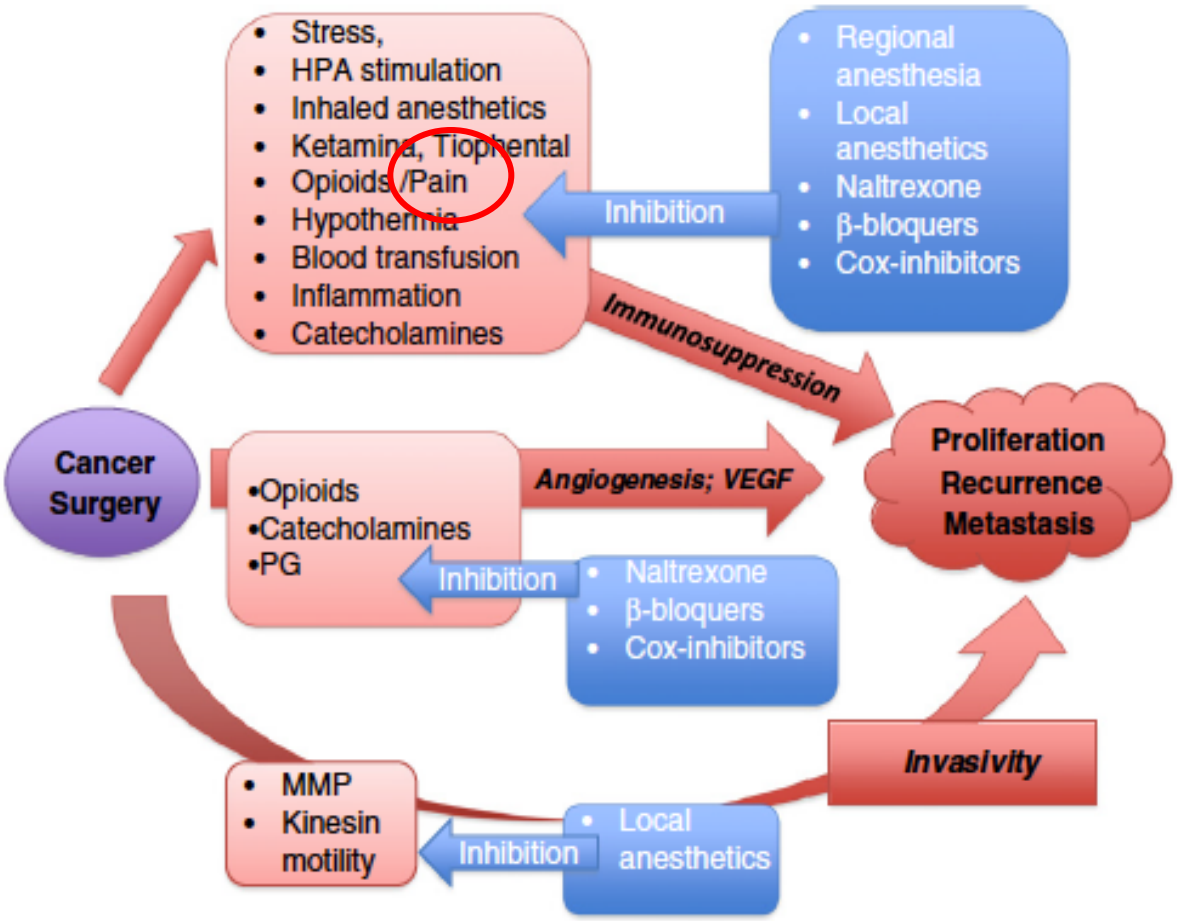
Course:

Analgezia pacientului neoplazic supus chirurgiei. Locul analgeticelor sistemice.

Country:Romania

Speaker: Simona Mărgărit

UMF "Iuliu Haţieganu " Cluj Napoca



Influenta chirurgiei, anesteziei, medicatiei si altor factori perioperatorii asupra recidivei tumorale locale, proliferarii si metastazarii.

Cassinello F, Prieto I, del Olmo M, Rivas S, Strichartz GR, Cancer surgery: how may anesthesia influence outcome? J Clin Anesth 2015; 27, 262–272

Consecintele durerii netratate/tratate inadecvat la pacientul neoplazic

- Durerea postchirurgie determina imunosupresia care influenteaza recidiva tumorala, metastazarea
- Durerea stimuleaza eliberarea de opioide endogene care au efect direct asupra celulelor neoplazice - stimuleaza cresterea tumorala

Rittner HL, Brack A, Stein C. Pain and the immune system. Br J Anaesth 2008 ;101(1):40e4
Page GG, Blakely WP, Ben-Eliyahu S. Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. Pain 2001 ;90(1e2):191e9.
Lennon FE, Moss J, Singleton PA. The mu-opioid receptor in cancer progression: is there a direct effect? Anesthesiology 2012 ;116(4):940e5

ANALGEZIA

"top priority"

creste perioada de supravietuire fara recidiva tumorala sau metastaze

modele animale

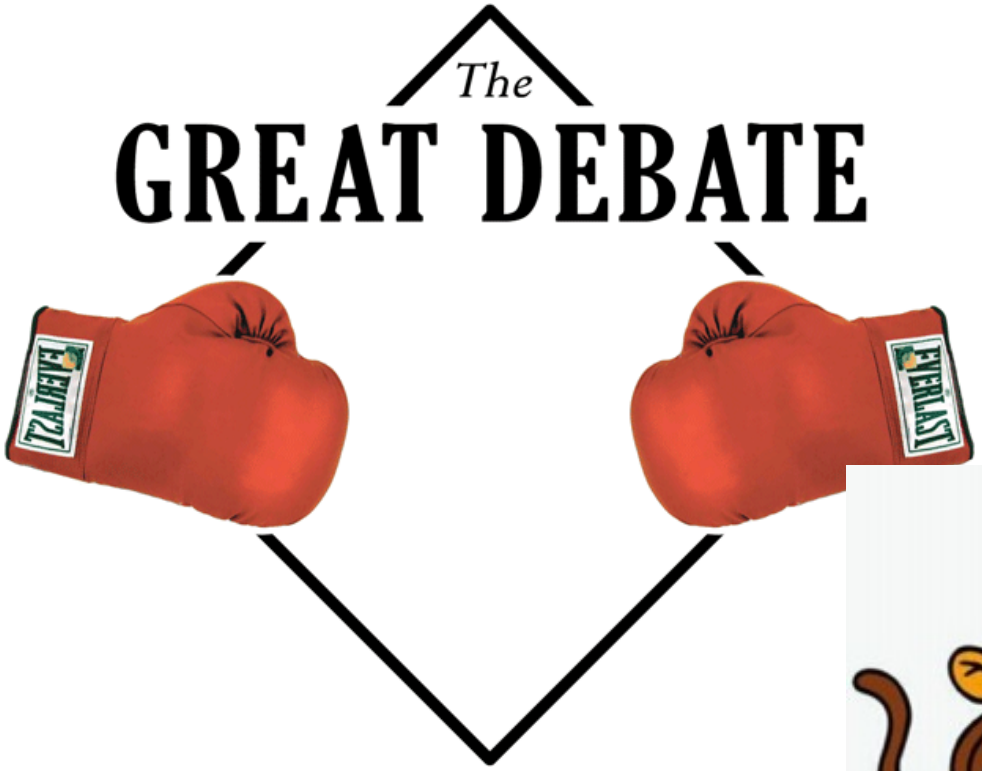
studii umane

Page GG, Blakely WP, Ben-Eliyahu S. Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. Pain 2001 ;90(1e2):191e9.
Macfarlane GJ, McBeth J, Silman AJ. Widespread body pain and mortality: prospective population based study. BMJ 2001 ;323(7314):662e5.
Wong GY, Schroeder DR, Carns PE, et al. Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial. JAMA 2004 r 3;291(9):1092e9.

Care este cea mai buna modalitate de analgezie?

Analgezia sistemica

Tehnici de analgezia locoregionala



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LOCUL ANALGETICELOR SISTEMICE

☆ asigura controlul adecvat al durerii

✧produc imunosupresia sistemelor de aparare imuna implicate in mentinerea sub control a celulelor canceroase

✧efect negativ asupra sistemului endocrin si astfel scade raspunsul gazdei la tumora

✧efect direct asupra celulelor tumorale

Gottschalk A, Sharma S, Ford J, et al. Review article: the role of the perioperative period in recurrence after cancer surgery. Anesth Analg 2010 1;110(6):1636e43.

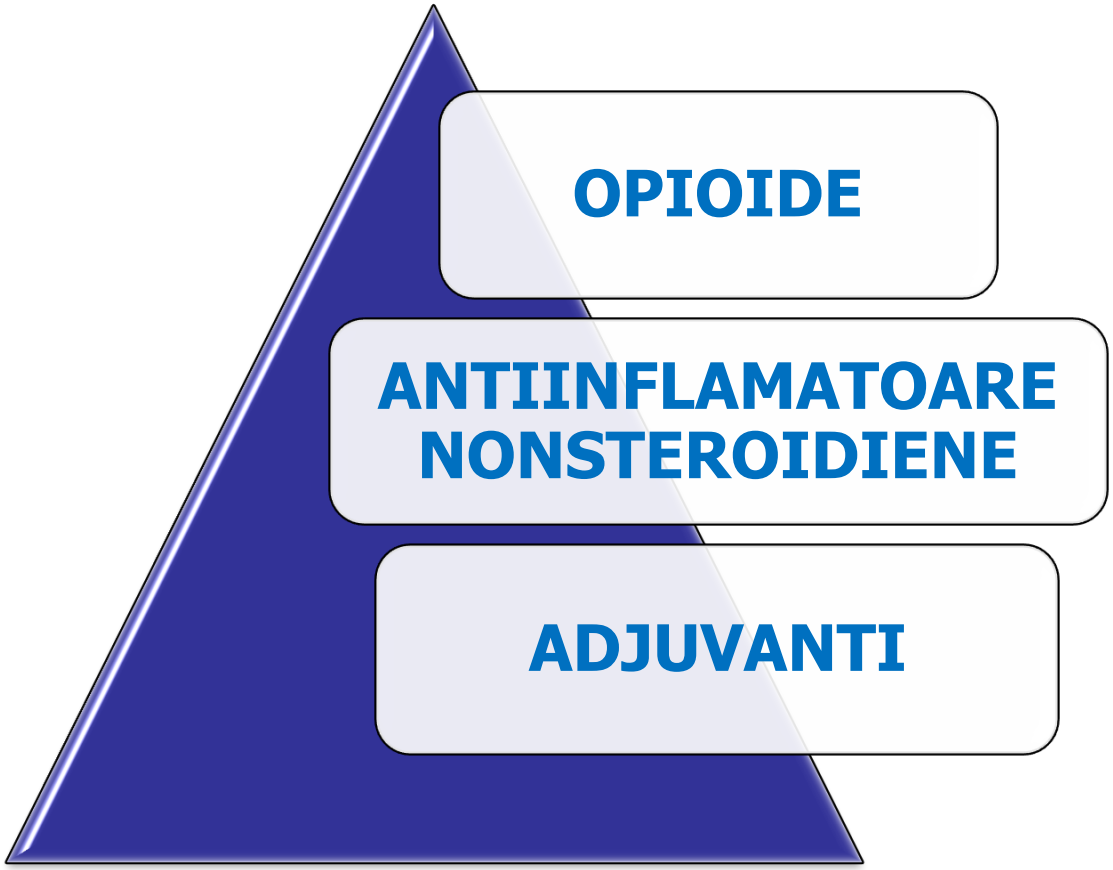
Tavare AN, Perry NJ, Benzonana LL, et al. Cancer recurrence after surgery: direct and indirect effects of anesthetic agents. Int J Cancer 2012 15;130(6):1237e50.

Mao L, Lin S, Lin J. The effects of anesthetics on tumor progression. Int J Physiol Pathophysiol Pharmacol 2013;5(1):1e10.

Heaney A, Buggy DJ. Can anaesthetic and analgesic techniques affect cancer recurrence or metastasis? Br J Anaesth 2012109(Suppl. 1):i17e28.

Snyder GL, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. Br J Anaesth2010 ;105(2):

ANALGETICE SISTEMICE



OPIOIDE

- "gold standard" în managementul durerii acute postoperatorii dar si in scop paleativ la pacientul neoplazic DAR.....

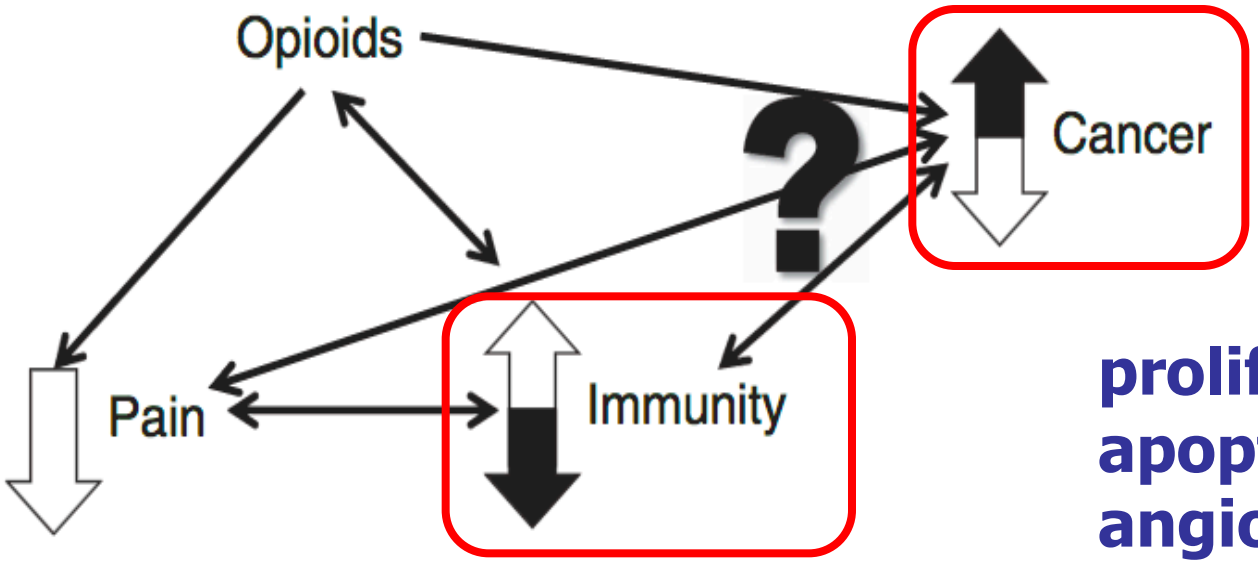
  - argumente din studii experimentale si studii clinice retrospective vin sa sugereze că opioidele facilitează progresia cancerului si reduc supravietuirea pe termen lung

OPIOIDELE

FULL PAPER
BJC
British Journal of Cancer (2014) 111, 866–873 | doi: 10.1038/bjc.2014.384
Keywords: opioids; morphine; neoplasms; immunity; NK cells; T cells

Effects of opioids on immunologic parameters that are relevant to anti-tumour immune potential in patients with cancer: a systematic literature review

J W Boland[*,1], K McWilliams[2], S H Ahmedzai[3] and A G Pockley[4]
[1]Hull York Medical School, University of Hull, Hull HU6 7RX, UK; [2]Palliative Medicine Research Department, Beatson Oncology Centre, Glasgow G11 0YN, UK; [3]Department of Oncology, The Medical School, University of Sheffield, Sheffield S10 2RX, UK and [4]John van Geest Cancer Research Centre, Nottingham Trent University, Nottingham NG11 8NS, UK



proliferarea tumorala
apoptoza
angiogeneza
metastazarea

Efectul opioidelor :

1. **imunomodulator** (direct sau indirect)
2. direct asupra **celulor tumorale** si din micromediul tumoral

Boland JW, McWilliams K , Ahmedzai SH, Pockley AG. Effects of opioids on immunologic parameters that are relevant to anti-tumour immune potential in patients with cancer: a systematic literature review. *Brit J Cancer* 2014; 111, 866–873
Meserve JR, Kaye AD, Prabhakar A, Urman RD. The role of analgesics in cancer propagation.. Best Pract Res Clin Anaesthesiol. 2014 ;28(2):139-51

BJA

British Journal of Anaesthesia, 115 (S2): ii34–ii45 (2015)

doi: 10.1093/bja/aev375
Regional Anaesthesia

Regional anaesthesia and analgesia: relationship to cancer recurrence and survival

T. Tedore*

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Can J Anesth/J Can Anesth (2016) 63:184–192
DOI 10.1007/s12630-015-0523-8

REVIEW ARTICLE/BRIEF REVIEW

Can anesthetic-analgesic technique during primary cancer surgery affect recurrence or metastasis?

Les techniques d'anesthésie et d'analgésie lors d'une chirurgie de cancer primitif peuvent-elle affecter la récurrence ou la métastase?

Kathryn Byrne, MD · Kirk J. Levins, PhD · Donal J. Buggy, MD

Cancer Cell & Microenvironment 2016; 3: e1159. doi: 10.14800/ccm.1159; © 2016 by Juan P. Cata, et al.
http://www.smartscitech.com/index.php/ccm

REVIEW

Opioids and cancer recurrence: A brief review of the literature

Juan P. Cata[1,2,4], Dario Bugada[3,4], Maurizio Marchesini[4,5], Manuela De Gregori [4,6], Massimo Allegri[3,4]

[1]Department of Anesthesiology and Perioperative Medicine, MD Anderson Cancer Center, Houston, Texas, 77030, USA
[2]Anesthesiology and Surgical Oncology Research Group, Houston, Texas, 77401, USA
[3]Department of Surgical Sciences, University of Parma, Parma, 43100, Italy
[4]SIMPAR Group, Parma, 43100, Italy
[5]Anesthesia Intensive Care and Pain Service Azienda Ospedaliera Universitaria Parma, 43100, Italy
[6]Pain Therapy Service Foundation IRCCS Policlinico San Matteo, Pavia, 27100, Italy

Best Practice & Research Clinical Anaesthesiology 28 (2014) 139–151

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journal homepage: www.elsevier.com/locate/bean

4

The role of analgesics in cancer propagation

Jonathan R. Meserve, MD, Senior Resident [a, *],
Alan David Kaye, MD, PhD, DABA, DABPM, DABIPP, Professor and Chairman [b], Amit Prabhakar, MD, MS, Senior Resident [b],
Richard D. Urman, MD, MBA, Assistant Professor [c]

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British Journal of Anaesthesia 105 (2): 106–115 (2010)
doi:10.1093/bja/aeq164

BJA

REVIEW ARTICLES

Effect of anaesthetic technique and other perioperative factors on cancer recurrence

G. L. Snyder[1,2*] and S. Greenberg[1,2]

[1] Department of Anesthesia and Perioperative Medicine and [2] Department of Oncology and Hematology, University of California San Francisco, 505 Parnassus Ave., San Francisco, CA 94143, USA

* Corresponding author. E-mail. gabrielsnyder@hotmail.com

European Society of Anaesthesiology ESA

REVIEW ARTICLE

CME

The Role of the Perioperative Period in Recurrence After Cancer Surgery

Antje Gottschalk, MD,*† Sonal Sharma, MD,* Justin Ford, MD,* Marcel E. Durieux, MD, PhD,* and Mohamed Tiouririne, MD*

A wealth of basic science data supports the hypothesis that the surgical stress response increases the likelihood of cancer dissemination and metastasis during and after cancer surgery. Anesthetic management of the cancer patient, therefore, could potentially influence long-term outcome. Preclinical data suggest that beneficial approaches might include selection of induction drugs such as propofol, minimizing the use of volatile anesthetics, and coadministration of cyclooxygenase antagonists with systemic opioids. Retrospective clinical trials suggest that the addition of regional anesthesia might decrease recurrence after cancer surgery. Other factors such as blood transfusion, temperature regulation, and statin administration may also affect long-term outcome. (Anesth Analg 2010;110:1636–43)

OPIOIDE

Efectul imunomodulator: imunosupresor/imunostimulator ??

- celule NK –antitumorale
- limfocite T CD8 citotoxice cu efect apoptotic

British Journal of Anaesthesia 105 (2): 106–115 (2010)
doi:10.1093/bja/aeq164

BJA

REVIEW ARTICLES

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* Corresponding author. E-mail. gabrielsnyder@hotmail.com

Morphine	Inhibits cellular immunity including NK cell activity in animal models Inhibits NK cell activity in humans
Fentanyl	Inhibits NK cell activity in humans
Tramadol	Stimulates NK cell activity in animal models Stimulates NK cell activity in humans

FULL PAPER

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REVIEW ARTICLE

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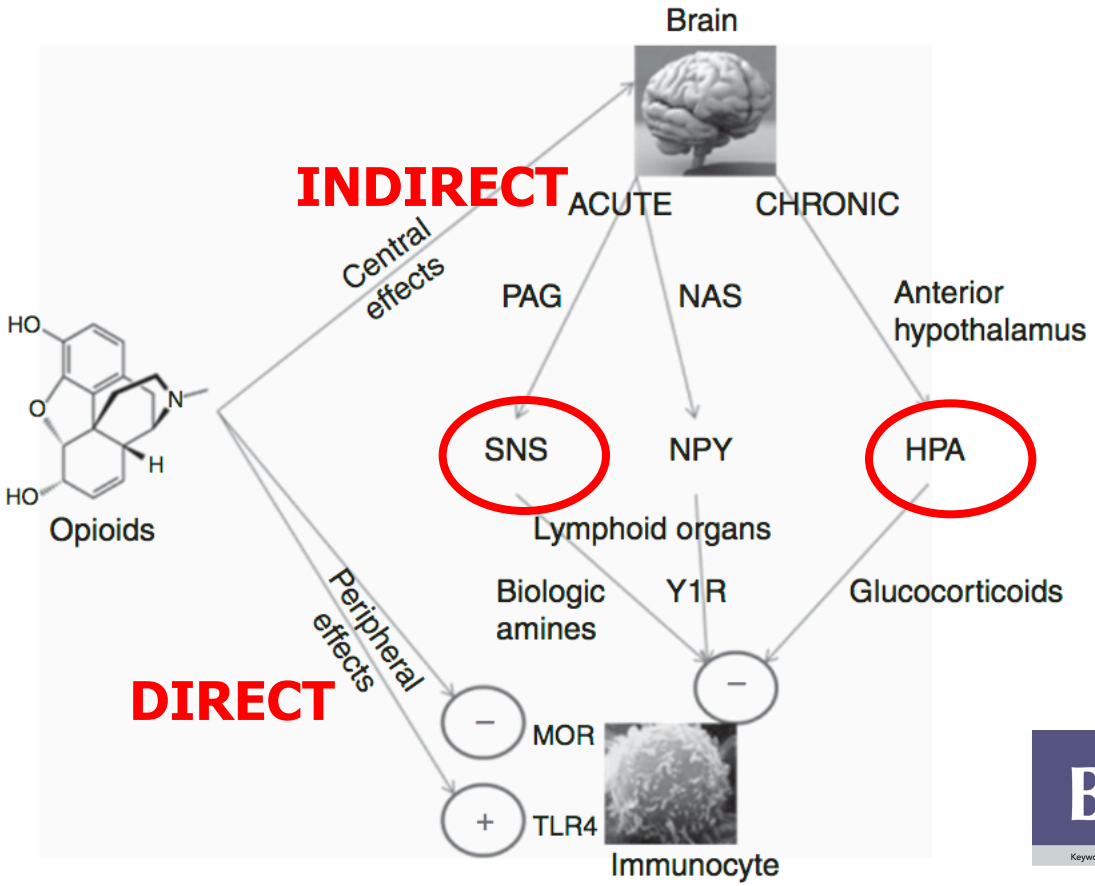
Opioids

- Opioids inhibit cellular and humoral immune function in humans[36]
- Morphine inhibits spontaneous and cytokine-enhanced NK cell cytotoxicity[35–37]
- In contrast, IV fentanyl increases NK cell cytotoxicity and circulating CD16(+) lymphocytes in humans[41]
- Opioid-induced promotion and stimulation of angiogenesis[39]

European Society of Anaesthesiology ESA

OPIOIDELE SI CANCERUL

EFECTUL IMUNOSUPRESIV AL OPIOIDELOR



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✧**Activated immune cells can also produce endogenous opioids**

OPIOIDE

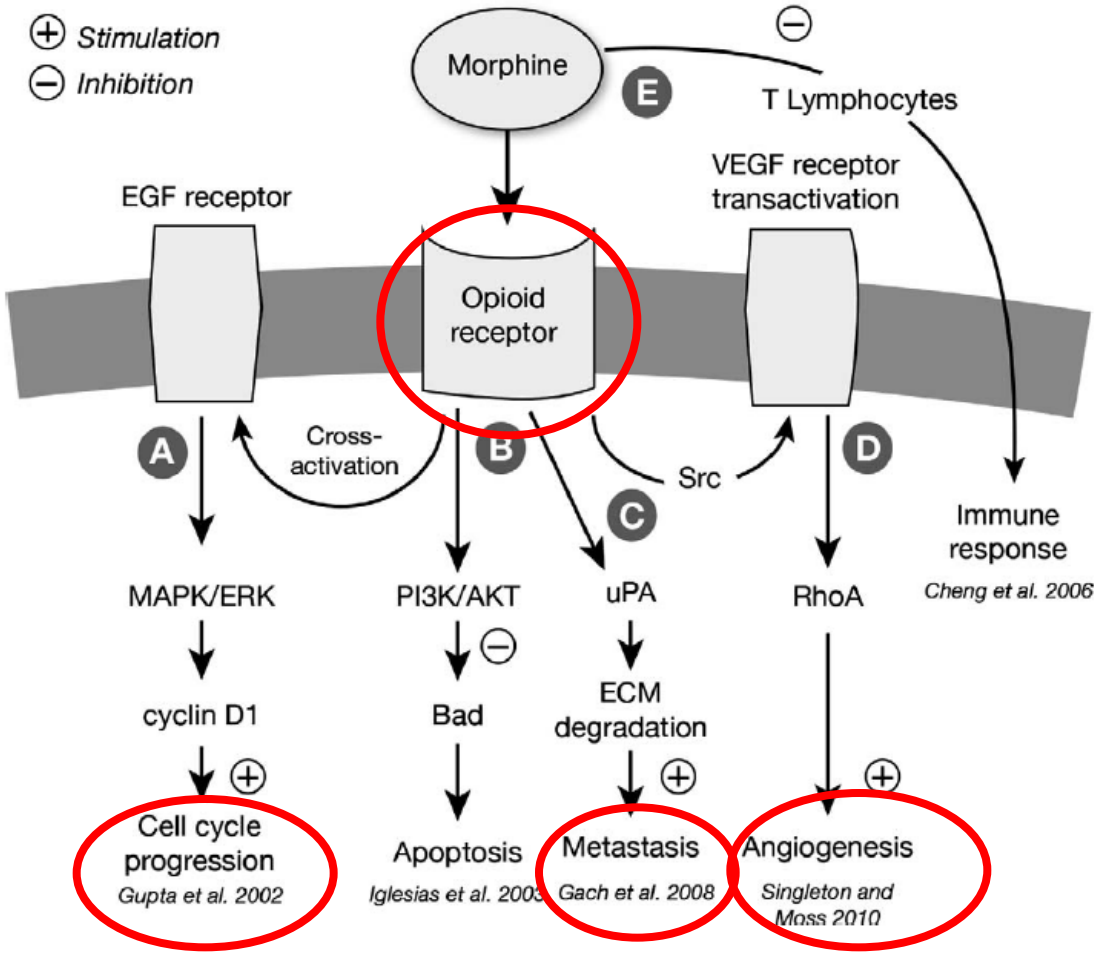
Efectul direct al opioidelor asupra celulelor tumorale si a celor din mediul tumoral

- ✧PROLIFERARE
- ✧METASTAZARE
- ✧ANGIOGENEZA
- ✧APOPTOZEI

prin - stimularea receptorilor μ pentru opioide (MORs)

- alte mecanisme

OPIOIDELE -efecte protumorale



- expresie crescută a MORs la nivelul celulelor tumorale

-activarea MORs determina angiogeneza VEGF dependenta

-MORs reglează cresterea tumorala si metastazarea prin intermediul opioidelor endogene

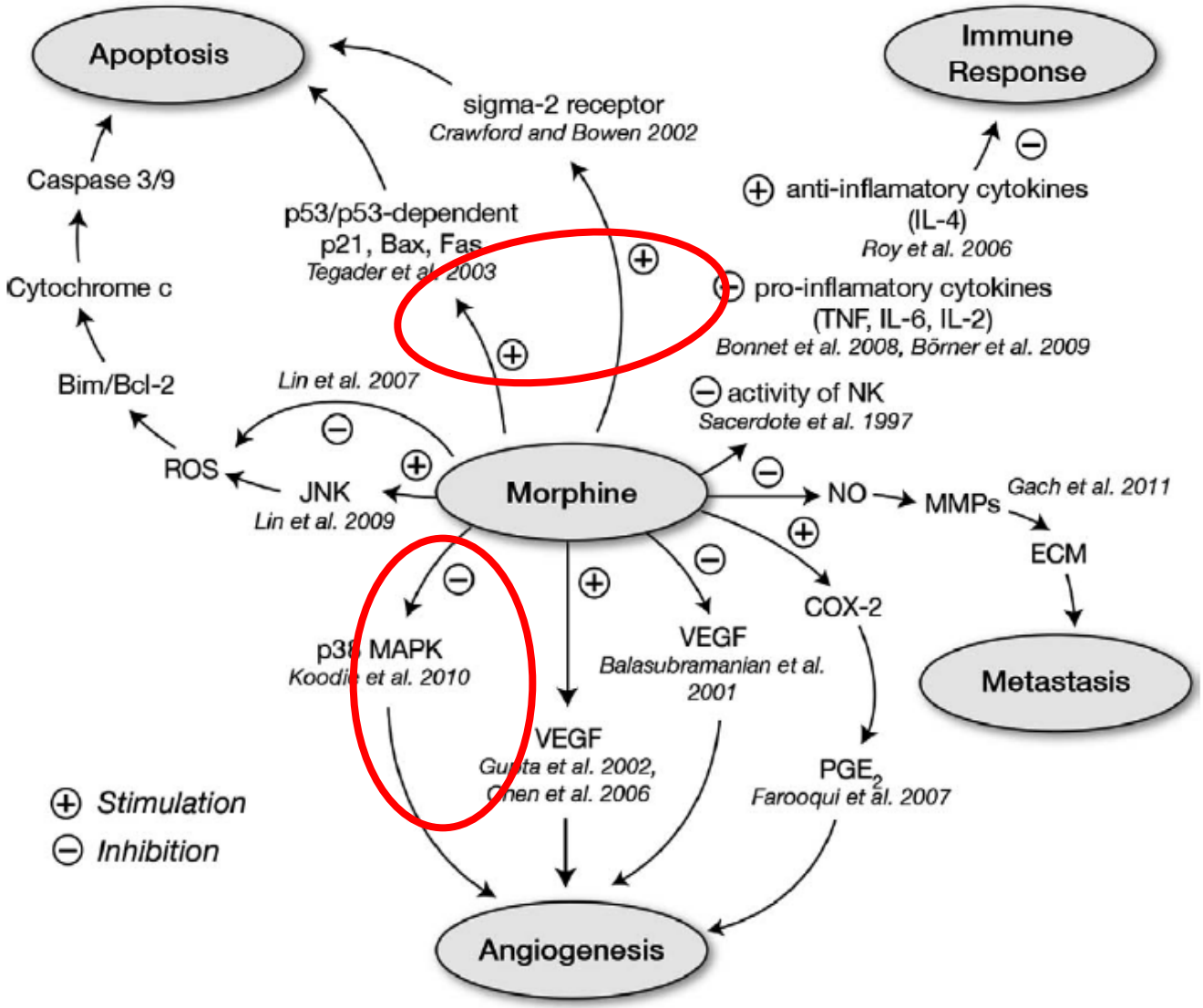
Gach K, Wyrebska A, Fichna J, et al. The role of morphine in regulation of cancer cell growth. Naunyn Schmiedeb Arch Pharmacol 2011;384(3):221e30

Lennon FE, Moss J, Singleton PA. The mu-opioid receptor in cancer progression: is there a direct effect? Anesthesiolog 2012;116(4):940e5.

Lennon FE, Mirzapoiazova T, Mambetsariev B, et al. Overexpression of the mu-opioid receptor in human non-small cell lung cancer promotes Akt and mTOR activation, tumor growth, and metastasis. Anesthesiology 2012;116(4):857e67.

Zylla D, Gourley BL, Vang D, et al. Opioid requirement, opioid receptor expression, and clinical outcomes in patients with advanced prostate cancer. Cancer 2013; 119: 4103-10.

OPIOIDE



Gach K, Wyrebska A, Fichna J, et al. The role of morphine in regulation of cancer cell growth. Naunyn Schmiedeb Arch Pharmacol 2011;384(3):221e30

OPIOIDE –efecte antitumorale

- morfina stimuleaza apoptoza in linii celulare neoplazice umane la doze terapeutice si doze crescute
- are efect antiproliferativ si pro apoptotic asupra diferitelor tipuri de celule neoplazice
- morfina nu faciliteaza angiogeneza, cresterea tumorala sau metastazarea
- administrarea preoperatorie de morfina reduce riscul de metastazare determinta de chirurgie
- morfina determina suprimarea cresterii tumorale si metastazarea

Kawase M, Sakagami H, Furuya K, et al. Cell death-inducing activity of opiates in human oral tumor cell lines. Anticancer Res 2002;22(1A):211e4.

Page GG, McDonald JS, Ben-Eliyahu S. Pre-operative versus postoperative administration of morphine: impact on the neuroendocrine, behavioural, and metastatic-enhancing effects of surgery.Br J Anaesth 1998; 81: 216–23

Welters ID, Menzebach A, Goumon Y, Cadet P, Menges T, Hughes TK, Hempelmann G, Stefano GB. Morphine inhibits NF-kapp aB nuclear binding in human neutrophils and monocytes by a nitric oxide-dependent mechanism. Anesthesiology 2000;92:1677–84

Sasamura T, Nakamura S, Iida Y et al. Morphine analgesia suppresses tumor growth and metastasis in a mouse model of cancer pain produced by orthotopic tumor inoculation. Eur J Pharmacol 2002; 441: 185–91

Doornebal CW, Vrijland K, Hau CS, et al. Morphine does not facilitate breast cancer progression in two preclinical mouse models for human invasive lobular HER2+ breast cancer. Pain 2015; 156: 1424–32

CEEA

BJP British Journal of Pharmacology

Themed Section: Opioids: New Pathways to Functional Selectivity

REVIEW

Comparison and analysis of the animal models used to study the effect of morphine on tumour growth and metastasis

B Afsharimani[1], C W Doornebal[2], P J Cabot[1], M W Hollmann[2] and M-O Parat[1]

British Journal of Pharmacology (2015) **172** 251–259

European Society of Anaesthesiology ESA

World Federation of Societies of Anaesthesiologists

Rodent model	Induced pain or surgical stress	Dose of morphine	Effect of morphine on tumour growth and metastasis	Reference
Walker 256 carcinoma cells cultivated in ascites, then injected in Sprague-Dawley rats Immuno-competent rats Ectopic (injection in the tail vein)	No	5 mg·kg^{-1} single i.p. injection at the time of tumour inoculation	Increased number of lung metastases	Simon and Arbo (1986)
Both syngeneic and allogeneic Immuno-competent mice Ectopic (s.c., i.p.)	No	10 mg·kg^{-1} s.c. once daily for 10 days	Promotion of tumour growth	Ishikawa *et al.* (1993)
Syngeneic Immunocompetent rats Injection of tumour cells in ileocecal vein	Yes (laparotomy)	Morphine sulfate (15 mg·kg^{-1} 4 doses over 24 h perioperatively)	Increased tumour burden	Colacchio *et al.* (1994)
Allogeneic Immuno-compromised mice Orthotopic breast tumour	No	0.714 mg·kg^{-1}·day^{-1} s.c. for 2 weeks, followed by 1.43 mg·kg^{-1}·day^{-1} for 3 weeks	Increased tumour volume after 32 days	Gupta *et al.* (2002)
Syngeneic A/J mice are immuno-competent but present a defect in macrophage function Ectopic (s.c. in right hind thigh)	Pain increases with tumour growth	0.714 mg·kg^{-1} day^{-1} for 7 days followed by 1 mg·kg^{-1}·day^{-1} for 7 days Morphine non-analgesic	Increased tumour weight and presence of metastases	Farooqui *et al.* (2007)
Syngeneic Immuno-competent rats Tail vein injection of tumour cells	Yes (laparotomy)	10 mg·kg^{-1} immediately and 5 h after surgery	Increased lung diffusion of tumour cells in the absence of surgery. Slightly decreased tumour load (non-statistically significant) in the presence of surgery.	Franchi *et al.* (2007)
Syngeneic colon adenocarcinoma Immuno-competent rats Injection of tumour cells in ileocecal vein	Yes (laparotomy)	20 mg·kg^{-1} morphine s.c. 1 day before and 2 days after tumour inoculation	Reduced tumour burden	Yeager and Colacchio (1991)
Syngeneic Immuno-competent rats Tail vein injection of tumour cells	Yes (laparotomy)	5 mg·kg^{-1} i.p. 30 min before surgery, 5 mg·kg^{-1} s.c. in slow-release suspension immediately after surgery 5–10 mg·kg^{-1} s.c. in slow-release suspension 5 h after surgery	Reduced tumour burden in the presence of surgical stress. No effect in the absence of surgical stress.	Page *et al.* (1993)
Syngeneic Immuno-competent rats Tail vein injection of tumour cells	Yes (laparotomy)	10 mg·kg^{-1} i.p. 30 min before surgery and 5 mg·kg^{-1} s.c. in slow-release suspension after surgery	Reduced tumour burden in the presence of surgical stress, No effect in the absence of surgical stress.	Page *et al.* (1994)
Syngeneic Immuno-competent rats Tail vein injection of tumour cells	Yes (laparotomy)	8 mg·kg^{-1} i.p. 30 min before surgery and/or 4 mg·kg^{-1} s.c. immediately after surgery in a slow-release suspension and/or 2 mg·kg^{-1} s.c. in a slow-release suspension 5 h after surgery	Reduced lung tumour burden in the presence of surgery in all treatment groups	Page *et al.* (1998)
Syngeneic Immuno-competent rats Tail vein injection of tumour cells	Yes (laparotomy)	10 mg·kg^{-1} i.p. at induction of anaesthesia	Reduced lung retention of tumour cells in the presence of surgical stress, but no statistical significance	Bar-Yosef *et al.* (2001)
Syngeneic Immuno-competent mice i.v. injection of tumour cells	no	10 mg·kg^{-1} i.p. for 6 days	Decreased lung metastases	Harimaya *et al.* (2002)
Syngeneic Immuno-competent mice Ectopic (melanoma cells s.c. in hind paw) even though the authors claim orthotopic	Yes (tumour-induced hyperalgesia)	5 and 10 mg·kg^{-1} s.c. daily for 6 days (days 16–21 post-inoculation) Analgesia was demonstrated	Reduced tumour growth and metastasis	Sasamura *et al.* (2002)
Allogeneic Immuno-compromised mice Ectopic (tumour cells inoculated s.c. in dorsal flank)	No	10, 20 and 30 mg·kg^{-1}·day^{-1} i.p. during first, second and third weeks after inoculation respectively Morphine concentrations checked in plasma after injection, 50–60 μM at 10–25 min, 0.9–3.4 μM at 1–2 h	Decreased tumour volume for breast cancer cell lines MCF7 and MDA-MB231, no effect for colon cancer HT-29	Tegeder *et al.* (2003)
Allogeneic Immuno-compromised (nude) mice Ectopic (LLC implanted in the right flank s.c.)	Not intentionally (but surgical insertion of the pellets)	Day of tumour inoculation: 75 mg morphine pellets implanted days 7–14 20 mg·kg^{-1}·day^{-1} i.p. Days 15–21, 30 mg·kg^{-1}·day^{-1} i.p.	Decreased tumour volume and wet weight	Koodie *et al.* (2010)
Syngeneic Immuno-competent mice Tail vein injection of tumour cells	No	10 mg·kg^{-1} i.p. every day for 3 days	Decreased number of tumour nodules	Afsharimani *et al.* (2014)

BJP British Journal of Pharmacology

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British Journal of Pharmacology (2015) **172** 251–259 251

Conclusions

- The mice should spontaneously develop ortho- topic primary tumours in an immuno-competent setting.
- The tumour models should reproduce the biology of *de novo* metastatic disease.
- Surgical resection of the primary tumour is desirable as part of the model.
- The doses of morphine used should be analgesic in mice
- The duration of morphine exposure should match post-operative analgesia regimens, avoiding unnecessary withdrawal as much as possible.
  - continuous administration of high doses of morphine that produce analgesia is more likely to result in prevention of tumour growth and metastasis, in rodent models.

CEEA

Can J Anesth/J Can Anesth (2016) 63:184–192
DOI 10.1007/s12630-015-0523-8

REVIEW ARTICLE/BRIEF REVIEW

Can anesthetic-analgesic technique during primary cancer surgery affect recurrence or metastasis?

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BJA

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[1]*Department of Anesthesiology and Perioperative Medicine, MD Anderson Cancer Center, Houston, Texas, 77030, USA*
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[3]*Department of Surgical Sciences, University of Parma, Parma, 43100, Italy*
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[5]*Anesthesia Intensive Care and Pain Service Azienda Ospedaliera Universitaria Parma, 43100, Italy*
[6]*Pain Therapy Service Foundation IRCCS Policlinico San Matteo, Pavia, 27100, Italy*

European Society of Anaesthesiology ESA

World Federation of Societies of Anaesthesiologists

OPIOIDE

Studiile clinice

Nu sunt studii prospective care sa demonstreze actiunea proliferativa, angiogenica sau prometastatica a opioidelor (in special morfina)

Trialuri clinice aflate in desfasurare:AG +opioide vs AG+anest regionala

- ☆ **cancer de san**
- ☆ **cancer colorectal**
- ☆ **cancer pancreatic**
- ☆ **melanom malign**

Buckley A, McQuaid S, Johnson P, Buggy DJ. Effect of anaes- thetic technique on the natural killer cell anti-tumour activ- ity of serum from women undergoing breast cancer surgery: a pilot study. Br J Anaesth 2014; 113 (Suppl. 1): i56–i62

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

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

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

OPIOIDE

Studiile clinice

- date retrospective privind implicarea receptorilor MORs in evolutia cancerului

- cancerul pulmonar cu celule mari - expresie crescuta de MOR
  - asociere opioide si scaderea perioadei fara recidiva
  - utilizarea dozelor crescute de opioid – factor de risc independent pentru recidiva sau metastazare

-

Cata JP , Keerty V , Keerty D, Feng L, Norman PH, Gottumukkala V, *et al*. A retrospective analysis of the effect of intraoperative opioid dose on cancer recurrence after non-small cell lung cancer resection. Cancer Med 2014; 3: 900-908.
Maher DP, Wong W, White PF, McKenna R, Jr., Rosner H, Shamloo B, *et al*. Association of increased postoperative opioid administration with non-small-cell lung cancer recurrence: a retrospective analysis. Br J Anaesth 2014; 113 Suppl 1: i88-94.

OPIOIDE

Studiile clinice

Cancer de san - date retrospective variate

- ✧ **blocul paravertebral/analgezia epidurala vs opioid sistemic pentru mastectomie – reduce riscul de recurentă**
- ✧ **utilizarea opioidelor nu a redus durata de supravietuire**
- ✧ **polimorfism genetic al receptorilor MOR (A118G) – scade mortalitatea**

Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiology 2006; 105: 660-664.

Cronin-Fenton DP, Heide-Jorgensen U, Ahern TP, Lash TL, Christiansen PM, Ejlertsen B, *et al*. Opioids and breast cancer recurrence: A Danish population-based cohort study. Cancer 2015; 121: 3507-3514.

Forget P, Vandenhende J, Berliere M, Machiels JP, Nussbaum B, Legrand C. Do intraoperative analgesics influence breast cancer recurrence after mastectomy? A retrospective analysis. Anesth Analg 2010; 110: 1630-1635.

Cieslinska A, Sienkiewicz-Szlapka E, Kostyra E, Fiedorowicz E, Snarska J, Wronski K, *et al*. mu-Opioid receptor gene (OPRM1) polymorphism in patients with breast cancer. Tumour Biol 2015; 36: 4655-4660.

Bortsov AV, Millikan RC, Belfer I, Boortz-Marx RL, Arora H, McLean SA. mu-Opioid receptor gene A118G polymorphism predicts survival in patients with breast cancer. Anesthesiology 2012; 116: 896-902.

OPIOIDE

Studiile clinice

- Cancer prostatic -date variate
- analgezia epidurala reduce cu 60 % riscul de recurenta
- reducerea consumului de fentanil nu infl durata supravietuirii
- sufentanilul creste recurenta
- cancerul prostatic avansat cresterea expresiei MOR asociată cu reducerea supravietuirii
- utilizarea dozelor crescute de opioid –asociere cu reducerea supravietuirii

Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence. Anesthesiology 2008; 109: 180–7

Scavonetto F, Yeoh TY, Umbreit EC, Weingarten TN, Gettman MT, Frank I, *et al*. Association between neuraxial analgesia, cancer progression, and mortality after radical prostatectomy: a large, retrospective matched cohort study. Br J Anaesth 2014; 113 Suppl 1: i95-102.

Forget P, Tombal B, Scholtes JL, Nzimbala J, Meulders C, Legrand C, *et al*. Do intraoperative analgesics influence oncological outcomes after radical prostatectomy for prostate cancer? Eur J Anaesthesiol 2011; 28: 830-835.

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Consensus statement from the *BJA* Workshop on Cancer and Anaesthesia

D. J. Buggy[1*], A. Borgeat[2], J. Cata[3], D. G. Doherty[4], C. W. Doornebal[5], P. Forget[6], V. Gottumukkala[7], A. Gottschalk[8], A. Gupta[9], K. Gupta[10], T. G. Hales[11], H. C. Hemmings[12], M. W. Hollmann[5], A. Kurz[13], D. Ma[14], M. O. Parat[15], D. I. Sessler[13], G. Shorten[16] and P. Singleton[17]

- **Datele existente asupra rolului opioidelor in cancer sunt contradictorii cel mai probabil datorita utilizării unor modele experimentale diferite**

- **Administrarea opioidelor pe termen lung in doze subanalgetice la soareci care nu sunt supusi chirurgiei sugereaza stimularea cresterii tumorale**

- **Modelele animale pe soareci care reproduc conditiile perioperatorii utilizand doze analgetice de opioid sugereaza efectul protector al opioidelor in cancer sau lipsa efectului asupra celulelor neoplazice**

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- **Morfina nu pare sa stimuleze initierea tumorilor si nu exista evidente ca analgezia cu morfina produce cancer**
- **Ramane neclar daca opioidele cresc riscul de recidiva sau metastazare dupa chirurgia neoplazica**
- **Datele existente pana la aceasta data sunt insuficienta pentru a determina schimbarea practicii clinice**

Antiinflamatoarele nonsteroidiene neselective (AINS)
coxibi

AINS /COXIBII

Inhibitoare COX implicate in sinteza de PG

PG –imunosupresoare

PGE2

- efect inhibitor asupra celulelor NK citotoxice din mediul tumoral
  - creșterea tumorală și metastazare
- accentuează migrarea si invazia tumorala prin activarea receptorul factorului de creștere epitelial (EGFR)
- promoveaza angiogeneza
- inhiba apoptoza

Heaney A Buggy DJ. Can anaesthetic and analgesic techniques affect cancer recurrence or metastasis? Br J Anaesth 2012; 109 (S1): i17–i28

Tedore T. Regional anaesthesia and analgesia: relationship to cancer recurrence and survival. Br J Anaesth 2015: 115 (S2): ii34–ii45

Iñiguez MA, Rodríguez A, Volpert OV, Fresno M, Redondo JM. Cyclooxygenase-2: a therapeutic target in angiogenesis. Trends Mol Med 2003; 9: 73–8.

AINS/COXIBII

Blocarea sintezei de PG

- ☆ efect protector antineoplazic
- ☆ efect de reducere a recurenței la pacientul neoplazic.

AINS/COXIBII

- expresia COX -2 este crescută în diferite tipuri de cancer: colon, mamar, pulmonar, prostatic, stomac, pancreas și vezică urinară

- determină o rezistență crescută a celulelor neoplazice la apoptoză si sinteza crescuta de PG implicate in cresterea tumorala

Byrne K, Levins KJ, Buggy DJ. Can anesthetic-analgesic technique during primary cancer surgery affect recurrence or metastasis? Can J Anaesth 2016 63:184–192

Tedore T. Regional anaesthesia and analgesia: relationship to cancer recurrence and survival. Br J Anaesth 2015 ;115 Suppl 2:ii34-45

Roche-Nagle G, Connolly EM, Eng M, Bouchier-Hayes DJ, Harmey JH. Antimetastatic activity of a cyclooxygenase-2 inhibitor. Br J Cancer 2004; 91: 359–65.

AINS/COXIBI

Datele experimentale

Inhibitorii COX mai ales COX-2

- ☆ **reduc imunosupresia determinata de chirurgie si astfel potentialul de metastazare**
- ☆ **scaderea factorilor angiogenici**
- ☆ **inducerea apoptozei**
- ☆ **atenueaza imunosupresia determinata de opioide**

combinarea inhibitorilor COX mai ales COX-2 cu opioizii de tipul morfinei au prevenit creșterea tumorală, angiogeneza, metastazare și au crescut supraviețuirea

Farooqui M, Li Y, Rogers T, et al. COX-2 inhibitor celecoxib prevents chronic morphine-induced promotion of angiogenesis, tumour growth, metastasis and mortality, without compromising analgesia. Br J Cancer 2007; 97: 1523

Forget P, Bentin C, Machiels JP, Berliere M, Coulie PG, De Kock M. Intraoperative use of ketorolac or diclofenac is associated with improved disease-free survival and overall survival in conservative breast cancer surgery. Br J Anaesth 2014; 113(Suppl 1): i82-7.

Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of Anesthesia, analgesia, and cancer recurrence during randomised controlled trials. Lancet 2012; 379: 1591-601.

Adjuvanti

- ☆ **Ketamina**
- ☆ **Alfa 2 agonisti: clonidina, dexmedetomidina**

date neconludente

CONCLUZII

- ☆ **Analgezia pacientului supus chirurgiei neoplazice reprezinta o prioritate in managementul perioperator**
- ☆ **Rolul opioidelor in recidiva si metastazare tumorala ramane inca neclar**
- ☆ **Inhibitorii COX, mai ales coxibii au efecte antitumorale dovedite**
- ☆ **Asocierea opioidelor cu inhibitorii COX este benefica datorita faptul că inhibitorii COX previn progresia cancerului și atenuează efectele imunosupresoare ale opioidelor fără a afecta calitatea analgeziei.**

☆

Va multumesc !