesia	Cleveland Clinic, OH, USA Hospital Italiano de Buenos Aires, Argentina; University of Dusseldorf, Germany	December 2022

PVAA = paravertebral anaesthesia and GA = General analgesia.

Table 3) conserved the cytotoxic ability of the Natural-Killer immune cell and cancers apoptotic cell to a greater extent when compared to serum of the patients administered with standard volatile-based general anesthesia with opioid analgesia [31]. Myles and colleagues also reported their findings on a study carried out to ascertain the notion if performing epidural block for a cancer patient undergoing abdominal surgery is related to decreased cancer recurrence and enhanced survival [32,33]. Common IV induction agents include propofol, ketamine and thiopentone. The effects of these agents have been studied in an inoculation animal model of breast cancer. In one study, rats were injected with propofol, ketamine or thiopentone, and NK cell activity and resistance to metastasis were measured [34]. All agents except propofol reduced NK cell activity and increased lung metastases [35]. In a cell culture study, prostate cancer cells were exposed to propofol and isoflurane. The results found that propofol inhibited hypoxia-inducible factor-1a activation and partially reduced cancer cell malignant activities. An in vitro study carried out on breast cancer cells demonstrated that propofol reduced the expression of the neuro-epithelial cell transforming gene 1 (NET1), which is associated with promoting migration in adenocarcinoma in vitro and propofol also reduced cell migration in ER- positive and -negative breast cancer cells [36]. In a retrospective analysis of 2838 patients who underwent surgery for breast, colon or rectal cancer, there was no statistically significant difference and randomized controlled trials were recommended [37].

1.1.1. Potential targets for metastasis inhibition by the anesthesiologist

Surgical stress response seems to play an important role in the spread of cancer and metastasis, however the question remains if these harmful effects can be reduced by an administration of suitable choice of anesthetics drugs? Several researchers have extensively worked on the effect of anesthesia on the stress response to surgery [38]. Fig. 2 gives a summary of anesthetic interventions that affect pathways in connection with tumor progression [39].

1.2. Opioids

In palliative care, opioids have been identified as a keystone in the management of acute pain be it postoperative or cancer-associated pain [40]. However, there are strong claims from clinical trials and research studies stating that opioids have been identified as a major player in promoting the spread of cancer and reducing survival rate in cancer patients. Gupta et al. also reported that the proliferation and survival of cancerous cells is stimulated by the effects morphine via activation of mitogen-activated protein kinase and Akt signalling pathways in tumour cells [41]. In addition, Singleton et al. and Zylla et al. have demonstrated and reported the regulation of tumour growth and metastasis by the actions of l- opioid receptor (MOR) [42]. Several research has reported the overexpression of MOR in lung and in prostate cancer.

Furthermore the several reports on MOR association with tumour metastasis has been corroborated by Mathew and colleagues, in their report that demonstrated reduced spread of lung carcinoma in MOR knockout mice administered with opioid receptor antagonist naltrexone [43]. It should be noted that morphine does not affect tumour initiation form the onset, but somehow stimulates the spreading of an already established breast tumour as demonstrated recently by Nguyen and co-workers in a transgenic mouse study found to have a reduced survival rate in a mouse model of breast adenocarcinoma. Furthermore, in a recently carried out clinical trial study on a breast cancer patients with ClinicalTrials.gov number, NCT00418457 has demonstrated the association between anesthetic technique and the expression of immune cell in breast cancer tissue.They finally reported that patients that were administered with propofol-paravertebral anesthesia had increased NK cell infiltration expression when compared to patients administered with standard vapour general anesthesia with opioid analgesia [44]. Conclusively this report implies that anesthetic technique maybe associated with immune function in breast cancer tissue.

1.3. Anesthetics drugs effect on cancer cell biology

There have been several studies on the link between anesthetics drugs and some cell signaling, like with Hypoxia Inducible Factors (HIFs), anesthetic drugs like isoflurane and desflurane, and the noble gas have been demonstrated to up-regulate HIFs thereby giving anesthetics drugs tissue-protective properties functions [45]. Several researchers have worked extensively on the biology of HIFs, however Fig. 1 gives a summary of its biology.

These transcription factors have been demonstrated to be involved in regulating a wide range of genes like genes that control angiogenesis, metabolism and also counteract the changes in physiological states [47]f. The HIF system has been identified as been important to the modification and existence of healthy cells; it has also been implicated in promoting the growth and survival of cancer cells [48]. In addition, HIF-1a and HIF-2a indirectly and directly promotes tumorigenesis and metastasis via its broad range of genes it regulates [49] (Table 4).

1.4. Clinical proof of an association between cancer recurrence and regional anaesthesia

Several researchers have reported and identified the association between regional anaesthesia during cancer surgery for different kind of tumours based on their recurrence and metastases, though some of these evidences still remains conflicting.

Table 5 provides a summary of both past and on going randomized, clinical and controlled trials intended to assess non-cancer outcomes.

2. Conclusion

It should be noted that for any cancer surgery, its primary focus is on total clearance and resection. Unexpectedly anesthetic agents have been demonstrated to mitigate pro-metastatic activities that occur during cancer surgery as a result of immune responses to physiological and anatomical trauma. No conclusive reports have established a link between anaesthetic technique and cancer recurrence; however, only randomized, clinical trials can provide us such link. However a good working combination of anesthetic agents and techniques may be the key in improving surviving rate of cancer patients.

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