

淋巴瘤 簡介及治療方法

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血液及血液腫瘤科專科醫生

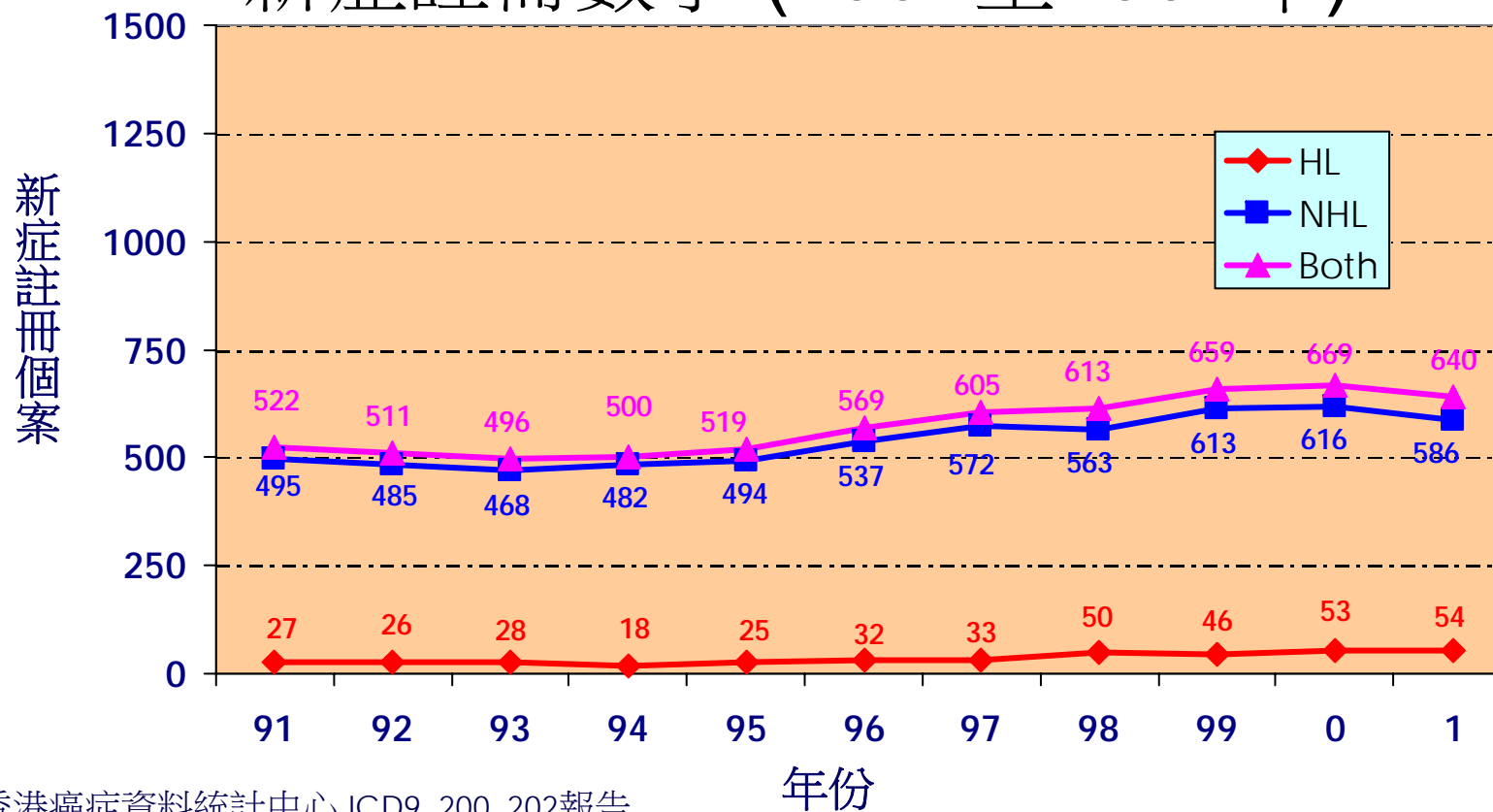
9/3/2008



淋巴瘤在香港的情況 (Lymphomas in Hong Kong)

- 發病率：全港第 9 位最常見的癌病
- 2001 年有 620 宗病例
- 較 1991 年 (520 宗) 增加約 20%
- 可以在半年至二年內令病人死亡
- 死亡率在最近十年上升近 80% (增至 2001 年的 312 例)
- 早期的治癒率達 80-90%

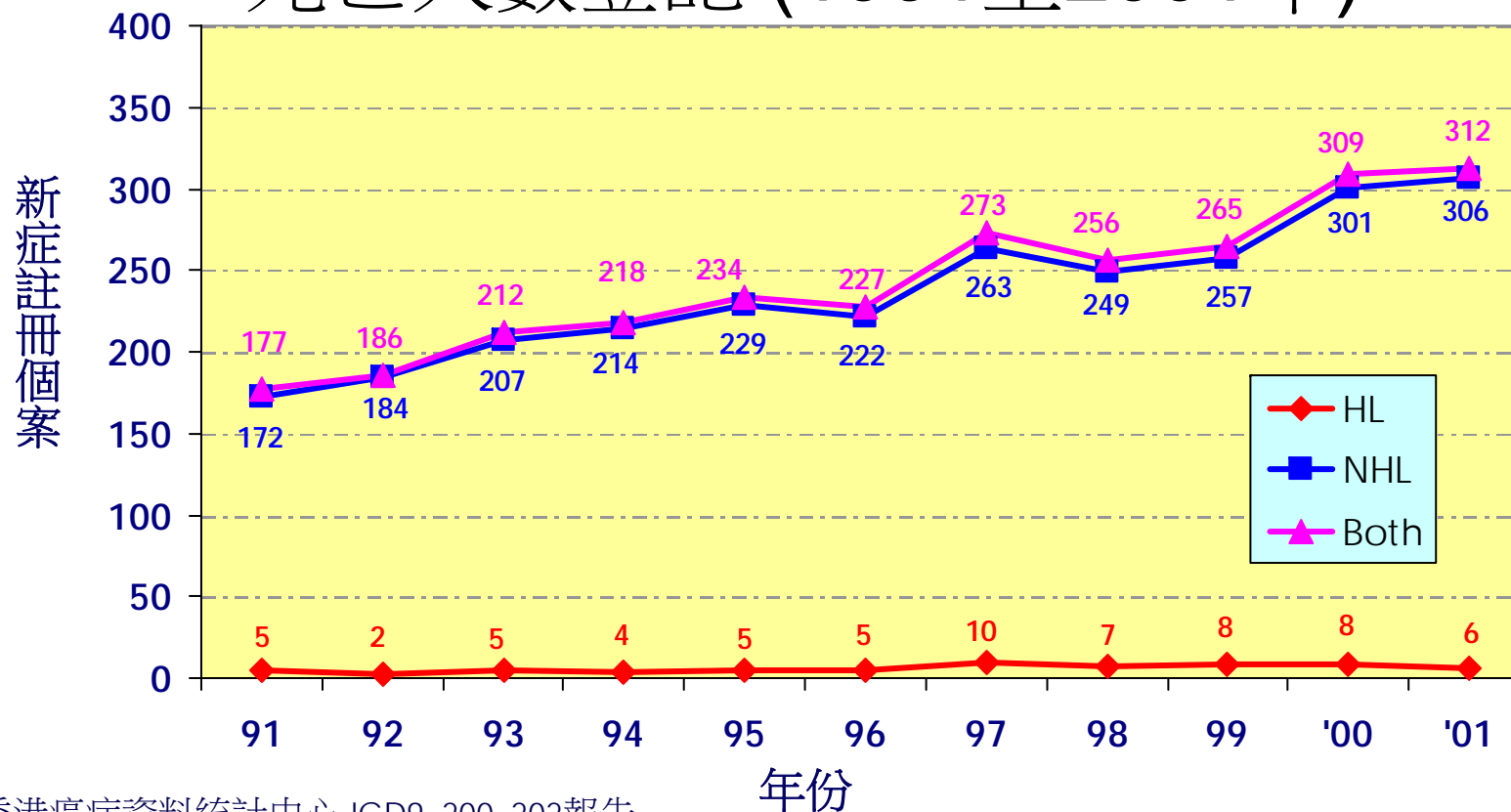
本港所有年齡的患淋巴瘤人士 新症註冊數字 (1991至2001年)



參考：香港癌症資料統計中心 ICD9 200, 202報告

2004年新症共 594 人
(佔癌症新症人數 2.6%)

本港所有年齡的患淋巴瘤人士 死亡人數登記 (1991至2001年)



參考：香港癌症資料統計中心 ICD9 200, 202報告

2004年 286 死亡個案
(佔癌症死亡人數2.4%)

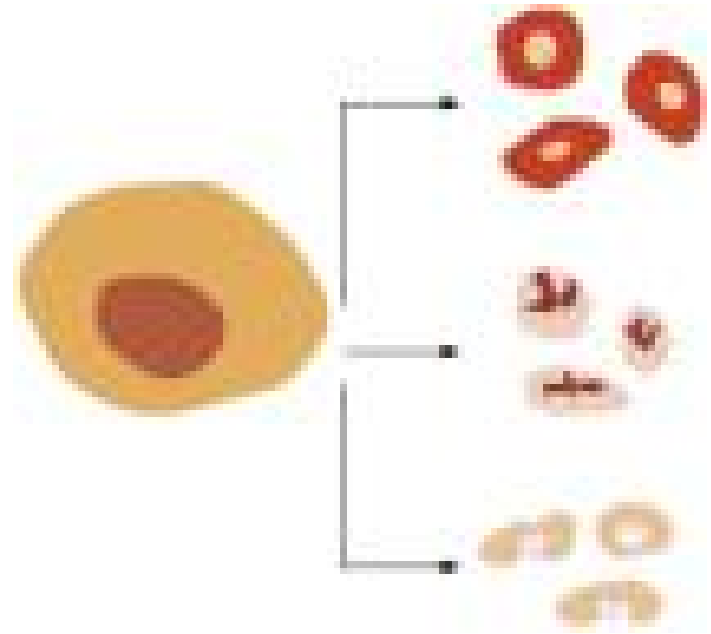
Table 3. Sex Ratio, Median Age and Cumulative Risk for 20 Leading Cancer Sites in 2000

Incidence

Rank	ICD-9	Site	Sex ratio		Median age at diagnosis		Cumulative risk of developing cancer	
			Male	Female	Male	Female	Male	Female
					(yrs)	(yrs)	(1 in)	(1 in)
1	162	Lung	2.1	1	70	73	15	38
2	153	Colon	1	1	70	71	38	43
3	174	Female breast	-	-	-	50	-	23
4	155	Liver	3.4	1	61	70	30	110
5	154	Rectum	1.5	1	69	70	54	90
6	147	Nasopharynx	2.4	1	48	47	53	131
7	151	Stomach	1.8	1	69	72	56	128
8	185	Prostate	-	-	74	-	63	-
8	188	Bladder	3.2	1	71	78	79	415
10	200,202	Non-Hodgkin's lymphoma	1.3	1	64	66	110	168
11	150	Oesophagus	4.2	1	67	73	80	442
12	173	Non-melanomatous skin	1	1.2	70	76	166	204
13	180	Cervix uteri	-	-	-	53	-	94
14	193	Thyroid	1	3.7	46.5	45	472	143
15	182	Corpus uteri	-	-	-	54	-	106
16	183	Ovary etc.	-	-	-	50	-	125
17	157	Pancreas	1.2	1	69	72.5	214	288
18	204-208	Leukaemia	1.1	1	52	44.5	228	298
19	189	Urinary except bladder	1.6	1	64	66.5	209	298
20	156	Gallbladder etc.	1	1.1	73	74	369	344
	140-208	All sites	1.2	1	67	65	4	5

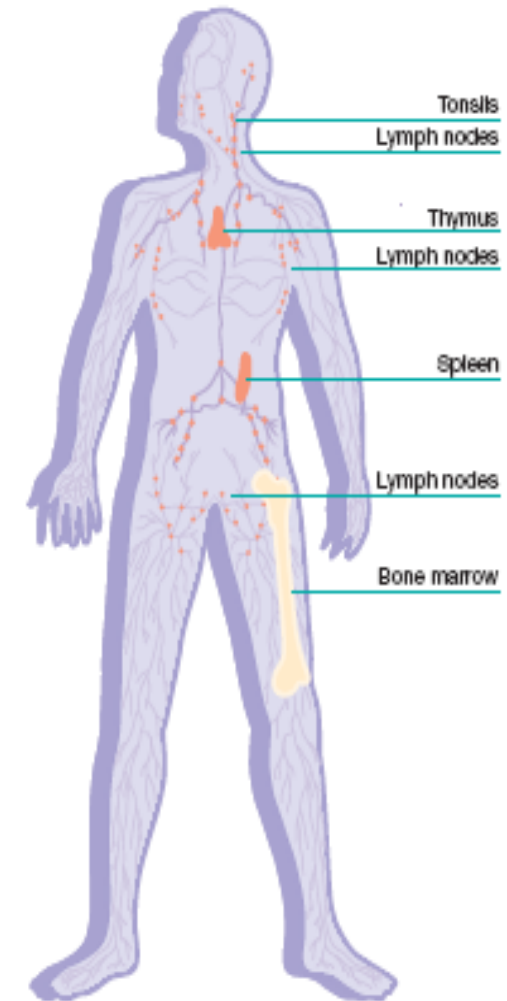
基本概念(一)：血球的種類

- 紅血球
- 白血球
 - 中性粒細胞 (Neutrophil)
 - 淋巴細胞 (Lymphocyte)
 - 嗜酸性細胞 (Eosinophil)
 - 嗜鹼性細胞 (Basophil)
 - 單核細胞 (Monocyte)
- 血小板

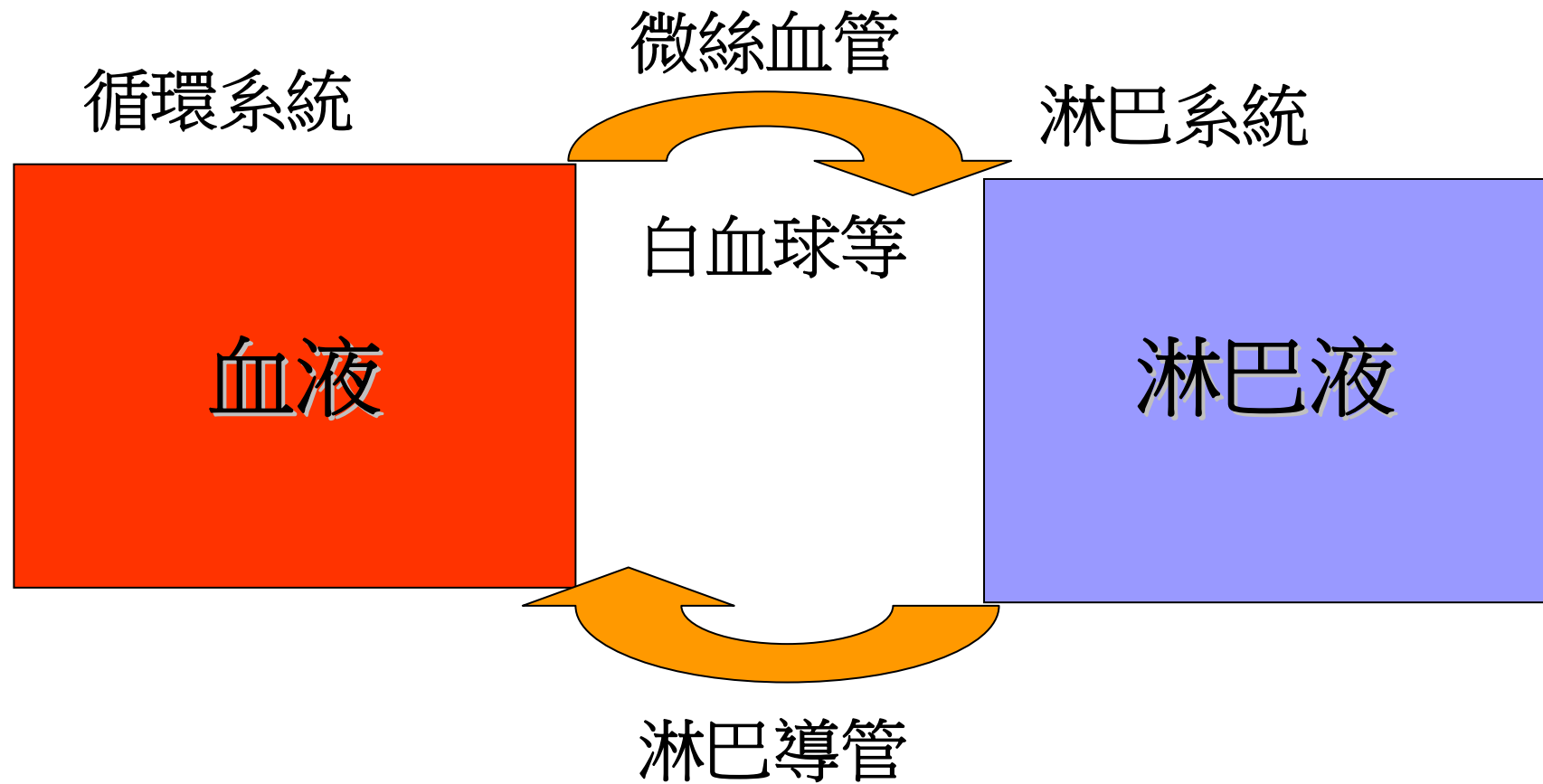


基本概念(二)：三個有關的系統

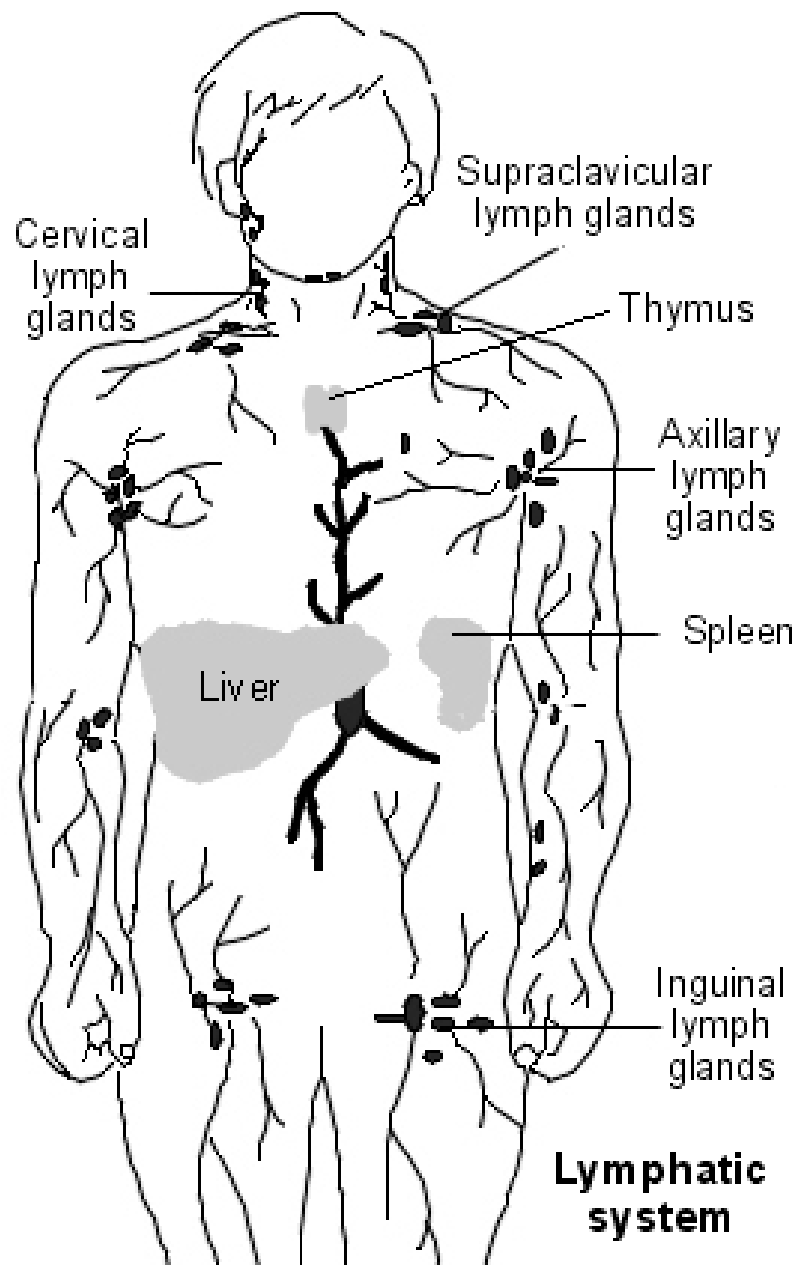
- 血液系統
 - 血液、骨髓、肝、脾
- 循環系統
 - 心、動脈、靜脈、微絲血管
- 淋巴系統
 - 淋巴管、淋巴結、淋巴結群
 - 淋巴組織：大量淋巴細胞之網狀組織，分佈在脾、胸腺及消化，呼吸管道上，包括 Waldeyer's Ring



基本概念(三)：三個有關的系統



淋巴系统

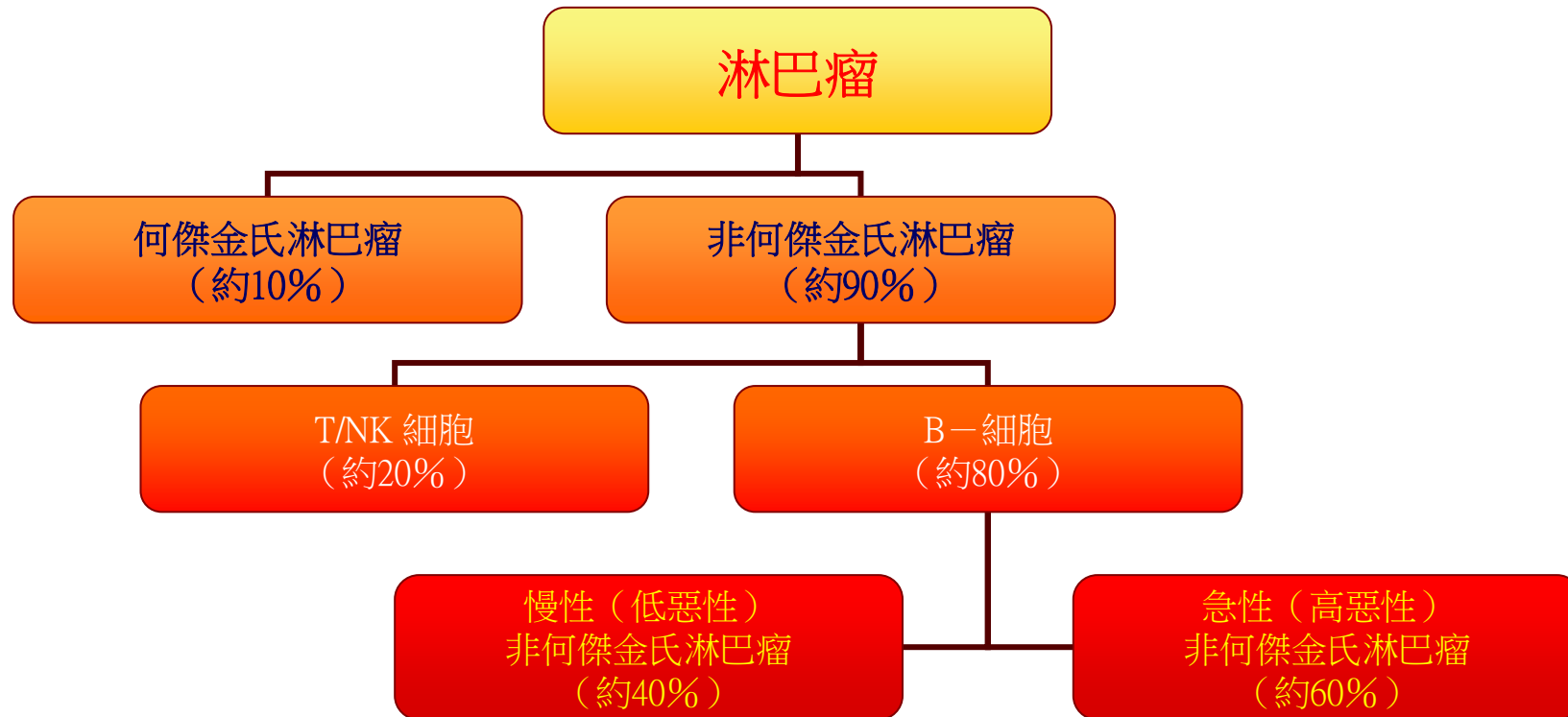




淋巴癌的種類

- 種類非常繁多
- 主要分為
 - 何傑金病 (Hodgkin's Disease)
 - 非何傑金淋巴瘤 (Non-Hodgkin's Lymphoma)
- 香港以非何傑金淋巴瘤患者居多

惡性淋巴瘤分類



以上百分比適用於香港情況

淋巴癌的分類

- 何傑金氏病
- 非何傑金氏病：這是起源自一大群不同類型淋巴血球白腫瘤

有多種非常繁複的分類方法：

- 病情快慢
 - 低惡性、高惡性
- 細胞起源
 - B，T 淋巴球、NK 細胞





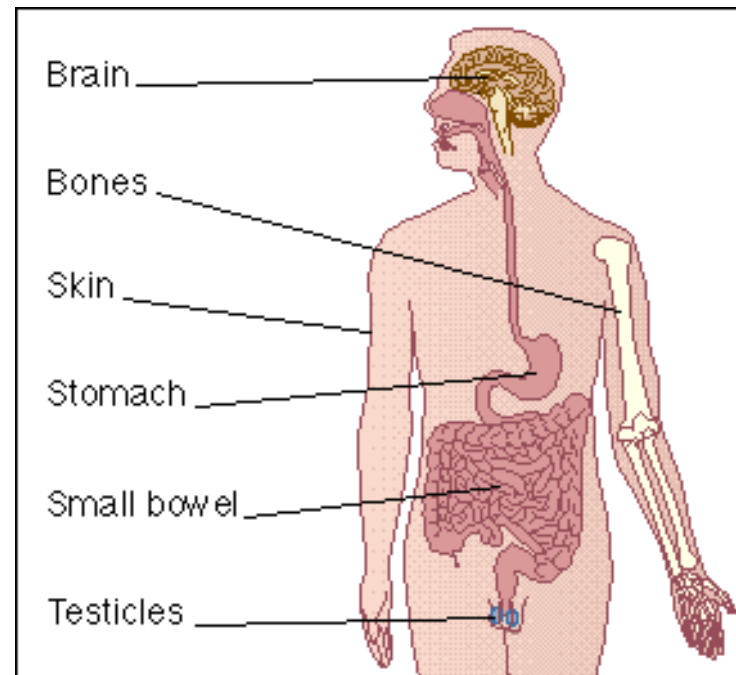
淋巴癌的成因

- 至今仍未完全了解
- 研究顯示可能成因
 - 遺傳基因病變
 - 病毒感染
 - 化學藥物
 - 體內免疫系統失常

淋巴癌病徵的總括

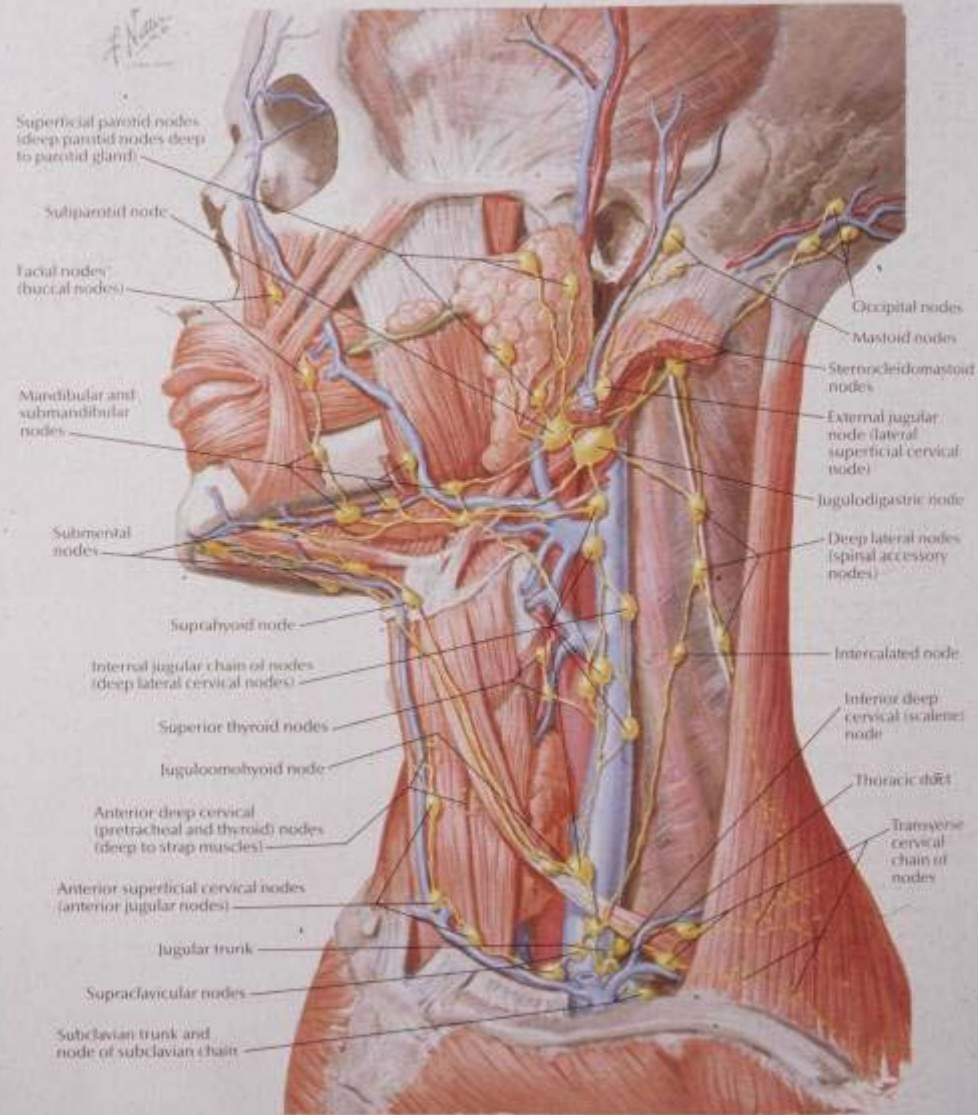


- 腫瘤引起的病徵
 - 淋巴結腫大
 - 淋巴結以外器官病發
 - 腸胃
 - 鼻孔、鼻咽
 - 眼睛
 - 皮膚
 - 中樞神經系統
 - 腮腺、甲狀腺
 - 睪丸



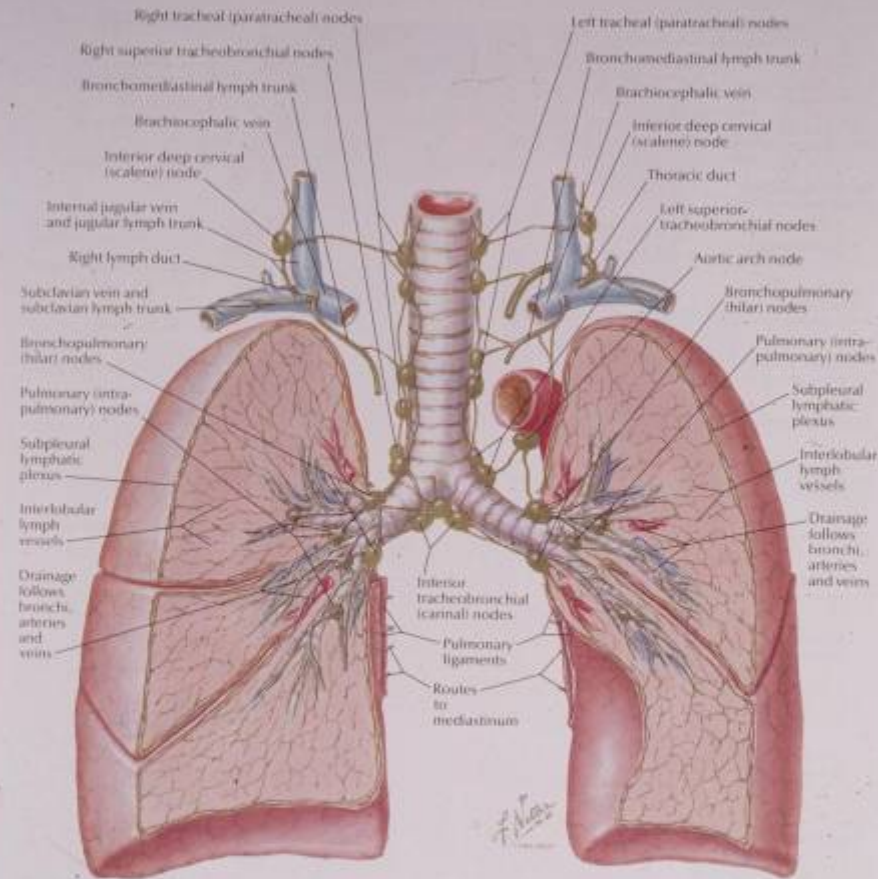
Lymph Vessels and Nodes of Oral and Pharyngeal Regions

SEE ALSO PLATE 197



Lymph Vessels and Nodes of Lung

SEE ALSO PLATES 66, 169, 227



Drainage routes

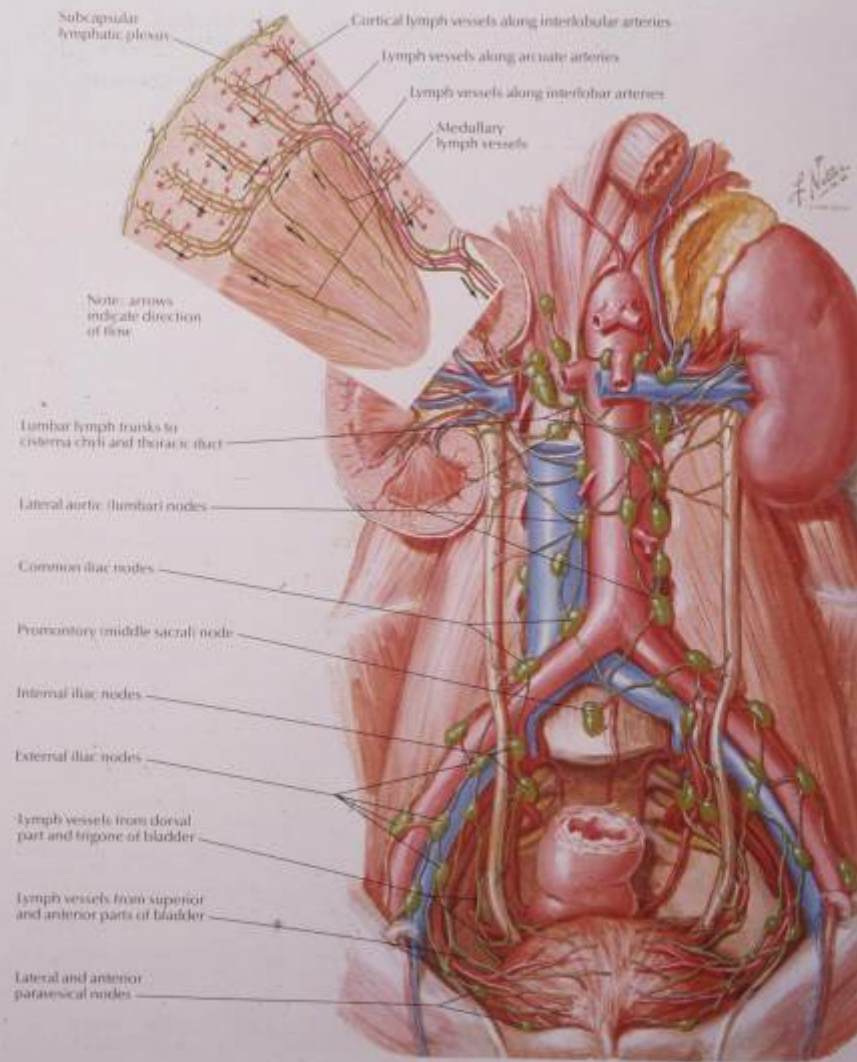
Right lung: All lobes drain to intrapulmonary and bronchopulmonary (hilar) nodes, then to inferior tracheobronchial (carinal) nodes, right superior tracheobronchial nodes and to right tracheal nodes on way to brachiocephalic vein via bronchomediastinal lymph trunk and/or scalene node.

Left lung: Upper lobe drains to pulmonary and hilar nodes, carinal nodes, left superior tracheobronchial nodes, left

tracheal nodes and/or aortic arch node, then to brachiocephalic vein via left bronchomediastinal trunk and thoracic duct. Left lower lobe drains also to pulmonary and hilar nodes and to carinal nodes, but then mostly to right superior tracheobronchial nodes, where it follows same route as lymph from right lung.

Lymph Vessels and Nodes of Kidneys and Urinary Bladder

SEE ALSO PLATES 301, 383



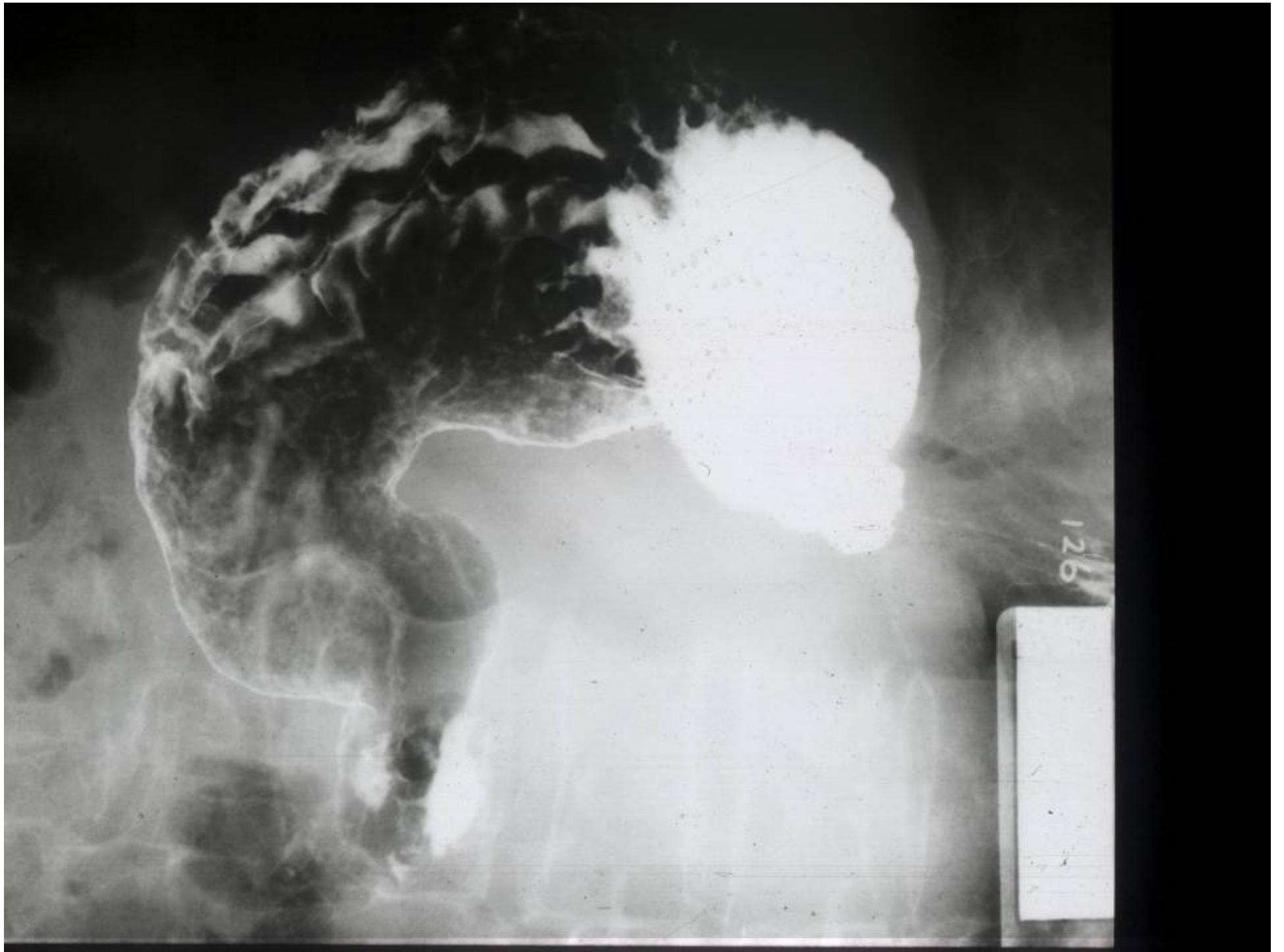
淋巴癌病徵的總括

■ B 症狀

- 6 個月內體重輕 10% 或以上
- 發燒
- 夜間盜汗















0.0mm
Tilt: 4.0
AX
2 [13,42] mean 33.10, sd 4.38, area 11mm
77 V/L

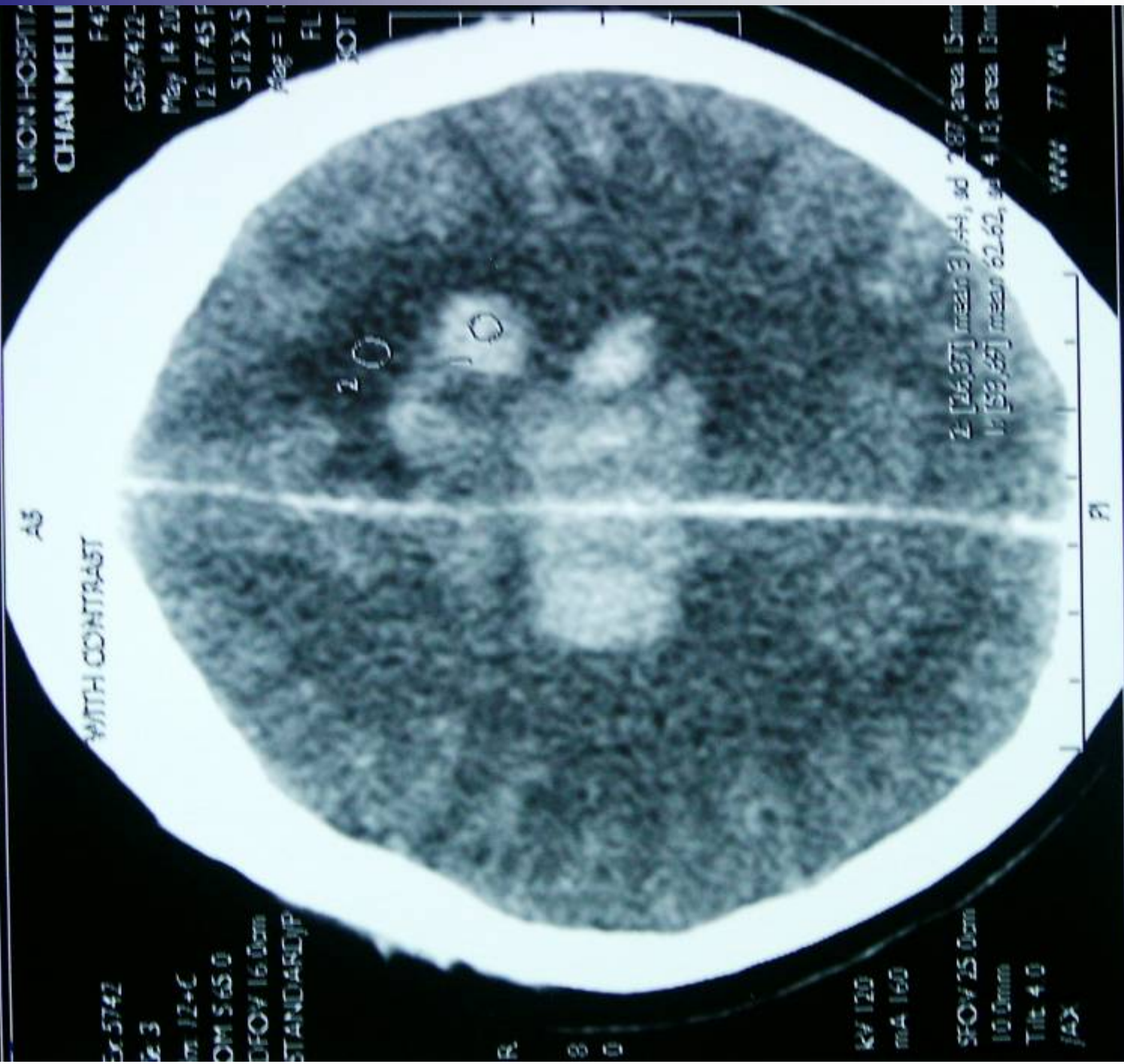
UNION HOSPITAL
CHAN MEI LI
F42

GS57422-
May 14 20
12 17 45 F
512 X 5
Mag = 1
FL
ROT

A5

WITH CONTRAST

EX 5742
Z 3
m 12+C
OM 5 65 0
DFOV 16.0cm
STANDARD/PP



R
8
0

KV 120
mA 160
SFOV 25.0cm
10.0mm
Tilt: 4.0
/AX

2 [26,37] mean 31.44, sd 2.87, area 15mm
1 [59,69] mean 62.62, sd 4.13, area 13mm
77 V/L

P1

UNION HOSPITAL
CHAN MEI LI
F42
GS57422-

A5

EX 5742
263

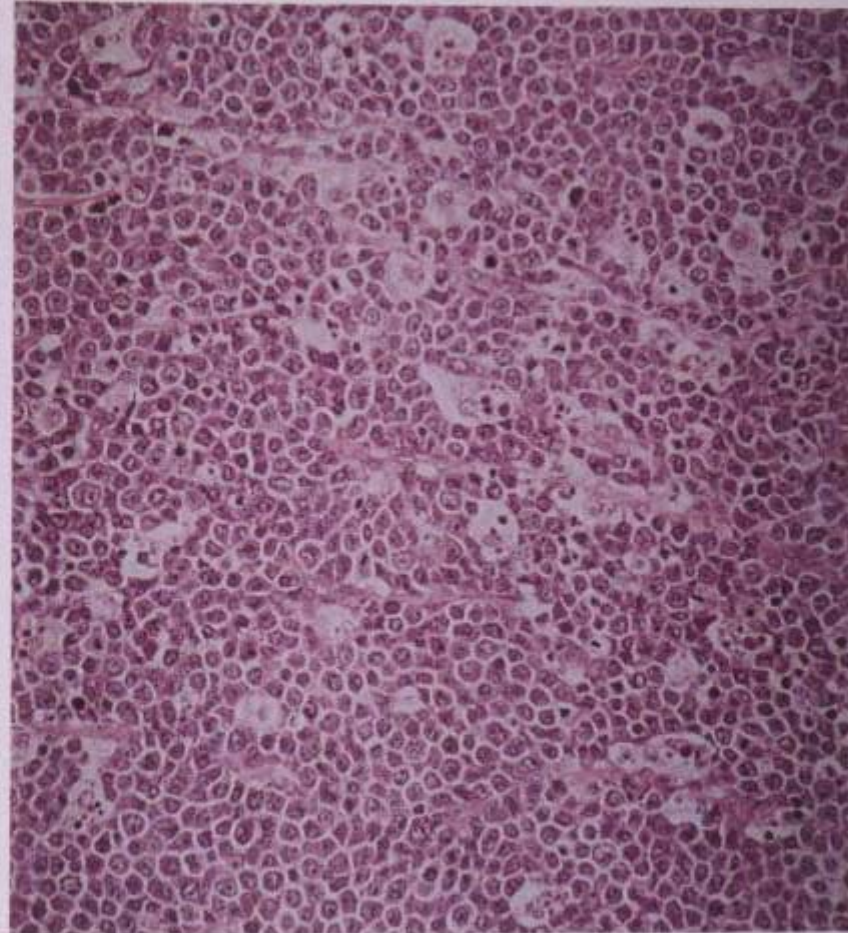


Fig. 13.13 Burkitt's lymphoma: characteristic facial swelling due to extensive tumour involvement of the mandible and surrounding soft tissues.

Fig. 13.14 Burkitt lymphoma: histological section of lymph node showing sheets of lymphoblasts and 'starry sky' tingible body macrophages.



徵狀

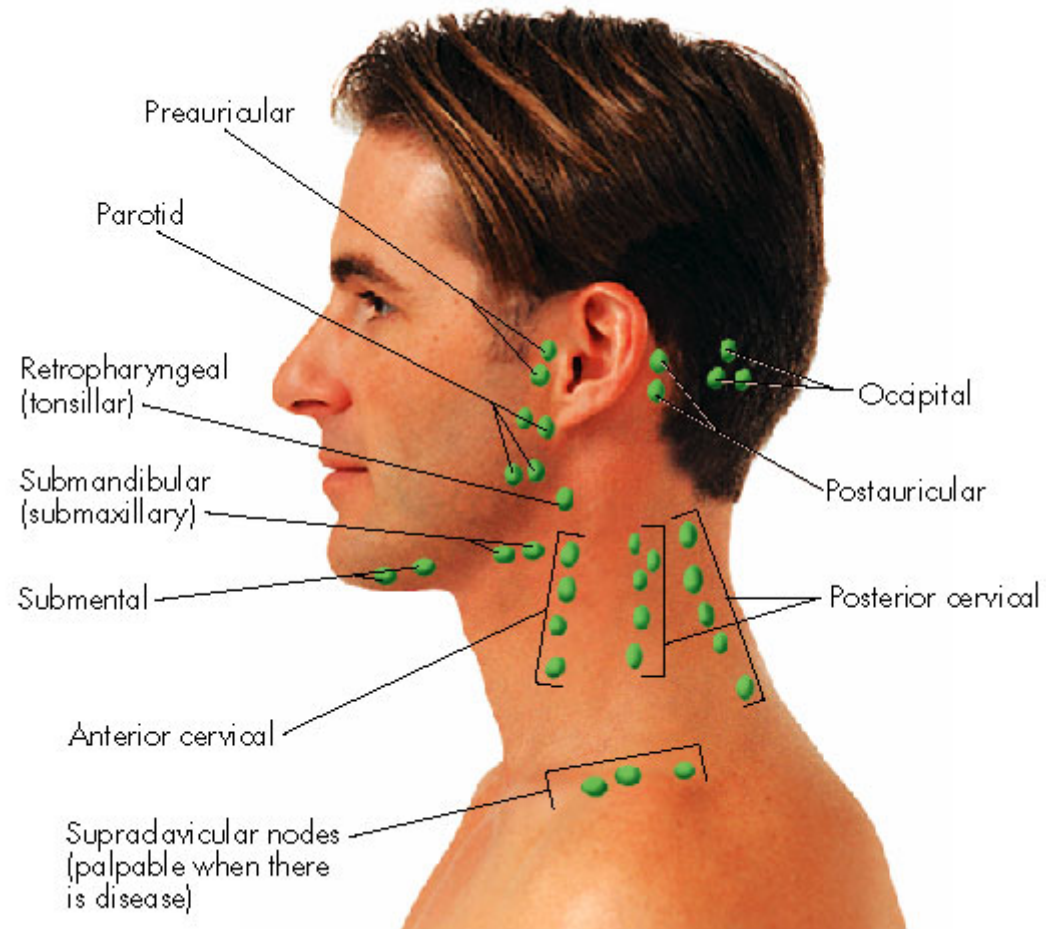
- 無痛性淋巴結腫大（頸部，腋下等）
- 體重下降
- 發熱
- 冒汗
- 持續咳嗽，氣喘，胸部疼痛
- 腹脹，腹痛



診斷

- 臨牀檢查
- 血液樣本化驗
- 淋巴結切除病理分析
- X光檢查
- 電腦掃描
- 抽取骨髓

臨牀檢查



臨牀檢查

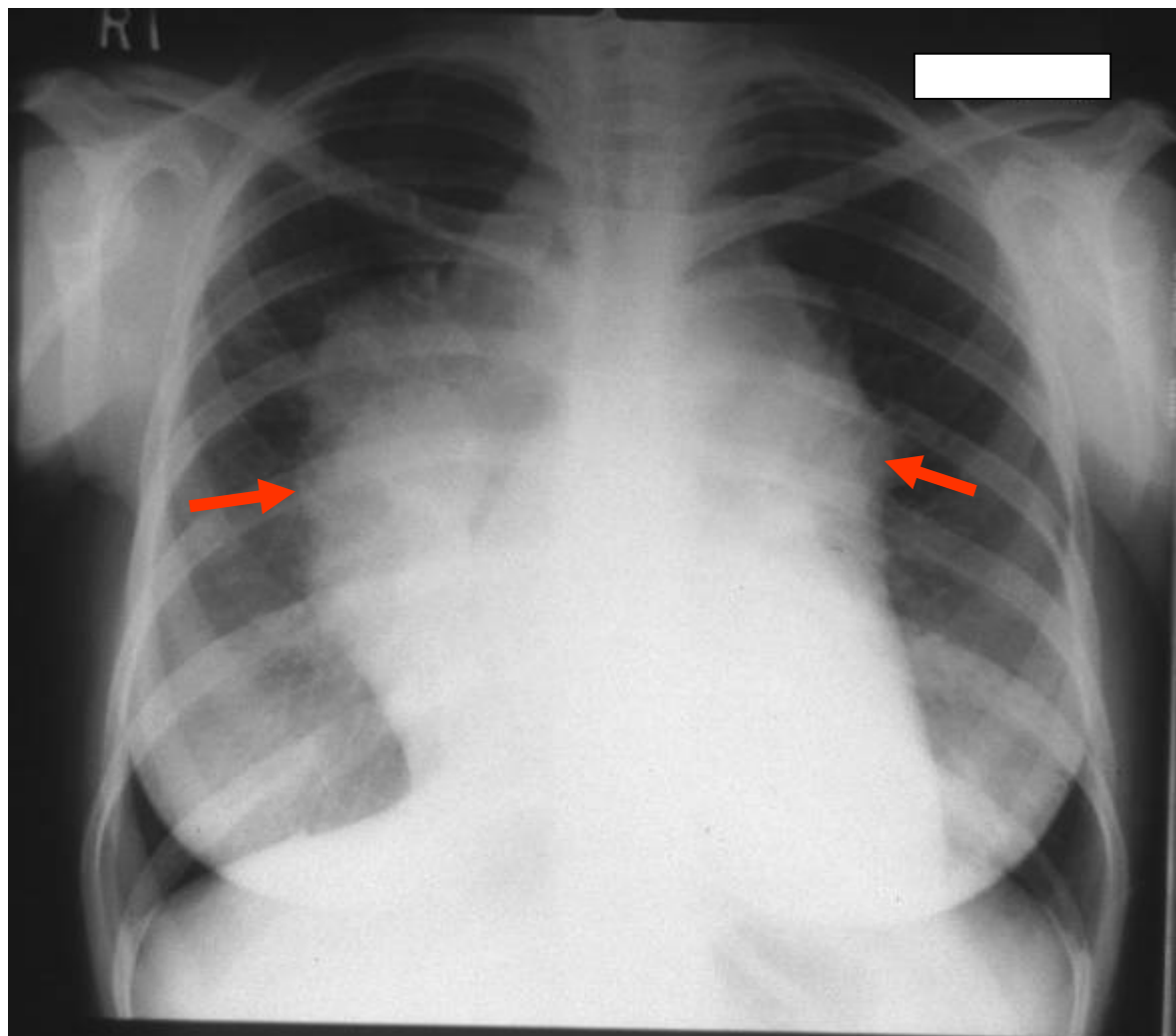


Normal spleen

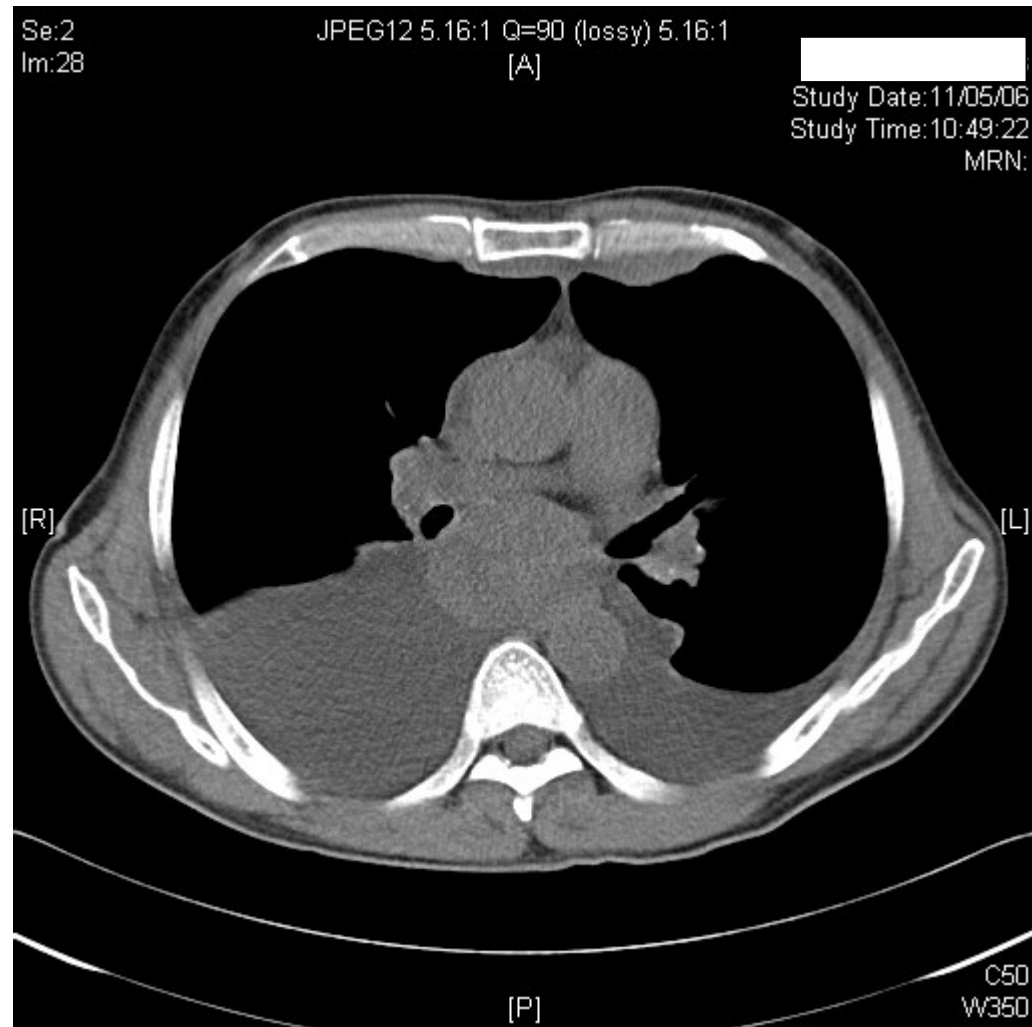


Splenomegaly

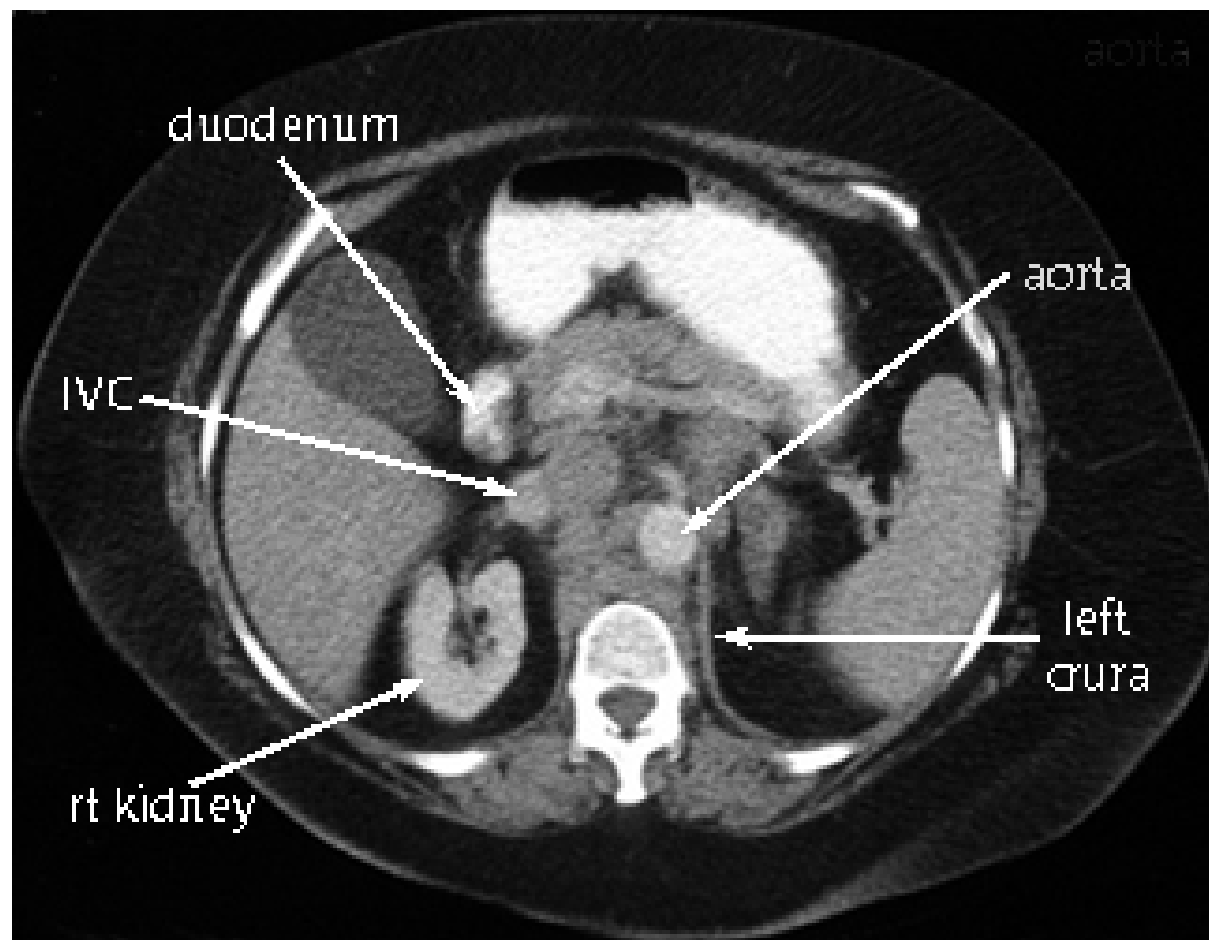
X光檢查



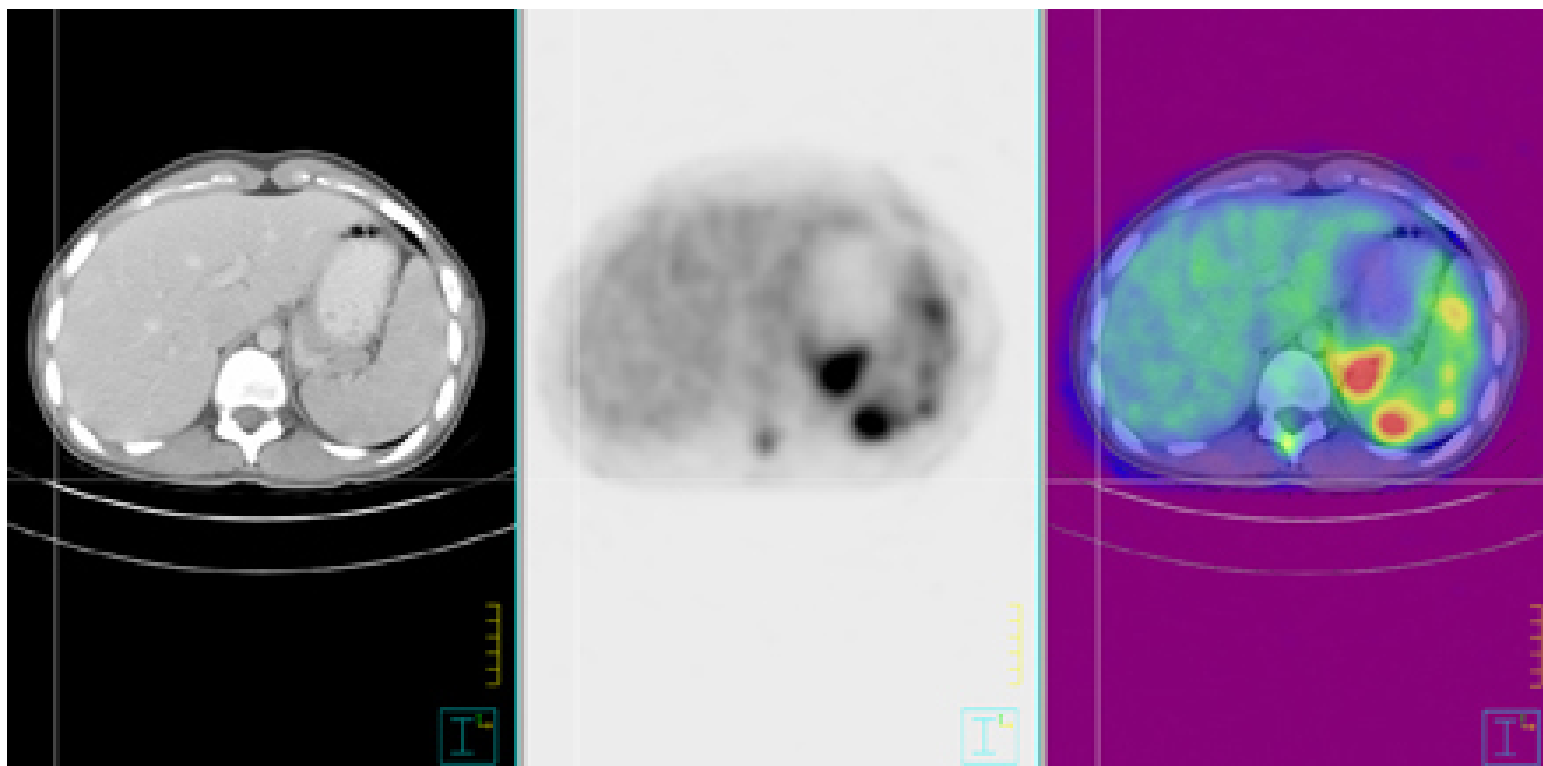
電腦掃描



電腦掃描



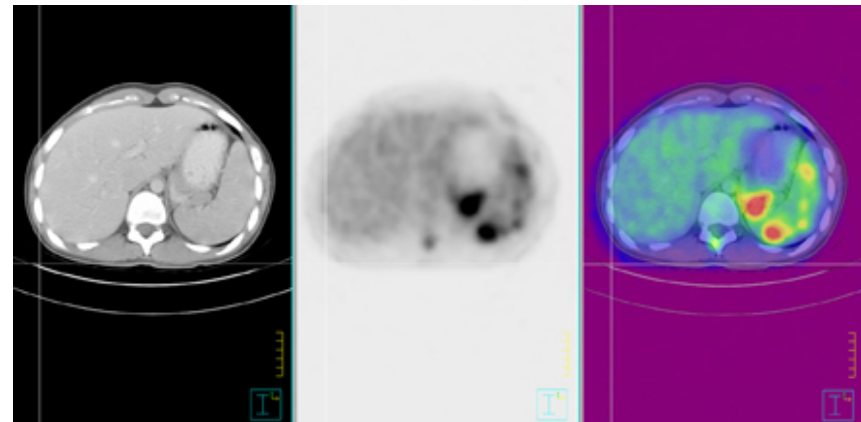
正電子素描 (PET Scan)



正電子素描 (PET Scan)

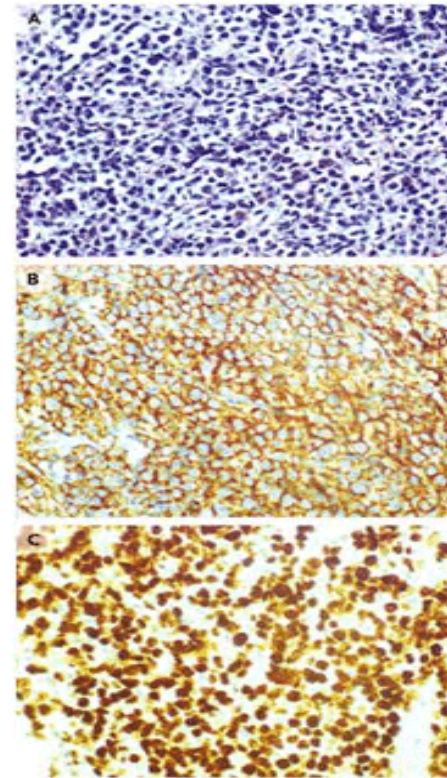
■ 徵狀

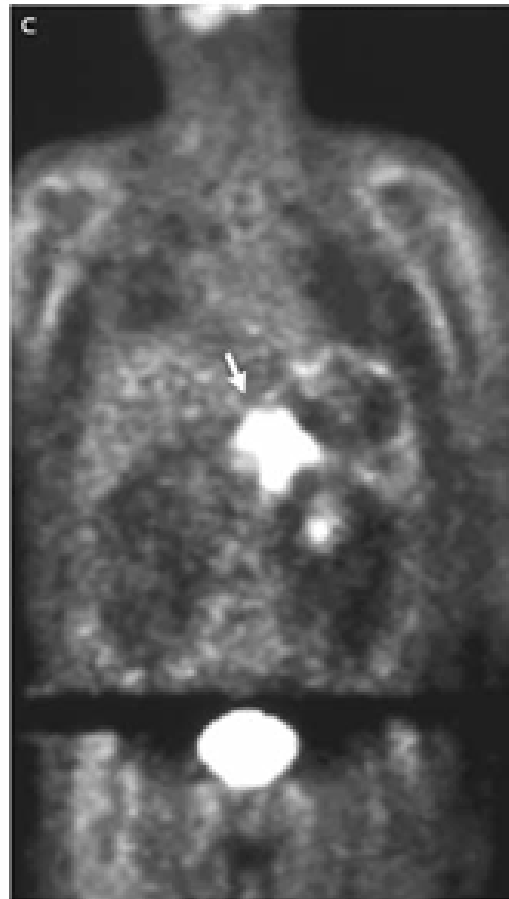
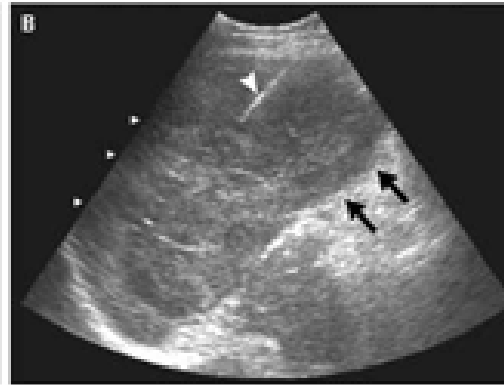
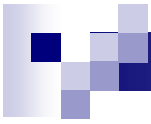
- 無痛性淋巴結腫大（頸部，腋下等）
- 體重下降
- 發熱
- 冒汗
- 持續咳嗽，氣喘，胸部疼痛
- 腹脹，腹痛



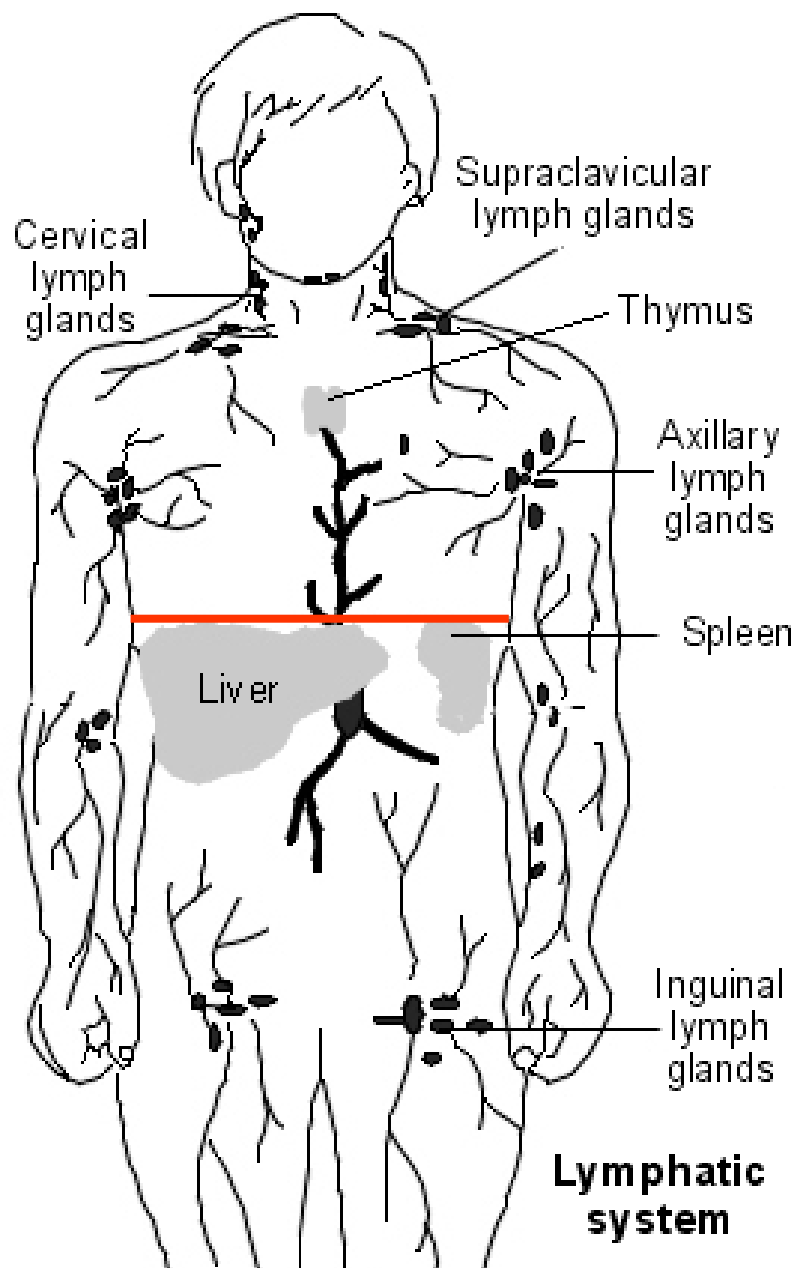
脾臟穿刺活檢（Needle Biopsy）

- H-E 染色見彌散性大淋巴細胞
- Immunoperoxidase 染色見癌細胞呈B-細胞抗原CD20
- 80%細胞見增生抗原Ki-67
- 彌散性大B-細胞淋巴瘤





分期



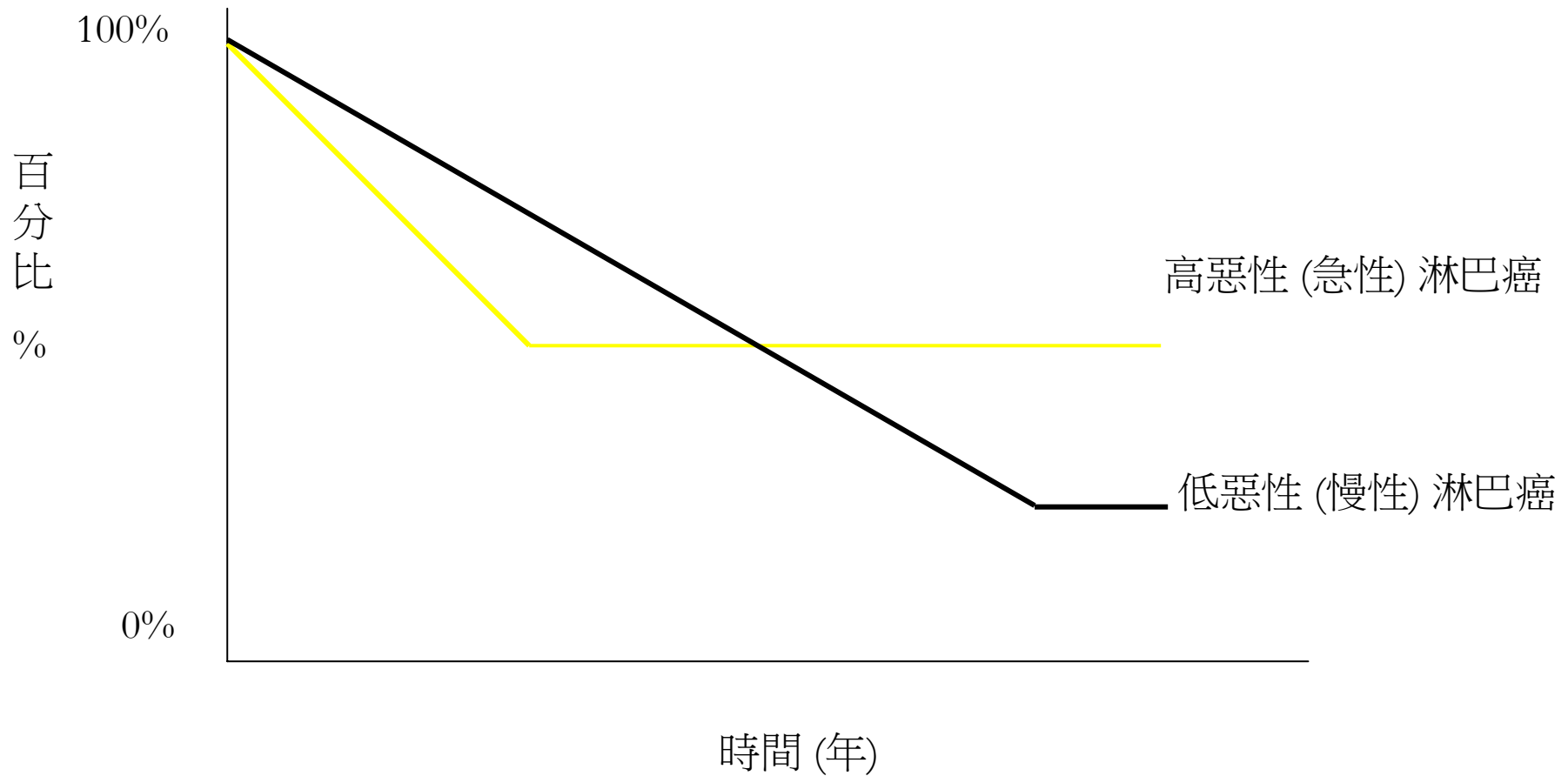



非何傑金氏淋巴瘤的特性

- 發病率：全港第 9 位最常見的癌病
- 病人：年老病人較多 (45 – 60)
- 病理及特徵
 - 淋巴結腫大，較多非順序擴散現象
 - 淋巴結以外的淋巴器官常見受影響
 - **B** 症狀較少見

復發的機會與時間性

圖：處於“完全緩解”狀況中病人的百分比





常見非何傑金氏淋巴瘤

■ 低惡性

- 濾泡性淋巴瘤 (Follicular centre cell)
- MALT 型結外邊緣區細胞淋巴瘤 (MALTOMA)
- 套細胞淋巴瘤 (Mantle Cell Lymphoma)

■ 高惡性

- 彌漫性大 B 細胞淋巴瘤 (Diffuse Large B-Cell Lymphoma)
- T 和 NK/T 型 (Peripheral T-cell Lymphoma)

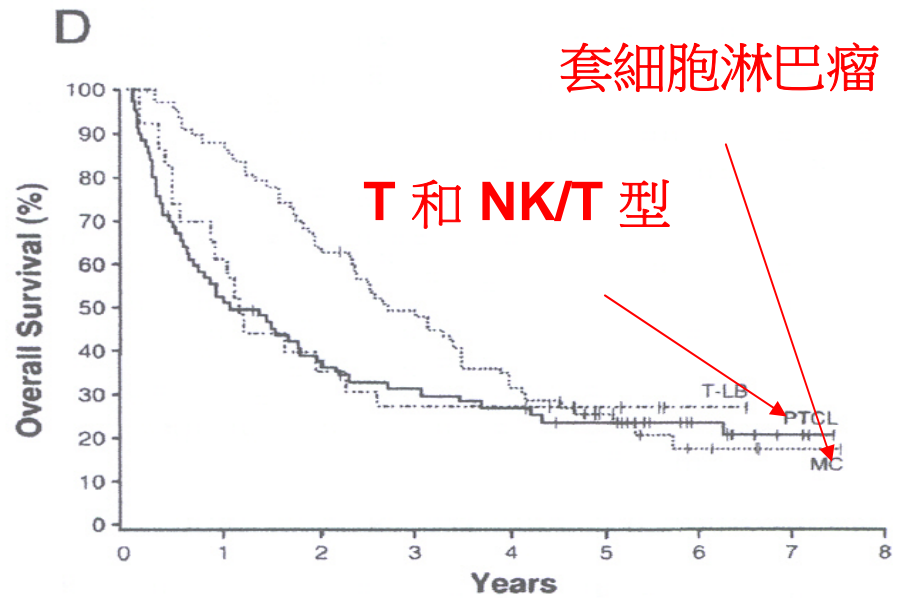
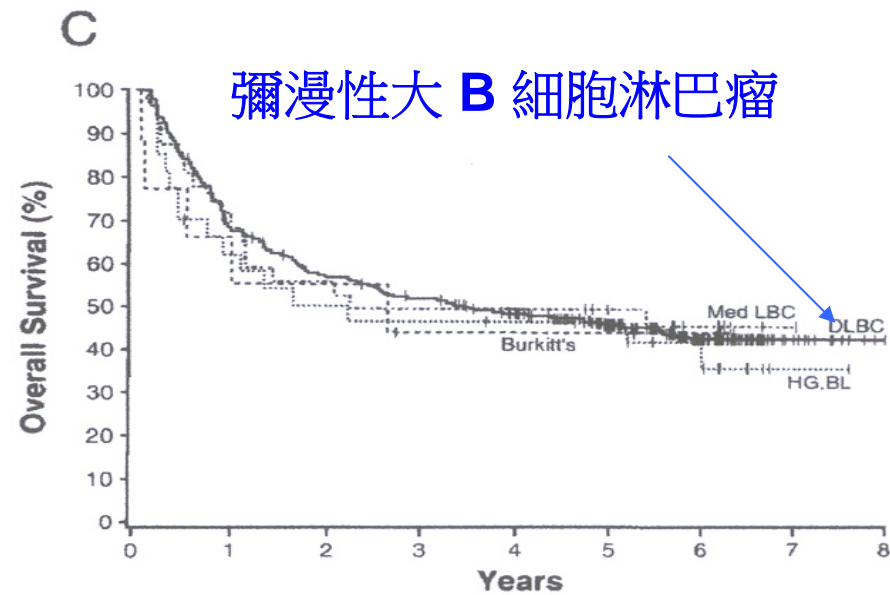
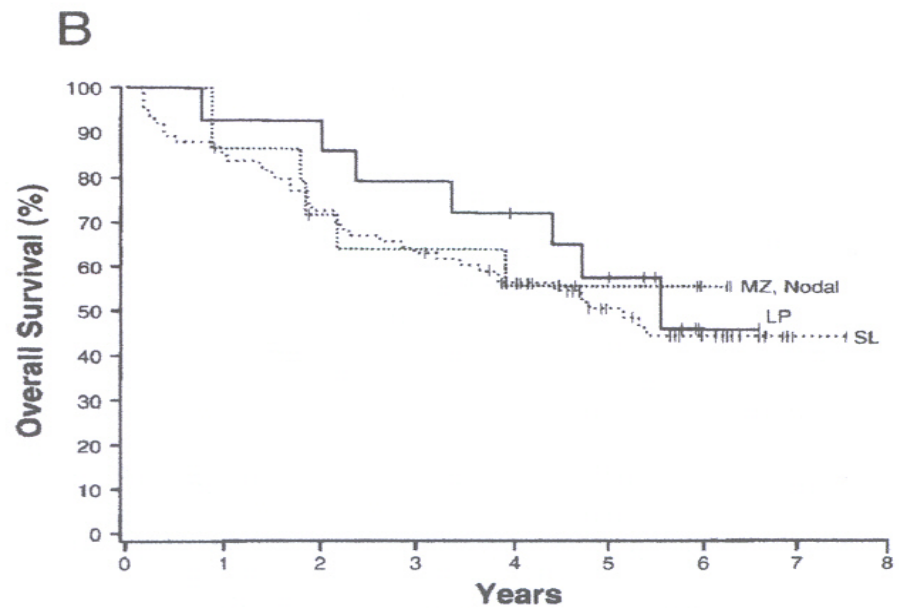
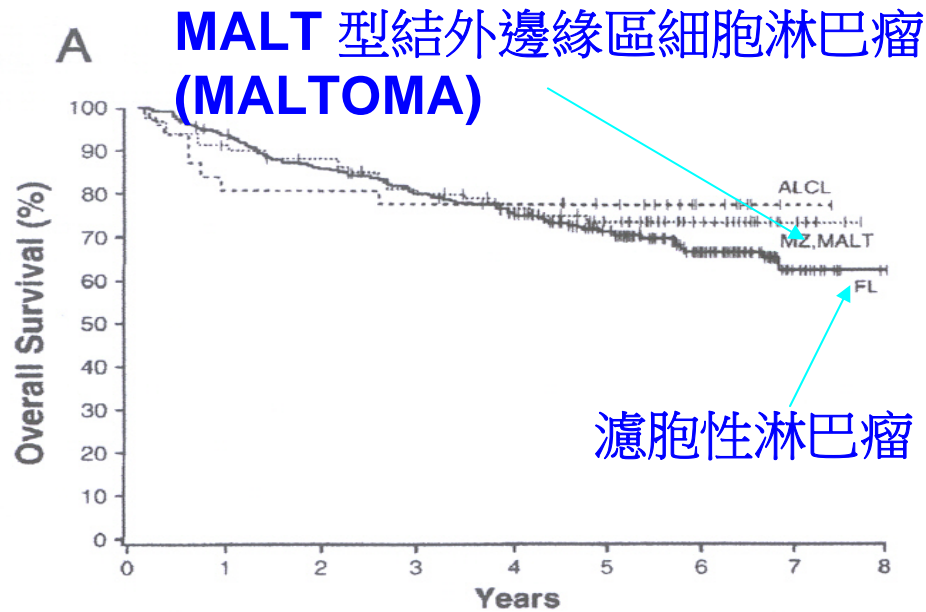


Fig 1. NHLs with a 5-year overall survival of greater than 70% (A), 50% to 70% (B), 30% to 49% (C), and less than 30% (D); ALCL, anaplastic large T/null-cell lymphoma; MZ, MALT, marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue; FL, follicular lymphoma; MZ, nodal, marginal zone B-cell lymphoma of nodal type; LP, lymphoplasmacytoid lymphoma; SL, small lymphocytic lymphoma; Med LBC, primary mediastinal large B-cell lymphoma; DLBC, diffuse large B-cell lymphoma; HG, BL, high-grade B-cell Burkitt-like lymphoma; T-LB, precursor T-lymphoblastic lymphoma; PTCL, peripheral T-cell lymphoma; MC, mantle cell lymphoma.




治療

- 考慮因素
 - 淋巴瘤的種類
 - 癌症分期
 - 年齡
 - 身體狀況及其他疾病



治療可用方法

- 化學治療
- 抗體治療
- 放射治療
- 血幹細胞移植



治療方案

- 生長緩慢非何傑金淋巴瘤
 - 如無任何病徵，可予觀察
 - 如有徵狀，建議化學治療或抗體治療
 - 第一，二期患者可考慮放射治療



治療方案

- 何傑金病及生長快速的非何傑金淋巴瘤
 - 建議化學治療 ± 抗體治療（非何傑金淋巴瘤）
 - 需要時結合放射治療



化學治療

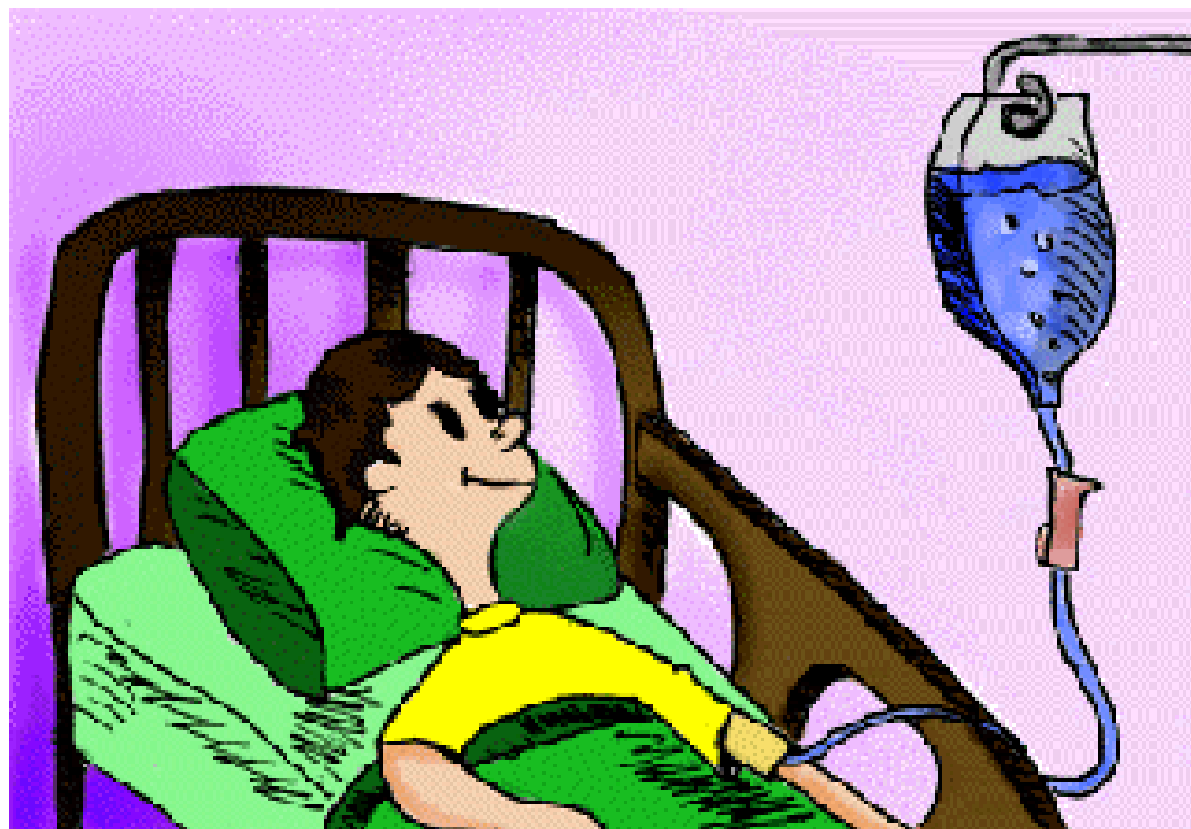
- 方法

- 口服

- 靜脈注射

- 脊髓液注射

化學治療

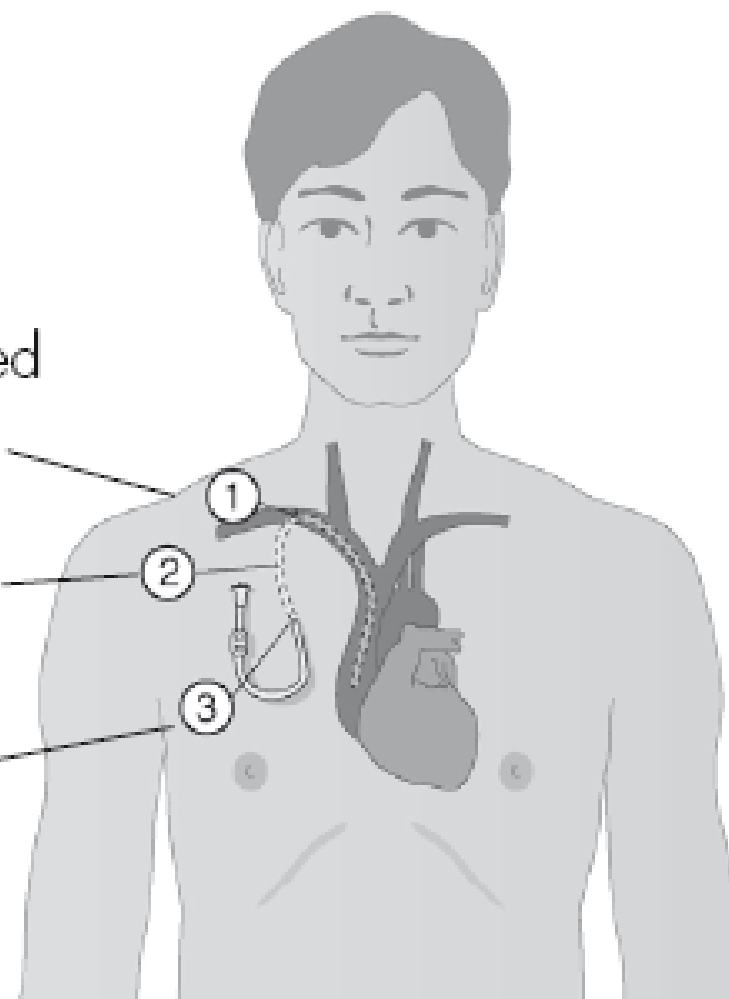


化學治療

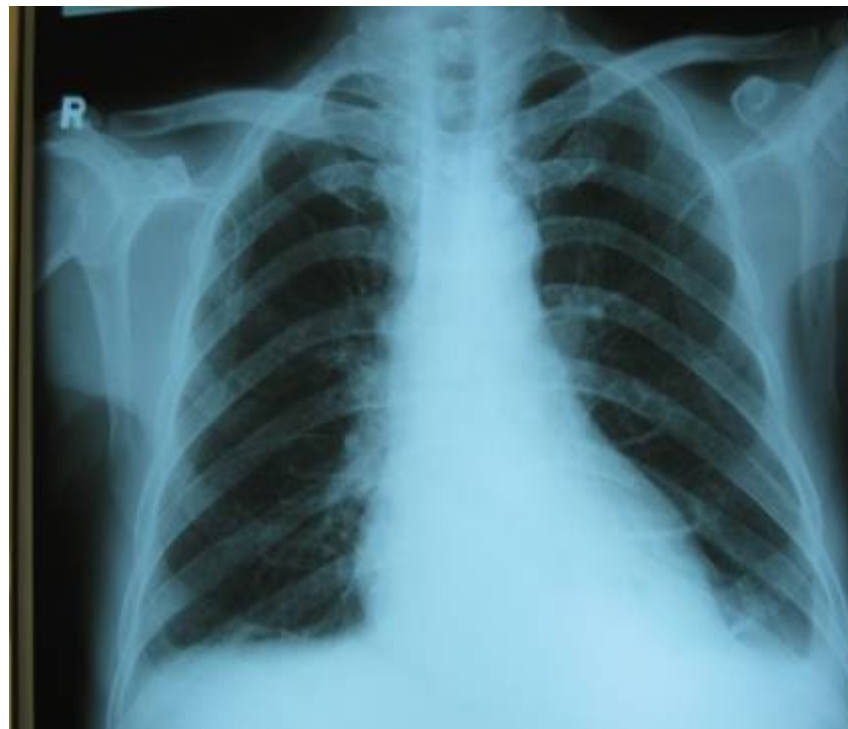
Central line is inserted
into your chest here

The line is tunnelled
under your skin

The line comes
out here



化學治療





化療副作用

- 血細胞

- 感染
- 出血
- 疲累

- 髮根

- 脫髮

- 消化系統

- 嘔吐
- 粘膜炎



抗體（標靶）治療

- 利用抗體辨認獨特抗原的能力
- 刺激免疫系統清除癌細胞

- 常見副作用
 - 發燒
 - 頭痛
 - 疲倦
 - 噁心

- 其他副作用
 - 氣喘
 - 血壓下降
 - 皮膚出疹

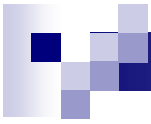
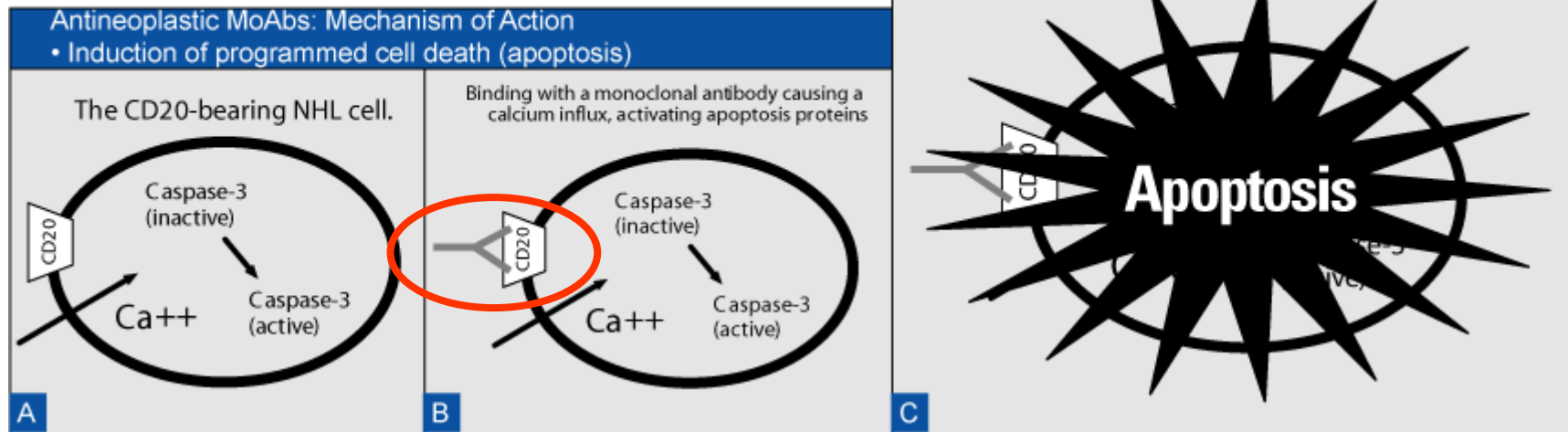


Figure 4





放射治療

- 利用治療機器所產生出來的高能量輻射
- 從遠距離照射到患處
- 消滅癌細胞

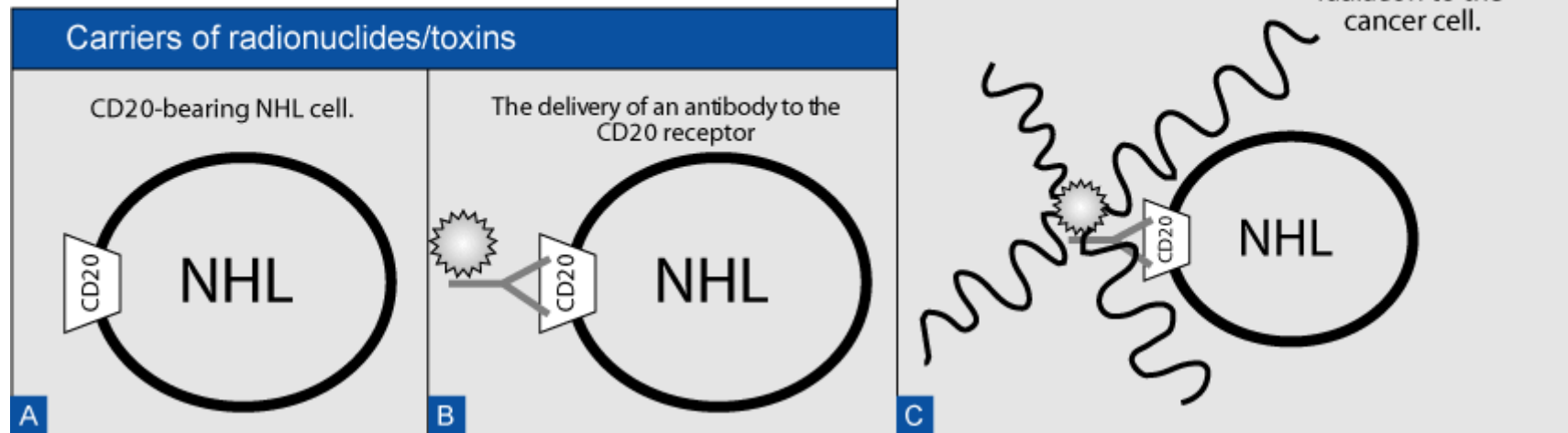
- 局部
- 全身



放射治療

- 副作用視乎治療位置
- 腹部
 - 噁心
 - 嘔吐
 - 腹瀉
- 肺部
 - 咳嗽
 - 氣喘
- 皮膚
 - 泛紅
 - 乾躁
 - 疼痛
- 疲倦

Figure 3



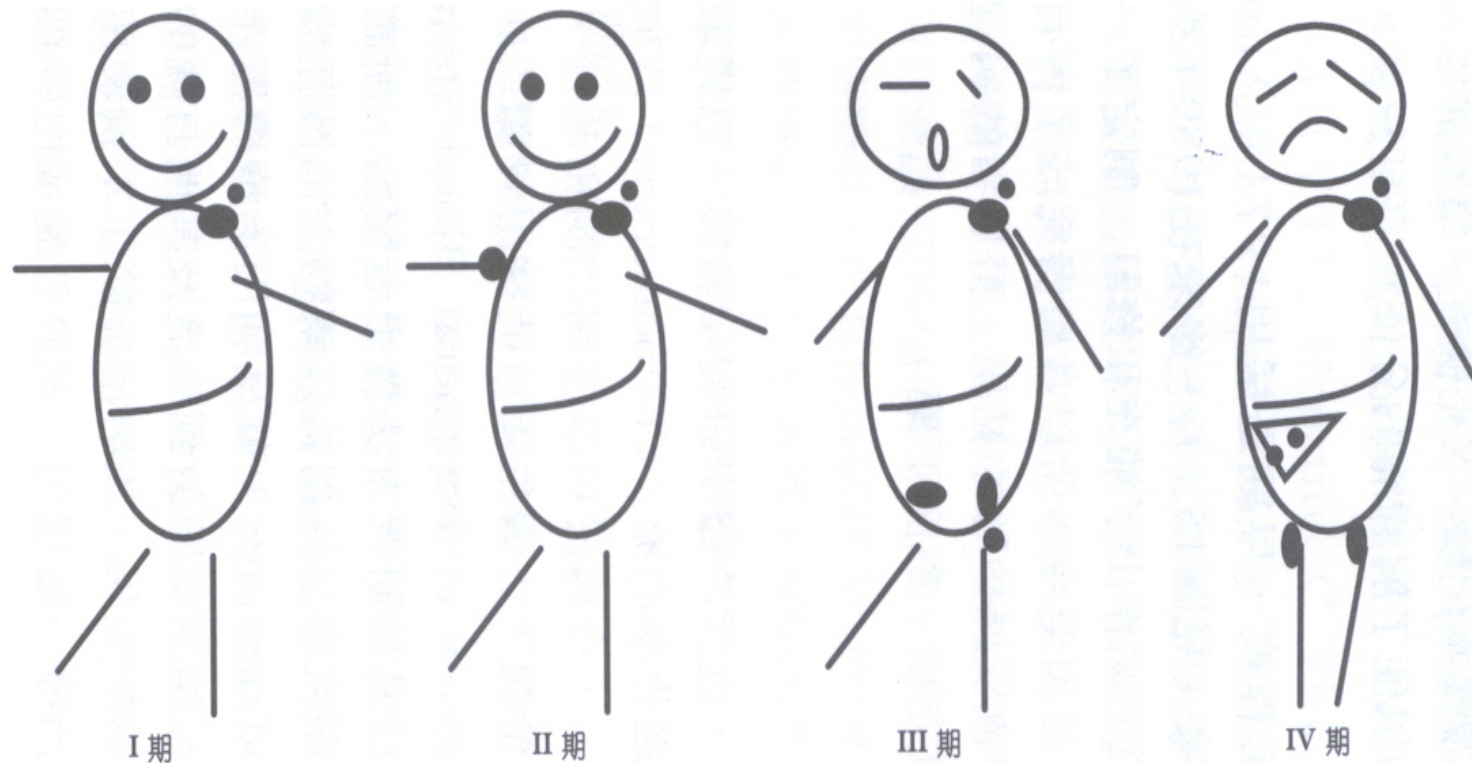


圖15.2：淋巴瘤的分期，Ann Arbor System 1971

I 期：單一個淋巴腺部位患上腫瘤或單一個淋巴結外器官患上淋巴腫瘤〔IE 期〕。

II 期：在同側的橫膈肌以上或以下的兩組或以上淋巴腺部位患上腫瘤。

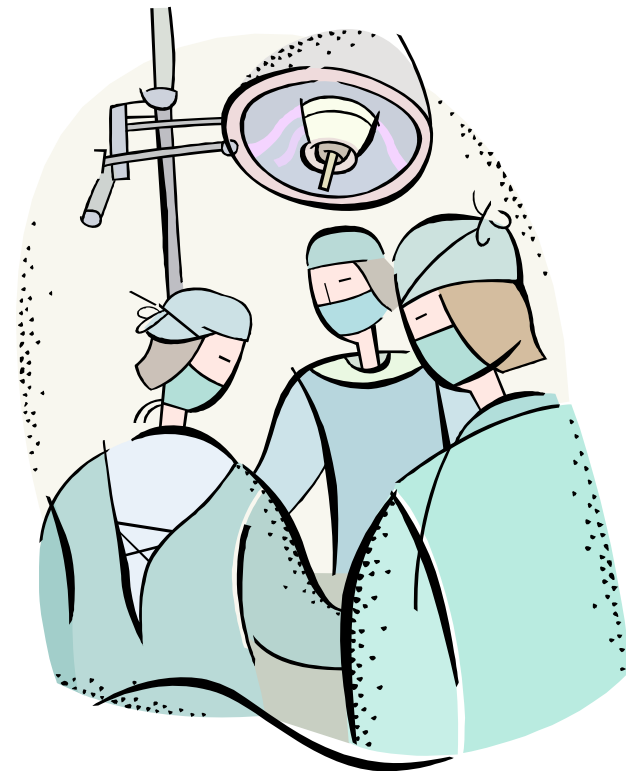
III 期：橫膈肌以上和以下同時兩組或以上的淋巴腺部位患上腫瘤。

IV 期：一個或多個淋巴腺外的器官〔例如：肝臟、中樞神經系統和骨髓〕被腫瘤侵犯。

* 各期還按有或沒有特定的症狀而分為 A 或 B。無症狀者為 A，有以下症狀者為 B：體重減輕超過 10% 以上，經常發熱 38°C 以上；經常出汗。

手術在治療中扮演的角色

- 診斷
- 治療緊急之併發症
 - 腸胃出血，穿破
 - 脊髓神經受壓
- 主治方法：**MALTOMA**



主治方法(一)：化學治療

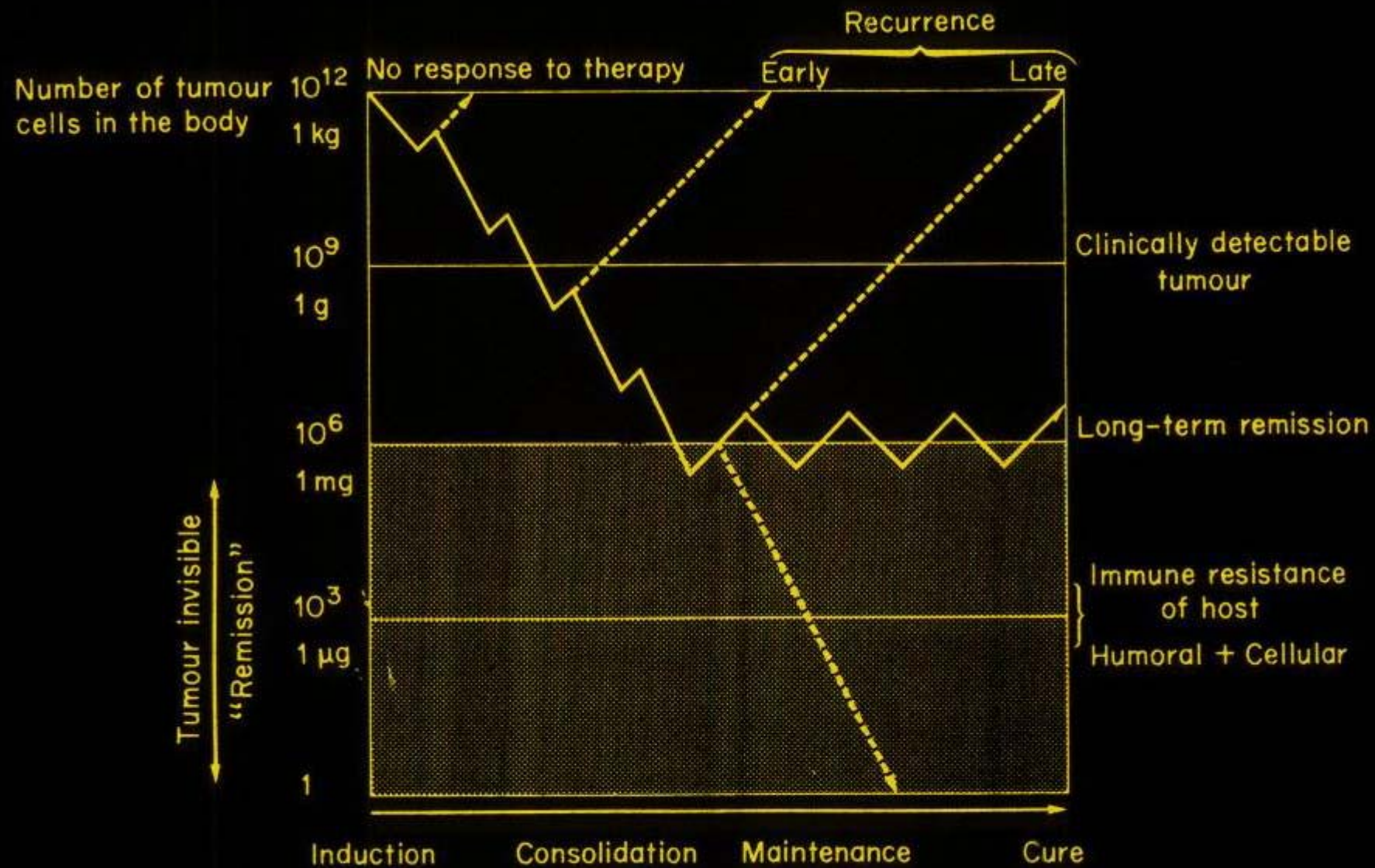
- 聯合化 / 放療法
- 週期性聯合治療
 - CHOP / CEOP
 - ProMACE-CytaBOM
 - CVP
 - Chlorambucil



主治方法(一)：化學治療

- “抗癌藥”的作用
 - 阻止細胞分裂
 - 減慢細胞循環速度，生長快的細胞最受影響
 - 癌細胞
 - 正常細胞 (血球，毛囊細胞，腸胃細胞，生殖細胞)

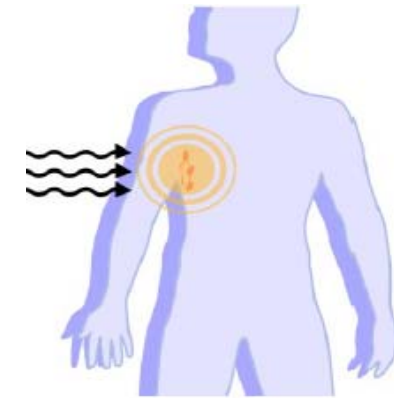




Diagrammatic representation of the reduction of the number of tumour cells in the body with therapy.

主治方法(二)：放射治療

- 主治角色
 - 早期何傑金氏病
 - 早期低惡性非何傑金氏淋巴瘤
- 輔助角色
 - 聯合療法 (通常作化療後的輔助治療)
- 原理
 - 破壞細胞分裂
- 副作用
 - 只局限於放療範圍內正常組織的反應







非何傑金氏淋巴瘤

■ 治療

□ 低惡性：姑息性治療

(早期，尤其是 **MALTOMA**：放療 / 手術)

□ 高惡性：

■ 早期：三期化療 + 放療

■ 晚期：六至八期化療 +/- 放療

(NK / T 鼻孔淋巴瘤例外)



非何傑金氏淋巴瘤

■ 治療

- 低惡性：姑息性治療 - 六至八期化療
(早期，尤其是 **MALTOMA**：放療 / 手術)
- 高惡性：
 - 早期：三期化療 + 放療
 - 晚期：六至八期化療 +/- 放療
(**NK / T 鼻孔淋巴瘤**例外)



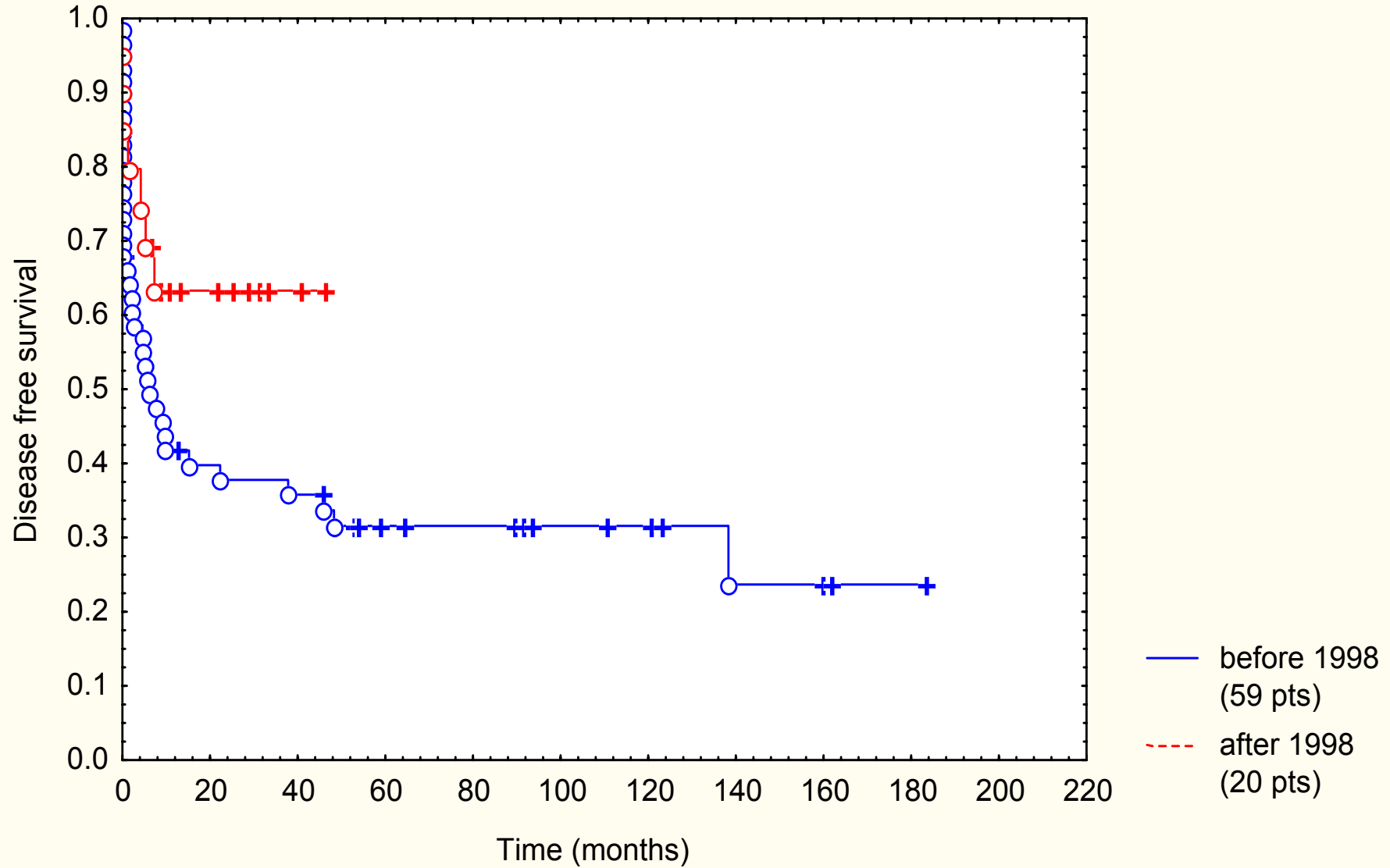
嶄新的治療方法

- 加大化療劑量
 - 自體或同種骨髓移植
 - CHOP-14
- 新藥
 - 如 GEMCITABINE, FLUDARABINE
- 抗體治療
 - CD20 單克隆抗體 (+/- 放射療素)

Disease free survival

p = 0.083

T 和 NK/T 型

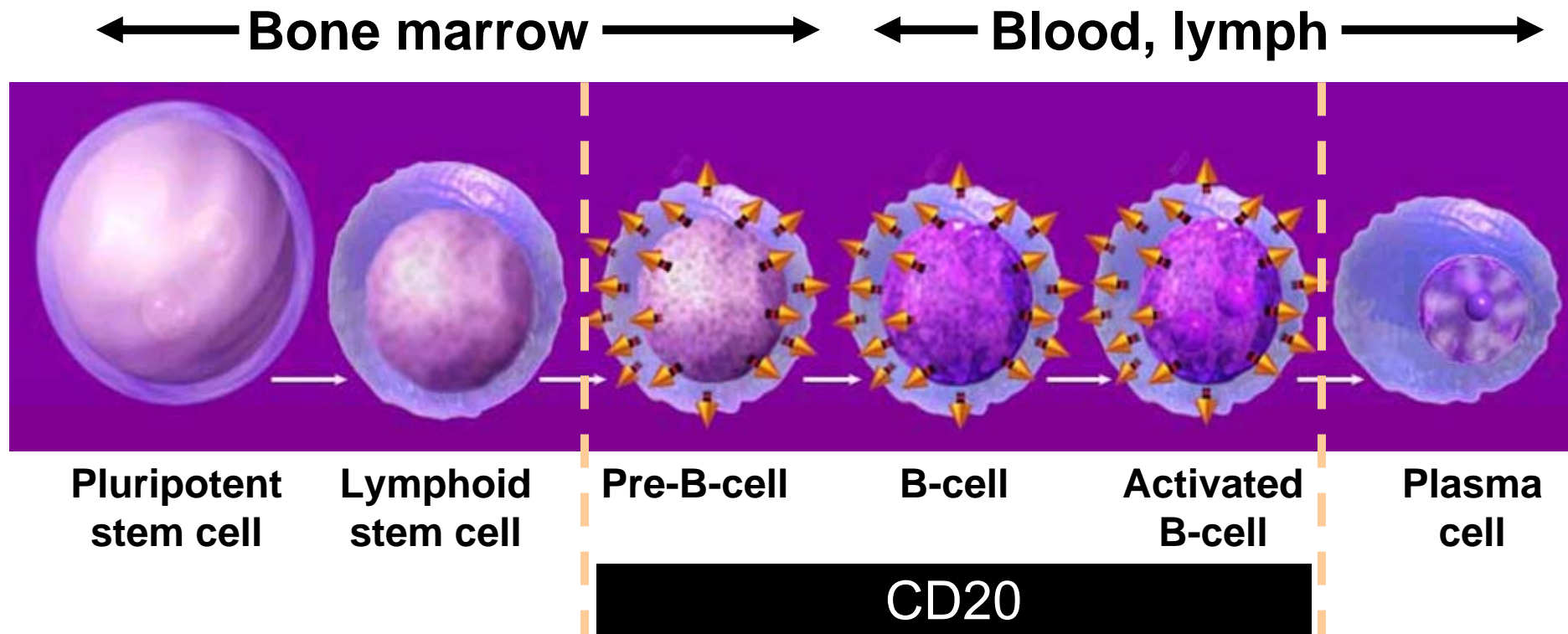




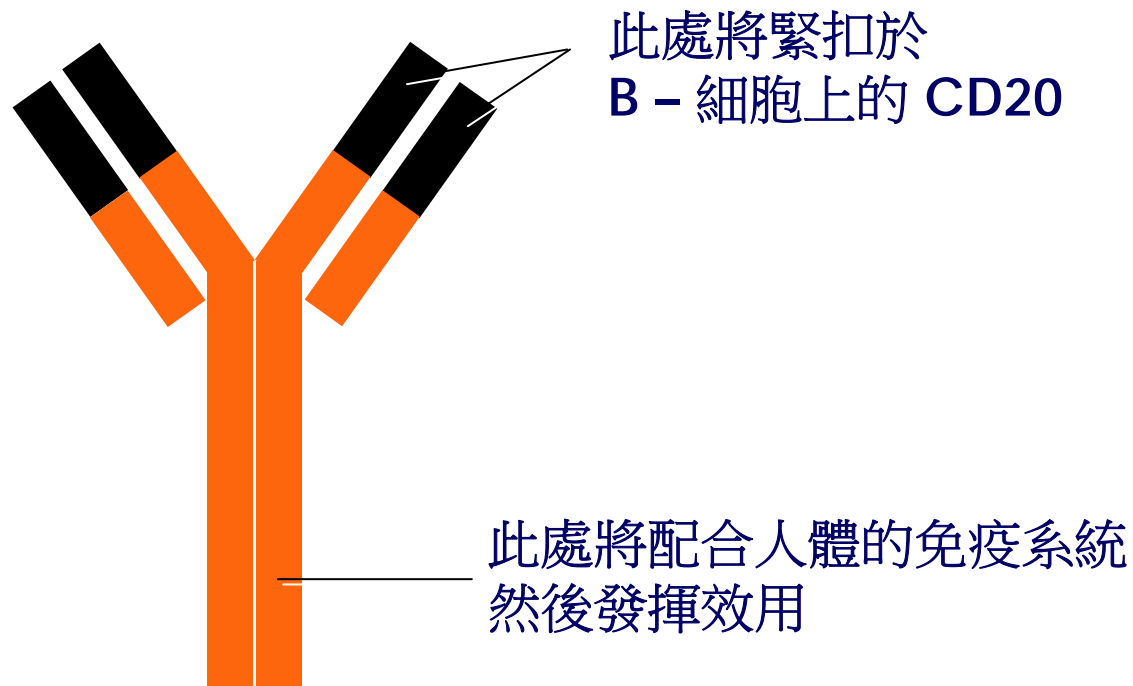
單克隆抗體

- 結合目標蛋白質以進行：
 - 毀滅癌細胞
 - 引入患者本身的免疫系統以進行攻擊
- 單一使用或加入化學療法一併使用
- **Eg: CD20**抗原, **CD52**抗原, 或帶有放射性的單克隆抗體

CD20 Expression in B-Cell Development



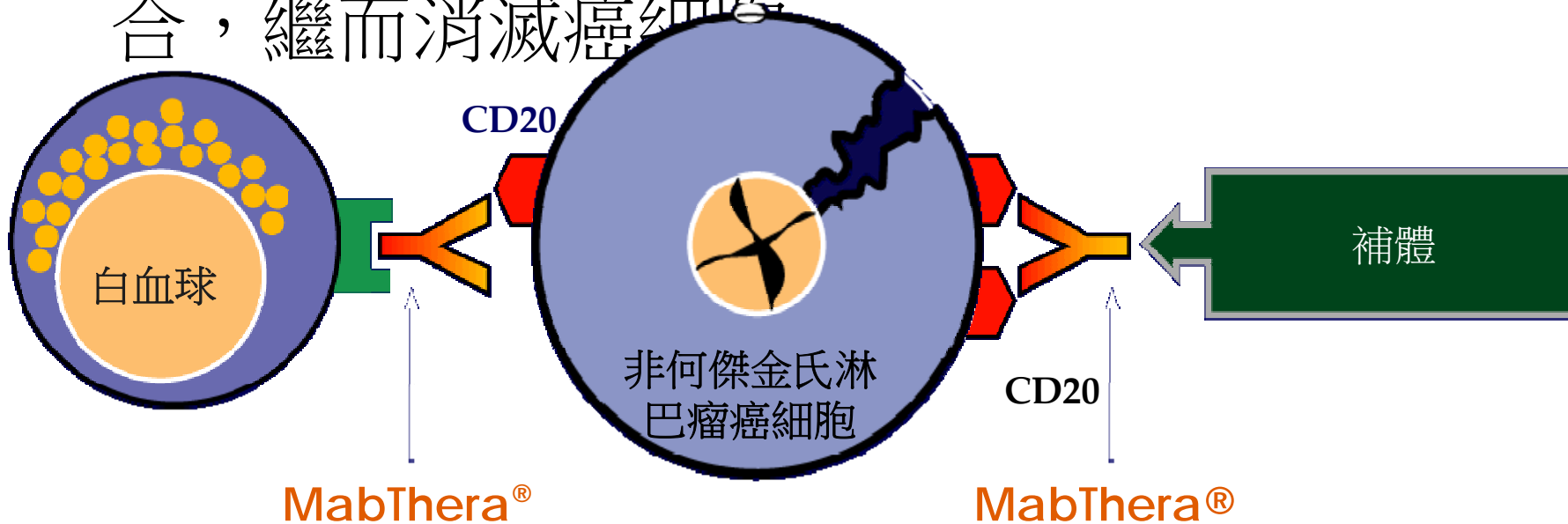
MabThera[®]：針對-CD20 的單克隆 抗體



上圖取材自Rybak et al. *Proc Natl Acad Sci USA*. 1992;89:3165.

MabThera[®]如何發揮療效

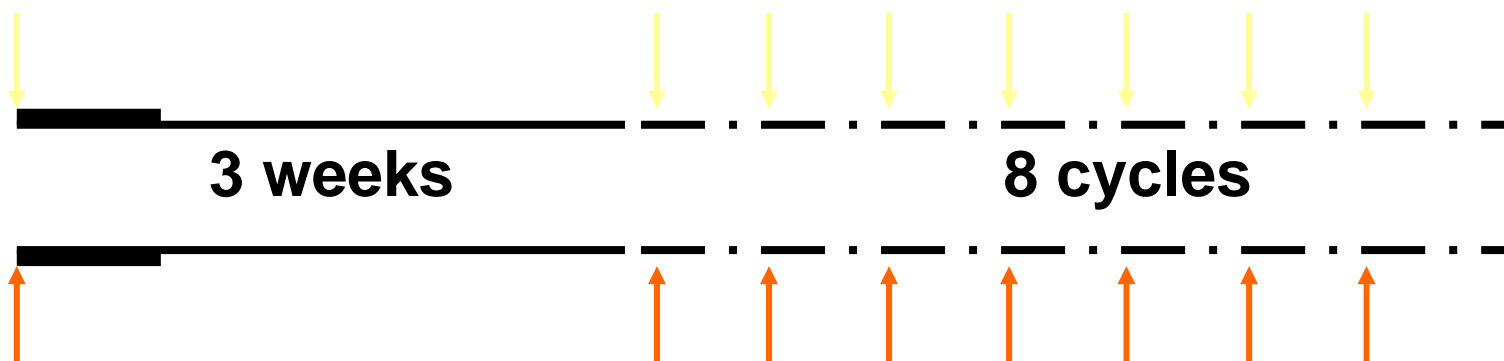
- **Rituximab**與患者體內的免疫細胞互相配合，繼而消滅癌細胞



GELA-LNH 98.5: 弥漫性大 B 细胞

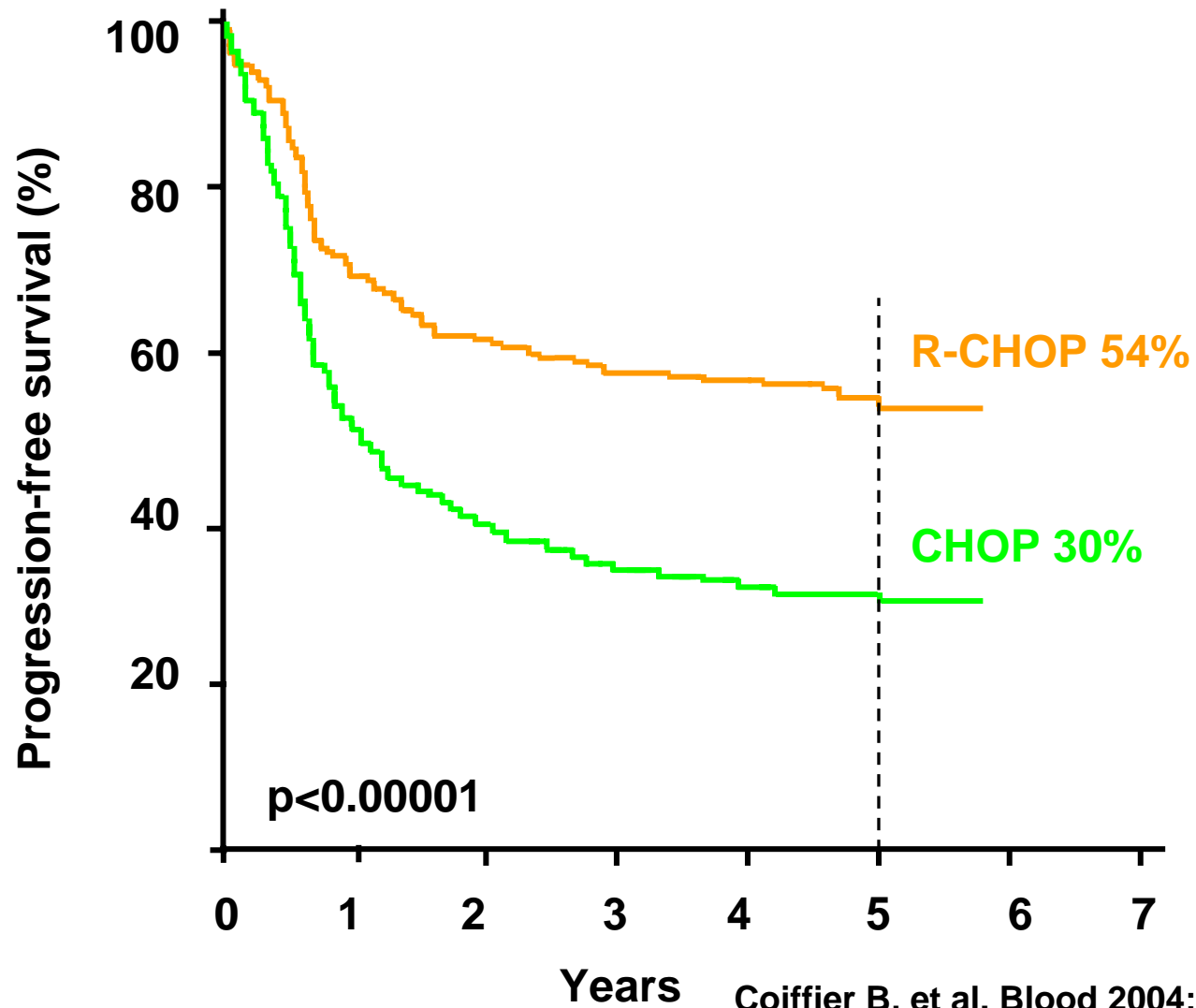
淋巴瘤 GELA phase III trial

Cyclophosphamide 750mg/m²
Doxorubicin 50mg/m²
Vincristine 1.4mg/m²
Prednisone 40mg/m²/day x 5 days



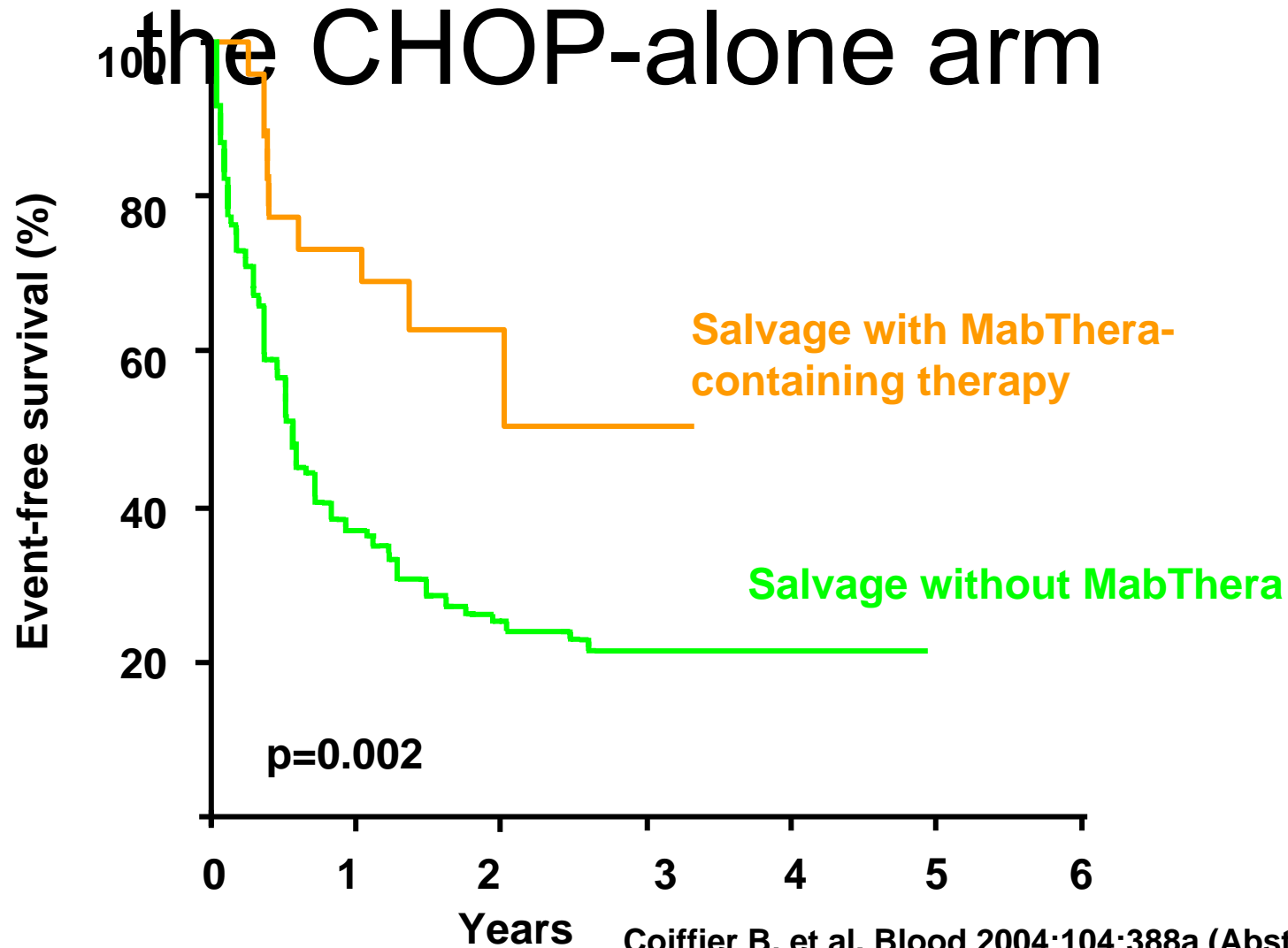
MabThera + CHOP 375mg/m²

GELA-LNH 98.5: 5-year PFS



Coiffier B, et al. Blood 2004;104:388a (Abstract 1383)

GELA-LNH 98.5: OS after salvage therapy for patients in the CHOP-alone arm

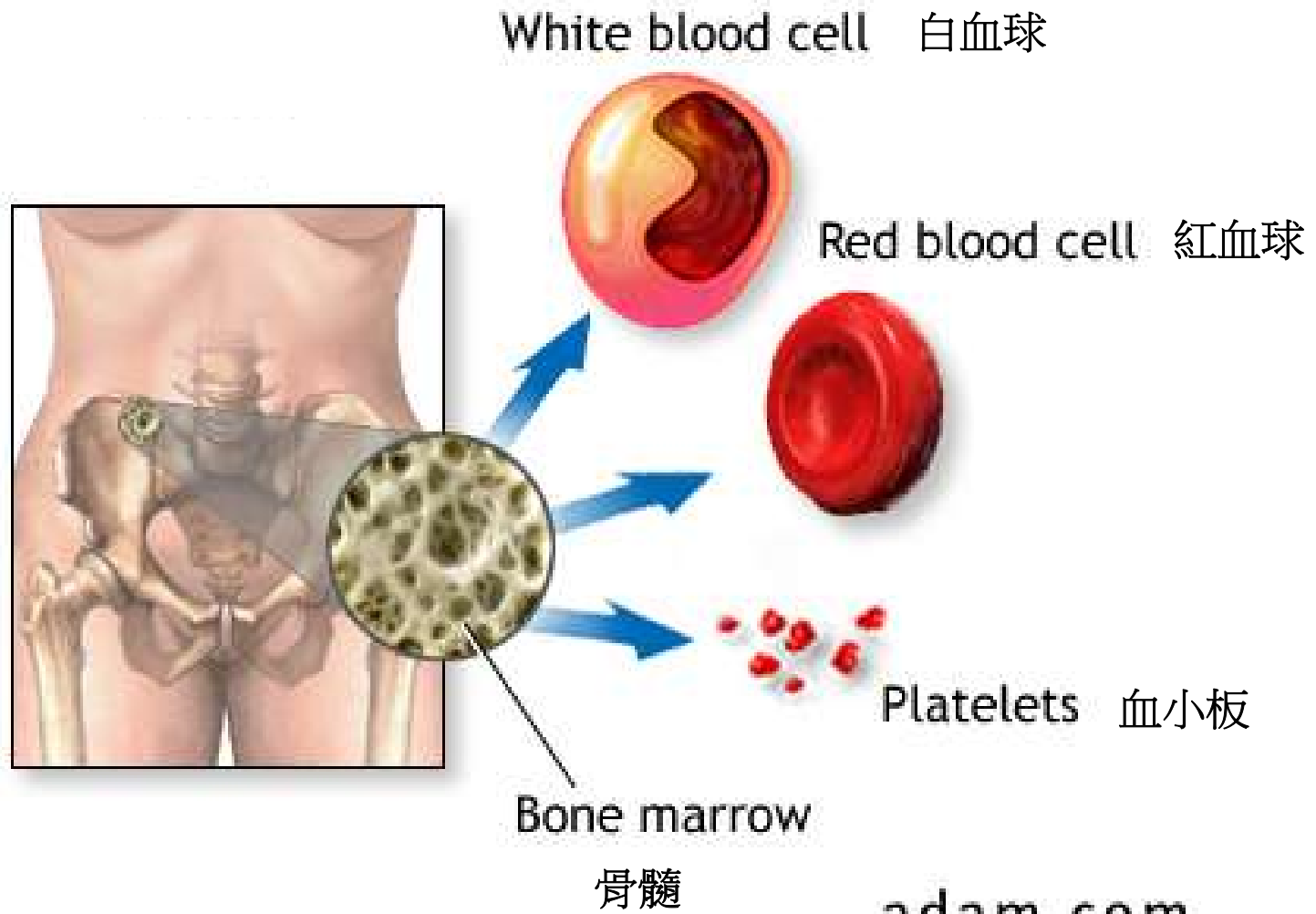
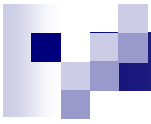




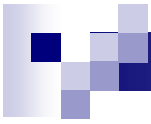
血幹細胞移植 (Stem Cell Transplant)

- 利用較高劑量的化學治療或放射治療
- 然後植入來自患者的血幹細胞（自身血幹細胞移植）
- 治療風險較高
- 通常應用在復發病患者上

- 自身或異體



adam.com



血細胞的製造

Blood Cell Production

多能造血幹細胞

Pluripotent Stem Cell

髓幹細胞

Myeloid Stem Cell

淋巴幹細胞

Lymphoid Stem Cell

Various precursor or blast cells

Blast cells

骨髓中
In bone marrow

血液
Cells passed into blood



Neutrophil



Eosinophil



Basophil
(Mast cell)



Monocyte
(Macrophage)



Platelets
血小板



Erythrocyte
(Red blood cell)

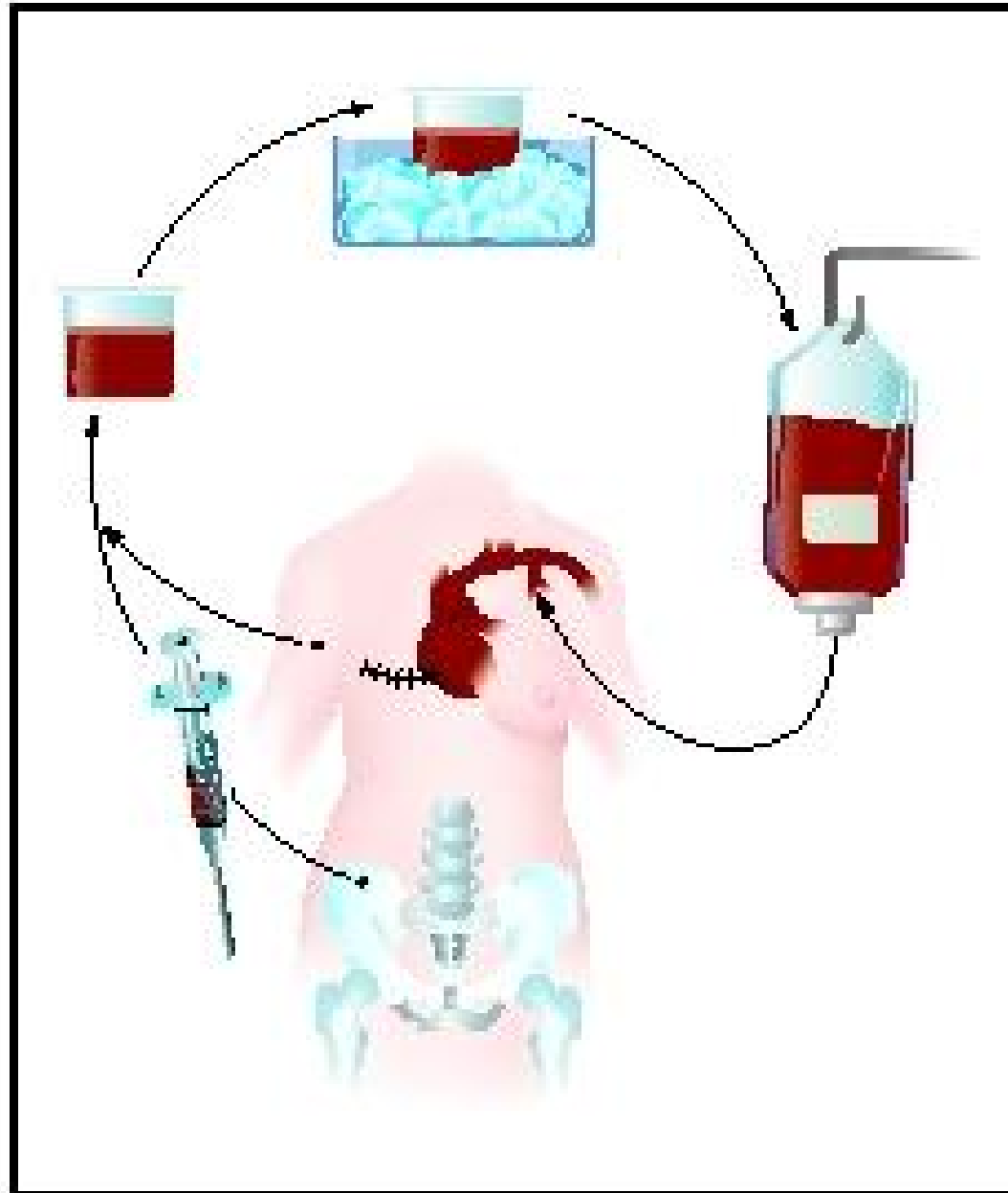
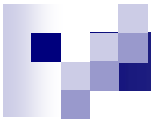


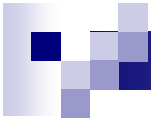
Lymphocyte

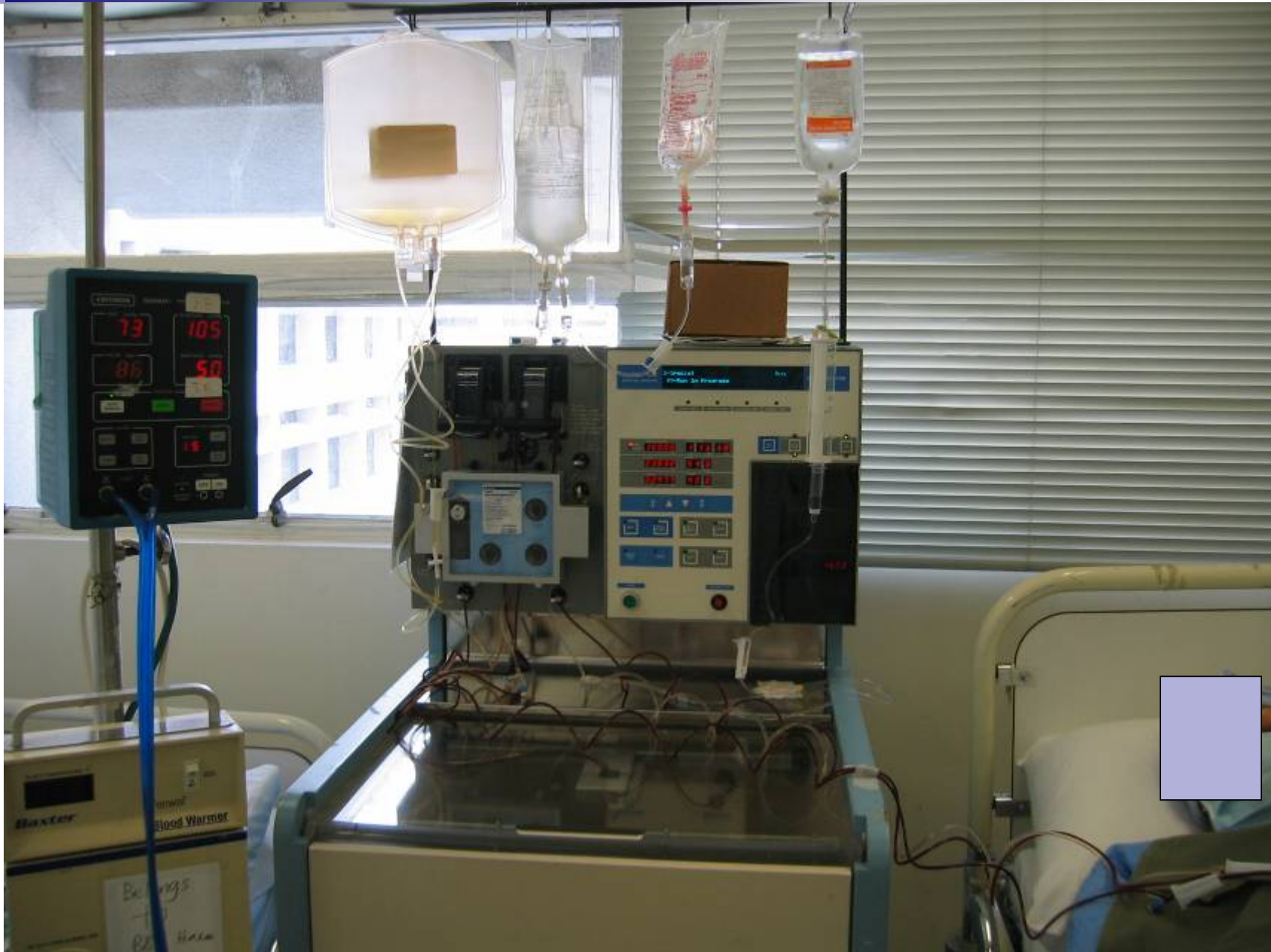
白血球

紅血球

淋巴白血球

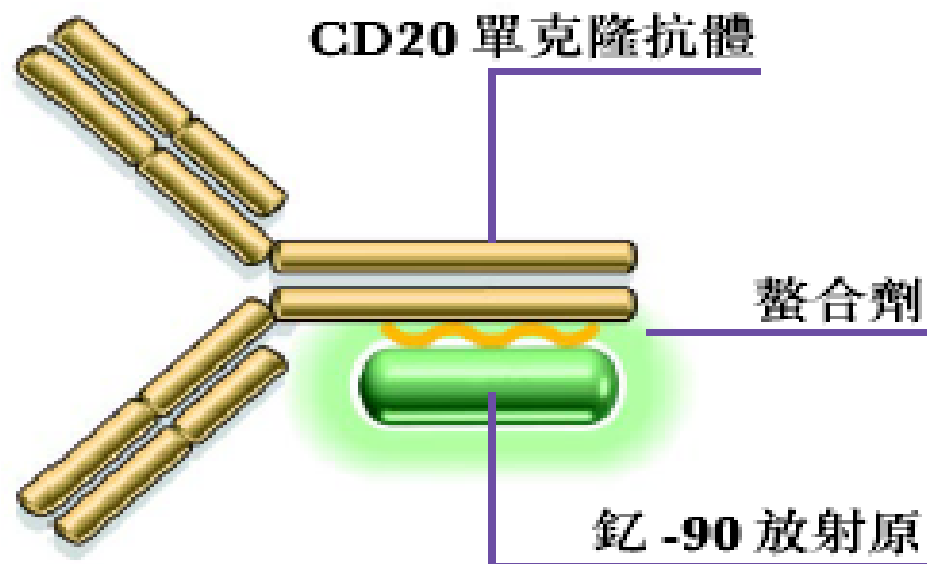




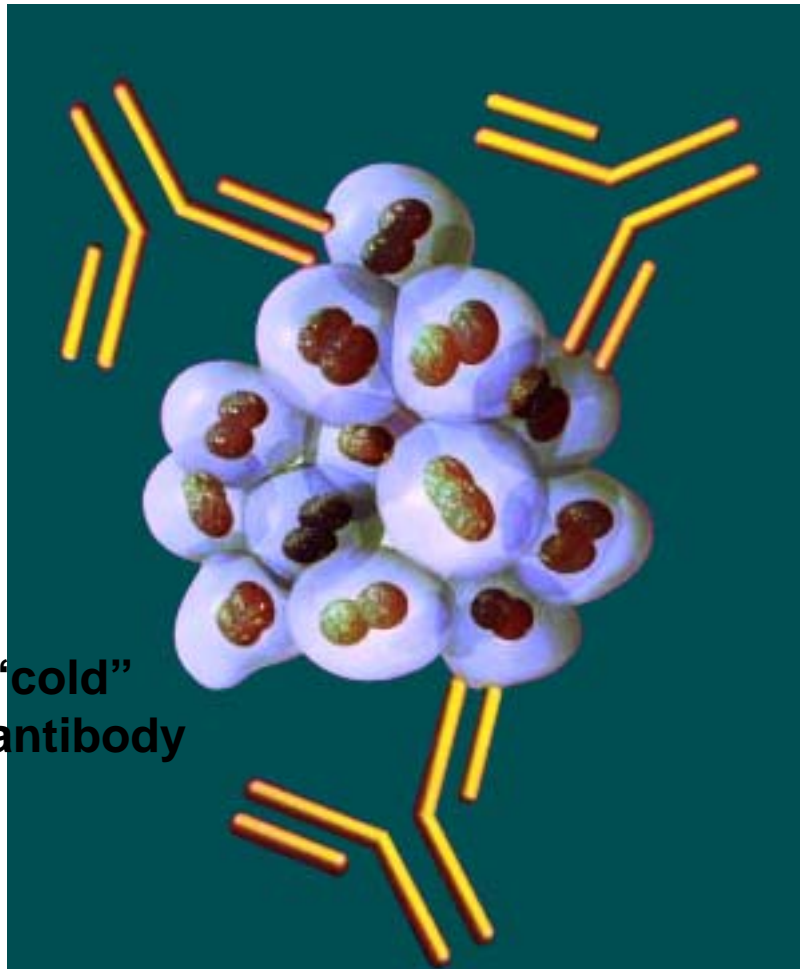


放射免疫治療 (Radioimmunotherapy, RIT)

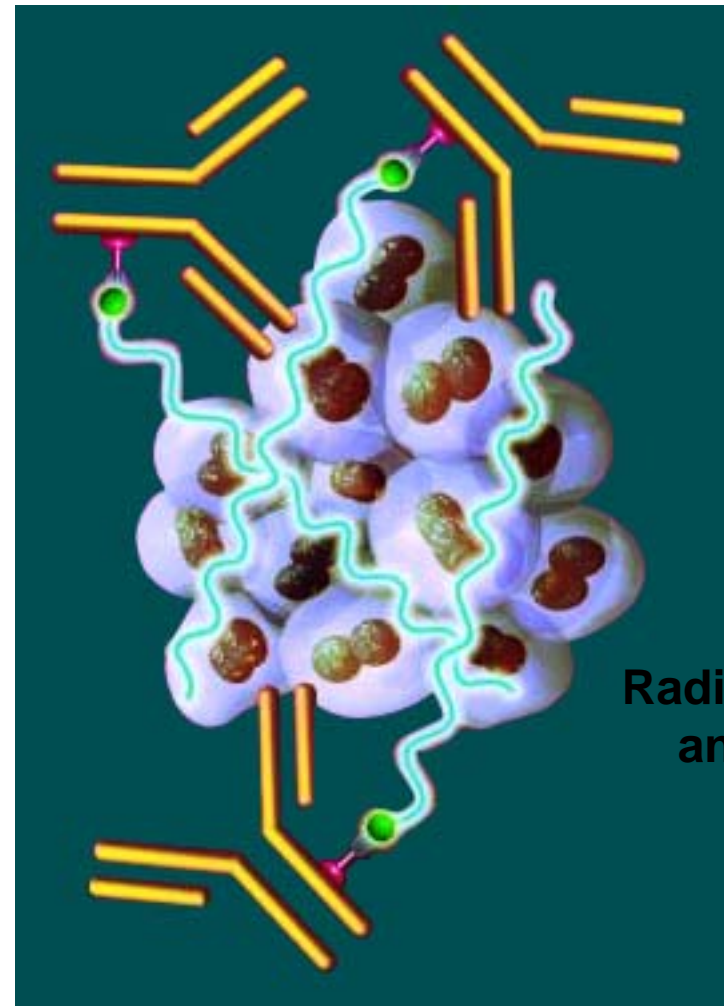
- 犀服靈® 的組成
- CD20 單克隆抗體 (CD20 monoclonal antibody)
- 金乙-90 放射原 (Yttrium-90)
- 螯合劑 (chelator)



Radioimmunotherapy exhibits a “Cross-fire Effect”



“cold”
antibody

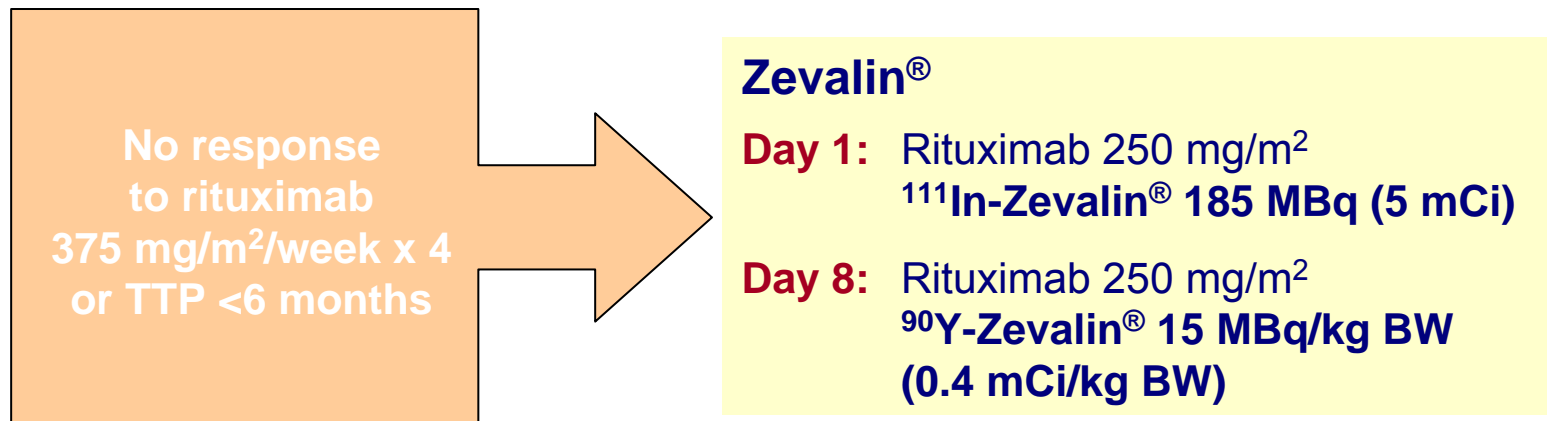



Radiolabelled
antibody



Rituximab-Refractory Trial: Study Design

Objective: Zevalin[®] in rituximab-refractory follicular CD20+ NHL patients versus last rituximab and last chemotherapy treatments





Rituximab-Refractory Trial: Response to Zevalin[®]

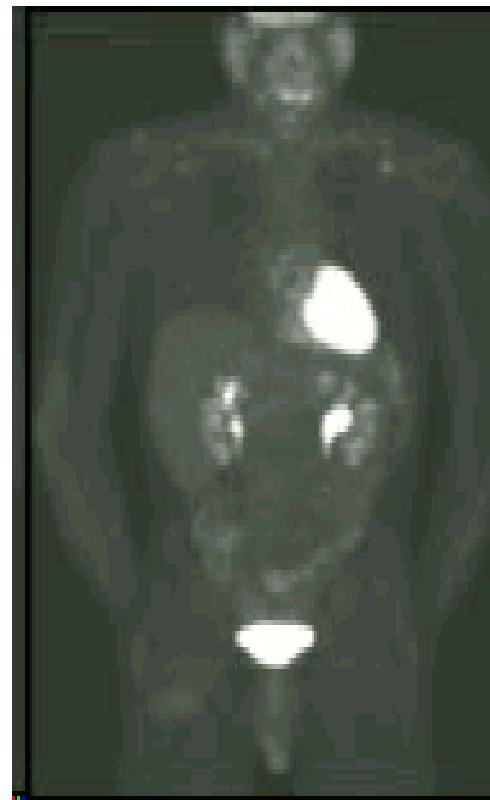
- ORR 74%, CR 15%:
 - Significantly better than prior rituximab (ORR 32%, $P < 0.01$)
 - Similar to last chemotherapy (ORR 67%, $P = 0.32$)
- Median TTP in responders 8.7 months (range, 1.7–25.9+)

Tumour Response with Zevalin®

FDG PET Scans

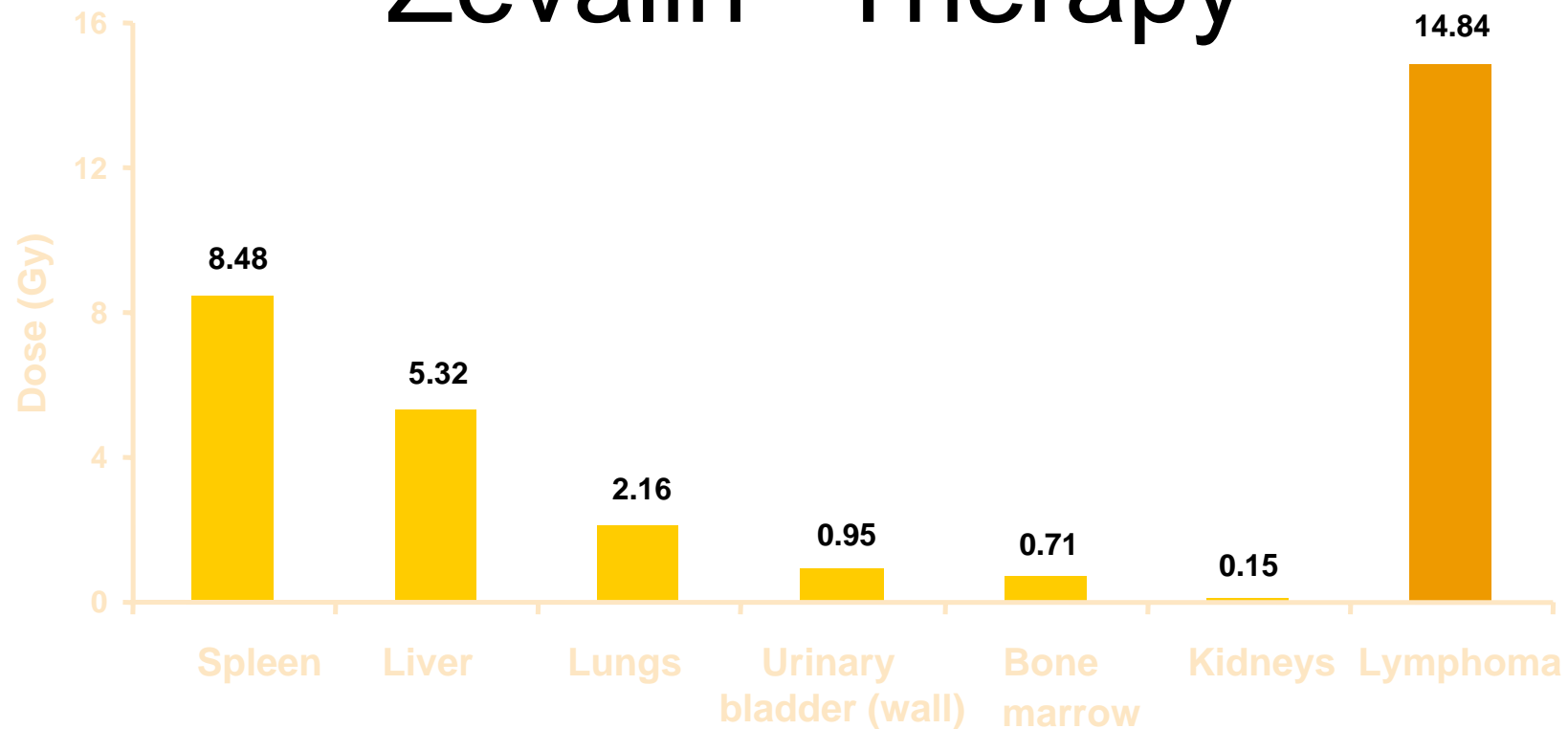


Before



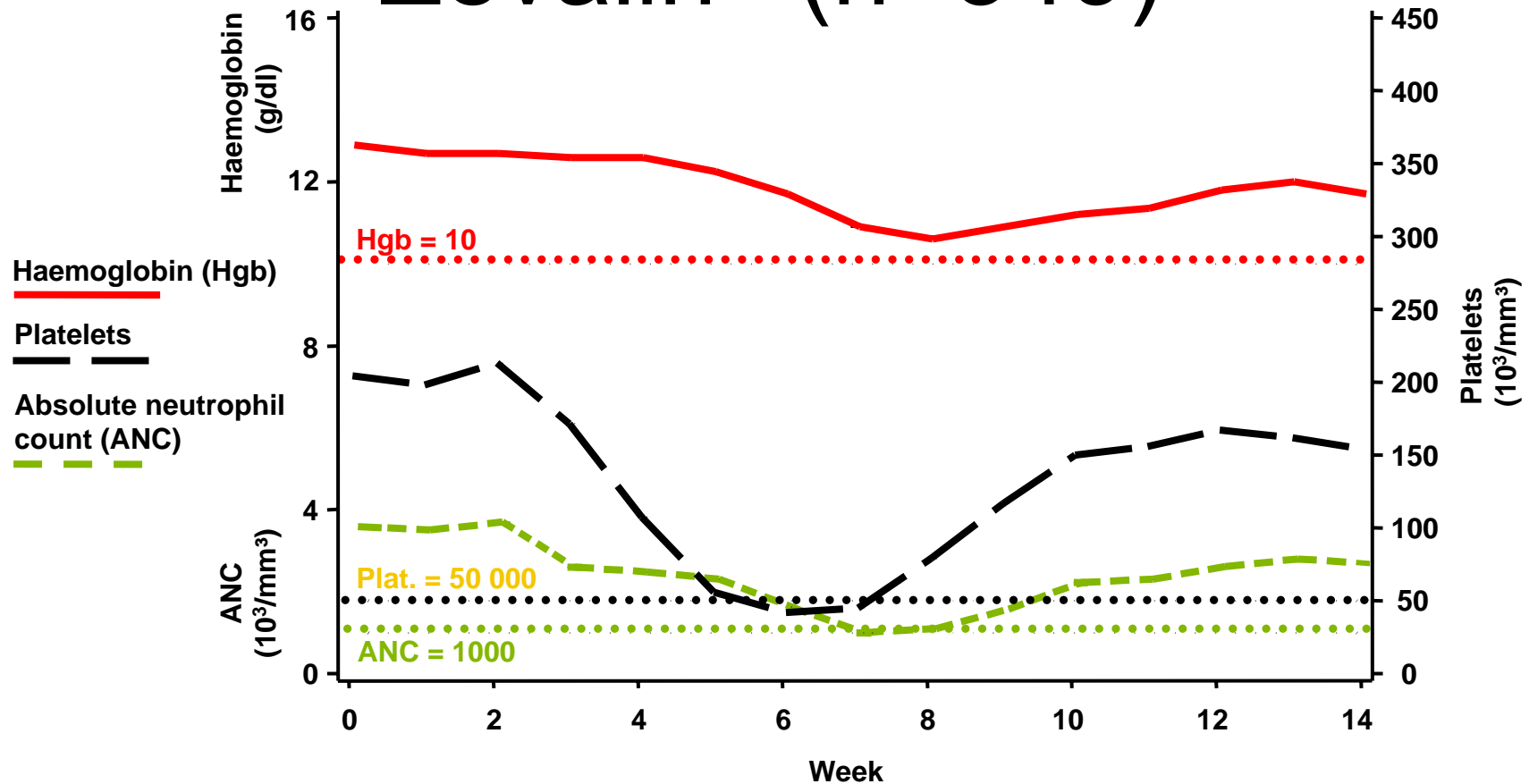
After

Estimated Radiation Doses to Organs during Zevalin[®] Therapy*



* Dosimetry in 72 patients in a phase III study

Median Haematologic Counts following Treatment with Zevalin[®] (n=349)





Zevalin[®] is highly Effective and Well Tolerated also in Geriatric Patients

- Retrospective analysis of 211 patients with B-NHL

- Age:

 - n=113 < 60 years

 - n= 58 between 60 and 69 years

 - n= 40 ≥ 70 years

- The trial data revealed no difference between age groups regarding efficacy (ORR 71% - 80%)

Schilder RJ et al. J Clin Oncol 23(16S):575s, abstr 6562 (2005)



EU Authorisation 2004

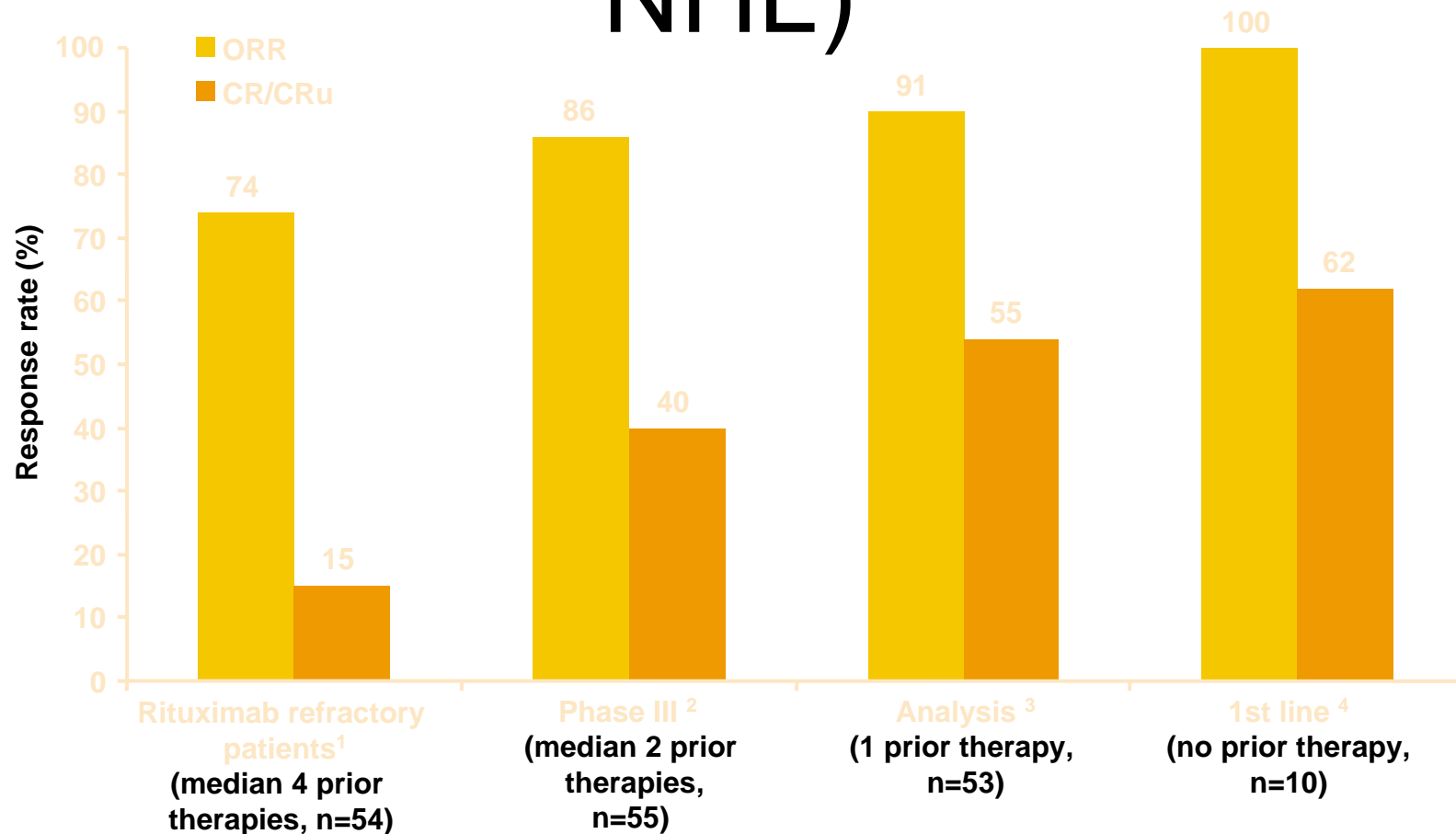
■ Indication:

The ^{90}Y -radiolabelled Zevalin[®] is indicated for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL).

■ Contraindications:

- Hypersensitivity to ibritumomab tiuxetan, to yttrium chloride, to rituximab, to other murine proteins or to any of the excipients.
- Pregnancy and lactation.

Earlier Treatment Associated with Higher Efficacy (follicular NHL)



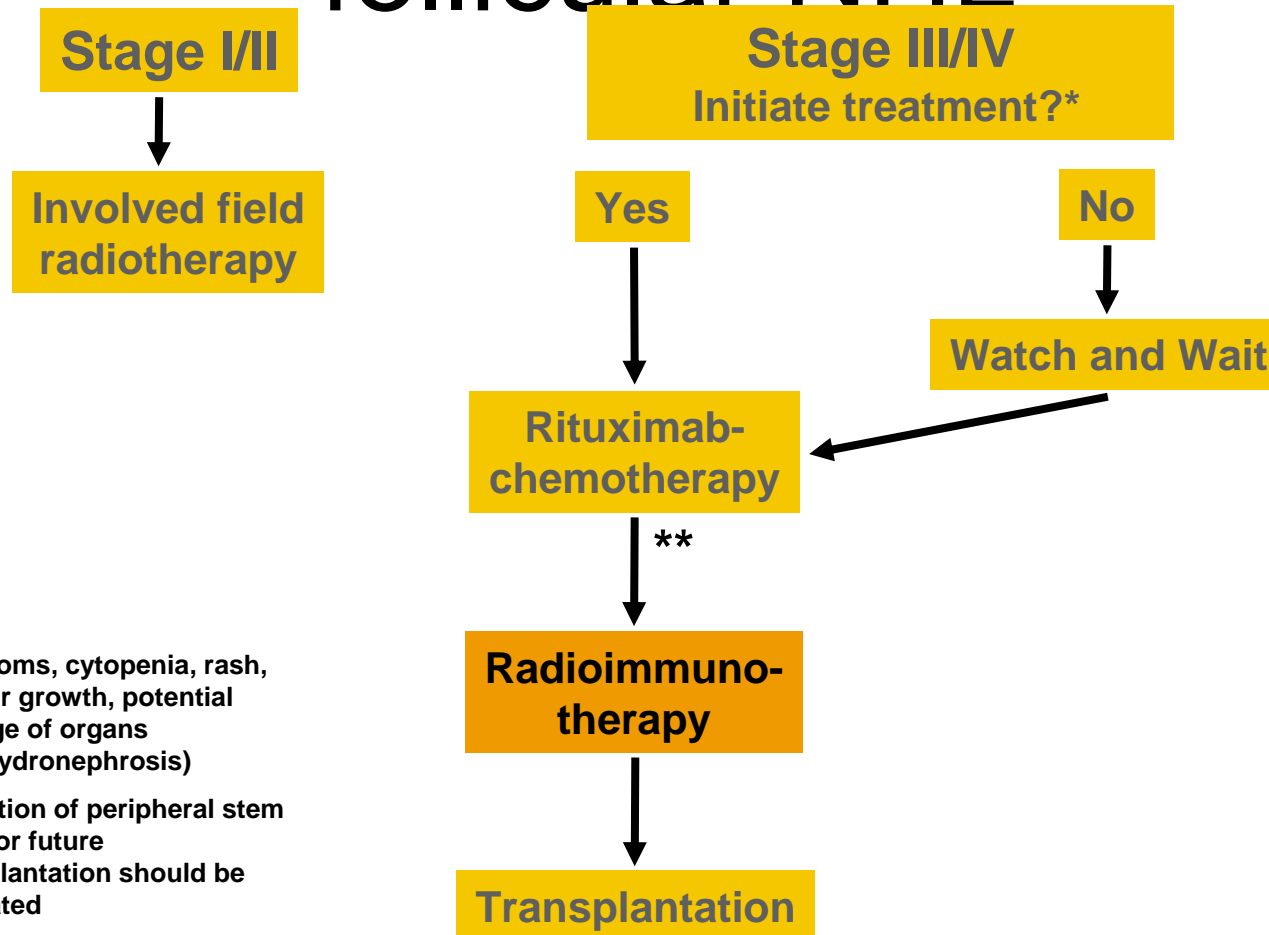
¹Witzig TE et al. J Clin Oncol 20:3262-3289 (2002)

²Gordon LI et al. Clin Lymphoma 5:98-101 (2004)

³Emmanouilides C et al. Blood 102(11):306b-307b, abstr 4949 (2003)

⁴Sweetenham JW et al. Blood 104(11), abstr 2633 (2004)

Treatment Algorithms for follicular NHL



* Symptoms, cytopenia, rash, tumour growth, potential damage of organs (e.g. hydronephrosis)

** Collection of peripheral stem cells for future transplantation should be evaluated



Zevalin's Contribution to the Improvement of NHL Treatment

- Treatment is generally well tolerated, with manageable haematologic toxicity, also in elderly patients
- High CR rates with long-term responses, even in patients with relapsed disease
- Perspectives:
 - Early use in follicular and non-follicular indolent lymphoma (consolidation)
 - Other CD20-positive NHL:
 - MCL
 - DLBCL
 - MALT gastric NHL
 - Targeted radiotherapy as conditioning regimen for stem



治療期間的護理

■ 避免感染

- 減少到人煙稠密的公共場所
- 避免接觸患上感冒或其他傳染病的親友
- 房間，衣物，用具要經常整理及保持清潔
- 切勿食用未經煮熟的食物
- 如有發燒，應即求診治理



非常清潔膳食

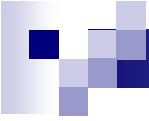
食物的選擇 - 魚，肉類及海產

■ 可以進食

- 新鮮及急凍的肉或魚類，以適當的煮食方法煮至全熟

■ 避免進食

- 半生熟肉食、凍食熟肉、冷盤
- 魚生
- 鹹魚、蝦米、蠔豉
- 外賣熟食（例如：叉燒）
- 豬牛肉乾、肉鬆、魷魚絲



非常清潔膳食


食物的選擇－蛋類

■ 可以進食

- 可煎、炒或焗至全熟，尤其是蛋黃。蒸水蛋要用大量沸水煮最少10分鐘

■ 避免進食

- 半生熟蛋、生蛋、鹹蛋、皮蛋




非常清潔膳食 食物的選擇－奶類

■ 可以進食

- 保鮮紙盒裝，膠樽，印UHT（高溫處理）字樣之奶類飲品
- 獨立包裝芝士片
- 細罐裝淡奶
- 細罐裝之奶粉及營養補充劑。注意保持罐蓋密封，以防潮濕

■ 避免進食

- 鮮奶、需要冷藏之盒奶，含活乳酸菌之奶類飲品，雪糕、芝士茸、鮮忌廉



非常清潔膳食

食物的選擇－五穀類

■ 可以進食

- 新鮮煮熟之飯、粉麵、粥、麥皮
- 獨立包裝之早餐穀類、餅乾
- 獨立包裝之清蛋糕

■ 避免進食

- 外賣炒粉麵、湯粉麵、粥品
- 大盒裝及曾經開啓之早餐穀類
- 散裝餅乾、夾心餅、威化餅
- 散裝或含忌廉之蛋糕、蛋卷、蛋撻



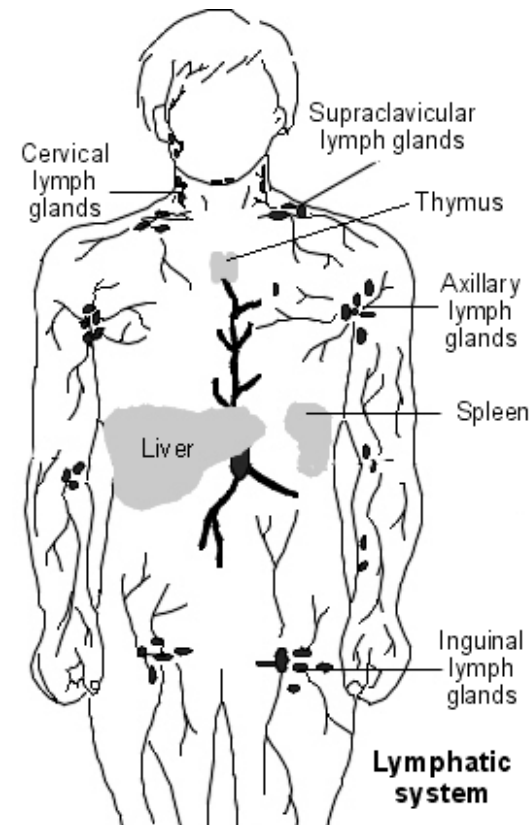
治療期間的護理


- 保持個人衛生
- 均衡飲食，良好營養狀況
- 適量的運動和休息
- 家人的支持，關懷和鼓勵

復遺症

~ 放射治療 ~

- 視乎接受電療之部位
- 甲狀腺功能減退
- 冠心病
- 繼發性腫瘤
 - 肺
 - 乳房
 - 胃部
 - 甲狀腺





復遺症 ~ 化學治療 ~

- 視乎需用藥物及其組合
- 心肌病（**Doxorubicin**）
- 肺纖維化（**Bleomycin**）
- 神經線受損（**Vincristine**）