癌症疼痛新認識

- 癌症疼痛是常見症狀之一，癌症評核已將癌症疼痛控制列為重點，於是住院癌症病人都要評估，稱為第五生命徵象。
- 雖然現今文獻呈現癌症疼痛控制可以達80~90%，但仍然超過一半癌症病人遭受疼痛困擾。
- 醫療人員繼續教育與民眾破除迷思是癌症疼痛控制的關鍵

正確的癌症疼痛控制觀念

- 了解疼痛控制對癌症病人的影響
  - 免疫系統與存活期的影響
  - 能量消耗
  - 社心靈影響
  - 醫療自主權
  - 麻醉疼痛用藥調整

疼痛對癌症病人不止是影響生活品質，還會損害免疫系統與減少存活期。

Baseline quali
a meta-analy
clinical trials

Chantal Quinten, Corneel Coens,
Andrew Bottomley, on behalf of

Summary

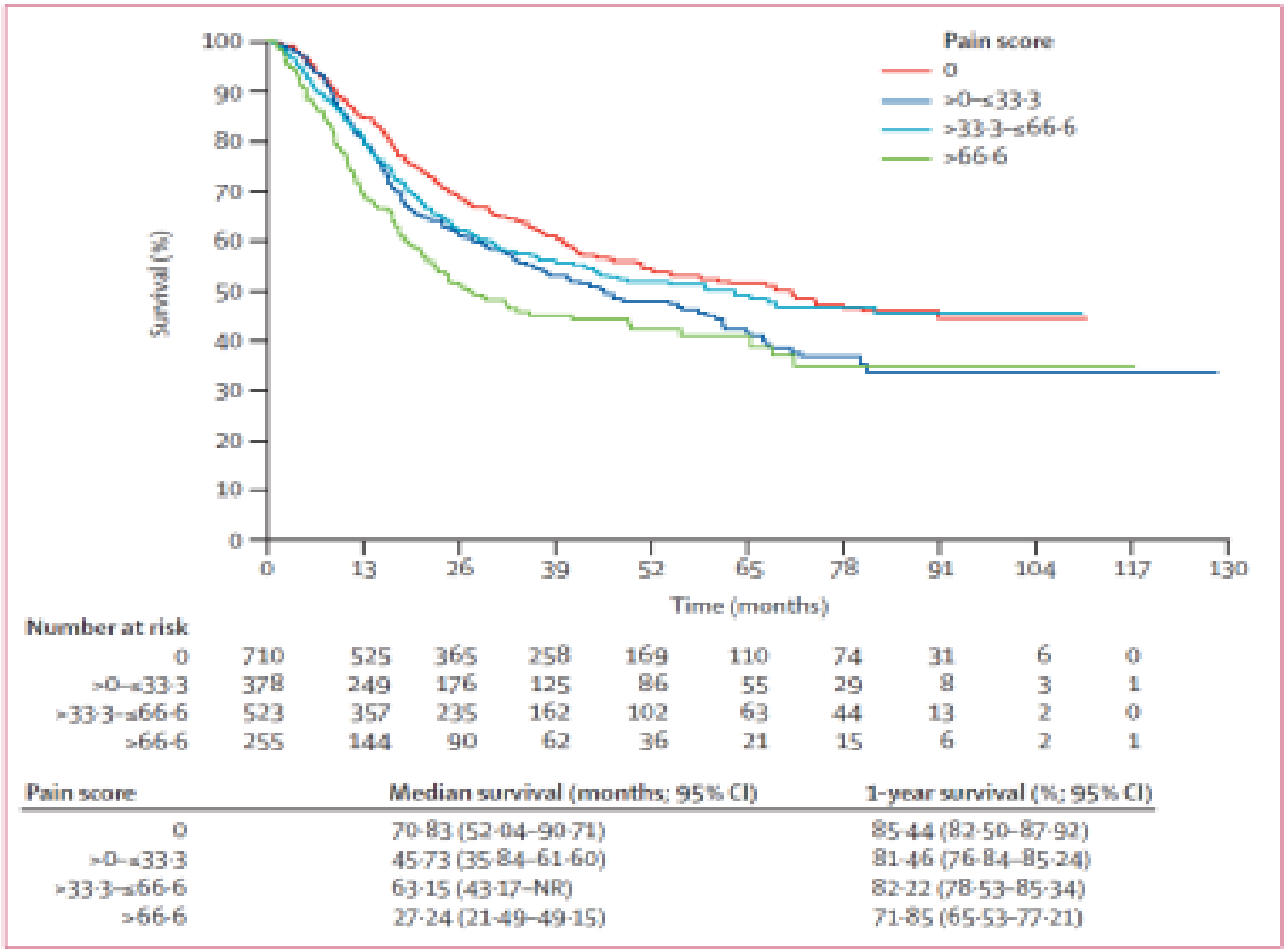
Background Although ind
factor for survival, contrac
We examined whether HF
different disease sites.

Methods We selected 30 r
Cancer (EORTC) started
cancer sites. Patients were
core quality of life questio
(men *vs* women), and clin
cancer site. We assessed
scales with Cox proportio

Findings In the stratified
parameters of physical f
p<0·0001), and appetite l
the parameters age (1·17
1·49–1·93; p<0·0001), bu
HRQOL parameters and
survival by 6% relative to
predicted and observed
sociodemographic, clinica

Interpretation The result
sociodemographic and cli
with cancer.

Funding Merck KGaA, EO



Number at risk

0	710	525	365	258	169	110	74	31	6	0
>0–≤33·3	378	249	176	125	86	55	29	8	3	1
>33·3–≤66·6	523	357	235	162	102	63	44	13	2	0
>66·6	255	144	90	62	36	21	15	6	2	1

Pain score	Median survival (months; 95% CI)	1-year survival (%; 95% CI)
0	70·83 (52·04–90·71)	85·44 (82·50–87·92)
>0–≤33·3	45·73 (35·84–61·60)	81·46 (76·84–85·24)
>33·3–≤66·6	63·15 (43·17–NR)	82·22 (78·53–85·34)
>66·6	27·24 (21·49–49·15)	71·85 (65·53–77·21)

Figure 2: **Overall survival curves stratified by QLQ-C30 pain score**
QLQ-C30=the European Organisation for Research and Treatment of Cancer quality-of-life core questionnaire.
NR=not reached.

無意義的忍痛是消耗自身能量

- **Cancer pain can be reduced, so that you can enjoy your normal routines and sleep better.**

  好的疼痛控制是可以維持身體活動力和改善睡眠

- **It may help to talk with a palliative care or pain specialist. 照會安寧團隊有幫助**

癌症疼痛控制
對病人社心靈的影響

- 生活品質差
- 癌症治療成效下降
- 容易憂鬱
- 容易想到自殺
- 負面的生命教育

不好的疼痛控制對癌症病人是醫療自主權的迫害

- 讓癌症病人決定個人化疼痛控制計畫
  - 希望疼痛控制程度（白天與晚上）
  - 選擇平時疼痛控制方式與藥劑
    （方式有口服、貼片、靜脈、皮下或其他）
    （藥劑有嗎啡 或 NSAIDs 等）
  - 選擇突發性疼痛用藥自主權
    （由病人主觀決定要不要）

了解一般人對嗎啡的害怕
Opioid phobia

- 毒品?
- 上癮?
- 以後沒有止痛藥用?
- 表示死亡接近了?
- 宗教上或信仰上禁忌?

嗎啡會不會產生耐受性?

- 可能，劑量會隨治療時間增加
- 依文獻報告，可知劑量增加並非全因耐受性，也和病情變化有密切的關係。

幫助癌症病人疼痛控制五步驟

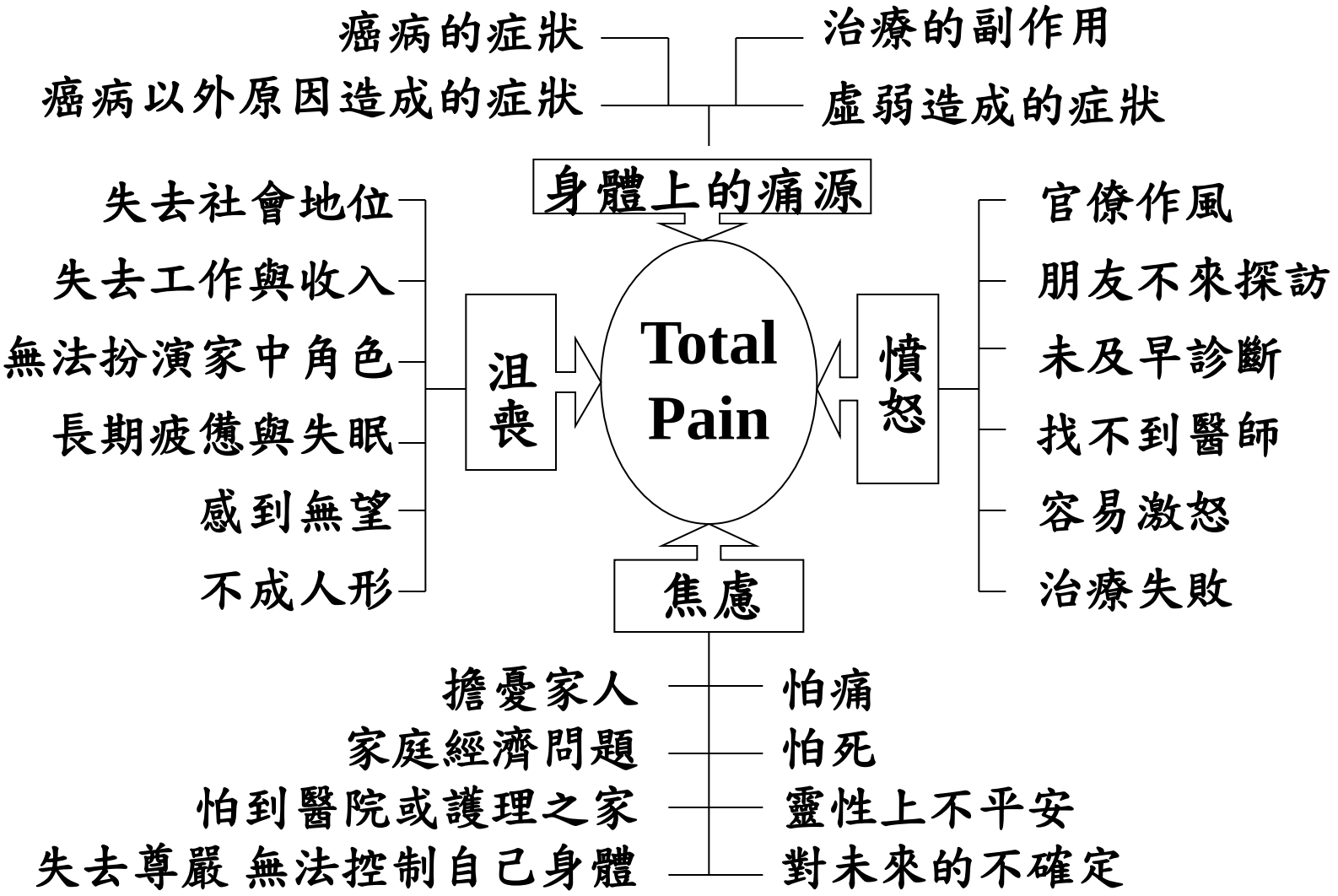
1. 疼痛評估
2. 用藥了解
3. 對疼痛議題的擔心與迷思
4. 輔助療法、舒適護理與翻身擺位
5. 社心靈協助

癌症病人疼痛表達差異大！

- **Pain is an unpleasant sensory（感覺）and emotional（情緒） experience associated with actual or potential tissue damage.**
  Association for the Study of Pain, IASP 19

- **Patient's description of pain is from "hurt" to " discomfort"（很痛到不舒服）.**

疼痛的全貌（Total Pain）



讓癌症病人或家屬描述疼痛

- 那裡痛？ 痛多久了？
- 怎麼痛的？(刺痛或悶痛或抽痛…)
- 一直痛還是一陣一陣的痛？
- 痛的時候你怎麼辦？（吃藥或…）效果如何？(包括吃那些藥的效果)
- 告訴病人要勇於和醫療人員討論您的疼痛情形，因為醫療人員要靠您表達對疼痛的感受來調藥與給予建議。

疼痛原因分辨

- 癌症本身疾病造成(依據疼痛部位與病史，必要時影像檢查資料佐證)
- 姿勢不良或局部血液循環不佳
- 之前癌症治療引起：開刀、放射線治療、化學藥物治療等
- 目前用藥副作用：便秘、黏膜潰瘍等
- 注意癌症骨轉移可能引起骨折
- 非癌症引起，如關節炎、痛風、十二指腸潰瘍、沮喪或焦慮等。

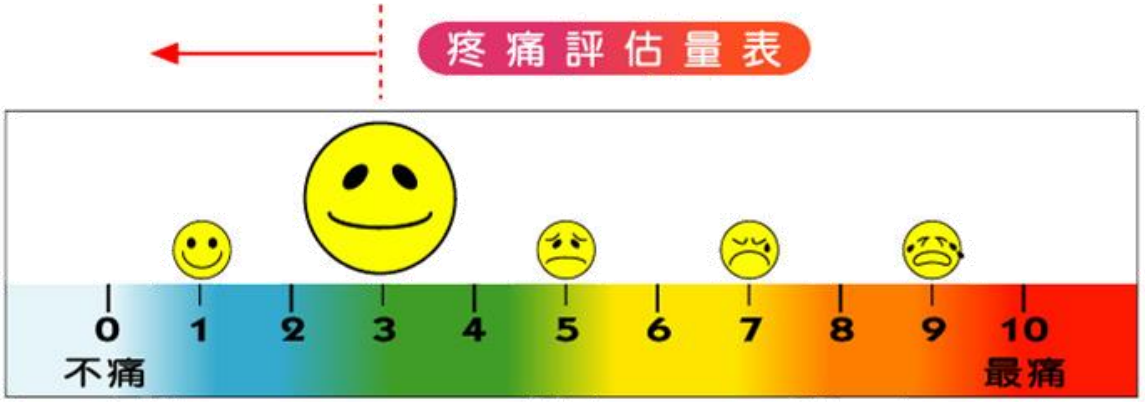
麻醉疼痛用藥調整

- 醫師應以簡單與長效藥物優先
- 配合短效藥物來處置突發性疼痛
- 面對長期使用中重度疼痛麻醉藥物病人，要適時轉換藥物種類來避免麻醉藥物之耐受性問題。
- 注意藥物遵從性

癌症疼痛藥物處置原則

1. 常規的止痛藥多數根據[世界衛生組織(World Health Organization)的依階段給藥、口服優先、按時給藥三原則]。

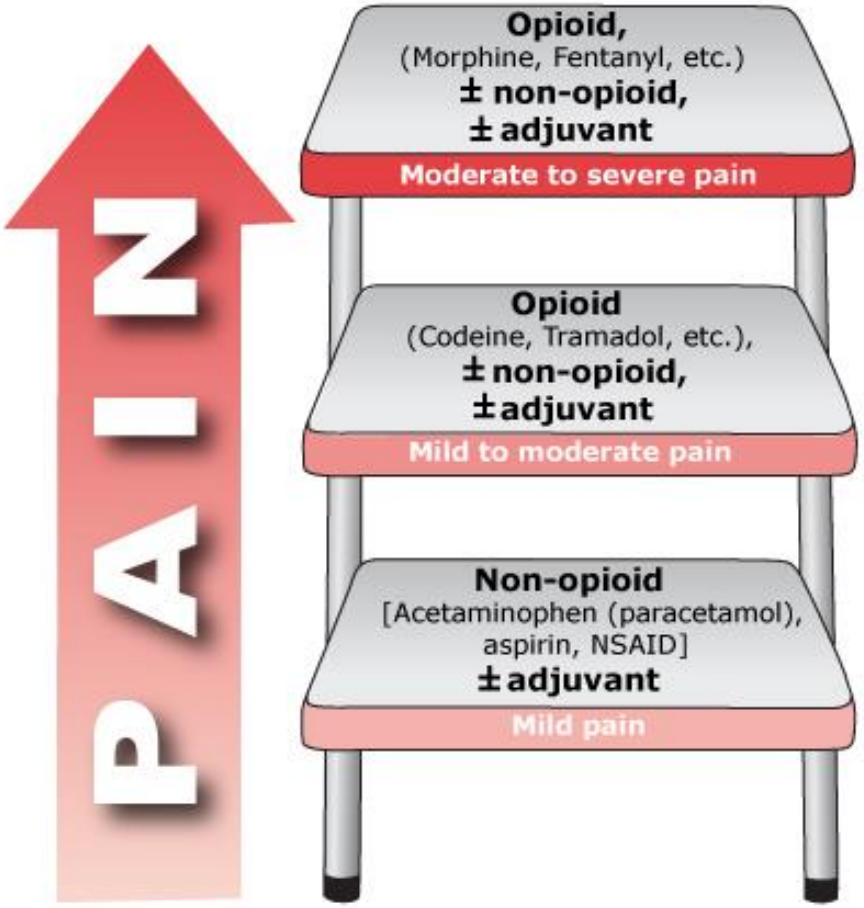
2. 困難案例時可根據詳細的疼痛評估和病人所經歷的疼痛特性，來選擇合適的治療藥物。



WHO has developed a three-step "ladder" for cancer pain relief. <1996>

- By the ladder
  依階段給藥
- By the mouth
  口服優先
- By the clock
  照時給藥

口服與貼片



National Comprehensive Cancer Network®

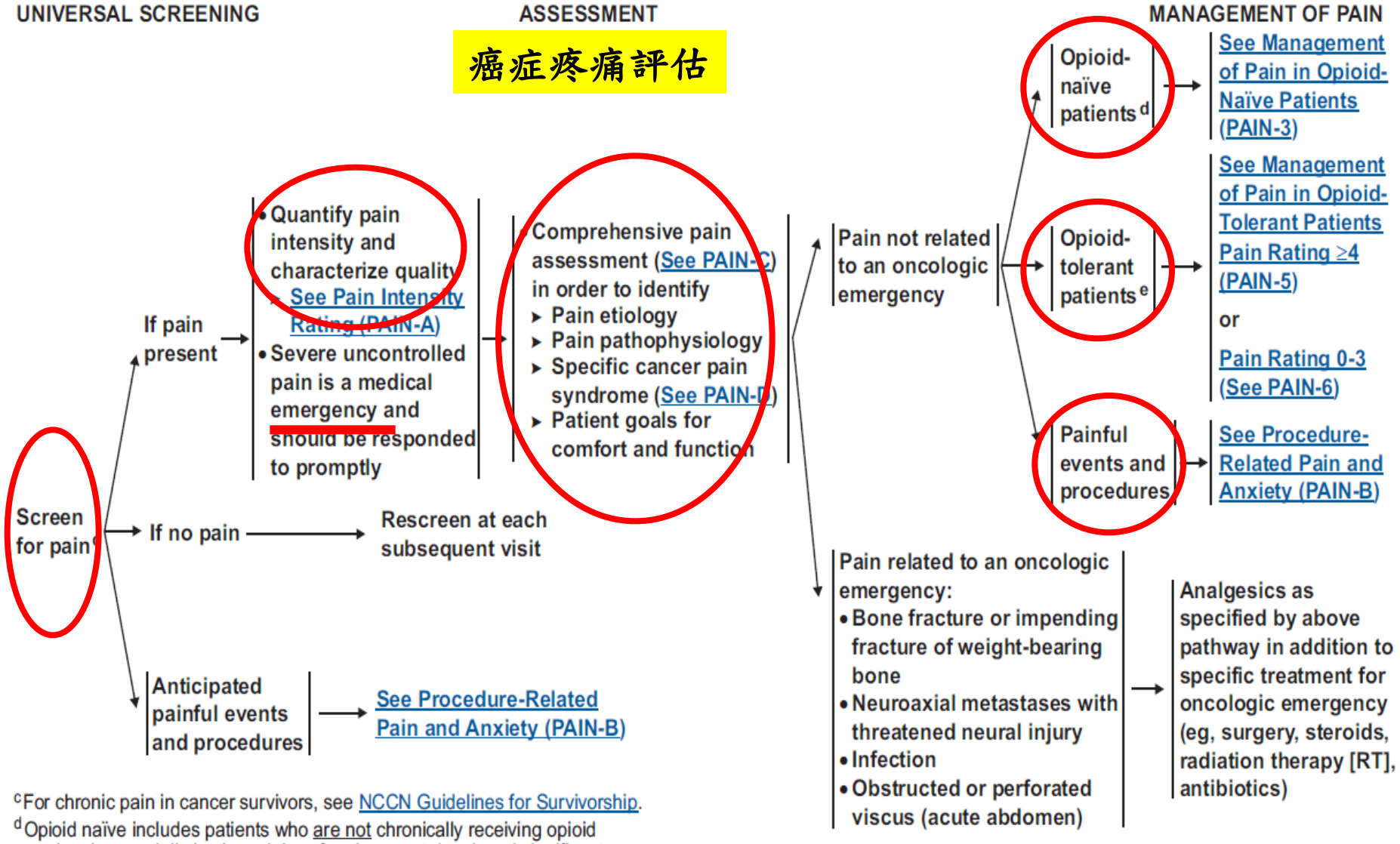
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Adult Cancer Pain

Version 2.2014

NCCN.org

Continue



[c] For chronic pain in cancer survivors, see NCCN Guidelines for Survivorship.

[d] Opioid naïve includes patients who are not chronically receiving opioid analgesic on a daily basis and therefore have not developed significant tolerance. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

[e] Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

從未用過麻醉性止痛藥之癌症病人

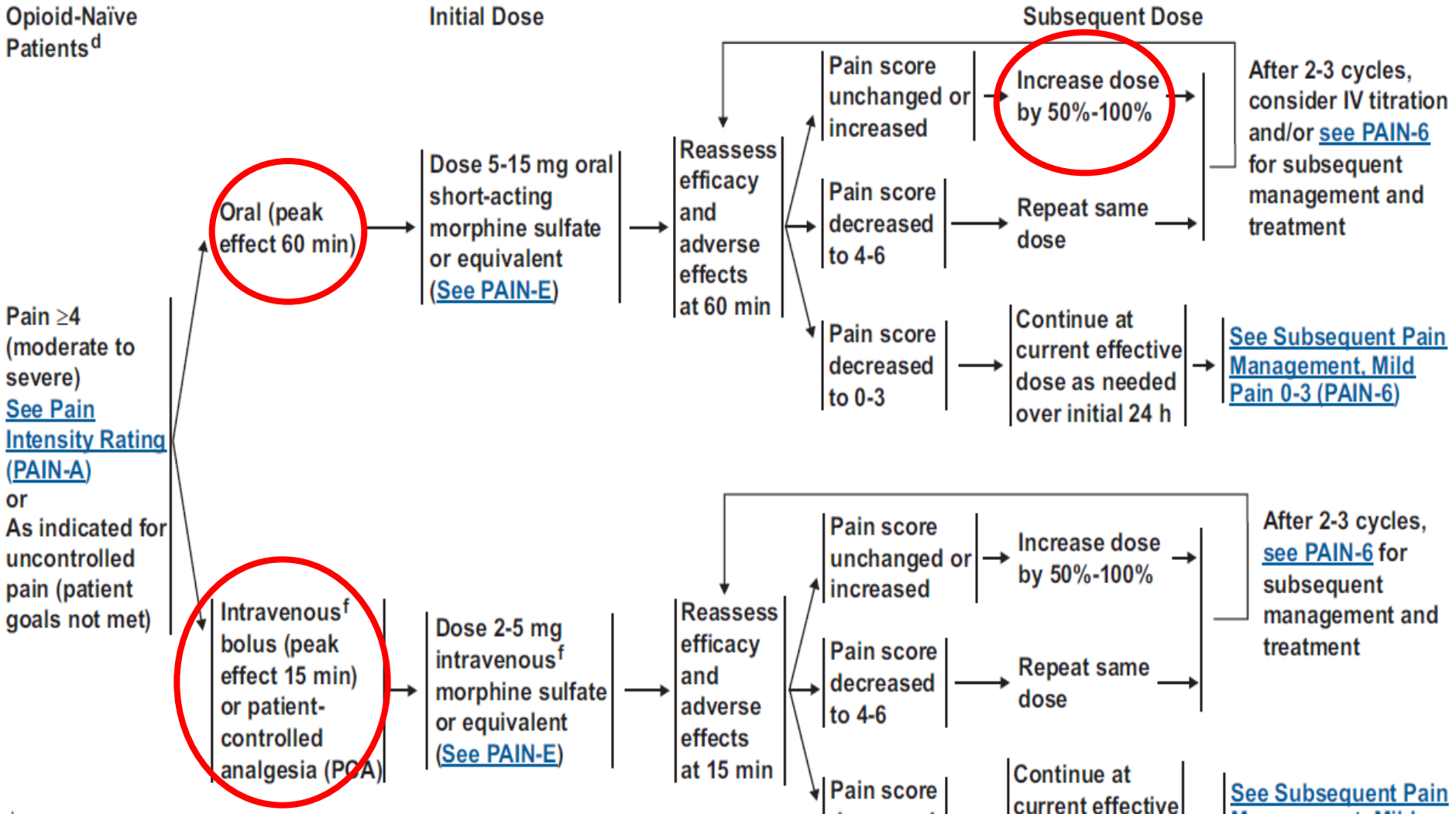
PAIN INTENSITY See Pain Intensity Rating (PAIN-A)	MANAGEMENT OF PAIN IN OPIOID-NAÏVE PATIENTS[d]		
For *ALL* levels of pain	• For opioid principles, prescribing, titration, and maintenance, see PAIN-E • Anticipate and treat analgesic adverse effects (See PAIN-F) • Consider adding adjuvant analgesics (See PAIN-G) for specific pain syndrome (See PAIN-D) • Provide psychosocial support (See PAIN-H) • Provide patient and family/caregiver education (See PAIN-I) • Optimize integrative interventions (See PAIN-J) • Consider nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen (See PAIN-K) • For acute pain crisis, consider hospital admission to achieve patient-specific pain goals	Reevaluate pain at each contact and as needed to meet patient-specific goals for comfort, function, and safety	See Ongoing Care (PAIN-7)
Severe Pain 7-10	• See management for *all* levels of pain above AND • Rapidly titrate short-acting opioid, see PAIN-4 for initiating short-acting opioids ▸ Begin bowel regimen (See PAIN-F)		
Moderate Pain 4-6	• See management for *all* levels of pain above AND • Titrate short-acting opioid, see PAIN-4 for initiating short-acting opioids ▸ Begin bowel regimen (See PAIN-F)		
Mild Pain 1-3	• See management for *all* levels of pain above AND • Consider titrating short-acting opioid (See PAIN-E) ▸ Begin bowel regimen (See PAIN-F)	Reevaluate pain at each contact and as needed to meet patient-specific goals for comfort, function, and safety	See Ongoing Care (PAIN-7)

[d]Opioid naïve includes patients who are not chronically receiving opioid analgesic on a daily basis and therefore have not developed significant tolerance. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

INITIATING SHORT-ACTING OPIOIDS IN OPIOID-NAÏVE PATIENTS[d]

從未用過麻醉性止痛藥之癌症病人

Monitor for acute and chronic adverse effects. (See Management of



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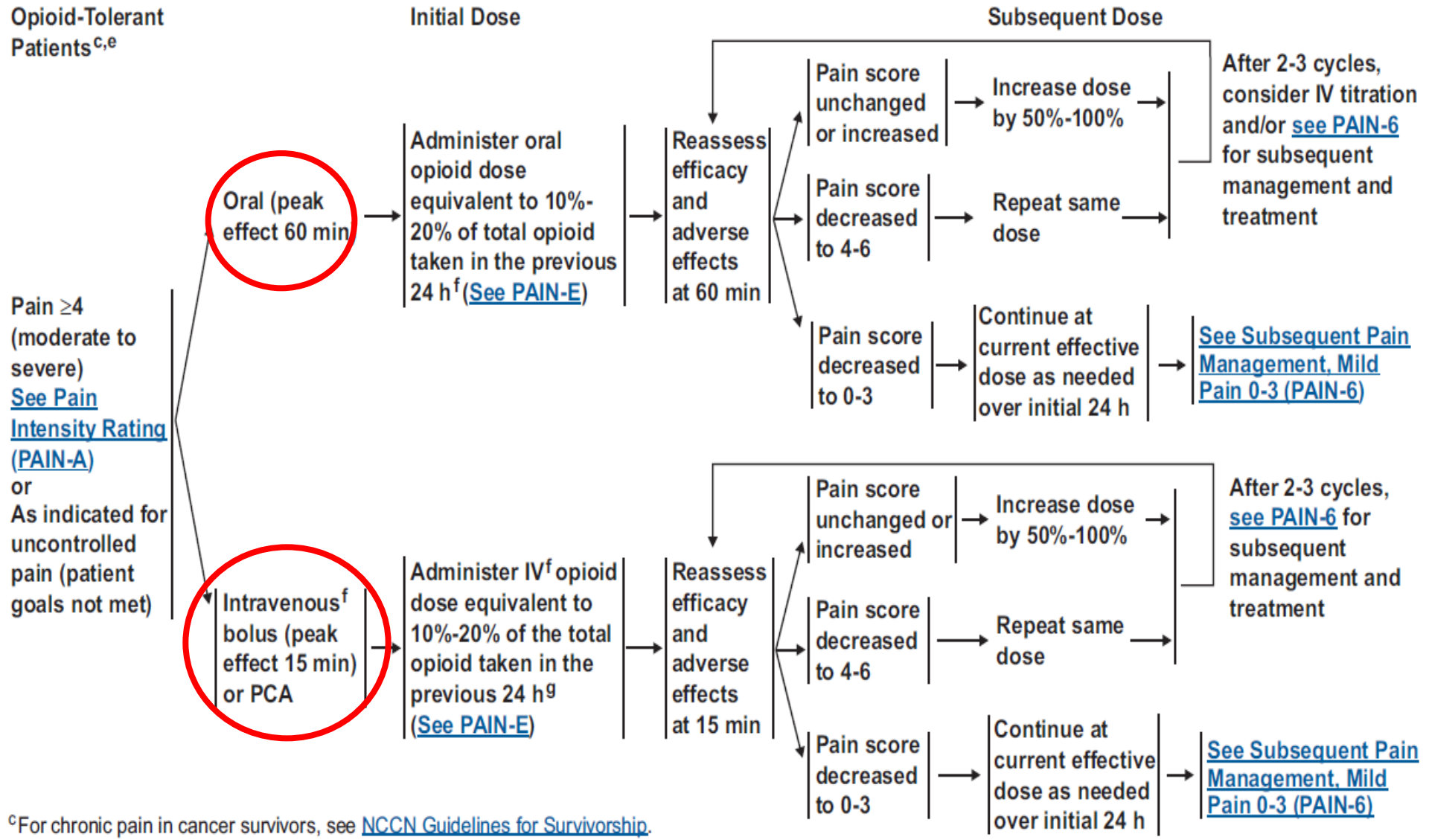
[f]Subcutaneous can be substituted for intravenous; however, peak effect subcutaneously is usually 30 min.

MANAGEMENT OF PAIN IN OPIOID-TOLERANT PATIENTS[e]

Monitor for acute and chronic adverse effects. (See Mana

使用過麻醉性止痛藥之癌症病人



[c] For chronic pain in cancer survivors, see NCCN Guidelines for Survivorship.

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[f] Subcutaneous can be substituted for intravenous; however, peak effect subcutaneously is usually 30 min.

[g] Not including transmucosal fentanyl dose.

COMPREHENSIVE PAIN ASSESSMENT

- Patient's self report of pain is the standard of care. If the patient is unable to verbally report pain, an alternative method to obtain pain rating and response should be utilized (See PAIN-A 2 of 2).
- The goal of the comprehensive pain assessment is to find the cause of the pain and identify optimal therapies. Individualized treatment of the pain is based on the characteristics, cause of pain, the patient's clinical condition, and patient-centered goals of care.
- The etiology and pathophysiology of the pain should be investigated, including medical history (including psychosocial factors), physical exam, laboratory tests, and imaging studies.
  - Etiology factors may include direct involvement of cancer itself, cancer the coincidental or noncancer pain (eg, arthritis).
  - Pathophysiology factors may include nociceptive, neuropathic, visceral, e

完整癌症疼痛評估：
是以癌症病人認為的疼痛
與對疼痛處置喜好為重點

- Pain experience
  - Location, referral pattern, radiation of pain(s)
  - Intensity See Pain Intensity Rating (PAIN-A)
    - Last 24 hours and current pain
    - At rest and with movement
  - Interference with activities
    See Impact of Pain Measurement (PAIN-C 3 of 3)
    - General activity, mood, walking ability, work ability, relationship with others, sleep, appetite, and enjoyment of life
  - Timing: onset, duration, course, persistent, or intermittent
  - Description or quality
    - Aching, stabbing, throbbing, or pressure often associated with somatic pain in skin, muscle, and bone
    - Gnawing, cramping, aching, or sharp pain often associated with visceral pain in organs or viscera
    - Burning, tingling, shooting, or electric/shocking pain often associated with neuropathic pain caused by nerve damage
  - Aggravating and alleviating factors
  - Other current symptoms; symptom clusters
  - Current pain management plan, both pharmacologic and non-pharmacologic. If medications are used, determine:
    - What medication(s), prescription and/or over the counter?
    - Dose, route of administration, frequency?
    - Current prescriber?

Pain e

  - Response to current therapy
    - Pain relief
    - Patient adherence to medication plan
    - Medication adverse effects such as constipation, sedation, cognitive slowing, nausea, and others
  - Breakthrough pain is episodic pain not controlled with existing pain regimen; see breakthrough pain on PAIN-E 3 of 10.
  - Prior pain therapies
    - Reason for use, length of use, response, reasons for discontinuing, and adverse effects encountered
  - Special issues relating to pain
    - Meaning and consequences of pain for patient and family/caregiver
    - Patient and family/caregiver knowledge and beliefs surrounding pain and pain medications
    - Cultural beliefs toward pain, pain expression, and treatment
    - Spiritual, religious considerations, and existential suffering
    - Patient goals and expectations regarding pain management
    - Assess for use of alternative or complementary therapies and screen for potential adverse interactions or effects

Continued on PAIN-C 2 of 3

癌症疼痛非藥物處置

- 舒適護理：翻身、擺位、…
- 輕柔按摩或淋巴按摩
- 適當熱敷或冷敷
- 經皮神經電刺激器(TENS)
- 芳香療法
- 陪伴
- 冥想療法
- 適切宗教幫助
- 藝術治療、音樂治療等

NCCN ADULT CANCER PAIN GUIDELINES

Table 2 Recommended Dose Conversion from Morphine to Transdermal Fentanyl

Transdermal Fentanyl	Morphine	
	IV/SubQ *	Oral
12 mcg/h	10 mg/d	30 mg/d
25 mcg/h	20 mg/d	60 mg/d
50 mcg/h	40 mg/d	120 mg/d
75 mcg/h	60 mg/d	180 mg/d
100 mcg/h	80 mg/d	240 mg/d

臺中榮總緩和醫療中心

Fentanyl TTS 25 ug/hr q3d

=口服 Morphine 10mg tab q4h

=口服 Morphine 30mg tab q12h

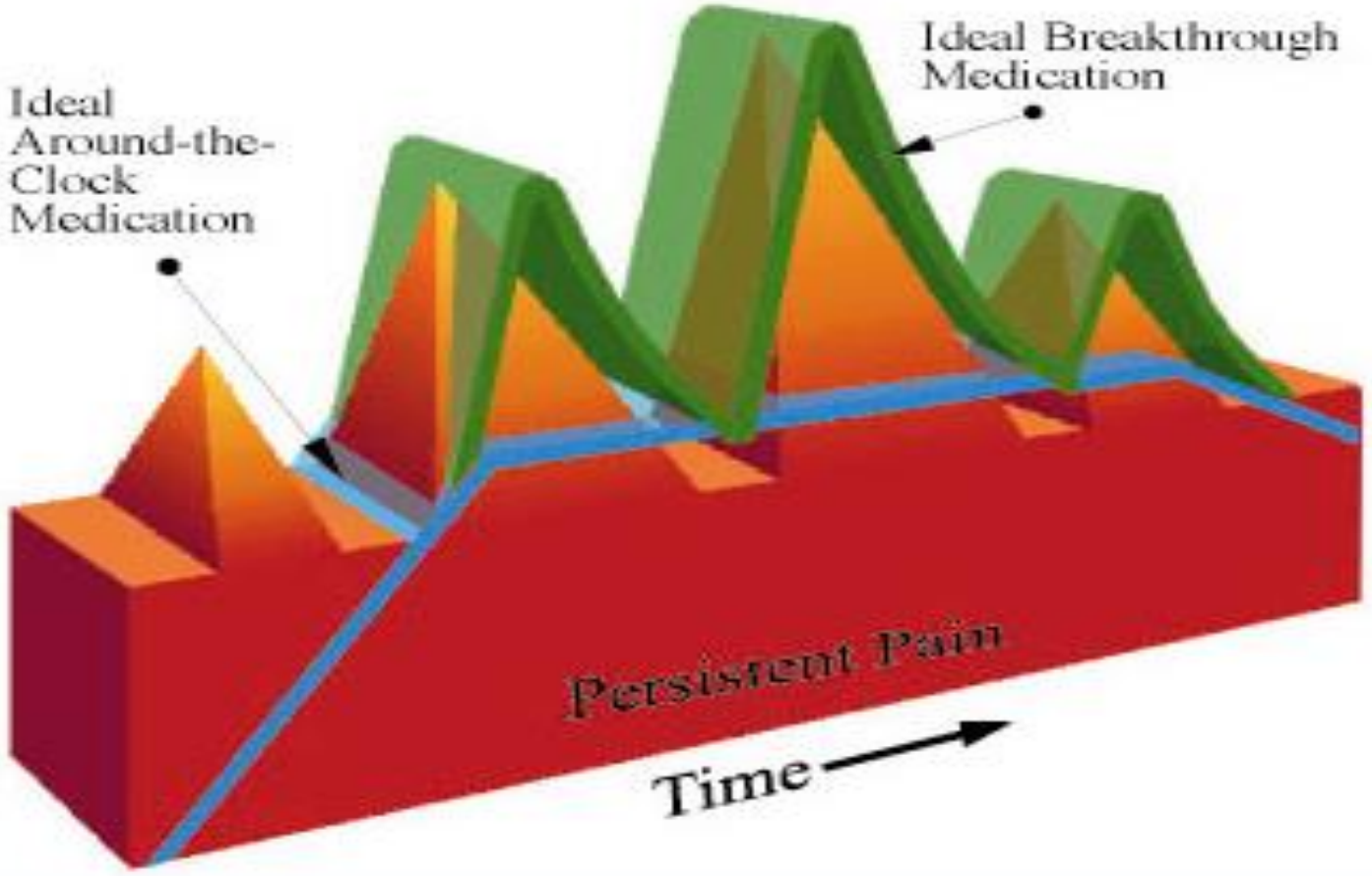
=針劑 Morphine 3mg sc q4h

為甚麼會發生突發性疼痛？

- 目前詳細病理機轉尚未清楚，可能原因有三種：
  - 嗎啡藥效時間要到了
  - 活動性疼痛
  - 原來疼痛控制不好
- 一般是發生在中重度癌症疼痛病人身上
- 前一日超過三次突發疼痛要調總劑量

To Control the incidence of Breakthrough Pain as less as possible

疼痛藥物調整要考慮突發性疼痛



突發性疼痛調藥原則

- 以一日常規疼痛藥物口服總劑量之1/6~1/10為參考，準備備用藥。

  －例如：Fentanyl 25 ug/hr q3d and Morphine 10mg tab 1# q4hprn.

- 昨日超過三次突發性疼痛應考慮增加每日疼痛藥物口服總劑量，必要時備用藥劑量也增加。

Do Strong Opioids Shorten Live?
用嗎啡會縮短生命？

Duration of hospitalisation on the PCU For patients with/without opioids			Days
Consumption of opioids	No	Median	10,00
		Interquartile Range	15,25
	Yes	Median	14.00
		Interquartile Range	26,75

好的癌症疼痛控制要點

- 相信病人
- 同理心溝通
- 注重完整疼痛評估
- 適當的突發性疼痛控制
- 盡可能密切的追蹤癌症疼痛藥物控制的反應
- 學習非藥物的癌症疼痛控制方法

癌症病人化學治療(化療)後的噁心嘔吐

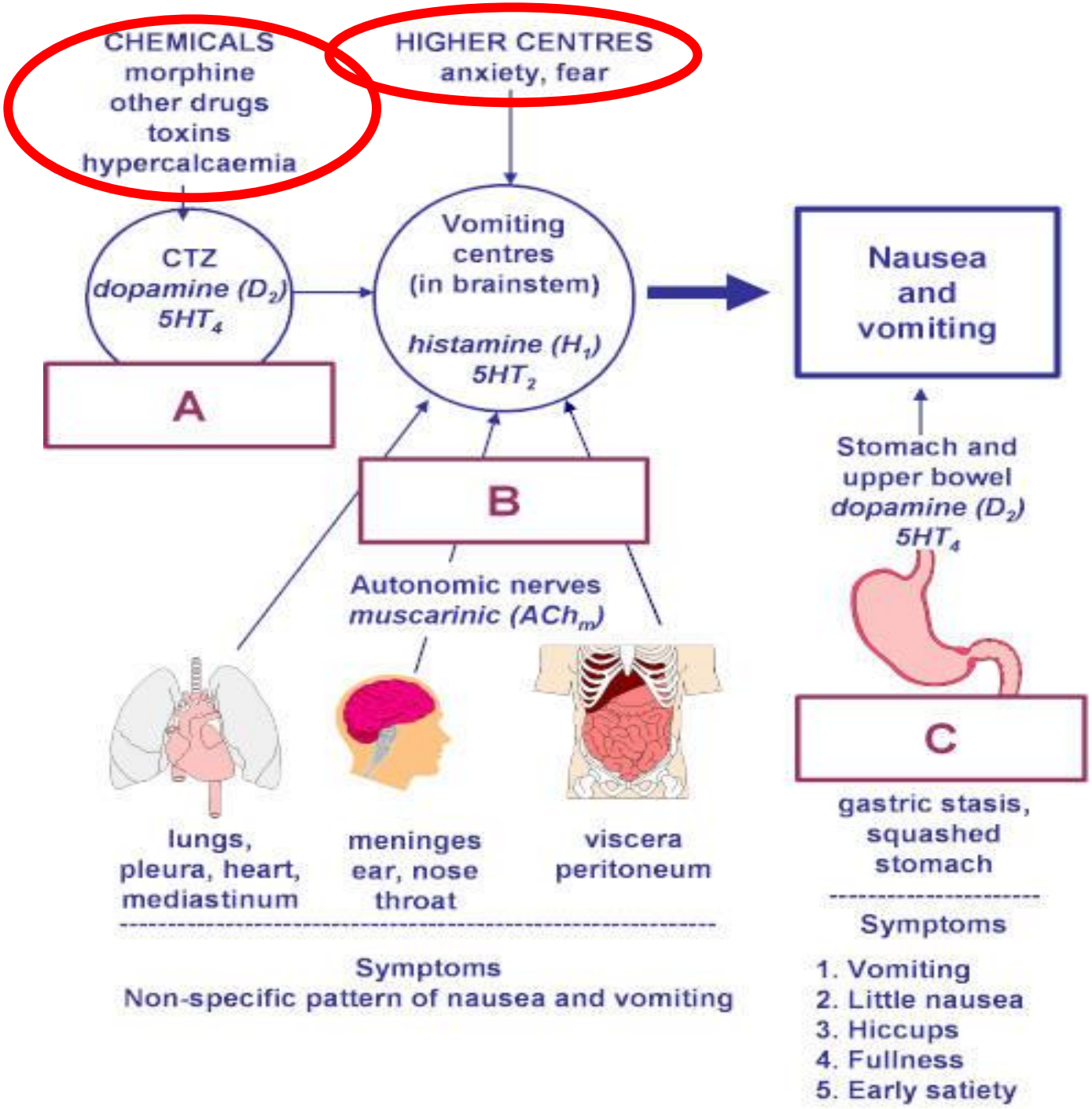
- 好的化療品質包括控制好病人因藥物引起之症狀，尤其是噁心嘔吐控制。
- 了解化療會引起之噁心嘔吐風險，給予全程管控是必要的。
- 首先了解化療藥物的高、中、低致吐性，接著依噁心嘔吐風險時程選擇適合的止吐藥，與最後追蹤評估成效。

噁心及嘔吐的生理機轉

- 1953年証實人腦中存有嘔吐中樞，可接收人體中各組織所傳來的嘔吐神經傳導，
  - 嘔吐中樞位於延腦，接受嘔吐的神經傳導物質(Serotonin、Dopamine、Histamine、Acetylcholine、Substance P）引起嘔吐。
  - 化學受體刺激區（Chemoreceptor trigger zone，CTZ）也在同時期被發現位於腦部最後區，接近第四腦室底的附近，可接收嘔吐的訊息傳入(最重要訊息是來自腸道中的迷走神經)，再傳嘔吐中樞引發嘔吐。

- 迷走神經是啟動嘔吐最重要的神經傳導，當腸道內皮細胞因化療而受損時，會分泌最重要的嘔吐神經傳導物質Serotonin（5-Hydroxy tryptamine，5HT），藉由迷走神經上的5-HT3受體，刺激腦部中的CTZ發生嘔吐作用。

- 迷走神經的傳導末端是位於腦部中的孤立束核，它會分泌另一種嘔吐傳導物質substance P，來活化Neurokinin-1（簡稱NK-1）受體，進一步刺激CTZ發生的嘔吐作用，瞭解噁心嘔吐的機轉，對止吐藥物的沿革發展的認識是非常重要的。

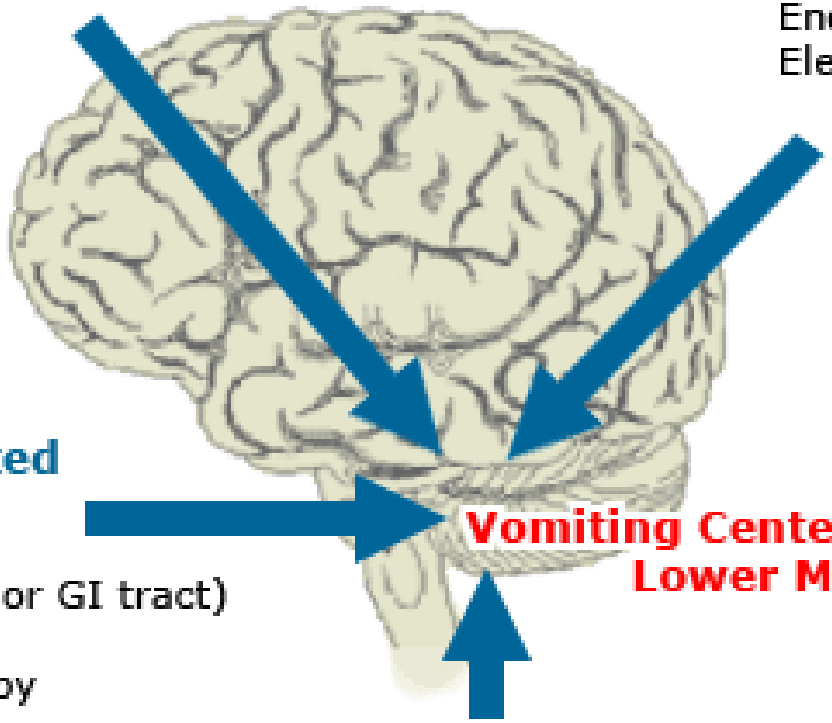

CHEMICALS
morphine
other drugs
toxins
hypercalcaemia
HIGHER CENTRES
anxiety, fear
CTZ
dopamine (D2)
5HT4
Vomiting
centres
(in brainstem)
histamine (H1)
5HT2
Nausea
and
vomiting
A
B
Stomach and
upper bowel
dopamine (D2)
5HT4
Autonomic nerves
muscarinic (AChm)
C
lungs,
pleura, heart,
mediastinum
meninges
ear, nose
throat
viscera
peritoneum
gastric stasis,
squashed
stomach
Symptoms
Non-specific pattern of nausea and vomiting
Symptoms
1. Vomiting
2. Little nausea
3. Hiccups
4. Fullness
5. Early satiety

Physiologic

Constipation
Gastric Stasis/Outlet Obstruction
Brain Metasteses
Increased Intercranial Pressure
Bowel/Instestinal Obstruction
Hepatomegaly
Oral Thrush
Cough

Metabolic

Uremia
Endocrine Imbalance
Electrolyte Imbalance:
- Hypercalcemia
- Hyponatremia



Treatment Related

Chemotherapy
Radiation Therapy
(especially to brain or GI tract)
Medications:
Initial Opioid Therapy
Antibiotics
Aspirin/NSAIDS
Carbamazepine
Steroids
Expectorants

Vomiting Center of the Brain: Lower Medula

Emotional/Spiritual/Psychological

Anticipatory N&V (prior to chemotherapy)
Meaning of Illness
Loss of Personhood
Role Change
Suffering
Anziety/Fear
Fatigue

依引起噁心嘔吐程度將化療藥物分成三類

1. 高致吐性：會讓90%以上的病人發生噁心嘔吐的化療藥物

2. 中致吐性：使30~90%病人發生噁心嘔吐的化療藥物

3. 低致吐性：使10~30%病人發生噁心嘔吐的化療藥物

化療引起的噁心嘔吐風險時程分為三種

1. 急性：化療後24小時內發生；
2. 延遲性：化療後第2~5天發生；
3. 預期性：因前次化療引起的噁心嘔吐不舒服感覺，在即將化療前發生預期性噁心嘔吐。

常見化療藥物的致吐性：

- 高致吐性：Cisplatin ≧ 50 mg/㎡、Mechlortamine、Streptozocin、Carmustine > 250 mg/㎡、Cyclophosphamide > 1500 mg/㎡、Dacarbazine
- 中高玫吐性：Cisplatin < 50 mg/㎡、Cytarabine > 1000 mg/㎡、Carboplatin、Oxaliplatin、Ifosfamide、Carmustine ≦ 250 mg/㎡、Cyclophosphamide ≦ 1500 mg/㎡、Doxorubicin ≧ 60 mg/㎡、Epirubicin ≧ 90 mg/㎡

- 中低致吐性：Topotecan、Irinotecan、Procarbazine、Cyclophosphamide、Mitoxantrone、Gemcitabine、Liposomal doxorubicin、Docetaxel、Paclitaxel、Etoposide、Teniposide、Methotrexate 50-250 mg/㎡、Mitomycin、Fluorouracil < 1000 mg/㎡
- 低致吐性：Bleomycin、Busulfan(Not for high dose therapy)、Chlorambucil、Fludarabine、Hydroxyurea、Methotrexate ≦ 50 mg/㎡、Vincristine/Vinblastine/Vinorelbine

常用止吐藥物介紹

- 第一類Phenothiazine，在1963年証實可有效控制輕至中度致吐性化療引起的噁心及嘔吐，如Chlopromazine (wintermine)，可針對5-Fluorouracil化療使用，但劑量增加容易會有錐體外徑路症候群、嗜睡、四肢無力的副作用，所以在1990年後已少使用；

- 第二類Butyrophenones，包括有haloperidol, droperidol等作用於Dopamine受體的藥物，只能控制中致吐性化療的止吐效果，但因副作用大，較少使用；

常用止吐藥物介紹

- 第三類類固醇，其作用機轉尚不明確，可能是前列腺素（Prostaglandin）有關，可單獨用於輕至中度致吐性化療，但對高致吐性藥物如Cisplatin止吐效果不佳，通常需合併Dexamethasone 20mg靜脈注射及5-HT3抑劑劑，才有較佳的止吐效果；
- 第四類Benzodiazepines，如lorazepam及alprazolam，雖然止吐效果差，但可讓病人有鎮靜的效果，對預期性嘔吐或對化療焦慮的病人可使用；

常用止吐藥物介紹

- 第五類Substituted Benzamides，以Metoclopramide（Primperam）為主，可用於胃蠕動不良引起嘔吐的病患，對接受高致吐性Cisplatin化療引起的嘔吐有效，但會增強抗dopamine受體的副作用發生，如錐體外徑路症候群、焦慮及憂鬱的症狀，可是它的抗Serotonin的效果是後來發展專一性的止吐藥物的里程碑。

常用止吐藥物介紹

- 在1990年5-HT3受體抑制劑的第一代止吐藥，有專一性抗Serotonin的效果，化療引起的噁心及嘔吐非常有效，且沒有Dopamine受體的刺激作用，但價格比Metoclopramide貴10倍以上，適用於高致吐性化療，主要藥物Ondansetron（Zofran）、Dolasetron（Anzemet）、Tropisetron（Navoban）及Granisetron（Kytril），第二代的藥物包括有Palonosetron，半衰期達40小時以上，比第一代的藥物更有效的控制延遲性嘔性。

5-HT3受體抑制劑

- 使用此類藥物須注意下列特點：
  - 第一，儘量使用低且有效的藥物劑量，因為再高的劑量，因5-HT3受體飽和而失效；
  - 第二，口服及靜脈注射均有同等藥效。
  - 第三，儘量使用單次劑量，勿分成多次劑量使用。

常用止吐藥物介紹

- 最新止吐藥就是NK-1受體抑制劑Aprepitant，可抑制substance P作用NK-1受體而導致的嘔吐，可用於高致吐性化療與延遲性嘔吐，在第三期的雙盲臨床試驗中，實驗組使用合併Aprepitant、Ondansetron及Dexamethasone，對照組只使用Ondansetron及Dexamethasone，結果兩組的完全控制嘔吐率為73%比52%（P < 0.001），證實多加了Aprepitant，更能有效的控制急性及延遲性嘔吐。

化學治療的止吐藥使用

- 預防性的投與止吐藥通常是在化學治療前30-60分鐘投與，如果病患出現噁心/嘔吐症狀，治療最好改由靜脈注射。
- 高~中高致吐性化療藥物，建議合併Serotonin antagonists 及類固醇使用；
- 中致吐性化療藥物，通常在Serotonin antagonists 、類固醇或dopamine antagonists中擇一使用，且不一定需要預防性投與；
- 低致吐性化療藥物者不需要預防性投與

延遲性噁心/嘔吐反應

- 是讓病人接受化學治療滿意度下降主因之一
- 以連續數日的化療為例，在治療當日視同急性反應之處理原則，而延遲性反應則於1-2天後投與。
- 一般延遲性噁心/嘔吐的控制是比照高~中高致吐性化療藥物，建議合併Serotonin antagonists 及類固醇使用，必要時可以與NK-1受體抑制劑一起使用。

化療較容易引起噁心及嘔吐的因子

- 年齡小於50歲
- 女性
- 長期喝酒
- 曾因化療有噁心及嘔吐症狀
- 容易有動暈症
- 焦慮的病患。

提醒

- 即使止吐藥物已有許多進展且有訂定止吐治療準則，仍然有很多癌症病人受化療引起噁心及嘔吐所苦，甚至發生危險。主要的因素為醫護人員忽略這個問題的嚴重性，例如：未能即時更新止吐藥物新知、少了好的衛教資料與方式、以及好的評估方式與處置，以為病人均已得到良好的止吐控制，其實不然，尤其是延遲性嘔吐的控制，仍待加強。