Cancer children: understanding acute and chronic pain

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GUSTAVE ROUSSY
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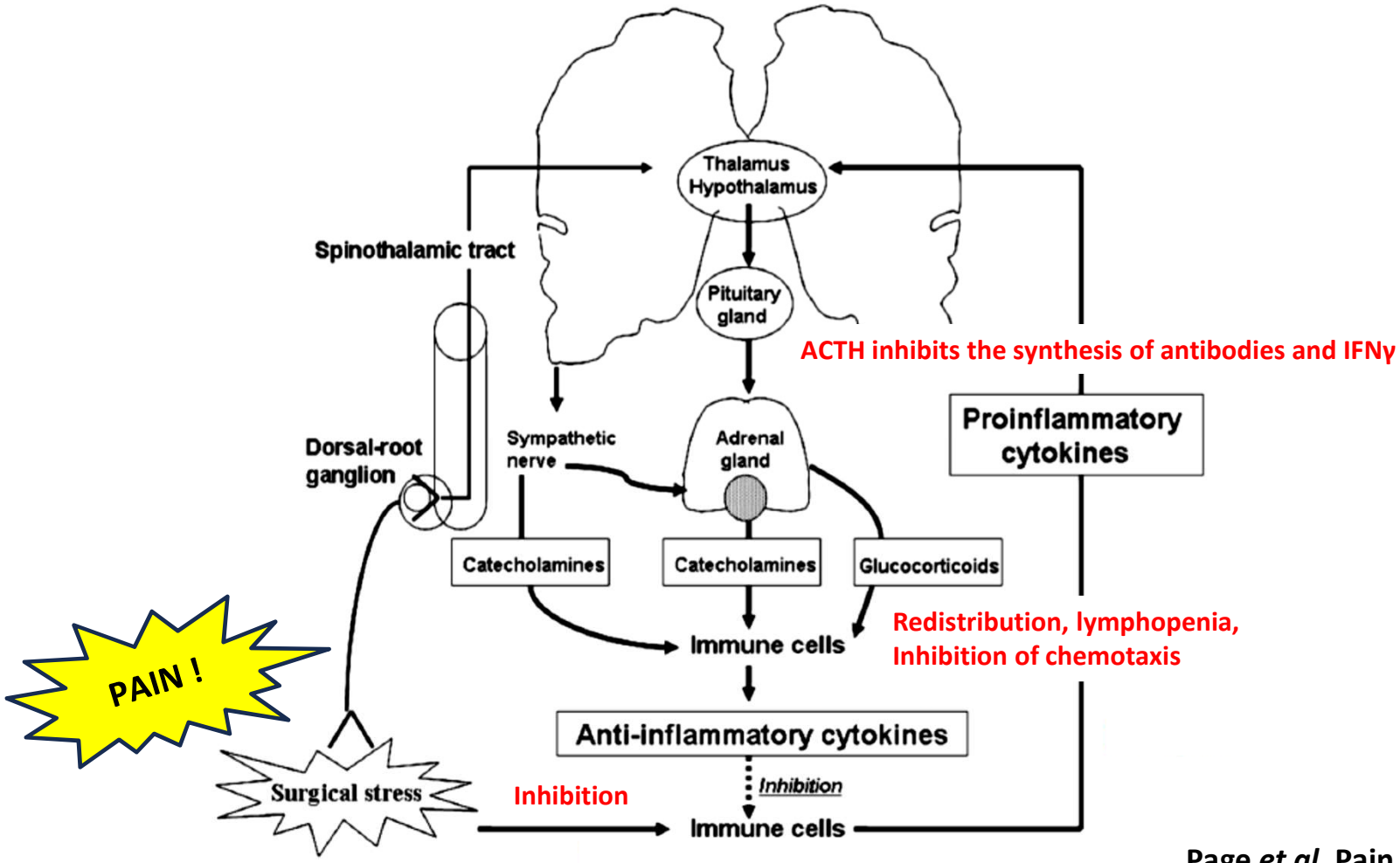
GRAND PARIS

No conflict of interest

Acute pain is immunosuppressive

Glucocorticoid stress

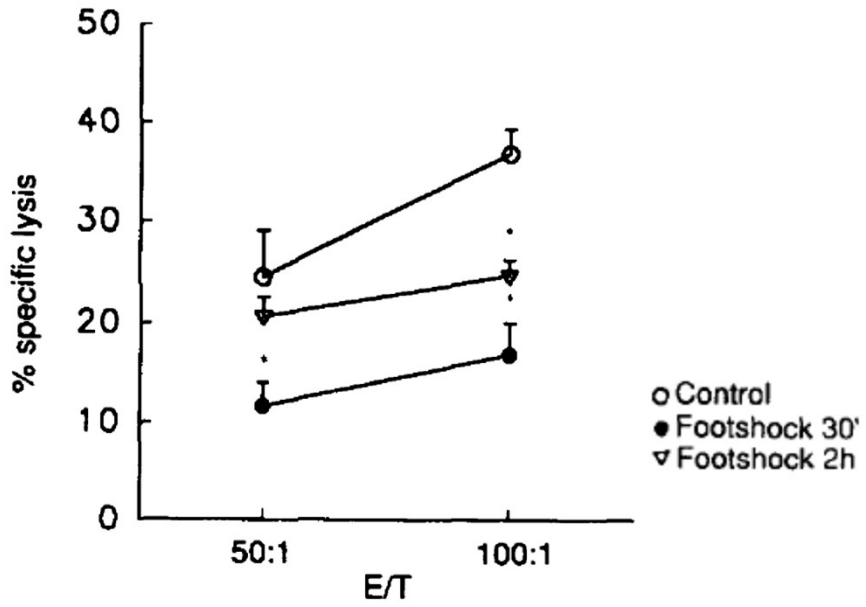


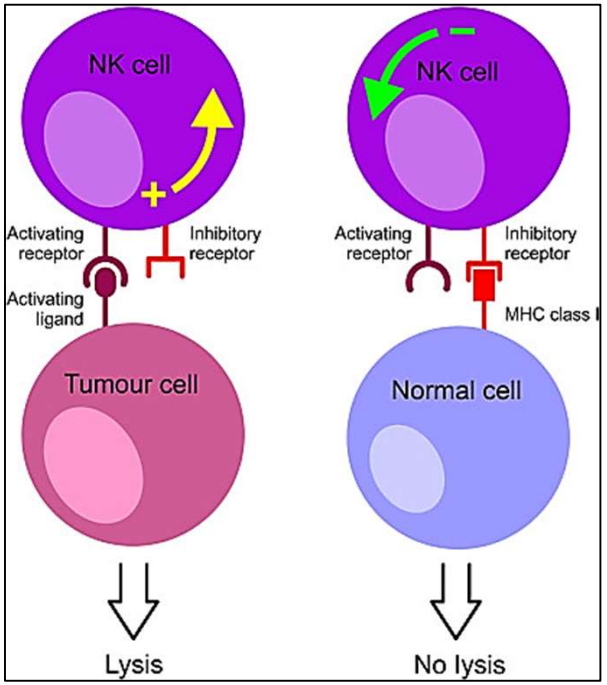
Glucocorticoid stress

Page *et al.* Pain 2001
Sacerdote *et al*. Brain Behav Immun 1994
Guillemin *et al*. Science 1977
Baker *et al*. Br Med J 1985

Acute pain is immunosuppressive

Acute pain decreases the activity of Natural Killer cells.



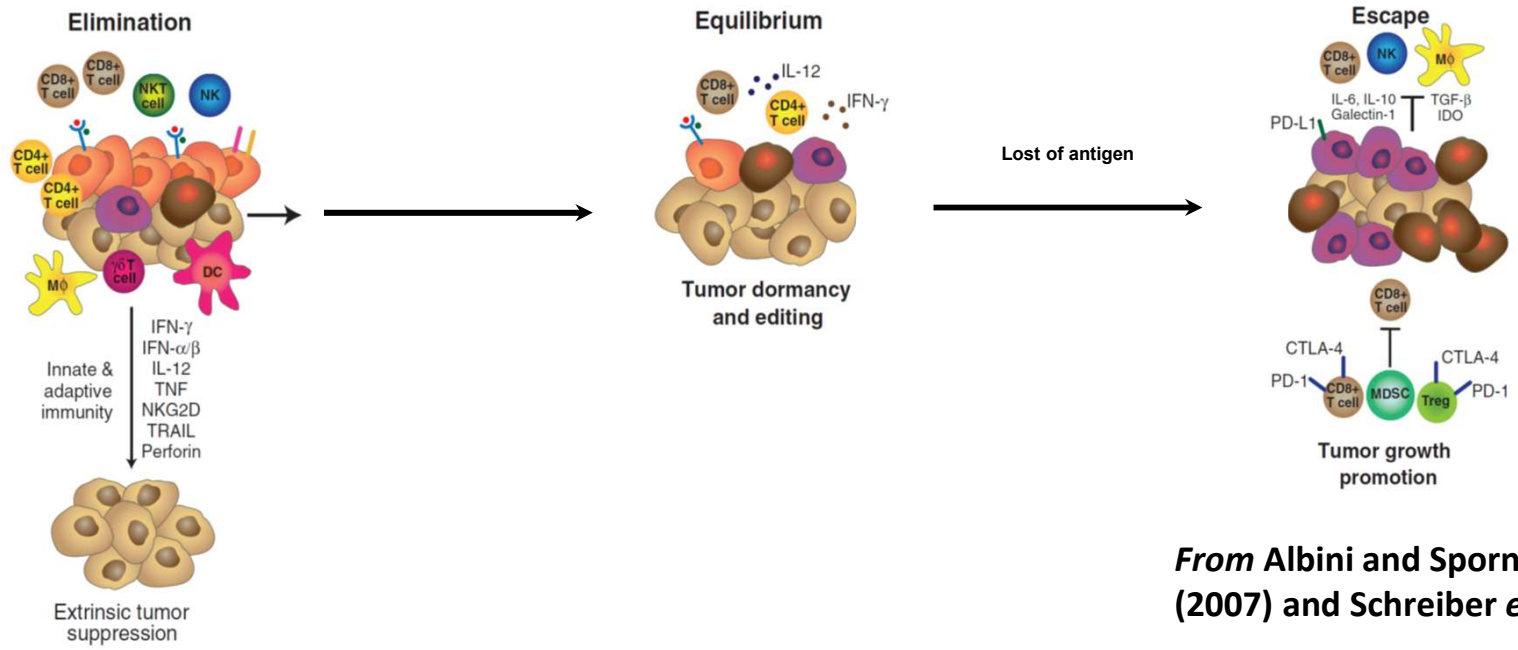


Natural Killer cells-an overview ScienceDirect Topics 2019

Electrical stress of 1.6 mA applied on paw of rat for 1s every 5s during 20 min. Blood samples 30min and 2h after stress to assess NK activity.

Sacerdote *et al.* Brain, Behavior and Immunity 1994

Acute pain modifies tumor microenvironment



***From* Albini and Sporn. Nat Rev Cancer (2007) and Schreiber *et al*. Science (2011)**

Surgical pain decreases the activity of T and NK lymphocytes, neutrophils, dendritic cells and macrophages. Pain also changes the tumor microenvironment and the tumor infiltrating leucocytes by altering the chemotaxis.

Glucocorticoid stress impairs anti-tumor immune response

ARTICLES
https://doi.org/10.1038/s41591-019-0566-4
nature medicine

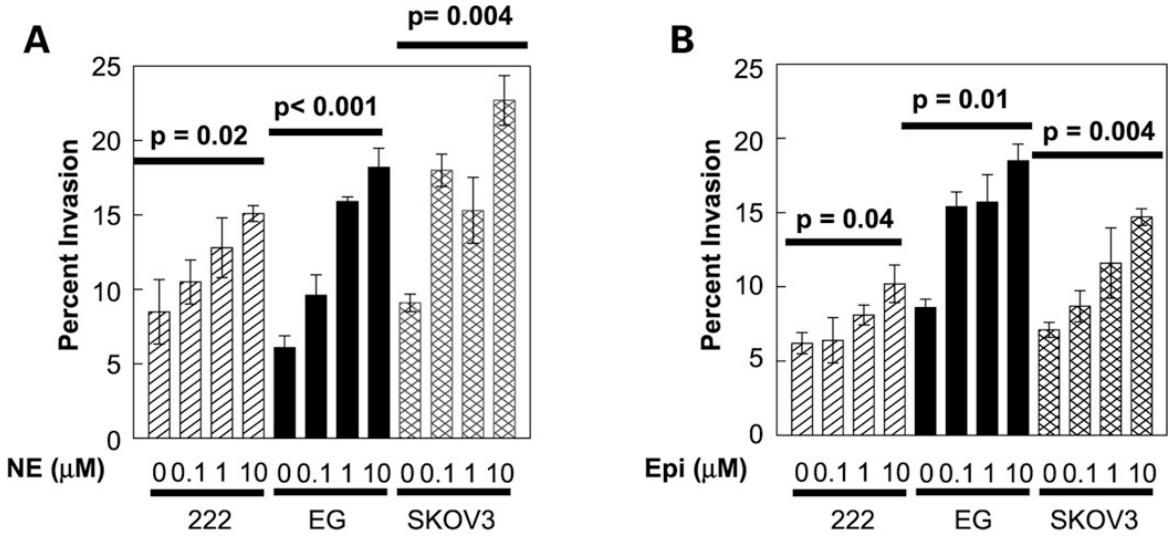
Stress–glucocorticoid–TSC22D3 axis compromises therapy-induced antitumor immunity

Heng Yang[1,2,22], Lin Xia[1,2,22], Jian Chen[3,22], Shuqing Zhang[1,2], Vincent Martin[4], Qingqing Li[1,2], Shangqing Lin[1,2], Jinfeng Chen[1,2], Joseph Calmette[5], Min Lu[6], Lingyi Fu[7], Jie Yang[7], Zhizhong Pan[7], Kuai Yu[7], Jingjing He[7], Eric Morand[8], Géraldine Schlecht-Louf[5], Roman Krzysiek[5,9], Laurence Zitvogel[1,2,10,11,12], Boxi Kang[13], Zeming Zhang[13], Andrew Leader[14], Penghui Zhou[7], Laurence Lanfumey[4], Minxin Shi[3], Guido Kroemer[1,2,15,16,17,18,19,20,21,23*] and Yuting Ma[1,2,23*]

NATURE MEDICINE | VOL 25 | SEPTEMBER 2019 | 1428–1441

Acute pain increases the rate of catecholamines

- High plasma level of epinephrine and norepinephrine in per- and postoperative period.
- Catecholamines are immunosuppressive and their concentrations are inversely correlated with the activity of lymphocytes.
- Relation between neurotransmettors and tumor cells, which express adrenoceptors (breast, ovary tumor cells…).

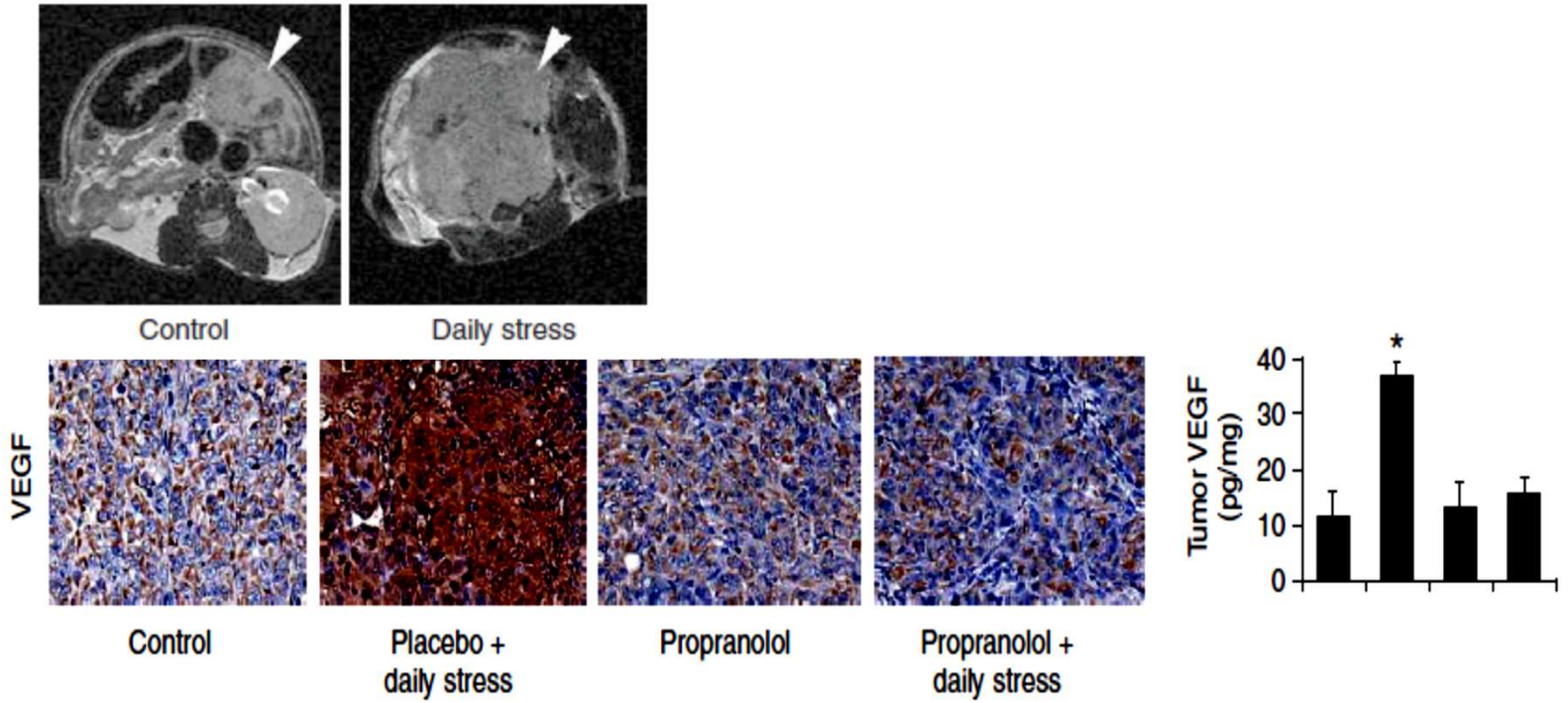


Sood *et al*. Clin Cancer Res 2006

- Catecholamines increase the proliferation, invasion and survival of tumor cells by favoring MMP, STAT3 and the secretion of VEGF.

Administration of exogenous catecholamines during per- and postoperative period might impact on oncological outcomes? The question remains open…

- Murine orthotopic ovary cancer (HeyA8 cells expressing beta-adrenoceptors)
- Mice were stressed for 2-6h daily (stuck in a falcon tube). Size and weight of adrenal glands + assessment of norepinephrine and corticosterone
- Significant increase in beta-adrenergic activity, VEGF, MMP2, MMP9

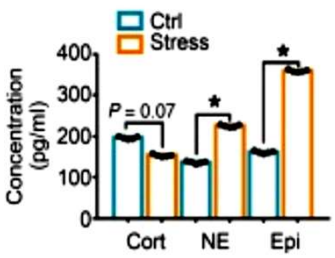


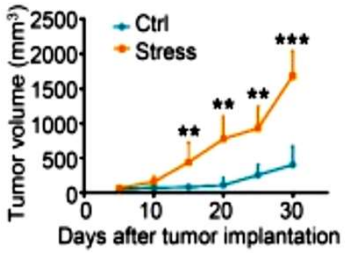
Thaker *et al.* Nat Med 2006

JCI The Journal of Clinical Investigation
Published by The American Society for Clinical Investigation | Founded 1908

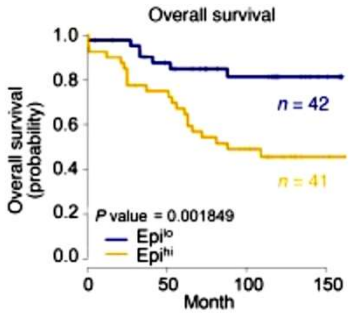
Stress-induced epinephrine enhances lactate dehydrogenase A and promotes breast cancer stem-like cells

Murin breast cancer
Mice were stressed
(claustrophobia model)





83 patients with breast cancer
No difference for: TNM and hormones receptors



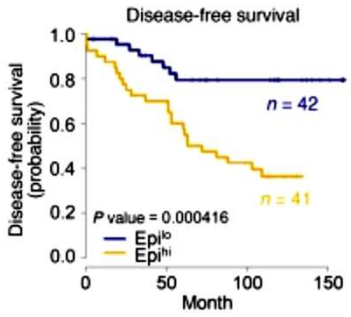


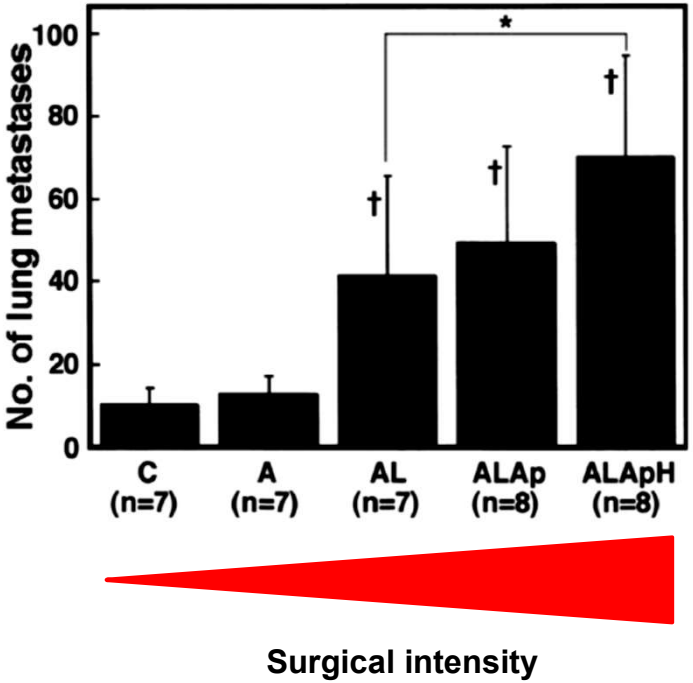
Table 6. Results of multivariate Cox proportional hazards analysis for overall survival and disease-free survival in breast cancer patients

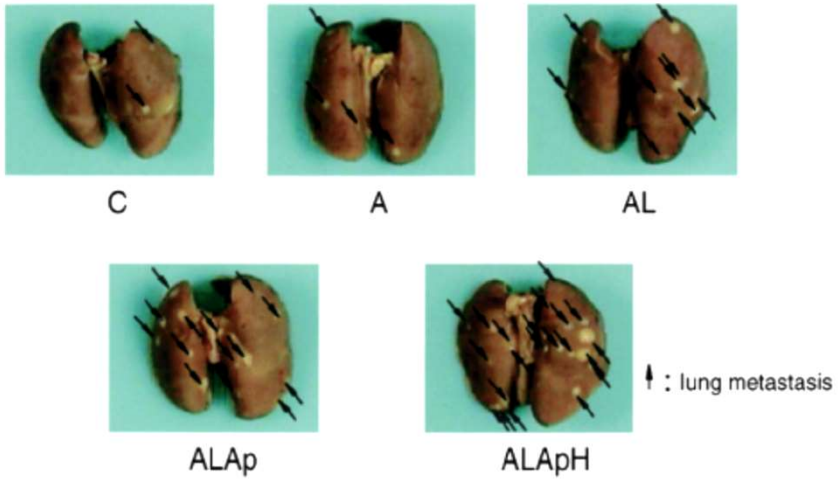
Variable	For OS			For DFS		
	Hazard ratio	95% Confidence interval	*P*	Hazard ratio	95% Confidence interval	*P*
HER2 <−/+ (vs. ≥−/+)	0.679	0.235–1.966	0.476	1.174	0.437–3.150	0.751
PR ≤+ (vs. ≥++)	0.872	0.326–2.329	0.785	1.023	0.410–2.553	0.961
ER ≤+ (vs. ≥++)	0.886	0.362–2.168	0.79	0.953	0.411–2.209	0.910
Tumor stage $T_1 + T_4$ (vs. $T_2 + T_3$)	1.884	1.110–3.199	0.019	2.343	1.415–3.882	0.01
Node stage $N_0 + N_1$ (vs. $N_2 + N_3$)	1.350	0.883–2.064	0.165	1.787	1.188–2.689	0.05
Epi^{lo} (vs. Epi^{hi})	0.322	0.125–0.828	0.019	0.171	0.063–0.465	0.01

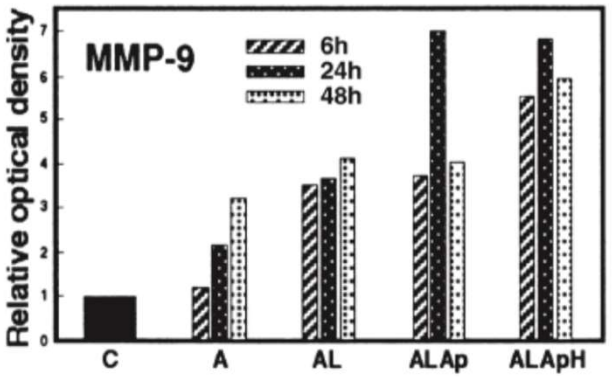
n = 83. OS, overall survival; DFS, disease-free survival. <−/+ , $HER2^-$; ≥−/+, $HER2^+$; ≤+,PR^- or ER^-; "≥++, PR^+ or ER^+.

Acute/surgical pain and oncological outcomes

Surgical pain increases metastases



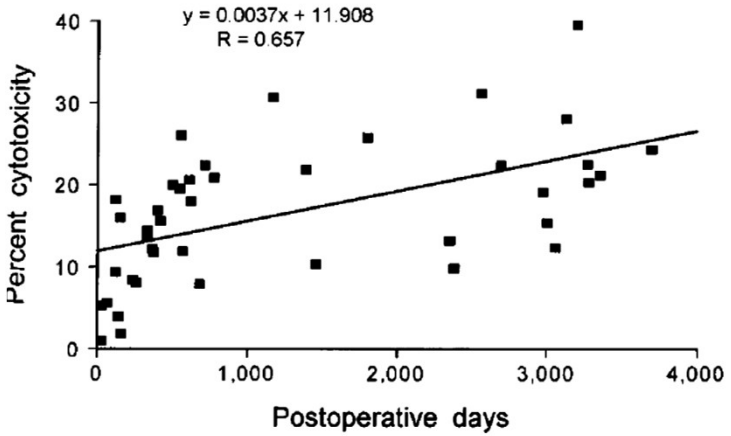


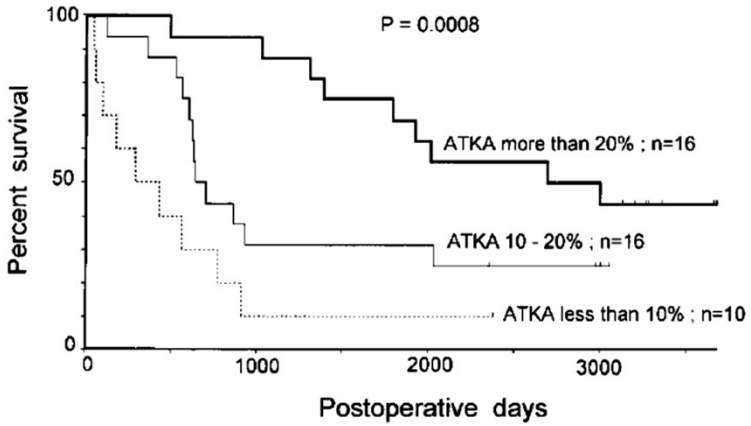


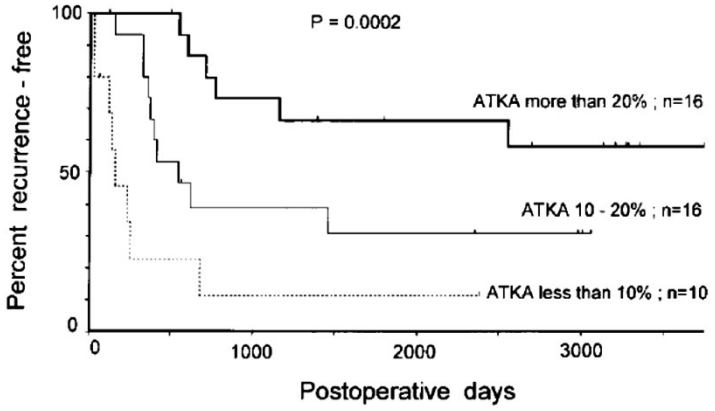
Tsuchiya *et al.* Surgery 2003

Correlation between surgery, NK cells and survival

42 patients operated for NSCLC lung cancer. Culture of cancer cells.
Post-operative period: co-culture with lymphocytes (blood sample)
Assessment of cytotoxicity of lymphocytes.



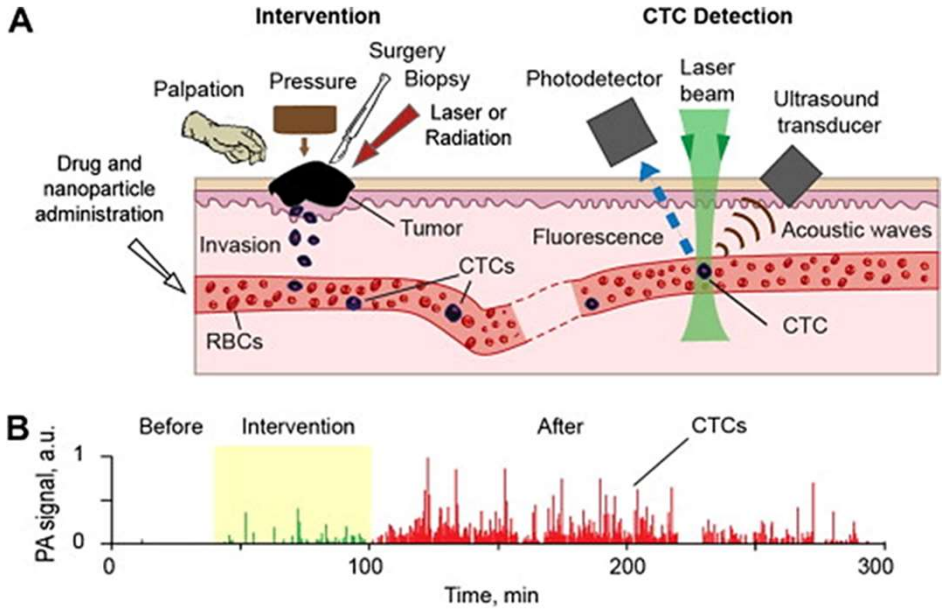




ATKA: autologous tumor killing activity

Fujisawa *et al.* Cancer 1997

Surgery is a physical factor of tumor cells spread



CTC: circulating tumor cells

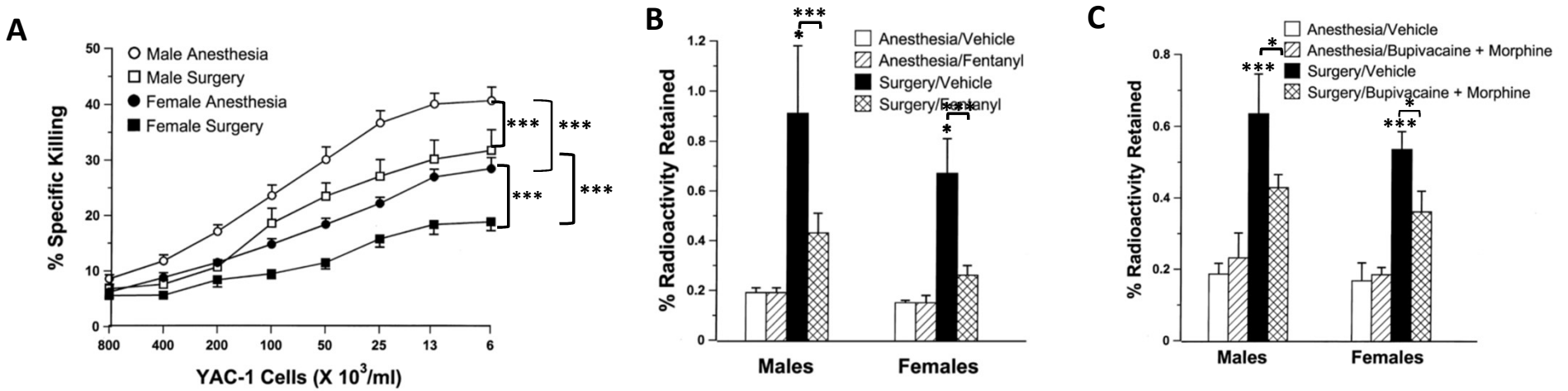
- Surgery is immunodeficient and promotes the migration of residual circulating tumor cells
- CTC are either controlled by the immune system or hidden in postoperative adhesions
- If immune system failure (ageing, drugs…), CTC can proliferate, promote metastases or return to the site of primary tumor ("**Tumor self-seeding**" process).
- Add an adjuvant during oncological surgery is expected to control CTC and improve survival

Fidler *et al.* Nat Rev Canc 2003

Optimal control of pain could improve oncological outcomes?

Preclinical data

Rat model: laparotomy (4 cm) under halothane 2% + externalization of 10 cm of the small intestine + tissue damage



Co-culture NK cells from rats with YAC-1 cells

- **Surgery decreases NK activity**
- **Difference between male and female**

Injection of radiolabeled MADB tumor cells. Removal of lungs. % radiolabeled lung metastases

- **Surgery increases lung metastases.**
- **Pain control (fentanyl *s.c.* or bupivacaine+morphine *i.t.*) decreases lung metastases.**

Page *et al.* Pain 2001

Neuraxial anesthesia perfectly controls glucocorticoid stress

British Journal of Anaesthesia 1991; **67**: 729–734

PROTEIN METABOLISM AFTER ABDOMINAL SURGERY: EFFECT OF 24-H EXTRADURAL BLOCK WITH LOCAL ANAESTHETIC

F. CARLI, J. WEBSTER, M. PEARSON, J. PEARSON, S. BARTLETT, P. BANNISTER AND D. HALLIDAY

17 patients operated for recto-sigmoid resection
2 groups: GA versus GA + bolus of bupivacaine (intrathecal)

TABLE V. *Urinary excretion (mean (SD)) of urea nitrogen, creatinine, adrenaline, noradrenaline and cortisol in the two groups*

	Before surgery	After surgery			
	Day −1	Day +1	Day +2	Day +3	Day +4
Urea nitrogen (mmol day^{-1})					
Control	84 (9)	124 (12)	126 (19)	119 (16)	113 (16)
Extradural	81 (14)	84 (17)	84 (18)	90 (18)	89 (17)
Creatinine (mmol day^{-1})					
Control	6 (3)	13 (5)	14 (6)	12 (5)	12 (5)
Extradural	5 (3)	10 (4)	10 (5)	10 (5)	8 (4)
Adrenaline (μmol day^{-1})					
Control	0.05 (0.03)	0.31 (0.13)	0.02 (0.08)	0.12 (0.04)	0.10 (0.04)
Extradural	0.04 (0.03)	0.09 (0.03)	0.06 (0.03)	0.04 (0.03)	0.04 (0.02)
Noradrenaline (μmol day^{-1})					
Control	0.15 (0.04)	0.43 (0.16)	0.41 (0.15)	0.36 (0.14)	0.36 (0.13)
Extradural	0.19 (0.08)	0.23 (0.08)	0.21 (0.09)	0.20 (0.08)	0.18 (0.07)
Cortisol (nmol day^{-1})					
Control	379 (162)	3391 (760)	—	2235 (643)	—
Extradural	412 (125)	2970 (410)	—	2127 (782)	—

Carli *et al*. BJA (1991)

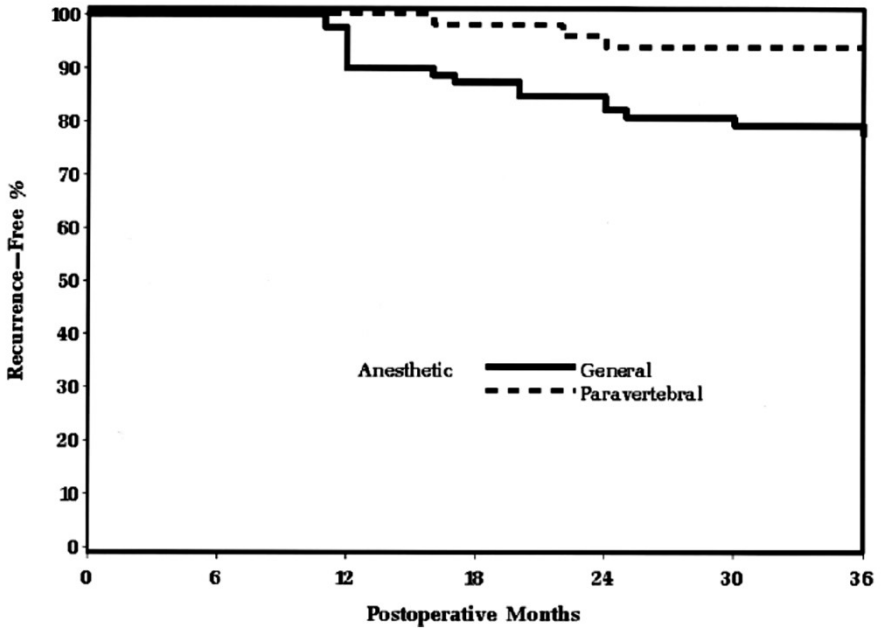
Retrospective study

- 129 mastectomies for breast cancer
- 2 groups: -PVB (T2-T3): bolus levobupivacaine 0.25% 0.2ml/kg + catheter for 48h
  -IV morphine pump
- Lower pain scores in PVB group

Table 1. Anesthetic and Surgical Factors

	Paravertebral (n = 50)	General Anesthesia (n = 79)	*P* Value
Age, yr	57 [51–64]	56 [50–64]	0.95
Time from surgery to recurrence or last follow-up, months	36 [24–36]	36 [24–40]	*
Duration of surgery, min	90 [69–120]	90 [60–105]	0.35
Intraoperative blood loss, ml	100 [100–200]	100 [100–100]	0.017
Pain score 4 h, Likert score	1 [0–3]	3 [2–5]	0.02
Pain score 24 h, Likert score	1 [0–2]	2 [0–4]	0.04

Exadaktylos *et al.* Anesthesiology 2006



- At 36 months: no relapses for 94% group PVB *vs* 77% group morphine (p=0.007)
- Local recurrences (1 patient group PVB vs 11 patients), distant recurrences (2 patients group PVB *vs* 8 patients)

Beneficial pain control? Or direct effect of local anesthetics?

Pro-tumor activity of opioids?

Exadaktylos *et al*. Anesthesiology 2006

Retrospective study

- 225 patients, prostatectomy by laparotomy
- 2 groups: -thoracic epidural (T11-T12): bolus then continuous infusion for 2-3 days
  -IV morphine pump
- No information for pain

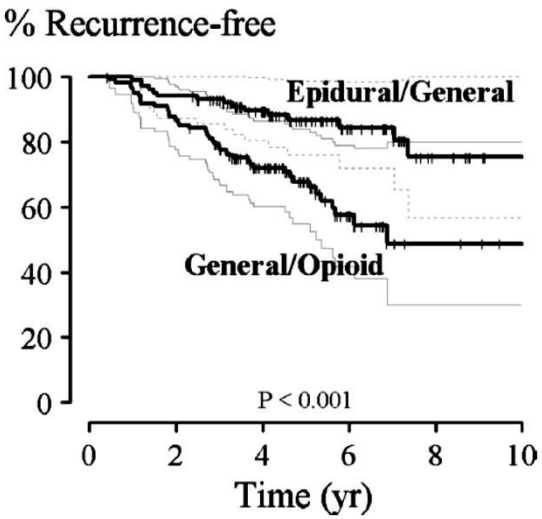


Table 4. Multivariable Association with Recurrence: Cox Regression Model

Model Factor*	Reference or Units	Hazard Ratio (95% CI)	*P* Value
Epidural–general	General–opioids	0.43 (0.22–0.83)	0.012
Tumor size	Per 10 percent of prostate	1.17 (1.03–1.34)	0.01
Gleason score	1	1.19 (1.08–1.52)	0.004
Margin = yes	No	1.49 (0.77–2.87)	0.24
Preoperative PSA status	1	1.02 (1.00–1.04)	0.054
Date of surgery	NA	NA	0.28

Beneficial effect of pain control?

Direct effect of local anesthetics? No, injection very far from tumor site and low plasma level of local anesthetics. Pro-tumoral effect of opioids?

Biki *et al.* Anesthesiology 2008

How to treat oncological acute and chronic pain in children ?

Types of pain in cancer children

Causes:
- Tumor (64%) : invasion, compression, nerve injury
- Treatment (20.3%): chemotherapy, radiotherapy
- Acts: punction, injection, surgery, IV
- Other: psychological pain, anticipation of pain

Symptoms:
- Nociceptive pain (visceral or somatic): postsurgery, inflammation, healing
- Neuropathic pain: nerve compression/injury, chemotherapy-induced neuropathy, paraneoplastic neuropathy…
- Psychological pain: stress, …
- Dysfunctional pain: phantom limb pain
- Mixed pain

Opioids do not work for all types of pain !

Marec-Bérard P, *et al.* Arch Pediatr 2005
Ljungman G, *et al.* Pediatr Hematol Oncol 2000

Pain prevalence in cancer children

Prospective study (1995-1996) including 160 children (10-18 y/o) from the pediatric department of Memorial Sloan-Kettering Cancer Center (New York):

- Pain (49.1%)
- Lack of energy (49.7 %)
- Pain in hospitalized children (84.4%)
- Moderate-severe pain (86.6%)

Pain prevalence according to the type of cancer:

- leukemia: 43.8 %;
- lymphoma: 26.9 %;
- solid tumor: 63 %;
- CNS cancer: 50 %.

Collins JJ, *et al.* J Pain Symptom Manage 2000

Oncological pain in cancer children: opioids ?

-Efficiency and side effects of opioids to treat oncological pain in children (0-17 y/o) ? No conclusion

Wiffen PJ, *et al.* Cochrane Database Syst Rev 2017

-**Oral morphine** is the most prescribed opioid (gold standard).
-**Hydromorphone** (extended release): AMM for children >7 y/o in case of refractory pain and/or morphine intolerance.
-**Fentanyl** transdermal patch: AMM for children. However, pills and intranasal injection are safe and well tolerated.

Coombes L, *et al.* Scand J Pain 2017
Murphy A, *et al*.Cochrane Database Syst Rev 2014

-**Methadone** (synthetic opioid, µOR agonist, NMDA antagonist, and inhibitor of serotonin/norepinephrine reuptake): nociceptive and neuropathic pain. High level of interindividual variability, long half-life (15–60 h), high risk of release and overdose. Good efficiency and rare side effects. No AMM for children<15 y/o.

Habashy C, *et al.* Paediatr Drugs 2018
Madden K, *et al.* Pediatr Blood Cancer 2017
Rasmussen VF, *et al*. Pediatr Blood Cancer 2015
Davies D, *et al.* Pediatr Blood Cancer 2008

-**Oxycodone**: no AMM for children <12 y/o. Scarcity of data.
-**Tapentadol**: AMM for pain (moderate-severe) in children>2 y/o in case of opioid failure.

Wang, *et al.* J Pharm Sci. 2025
Eissa, *et al.* J Pain Res. 2021
Beuter, *et al.* J Pain Res. 2019

Co-analgesics for cancer children

- **Corticoids**: anti-inflammatory agent. Indications: neurological syndromes (meningitis, medullary compression, ICP).

  Who guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents (2018)
  https://apps.who.int/iris/bitstream/handle/10665/279700/9789241550390-eng.pdf

- **Ketamine**: NMDA antagonist (0.5 to 2 mg/kg/d continuous IV). Synergic effect with opioids. Side effects: dysphoria and laryngospasm.

  Courade M, *et al.* BMJ Support Palliat Care 2019

- **Biphosphonates**: efficient for bone metastases, well-tolerated, mineralization improvement, and decrease in opioid consumption.

  Anghelescu DL, *et al.* Am J Hosp Palliat Care 2019

Interventional radiology for cancer children

-**No consensus** (scarcity of data). Interventional strategies for palliative care, refractory pain, side effects.

Shah RD, *et al*. Pain Pract 2020
Anghelescu DL, *et al*. Pediatr Anesth 2020
Galloway K, *et al*. Med Pediatr Oncol 2000

-**Issues**: technical specificity, no inclusion of children in large cohorts or in RCTs, lack of procedure for children, and risk of sedation/GA and irradiation.

-**Place for percutaneous procedures**: curative and palliative care in association with chemo-radiotherapy (e.g. radiofrequency, microwaves, cryoablation, intratumoral injection, neurolyse, and cimentoplasty). Decrease the incidence of chronic pain.

Filippiadis DK, *et al.* Presse Med 2019
Gómez FM, *et al.* Pediatr Radiol 2014
Gandhi S, *et al.* J Pediatr Hematol Oncol 2005

-Interventional procedures seem to be safe and efficient to treat cancer pain in children. However, large RCTs are required to support their use in oncological children.

Loco-regional anesthesia for cancer children

-Locoregional anesthesia in children: for chronic/refractory pain or intolerance to current analgesics. SFAR/SFETD (grade 2+)

Forero M, *et al.* Reg Anesth Pain Med 2020
Beloeil H, *et al.* RFE SFAR-SFETD. Doul Analg 2013

-Loco-regional analgesia is frequent and safe in children (with US). Catheter is easy to implement. Tunnelling of catheter is associated with fewer complications (grade 2 RFE SFAR).

Bomberg H, *et al.* Br J Anaesth 2020

-Epidural and intrathecal route of administration can be indicated in oncological children. Intrathecal catheter is exceptional in children.

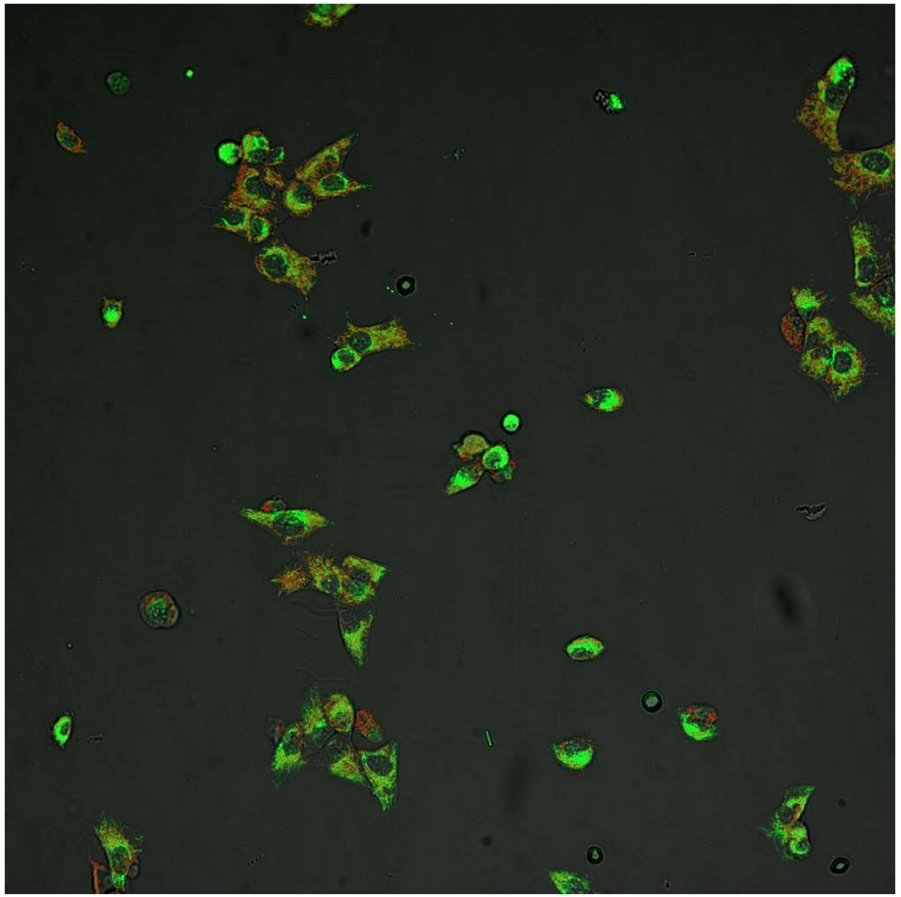
Rork JF, *et al.* J Pain Symptom Manage 2020
Galloway K, *et al.* Med Pediatr Oncol 2000

-Decrease the incidence of chronic pain.

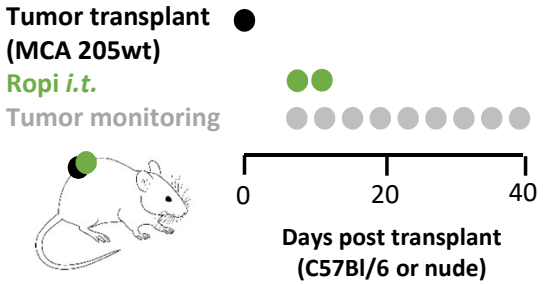
Local anesthetics and antitumor property

Anti-tumor direct effect

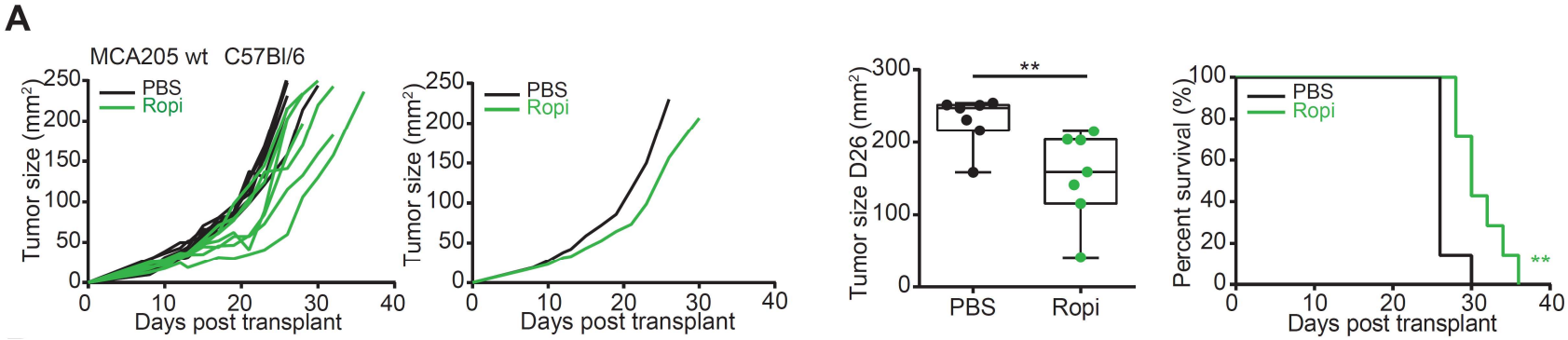
U2OS human osteosarcoma cells treated with ropivacaine



Local anesthetics decrease tumor growth

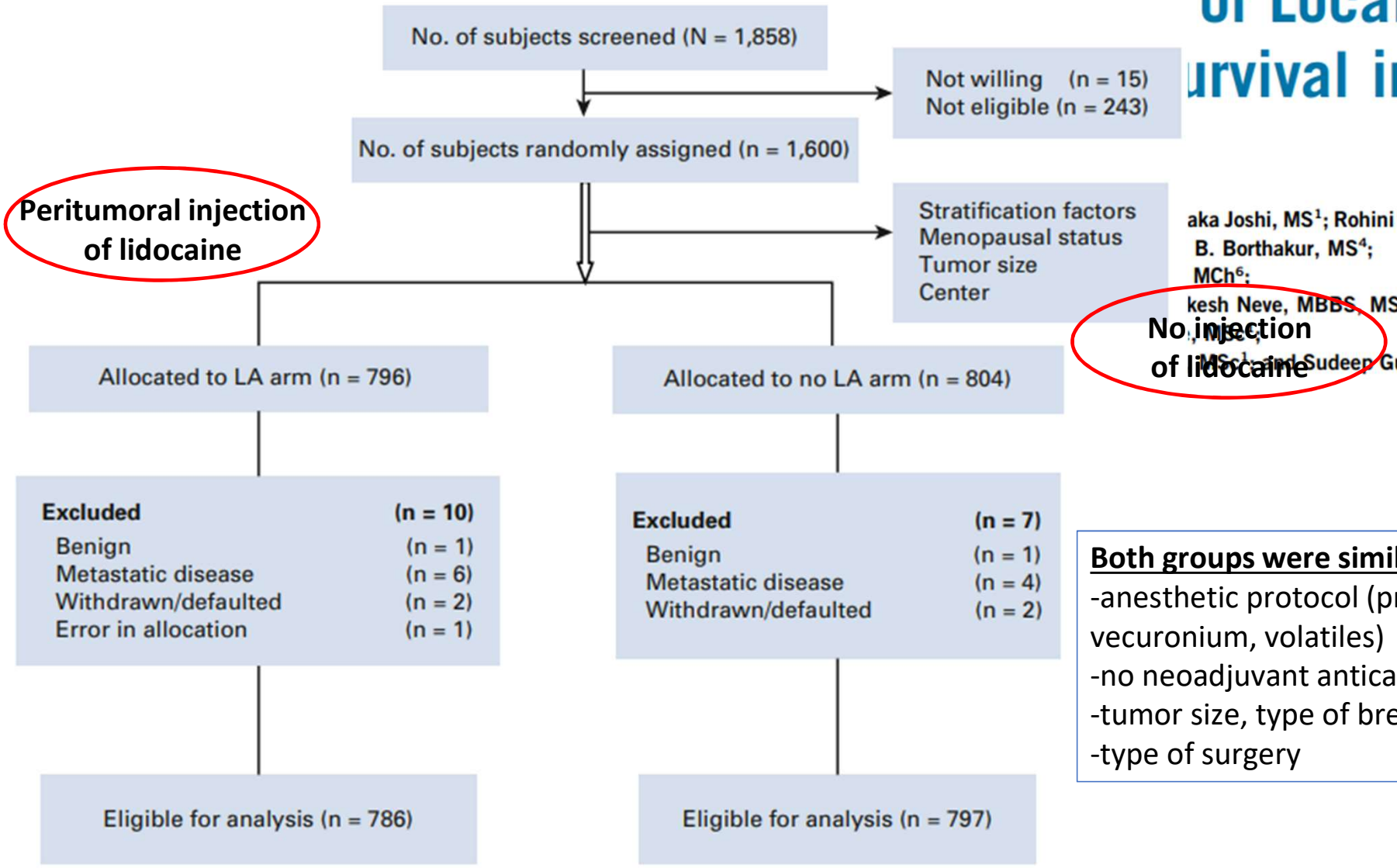


immunocompetent



Bezu, *et al*. JITC 2022

Effect of Peritumoral Infiltration of Local ... urvival in Early



aka Joshi, MS[1]; Rohini Hawaldar, BSc, DCM[1];
B. Borthakur, MS[4];
MCh[6];
kesh Neve, MBBS, MS, DNB[9];
, MBBS,
MSc[1], and Sudeep Gupta, MBBS, MD, DM[1]

Both groups were similar

-anesthetic protocol (propofol, fentanyl vecuronium, volatiles)
-no neoadjuvant anticancer therapy
-tumor size, type of breast cancer, TNM
-type of surgery

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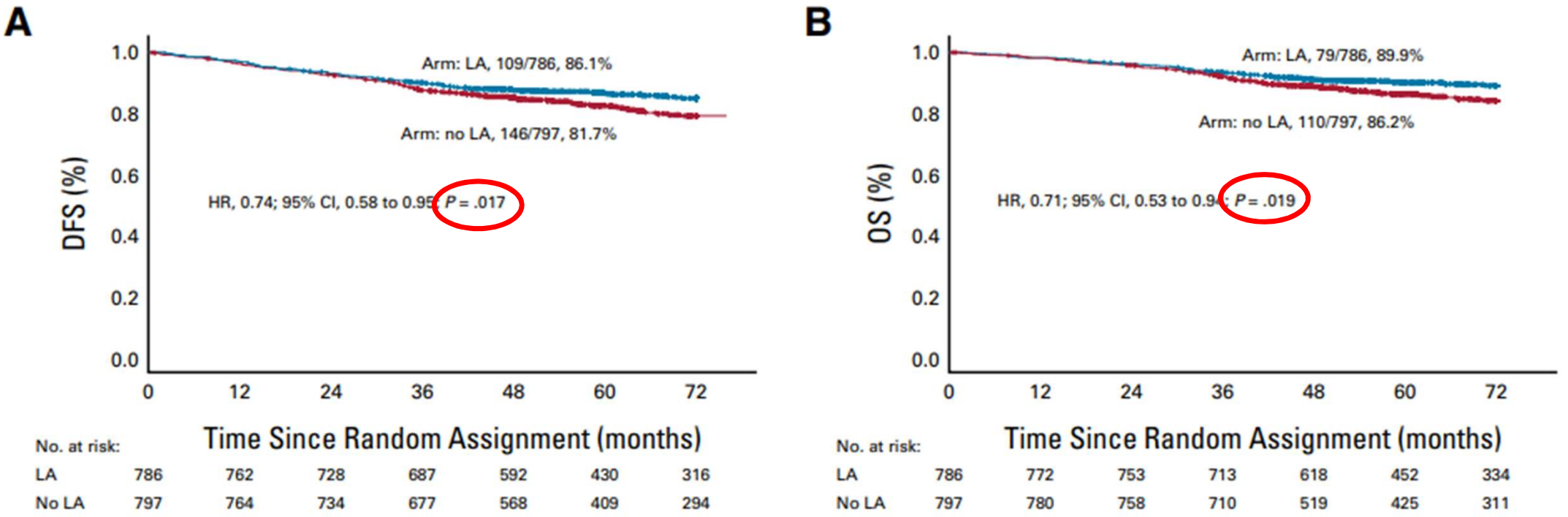
3318 Volume 41, Issue 18

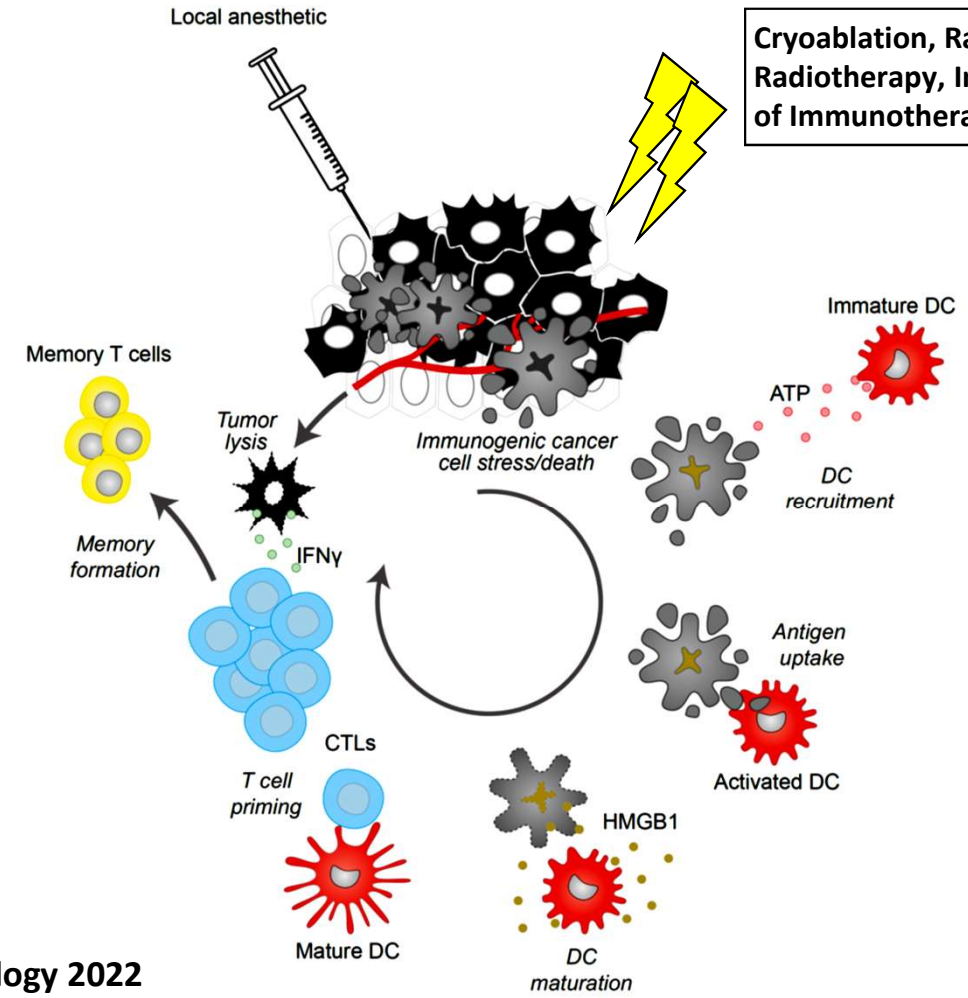


Local injection of anesthetics (lidocaine) improves 5-year OS and DFS

Abscopal effect of interventional radiology and local anesthetics

Direct treatment of primary tumor (intratumoral injection, interventional radiology) stimulates the immune system, which has the capacity to recognize and kill secondary tumors at distant organs.

Yu Z, *et al.* Oncotarget. 2014
Formenti SC, *et al.* Nat Med. 2018
Waitz R, *et al.* Cancer Res. 2012
Shi L, *et al.* Clin Cancer Res. 2016
Bezu L, *et al*. JITC 2022



Adapted from Bezu L. *et al* OncoImmunology 2022

From opioid-based to personalized analgesia

Causes of pain	Analgesics	Route of administration
Neuropathic pain	Antidepressants Anticonvulsivants	PO, IV
	Corticoids	PO, IV, IA, IT
	Bi-phosphonates	PO, IV
Compression Nerve injury Metastatic fracture	Neurostimulation Infiltration Cimentoplasty Alcoholization Sympatholysis	Surgery Interventional radiology
Post-surgery Chronic pain and palliative care	Loco-regional block	Peri-neural IT
Miscellaneous	Acupuncture Hypnotherapy, sophrology, musicotherapy Physiotherapy Photobiomodulation	SC

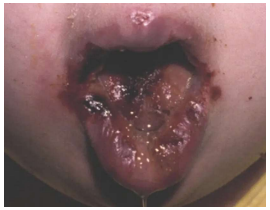
WHO Guidelines for cancer pain management. https://www.who.int/publications/i/item/9789241550390

Photobiomodulation

Laser/LED with low energy
Anti-inflammatory and analgesic property

Photobiomodulation

Prevention and treatment of mucositis
Reduction in the incidence of mucositis from 66.67% to 6.67% ($p<0.05$) in pediatric patients



Lavaee *et al.* BMC Cancer 2025

Conclusions

-Acute/surgical pain is immunosuppressive (glucocorticoid stress, decrease in NK activity).
-Acute/surgical pain impacts oncological outcomes negatively (no control of residual cancer cells, recurrences).
-Optimal pain control could improve cancer prognosis.
-Specific analgesics/procedures (local anesthetics, interventional radiology) boost the immune system and deserve to be implemented in cancer children.
-Large randomized controlled trials including cancer children are required in onco-anesthesia.

➡ Need to advance pediatric onco-anesthesia.

Thanks for your attention

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