癌症治療新方向和香港質子治療的臨床經驗

張天怡醫生
臨床腫瘤科醫生

1. 肺癌病理分類
2. 乳腺癌分類
3. 癌症分期
4. 肺癌治療
5. 乳腺癌治療
6. 質子治療
7. 影像引導放射治療
8. 基因測序
9. 香港質子治療臨床經驗

問答

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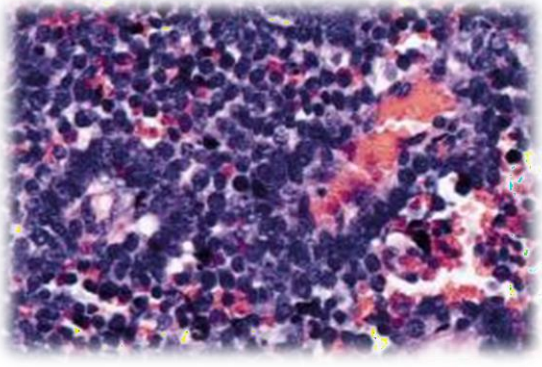
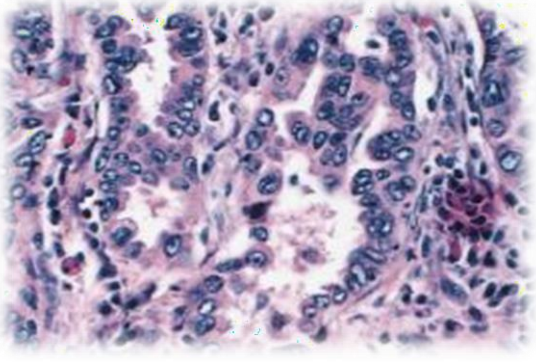
1. 肺癌的病理分類

- 以組織學為本，從顯微鏡下觀察細胞的樣式及分子標記來歸類
- 原發性肺癌大致分兩大類



小細胞(small cell carcinoma)



非小細胞肺癌(non-small cell carcinoma)

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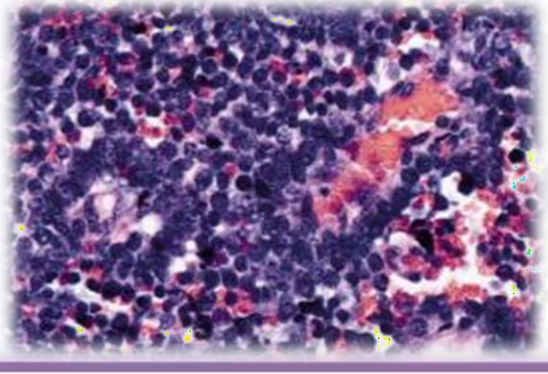
小細胞肺癌

- 約佔15%
- 生長速度極快、擴散能力高
- 確診時多已擴散
- 與吸煙關係密切
- 對電療及化療極敏
- 易生抗藥性
- 預後較差



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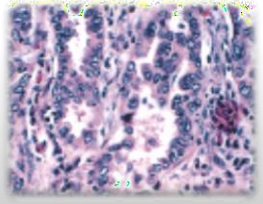
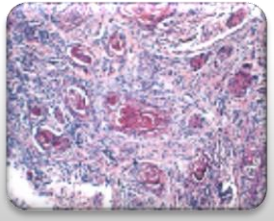
非小細胞肺癌



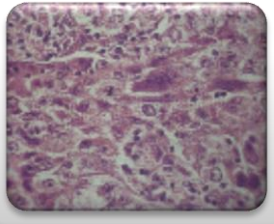
腺癌

- 約佔40%，非吸煙者較常罹患的類別
- 較常在週邊生長，常引發惡性肺腔積液



鱗癌

- 約佔25%，吸煙者較常罹患的類別
- 較常在中央生長



大細胞

- <10%, 低分化、沒明顯腺狀或鱗狀形態
- 可再細分多種不同類型

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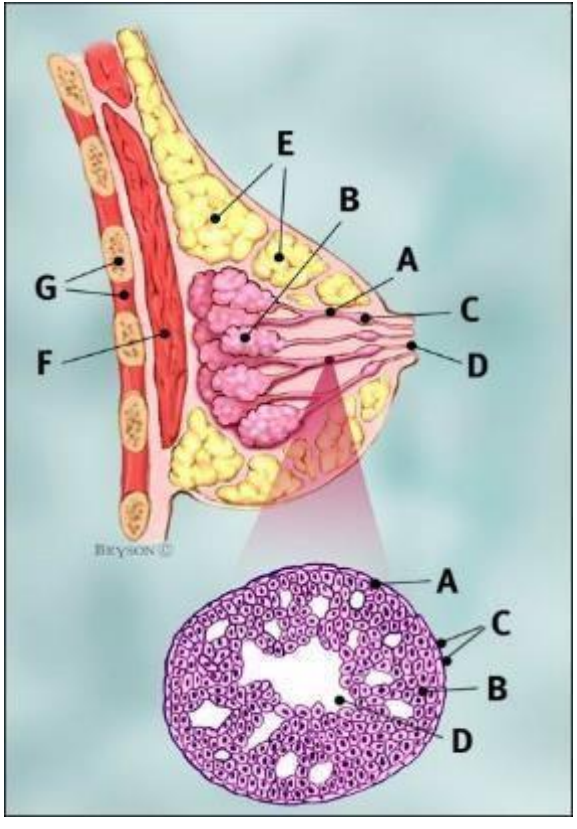
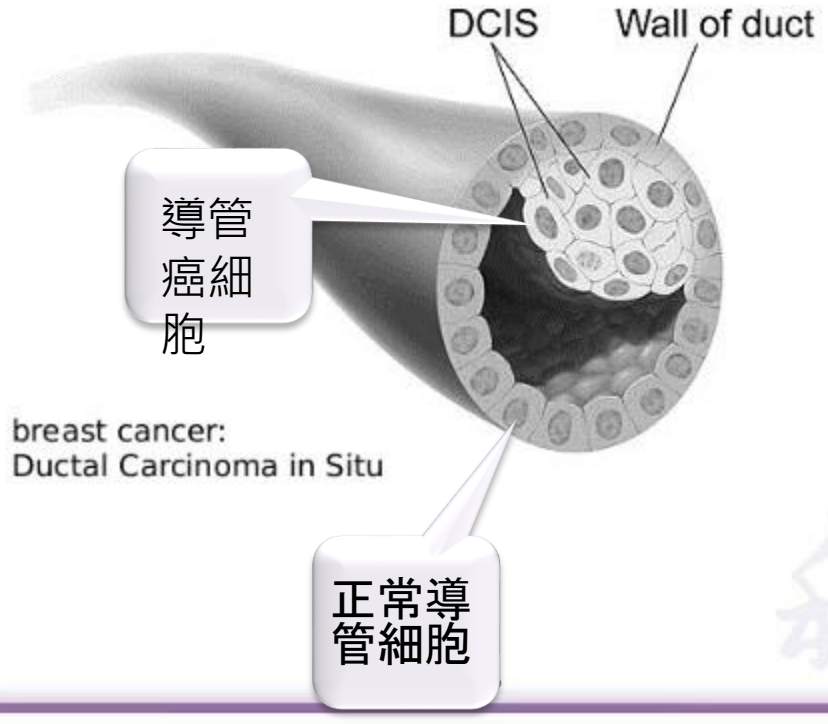
2. 乳癌的病理分類

導管原位癌（DCIS）





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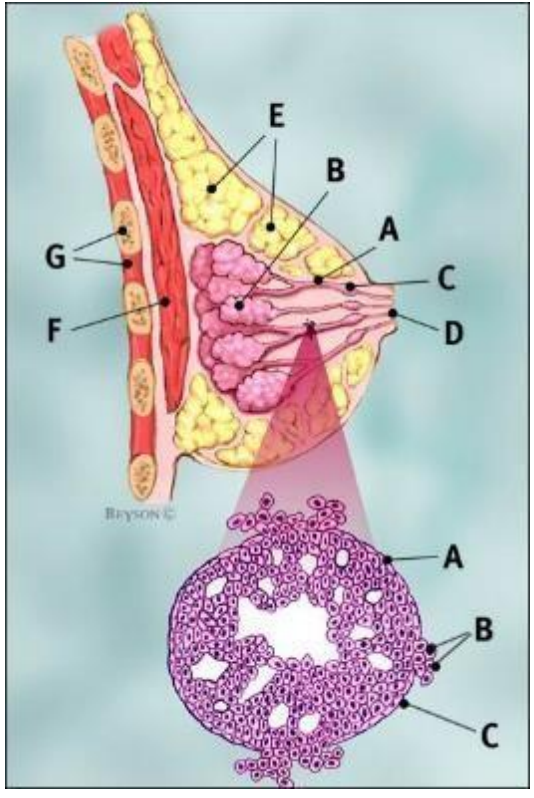
侵襲性導管癌癌



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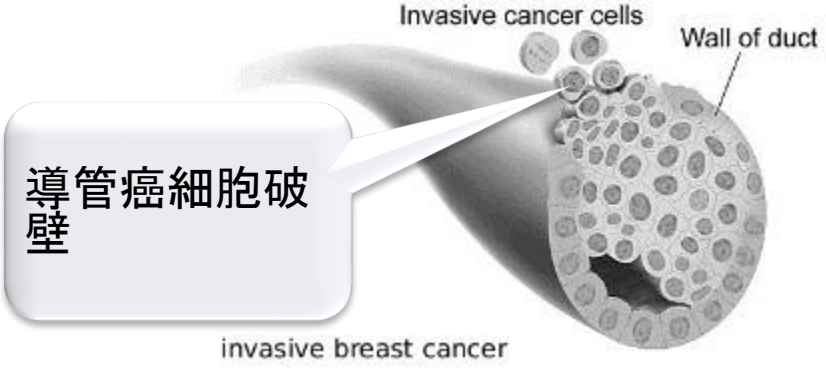

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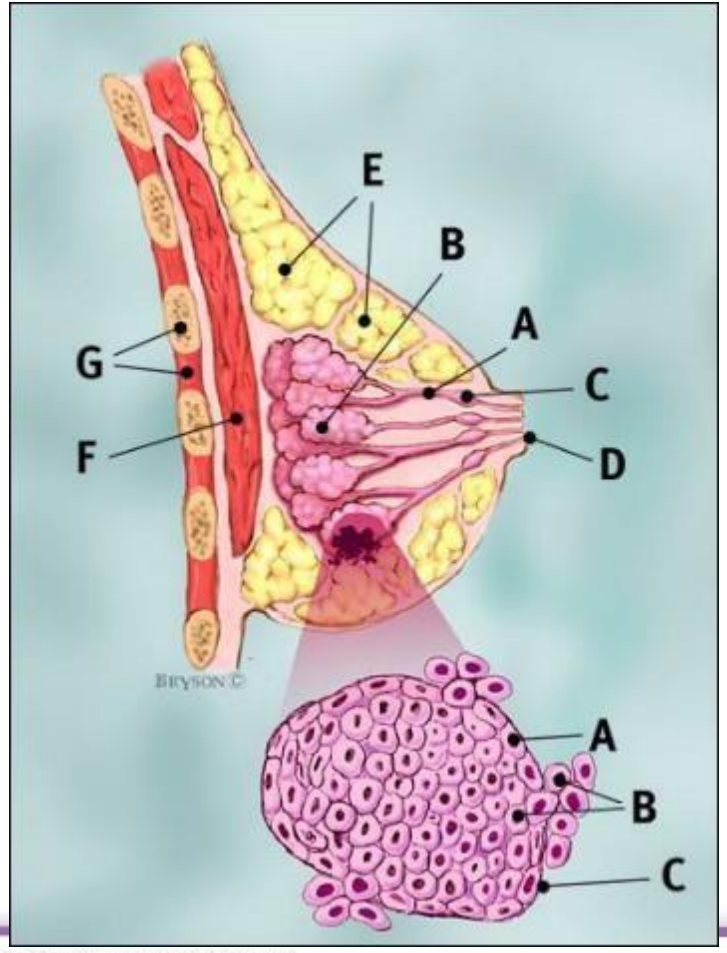
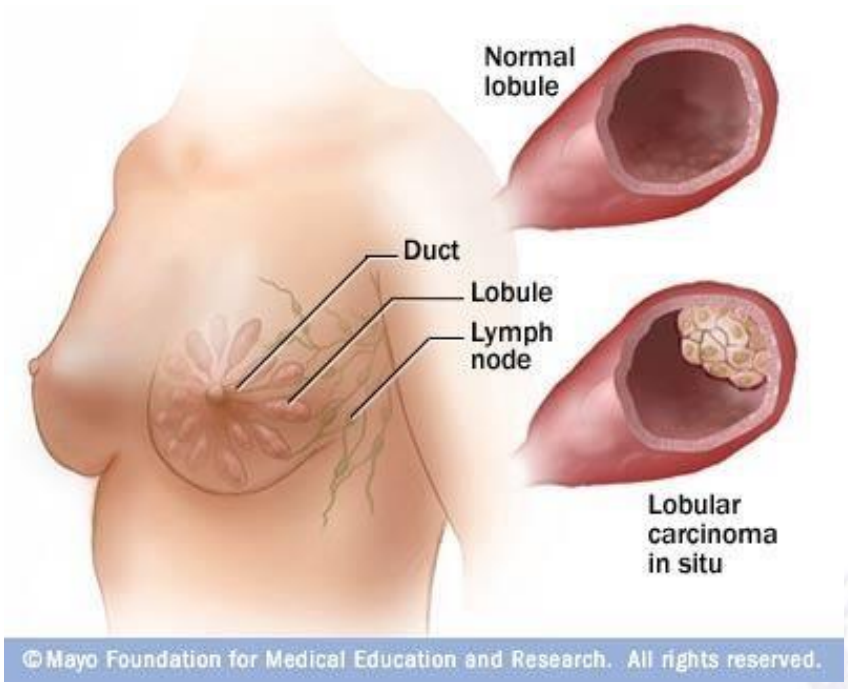
侵襲性小葉癌（ILC）





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乳癌的分類[1,2]

雌激素受體呈陽性(ER+)/
黃體素受體呈陽性 (PR+)
此類癌細胞的生長主要受荷爾蒙影響,
這類腫瘤生長速度一般較慢

79.5%

三陰性乳癌
荷爾蒙受體及HER2受體都呈陰性,
多見於年輕女性, 惡性也較高

12%

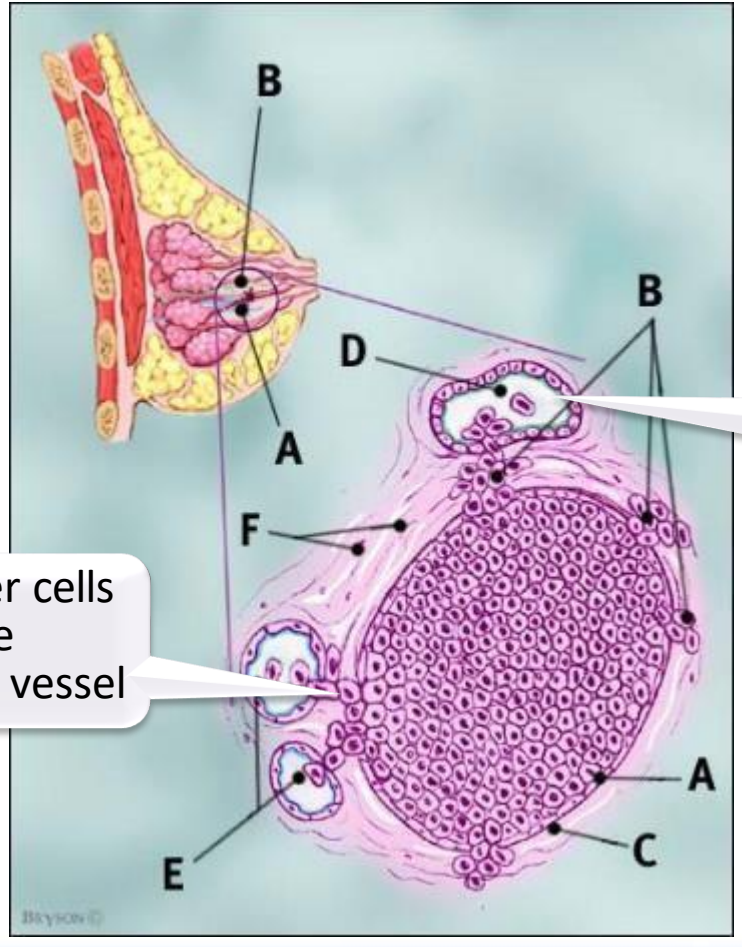


第二型人類上皮生長因子受體呈陽性
(HER2+)
癌細胞擁有較多HER2受體,
這類癌細胞的生長及擴散速度也較快

21.7%

1. American Cancer Society, 2016. Breast Cancer. Available at: <http://www.cancer.org/acs/groups/cid/documents/webcontent/003090-pdf.pdf> [Accessed: August 8, 2016].
2. Hong Kong Breast Cancer Foundation. Hong Kong Breast Cancer Registry Report No. 7. 2015.

癌症也可侵襲淋巴或血管 - 轉移性乳腺癌



Cancer cells invade lymph duct

Cancer cells invade blood vessel

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3. 癌症的分期 (TNM Staging)

- 國際癌病協會(UICC)制定的分期標準
- 根據腫瘤(Tumor) 範圍 、淋巴結(Node) 及有否遠程擴散(distant Metastases) 劃分
- 醫生會因應分期從而:
  - 制定治療方案
  - 與病人討論預後(Prognosis)
  - 作研究及分析用途



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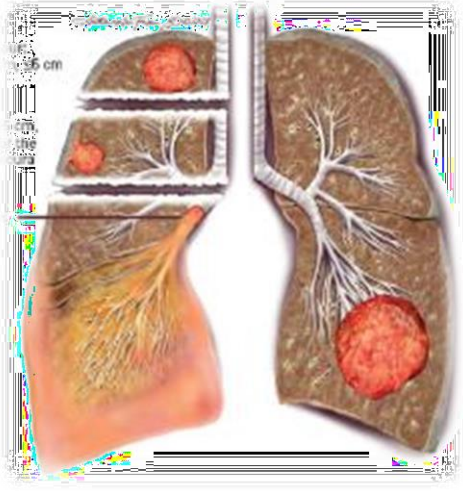
肺癌的分期



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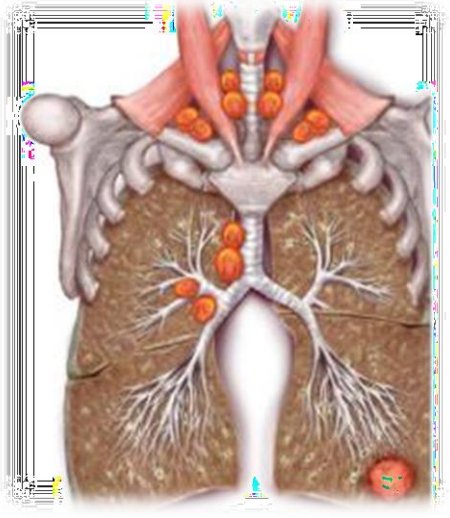

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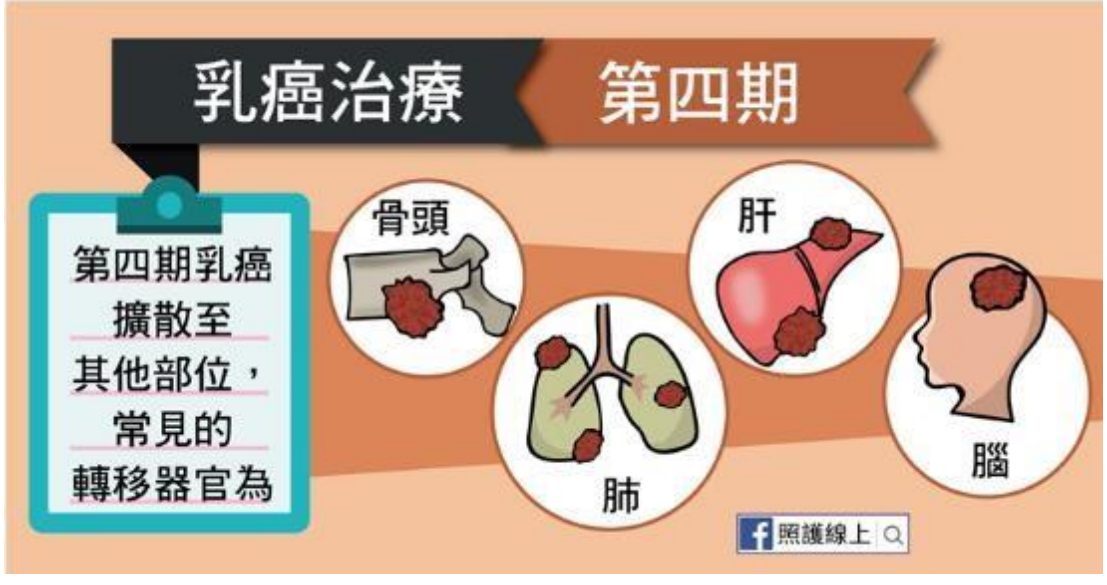
乳癌的分期

- 主要分零至四期
- 數字小代表屬早期，而數字越大代表屬越接近晚期
- 第四期代表癌細胞已經由乳房擴散至其他器官



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乳癌的分期

癌症期數	簡介
第0期	原位癌
第一期	腫瘤少於二厘米，沒有淋巴結影響
第二期	腫瘤二至五厘米, +/-淋巴結受影響
第三期	視乎腫瘤的大小及淋巴結受影響的幅度；腫瘤受影響的幅度越大，越多淋巴結受到癌細胞影響，癌症期數越後
第四期	腫瘤已擴散至乳房以外的器官及組織

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Reference:
Smart Patient, Hospital Authority. Available at: http://www21.ha.org.hk/smartpatient/tc/cancerin_focus/details.html?id=153 (Accessed on 12th

4.常見癌症的治療方法–肺癌治療

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肺癌的成因



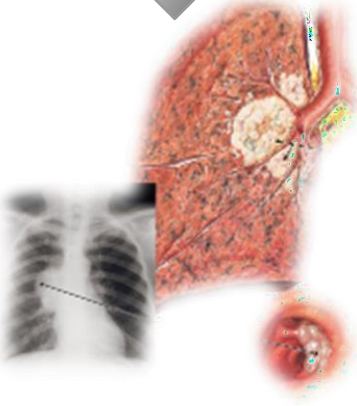
吸煙



家族史
基因缺陷



空氣污染
碳氫化合物





石綿
砷、 氯乙烯



氡氣
輻射

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非小細胞肺癌治療概略

分期 (UICC 7th Ed.)	一般建議方法	可考慮的其他方案
I	外科手術	• 放射治療(電療) • 立體定位放射治療(SBRT)
II	外科手術+ 化學治療(化療)	放射治療(電療)
IIIA	化療 +電療	• 化療 +電療 +手術 • 化療+手術
IIIB	化療+電療	
IV	標靶治療、化療 +/- 電療	

* 任何分期的病者，如條件合適，皆有可能受邀加入臨床研究計劃

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小細胞肺癌治療概略

- 侷限期小細胞肺癌(Limited Stage SCLC)
  - 胸腔電療 + 同步化療 + 全腦電療

- 擴散期小細胞肺癌 (Extensive Stage SCLC)
  - 化療+全腦電療 +/- 胸腔電療

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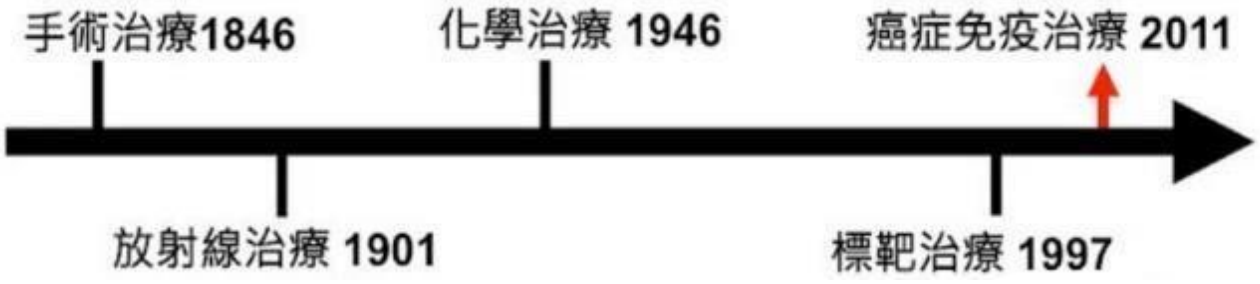
腫瘤療法的歷史



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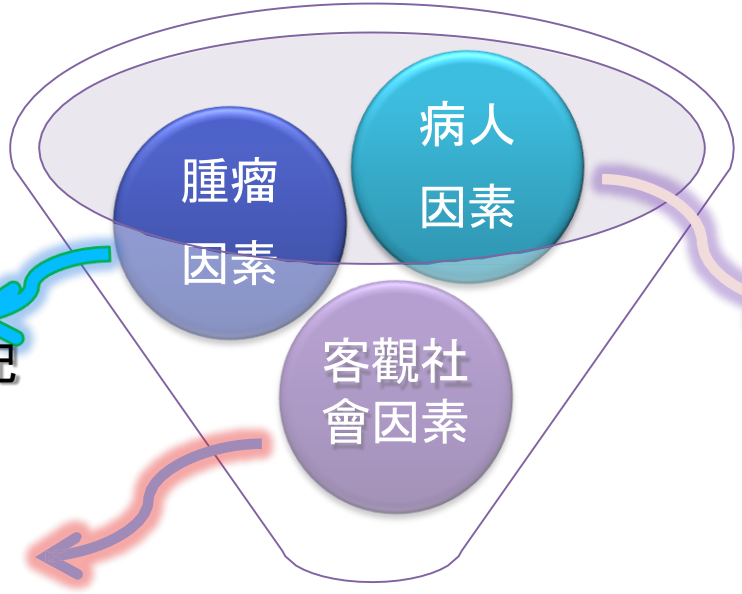
制定治療方針



腫瘤分期、病理
分類、分子生物標記

年齡、健康狀況
主觀意願、 取向
及信念

家庭狀況、週邊
的支援、經濟考慮、
醫院設備

最終治療方案

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化學治療

- 透過抗癌藥物去抑制快速生長細胞的分裂、生長
- 可適用於手術前後輔助性治療、與電療同步作根治性治療，或作舒緩治療。
- 常見的副作用: 脫髮、嘔吐、噁心、疲倦、骨髓工能下降、麻痺、肝腎工能受損、感染等
- 現代的化療，副作用已大大減少，也有一些輔助藥物能減低化療的副作用

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化學治療

一般常用之一線化療

- 鉑類藥物(cisplatin 順鉑、carboplatin 卡鉑) +
  - 吉西他濱(Gemcitabine)
  - 紫杉醇(Paclitaxel)
  - 多西紫杉醇 (Docetaxel)
  - 培美曲塞(Pemetrexed)
  - 長春瑞濱 (Vinorelbine)
  - 依附泊苷 (Epotoside)

常用之二線化療

- 培美曲塞 (Pemetrexed)
- 多西紫杉醇 (Docetaxel)



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化療常見的副作用

嘔吐

- 影響腦部內的「嘔吐中心」， 令患者覺得噁心
- 最常於化療一星期後發生
- 心理因素亦可能引發嘔吐
- 醫生會為病人處方止吐藥物

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化療常見的副作用

脱髮

- 不少患者接受化療後會掉髮
- 建議患者於治療前剪短頭髮及可配戴假髮
- 完成化療後， 頭髮便會慢慢重生

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化療常見的副作用

感染

- 接受化療後，患者的白血球水平會有機會下降，一般而言，約2 至3 星期後便會回升
- 若白血球水平長期維持在低水平，患者受感染的機會便會大大增加，常見的症狀如發燒、 咳嗽等
- 醫生會視乎情況為病人注射俗稱「升白針」的白血球生成素
- 治療期間， 應盡量避免到人多擠迫的地方，及避免與動物及傳染病患者接觸， 並要勤洗手及保持口腔清潔， 以減低出現感染的機會

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個人化治療的重要性

- 隨着分子生物醫學的急速發展，愈來愈多針對特定細胞受體的藥物面世
- 肺癌的分類，亦在組織學上再加入分子、基因分析
- 透過找出特別的生物標記，使醫生能制定出更個人化、療效更佳，更少副作用的治療

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標靶治療

- 針對癌細胞表面的生長因子受體，從而干擾癌細胞內的生長訊號
- 為一些有特殊靶點的病人， 提供另一個有效而低毒性的新選擇

- 現時已經認可用於肺癌的標靶藥物，主要針對:
  - 上皮生長因子受體(EGFR)
  - 間變性淋巴瘤激酶(ALK)
  - 酪胺酸激酶(ROS-1)
  - 惡性黑素瘤(BRAF)
  - 抗細胞死亡配體-1 (PD-L1)

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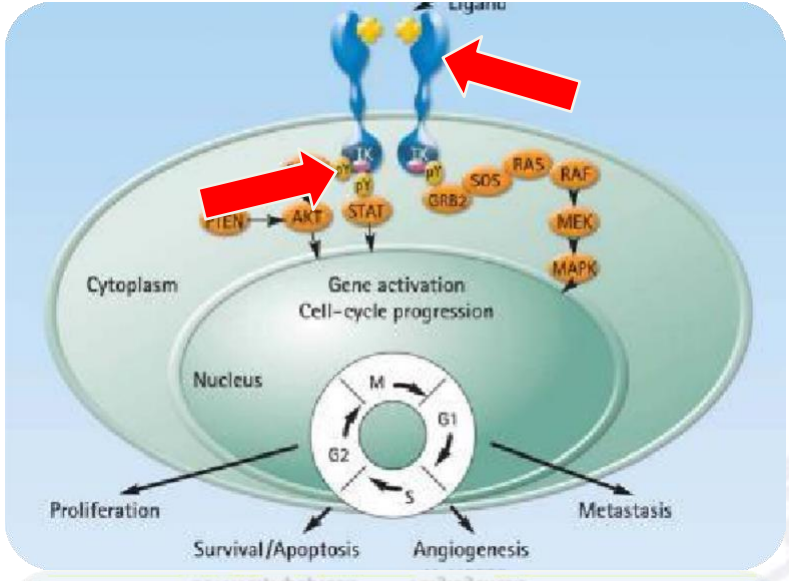
標靶治療

- 上皮生長因子會發放訊息使細胞生長、 血管增生、擴散
- 透過抑制上皮生長因子受體(EGFR)來干擾癌細胞生長訊號，使癌細胞凋謝死亡
  - 酪胺酸激酶抑制劑 (Tyrosine kinase inhibitor, TKI)
  - EGFR 單株抗體 (Monoclonal antibody)



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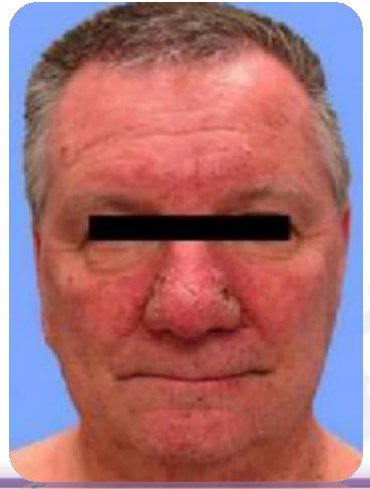
Eur J Cancer 2001;37 Suppl 4:S16-S22.

標靶治療

- 在香港認可的 TKIs
  - 吉非替尼(Gefitinib)
  - 厄洛替尼 (Erlotinib)
  - 阿法替尼(Afatinib)
  - 奧希替尼 (Osimertinib)



- 常見的副作用:
  - 肚瀉
  - 皮疹、 暗瘡
  - 眼捷毛生長異常
  - 肝功能受損
  - 間質性肺炎



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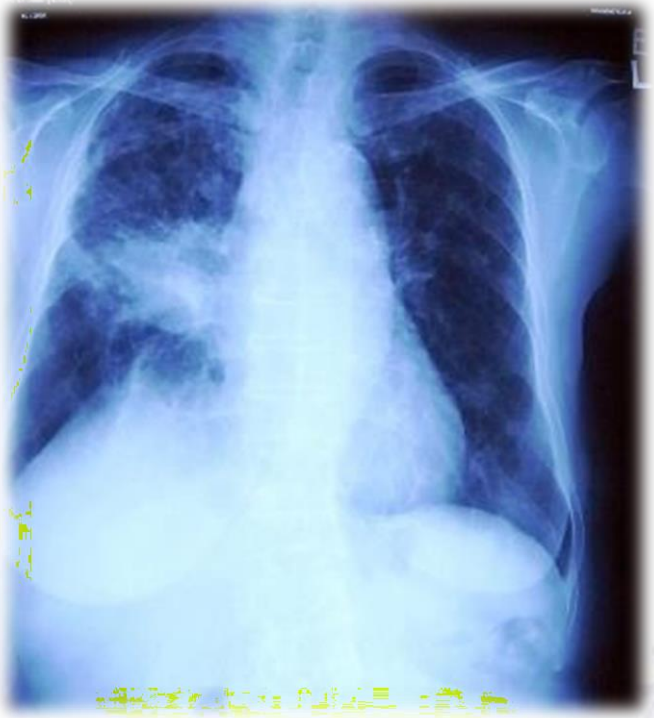
標靶治療



剛診斷肺癌時



使用酪胺酸激酶抑制劑
一個月後

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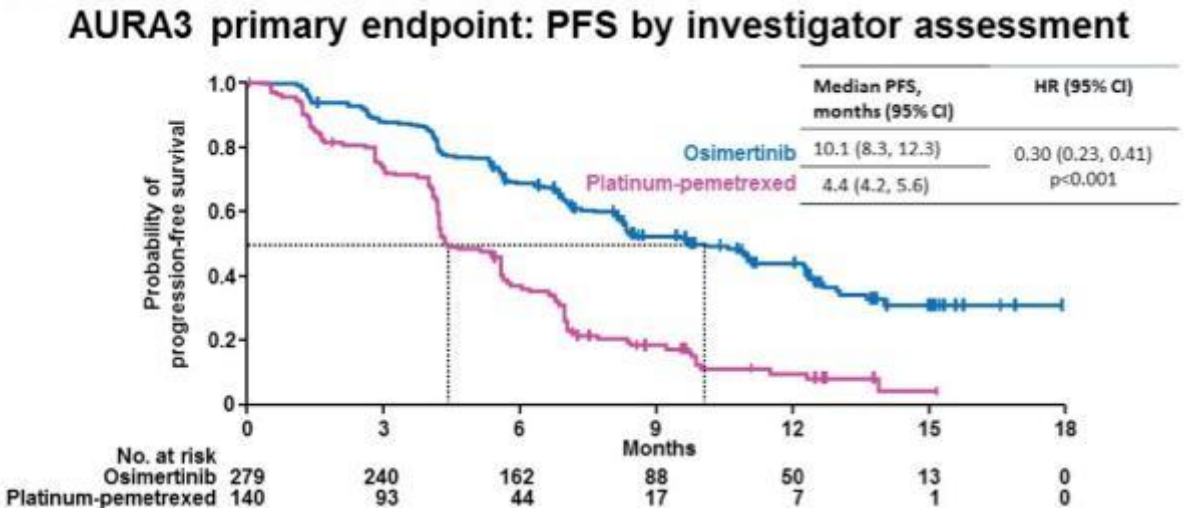
標靶治療

- 奧希替尼 (Osimertinib)治療EGFR T790M突變陽性的非小細胞肺癌
- 臨床試驗療效比於標準化療



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- 近三分之二的EGFR突變陽性病人, 經EGFR-TKI治療後發展為T790M耐藥突變
- 奧西替尼是第三代EGFR酪氨酸激酶抑制劑
- 抑制EGFR敏感性和EGFR T790M抗性突變, 在中樞神經系統（CNS）中有效果

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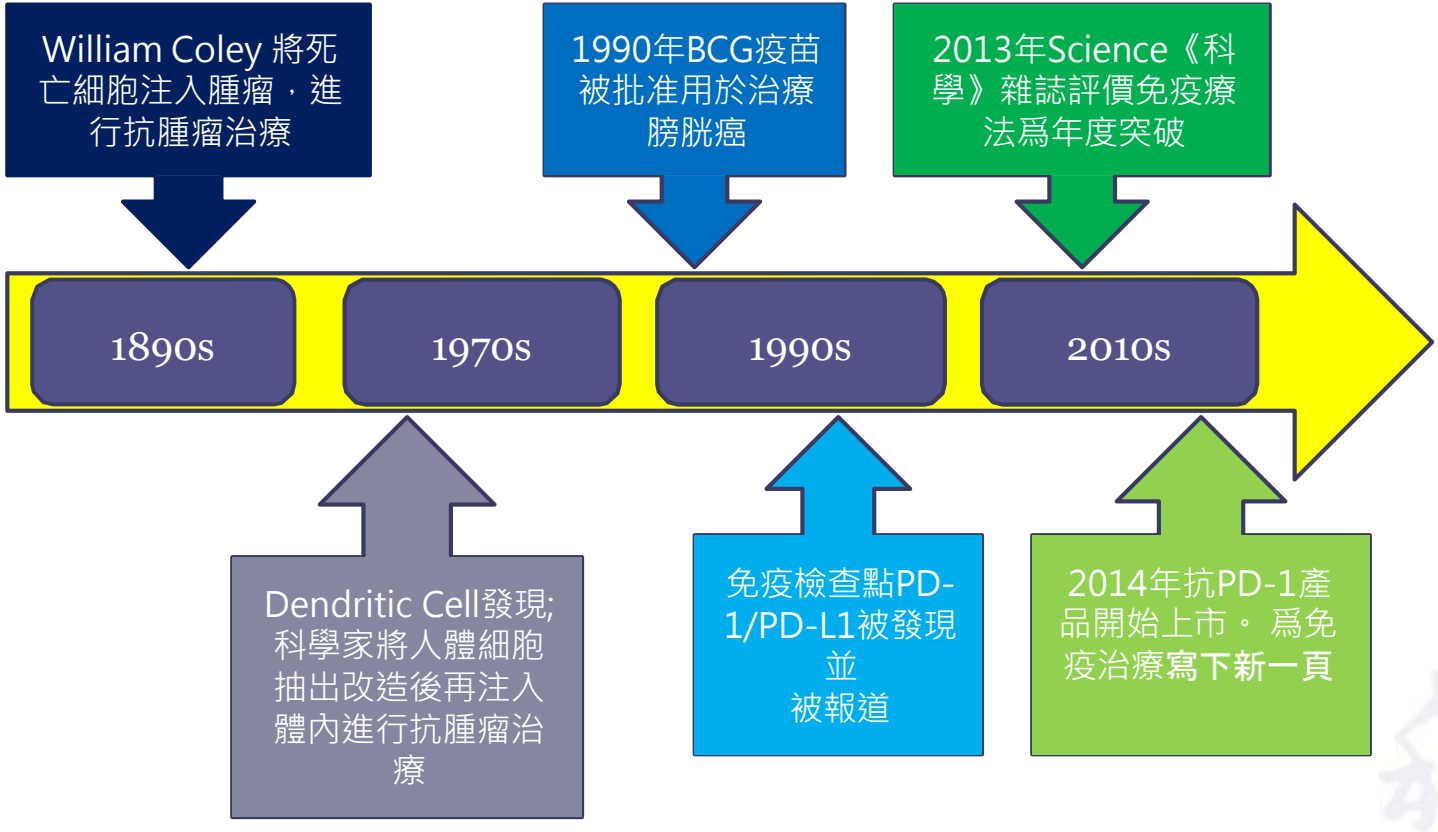
免疫療法的歷史



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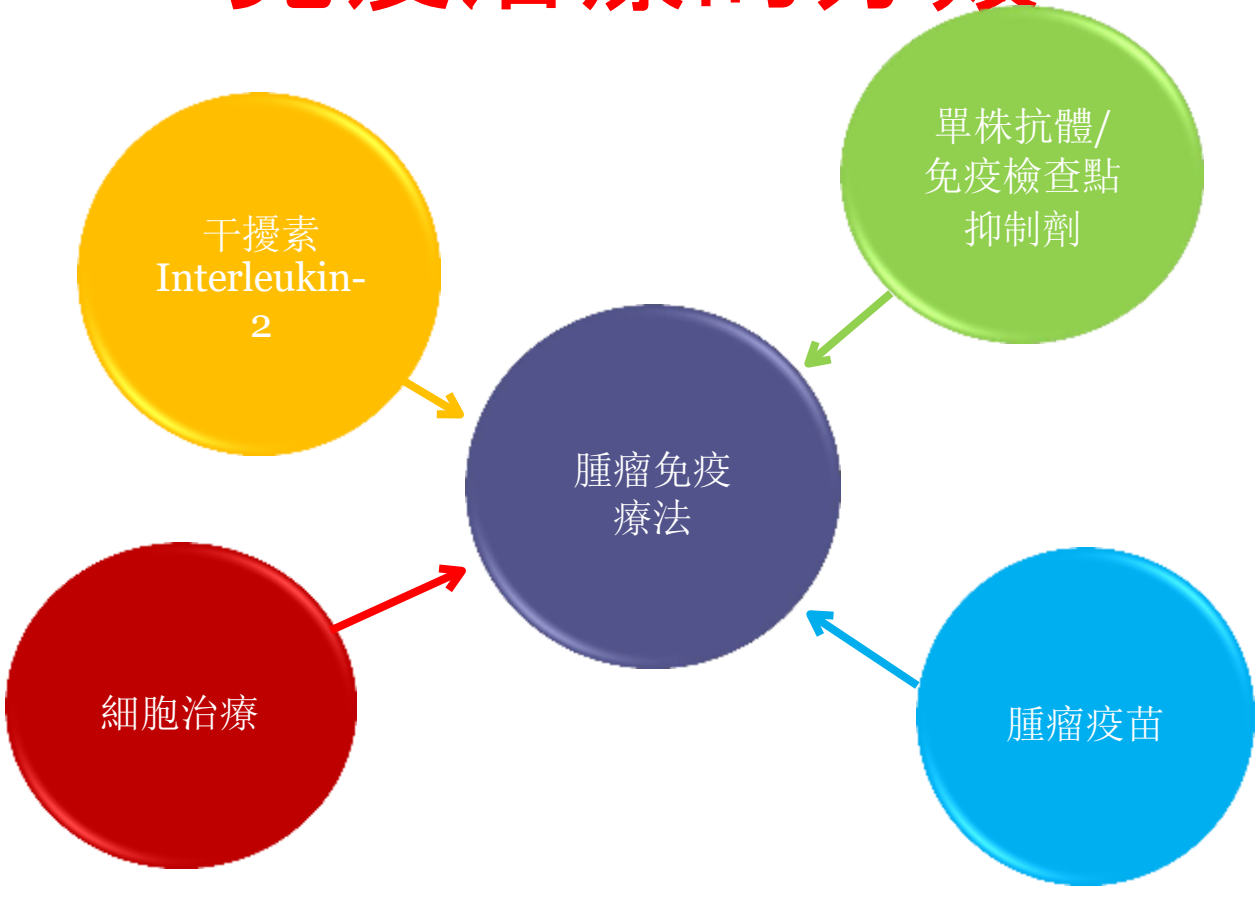
免疫治療的分類



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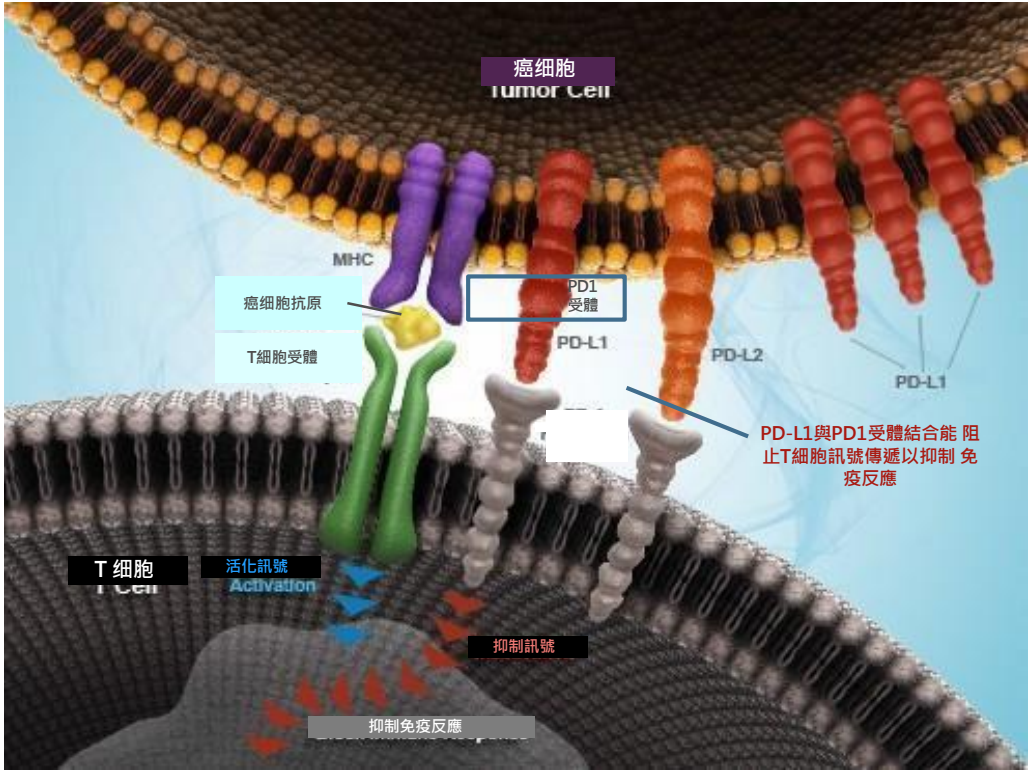
癌細胞如何抑制免疫系統的反應?



- T 細胞(白血球細胞的一種) 上的PD-1受體, 一旦與其他細胞上的PDL1蛋白結 合,便會產生抑制訊號,T細胞便會停止攻擊。
- 狡猾的癌細胞會表現出PDL1蛋白, 並與T細胞上的PD-1受體結合, 令T細胞不會對癌細胞作出攻擊

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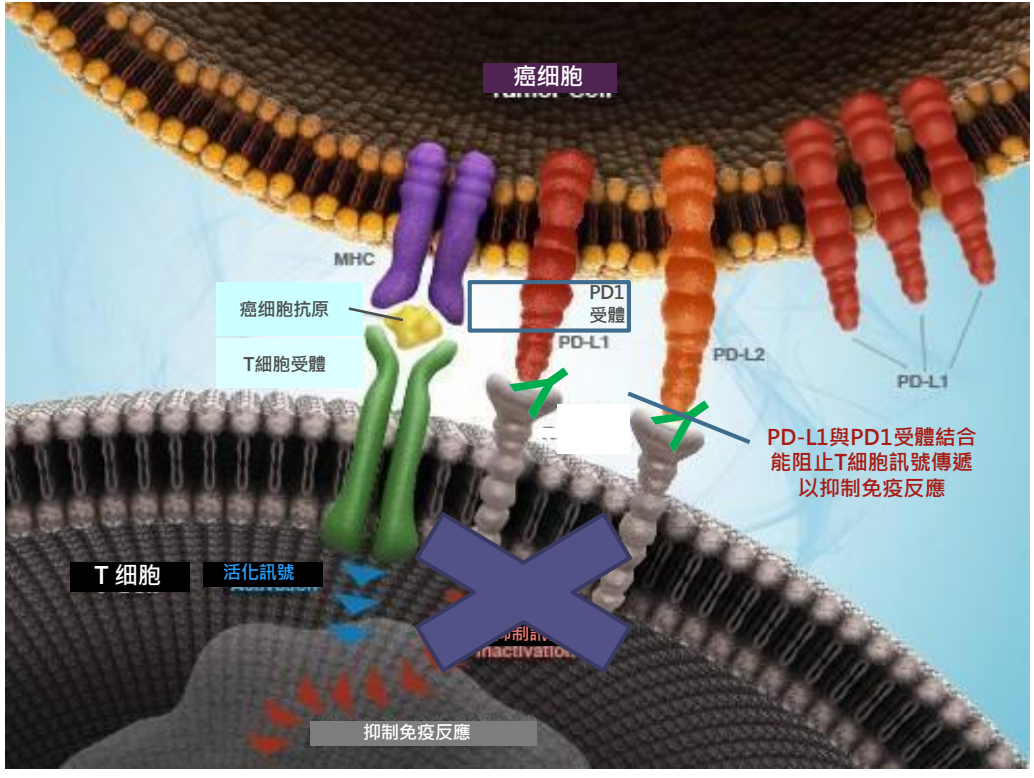
抗PD-1藥物的作用



抗PD-1藥物原理乃 刺激白血球認知癌細 胞,阻斷T細胞與腫瘤 細胞之間PD-1/PD- L1信號通路,透過自 身免疫力攻擊癌細胞。

Y 抗PD-1藥物，例如Pembrolizumab

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▼ PD-L1 蛋白

▼ PD-1 受體

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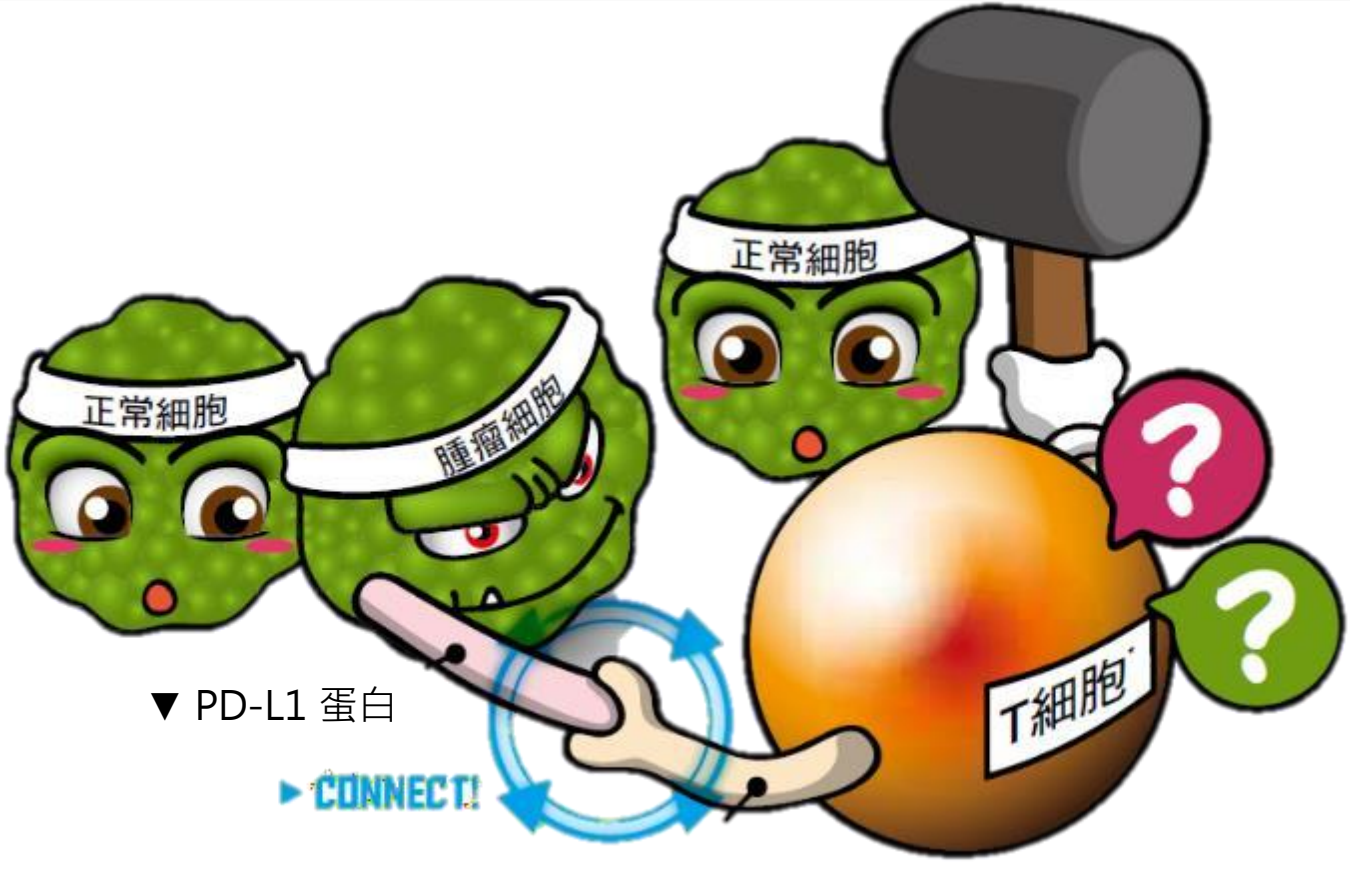

▼ PD-L1 蛋白

▼ PD-1 受體

*T 細胞為白血球細胞的一種

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▼ PD-L1 蛋白

▼ PD-1 抑制劑

▼ PD-1 受體

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*T 細胞為白血球細胞的一種

Anti-PD-1和anti-PD-L1藥物概觀

產品	Pembrolizumab [a]	Nivolumab [a]	Avelumab [a]	Atezolizumab [b]	Durvalumab [a]
類別	Anti-PD-1	Anti-PD-1	Anti-PD-1	Anti-PD-L1	Anti-PD-L1
公司	MSD	BMS	EMD serono & Pfizer	Roche	AstraZeneca
使用頻率	Q3W	Q2W	Q2W	Q3W	Q2W
獲得美國FDA批准在非小細胞肺癌患者使用	✓ 一線 (TPS> 50%)和二線	✓ 二線		✓ 二線	

Pembrolizumab目前在香港只獲得二線非小細胞肺癌和一線黑素瘤的註冊。 有關顯示詳細信息，請參閱每個產品的包裝插頁。

a根據各產品US Prescribing Information 2017 [25, 26, 28, 29]

b根據Atezolizumab US Prescribing Information 2016 [27]

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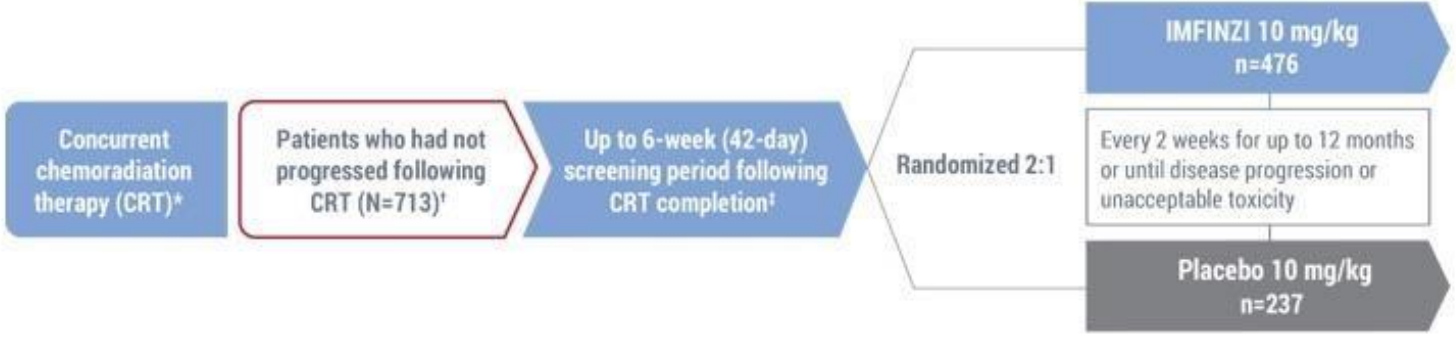
免疫療法與第三期肺癌

The PACIFIC study was a randomized, double-blind, placebo-controlled, international study of 713 patients with unresectable Stage III (locally advanced) NSCLC[1,2]



在第三期放化療之後，接受一年的免疫治療

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免疫療法與第三期肺癌

Baseline demographics[1,2]		
Gender	70% Male	30% Female
Age	55% Below age 65	45% Age 65 & older
Smoking history	91% Current/ former smoker	9% Never smoked

Disease characteristics[2]		IMFINZI	Placebo
Stage at diagnosis#	IIIA	53%	53%
	IIIB	45%	45%
Histology	Squamous	47%	43%
	Non-squamous	53%	57%
PD-L1 expression**	25% or more	24%	19%
	Less than 25%	39%	44%
	Unknown	37%	37%
EGFR mutation††	Positive	6%	6%
	Negative	66%	70%
	Unknown	28%	24%

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提升無變化存活率16.8 vs 5.6月

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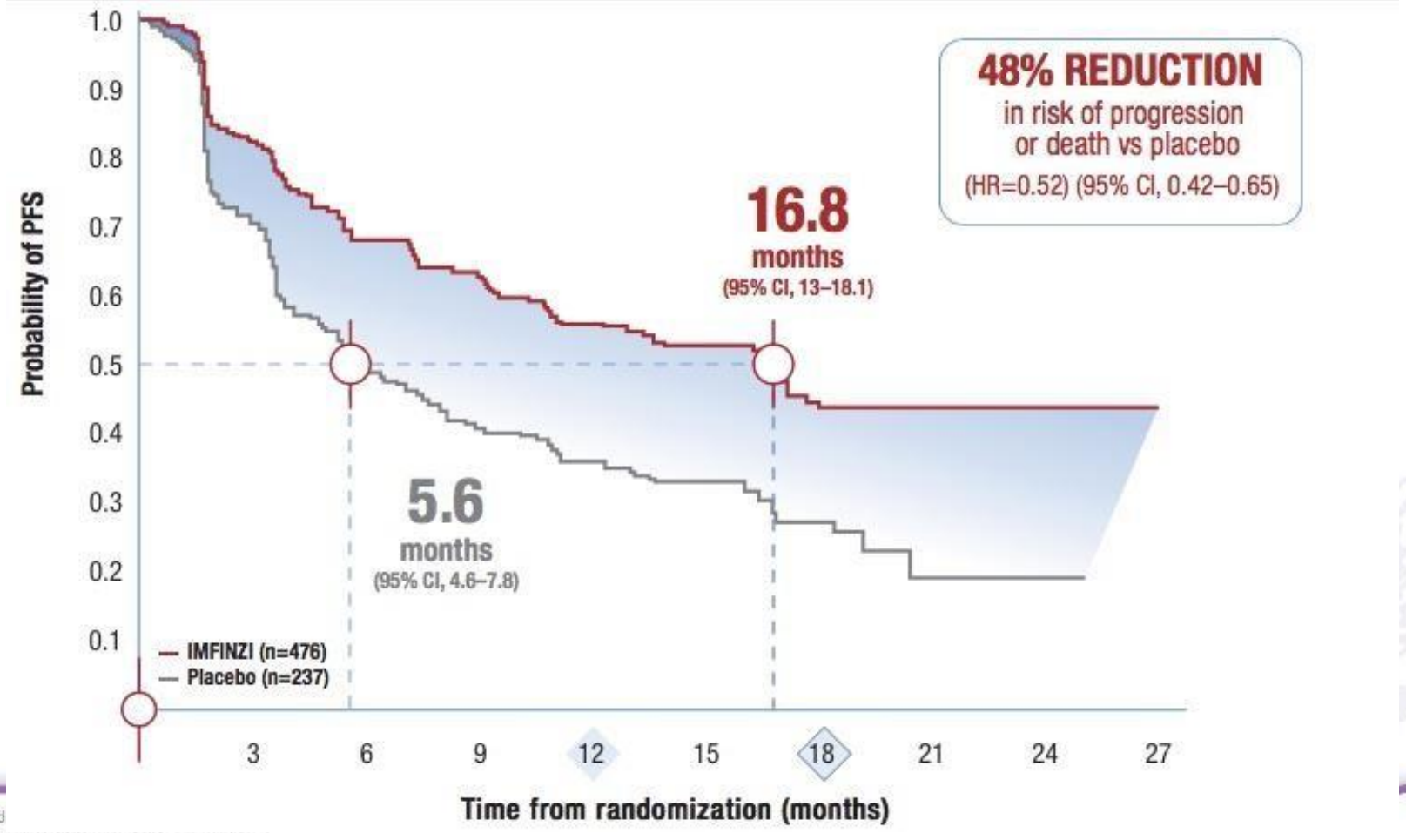

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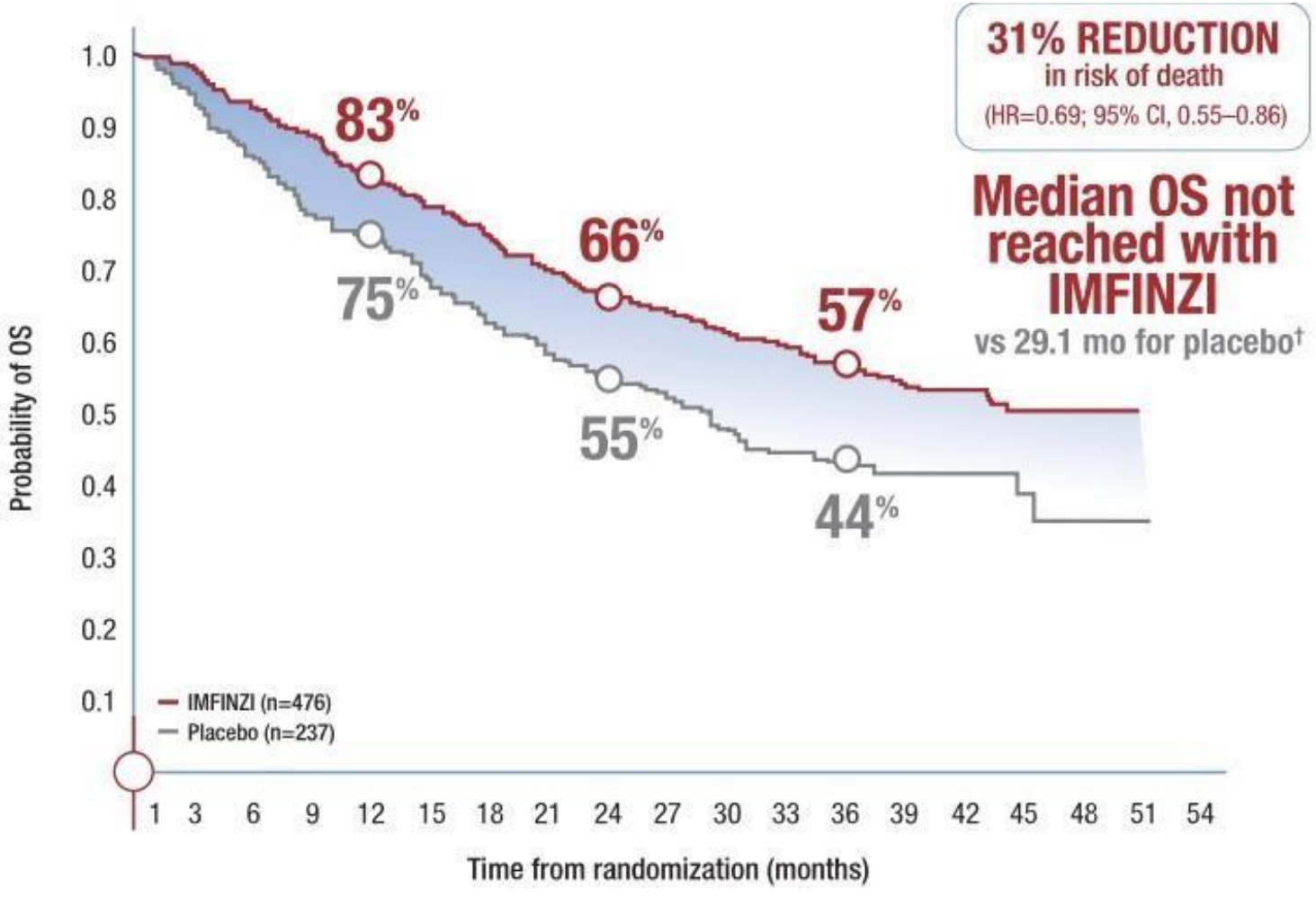
提升整體存活率



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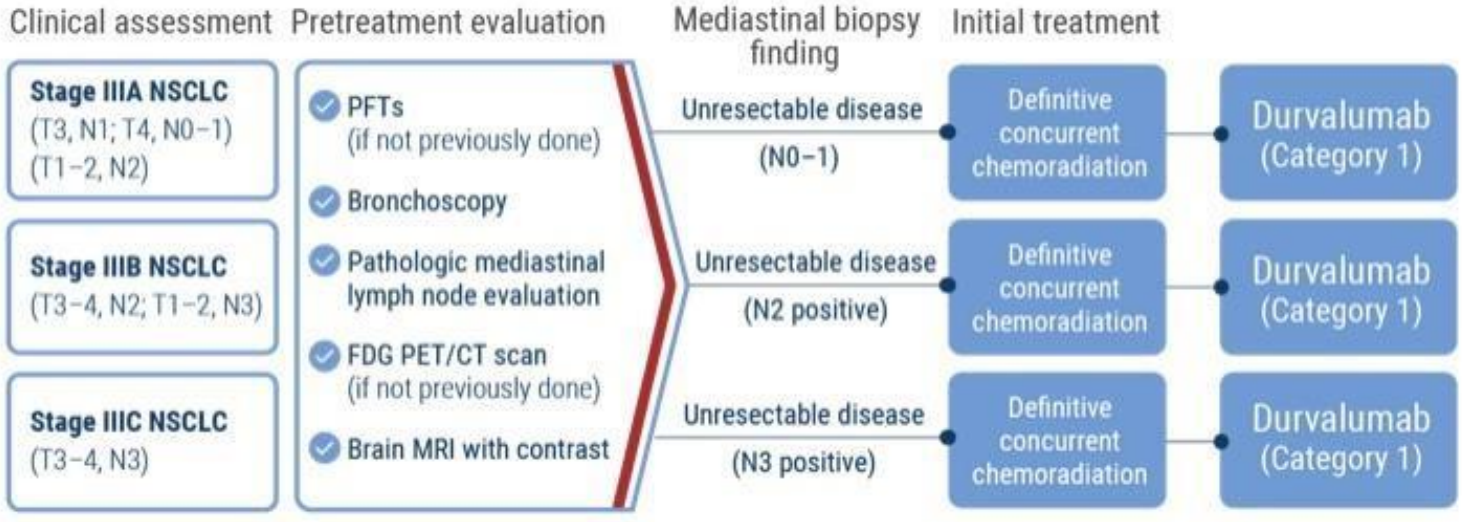
NCCN 第三期肺癌治療包括免疫治療

Stage III NSCLC whose disease has not progressed following chemoradiation therapy†5



- NCCN recommends multidisciplinary evaluations be done before treatment[5]

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副作用

Adverse Reaction	IMFINZI (n=475)		Placebo (n=234)	
	All Grades	Grades 3–4	All Grades	Grades 3–4
Respiratory, thoracic, and mediastinal disorders				
Cough/Productive cough	40%	0.6%	30%	0.4%
Pneumonitis†/Radiation pneumonitis	34%	3.4%	25%	3.0%
Dyspnea‡	25%	1.5%	25%	2.6%
Gastrointestinal disorders				
Diarrhea	18%	0.6%	19%	1.3%
Abdominal pain§	10%	0.4%	6%	0.4%
Endocrine disorders				
Hypothyroidism‖	12%	0.2%	1.7%	0%
Skin and subcutaneous tissue disorders				
Rash¶	23%	0.6%	12%	0%
Pruritus#	12%	0%	6%	0%
General disorders				
Fatigue**	34%	0.8%	32%	1.3%
Pyrexia	15%	0.2%	9%	0%

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免疫療法的研究-第四期肺癌

- KEYNOTE-001研究是一項評價Pembrolizumab治療非小細胞肺癌的有效性和安全性的第一期臨床研究。

- 這項研究的主要目標是評估Pembrolizumab治療非小細胞肺癌病人中的緩解率 (ORR)。

- 這項研究招攬了495名晚期非小細胞肺癌患者(包括沒有接受過任何治療和接受過治療)。

- 劑量方案為: 2mg/kg Q3W、10mg/kg Q3W或 10mg/kg Q2W, 直至疾病進展、死亡、退出研究或無法 耐受毒性。

- 不同劑量組間在有效性和安全性方面無明顯差異
- 美國FDA及香港衛生署批准Pembrolizumab的治療劑量為2mg/kg Q3W。[25,36]

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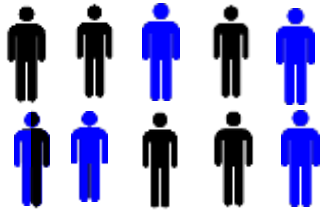
根據Pembrolizumab US及 HK Prescribing Information 2017 [25, 36]

Pembrolizumab為醫生處方藥物, 有關藥物療效或其他詳情, 敬請諮詢醫生之專業意見.

免疫治療法在**非小細胞肺癌的有效性**

2015年4月19日發表在《新英格蘭醫學雜誌》上的KEYNOTE-001研究結果顯示, 抗PD-1藥物 Pembrolizumab對晚期非小細胞肺癌有持久的抗腫瘤 活性。

有腫瘤PD-L1高表達(≥50%) 的患者中緩解率高達 (n=73):



45%

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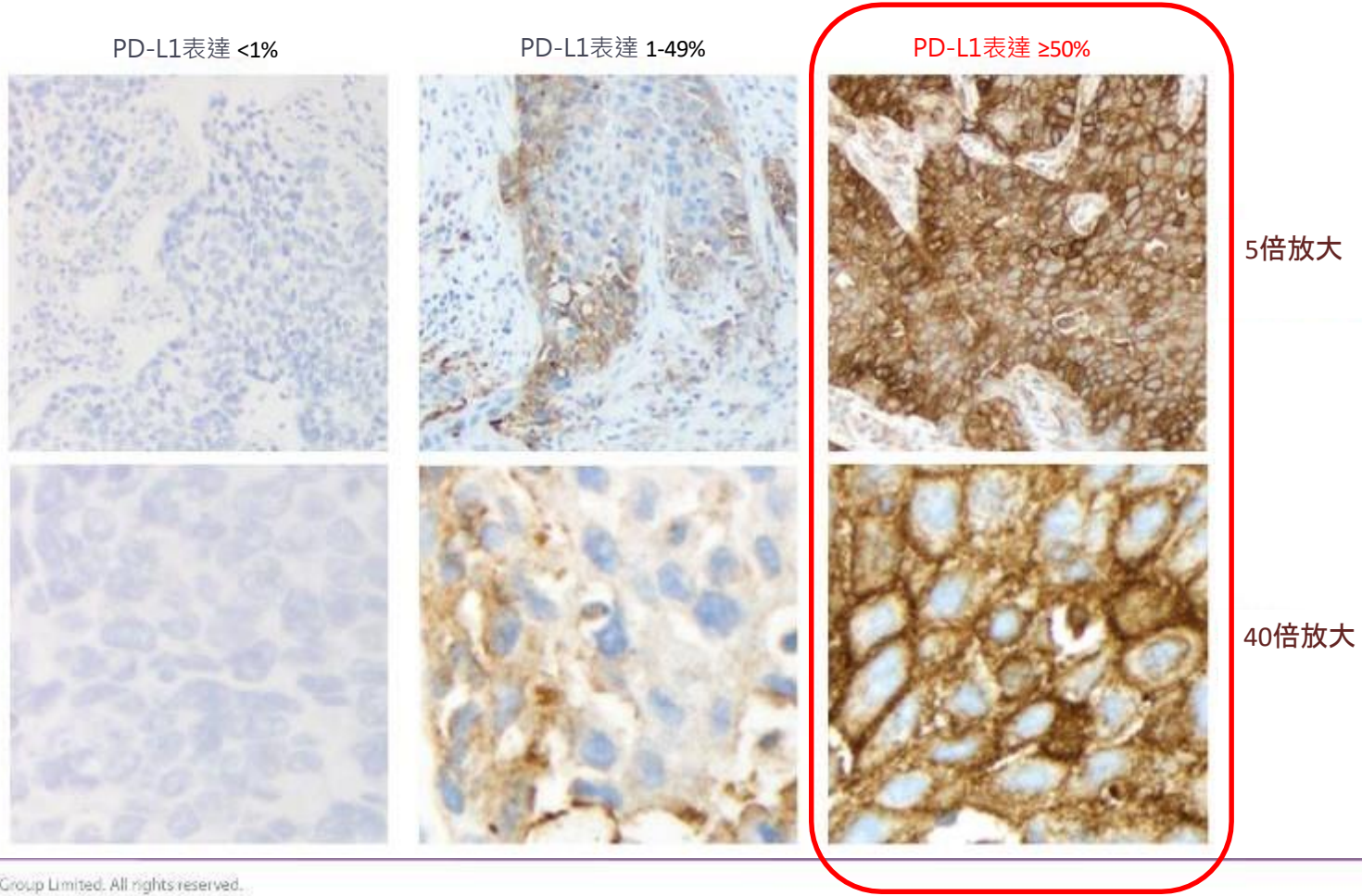
PD-L1 免疫組織化學染色(非小細胞肺癌樣本)
臨床試驗分析



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Garon EB et al. *N Engl J Med* 2015;372:2018-28.

免疫治療法在**非小細胞肺癌的安全性** [35]

該研究的毒性反應是可控的, 3級以上(嚴重)不良反應發生 率為**9.5%** (47/495)。

最常見的不良反應為疲乏、皮膚痕癢和食欲不振。

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Pembrolizumab為醫生處方藥物, 有關藥物療效或其他詳情, 敬請諮詢醫生之專業意見.

免疫療法的研究-肺癌 (2):

KEYNOTE-010 [37]



	共同主要終點		次要終點	
	生存時間中位數OS (腫瘤PD-L1 表達 ≥50%)	生存時間中位數 PFS (腫瘤PD-L1 表達≥50%)	總緩解率 (ORR) (腫瘤PD-L1 表達≥50%)	3-5級不良反應 發生率(腫瘤PD-L1 表達 ≥50%)
Pembrolizumab (2mg/kg), n=345	14.9 個月	5.0 個月	30%	13%
Pembrolizumab (10mg/kg), n=346	17.3 個月	5.2 個月	29%	16%
Docetaxel, n=343	8.2 個月	4.1 個月	8%	35%
P-value	P≤0.0002（2mg與Docetaxel比較）	P≤0.0001（2mg與Docetaxel比較）	P<0.0001（2mg與Docetaxel比較）	N/A

對於PD-L1 高表達和接受過第一線含鉑化療後惡化的晚期非小細胞肺癌患者，
Pembrolizumab 比 Docetaxel 能有效提高46%存活率， HR: 0.54 (P=0.0002) 。

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Pembrolizumab的註冊劑量為2 mg/kg Q3W.

Pembrolizumab為醫生處方藥物, 有關藥物療效或其他詳情, 敬請諮詢醫生之專業意見.

其他免疫療法及於**非小細胞肺癌的**用途

- Nivolumab用於治療二線非小細胞肺癌患者(接受含鉑化療後有惡化或帶有EGFR/ALK基因突變而接受目標靶治療後有惡化的患者)
- Atezolizumab 用於治療二線已擴散的非小細胞肺癌患者 (接受含鉑化療一線化療期間或之後有惡化的患者)

Nivolumab及Atezolizumab 為醫生處方藥物, 有關藥物療效或其他詳情, 敬請諮詢醫生之專業意見.

根據Nivolumab US Prescribing Information 2017 [26]

根據Atezolizumab US Prescribing Information 2016 [28]

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免疫療法的副作用

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- 疲勞是最常見的副作用，同時還會可能有發燒，發冷，噁心與注射部位的反應。患者接受免疫治療需要觀察潛在的副作用如：

- 肺炎
- 結腸炎
- 肝炎與腎炎
- 皮疹
- 內分泌疾病包括甲狀腺異常與腎上腺功能不全

- 幸運的是，如此大範圍的副作用能夠通過免疫抑製藥物控制，如皮質類固醇藥與抗組胺藥，它們能夠抑制炎症的過度反應

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5. 乳腺癌治療

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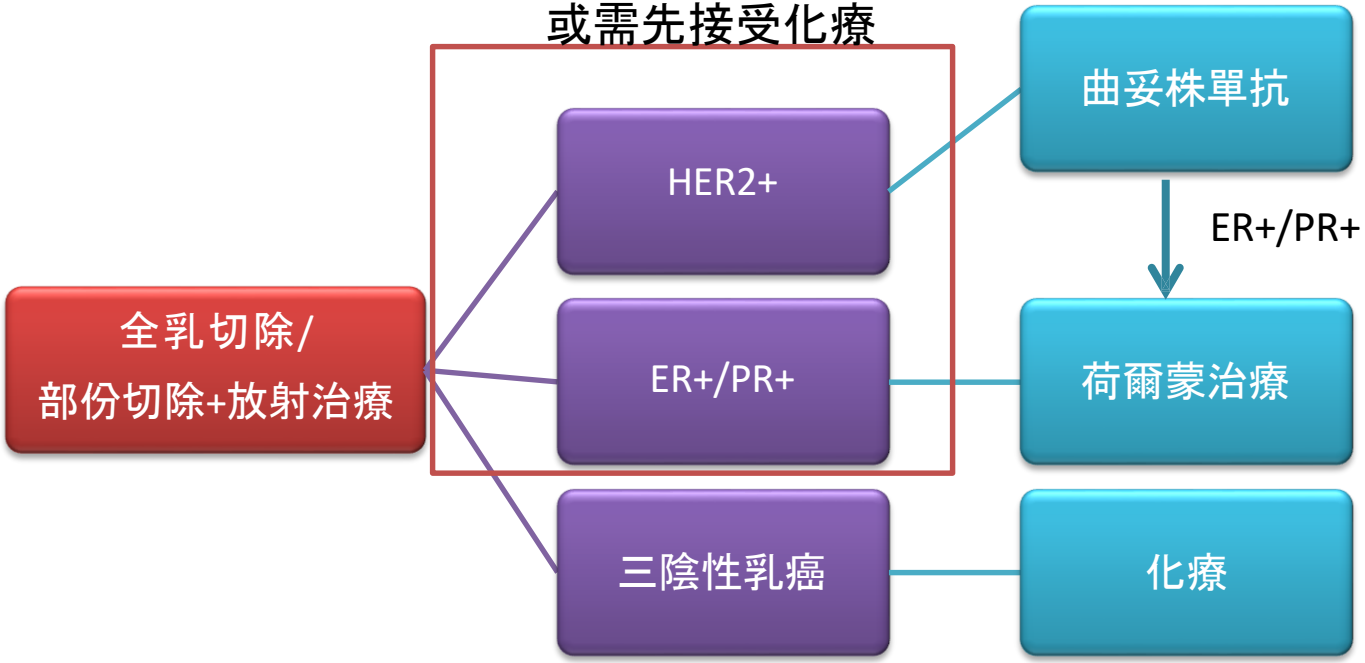
不同期數的乳癌治療方法[1]
(第I期)



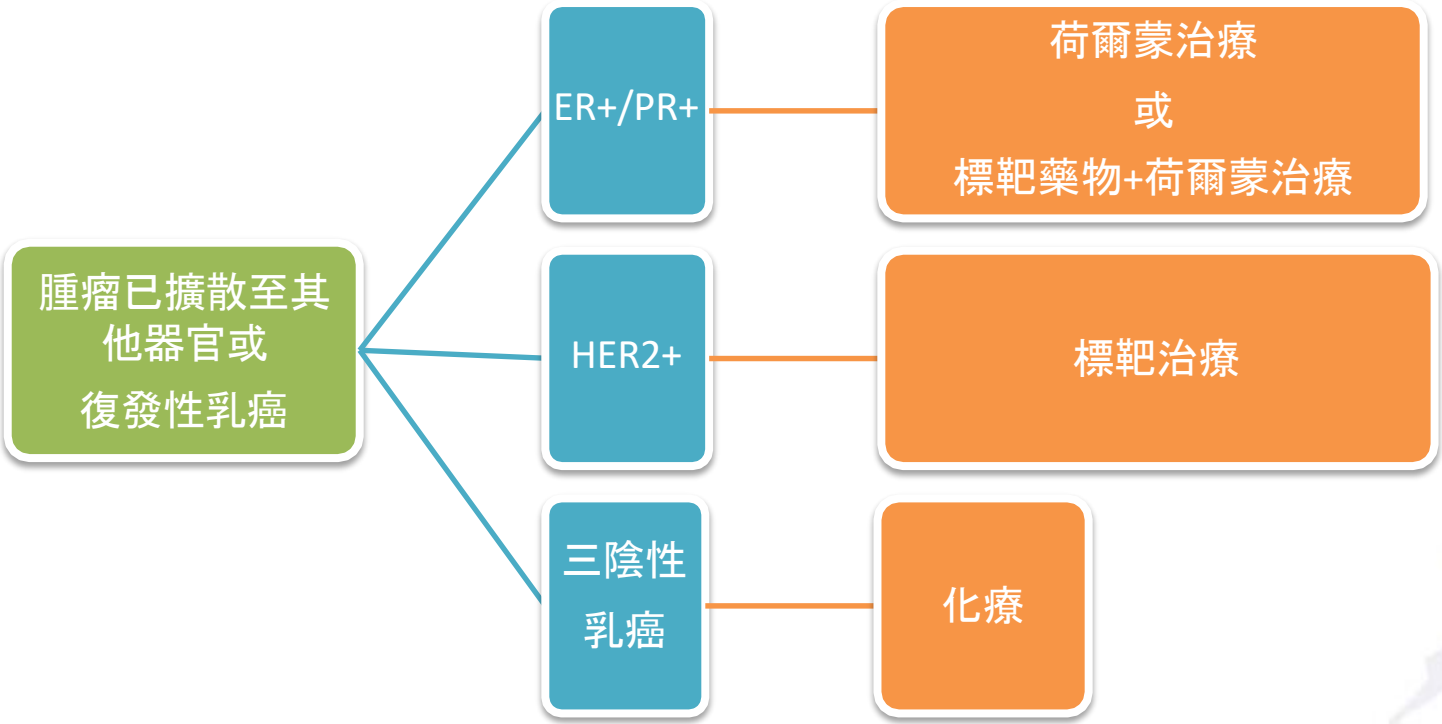
1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®):Breast Cancer. Version 2.2016.

不同期數的乳癌治療方法 (第II/III期)[1]

- 與治療方與第I期相似
- 如欲進行局部切除手術，需要在手術前接受化療/荷爾蒙/曲妥株單抗治療，視乎乳癌類型而定

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®):Breast Cancer. Version 2.2016.

不同期數的乳癌治療方法 (第IV期)[1]

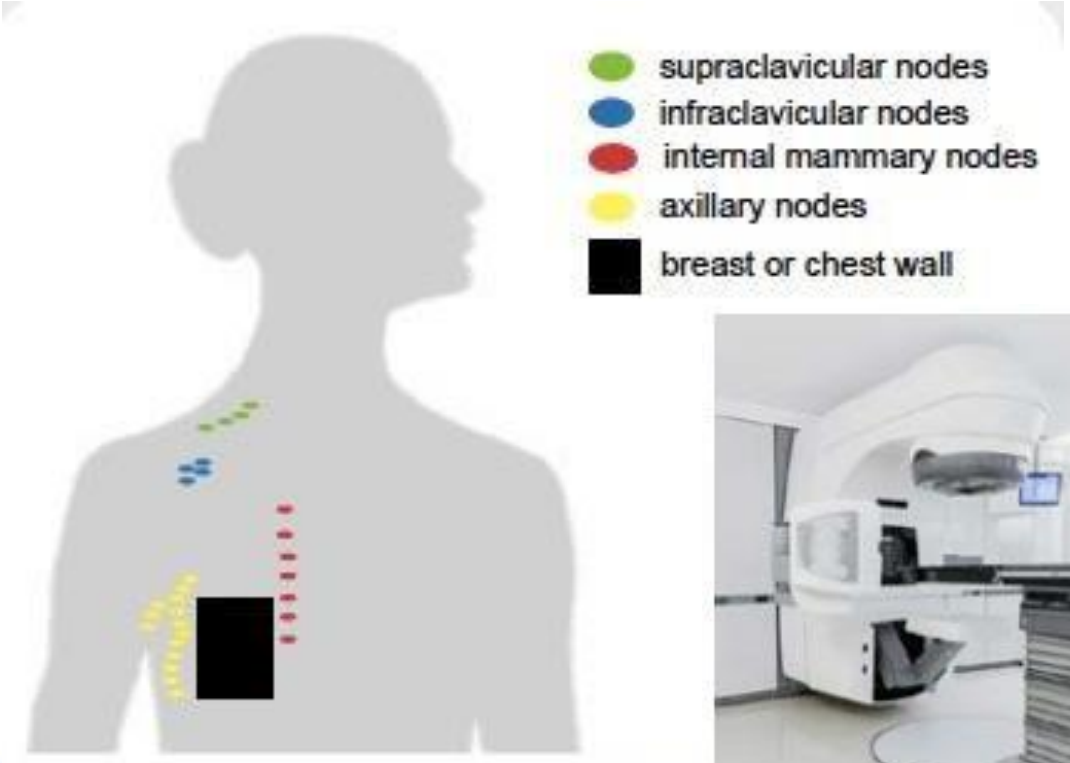


- 倘若晚期乳癌患者乳房出現潰爛或傷口，也可考慮再加手術或電療處理

1. American Cancer Society, 2016. Breast Cancer. Available at: <http://www.cancer.org/acs/groups/cid/documents/webcontent/003090-pdf.pdf> [Accessed: August 8, 2016].

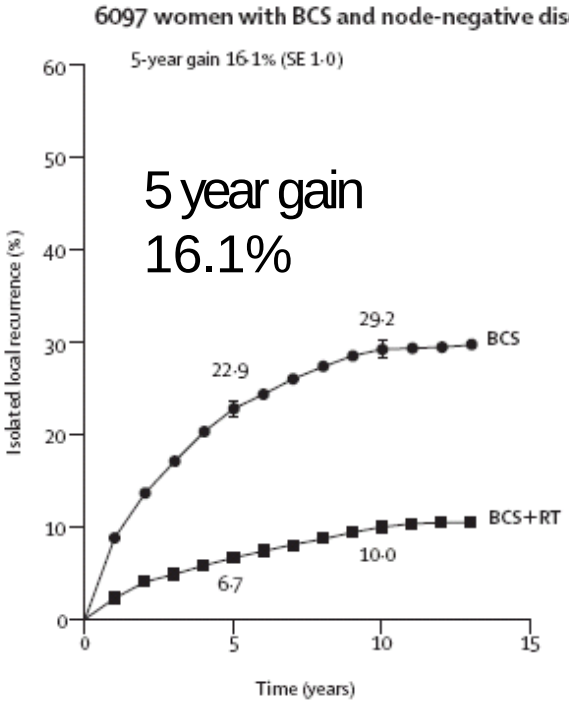
放射治療

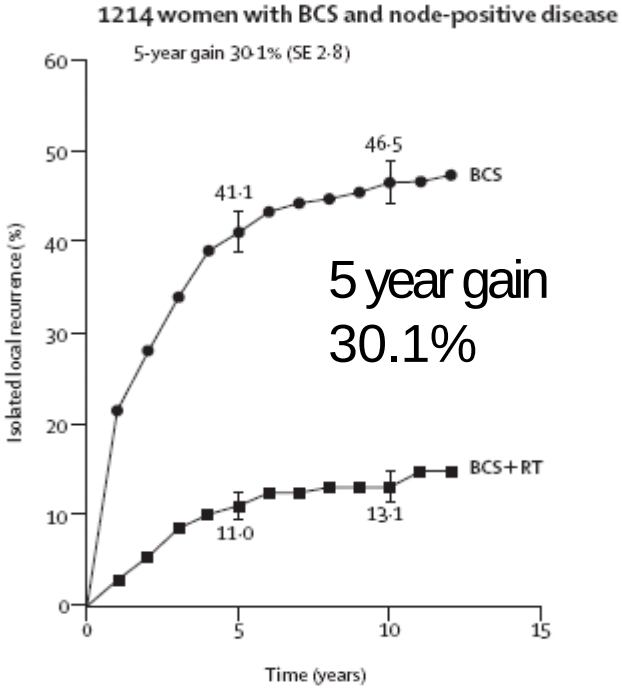
利用高能量的射線照射受腫瘤受影響的部位，直接殺死癌細胞





在局部切除手術患者，加上放射治療能減少原位復發達三成





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EBCTCG meta-analysis. Lancet 2005; 366: 2087–2106

放射治療適用情況

- 局部切除手術患者 (原位癌侵襲性導管癌癌)
- 完成全乳切除手術但腫瘤較大或淋巴結已受癌細胞影響的患者

- 副作用
- 乳房腫脹
- 受照射的位置發紅、長出水泡或脫皮
- 疲倦
- 部份手臂神經受損
- 淋巴水腫(腋下放射治療)

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化學治療

- 小紅莓類 Adriamycin, Epirubicin
- 紫杉醇類Taxol, Taxotere
- 鉑金類 cisplatin, carboplatin
- 吉西他濱 (gemcitabine)
- 卡培他濱 (capecitabine)

- 適用情況
- 手術後：消滅肉眼看不見的癌細胞，降低復發機會
- 手術前：縮小腫瘤，降低手術的創傷性
- 晚期乳癌：控制病情

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化學治療有甚麼副作用可能會出現？

可能出現的副作用	應對方法
噁心和嘔吐	如有需要，可服用醫生處方的止噁心藥物 避免進食油膩、辛辣、酸的食物 服用抗酸劑，以紓緩不適
疲倦	多做簡單的運動 多休息
便秘	多吃高纖維的食物，例如水果和蔬菜 每天喝八至十杯不含酒精的飲料 如有需有，可服用醫生處方的藥物，例如大便柔軟劑，以紓緩便秘的問題
脫髮	在療程開始前訂製一個跟原來髮質相似的假髮 可考慮佩戴帽子或頭巾 使用溫和的洗髮露 避免電髮和染髮

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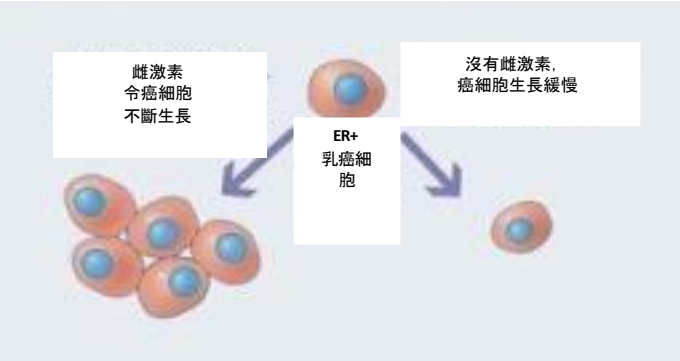
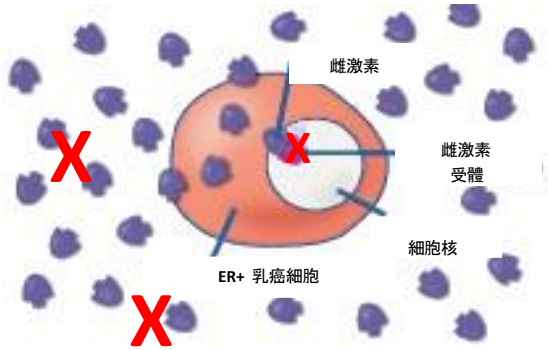
荷爾蒙治療[1]

- 荷爾蒙受體呈陽性**(ER+/PR+)**患者的腫瘤受到荷爾蒙刺激，會不斷生長



- 荷爾蒙治療
  - 阻截荷爾蒙接觸腫瘤
  - 降低體內荷爾蒙數量



- 適用情況：
  - 手術前
  - 於手術後降低復發機會
  - 乳癌復發
  - 乳癌擴散至身體其他地方

1. American Cancer Society, 2016. Breast Cancer. Available at: <http://www.cancer.org/acs/groups/cid/documents/webcontent/003090-pdf.pdf> [Accessed: August 8, 2016].

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常見的荷爾蒙治療[1]

選擇性雌激素受體調節劑 **(SERM):** 阻截荷爾蒙接觸腫瘤	芳香環轉化**酶抑制劑(AI):** 降低體內荷爾蒙數量	抑制卵巢功能
更年期前或更年期後患者	更年期後患者	未達更年期者
他莫昔芬(tamoxifen) 法洛德(Fulvestrant)	Exemestane Letrozole Anastrozole	切除卵巢 促性腺釋放激素類似物(LHRH analog)，以抑制卵巢製造雌性荷爾蒙

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1. American Cancer Society, 2016. Breast Cancer. Available at: <http://www.cancer.org/acs/groups/cid/documents/webcontent/003090-pdf.pdf> [Accessed: August 8, 2016].

荷爾蒙治療副作用[1]

選擇性雌激素受體調節劑(SERM)	芳香環轉化酶抑制劑(AI)
疲倦 潮熱 陰道乾涸或出現分泌物 情緒化	
患上子宮內膜癌、子宮癌及深層靜脈栓塞的機會增加	肌肉疼痛、關節痛、骨質疏鬆及骨折

1. American Cancer Society, 2016. Breast Cancer. Available at: <http://www.cancer.org/acs/groups/cid/documents/webcontent/003090-pdf.pdf> [Accessed: August 8, 2016].

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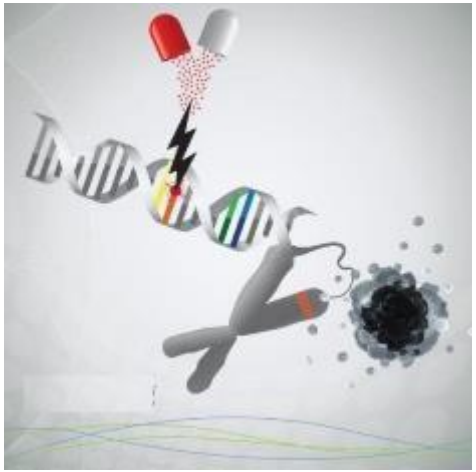
標靶藥物治療[1]

- 針對癌細胞的特點進行攻擊，不會如化療般針對所有快速生長的細胞
- 在大部份情況下，標靶藥物的副作用較化療輕



網上圖片

1. American Cancer Society, 2016. Breast Cancer. Available at: <http://www.cancer.org/acs/groups/cid/documents/webcontent/003090-pdf.pdf> [Accessed: August 8, 2016].

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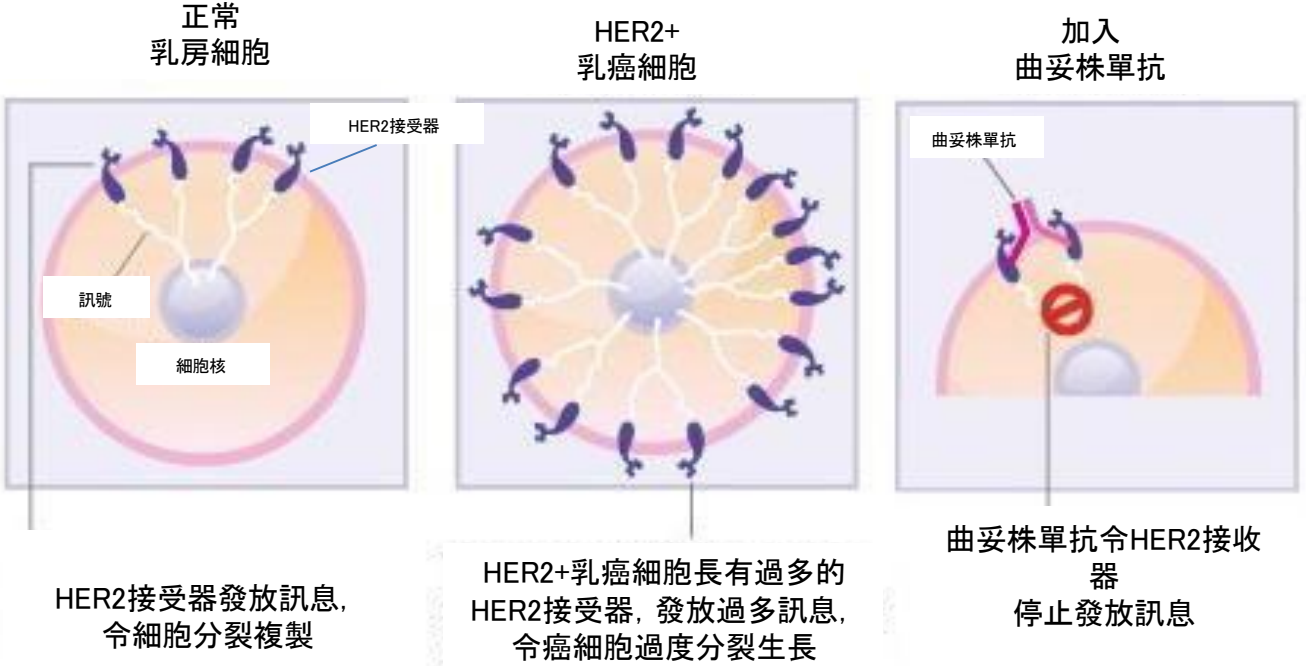
常見的乳癌標靶藥物[1]

適用於**HER2+**乳癌患者	適用於**ER+**乳癌患者**(**更年期後**)**
•曲妥株單抗Trastuzumab (靜脈滴注) •拉帕替尼Lapatinib(口服) •T-DM1(靜脈滴注) •帕妥珠單抗Pertuzumab(靜脈滴注)	•帕博西尼Palbociclib (口服) •依維莫司Everolimus(口服)

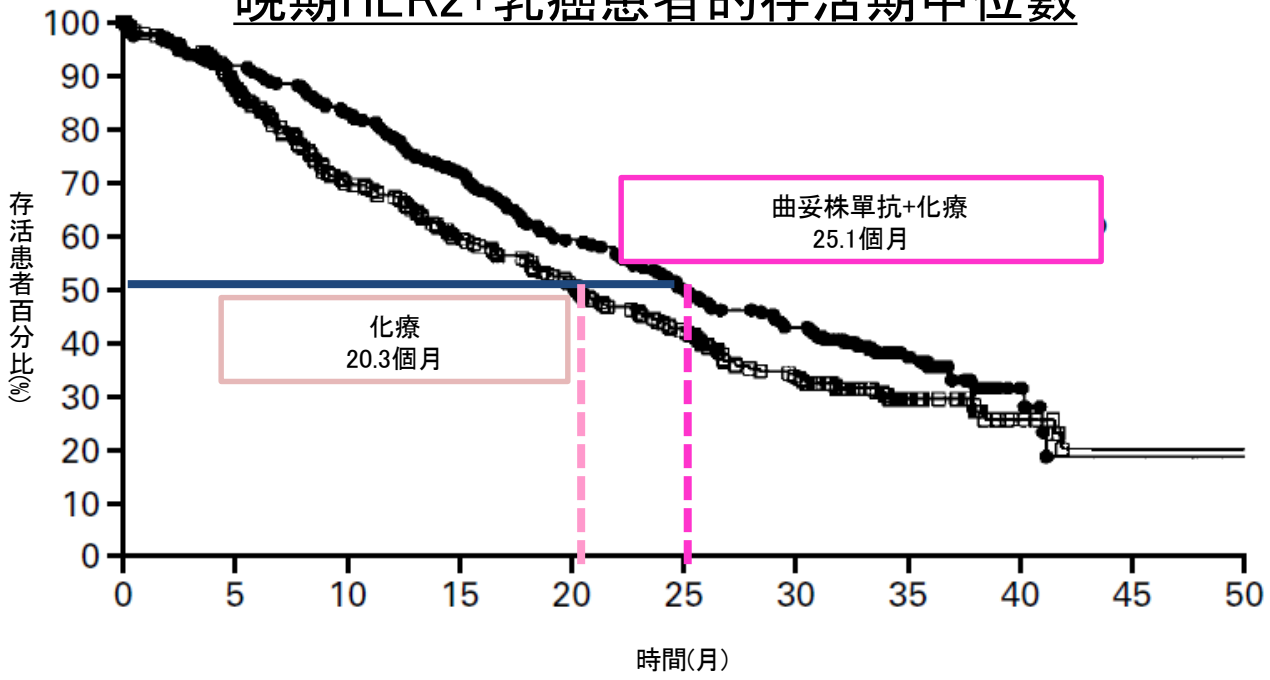
1. American Cancer Society, 2016. Breast Cancer. Available at: <http://www.cancer.org/acs/groups/cid/documents/webcontent/003090-pdf.pdf> [Accessed: August 8, 2016].

適用於HER2+乳癌患者的標靶藥物-曲妥株單抗[1, 2]



1. Albanell J et al. Adv Exp Med Biol. 2003;532:253-68.
2. Yeon CH et al . Invest New Drugs. 2005 Oct;23(5):391-409.

曲妥株單抗
可增加晚期HER2+乳癌患者壽命[1]



1. Slamon Dj et al. N Engl J Med 344 (11): 783-92, 2001.

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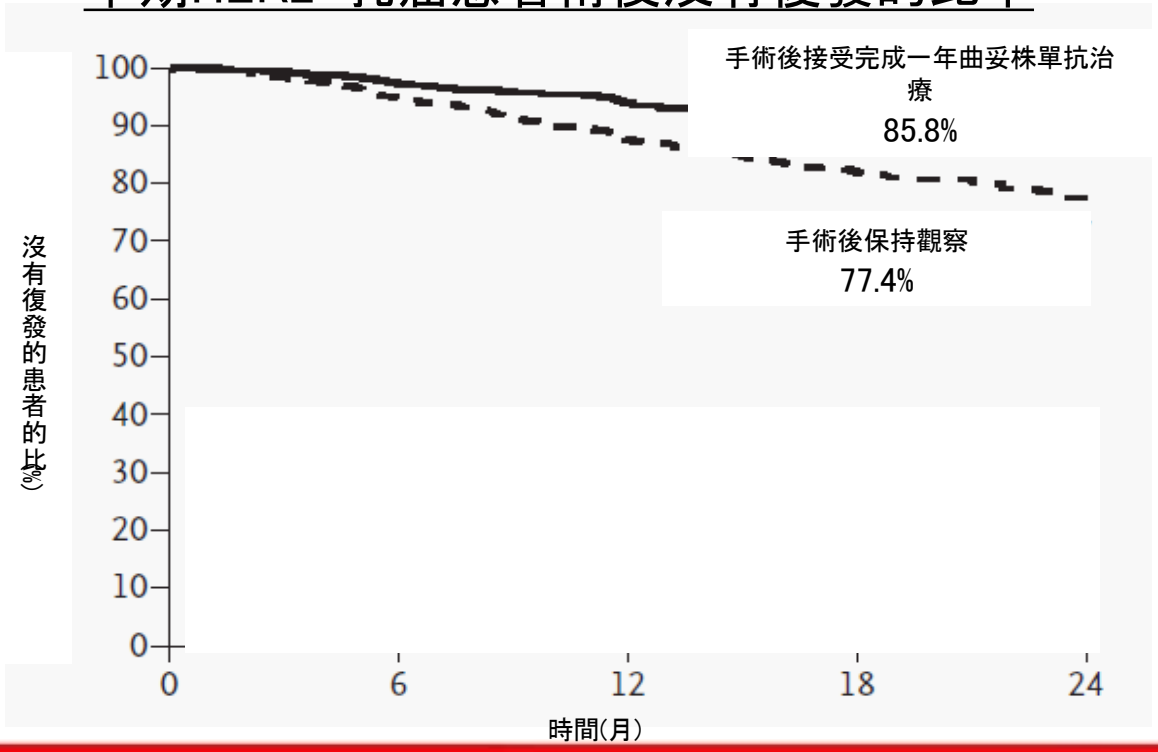
曲妥株單抗可減少
早期HER2+乳癌患者復發機會[1]

早期HER2+乳癌患者術後沒有復發的比率



1. Piccart-Gebhart MJ et al. N Engl J Med. 2005 Oct 20;353(16):1659-72.

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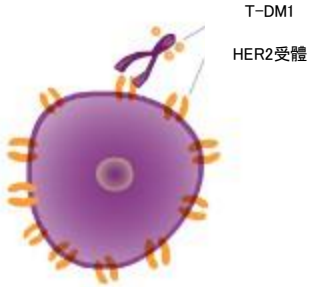
適用於HER2+乳癌患者的標靶藥物-T-DM1[1]

- T-DM1由抗體(曲妥株單抗)及抗細胞有絲分裂的化療組成

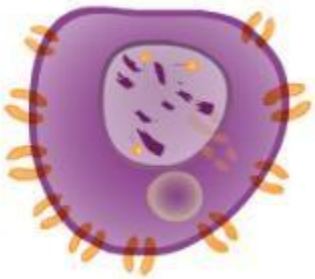
①T-DM1的抗體部份黏上HER2受體，阻止癌細胞繼續生長



②T-DM1黏上HER2受體後，會進入癌細胞



③T-DM1進入癌細胞後，抗體上的化療藥物會在癌細胞內釋放



④化療藥物進入癌細胞後，發揮破壞力，令癌細胞死亡



1. KADCYLA Prescribing Information. Genentech, Inc. 2016.

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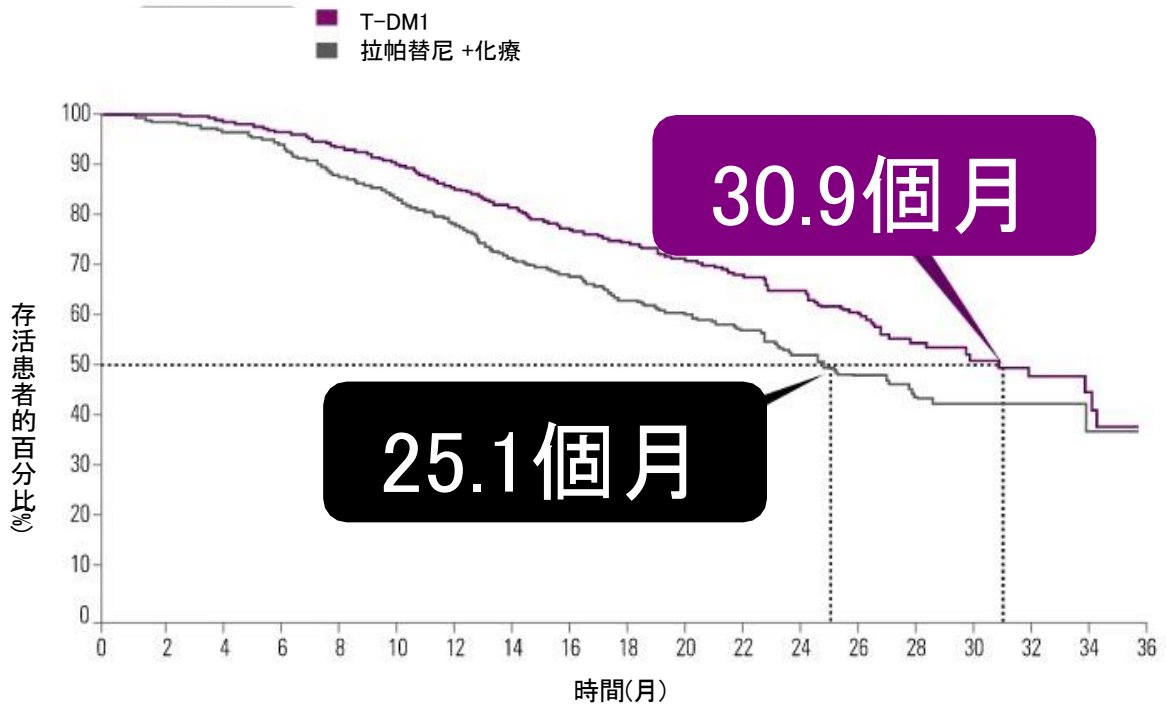
T-DM1可增加HER2+復發性乳癌患者的壽命[1]

HER2+乳癌復發性患者的存活期中位數



1Verma S et al. N Engl J Med. 2012 Nov 8;367(19):1783-91.

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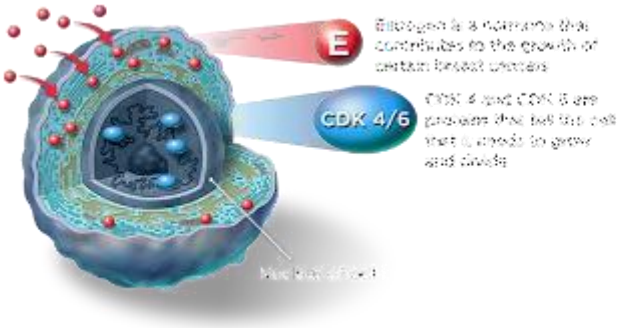
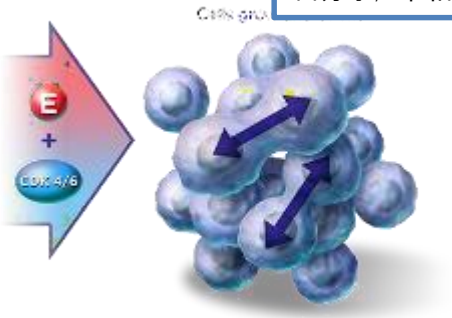
適用於ER+乳癌患者的標靶藥物-帕博西尼

①雌激素會刺激帶有荷爾蒙受體(ER+)的乳癌細胞生長[1-3]

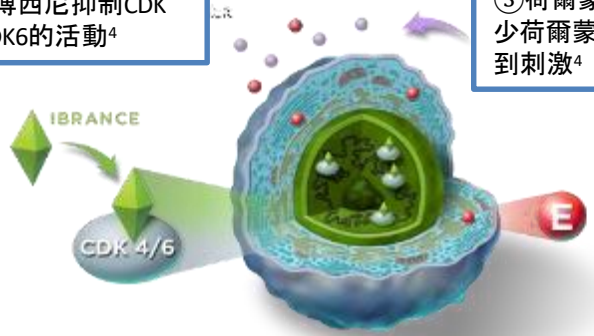


②當荷爾蒙體受到刺激，會激活細胞核內的CDK 4及CDK6這兩個蛋白分子，令細胞不斷分裂增生[1-3]



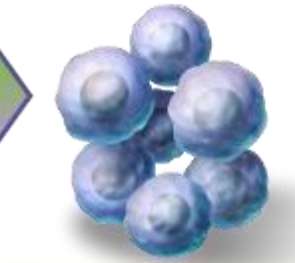
③荷爾蒙藥物減少荷爾蒙受體受到刺激[4]

④帕博西尼抑制CDK 4及CDK6的活動[4]



荷爾蒙藥物
+
帕博西尼

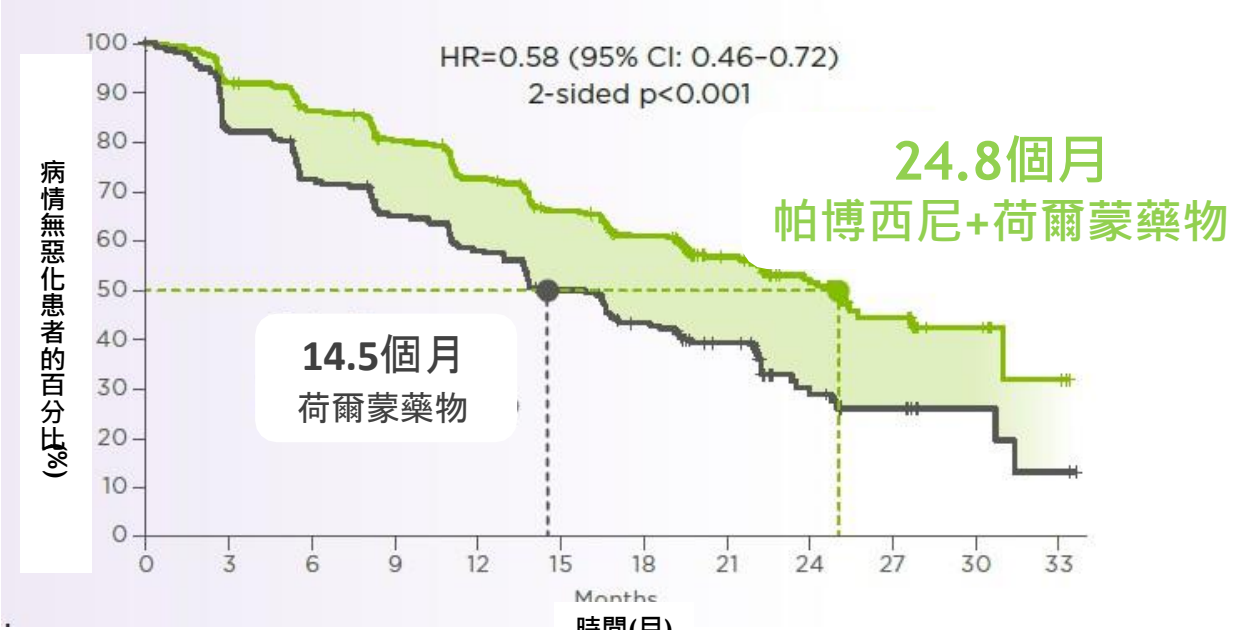
⑤ 當帕博西尼與荷爾蒙藥物一同使用時，可減慢乳癌細胞生長[4]



1. Prall OWJ et al. J Biol Chem. 1997;272(16):10882-10894. 2. Altucci L et al. Oncogene. 1996;12:2315-2324. 3. Weinberg RA. pRb and control of the cell cycle clock. In: The Biology of Cancer. 2nd ed. New York, NY: Garland Science; 2014. 4. IBRANCE® (palbociclib) Prescribing Information. New York, NY: Pfizer Inc. Feb 2015.

帕博西尼可增加ER+晚期乳癌患者的無惡化存活期多於兩年[1]

ER+晚期乳癌患者的無惡化存活期中位數



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1.Finn RS *et al.* Palbociclib and letrozole in Breast Cancer. *N Engl J Med* 2016;375:1925-36

帕博西尼的服用方法及副作用

服用方法[1]

- 口服藥物，與荷爾蒙藥物一同服用
- 連續服用21天後暫停7天，然後再重覆上述療程，期間毋須停止服用荷爾蒙藥物



副作用[2]

白血球細胞減少，貧血、疲倦、上呼吸道感染等



1. IBRANCE® (palbociclib) Prescribing Information. New York, NY: Pfizer Inc. Feb 2015.
2. Finn R et al. *Lancet Oncol.* 2015;16(1):25-35.

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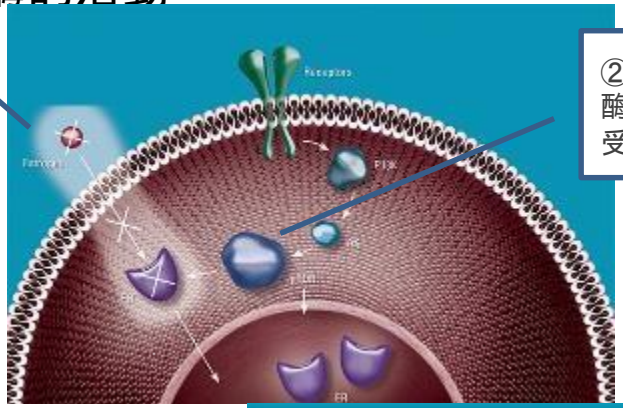
適用於ER+乳癌復發患者的標靶藥物-依維莫司[1-4]

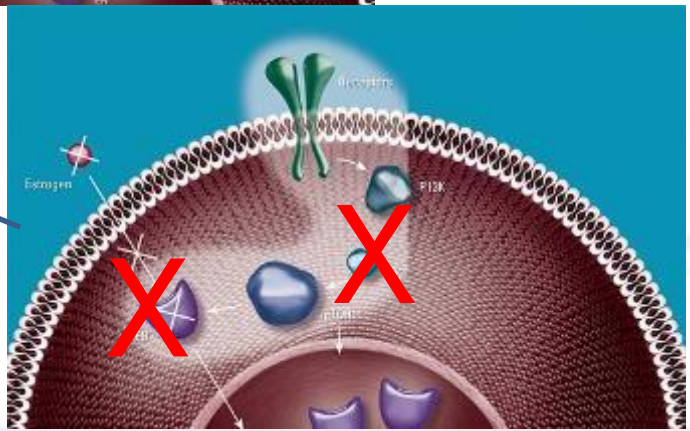
❖依維莫司可控制mTOR激酶的活動

①ER+乳癌細胞的雌激素受體受到刺激，會令癌細胞不斷生長



②約70%乳癌細胞的mTOR激酶發生突變，會影響雌激素受體，令癌細胞繼續增生

③以AI類荷爾蒙藥物減少雌激素，加上控制mTOR激酶的依維莫司，雙管齊下，控制乳癌細胞生長



1. Miller TW et al. J Clin Invest. 2010;120(7):2406-2413. 2. Miller TW et al. Breast Cancer Res. 2011;13(6):224.
3. Di Cosimo S et al. Nat Rev Clin Oncol. 2010;7(3):139-147. 4. Afinitor [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2016.

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6. 質子治療

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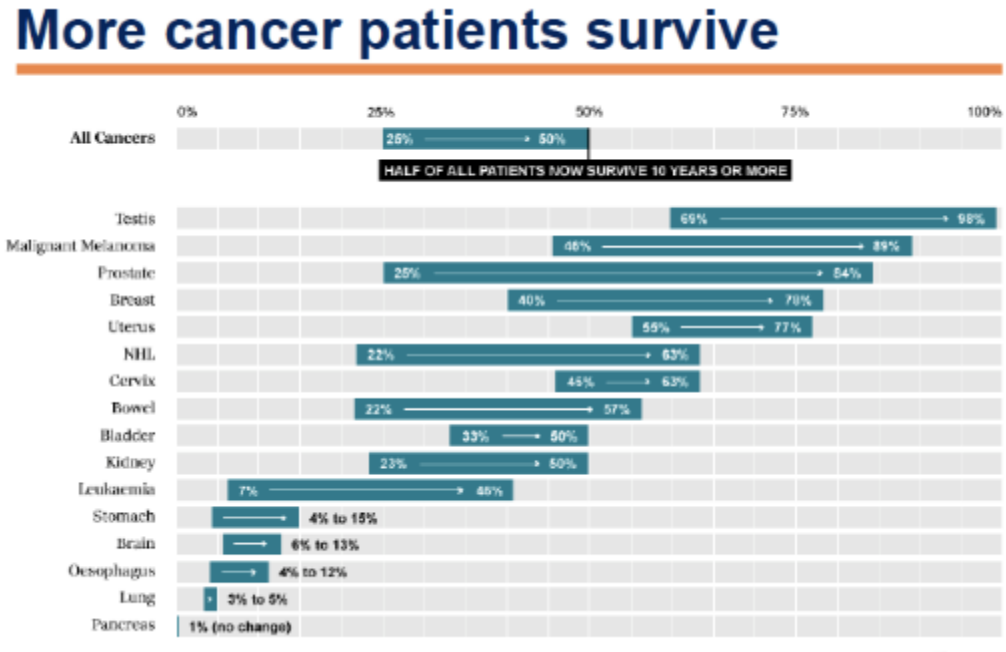
癌症存活率增加



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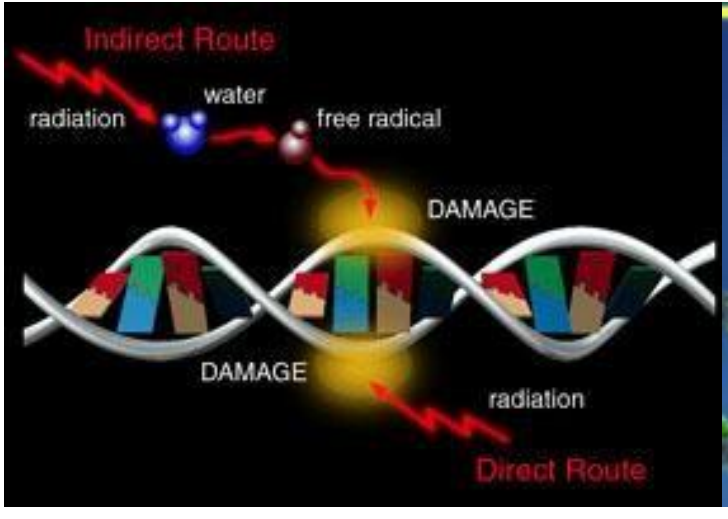
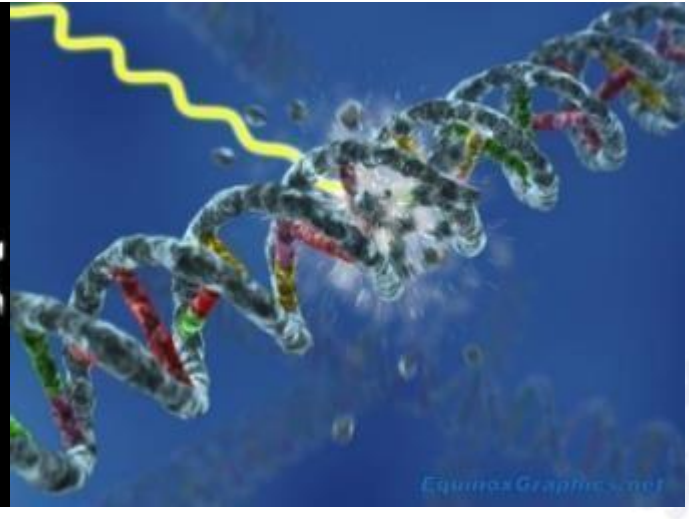
放射治療如何運作

- 儘管所需劑量不同，但科學界普遍認為，所有生物組織均可被輻射殺死
- 因此，我們將放射治療用於癌症治療





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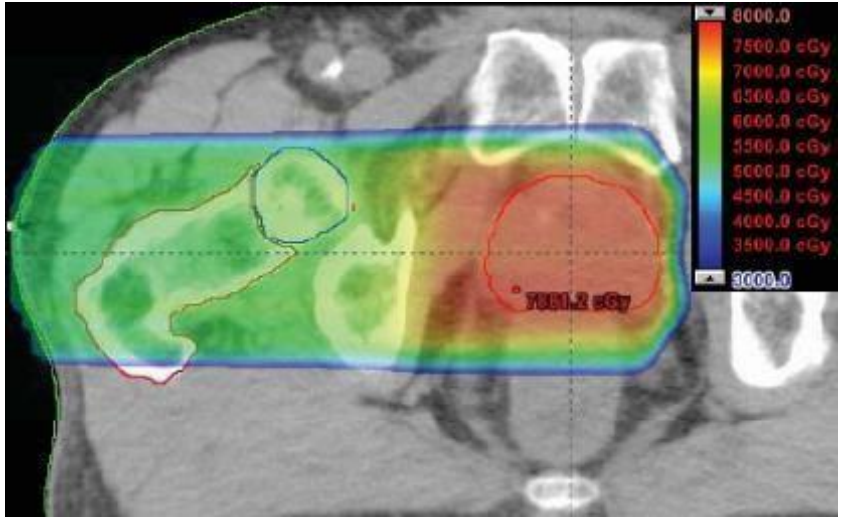
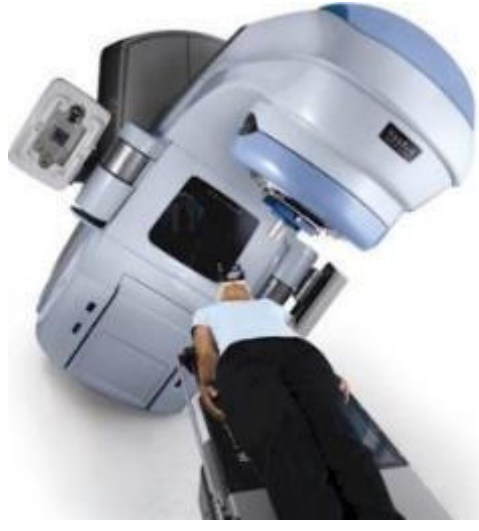
放射治療如何運作

在放射治療中，我們將放射治療從體外施加到患者體內，沿路徑的組織也會受到損害。





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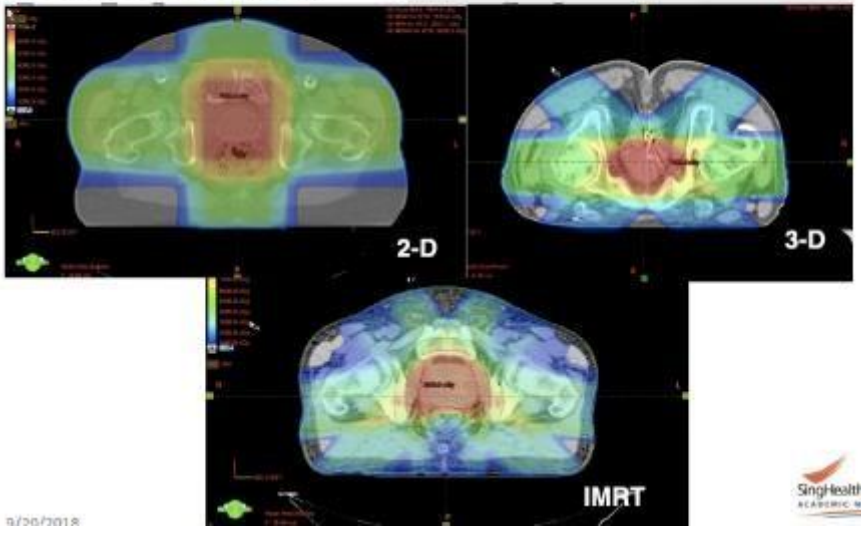
先進的電療技術: 2D/3D/IMRT

The Evolution of Conformal Radiotherapy

Improving conformality comes with very high cost; more normal tissue are exposed to radiation



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質子治療是甚麼？

- 質子治療是放射治療技術之一
- 傳統放射治療利用X光射線破壞腫瘤細胞
- 而質子治療主要利用氫氣作原料，分離氫氣中的質子及電子，加速質子集中破壞癌細胞

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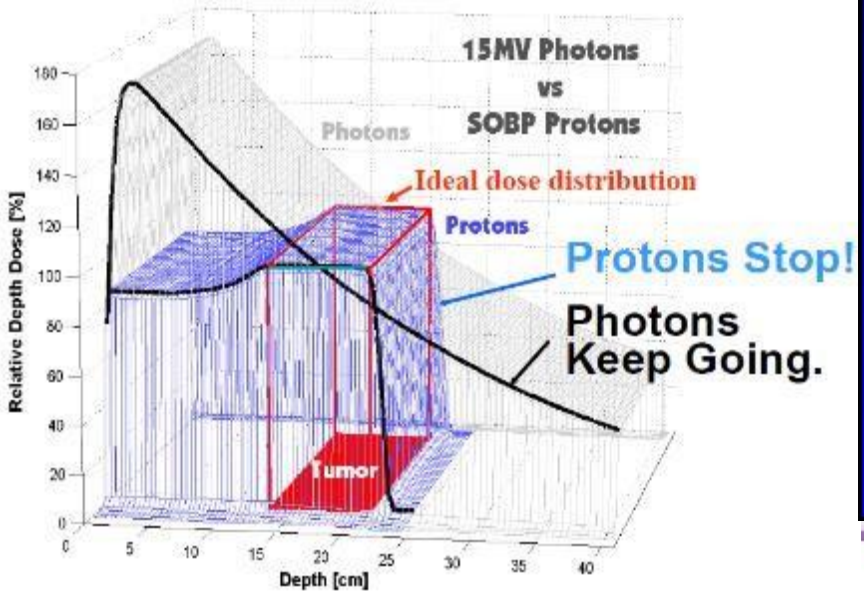
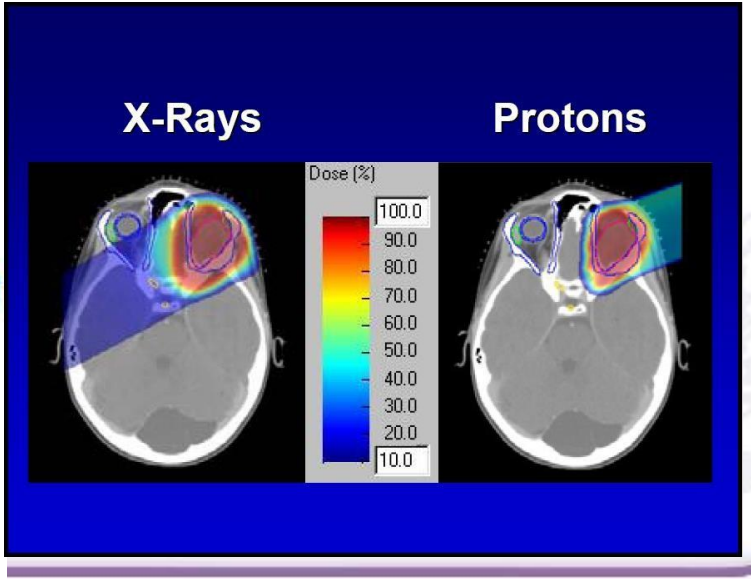
質子治療是甚麼？

- 基於質子獨有的物理特性，質子放射線穿越人體的初段射程期間，在正常組織中只釋放非常低的輻射





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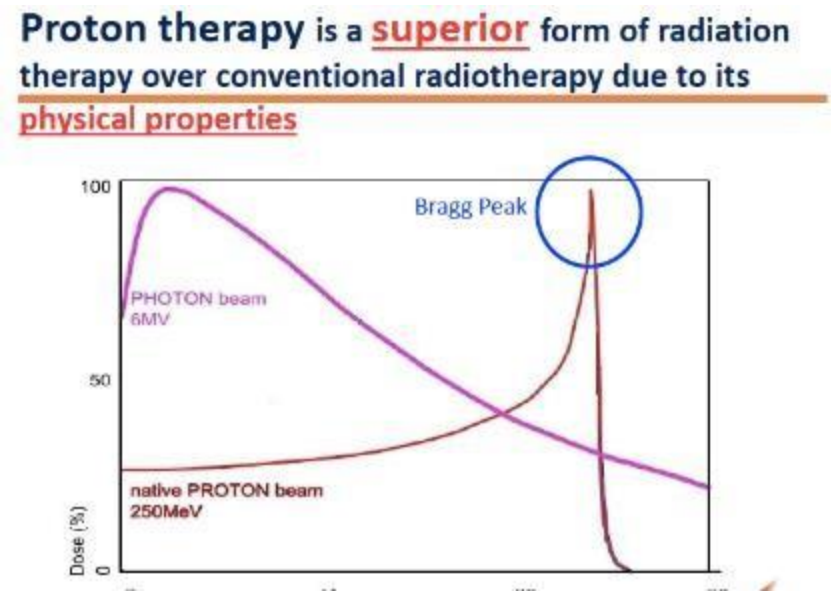
質子治療 vs.傳統(利用X光射線)放射治療



- 直至抵達指定腫瘤位置時，才釋放高劑量輻射，重點破壞腫瘤
- 物理學上稱為布拉格峰(Bragg Peak)
- 較深入的正常組織，則不會接受到任何輻射

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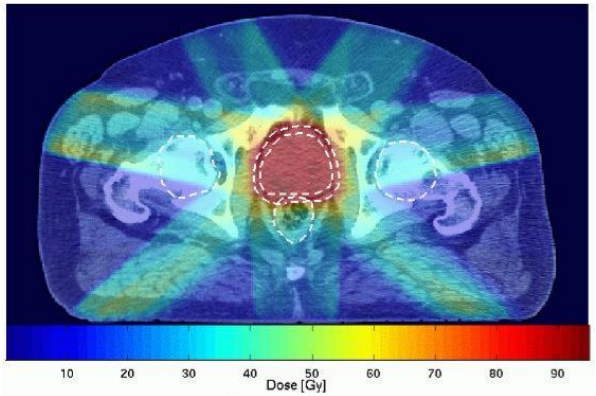
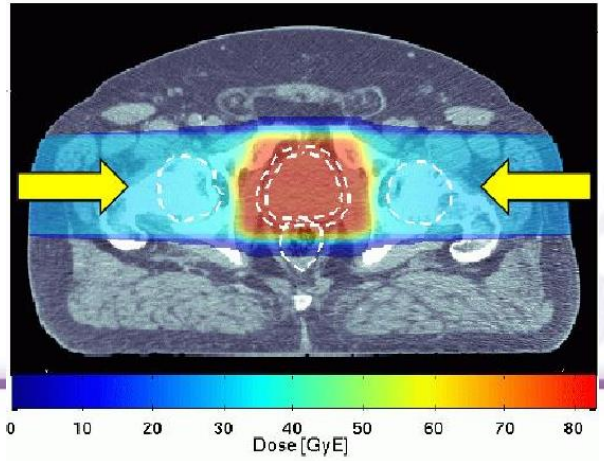
質子治療優勢

- 傳統放射治療→ 許多X射線束以不同角度入射並聚焦在腫瘤上→ 大面積正常組織照射
- 質子治療→使用的光束更少→小面積正常組織照射

IMRT



Protons



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臨床效益

- 對正常組織的顯著較低劑量，導致較低的副作用/並發症
- 如果發生復發，則再次照射的可能性更高
- 利用“無出口劑量”的物理特性，更好地治療關鍵器官附近的腫瘤
- 使放射劑量逐步提高，提高腫瘤控制率

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小兒患者的臨床獲益

- 減少對正常組織的輻射劑量對小兒患者至關重要
- 兒童放射療法的後期效果可能很嚴重
- 輻射會抑制任何組織的生長和發育
- 腦放射治療會影響神經認知功能，包括智商，學習，注意力，信息處理速度，視覺空間運動和記憶等
- 放射治療誘發的惡性腫瘤

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質子治療的歷史

- **1930** – Ernest Lawrence發明迴旋加速器
- **1946** – Robert R. Wilson建議高能質子可能是一種有效的治療方法
- **1961** –哈佛迴旋加速器實驗室與MGH合作進
- **1970's** – MGH對混合質子/光子治療前列腺癌進行了首次研究
- **1980's** –加利福尼亞州的Loma Linda醫療中心的第一個專用臨床PT設施上開始設計和建造
- **1950's - 2017** –全世界有超過170,000名患者接受了質子治療

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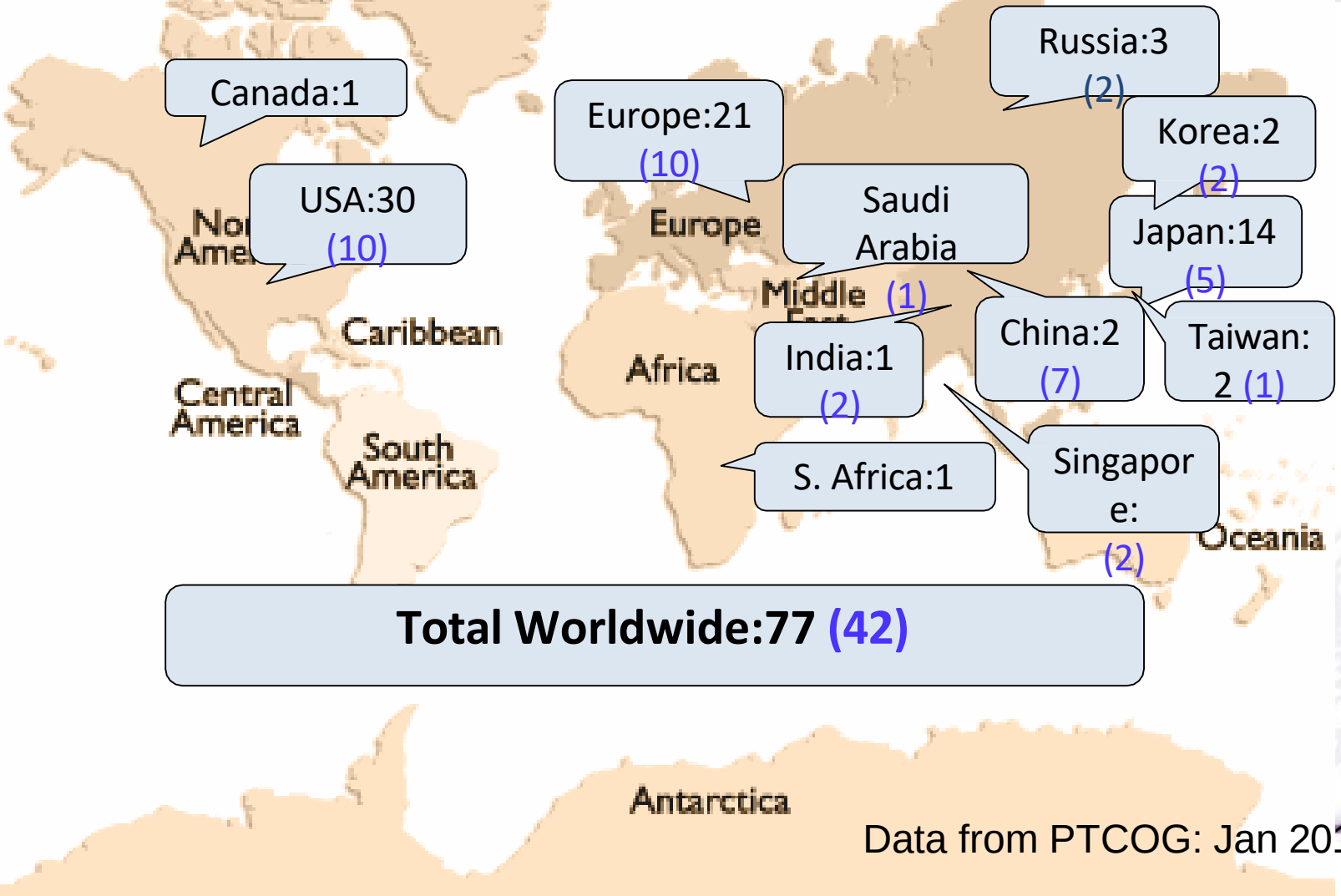
全球質子治療中心正在運營



Data from PTCOG: Jan 2019

HKSH Radiation Therapy Centers



Happy Valley Center



AKN 5 Center



AKN 3 Center

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用於小兒，眼，頭驢，重電

Accepted indications

- Pediatric CNS/solid tumors (medullobastoma)
- Ocular melanoma
- Skull base tumors (deep-seated chordomas, chondrosarcomas, para-spinal location, sacral chordomas)
  - Locally infiltrative, where local control is important, surgery with clear margins not possible/unlikely
  - Dose escalation while sparing critical organs
- Re-irradiation

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副作用減少

Toxicity Reduction by protons (retrospective analysis)

NSCLC treated with radiation therapy + chemotherapy at M.D. Anderson[1,2]

	3D CRT	IMRT	Protons
Dose	63 Gy	63 Gy	74 CGE
% patients stage IIIA-B2[2]	*87%*	*91%*	*87%*
Toxicity			
Esophagitis – G3+	*18%*	*44%*	*5%*
Pneumonitis – G3+	*30%*	*9%*	*2%*

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7. 影像引導放射治療

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Cyberknife M6導航刀

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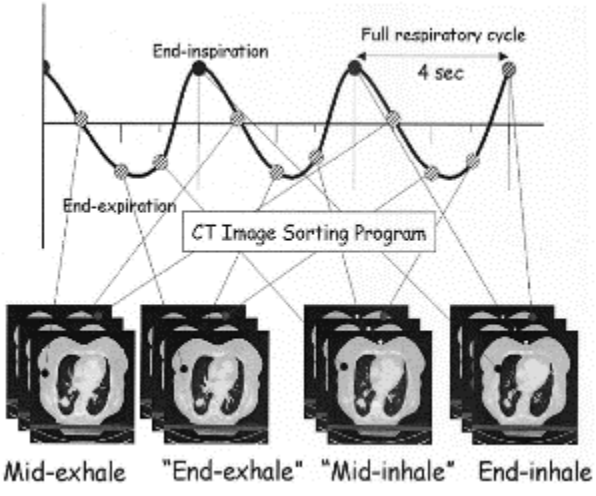
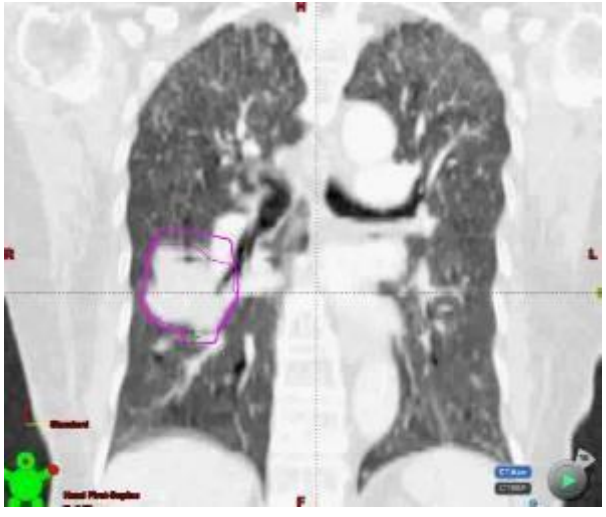
影像
導航的重要性





4D-CT ITV Based Approach

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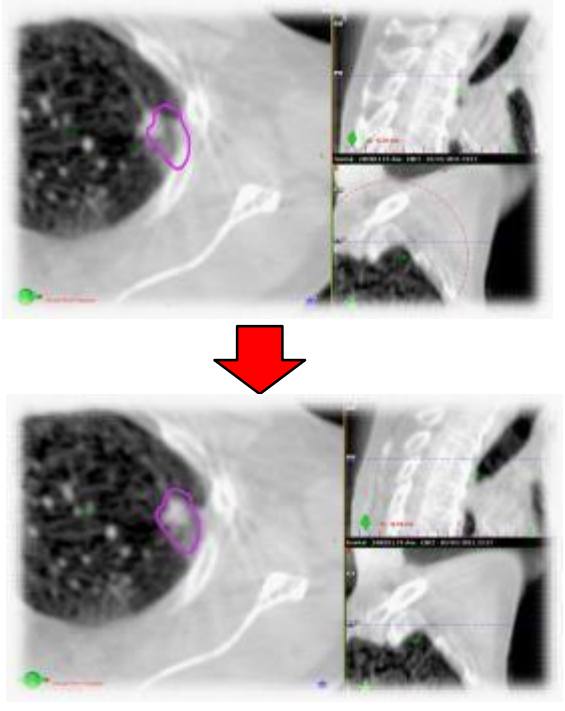
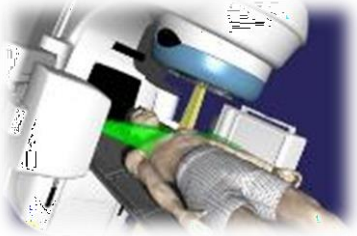
Image Guidance





Cone beam CT



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M6導航刀

- 機械臂放射外科手術系統
- 可用作治療任何部位的腫瘤
- 為病人提供除外科手術外另一種治療方案



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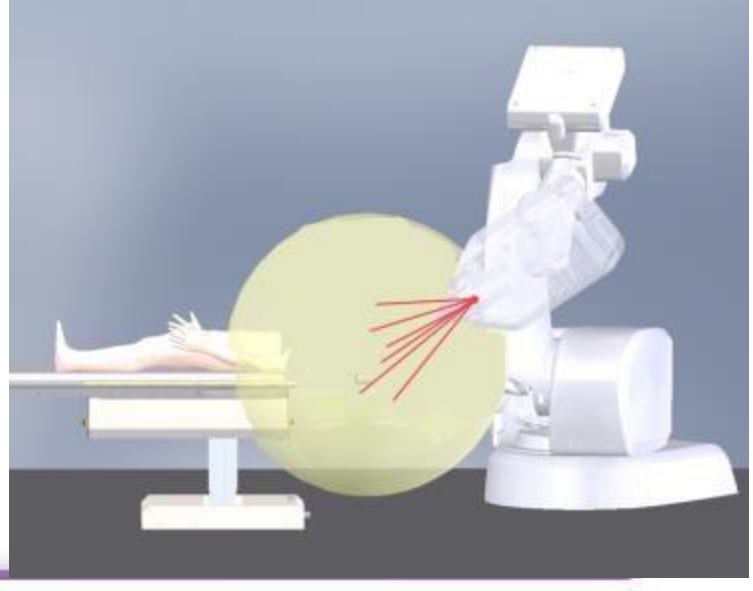
M6導航刀



- 多葉式準直儀
- 作出光束整型、無間斷的影像導引
- 非等軸旋轉非同面的治療方式
- Accuray Inc, Sunnyvale, CA, USA
- 腫瘤追蹤功能、機械活動能力及優良準直功能，使M6導航刀能在治療中自動作出修正



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M6導航刀

- 腫瘤追蹤功能、機械臂活動能力及優良準直功能，使M6導航刀能在治療中自動作出修正
- 就算治療靶區因呼吸作出位移，治療亦可維持高精準度



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M6導航刀

- 全世界已治療了100,000多名患者，並安裝了244個系統。
- 用於治療全身腫瘤包括:
  - 頭頸癌
  - 前列腺癌
  - 肺，脊柱，肝臟，胰腺和其他顱外腫瘤

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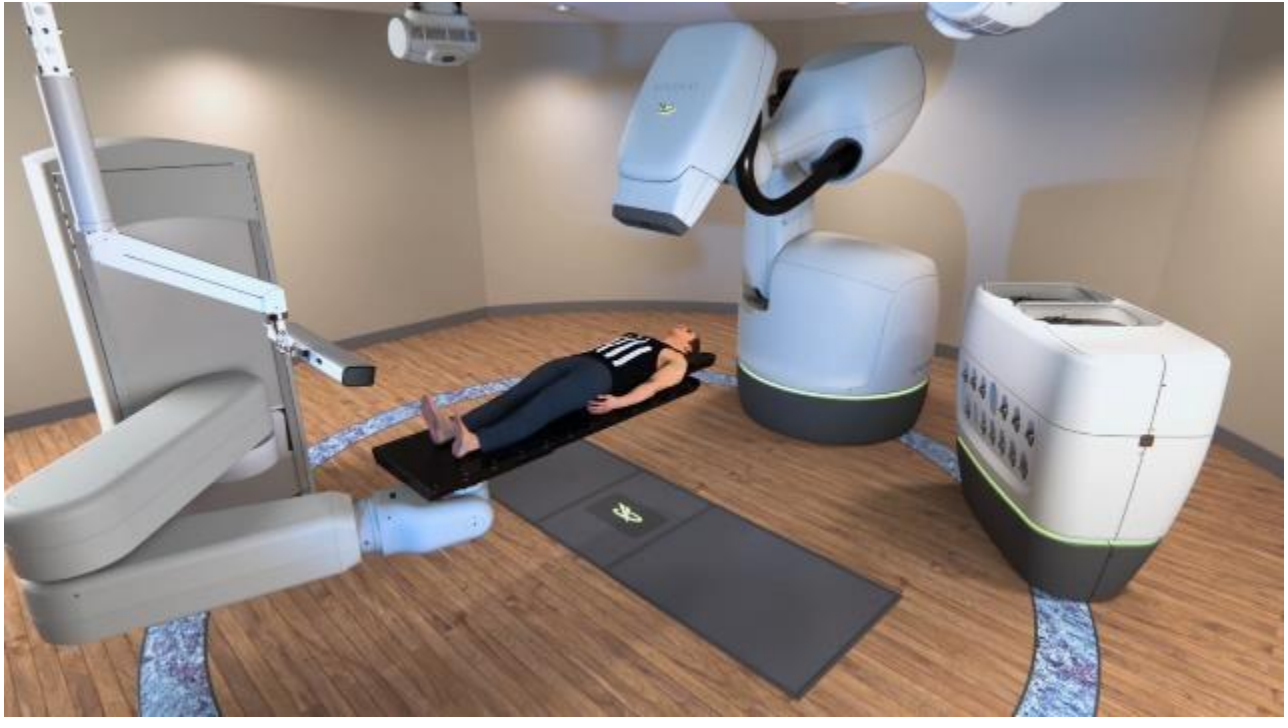
Accuray Expertise in Motion Tracking and Correction

The CyberKnife® System – Treatment delivery



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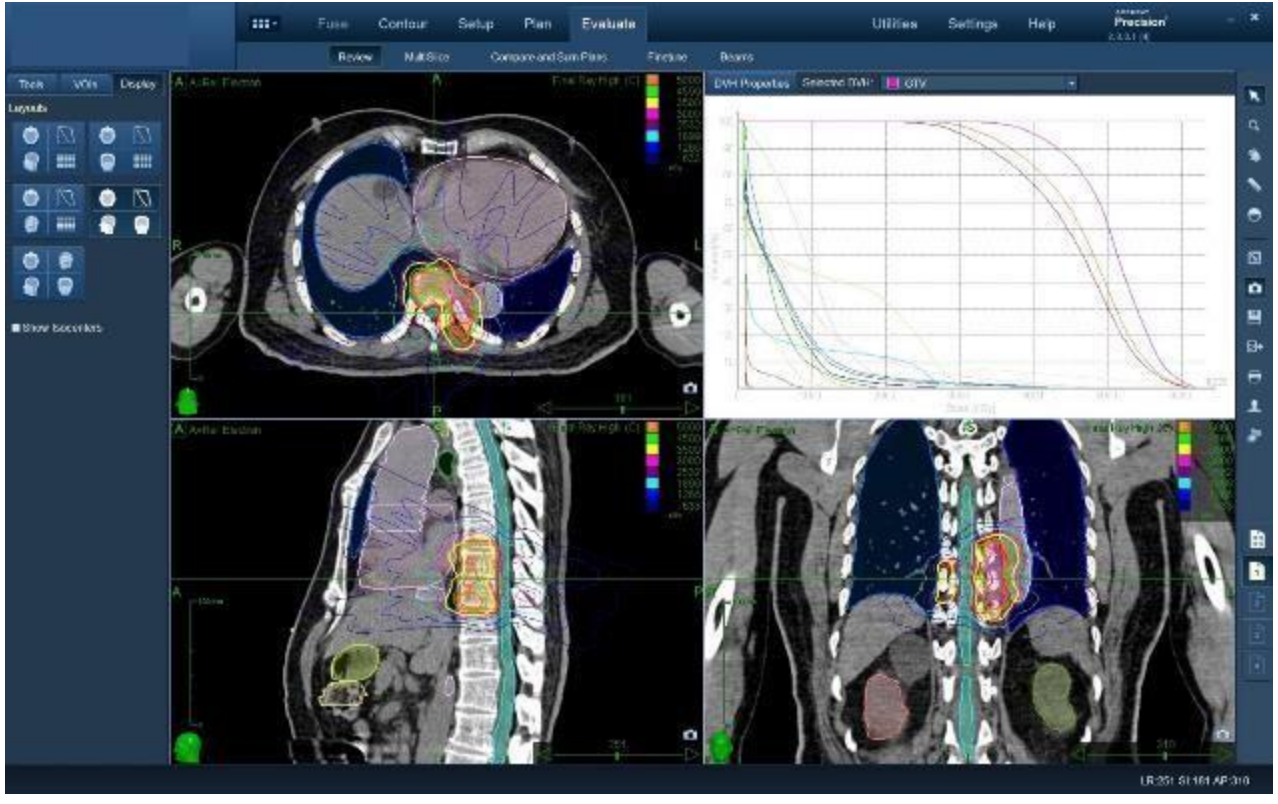
脊柱轉移



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腦轉移



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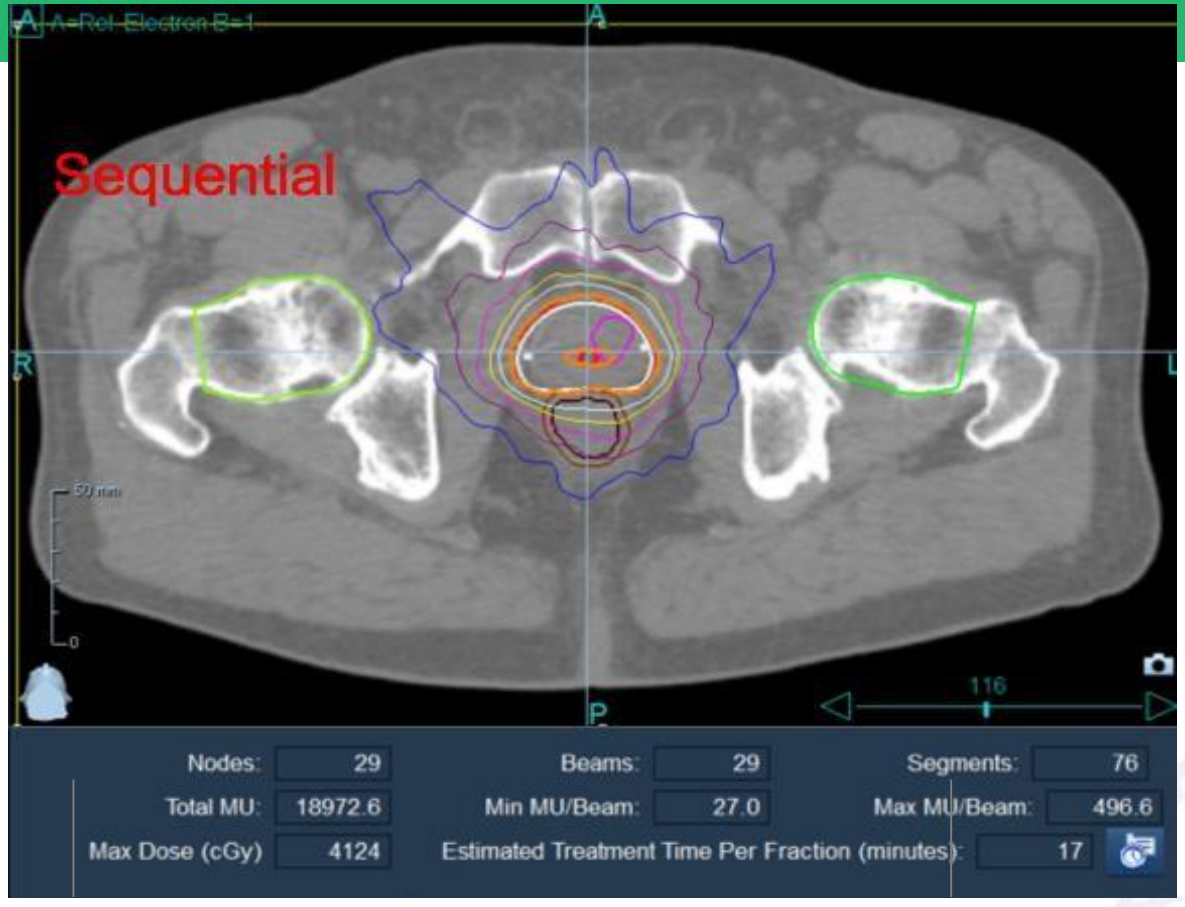
前列腺癌™



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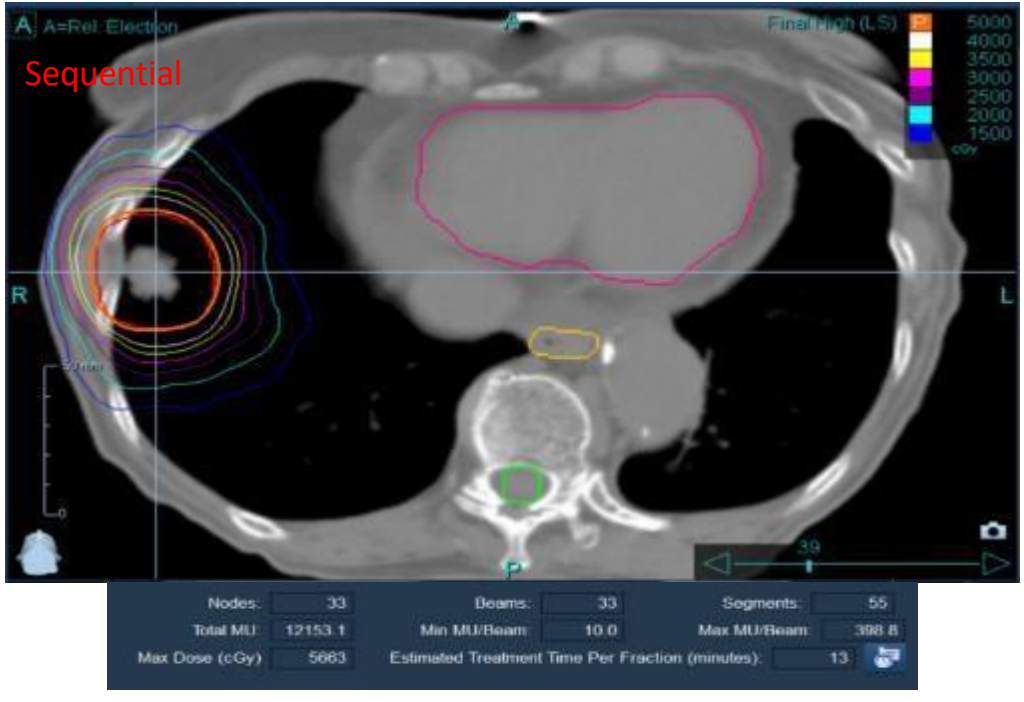
肺癌



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胰腺癌



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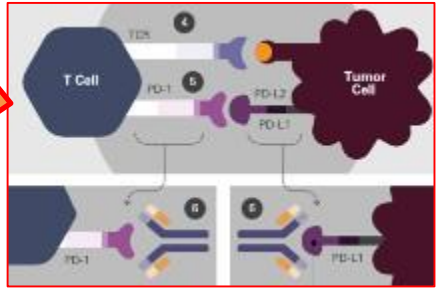
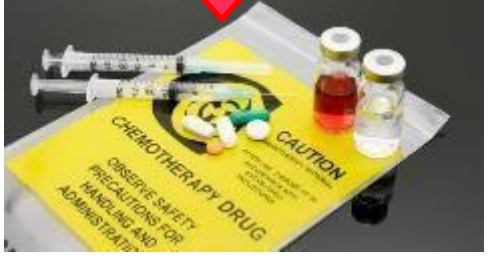
傳統癌症治療 與 精準癌症治療













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癌症基因及相關分子學檢測

檢測目標

(1)基因變異

- 單一基因變異
- 熱點組合
- 全面基因體分析

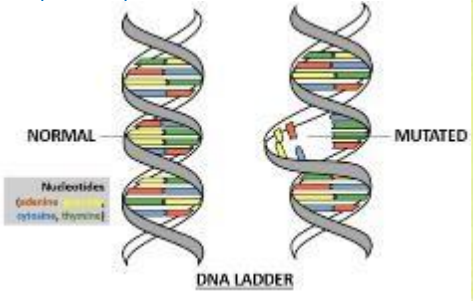
(2)染色體病變

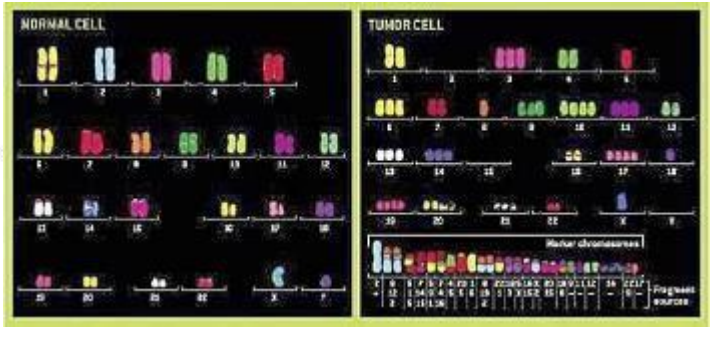
- 細胞遺傳學
- 螢光原位雜交

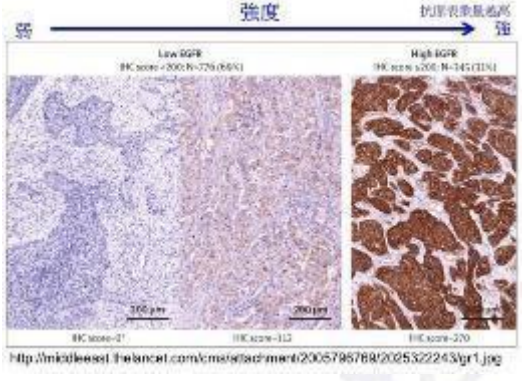
(3)蛋白表達

- 免疫組織化學染色法（IHC）

檢測方法







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8. 基因排序

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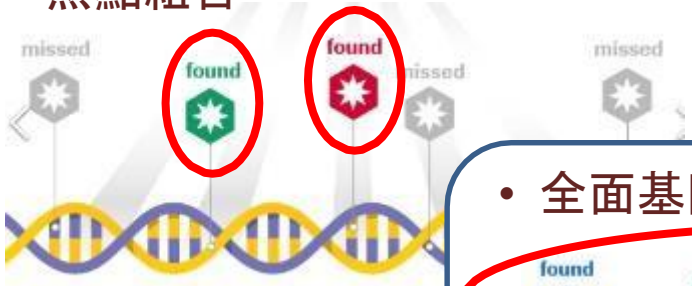
基因變異檢測

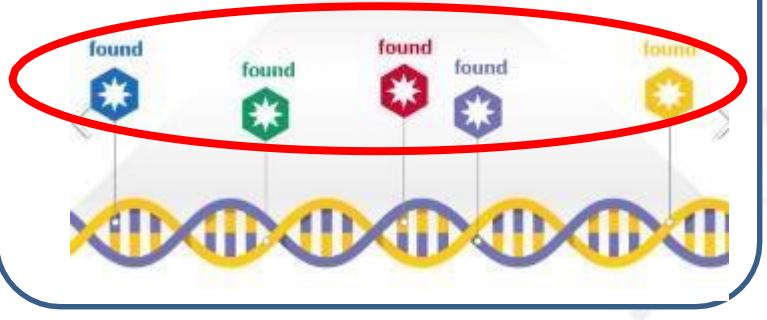
- 單一基因變異



- 熱點組合



- 全面基因體分析



低

個人化治療精準度

高

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全面基因體分析：更精準個人化治療

每位患者的癌症都是獨一無二的





次世代定序
（**Next Generation Sequencing, NGS**）
可以同時進行大量基因排序

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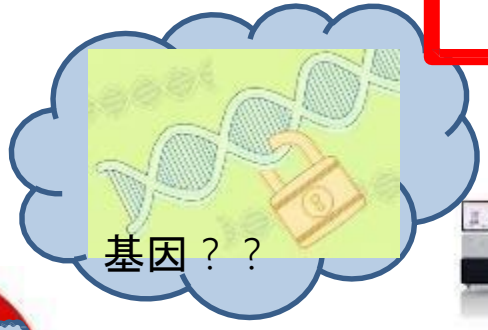
次世代定序（Next Generation Sequencing, NGS)

破解基因的密碼







測序儀 =



基因排序



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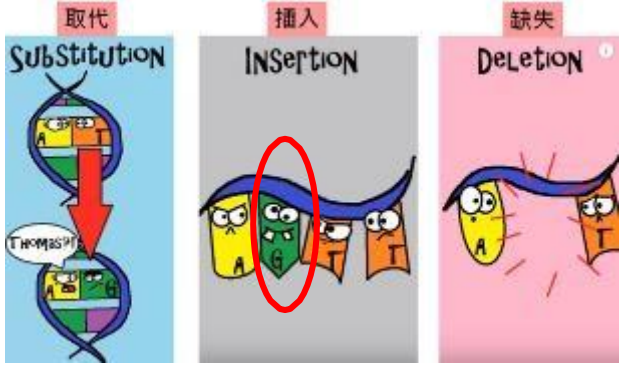
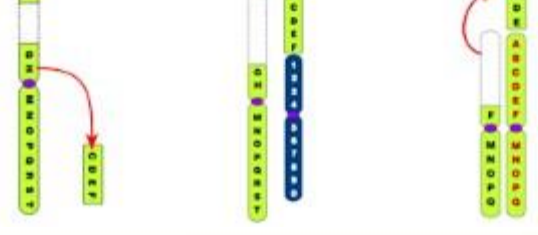
全面基因體分析：可以知道什麼？

1. 數百個個別基因有沒有變異？

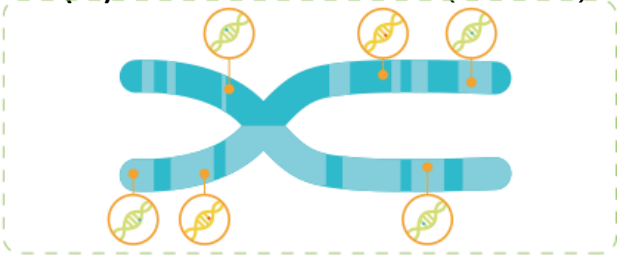


基因或大片刪除　基因體重排　基因或大片段複製

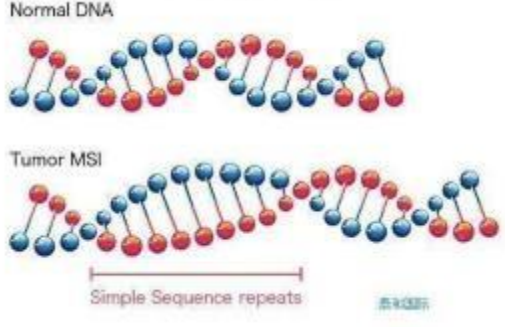


2. 整體性資料

(A) 腫瘤突變負荷（TMB）



(B) 微衛星不穩定性（MSI）



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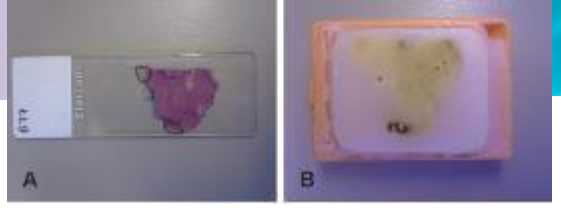
全面基因體分析：是怎樣做的？



1. 醫生建議進行分析

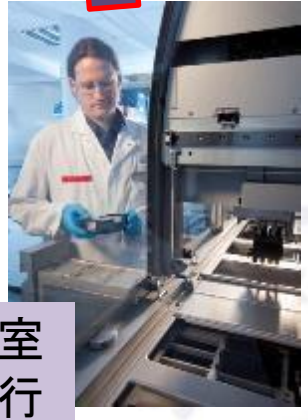
2. 生物科技公司向醫院病理科





3. 檢體送到實驗室，提取DNA，進行次世代定序





4. 生物資訊分析團體進行分析





5. 醫生講解報告

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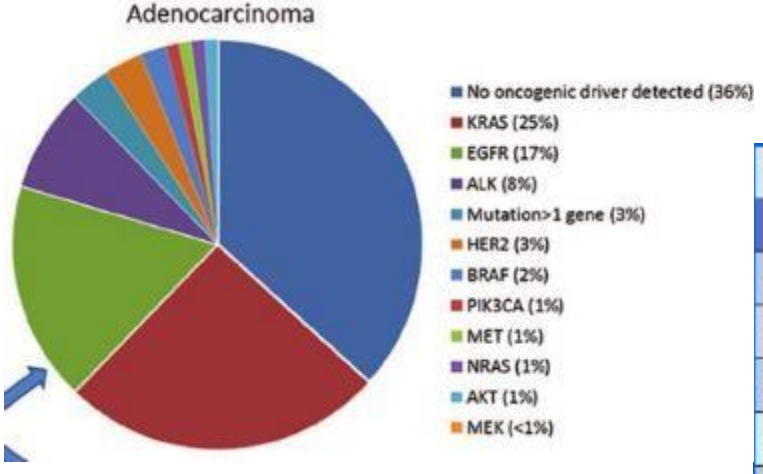
全面基因體分析：病人得到什麼？



癌症基因變異

針對癌症基因變異，再選用相對的治療

Targeted treatments are standard of care for many cancers	
Drug	**Gene**
Crizotinib	ALK
Ponatinib, Bosutinib, Dasatinib, Imatinib, Nilotinib, Omacetaxine	BCR/ABL1
Dabrafenib, trametinib, Vemurafenib	BRAF
Afatinib, Cetuximab, erlotinib, Panitumamab	EGFR
Trastuzumab, Everolimus, Lapatinib, Pertuzumab	HER2
Imatinib	KIT
Cetuximab, Panitumumab	KRAS
Ibritumomab, obinutuzumab, Ofatumumab, Rituximab, Tositumomab	MS4A1

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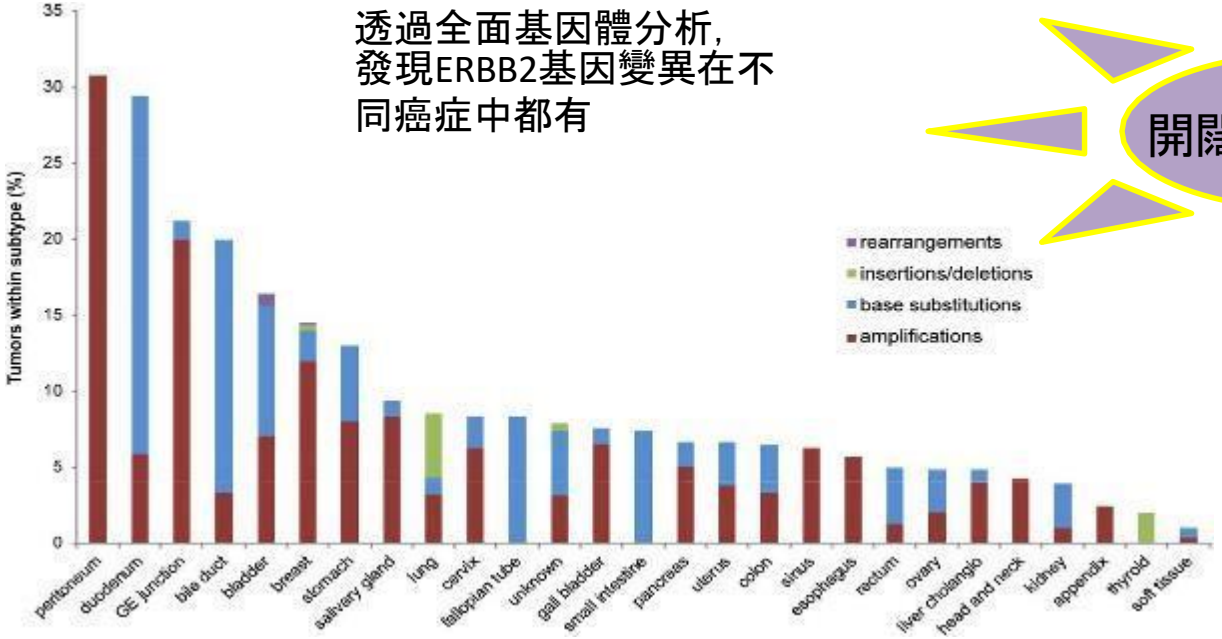
全面基因體分析：病人得到什麼？

透過全面基因體分析，
發現ERBB2基因變異在不同癌症中都有





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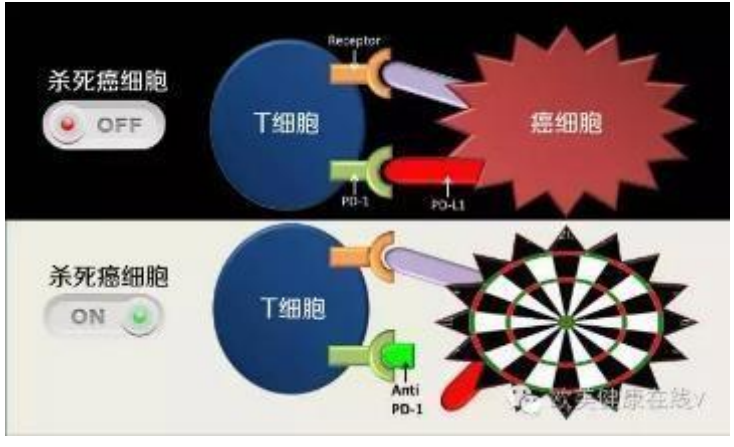
全面基因體分析：病人得到什麼？

標靶藥物／免疫治療方案是否<u>真的</u>有效？







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全面基因體分析：誰適合？

- 希望及早選用標靶藥物／免疫治療的病人
  - 確診各類癌症，需要基因檢測選擇標靶藥物方案指導
  - 檢測標靶藥物／免疫治療方案是否有效



- 較複雜的癌症病人
  - 已接受過常規標準化療，放射治療，標靶治療，但病情仍然惡化，需要進一步尋求進一步治療方法
  - 已經做過基因檢測，但因結果不全面／其他原因，未有找到適合的藥物
  - 原發位置不明的癌症
  - 罕見癌症
  - 同時有兩種以上的癌症



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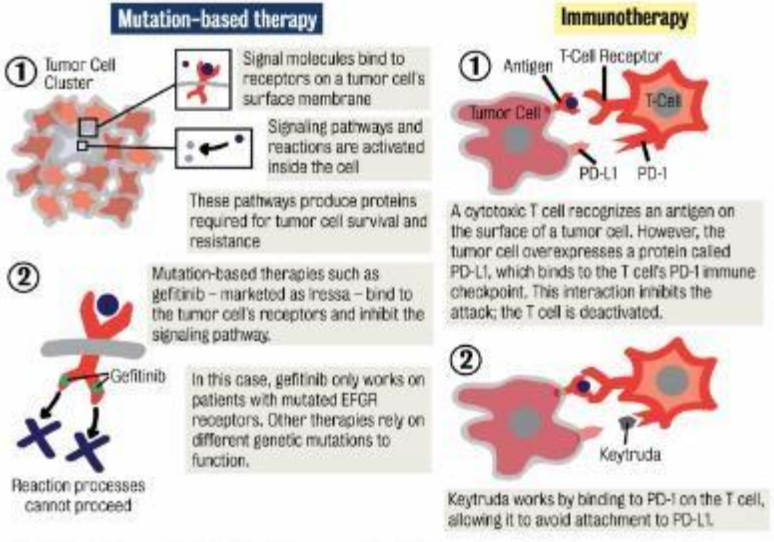
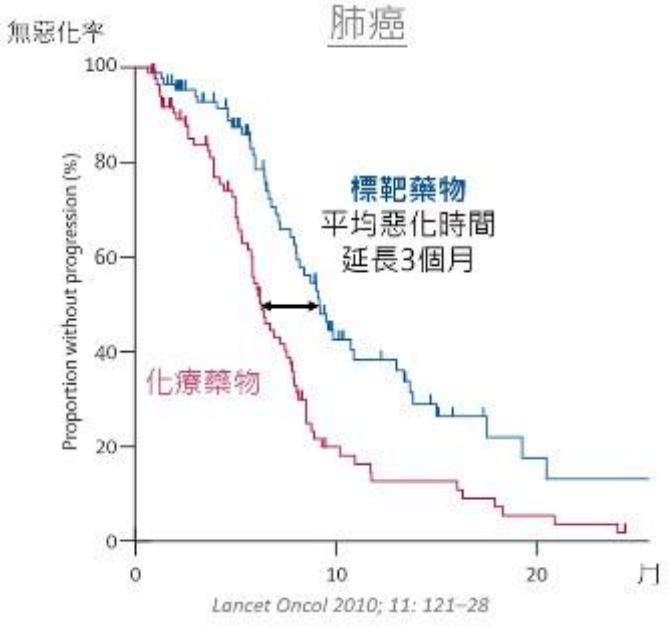
肺癌

FDA APPROVES IMMUNOTHERAPY-BASED DRUG FOR LUNG CANCER TREATMENT

The drug pembrolizumab, marketed as Keytruda, underwent 4 years of testing before receiving first-line approval for the treatment of non-small cell lung cancer (NSCLC). Keytruda is an immunotherapy-based drug, in contrast to older classes of drugs called signal-transduction inhibitors.



SOURCE: The National Cancer Institute, Dr. Edward Garon. Graphic reporting by Allison Ong, Brain reporter. Graphic by William Zou, assistant Graphics editor



Lancet Oncol 2010; 11: 121–28

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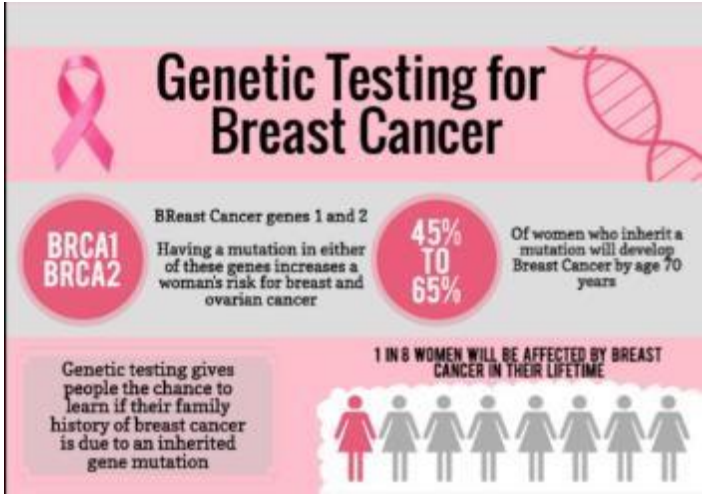
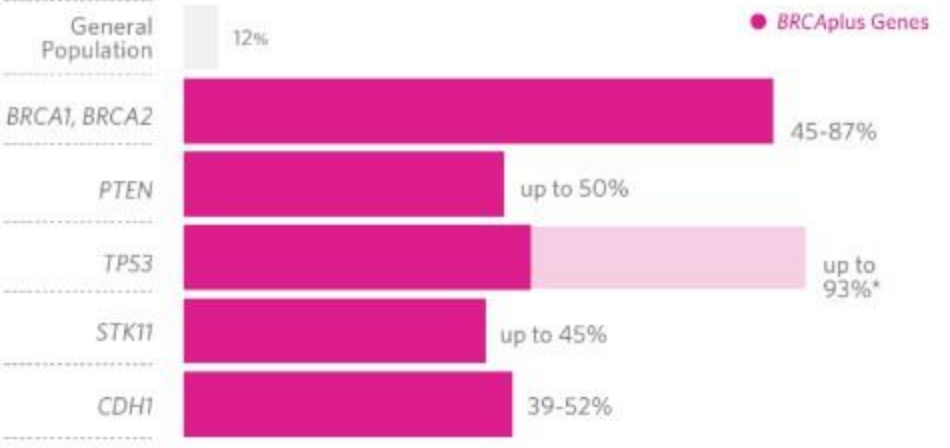
乳癌









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大腸癌

Colon Cancer At-A-Glance*

Colon cancer is the second leading cause of cancer-related death in the U.S.

On average, your risk is about 1 in 20, although this varies widely according to individual risk factors.

50+

90% of new cases occur in people 50 or older.

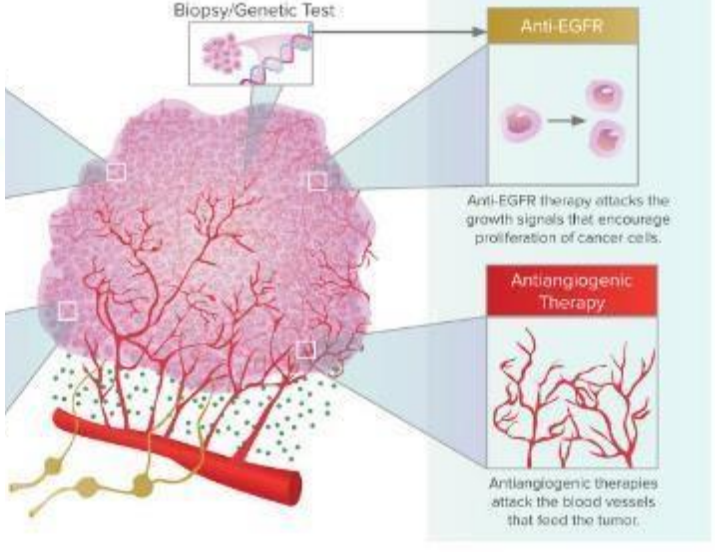
People with a first-degree relative (parent, sibling or offspring) who has colon cancer have two to three times the risk of developing the disease.

There are currently more than one million colon cancer survivors in the U.S.

*Source: American Cancer Society

Treatments for Stage IV Metastatic Colorectal Cancer

Because there are many treatment options for mCRC, you and your doctor will work together to select the proper treatment that will give you the most benefit.



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肺癌實例

- F/70
- Adenoid cystic carcinoma 罕見病理，乳癌病史
- 第四期轉移，到肺及腦部
- 化
- N

GENOMIC ALTERATION	DRUG THERAPY	EFFECT
ARID1A heterozygous deletion	RUCAPARIB, OLAPARIB, NIRAPARIB	SENSITIVE
PIK3R1 (Asn564Asp)	EVEROLIMUS, TEMSIROLIMUS	SENSITIVE

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胃癌實例

- F/40
- 第四期(轉移到腹腔)
- 接受傳統化療及標把治療
- NGS全面基因體分析:

Genomic Alteration	Drug therapy	Effectiveness
TP53	Bevacizumab Pazopanib	Sensitive
ATM	Rucaparib Niraparib Olaparib	Sensitive
TMB (tumor mutation burden) HIGH 18.0 mutations/megabase	Pembrolizumab (stomach cancer) Durvalumab Nivolumab Atezolizumab Avelumab	Sensitive

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總結

- 新的治療方法目標是提升存活率，改善生活質素
- 全面基因體分析 **(Next generation sequencing, NGS)**給予更精準個人化治療
- 要了解如何使用報告，和醫生詳細**說明內容**

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9. 香港質子治療的臨床經驗

Clinical experience of proton therapy in Hong Kong

養和東區醫療中心 質子治療中心主任
養和醫院 臨床腫瘤科名譽顧問醫生
臨床腫瘤科專科醫生
張天怡醫生

Dr. Amy Chang

Honorary Consultant in Clinical Oncology
Co-Director, Proton Therapy Centre
Hong Kong Sanatorium & Hospital

February, 2025



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質子的基礎 Basis of proton

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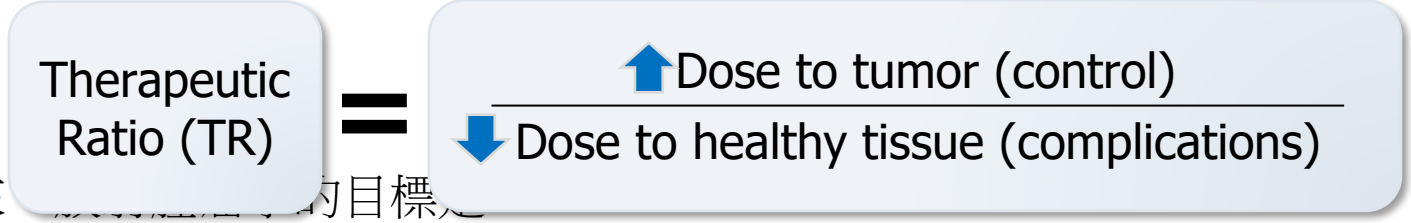
放射腫瘤學的目的是最大限度地提高治療率



100 年來[illegible]的目標是

- 在腫瘤中增加放射線（對照）
- 減少健康組織中的輻射（併發症）
- 這稱為治療比率（TR）

質子可以提高這個比例

Do as little harm as possible, while maintaining or even exceeding the expected efficacies for a proposed treatment/intervention

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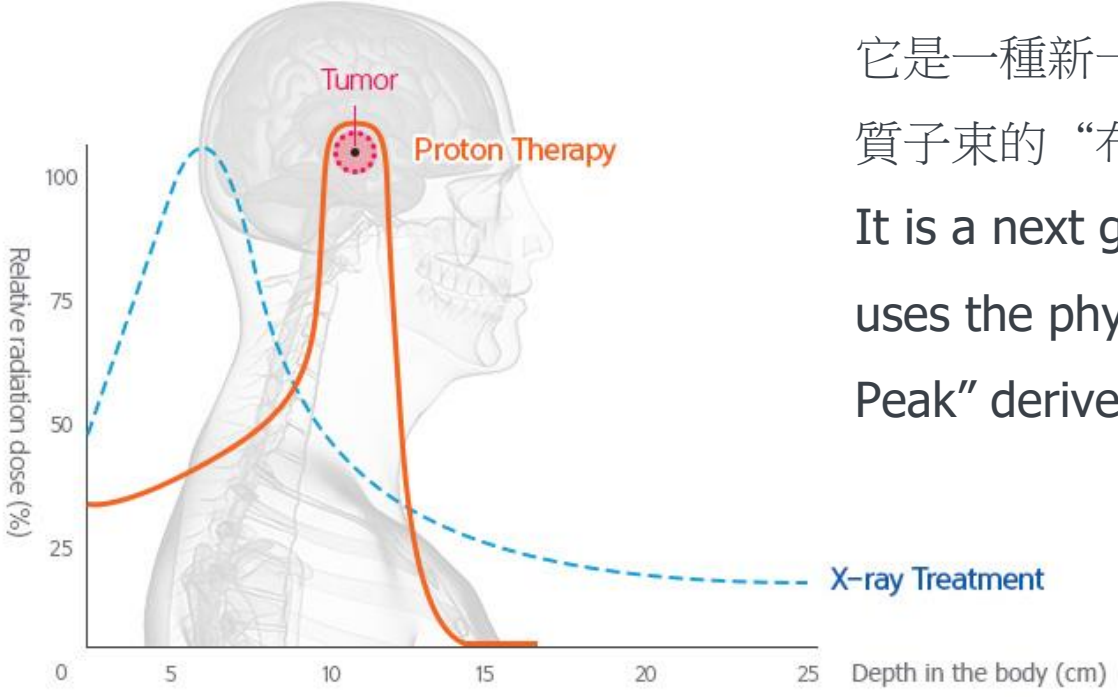
什麼是質子治療
What is Proton Therapy?



它是一種新一代放射療法，利用了源自質子束的“布拉格峰”的物理特性。

It is a next generation radiotherapy that uses the physical properties of “Bragg Peak” derived from the proton beam.

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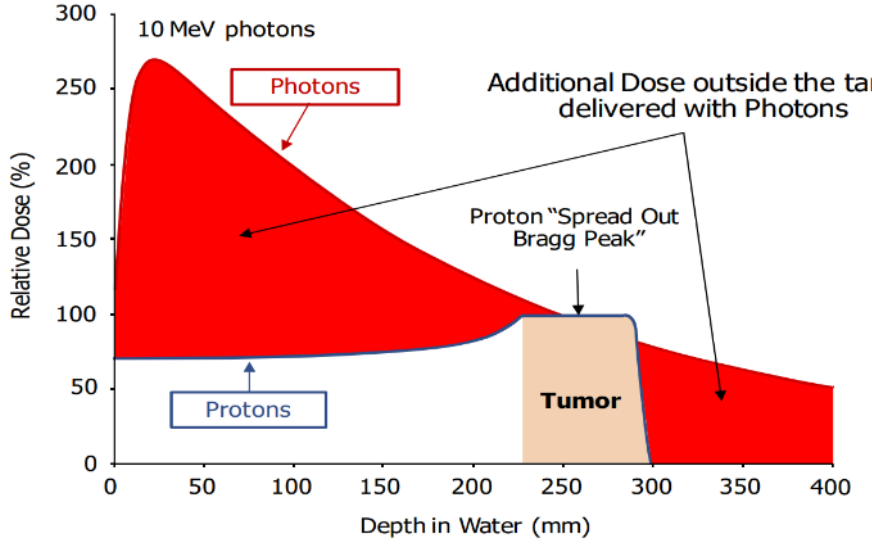
Why Protons?



產生一部分能量（出口劑量）

s a portion of its energy behind the tumor

當它穿透我們體內的正常組

量來殺死癌細胞，隨後，它

hen it reaches cancer tissues after

nense amount of radiation energy to kill the

cancer cells and subsequently, it disappears instantly

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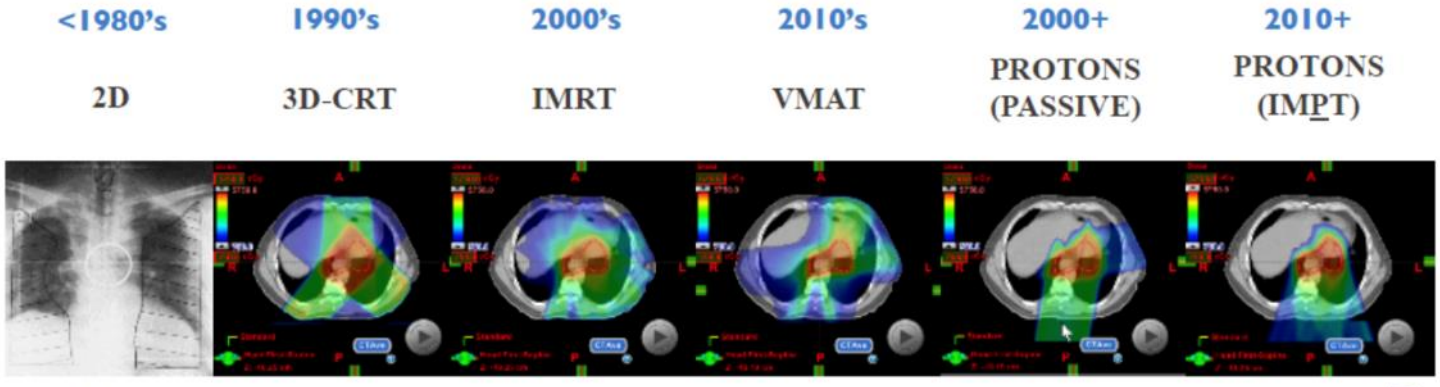
放射技術的發展減少了對食管癌心肺結構的不必要的輻射效應



Courtesy of Steven Lin, MD, PhD, MD Anderson Cancer Center

2D放射治療
3D放射治療
IMRT 調強放療
VMAT 容積弧放射治療
Protons
- 第一代質子（散射）
- 調強質子治療

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臨床應用Clinical applications

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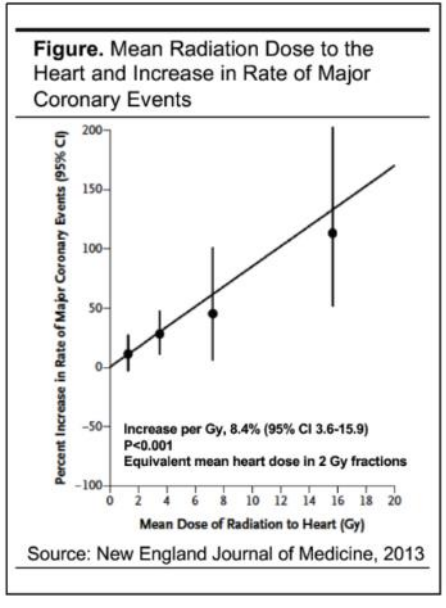
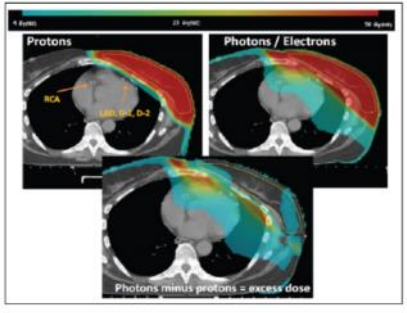
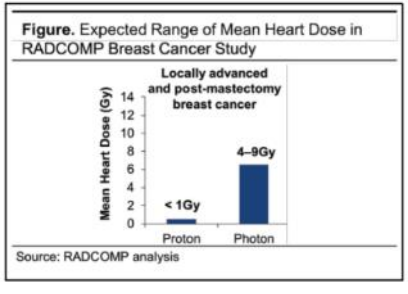
臨床應用：乳腺癌
Clinical Applications: Breast Cancer

Heart dose matters in breast cancer treatments







- 心臟平均輻射劑量與晚期冠狀動脈事件之間存在正相關關係
- 質子可以顯著減少平均心臟劑量

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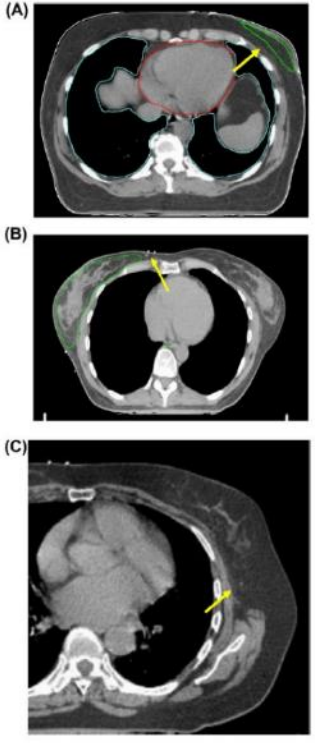
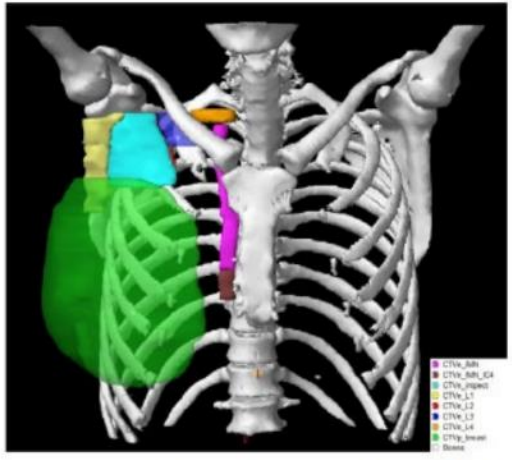


Fig. 3. (A) In relatively obese patients the CTVp_breast is positioned more ventrally in the caudal part of the breast due to fatty tissue. (B) It is often possible to identify medial mammary branches of the internal thoracic artery, and the CTVp_breast is positioned lateral to these vessels. (C) Arrow points at the lateral thoracic artery.

Increasing Complexity in Breast Cancer RT Planning



Offersen et el Rad and Oncol 114 (2015) 3-10

- 對於局部晚期乳腺癌，需要對局部淋巴結進行照射
- 這種複雜的輻射計劃將對心臟和肺部產生更多的劑量
- 質子療法是接受放射治療的局部淋巴結和左側乳腺癌的乳腺癌的推薦治療選擇

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Proton Beam Therapy (PBT) for Breast Cancer Patients

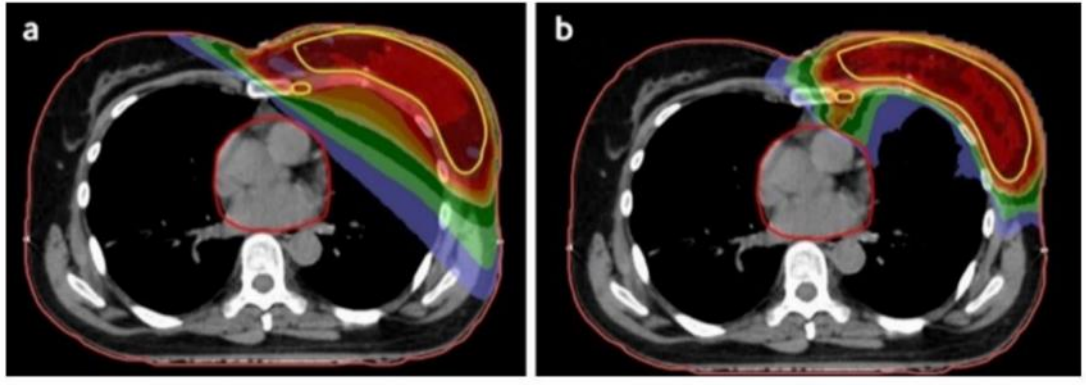

Fig 1 | Axial CT slices showing distribution of radiation dose in a patient being planned for either (a) volumetric modulated arc photon therapy in breath-hold or (b) proton beam therapy. In image B, the radiation dose colourwash can be seen to conform more closely to the target volumes (breast and internal mammary nodes outlined in yellow) leading to lower mean radiation doses to heart and lung

BMJ 2023;381:e072896

比較左側圖片（屏氣容積弧形治療, VMAT）
和右側圖片（質子療法, Protons）：

- 高劑量更符合目標體積（即左乳房和乳腺內淋巴　結，以黃色顯示）
- 導致心臟和肺部的平均劑量較低

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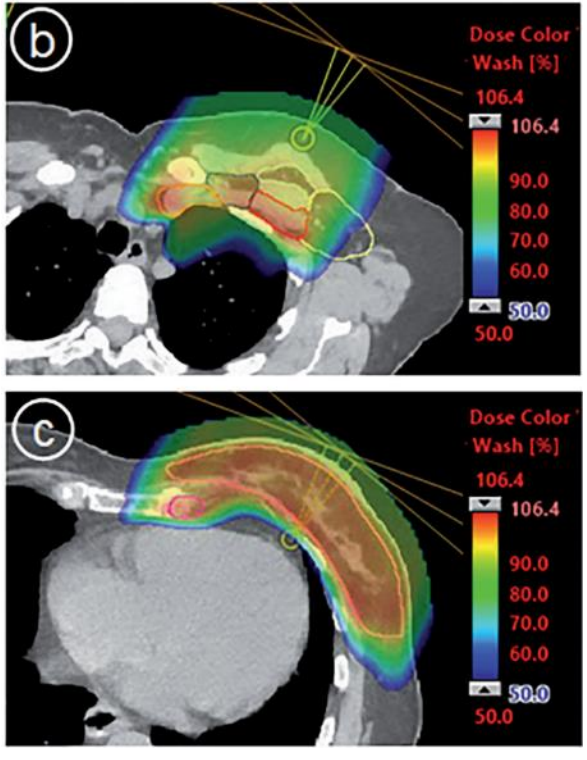
質子與光子乳腺放療的臨床研究結果
Clinical study results for proton versus photon breast radiotherapy

> 20 年的乳腺癌質子治療歷史，臨床結果可用

> 30 項臨床研究

> 1400 名患者

它可用於腫塊切除術或乳房切除術后，有或沒有區域淋巴結照射



Holt Red 2023
Gao Red 2023
Jensen Acta Oncol 2021

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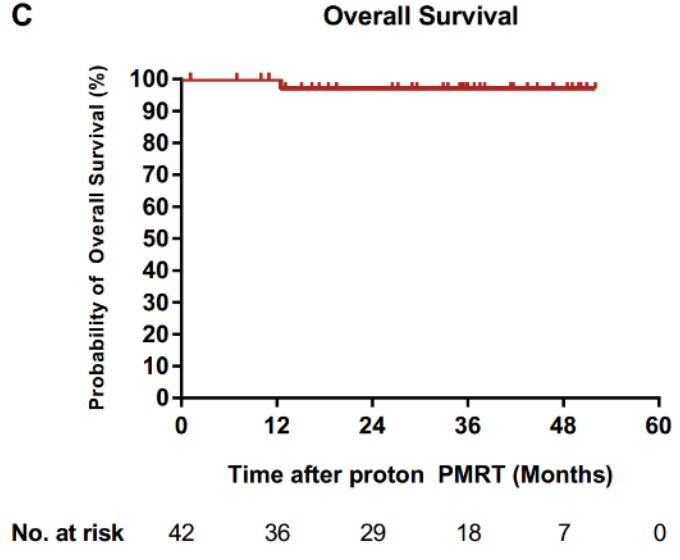
質子與光子乳腺放療的臨床研究結果
Clinical study results for proton versus photon breast radiotherapy

出色的局部區域疾病控制和生存結果
5 年總生存率 88%
5 年局部區域控制 98%
非常低（小於5%）嚴重（3級及以上）副作用
可與光子研究相媲美
心臟劑量減少80%以上，肺劑量減少50%



Jimerez 2019
Gao 2023

Luo JCO 2019

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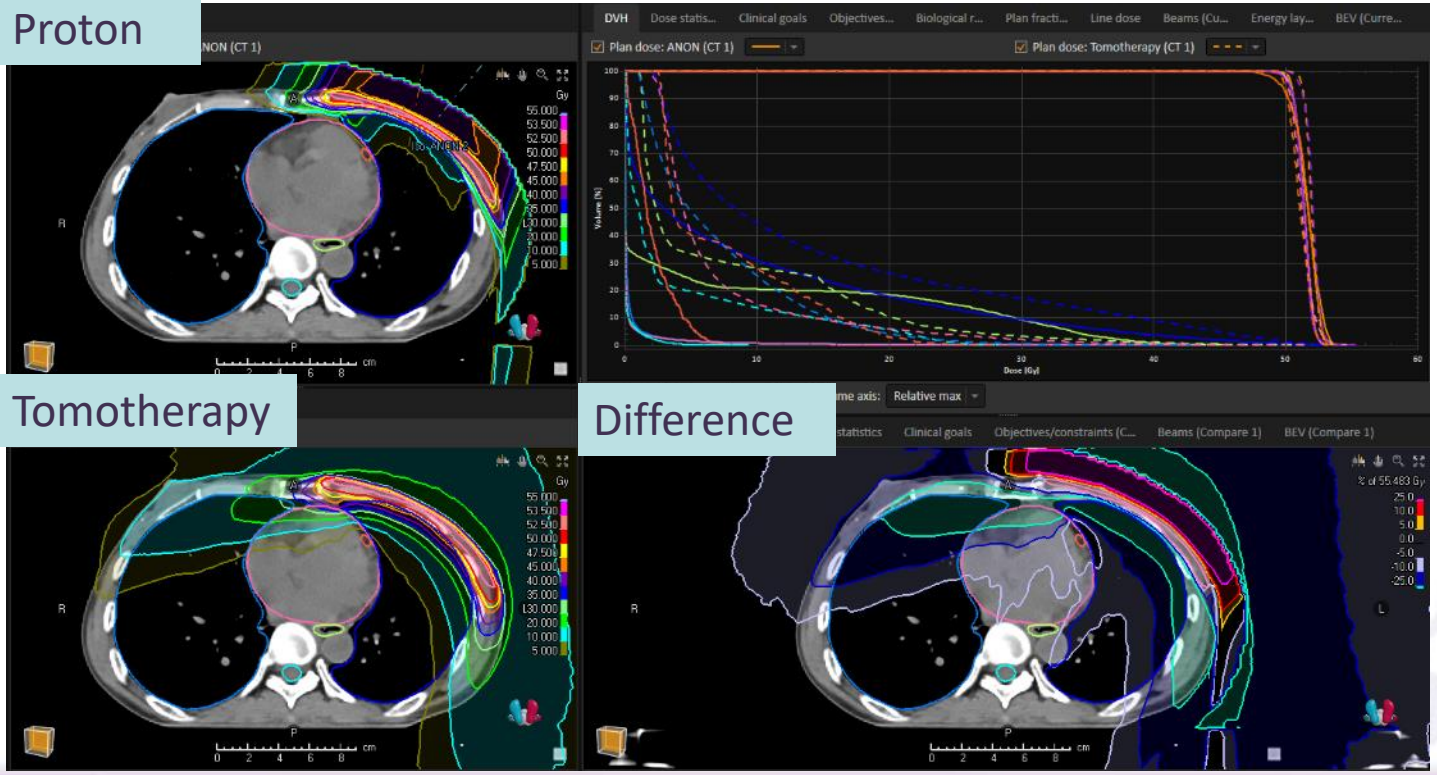
病例：乳房切除術后對左胸壁和區域淋巴結進行放療

Case : Post mastectomy radiotherapy to left chest wall and regional lymph nodes

質子治療

使用螺旋療法的常規放射治療



質子可以防止的過度輻射

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放療次數和建議
Number of fractions and recommendations

早期

Early stage (e.g. stage 1)

- 5次首選
- 15 次

局部晚期階段

Locally advanced stages (2-3)

- 15 次首選
- 25 次

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質子治療乳腺癌：總結
Proton for breast cancer: summary

減少對肺、心臟、食道的出口劑量 Reduce exit dose to lungs, heart, esophagus
減少晚期心血管事件 Reduce late cardiovascular events
最有益於：雙側乳房、再照射、需要局部淋巴結照射的晚期 Most beneficial in: bilateral breasts, re-irradiation, advanced stage requiring regional lymph node irradiation

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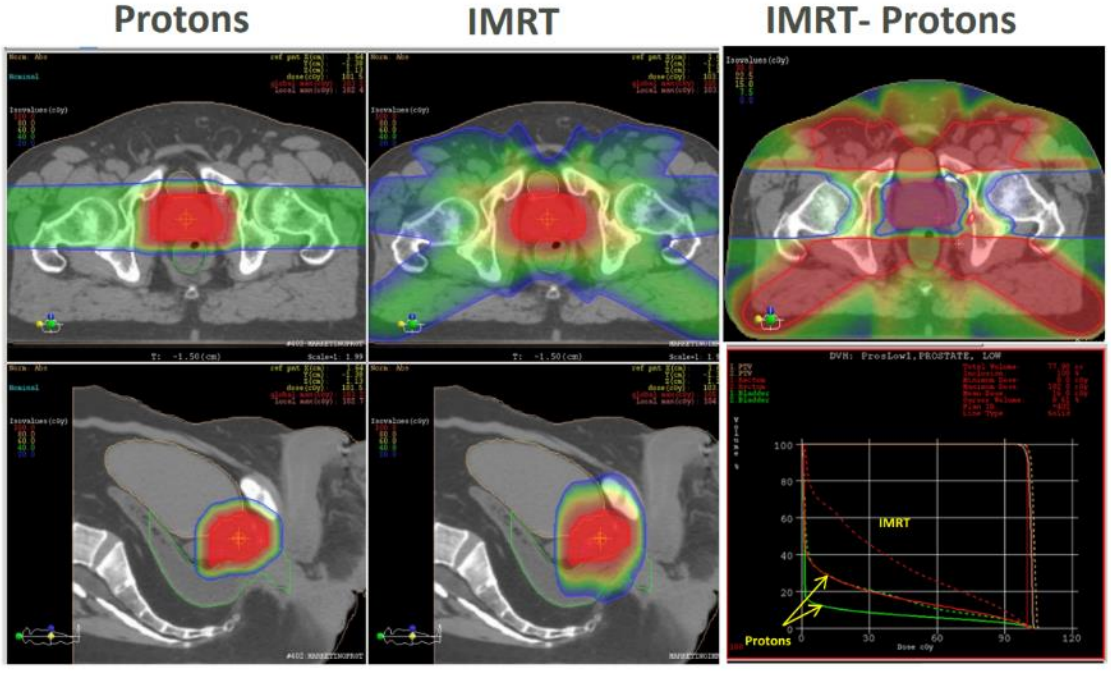
臨床應用：前列腺癌
Clinical applications: Prostate Cancer

- 與傳統的X射線（IMRT）相比，質子可以減少對膀胱、直腸、腸道和球的過量輻射
- 減少GI（胃腸道）、GU（泌尿生殖系統）和性功能的副作用



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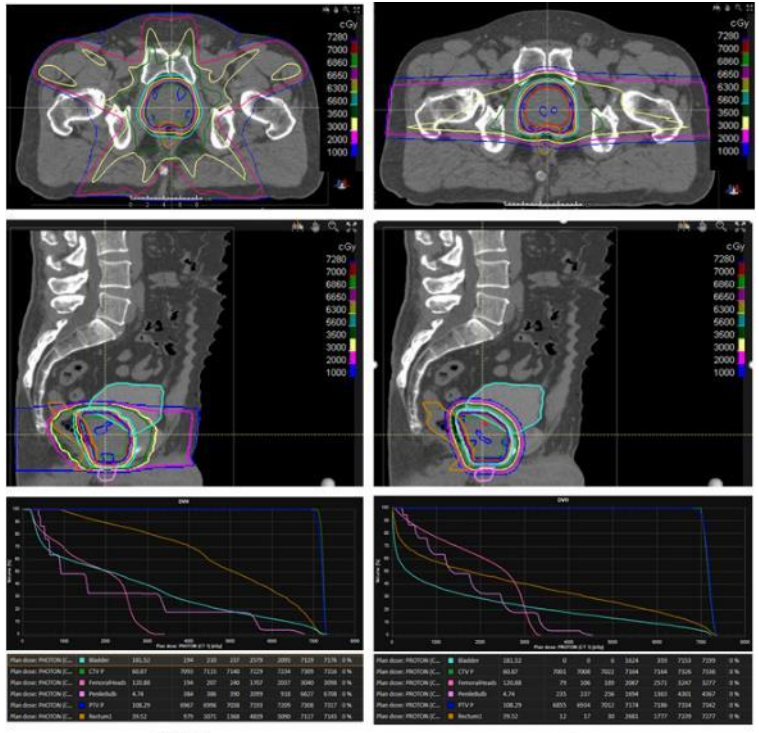
質子治療在前列腺癌中的優勢
Proton therapy advantages in prostate cancer

1. 減少低至中等劑量範圍
2. 照射到直腸和膀胱的體積減少 40-60%



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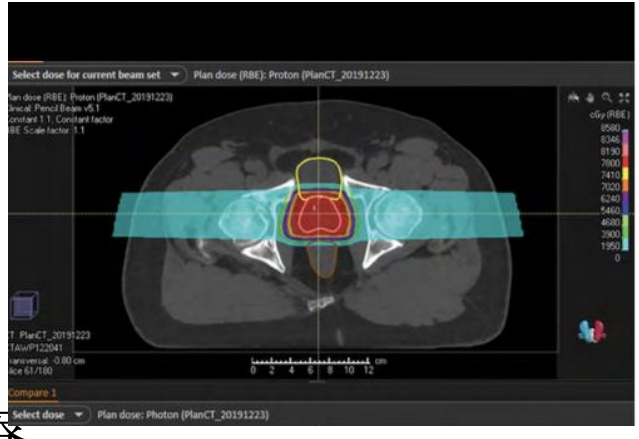
案例示例：
I 期前列腺癌
T1N0型
低風險
計劃 5 次質子治療





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質子治療前列腺癌：總結

顯著保留膀胱、直腸、腸道 Significant sparing to bladder, rectum, bowels

研究表明，與光子相比，效果相當，副作用最小 Studies showed equivalent effectiveness compared with photon and minimal side effects

每次治療時間短, 能夠減少次數（大分割）Short treatment time per session, hypofractionation)

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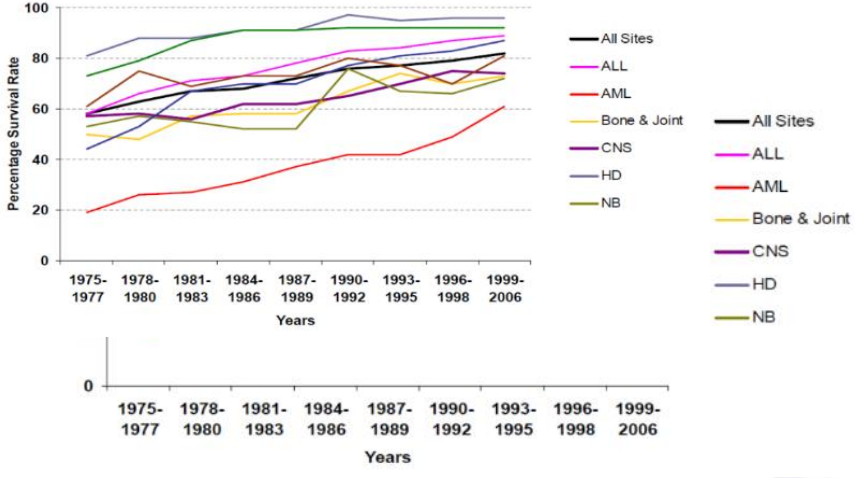
臨床應用：小兒癌症
Clinical applications: Pediatric Cancer

隨著技術的進步，兒童癌症的存活率正在增加

如果及早診斷，80%的患者可以治癒



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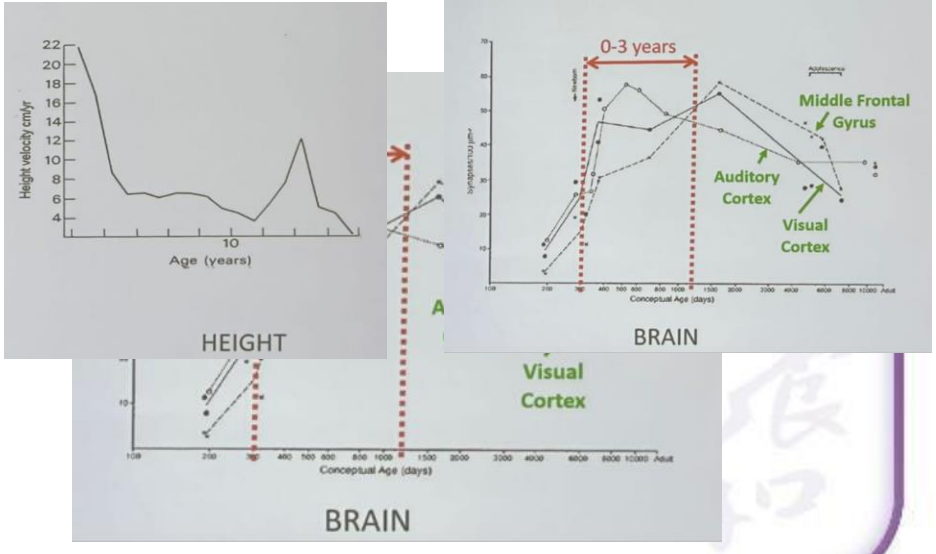
小兒放療的副作用
The toxicities of pediatric radiotherapy

放射治療是虱形癌患者根治性治療的重要組成部分

但是，即使是對幼兒的低劑量電離輻射也可能在治療后數年或數十年內導致晚期副作用

包括：

第二惡性腫瘤
生長障礙
功能結局下降
聽覺、視覺
神經認知
血管異常
內分泌腺



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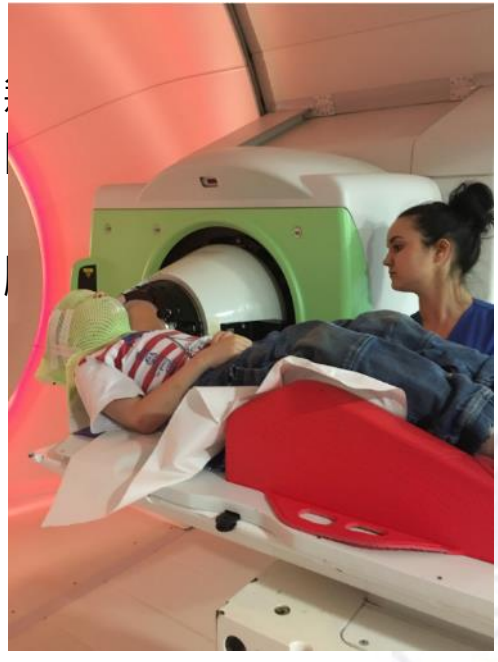
質子治療在兒科中的益處
Benefits of proton therapy in pediatrics

質子治療的優勢，治療率提高
目標腫瘤體積後面的特徵性劑量下降 (
將最大劑量遞送至腫瘤區域，並保護周
低劑量和中等劑量的傷害
減少急性和長期副作用以及繼發性惡性
質子的等效效率可與光子相媲美



Thomas BJR 2020

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第二惡性腫瘤的風險
Risks of second malignancy

20,000 名患者的兒童癌症倖存者
（1970-1986）
第二惡性腫瘤的數量增加了 2.3
第二惡性腫瘤的 30 年累積發病
9.3%，非黑色素瘤皮膚癌為 6.9
在20多年的所有原發性兒童癌症
訪中，風險仍然很高

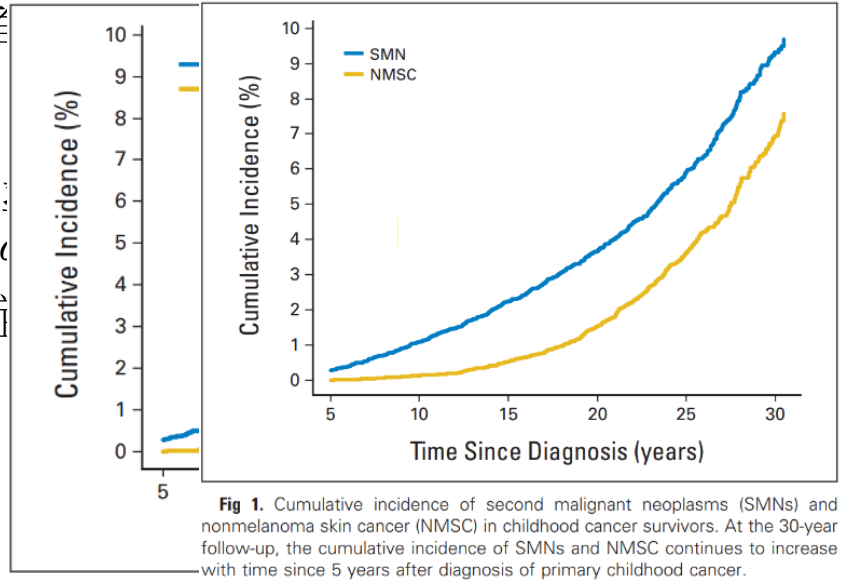

Fig 1. Cumulative incidence of second malignant neoplasms (SMNs) and nonmelanoma skin cancer (NMSC) in childhood cancer survivors. At the 30-year follow-up, the cumulative incidence of SMNs and NMSC continues to increase with time since 5 years after diagnosis of primary childhood cancer.

Fig 1. Cumulative incidence of second malignant neoplasms (SMNs) and nonmelanoma skin cancer (NMSC) in childhood cancer survivors. At the 30-year follow-up, the cumulative incidence of SMNs and NMSC continues to increase with time since 5 years after diagnosis of primary childhood cancer.

Meadows et al, JCO 2009

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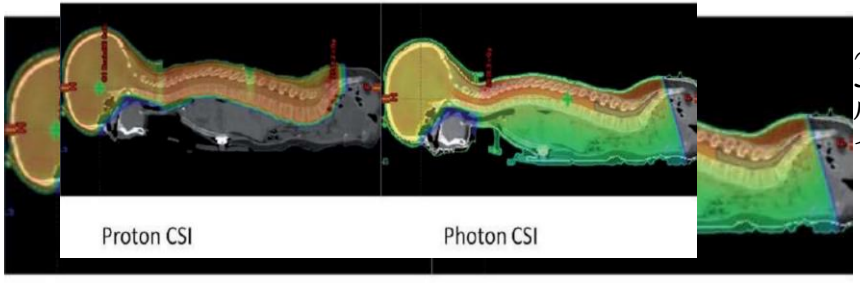
髓母細胞瘤 Medulloblastoma



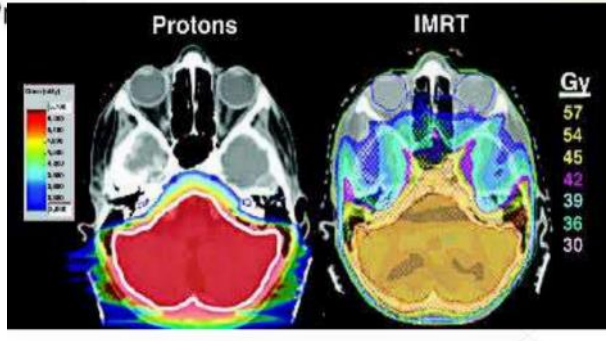


Fig: Proton therapy shows more healthy tissue sparing than IMRT *{Source: St. Clair, et al (2004)}*

35項研究比較了質子治療與光子治療
質子治療證明：

- 卓越的神經認知結果
- 甲狀腺功能減退症的發生率更低（23 vs 69%）
- 減少急性毒性（包括骨髓抑制、食管炎、腹瀉等）
- 10年內低中度惡性腫瘤（2.1-4.9% vs 8%）
- 10 年總生存率為 86%，兩者相似

Young et al, Red Journal, 2022

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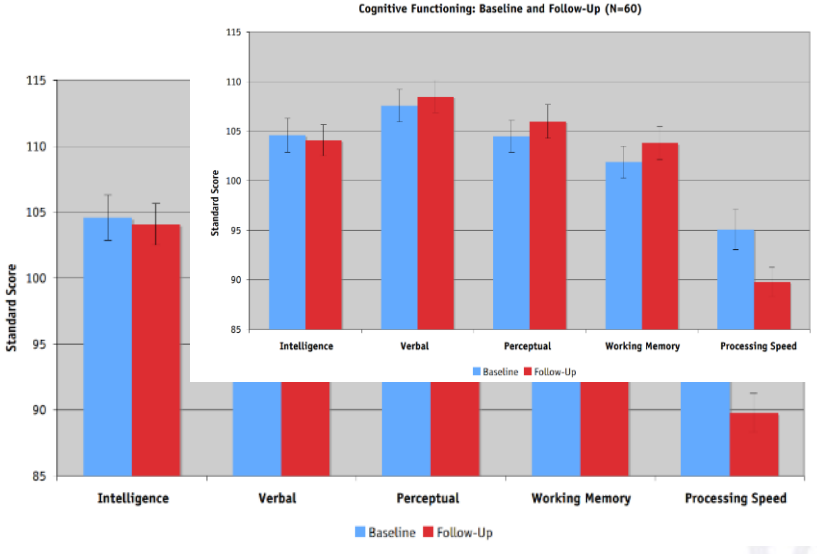
接受質子治療的腦腫瘤兒科患者認知結果的研究

Study of cognitive outcomes for pediatric patients with brain tumors receiving proton therapy

60 名年齡 6歲或以上的兒科患者歲患有腦瘤
平均隨訪 2.5 年
隨訪時，智商和其他參數（處理速度除外有顯著變化



Pulsifer Red Journal 2015

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小兒質子應用摘要
Summary for pediatric proton applications

兒童質子治療在腫瘤控制和減少急性和晚期副作用方面具有可喜的臨床結果

應鼓勵更多兒童接受質子治療

光子和質子治療之間的長期臨床結果和毒性比較正在等待

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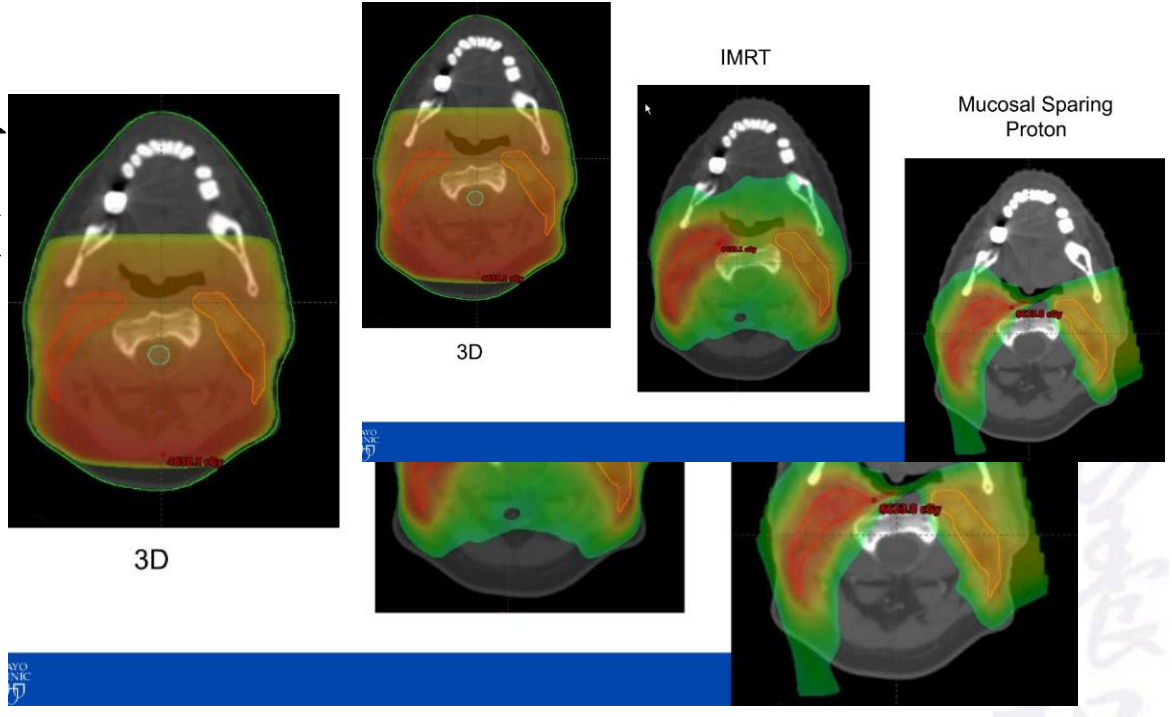
臨床應用：頭頸癌
Clinical Applications: Head and Neck Cancer

質子治療可減少對前口



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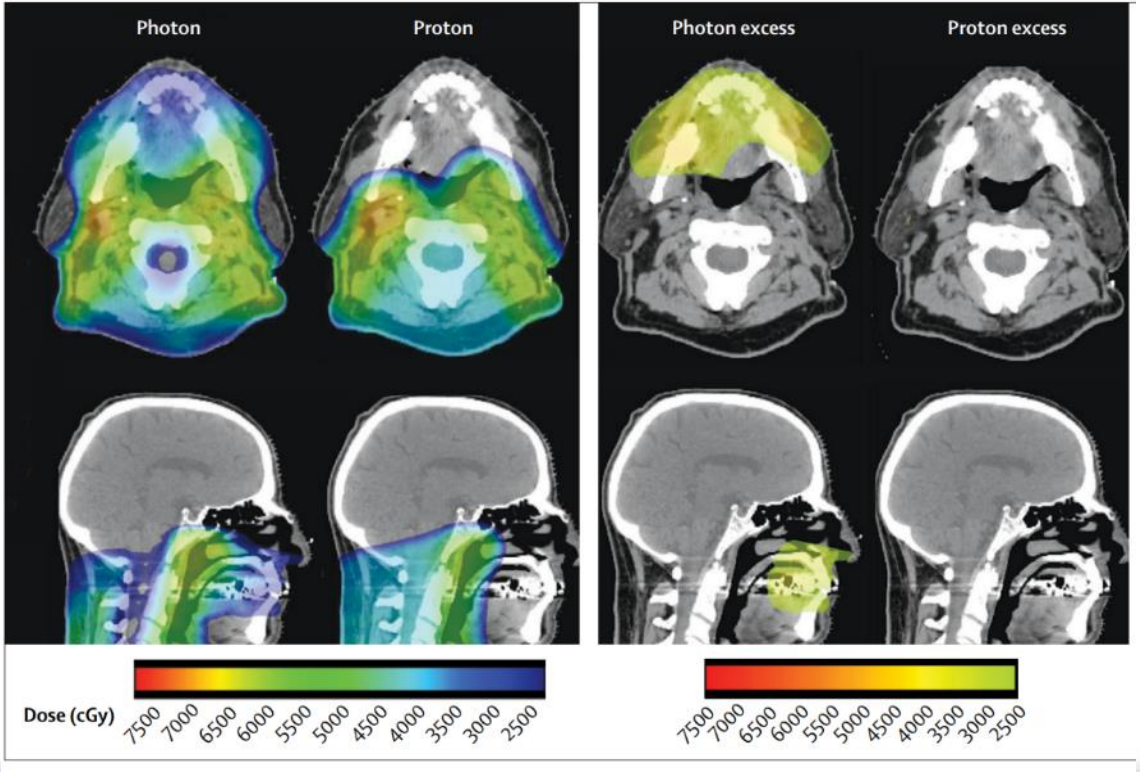
口咽癌
Oropharynx cancer



- 國際臨床試驗表明，插入飼管和感染風險以及住院治療的需求顯著降低
- 良好的生存率和低復發率

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Thank you

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