



BRESCIA, 11 MARZO 2017

Cure simultanee e di supporto:  
l'integrazione tra ospedale e territorio  
nella gestione delle patologie oncologiche rese croniche dai  
trattamenti

Definizione e gestione del  
breakthrough cancer pain.  
M.A. Venturini





NEO = νεοζ  
PLASIA = πλαθιαζ

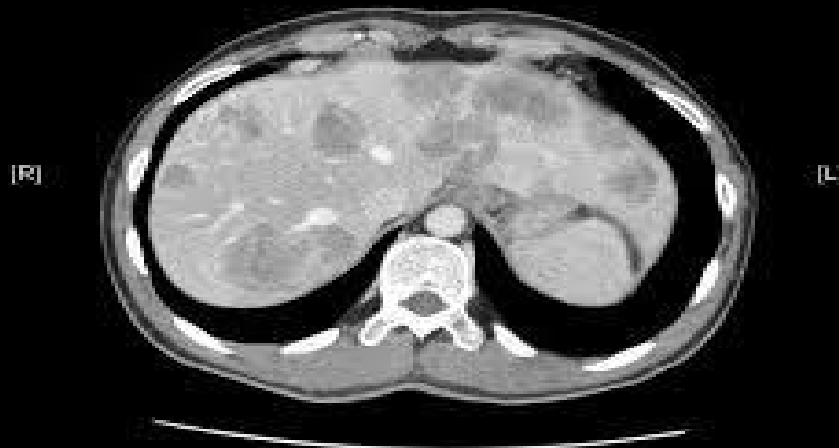
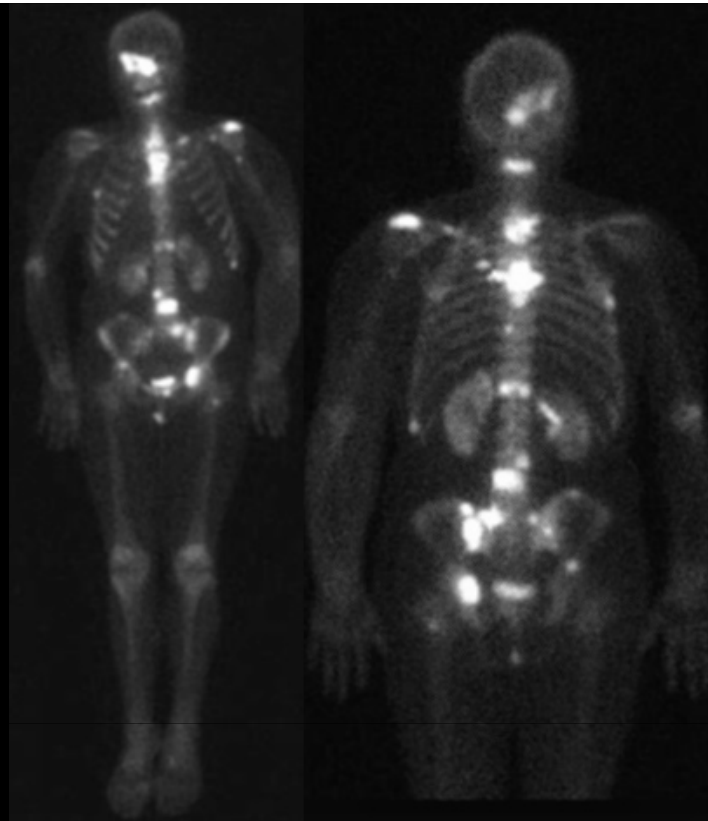




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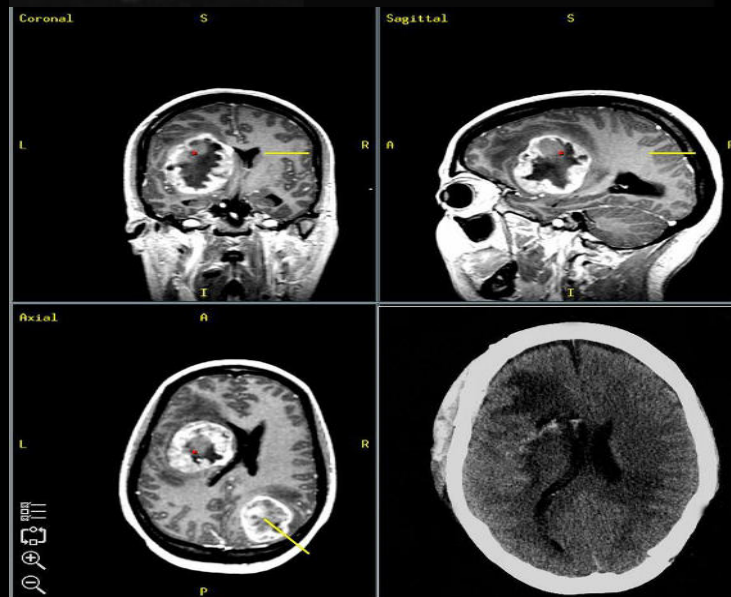


[R]

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FASE CONTRASTOGRAFICA

C40



**DOLORE  
SOMATICO  
NOCICETTIVO**

**DOLORE  
VISCERALE  
NOCICETTIVO**

**DOLORE  
NEUROPATICO**

**BACKGROUND  
PAIN**

**BREAKTHROUGH  
PAIN**

# Breakthrough pain: definition, prevalence and characteristics

Russell K. Portenoy<sup>1</sup> and Neil A. Hagen

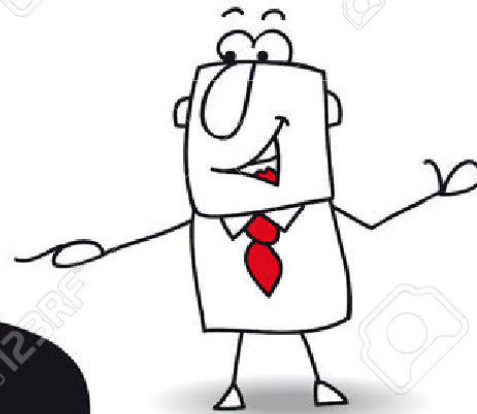
*Felix Sandoz, Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, NY (U.S.A.)*

*(Received 20 June 1989, revision received 1 December 1989, accepted 15 December 1989)*



Six

NINE



6

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RESEARCH ARTICLE

## Consensus and controversies in the definition, assessment, treatment and monitoring of BTcP: results of a Delphi study

J. Boceta<sup>1</sup> · A. De la Torre<sup>2</sup> · D. Samper<sup>3</sup> · M. Farto<sup>4</sup> · R. Sánchez-de la Rosa<sup>4</sup>

*Adv Ther* (2013) 30(3):298–305.  
DOI 10.1007/s12325-013-0013-8

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ORIGINAL RESEARCH

## Beyond the Traditional Definition of Breakthrough Pain: An Observational Study

Antonio Gatti · Maria Gentili · Vittorio Iorno · Massimo Mammucari · Giuseppe Tufaro · Marzia Lazzari · Alessandro Fabrizio Sabato

*Adv Ther* (2014) 31:657–682  
DOI 10.1007/s12325-014-0130-z

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REVIEW

## Breakthrough Cancer Pain (BTcP): a Synthesis of Taxonomy, Pathogenesis, Therapy, and Good Clinical Practice in Adult Patients in Italy

Furio Zucco · Cesare Bonezzi · Diego Fornasari



# Canadian recommendations for the management of breakthrough cancer pain

P. Daeninck MD,\* B. Gagnon MD,† R. Gallagher MD,‡ J.D. Henderson MD,§ Y. Shir MD,||  
C. Zimmermann MD PhD,¶ and B. Lapointe MD\*\*

Support Care Cancer (2016) 24:961–968  
DOI 10.1007/s00520-015-2951-y




REVIEW ARTICLE

## Breakthrough pain and its treatment: critical review and recommendations of IOPS (Italian Oncologic Pain Survey) expert group

Sebastiano Mercadante<sup>1,6</sup> • Paolo Marchetti<sup>2</sup> • Arturo Cuomo<sup>3</sup> •  
Massimo Mammucari<sup>4</sup> • Augusto Caraceni<sup>5</sup> • on behalf of the IOPS MS study Group

## What to Do, and What Not to Do, When Diagnosing and Treating Breakthrough Cancer Pain (BTcP): Expert Opinion

Working Group Nientemale DEI · R. Vellucci<sup>1</sup>  · G. Fanelli<sup>2</sup> · R. Pannuti<sup>3</sup> · C. Peruselli<sup>4</sup> · S. Adamo<sup>5</sup> · G. Alongi<sup>6</sup> · F. Amato<sup>7,8</sup> · L. Consoletti<sup>9</sup> · L. Lamarca<sup>10</sup> · S. Liguori<sup>11</sup> · C. Lo Presti<sup>12</sup> · A. Maione<sup>13</sup> · S. Mamei<sup>14</sup> · F. Marinangeli<sup>15</sup> · S. Marulli<sup>16</sup> · V. Minotti<sup>17</sup> · D. Miotti<sup>18</sup> · L. Montanari<sup>19,20</sup> · G. Moruzzi<sup>21</sup> · S. Palermo<sup>22</sup> · M. Parolini<sup>23</sup> · P. Poli<sup>24</sup> · W. Tirelli<sup>25,26</sup> · A. Valle<sup>27</sup> · P. Romualdi<sup>28</sup>

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**Cochrane  
Library**

Cochrane Database of Systematic Reviews

“It is very unusual to find a Cochrane Review of poor quality and we have never seen it before”, said Ruiz-Garcia et al. on their rapid response to the British Medical Journal [6] about Cochrane’s transparency and the use of fentanyl for the management of breakthrough pain in cancer patients.

Ruiz-Garcia V, Lopez-Briz E. <http://www.bmj.com/content/337/bmj.a3104/rr>. Accessed 21 Mar 2016.

**Pain in cancer**

Zeppetella G, Davies AN.

Opioids for the management of breakthrough pain in cancer patients.

Cochrane Database of Systematic Reviews 2015, Issue 8. Art. No.: CD004311.

DOI: 10.1002/14651858.CD004311.pub4.

[www.cochranelibrary.com](http://www.cochranelibrary.com)

## Comment on ‘What to Do, and What Not to Do, When Diagnosing and Treating Breakthrough Cancer Pain: Expert Opinion’

Raffaele Giusti<sup>1</sup> · Lucilla Verna<sup>2,3</sup> · Daniela Iacono<sup>1</sup> · Agnese Vannini<sup>3</sup> ·  
Corrado Ficarella<sup>2</sup> · Giampiero Porzio<sup>2,3</sup>

Nonetheless, on August 2015, the Cochrane Editorial Unit (CEU) advised that the [Cochrane systematic review](#) on the use of opioids for the management of BTcP in cancer patients [5] [should be withdrawn](#). In fact, according to the feedback provided by different authors on the Cochrane Library web page, the systematic review has turned out to be misleading.

# definizione



# BTcP = definizione

Episodio di  
dolore severo

*esacerbazione transitoria del  
dolore di intensità moderata-  
elevata*

Mercadante S et al (2015) Italian Oncologic Pain Survey (IOPS): a multi-centre Italian study of breakthrough pain performed in different settings. Clin J Pain 31:214-221

Davies A et al (2013) Breakthrough cancer pain: an observational study of 1000 European oncology patients. J Pain Symptom Manag 46:619-628

# BTcP = definizione

in pazienti oncologici  
che ricevono un  
**adeguato** trattamento  
antalgico con farmaci  
oppiacei

*tale da mantenere il dolore  
di base per la maggior  
parte della giornata sotto  
controllo, o di intensità  
lieve.*

Mercadante S et al (2015) Italian Oncologic Pain Survey (IOPS): a multi-centre Italian study of breakthrough pain performed in different settings. Clin J Pain 31:214-221

Davies A et al (2013) Breakthrough cancer pain: an observational study of 1000 European oncology patients. J Pain Symptom Manag 46:619-628



## Consensus:

✓ Terapia con farmaci oppioidi a regime e stabilizzata

¶ Il dolore di base ben controllato per la maggior parte della giornata

Consensus: ✓ Evento  
scatenante solo  
descrittivo

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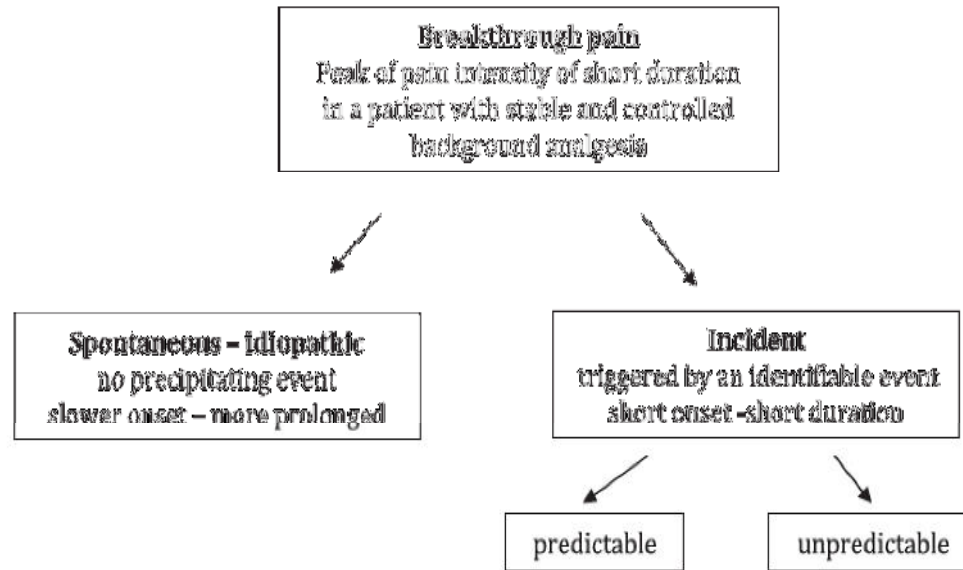


Figure 1. Breakthrough pain and principal subtypes.

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**NO** consensus

✓ Change in pain  
severity

?

Baseline pain rated  $\leq 4$  (NRS 0-10)

Acute pain episode  $> 7$

Mercadante S, Adile C, Torta R, Varetto A, Fulfaro F, Giarratano A, Casuccio A. Meaningful cut-off pain intensity for breakthrough pain changes in advanced cancer patients. *Curr Med Res Opin* 2013;29:93-7.

**NO** consensus

¶ Duration of the  
pain episode

# Disagreement



## End-of-dose failure ... another subtype of BTcp ?

Hwang SS, Chang VT, Kasimis B. Cancer breakthrough pain characteristics and responses to treatment at a VA medical center. *Pain*. 2003;101:55–64.

Haugen DF, Hjemstad MJ, Hagen N, et al. Assessment and classification of cancer breakthrough pain: a systematic literature review. *Pain*. 2010;149:476–82.

Simmonds MA. Management of breakthrough pain due to cancer. *Oncology (Williston Park)*. 1999;13:1103–8 (discussion 1110, 1113–1114).

Davies AN, Dickman A, Reid C, et al. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Eur J Pain*. 2009;13:331–8.

Payne R. Recognition and diagnosis of breakthrough pain. *Pain Med*. 2007;8(Suppl 1):S3–7.

Coluzzi PH. Cancer pain management: newer perspectives on opioids and episodic pain. *Am J Hosp Palliat Care*. 1998;15:13–22.

# Strumenti di diagnosi del BTcP:

## 1. Breakthrough Pain Questionnaire (BPQ)

Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. *Pain*. 1990;41:273–81.

## 2. Alberta Breakthrough Pain Assessment Tool (ABPAT)

Hagen NA, Stiles C, Nekolaichuk C, et al. The Alberta Breakthrough Pain Assessment Tool for cancer patients: a validation study using a delphi process and patient think-aloud interviews. *J Pain Symptom Manage*. 2008;35:136–52.

## 3. Mercadante simplified version ABPAT

Mercadante S, Amadori D, Apolone G, et al. Raccomandazioni per la gestione del Breakthrough cancer Pain (BTcP). *Riv Ital Cure Palliat*. 2010;10:17–23.

## 4. Breakthrough pain Assessment Tool (BAT)

Webber K, Davies AN, Zeppetella G, Cowie MR. Development and validation of the breakthrough pain assessment tool (BAT) in cancer patients. *J Pain Symptom Manage*. 2014;48(4):619–31.

Obiettivo terapeutico ?



# OBIETTIVO:

**3 – 4** episodi di BTcP die

se il dolore  
durante il resto del giorno  
è controllato

Mercadante S, Marchetti P, Cuomo A, Mammucari M, Caraceni A. IOPS MS study Group. Breakthrough pain and its treatment: critical review and recommendations of IOPS (Italian Oncologic Pain Survey) expert group. *Support Care Cancer* 2016;24:961–8.

Davies A, Buchanan A, Zeppetella G, Porta-Sales J, Likar R, Weismayr W, Slama O, Korhonen T, Filbet M, Poulain P, Mystakidou K, Ardavanis A, O'Brien T, Wilkinson P, Caraceni A, Zucco F, Zu Mond W, Andersen S, Damkier A, Vejlgard T, Nauck F, Radbruch L, Sjölund KF, Stenberg M. Breakthrough cancer pain: an observational study of 1000 European oncology patients. *J Pain Symptom Manage* 2013;46:619–28.

Portenoy RK, Payne D, Jacobson P. Breakthrough pain: characteristics and impact in patients with cancer pain. *PAIN* 1999;81:129–34.

Mercadante S. Breakthrough pain in cancer patients: prevalence, mechanisms and treatment options. *Curr Opin Anaesthesiol* 2015;28:559–64.

Mercadante S, Valle A, Porzio G, Aielli F, Adile C, Ficorella C, Raineri M, Giarratano A, Casuccio A. Relationship between background cancer pain, breakthrough pain, and analgesic treatment: a preliminary study for a better interpretation of epidemiological and clinical studies. *Curr Med Res Opin* 2013;29:667–71.

Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Eur J Pain* 2009;13:331–8.



Ma cosa dice il paziente ?

... proviamo a chiederglielo..



The acceptable number of BTcP  
episodes may be

**BETTER defined**

in terms of

**patient preference**

than a maximum frequency.

Patient preference  
in terms of

**ACTIVITY**

is a KEY influence  
on treatment decisions.

# BTcP prevedibile:

**PREVENIRE  
IL DOLORE:**

**pre-emptive  
analgesia**

Elevata compliance  
del paziente

Elevata capacità di  
comprensione del  
timing  
di assunzione del  
farmaco rescue  
in base all'onset-time  
del farmaco

BTcP

- prevedibile
- inizio graduale**
- durata > 60 min**

Onset time ...?

Durata d'azione anche  
lunga...

? morfina orale ...

BTcP

- poco prevedibile**
- inizio rapido**
- durata < 60 min**

Onset time il più breve  
possibile

Durata d'azione BREVE

? FNT transmucoso

Estrema eterogeneità di BTcP



tra i pazienti



Ma  
anche  
nello  
stesso  
paziente



...cambiano le preferenze

...e le necessità



**lo stato della malattia  
condiziona  
il TARGET della terapia**



**DRUGS...**



BTcP

Farmaco “al bisogno”

**OPPIACEO**



**OPIOID** drug

a formulation with a

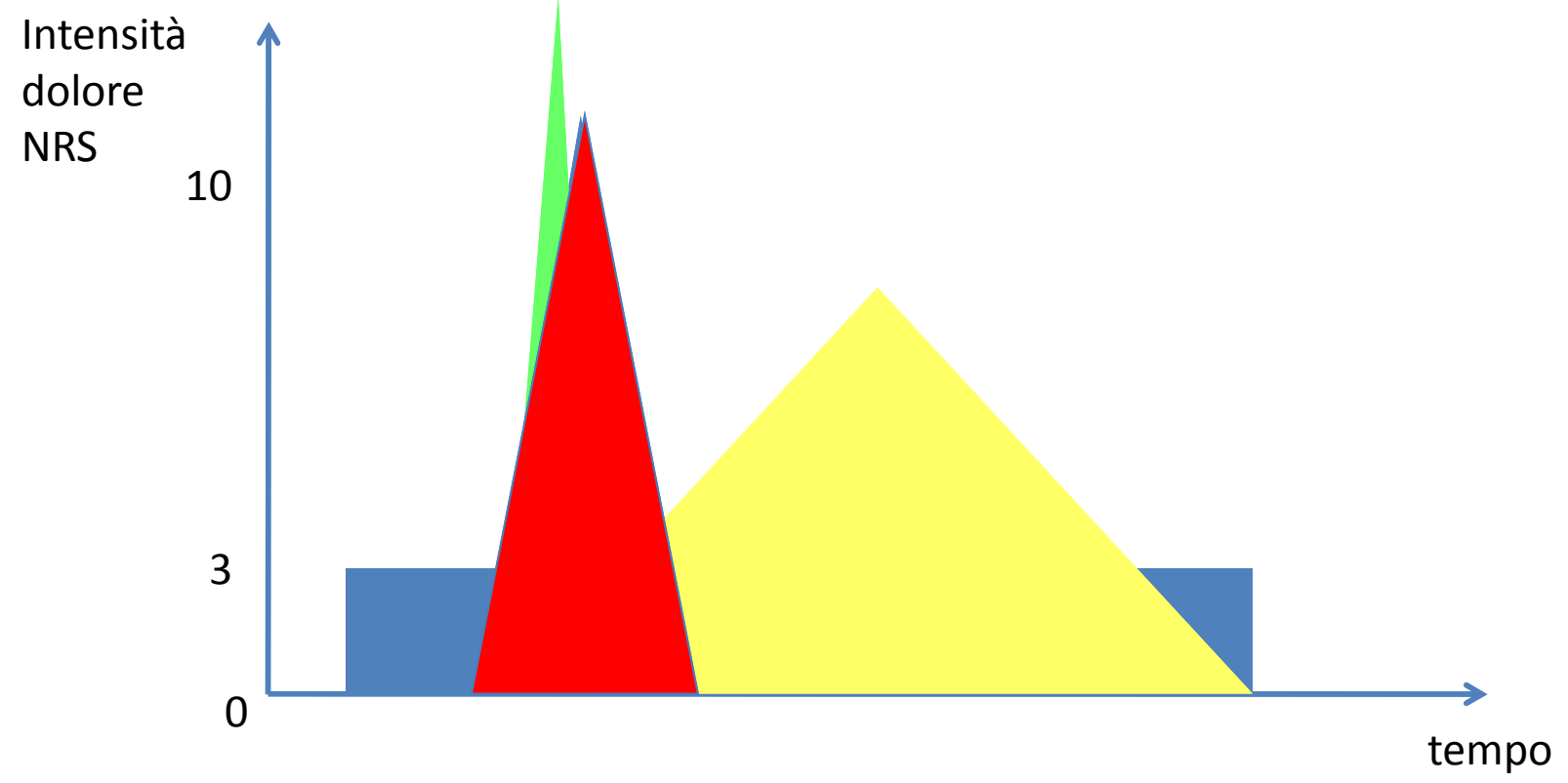
**TIME ACTION  
RELATIONSHIP**

**more consistent  
with the BTcP**

**1. identifica le caratteristiche  
temporali di QUEL BTcP**

**2. scegli il farmaco  
farmacocineticamente  
più adatto**

[conc efficace]



	analgesic onset (min)	availability	T max	dwell time
Morfina orale	30-45	30	120-180	NA
oral transmucosal fentanyl citrate OFTC	15-30	50	40	15
Fentanyl Buccal Tablet FBT	15	65	45	15
Sublingual fentanyl SLF	10-15	70	40	2
Fentanyl citrate sublingual	6	70		NA
Fentanyl buccal soluble film FBSF	15	65	60	2-5
Intranasal fentanyl spray INFS	5-10	80-90	20	NA
Fentanylpectin nasal spray FPNS	5-10	70	20	NA



# Quale formulazione scegliere ?

## Dipende...

Coluzzi P, Schwartzberg L, Conroy J, Charapata S, Gay M, Busch MA, Chavez J, Ashley J, Lebo D, McCracken M, Portenoy RK. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulphate immediate release (MSIR). *PAIN* 2001;91:123-30.

Davies A, Sitte T, Elsner F, Reale C, Espinosa J, Brooks D, Fallon M. Consistency of efficacy, patients acceptability, and nasal tolerability of fentanyl pectin nasal spray compared with immediate-release morphine sulphate in breakthrough cancer pain. *J Pain Symptom Manage* 2011;41: 358-66.

Corli O, Roberto A. Pharmacological and clinical differences among transmucosal fentanyl formulations for the treatment of breakthrough cancer pain: a review article. *Minerva Anestesiol* 2014;80:1123-34.

Mercadante S, Prestia G, Adile C, Casuccio A. Intranasal fentanyl versus fentanyl pectin nasal spray for the management of breakthrough cancer pain in doses proportional to basal opioid regimen. *J Pain* 2014;15: 602-7.

Mercadante S, Radbruck L, Davies A, Poulain P, Sitte T, Perkins P, Colberg T, Camba MA. A comparison of intranasal fentanyl spray with oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain: an open-label, randomized, crossover trial. *Curr Med Res Opin* 2009;25:2805-15.

Mercadante S, Caruselli A, Meli MR, Bellavia G, Tuttolomondo A, Casuccio A. Patients' acceptability of different fentanyl products for breakthrough cancer pain. *Clin Oncol (R Coll Radiol)* 2014;26:806.



numerosi RCT hanno concluso che  
le formulazioni di **FNT**  
sono migliori rispetto alla  
**morfina orale**  
per il trattamento della  
**maggior parte** degli episodi di BTcP

Ma nonostante ciò  
le linee guida del National  
Institute for Clinical Excellence  
NICE 2016 indicano  
**la MORFINA PER OS farmaco di  
PRIMA SCELTA**  
per il trattamento del BTcP

# Che dosaggio....?



# Che dose utilizzare ?

**A**

Iniziare con la dose più bassa ...

TITOLARE il farmaco...

Fino al raggiungimento della dose efficace

**B**

Dose proporzionale alla  
quantità di oppiaceo /die

# Relazione tra dose efficace e dose giornaliera

...NO

Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Eur J Pain* 2009;13:331-8.

Mercadante S. Rapid onset opioids for breakthrough pain: titrating or not titrating, this is the question. *Eur J Pain* 2011(suppl 2):443-8.

Mercadante S. The use of rapid onset opioids for breakthrough cancer pain: the challenge of its dosing. *Crit Rev Oncol Hematol* 2011b;80:460-5.

Mercadante S. Breakthrough pain: on the road again. *Eur J Pain* 2009;13:329-3.

Hagen NA, Fisher K, Victorino C, Farrar JT. A titration strategy is needed to manage breakthrough cancer pain effectively: observations from data pooled from three clinical trials. *J Palliat Med* 2007;10:47-55.

Mercadante S, Caruselli A, Meli MR, Bellavia G, Tuttolomondo A, Casuccio A. Patients' acceptability of different fentanyl products for breakthrough cancer pain. *Clin Oncol (R Coll Radiol)* 2014;26:806.

# A Iniziare con la dose più bassa TITOLARE fino alla dose efficace

->> sicurezza

- Prolungato periodo di dolore non controllato
- Ripetute somministrazioni
- Scoraggiamento, delusione e rifiuto del farmaco

# B Dose direttamente proporzionale alla dose giornaliera di oppiaceo

<< sicurezza

>> aggressivo

>> effetti collaterali:  
sopore e vomito

Hagen NA, Fisher K, Victorino C, Farrar JT. A titration strategy is needed to manage breakthrough cancer pain effectively: observations from data pooled from three clinical trials. *J Palliat Med* 2007;10:47–55.

Mercadante S, Gatti A, Porzio G, Lo Presti C, Aielli F, Adile C, Casuccio A. Dosing fentanyl buccal tablet for breakthrough cancer pain: dose titration versus proportional doses. *Curr Med Res Opin* 2012;28:963–8.

Mercadante S, Adile C, Cuomo A, Aielli F, Cortegiani A, Casuccio A, Porzio GP. Fentanyl buccal tablet versus oral morphine in doses proportional to basal opioid regimen for the management breakthrough pain: a randomized, cross-over, comparison study. *J Pain Symptom Manage* 2015;50:579–8.

Mercadante S, Prestia G, Casuccio A. The use of sublingual fentanyl for breakthrough pain by using doses proportional to opioid basal regimen. *Curr Med Res Opin* 2014;29:1527–32.

Mercadante S, Villari P, Ferrera P, Mangione S, Casuccio A. The use of opioids for breakthrough pain in acute palliative care unit by using doses proportional to opioid basal regimen. *Clin J Pain* 2010;26:306–9.

Mercadante S, Villari P, Ferrera P, Casuccio A, Mangione S, Intravaia G. Transmucosal fentanyl vs intravenous morphine in doses proportional to basal opioid regimen for episodic-breakthrough pain. *Br J Cancer* 2007; 96:1828–33.

Mercadante S, Ferrera P, Adile C, Casuccio A. Fentanyl buccal tablets for breakthrough pain in highly tolerant cancer patients: preliminary data on the proportionality between breakthrough pain dose and background dose. *J Pain Symptom Manage* 2011;42:464–9.

**Greater**  
**FLEXIBILITY**  
**in the selection of**  
**the STARTING**  
**DOSE**



**Pazienti che assumono  
ALTE dosi di oppiaceo**

episodi di BTcP  
molto frequenti  
molto “stressanti”



**Preferisci dose  
PROPORZIONALE  
alla dose die (1/6)**

**Pazienti che assumono  
BASSE dosi di oppiaceo**

Pazienti fragili, molto  
compromessi  
Numerose comorbidità



**Preferisci la  
TITOLAZIONE**

**Orally  
Short  
acting  
opioid**



**Rapid  
Onset  
Opioid**



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Andrea Bacci: Lamentation on Christ's Corpse (1498)



Μέτρον  
δοῦναι ἐπὶ πᾶσιν  
καριστόν.

Χρυσὰ ἔπη – Pitagora

