

# Der Tumorpatient: Perioperatives Management

Symposium «Der komplexe Schmerzpatient im perioperativen Setting»  
26. September 2019

Dr. med. Corinne Wanner Schmid

Oberärztin, Zentrum für Schmerztherapie, Institut für Anästhesiologie und Intensivmedizin STZ



**Stadt Zürich**

Stadthospital Waid und Triemli

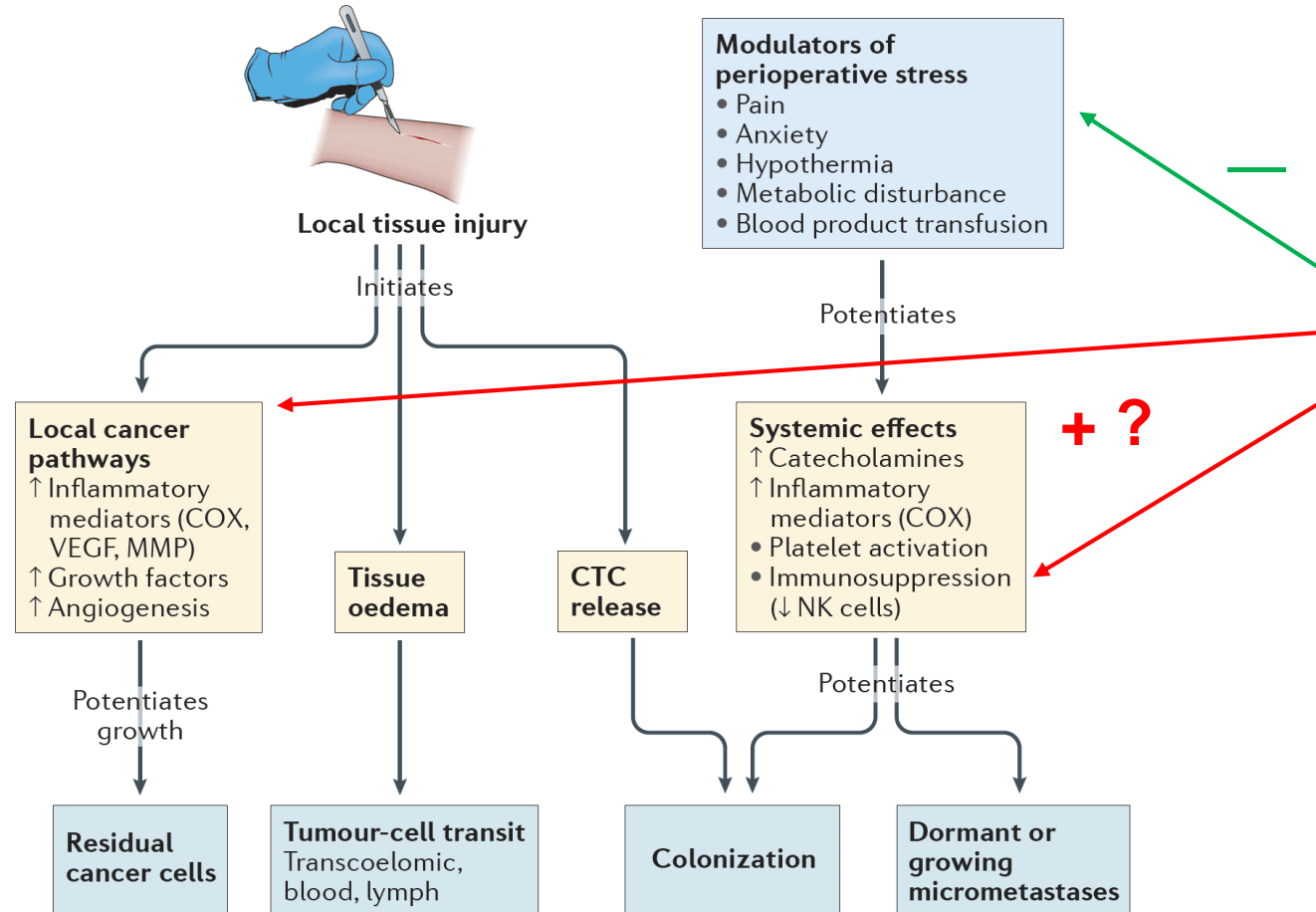
# Inhalt

**1. Anästhesie in der Tumorchirurgie**

**2. Tumorschmerzpatienten in der perioperativen Phase**

# Anästhesie in der Tumorchirurgie

«Seed- Soil»




„Anästhesie“

# Anästhesie in der Tumorchirurgie

## Inhalativa- Propofol

### **Anesthetic technique and cancer outcomes: a meta-analysis of total intravenous *versus* volatile anesthesia**

**Andrea Yap, FANZCA  · Maria A. Lopez-Olivo, PhD · Julia Dubowitz, MBBS · Jonathan Hiller, FANZCA · Bernhard Riedel, PhD · the Global Onco-Anesthesia Research Collaboration Group**

Can J Anesth/J Can Anesth (2019) 66:546–561

# Anästhesie in der Tumorchirurgie

**Hypothese** (in vitro/ Tier-experimentell)

- **Inhalativa:**

- Hypoxie -> Angiogenese↑, Zell- Proliferation ↑, - Migration ↑, - Invasion ↑
- Immunmodulation

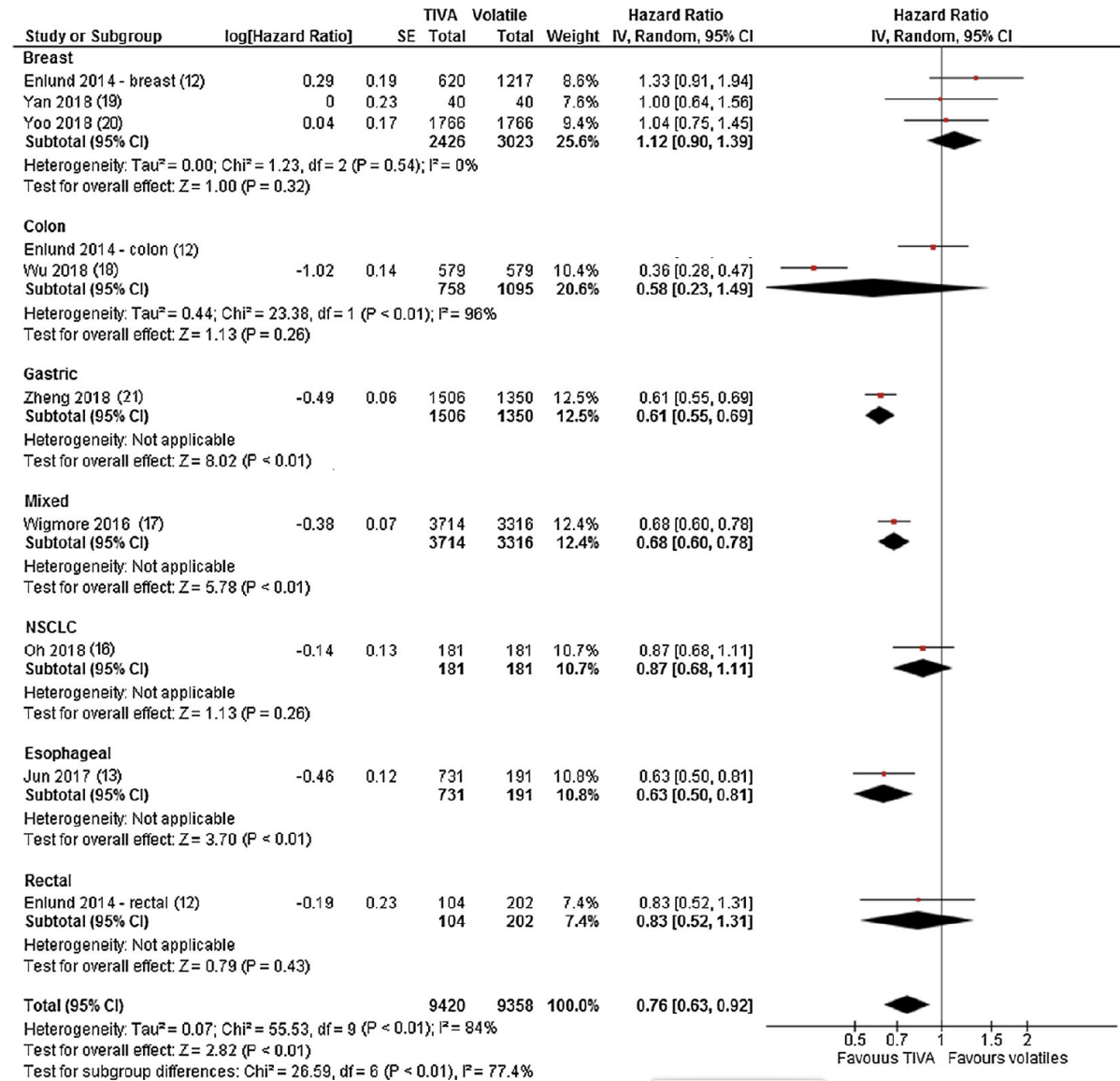
**=> „Preconditioning- Effekt“ (Zellschutz) begünstig Tumorzellen!**

- **Propofol:**

Zellproliferation↓, Apoptose und Immunantwort weniger beeinflusst

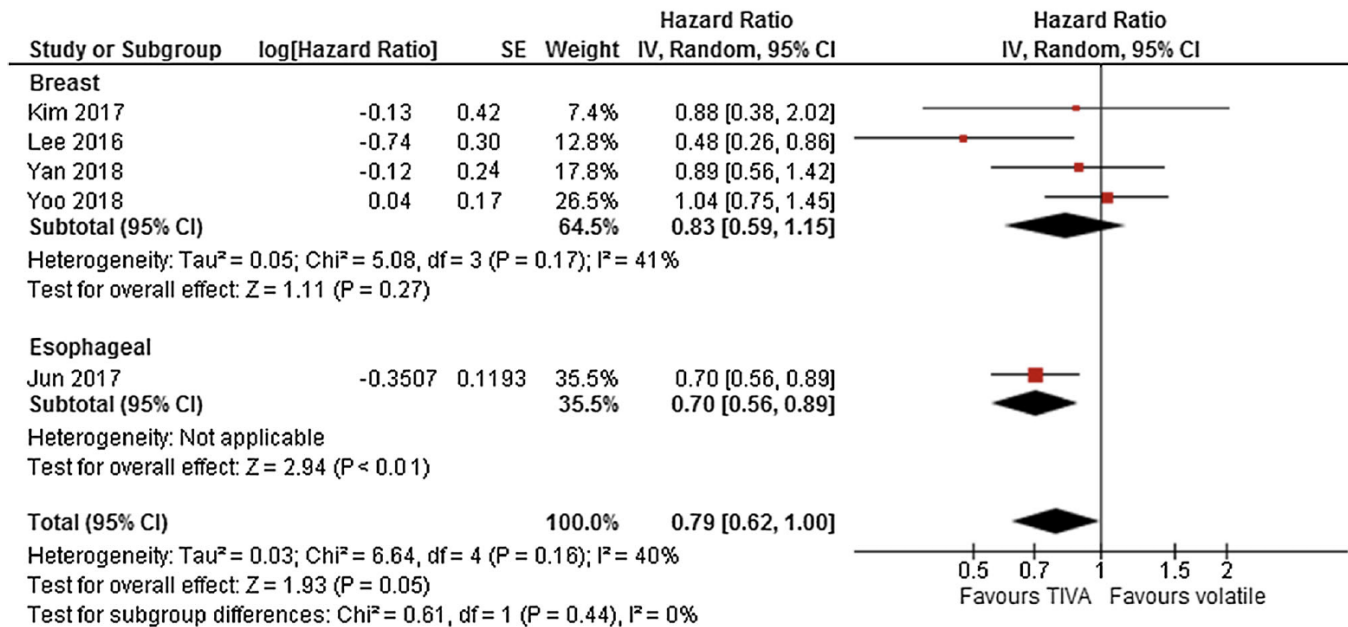
# Anästhesie in der Tumorchirurgie

## Gesamt- Überlebenszeit



# Anästhesie in der Tumorchirurgie

## Rezidiv- freies Überleben



**Correction to: Anesthetic technique and cancer outcomes: a meta-analysis of total intravenous versus volatile anesthesia**

Yap A. et al.; Can J Anesth (2019) 66:546–561

# Anästhesie in der Tumorchirurgie

## Resultate

The pooled results from this meta-analysis suggest that **TIVA use (compared with volatile anesthesia)** during cancer surgery is associated with **improved recurrence-free survival and overall survival** across **numerous cancer types**.

### Korrektur

...**data transcription error** relating to the Oh et al. study within our **recurrence-free survival analysis**.

..When removing the Oh et al. study (as an outlier), as described in our methods, the effect estimate is 0.79 (95% CI, 0.62 to 1.0; P = 0.05) **indicating a borderline protective effect** with an acceptable inconsistency score

**Breast cancer**... in this population, TIVA use was associated with an **improvement in recurrence-free survival but not overall survival**.



# Anästhesie in der Tumorchirurgie

## Limitationen !

- Eine RCT (80 Patienten), 9 retrospektive Studien
- **Heterogenität**
  - Studienpopulationen (Brustkrebs: Frauen, physischer Zustand, asiat. Population)
  - chirurgischer Technik (Invasivität)
  - Grading/ Staging Tumoren
  - Anästhesieverfahren, Bluttransfusionen

# Anästhesie in der Tumorchirurgie

**Analgetika ?**

# Anästhesie in der Tumorchirurgie

## Hypothese (in vitro/ Tier-experimentell)

- **Opioide**

- Tumorprogression und Metastasierung ↑, **aber:** auch gegenteiliger Effekt beschrieben!
- Morphin: Immunsuppression (nicht bei synthetischen Opioiden)

- **Lidocain iv/ Regionalanästhesie**

- Tumorzellwachstum ↓, Zellmigration ↓, Kolonisation ↓
- positive Immunmodulation (Lidocain)
- RA: Stressantwort ↓ (Schmerz ↓, Opioidverbrauch ↓, Immunsuppression ↓)

# Anästhesie in der Tumorchirurgie

## Analgetika

Special article

### Impact of perioperative pain management on cancer recurrence: an ASRA/ESRA special article

Andres Missair,<sup>1,2</sup> Juan Pablo Cata,<sup>3</sup> Gina Votta-Velis,<sup>4</sup> Mark Johnson,<sup>5</sup> Alain Borgeat,<sup>6</sup> Mohammed Tiouririne,<sup>7</sup> Vijay Gottumukkala,<sup>3</sup> Donal Buggy,<sup>5</sup> Ricardo Vallejo,<sup>8</sup> Esther Benedetti de Marrero,<sup>1,2</sup> Dan Sessler,<sup>9</sup> Marc A Huntoon,<sup>10</sup> Jose De Andres,<sup>11</sup> Oscar De Leon Casasola<sup>12</sup>

Reg Anesth Pain Med 2019;44:13-28.

# Anästhesie in der Tumorchirurgie

	Immunmodulation/ Immunsuppression				Tumorrezidiv			
	Empfehlung	Evidenz	Studien	Bem.	Empfehlung	Evidenz	Studien	Bem.
Morphin	strong -	average- strong?	(I) - A- H	3 klin. Studien, Immunmarker	strong -	weak- average	I - A - H	⊘ klin. Studien. "discrepancies"
Synthet. Opioide	strong +	weak- strong	H	2 klin. Studien, Immunmarker	strong -	?	?	
iv Lidocain	strong +	weak- average	I – H	(1 klin. Studie, Immunmarker)	weak +	strong	I	
Epidurale RA	strong +	strong	I - H	3 klin Studien, Immunmarker	weak +	strong	H	¾ RCT Immunmarker + retrosp. Studien "controversial"
Periphere RA	-	-	-		conflicting weak +/-	weak	H	retrosp. Studien inhomogen, Mix
Aspirin	-	-	-		strong +	average	H	*
NSAR	strong +	-	-		strong +	weak	I- H	1 RCT -, 1 retrosp. St. +
Ketamin	strong +	weak-average	H	1 Studie	-	weak, very limited human data	I –H	
Multimod. Analgesie	strong +	-	-		-	-	-	
α2- Agonisten	-	-	-		-	-	-	
Dexamethason	-	-	-		conflicting weak	weak	I - H	

# Anästhesie in der Tumorchirurgie

[Reg Anesth Pain Med](#). 2019 Jan;44(1):13-28. doi: 10.1136/rapm-2018-000001.

## Impact of perioperative pain management on cancer recurrence: an ASRA/ESRA special article.

[Missair A](#)<sup>1,2</sup>, [Cata JP](#)<sup>3</sup>, [Votta-Velis G](#)<sup>4</sup>, [Johnson M](#)<sup>5</sup>, [Borgeat A](#)<sup>6</sup>, [Tiouririne M](#)<sup>7</sup>, [Gottumukkala V](#)<sup>3</sup>, [Buggy D](#)<sup>5</sup>, [Vallejo R](#)<sup>8</sup>, [Marrero EB](#)<sup>9,2</sup>, [Sessler D](#)<sup>10</sup>, [Huntoon MA](#)<sup>11</sup>, [Andres J](#)<sup>12</sup>, [Casasola OL](#)<sup>13</sup>.

ASRA Practice Advisory on Neurologic Complications,<sup>9</sup> “recommendations that rely on limited clinical and animal data and, as such, the synthesis and interpretation of data by one group of experts, may differ from conclusions by another set of equally qualified experts.” The content of this document was approved by the ASRA and ESRA Board of Directors, as well as the ASRA Guidelines and Advocacy Regulatory Committee. “The recommendations contained herein do not define standard of care nor are they to be interpreted as guidelines. They are not intended to replace clinical judgment as applied to a specific patient scenario.”<sup>9</sup>



# Anästhesie in der Tumorchirurgie

Reg Anesth Pain Med. 2019 Jan;44(1):13-28. doi: 10.1136/rapm-2018-000001.

## Impact of perioperative pain management on cancer recurrence: an ASRA/ESRA special article.

Missair A<sup>1,2</sup>, Cata JP<sup>3</sup>, Votta-Velis G<sup>4</sup>, Johnson M<sup>5</sup>, Borgeat A<sup>6</sup>, Tiouririne M<sup>7</sup>, Gottumukkala V<sup>3</sup>, Buggy D<sup>5</sup>, Vallejo R<sup>8</sup>, Marrero EB<sup>9,2</sup>, Sessler D<sup>10</sup>, Huntoon MA<sup>11</sup>, Andres J<sup>12</sup>, Casasola OL<sup>13</sup>.

Summary: Analgesic techniques and influence on immunomodulation and immune cell function  
Recommendation of existing evidence

There is also strong evidence from animal and human data that morphine has negative effects on immune function (strong recommendation for not using, average to strong recommendation). Nonetheless synthetic opioids do not seem to impact immune function (strong recommendation for use, weak to strong evidence).

Summary: Perioperative opioids and cancer recurrence  
Recommendation of existing evidence

There is average laboratory evidence, from cell culture studies, that opioids may have a detrimental effect on cancer, tending to promote cancer cell migration and invasion. There is average animal data which suggest that opioids facilitate tumor spread and reduce disease-free survival in animal models of cancer. Clinically, there is weak evidence that opioids may increase the risk of metastasis in some solid tumor cancers. This emanates from prospective observational analysis of MOR expression in excised non-small cell lung cancer tissue, which shows an association between increased MOR expression in cancer tissue and metastasis (strong recommendation against use, weak to average evidence).

There are, however, discrepancies that may be due to the variability in experimental conditions, different animal models used, different doses of drug administered, and differing routes of administration. To extrapolate animal experimental data to patients, a standardized protocol applicable and transferable to humans should be applied.

# Anästhesie in der Tumorchirurgie

Cancer. 2015 Oct 1;121(19):3507-14. doi: 10.1002/cncr.29532. Epub 2015 Jul 24.

## **Opioids and breast cancer recurrence: A Danish population-based cohort study.**

Cronin-Fenton DP<sup>1</sup>, Heide-Jørgensen U<sup>1</sup>, Ahern TP<sup>2</sup>, Lash TL<sup>1,3</sup>, Christiansen PM<sup>4,5</sup>, Ejlertsen B<sup>5,6</sup>, Sjøgren P<sup>7</sup>, Kehlet H<sup>8</sup>, Sørensen HT<sup>1</sup>.

This large prospective cohort study provided **no clinically relevant evidence of an association between opioid prescriptions and breast cancer recurrence.**

Pain Manag. 2018 Sep 1;8(5):353-361. doi: 10.2217/pmt-2018-0029. Epub 2018 Sep 13.

## **Perioperative opioids and colorectal cancer recurrence: a systematic review of the literature.**

Diaz-Cambronero O<sup>1,2</sup>, Mazzinari G<sup>2,3</sup>, Cata JP<sup>4,5</sup>.

Our review indicates that there is **no conclusive evidence to avoid the use of opioids with the goal of reducing the risk of recurrence in colorectal cancer.**



# Anästhesie in der Tumorchirurgie

## Adäquate Schmerztherapie perioperativ wichtig! (Stressantwort)

Cancers (Basel). 2019 Apr 28;11(5). pii: E592. doi: 10.3390/cancers11050592.

### **How Anesthetic, Analgesic and Other Non-Surgical Techniques During Cancer Surgery Might Affect Postoperative Oncologic Outcomes: A Summary of Current State of Evidence.**

Forget P<sup>1</sup>, Aguirre JA<sup>2</sup>, Bencic I<sup>3</sup>, Borgeat A<sup>4</sup>, Cama A<sup>5</sup>, Condron C<sup>6</sup>, Eintrei C<sup>7</sup>, Eroles P<sup>8,9</sup>, Gupta A<sup>10</sup>, Hales TG<sup>11</sup>, Ionescu D<sup>12</sup>, Johnson M<sup>13</sup>, Kabata P<sup>14</sup>, Kirac I<sup>15</sup>, Ma D<sup>16</sup>, Mokini Z<sup>17</sup>, Guerrero Orriach JL<sup>18,19</sup>, Retsky M<sup>20</sup>, Sandrucci S<sup>21</sup>, Siekmann W<sup>22</sup>, Štefančić L<sup>23</sup>, Votta-Vellis G<sup>24</sup>, Connolly C<sup>25</sup>, Buggy D<sup>26,27</sup>.

Most experimental research, consisting of both cancer cell culture studies and in vivo animal models of cancer, suggest that opioids facilitate cancer cell proliferation (such as migration, invasion, and angiogenesis) and therefore could be detrimental in cancer patients [59–61]. However, some laboratory studies have shown the opposite effect i.e., opioids may have an inhibitory effect on cancer cells and, depending on the animal model used, may not always enhance tumor growth. On balance the evidence does not justify reduced perioperative opioid use, which could potentially lead to worse outcomes due to the negative impact of pain [62].

# Anästhesie in der Tumorchirurgie

## Does It Matter ??

- > 15 Millionen Menschen weltweit haben Krebs
- > 60% davon unterziehen sich einem chirurgischen Eingriff
- > 80% dieser Patienten erhalten Narkose

„Should the findings of the retrospective studies described in this Review be prospectively confirmed, considerable global economic and social **improvements in the outcomes of patients with cancer** can be achieved **at relatively little financial cost** but with potentially life-changing benefits that will bring about a paradigm shift in surgical cancer care“

# Anästhesie in der Tumorchirurgie

„RCT’s are very much needed!

Can J Anesth/J Can Anesth (2019) 66:491–494  
<https://doi.org/10.1007/s12630-019-01331-w>

EDITORIALS

## Can anesthesiologists affect cancer outcomes?

Jacob W. Nadler, MD, PhD · Timothy D. Quinn, MD · Elliott Bennett-Guerrero, MD

These are important and necessary,<sup>13</sup> as the medical literature has many examples of interventions that looked promising in retrospective analyses| but were later shown to be ineffective when subjected to the rigor of randomized-controlled trials, and in some cases, even being harmful.

Surgery is a critical piece of comprehensive cancer care, and the majority of cancer surgery requires general anesthesia. Our patients expect us to prevent awareness and minimize their pain, and at that we are enormously successful. But perhaps we will also learn in time that the choice of anesthesia drug influences cancer outcome. Such

# Tumorschmerzpatienten in der perioperativen Phase



# Tumorschmerzpatienten in der perioperativen Phase

## Präoperativ: Identifikation der Patienten und ihrer Probleme

- **Schmerzanamnese**
  - Ort, Dauer-/ Durchbruchschmerzen?
  - Neuropathische Schmerzen? Knochenmetastasen? Opioid- ind. Hyperalgesie?
  - Schmerzniveau? Progression Tumorerkrankung?
- **Medikation: Opioide, Analgetika und Co-Analgetika:**
  - Präparat(e)? Dosis? Toleranzentwicklung?
- **Schmerzverstärkende Faktoren:**
  - Somatisch?
  - Psychisch (z.B. Depression/ Angst)?

# Tumorschmerzpatienten in der perioperativen Phase

## Perioperativen Behandlungsplan erstellen!

- Ziele: **Analgesie- Stressantwort ↓- Opioid- Entzug vermeiden**
- **Multimodales Schmerzmanagement**
  - Operation?
  - Regionalanästhesieverfahren möglich ?
  - Co- Analgetika (Ketamin, Clonidin, Antiepileptika, Antidepressiva)?
  - Orale Gabe/ Resorption postoperativ gewährleistet?
- **Therapie der Nebenwirkungen/ weiterer beeinflussender Faktoren**

# Tumorschmerzpatienten in der perioperativen Phase

## Opioide

- **Patienten mit präoperativer Opioidtherapie: Entzug vermeiden!**
  - Entzugsprophylaxe: retardiertes Basis- Opioid weiter
  - keine Entfernung des Fentanyl-Pflasters im OP
  - Ø orale Gabe/ Resorption?
    - > Umstellung auf transdermale oder iv-Gabe (kontinuierlich, Boli, PCA)

# Tumorschmerzpatienten in der perioperativen Phase

## Opioide

- **Intra- postoperativ: zusätzlicher Bedarf an Opioiden zur Analgesie!**
  - Grund-/ Ruheschmerz:
    - > Dosis  $\uparrow$  retardiertes Basis- Opioid postoperativ oder
    - > kontinuierliche Infusion
  - Durchbruchsschmerz:
    - > kurzwirksames Opioid in Reserve (iv, sc, oral, buccal)
    - > in angepasster Dosis (Basis-Opioid)!



**Herzlichen Dank für die Aufmerksamkeit!**

