中 山 醫 學 大 學 附 設 醫 院

子 宮 體 癌 診 療 指 引

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臨床指引參考台灣國家衛生研究院、與美國 NCCN 版本
再依據中山醫學大學附設醫院婦癌小組經驗作編修
婦癌醫療小組

癌症委員會主任委員	癌症委員會執行長	癌症中心主任	團隊負責人

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	【懷疑有子宮外病灶】首次治療 (3)： 無	【懷疑有子宮外病灶】首次治療 (3) ：新增- ★全身性治療：意為化學治療或荷爾蒙治療或標靶治療或免疫療法(詳見P.18)
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	完整手術分期後之輔導治療 Stage IIIA： 無	完整手術分期後之輔導治療 Stage IIIA：新增- ★全身性治療：意為化學治療或荷爾蒙治療或標靶治療或免疫療法(詳見 P.18)
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	完整手術分期後之輔導治療： 無	完整手術分期後之輔導治療：新增- ★全身性治療：意為化學治療或荷爾蒙治療或標靶治療或免疫療法(詳見P.18)
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	2-2.子宮惡性肉瘤之臨床發現及處置：	2-2.子宮惡性肉瘤之臨床發現及處置：修訂為-

	1. Low-grade Endometrial Stromal sarcoma(ESS) 2. High-grade Undifferentiated sarcoma (HGUD) Or Leiomyosarcoma(LMS) (1&2分開)	(合併) Low-grade ESS or High-grade ESS or UUS or uLMS
	2-2.子宮惡性肉瘤之臨床發現及處置： 無	2-2.子宮惡性肉瘤之臨床發現及處置：新增- ★Systemic therapy：意為化學治療或荷爾蒙治療或標靶治療或免疫療法(詳見P.31)
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	High-grade ESS、UUS、uLMS： 無	High-grade ESS、UUS、uLMS：新增- ★Systemic therapy：意為化學治療或荷爾蒙治療或標靶治療或免疫療法(詳見 P.31)
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	2-3.子宮惡性肉瘤之復發處置： Disseminated disease→ →Low-grade ESS→Hormone therapy or Supportive care	2-3.子宮惡性肉瘤之復發處置：修訂為- Disseminated disease→Systemic therapy ± palliative RT or Supportive care

	→All others→Chemotherapy ± palliative RT or Supportive care	
	2-3.子宮惡性肉瘤之復發處置： 無	2-3.子宮惡性肉瘤之復發處置：修訂為- ★Systemic therapy：意為化學治療或荷爾蒙治療或標靶治療或免疫療法(詳見P.31)
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	2-3.子宮惡性肉瘤之復發處置： Prior RT→Surgical exploration + resection ± IORT ± hemotherapy or Hormone therapy (Low-grade ESS only) or Tumor-directed re-irradiation	2-3.子宮惡性肉瘤之復發處置：修訂為- Prior RT→Surgical exploration + resection ± IORT ± systemic therapy or Systemic therapy or Selected re-irradiation with EBRT and/or brachytherapy
	2-3.子宮惡性肉瘤之復發處置： 無	2-3.子宮惡性肉瘤之復發處置：新增- ★Systemic therapy：意為化學治療或荷爾蒙治療或標靶治療或免疫療法(詳見P.31)
第 31 頁	2-4.子宮惡性肉瘤之全身性治療： Hormonal therapy ★Medroxyprogesterone acetate ★Megestrol acetate ★Aromatase inhibitors(category 2B) ★GnRH analogs (category 2B) ★Tamoxifen (category 2B) Chemotherapy regimens The following agents can be used as single or in combination,as clinical appropriate：	2-4.子宮惡性肉瘤之全身性治療：修訂為- *Combination regimens:* ★ Docetaxel/gemcitabine (preferred for leiomyosarcoma) ★ Doxorubicin/ifosfamide ★ Doxorubicin/dacarbazine ★ Gemcitabine/dacarbazine ★ Gemcitabine/vinorelbine *Single-agent options:* ★ Dacarbazine

	★Doxorubicin ★Gemcitabine⁄docetaxel ★Other single agent options (category 2B)：Dacarbazine, Docetaxel, Epirubicin, Gemcitabine, Ifosfamide, Liposomal doxorubicin, and Paclitaxel could also be considered.	★ Doxorubicin ★ Epirubicin ★ Eribulin (category 2B) ★ Gemcitabine ★ Ifosfamide ★ Liposomal doxorubicin ★ Pazopanib ★ Temozolomide ★ Trabectedin ★ Vinorelbine (category 2B) ★ Docetaxel (category 3)

目 錄

一、 子宮內膜癌

1-1. 前言

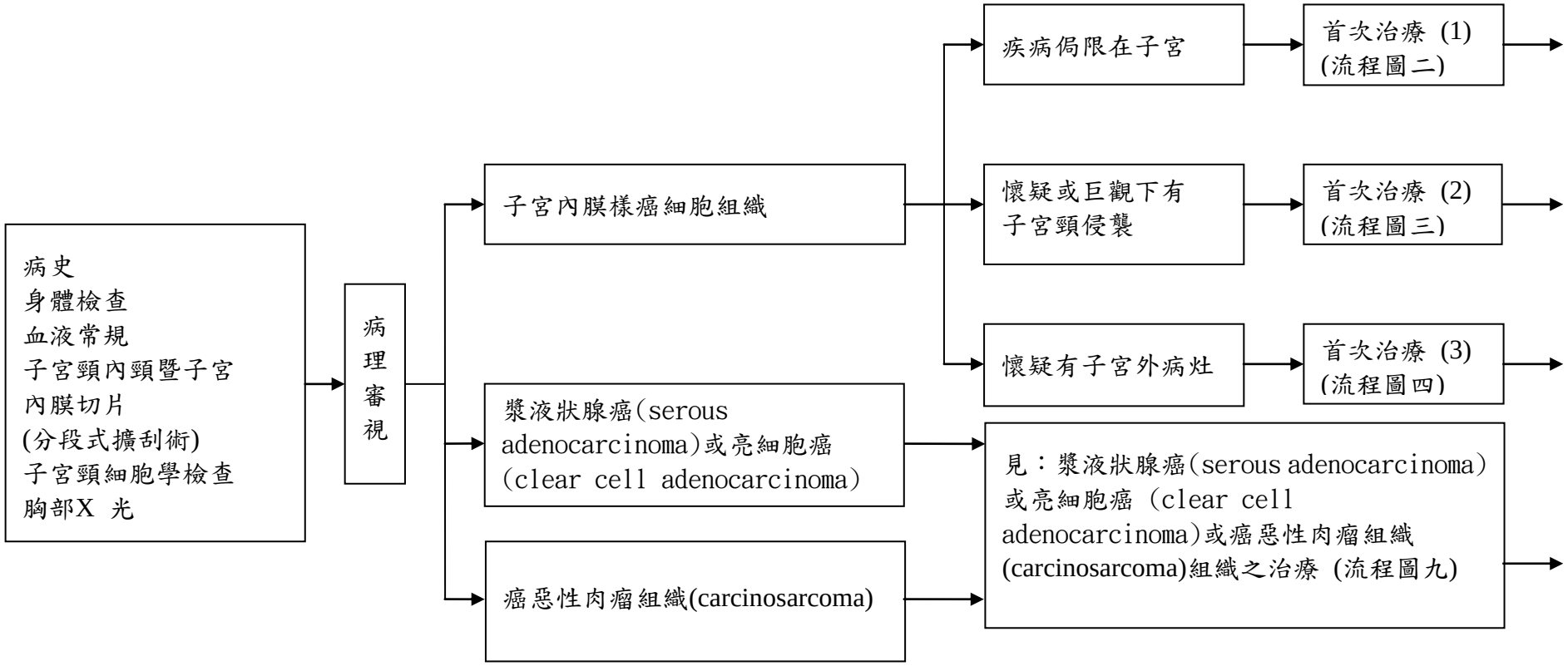
共識手冊內所提之各種診治意見，為原則性之建議，希望能為癌症患者及其家屬提供一個正確的指引；但對臨床醫師之醫療行為無絕對之法律性約束力！由於醫藥科技持續在進步，每位患者的病情亦不盡相同；醫師應就病人之病情做個別的考量，病人和家屬亦應與醫師溝通討論，以決定最適當之診治方式。

台灣大部分子宮內膜癌發生在停經後之女性，其好發的年齡中位值是在52-54歲，大部分病人其年齡在45-59歲之間。雖然 60% 的病例發生在50歲之後，但仍有15%的病例出現在40歲之前。子宮內膜癌可以發生在生育年齡及其後的任何一個年齡層，但比較好發於更年期或停經後的婦女。70-80%的子宮內膜癌診斷時僅侷限在子宮。其早期症狀主要為停經後之陰道出血，病患會因此早期就醫，與其他女性生殖道惡性腫瘤比較，有較高的存活率。

子宮內膜癌的危險因子包括有糖尿病、高血壓、肥胖、未有生育之婦女、初經年齡早而停經年齡晚、使用更年期荷爾蒙治療未合併黃體素之婦女、遺傳及種族因素、乳癌病患使用抗癌藥物治療者。

本子宮體癌診斷及治療指引的內容有子宮內膜癌、子宮惡性肉瘤及妊娠組織瘤等，其內容除了依據已發表的實證醫學證據及專家意見外，並參考國家衛生研究院子宮內膜癌臨床指引、美國 National Comprehensive Cancer Network (NCCN) 的 Practice Guide-lines in endometrial Cancer 2017版、FIGO Staging Classifications and Clinical Practice Guidelines in the Management of Gynecologic Cancer、及中山醫學大學附設醫院子宮體癌治療經驗進行編修。

1-2.子宮內膜癌之診斷與評估



流程圖一

1-3.子宮內膜癌之分期

FIGO 分期		TNM Categories
I	Tumor confined to corpus uteri (癌症侷限於子宮內)	T1
IA	No or less than half myometrium invasion (癌症沒有侵犯或小於一半以內子宮肌層)	T1a
IB	Invasion equal to or more than half of myometrium (癌症侵犯大於或等於一半子宮肌層)	T1b
II	Tumor invades cervical stroma,but does not extend beyond the uterus (癌症侵犯至子宮頸間質組織，但沒有超越至子宮外)	T2
III	Local and/or regional spread of the tumor (癌症局部或是區域性擴散)	T3
IIIA	Tumor invades the serosa of the corpus uteri and/or adnexa (癌症侵犯至子宮體漿膜層或是子宮附屬器官)	T3a
IIIB	vaginal and/or parametrical involvement (癌症侵犯至陰道或是子宮頸旁組織)	T3b
IIIC	metastases to pelvic and/or para-aortic lymph nodes (癌細胞轉移至骨盆腔或是主動脈旁淋巴結)	T3c
IIIC1	positive pelvic nodes (陽性骨盆腔淋巴結)	T3c1
IIIC2	positive para-aortic lymph nodes with or without positive lymph nodes (陽性主動脈旁淋巴結及/或陽性骨盆腔淋巴結)	T3c2
IV	Tumor invades bladder and/or bowel mucosa,and/or distant metastases (癌症侵襲膀胱或腸黏膜或遠處轉移)	T4
IV A	Tumor invasion of bladder and/or bowel mucosa (癌症侵犯膀胱或是腸黏膜)	T4a
IV B	Distant metastases,including intra-abdominal metastases and/or inguinal lymph nodes (遠處轉移，包括腹腔內轉移或是腹股溝淋巴結)	T4b

1-4.子宮內膜癌分期手術原則

★子宮全切除術與雙側卵巢全切除術(TH/BSO)為病灶明顯侷限在子宮內的子宮內膜癌之主要治療，除了少數個案有保留生育能力的意願而考慮保留生育的手術外(流程圖十一)，大多數局部晚期的子宮內膜癌患者都適用子宮全切除術與雙側卵巢全切除術。

★子宮切除術和附件切除可以透過開腹手術、陰道，或諸如腹腔鏡或機器人手術微創技術等方式進行。

★以肉眼評估腹膜、膈肌、漿膜表面，針對任何懷疑為病灶的部位進行切片檢查以排除子宮外的病灶有其重要性。

★雖然腹膜的細胞學檢查並不影響分期，但 FIGO 與 AJCC 仍建議能夠能夠採檢且有報告。

★當腫瘤的形態是 serous adenocarcinoma、clear cell adenocarcinoma、carcinosarcoma 時，通常會進行網膜的切片（omental biopsy）。

★骨盆腔或腹主動脈疑似或增大的淋巴結摘除對於排除淋巴結轉移的可能性而言有其重要性。

★對特定侷限於子宮內的子宮內膜癌分期手術而言，骨盆腔淋巴結的摘除與病理的評估仍是重要的部分，藉此可以鑑別重要的預後資訊且可能改變後續的治療決策。

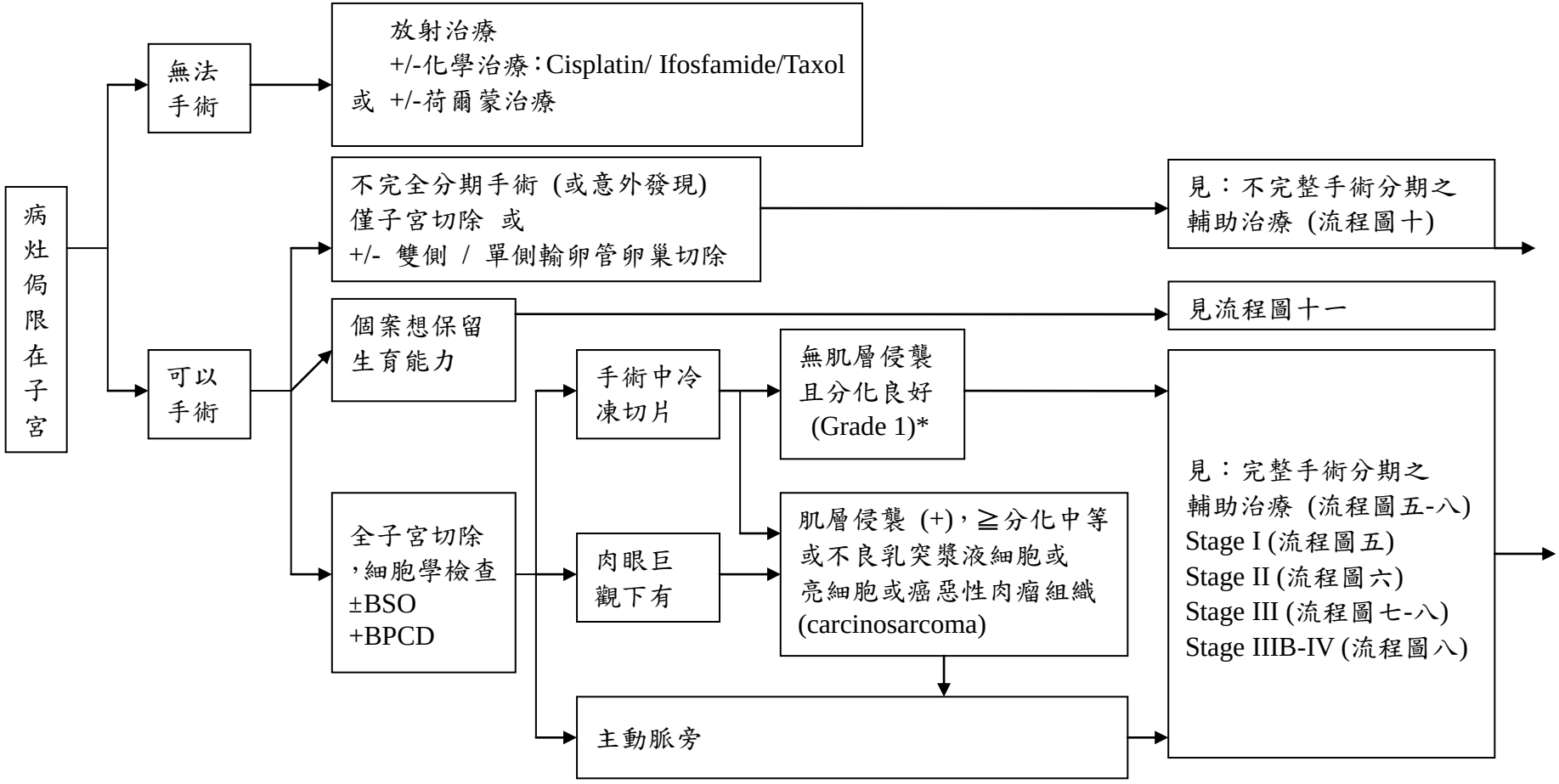
★從髂外(external iliac)、髂內(internal iliac)、閉孔(obturator)到髂總(common iliac nodes)的骨盆腔淋巴結都是分期手術中經常需要切除的。

★從 inframesenteric 和 infrarenal 區域針對腹主動脈淋巴結的評估，也可以用於決定特定高危險因子腫瘤的分期，例如 deeply invasive lesions，high-grade histology，和 serous adenocarcinoma、clear cell adenocarcinoma、carcinosarcoma 的分期。

★有些個案可能不適合接受淋巴結摘除術。

1-5. 子宮內膜癌之治療

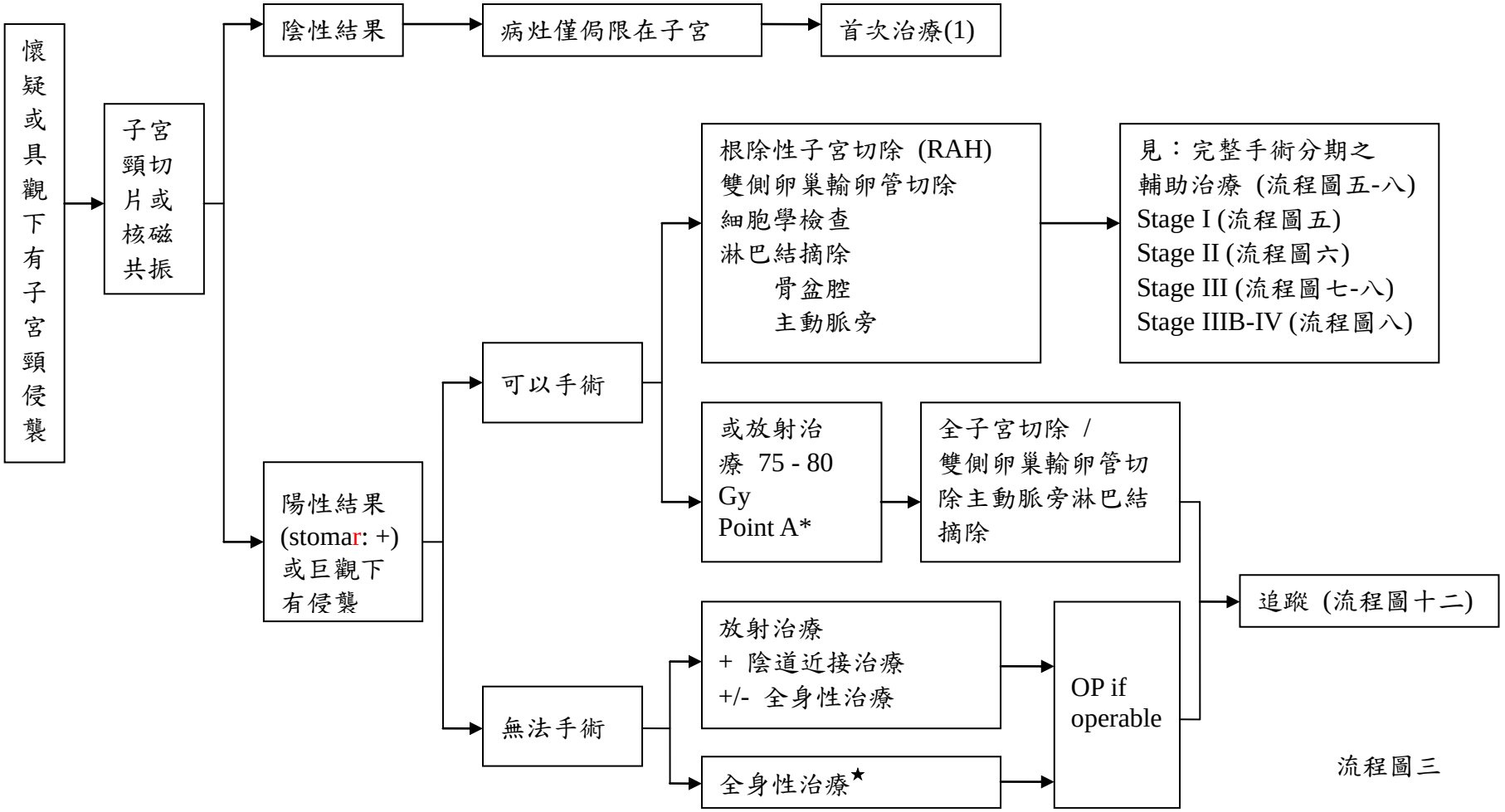
【疾病侷限在子宮】首次治療 (1)



流程圖二

＊：American College of Obstetricians and Gynecologists practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstet Gynecol 2005 Aug; 106:413-425.

【懷疑或巨觀下有子宮頸侵襲】首次治療 (2)

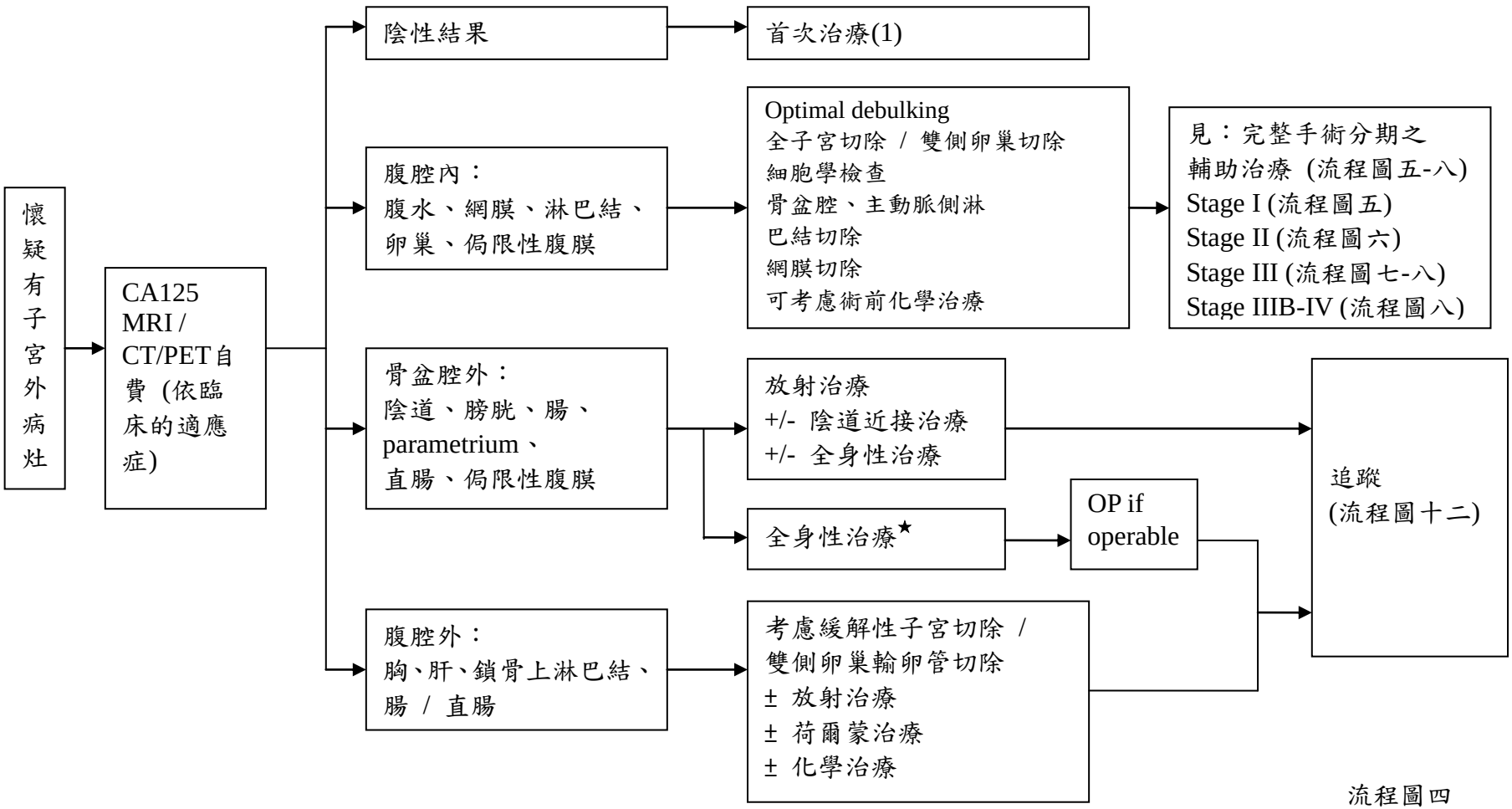


流程圖三

＊：仍未定論

★全身性治療：意為化學治療或荷爾蒙治療或標靶治療或免疫療法(詳見 P.18)

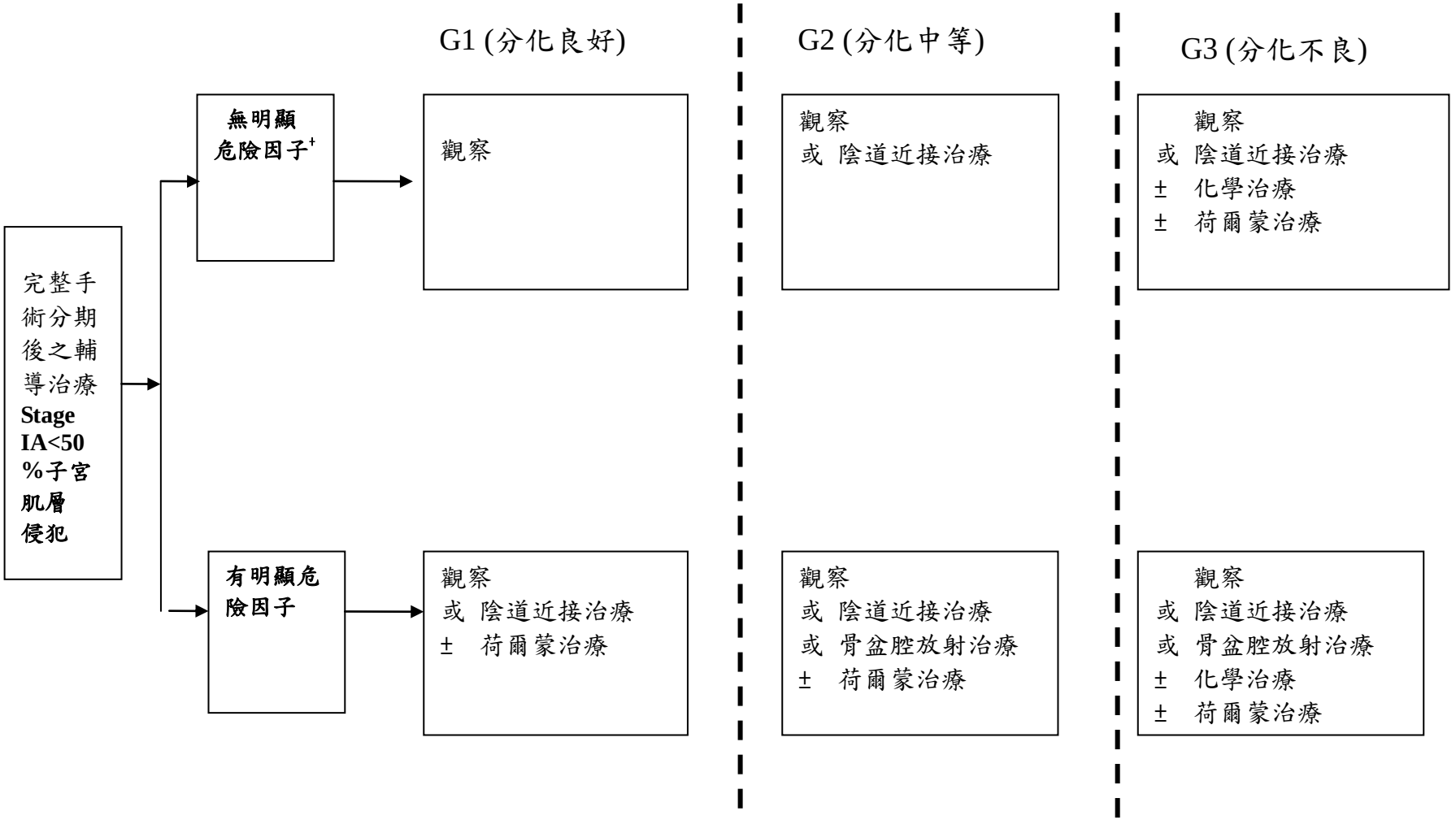
【懷疑有子宮外病灶】首次治療 (3)



流程圖四

★全身性治療：意為化學治療或荷爾蒙治療或標靶治療或免疫療法(詳見 P.18)

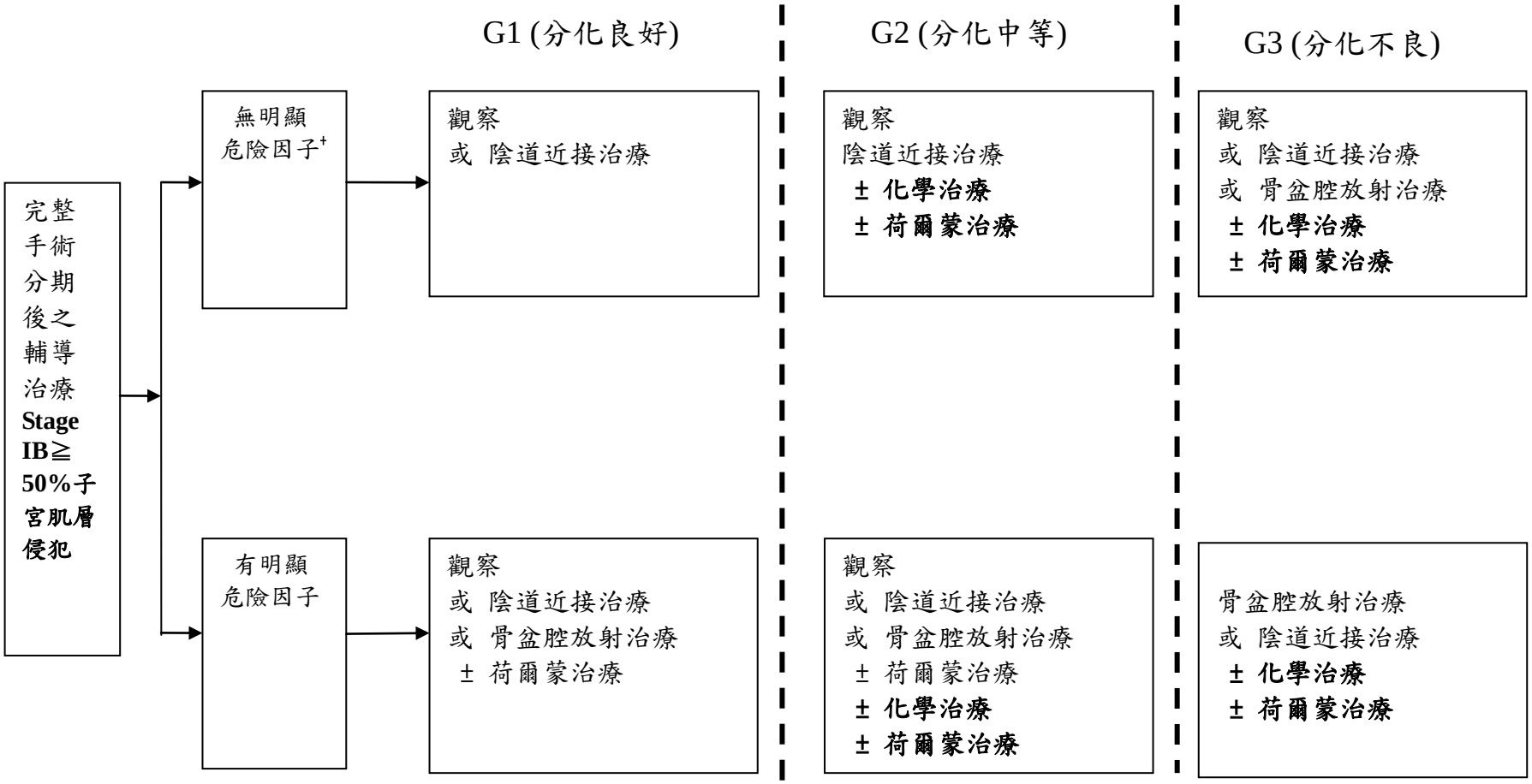
1-6. 子宮內膜癌完整手術分期後之輔導治療



流程圖五

＊：危險因子包括：年齡 60歲以上、淋巴血管腔侵襲、較大腫瘤 (2公分以上)、子宮下段侵襲、子宮頸腺體侵襲

＊：陰道頂部袖口端(viginal cuff)癒合即應儘快開始放射線治療，最好不超過術後12週。

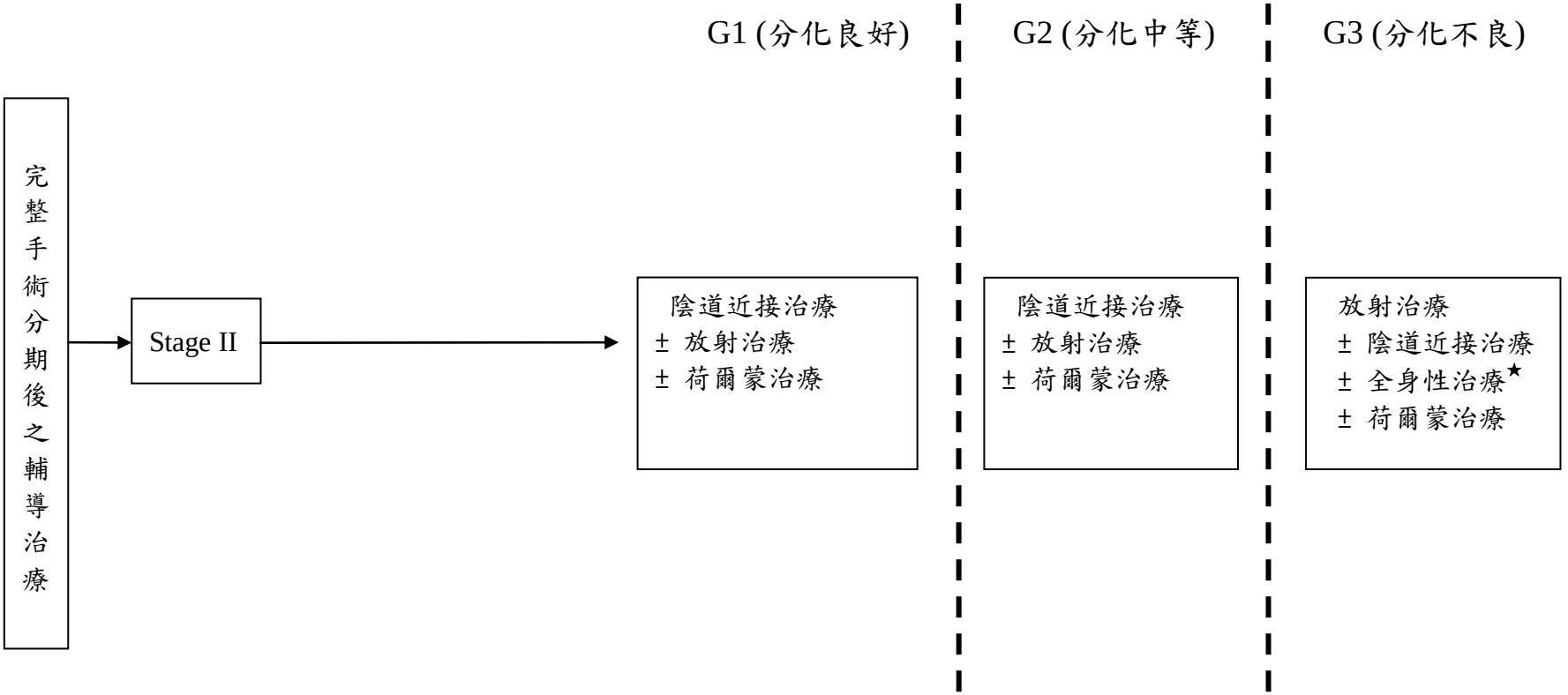


流程圖五

＊：危險因子包括：年齡 60歲以上、淋巴血管腔侵襲、較大腫瘤 (2公分以上)、子宮下段侵襲、子宮頸腺體侵襲

＊：陰道頂部袖口端(viginal cuff)癒合即應儘快開始放射線治療，最好不超過術後12週。

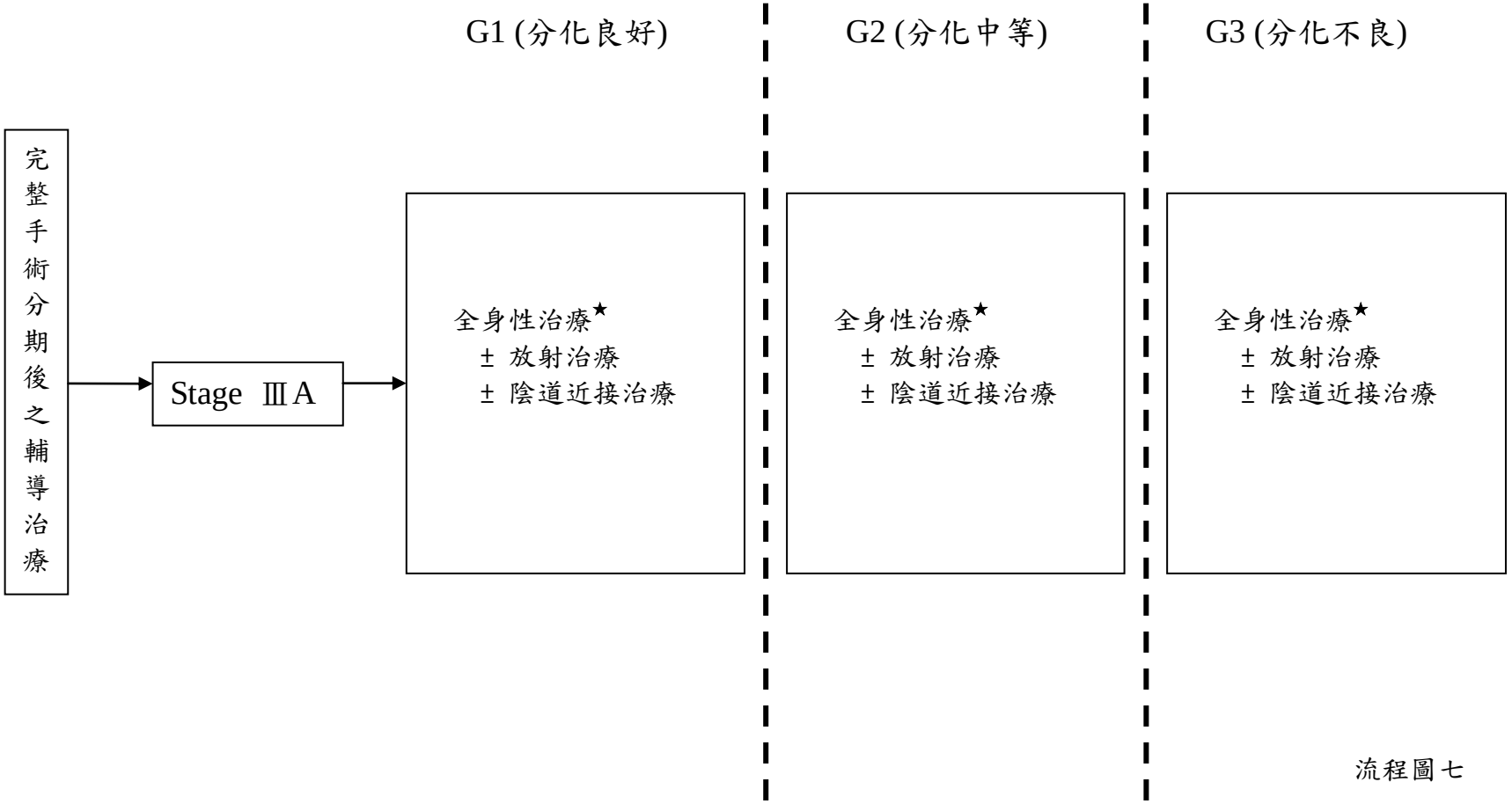
＊：針對放射線治療方式，醫師可選擇性以放射線治療為主要治療方式。



＊：觀察或陰道近接治療－可選擇在根除性子宮切除後邊緣無病灶，且無子宮外病灶。 流程圖六

＊：陰道頂部袖口端(viginal cuff)癒合即應儘快開始放射線治療，最好不超過術後12週。

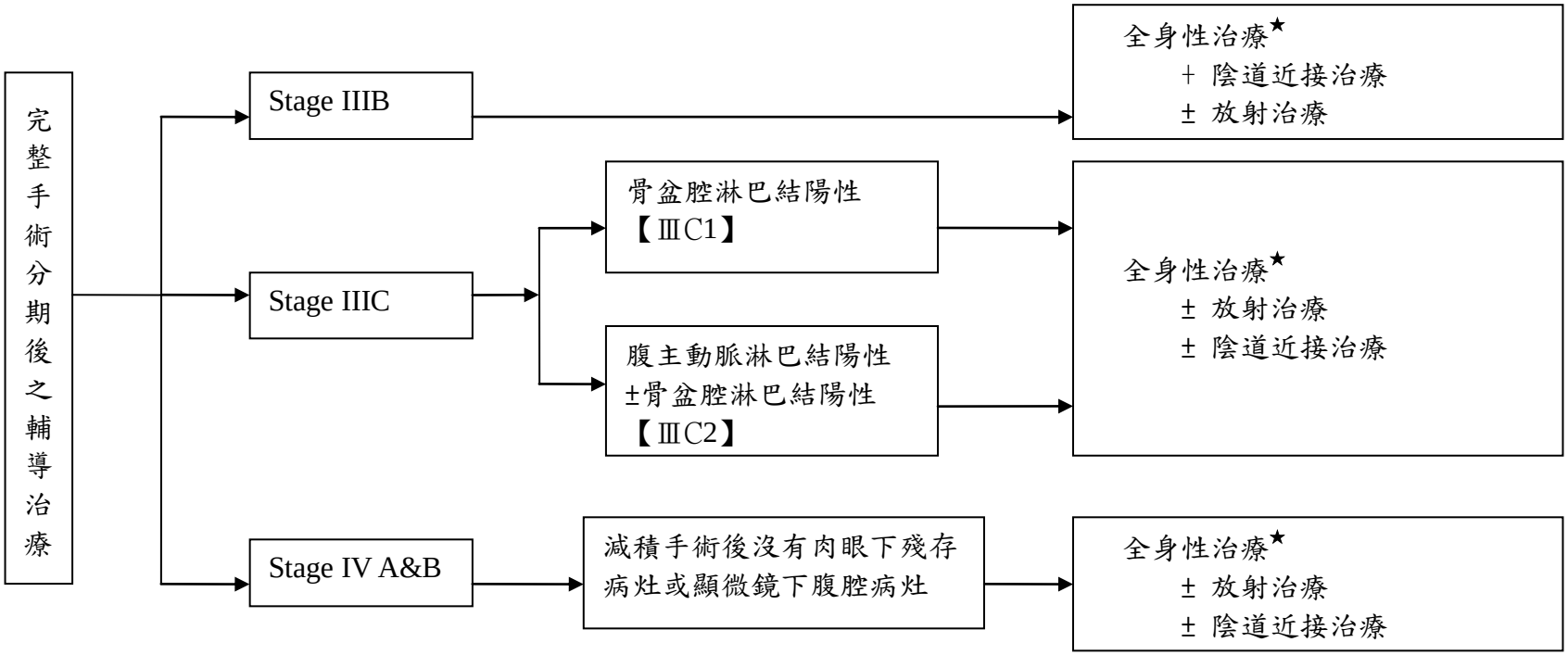
★全身性治療：意為化學治療或荷爾蒙治療或標靶治療或免疫療法(詳見P.18)。



流程圖七

＊：陰道頂部袖口端(viginal cuff)癒合即應儘快開始放射線治療，最好不超過術後12週。

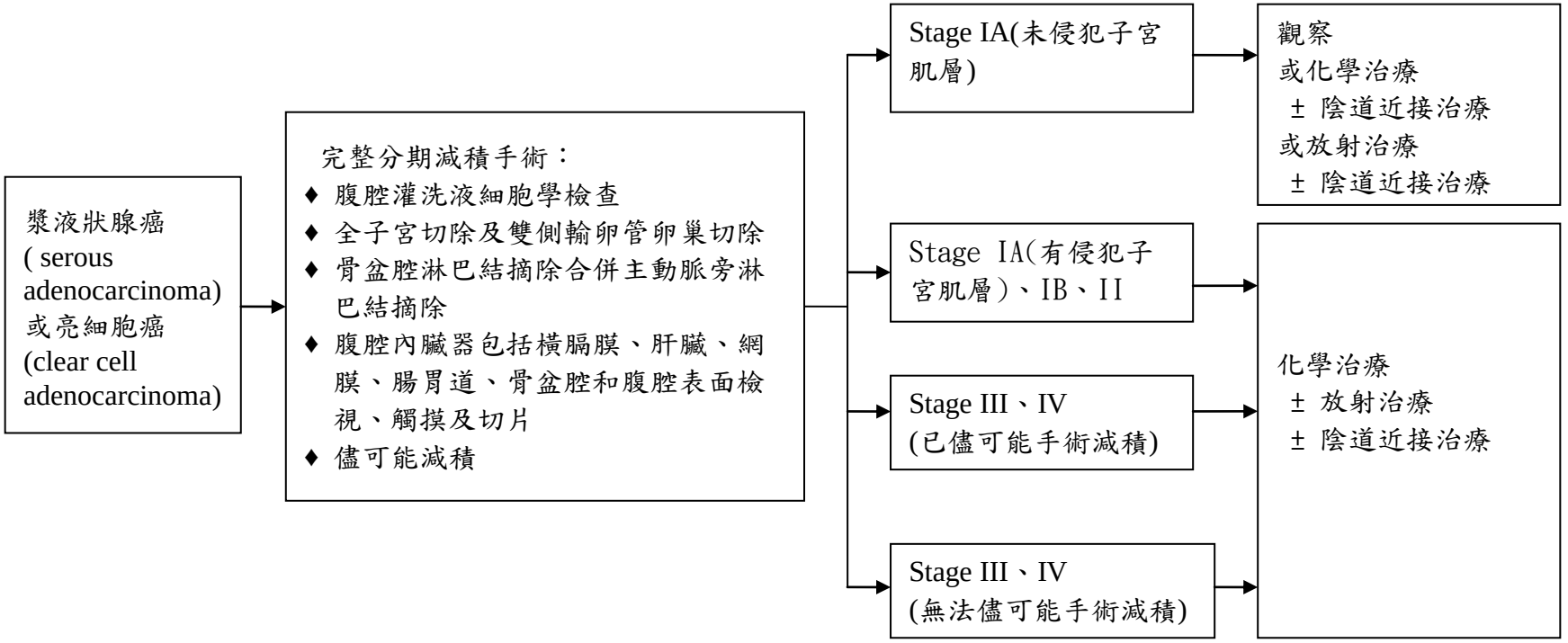
★全身性治療：意為化學治療或荷爾蒙治療或標靶治療或免疫療法(詳見 P.18)。



★全身性治療：意為化學治療或荷爾蒙治療或標靶治療或免疫療法(詳見P.18)。 流程圖八

1-7. 漿液狀腺癌(serous adenocarcinoma)或亮細胞癌(clear cell adenocarcinoma)

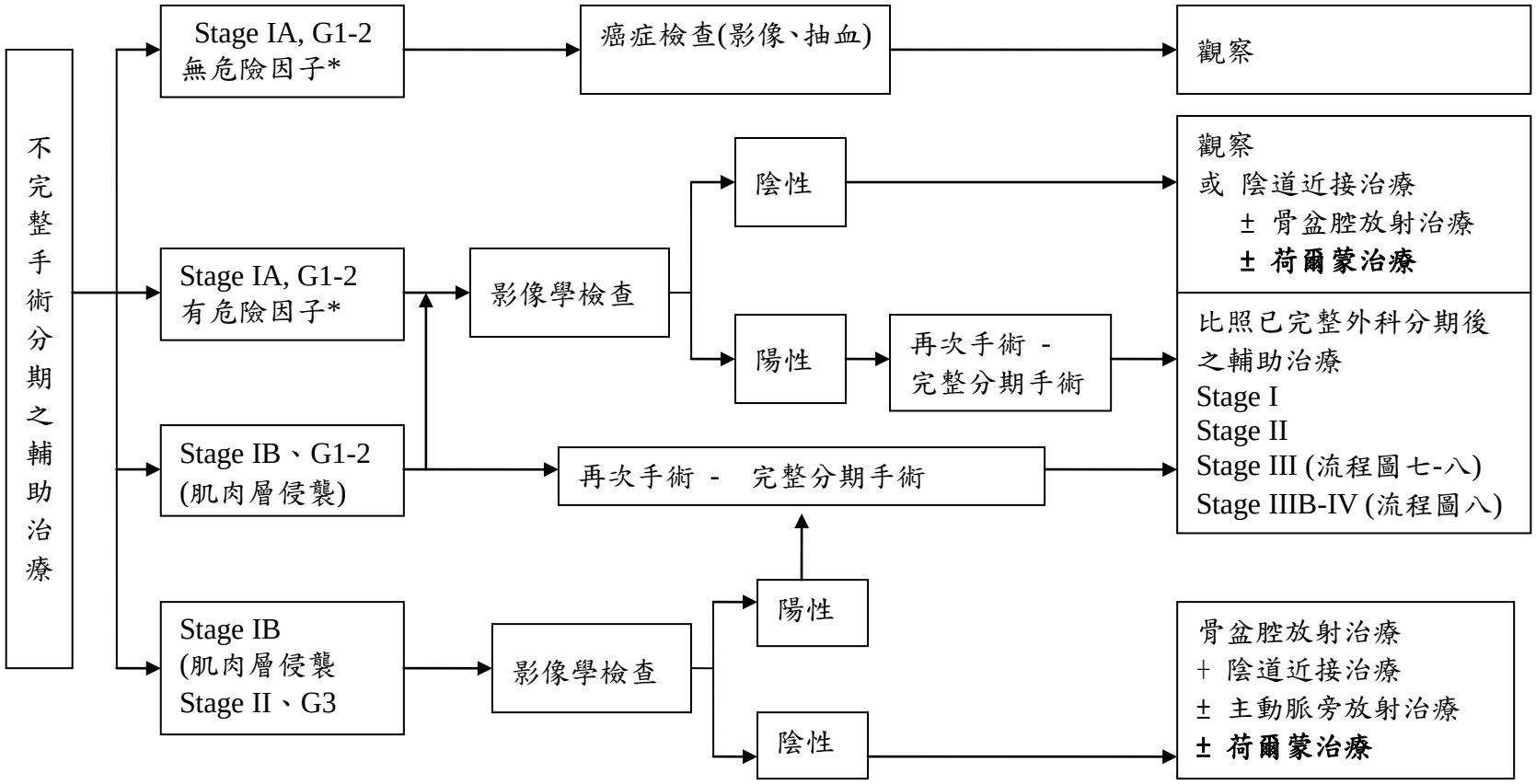
輔助治療



流程圖九

1-8.未接受完整手術分期之輔助治療

不完全分期手術 (或意外發現) 僅子宮切除或+/－雙側/單側輸卵管卵巢切除

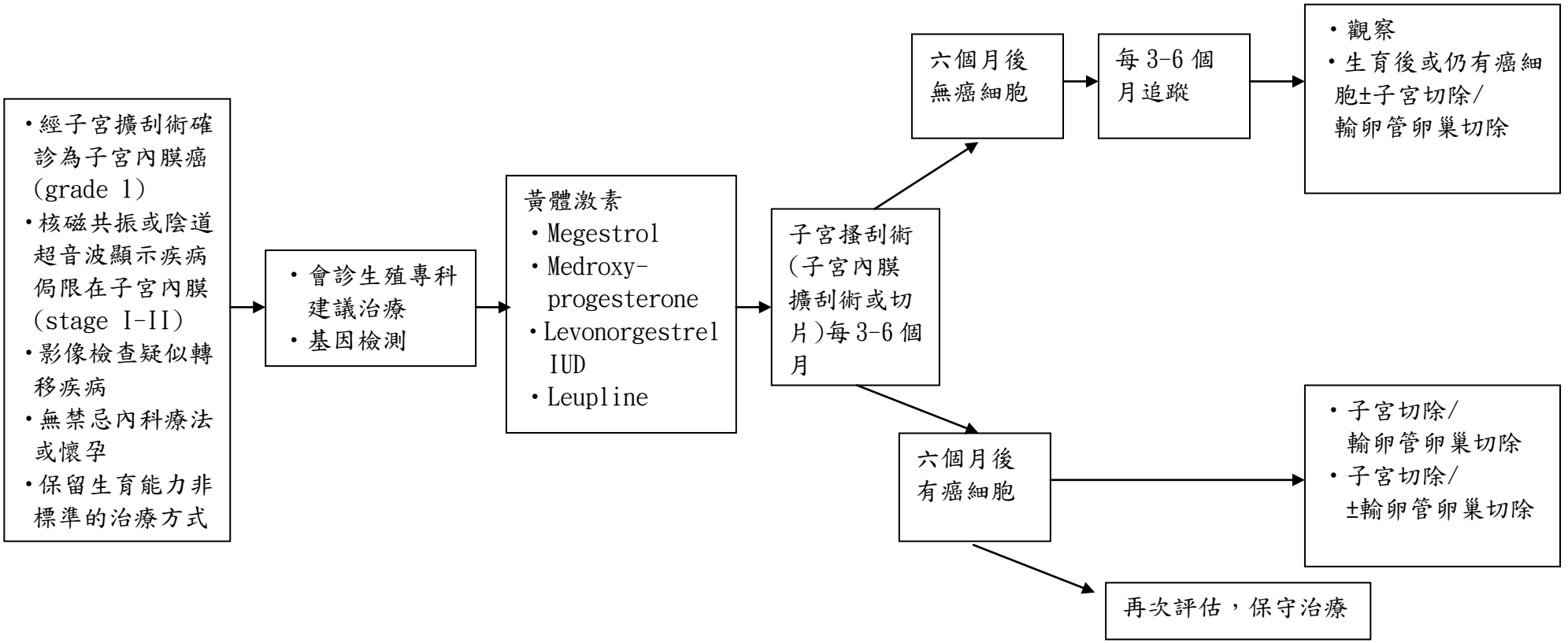


＊：危險因子包括：年齡 60歲以上、淋巴血管腔侵襲、較大腫瘤 (2公分以上)、子宮下段侵襲、子宮頸腺體侵襲

＊：年齡小於35歲、Stage IA、G1者，卵巢可不切除

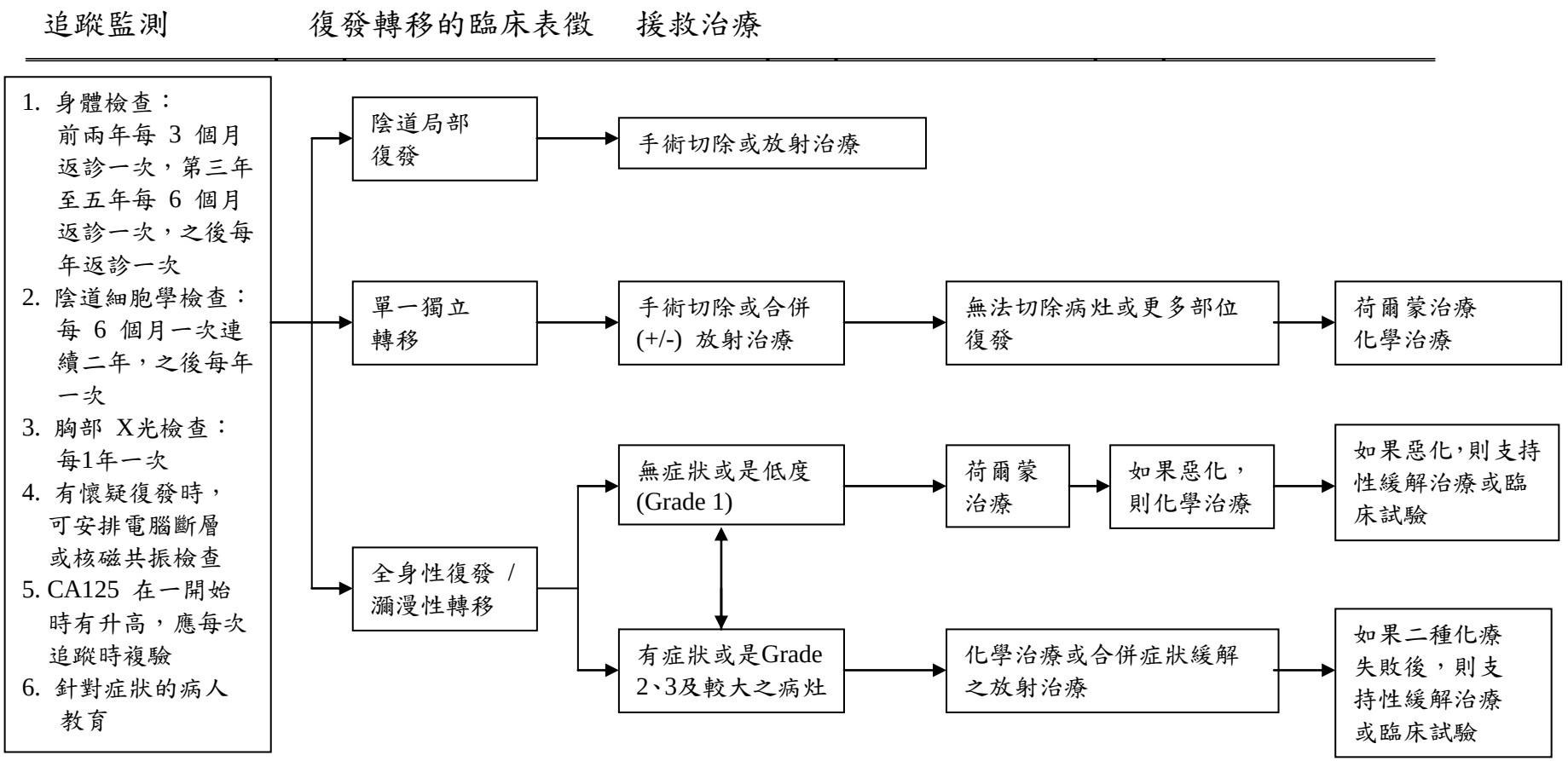
流程圖十

1-9.子宮內膜癌保留生育能力處置



流程圖十一

1-10.接續治療，追蹤及復發處置



流程圖十二

1-11. 子宮內膜癌之全身性治療

SYSTEMIC THERAPY FOR RECURRENT, METASTATIC, OR HIGH-RISK DISEASE
(STRONGLY ENCOURAGE PARTICIPATION IN CLINICAL TRIALS)

CHEMOTHERAPY REGIMENS

• Multi-agent chemotherapy regimens preferred, if tolerated

- ★ Carboplatin/paclitaxel
- ★ Cisplatin/doxorubicin
- ★ Cisplatin/doxorubicin/paclitaxel
- ★ Carboplatin/docetaxel
- ★ Ifosfamide/paclitaxel (category 1 for carcinosarcoma)
- ★ Cisplatin/ifosfamide (for carcinosarcoma)

• Single agents

- ★ Cisplatin
- ★ Carboplatin
- ★ Doxorubicin
- ★ Liposomal doxorubicin
- ★ Paclitaxel
- ★ Topotecan
- ★ Bevacizumab
- ★ Temsirolimus
- ★ Docetaxel (category 2B)
- ★ Ifosfamide (for carcinosarcoma)

HORMONE THERAPY

- ★ Megestrol/tamoxifen (alternating)
- ★ Progestational agents
- ★ Aromatase inhibitors
- ★ Tamoxifen
- ★ Leupline

荷爾蒙藥物的預防與治療有兩種：

(一) 荷爾蒙治療：針對 Advanced stage、recurrenced、palliative、有 high risk 的個案。

(二) 荷爾蒙預防，針對早期癌症病人，尤其是 IA、IB，雖經手術治療完全，但仍可給予預防性荷爾蒙。

Adjuvant chemotherapy

Epirubicin+Cisplatin

Epirubicin	60mg/m2 iv	d1
Cisplatin	60mg/m2 iv	d1
q3w x 6wks cycles		

Lissoni1, A. Gabriele1, G. Gorga2, S. Tumolo3, F. Landoni1, C. Mangioni1 and C. Sessa4. Cisplatin-, epirubicin- and paclitaxel-containing chemotherapy in uterine adenocarcinoma.Ann Oncol (1997) 8 (10): 969-972

Epirubicin+Carboplatin

Epirubicin	60mg/m2 iv	d1
Carboplatin	AUC (4-6) iv	d1
q3w x 6wks cycles		

F. Calero, E. Asins-Codoñerb, J. Jimenoc, F. et al. Epirubicin in advanced endometrial adenocarcinoma: a phase II study of the grupo ginecologico Español para el tratamiento oncologico (GGETO).European Journal of Cancer and Clinical Oncology, Volume 27, Issue 7, July 1991, Pages 864–866

Paclitaxel+Cisplatin

Paclitaxel	(135/175)mg/m2 iv	d1
Cisplatin	75mg/m2 iv	d1
q3w x 6wks cycles		

Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A Gynecologic Oncology Group study. Gynecol Oncol 2009;112:543-552.

Paclitaxel+Carboplatin

Paclitaxel	(135/175)mg/m2 iv	d1
Carboplatin	AUC (4-6) iv	d1
q3w x 6wks cycles		

Miller D, Filiaci V, Fleming G, et al. Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: a Gynecologic Oncology Group study [abstract]. Gynecol Oncol 2012;125:771.

Doxorubicin +Cisplatin

Doxorubicin	50mg/m^2 iv	d1
Cisplatin	75mg/m^2 iv	d1
q3w x 6 cycles		

Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A Gynecologic Oncology Group study. Gynecol Oncol 2009;112:543-552.

Doxorubicin +Carboplatin

Doxorubicin	50mg/m^2 iv	d1
Carboplatin	AUC (4-6) iv	d1
q3w x 6 cycles		

Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A Gynecologic Oncology Group study. Gynecol Oncol 2009;112:543-552.

Cisplatin+Ifosfamide

Cisplatin	50-100mg/m^2 iv	d1
Ifosfamide	3-5g/m^2 iv	d1
q3w x 6 cycles		

Howard D. Homesley, Virginia Filiaci, Maurie Markman, et al. Phase III Trial of Ifosfamide With or Without Paclitaxel in Advanced Uterine Carcinosarcoma: A Gynecologic Oncology Group Study.JCO February 10, 2007 vol. 25 no. 5 526-531

Carboplatin+Ifosfamide

Carboplatin	AUC (4-6) iv	d1
Ifosfamide	3-5g/m^2 iv	d1
q3w x 6 cycles		

A. Pawinski1, a, e, S. Tumolob, G. Hoeselc, A. Cervantesd, et al. Cyclophosphamide or ifosfamide in patients with advanced and/or recurrent endometrial carcinoma: a randomized phase II study of the EORTC Gynecological Cancer Cooperative Group.European Journal of Obstetrics & Gynecology and Reproductive Biology Volume 86, Issue 2, October 1999, Pages 179–183

Cisplatin + doxorubicin +paclitaxel (Taxol)*

Doxorubicin 45mg/m2 IV + cisplatin 50mg/m2 iv	d1
Paclitaxel 160mg/m2 3-hr iv	d2
Filgrastim 5mcg/kg SC.Repeat cycle every 3 weeks for max 7 cycles.	d3-12
Maximum BSA of 2.0 was used for calculations.	

1.NCCN Clinical Practice Guidelines in Oncology™. Uterine Neoplasms.v 2.2012. Available at: http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed February 24, 2012.
2.Fleming, GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol. 2004;22:2159–2166.

Ifosfamide (Ifex) + paclitaxel†

Paclitaxel 135mg/m2 administered as a 3-hr iv	d1
Ifosfamide 1.6g/m2/day iv (1.2g/m2/day if patient received prior radiation).	d1-3
Repeat cycle every 3 weeks for 8 cycles.	

1.NCCN Clinical Practice Guidelines in Oncology™. Uterine Neoplasms.v 2.2012. Available at: http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed February 24, 2012.
2.Homesley HD, Filiaci V, Markman M, et al. Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma:a Gynecologic Oncology Group study. J Clin Oncol.2007;25:526–531.

Bevacizumab (Avastin)

Bevacizumab 15mg/kg iv	d1
Repeat cycle every 3 weeks	

1.NCCN Clinical Practice Guidelines in Oncology™. Uterine Neoplasms.v 2.2012. Available at: http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed February 24, 2012.
2.Aghajanian C, Sill MW, Darcy KM, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. J Clin Oncol. 2011;29(16): 2259–2265.

Hormonal therapy

Megestrol

Megestrol	1 tad 40-100mg PO
QD x 6months	

1.Fiorica JV, Brunetto VL, Hanjani P, et al. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92:10-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14751131.
2.Pandya KJ, Yeap BY, Weiner LM, et al. Megestrol and tamoxifen in patients with advanced endometrial cancer: an Eastern Cooperative Oncology Group Study (E4882). Am J Clin Oncol 2001;24:43-46.Available at: http://www.ncbi.nlm.nih.gov/pubmed/11232948.

Medroxyprogesterone

Medroxyprogesterone	1 tad 5-10mg PO
QD x 6months	

1.Whitney CW, Brunetto VL, Zaino RJ, et al. Phase II study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92:4-9. Available at:http://www.ncbi.nlm.nih.gov/pubmed/14751130.
2.Thigpen JT, Brady MF, Alvarez RD, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. J Clin Oncol 1999;17:1736-1744. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561210.

Levonorgestrel IUD

Levonorgestrel IUD	Intrauterine Devise x1

Baker J, Obermair A, Gebski V, Janda M. Efficacy of oral or intrauterine device-delivered progestin in patients with complex endometrial hyperplasia with atypia or early endometrial adenocarcinoma: a meta-analysis and systematic review of the literature. Gynecol Oncol 2012;125:263-270. Available at:http://www.ncbi.nlm.nih.gov/pubmed/22196499.

Leupline

Leupline	375mg IM
qm x 6months	

1.A.R. Jeyarajah, M.D.C.J. Gallagher, M.D., Ph.D.P.R. Blake, M.D,et al.Long-Term Follow-up of Gonadotrophin-Releasing Hormone Analog Treatment for Recurrent Endometrial Cancer. Gynecologic Oncology Volume 63, Issue 1, October 1996, Pages 47–52
2. Tirso Pérez-Medina, M.D.José Bajo, M.D.Gonzalo Folgueira, M.D.,et al.Atypical Endometrial Hyperplasia Treatment with Progestogens and Gonadotropin-Releasing Hormone Analogues: Long-Term Follow-up. Gynecologic Oncology Volume 73, Issue 2, May 1999, Pages 299–304

1-12. 子宮內膜癌之放射線治療

- Adjuvant treatment
  - Whole pelvic irradiation: total 45-55Gy
  - IVBT boost: HDR 4-5Gy x 2-3 Fractions
  - IVBT alone: HDR 4-5 Gy x 6-8 Fractions
  - Consider dose escalation to gross disease

  IVBT：intravaginal brachytherapy
  HDR(high dose rate)

- Definitive
  - Whole pelvic irradiation: total 45-60Gy + HDR ICBT 4-5 Gy * 5-6 Fractions

  ICBT：intracavitary brachytherapy

*Prefer 3D CRT , IMRT, or IGRT(optional)

二、子宮惡性肉瘤

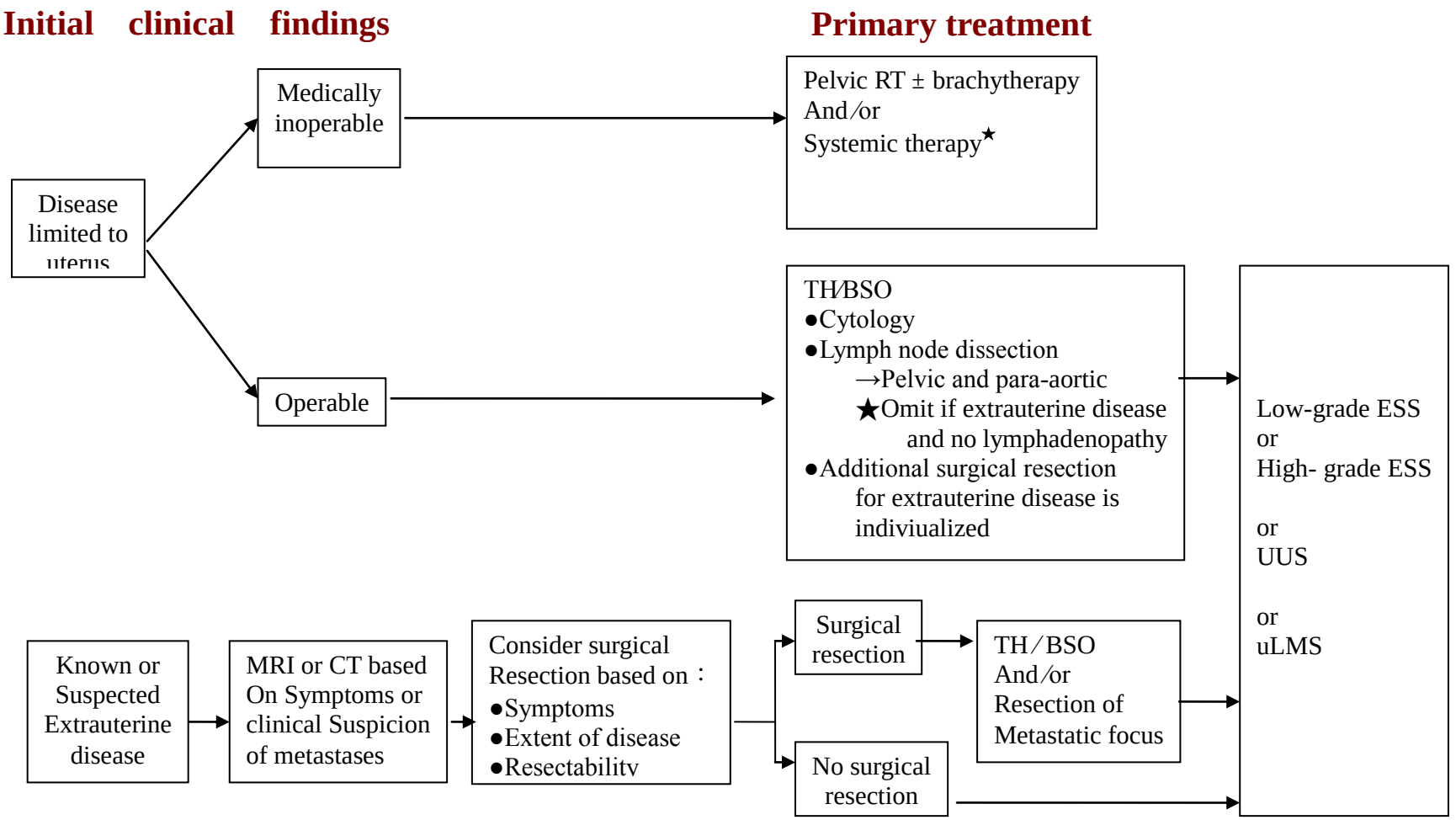
2-1.分期(Leiomyosarcoma and Endometrial Stromal Sarcoma)

FIGO 分期		TNM Categories
	Primary tumor cannot be assessed	Tx
	No evidence of primary tumor	T0
I	Tumor limited to the uterus	T1
IA	Tumor 5 cm or less in greatest dimension	T1a
IB	Tumor more than 5 cm	T1b
II	Tumor extends beyond the uterus, within the pelvis	T2
IIA	Tumor involves adnexa	T2a
IIB	Tumor involves other pelvic tissues	T2b
III	Tumor infiltrates abdominal tissues	T3
IIIA	One site	T3a
IIIB	More than one site	T3b
IIIC	Regional lymph node metastasis	N1
IVA	Tumor invades bladder or rectum	T4
IVB	Distant metastasis(excluding adexa, pelvic and abdominal tissue)	M1

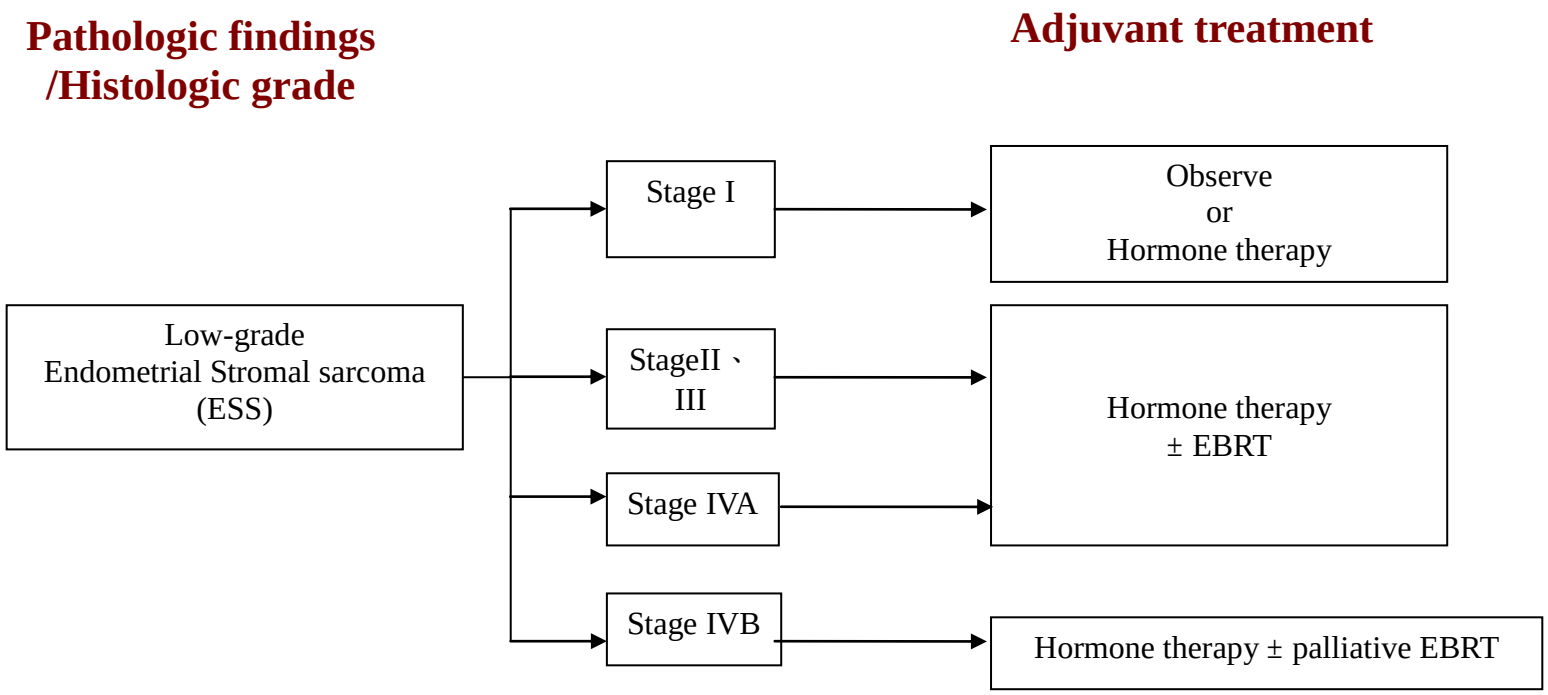
2-1.分期(Adenosarcoma)

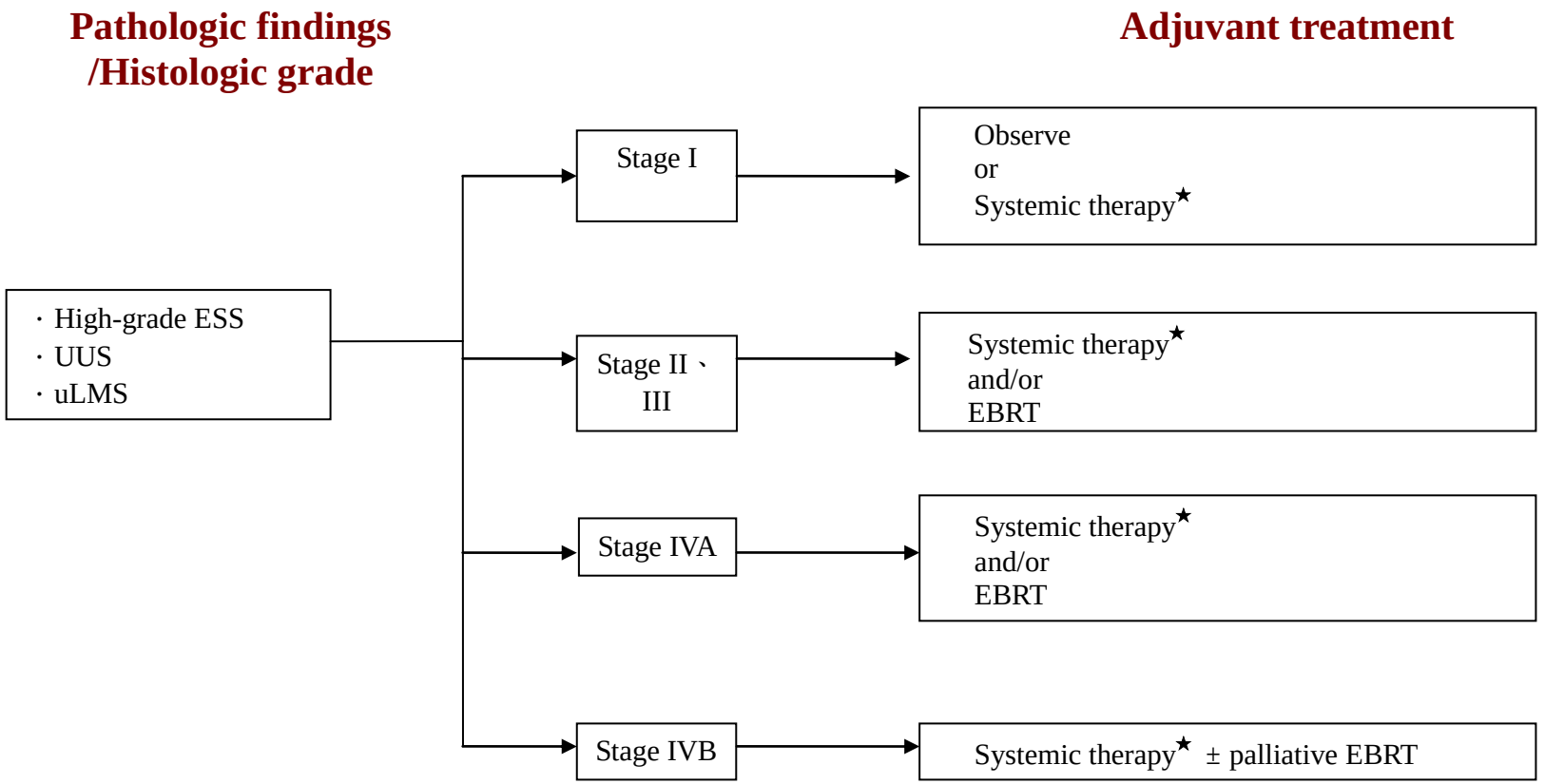
FIGO 分期		TNM Categories
	Primary tumor cannot be assessed	Tx
	No evidence of primary tumor	T0
I	Tumor limited to the uterus	T1
IA	Tumor limited to the endometrium/endocervix	T1a
IB	Tumor invades to less than half of the myometrium	T1b
II	Tumor extends beyond the uterus, within the pelvis	T2
IIA	Tumor involves adnexa	T2a
IIB	Tumor involves other pelvic tissues	T2b
III	Tumor involves abdominal tissues	T3
IIIA	One site	T3a
IIIB	More than one site	T3b
IIIC	Regional lymph node metastasis	N1
IVA	Tumor invades bladder or rectum	T4
IVB	Distant metastasis(excluding adexa, pelvic and abdominal tissue)	M1

2-2.子宮惡性肉瘤之臨床發現及處置



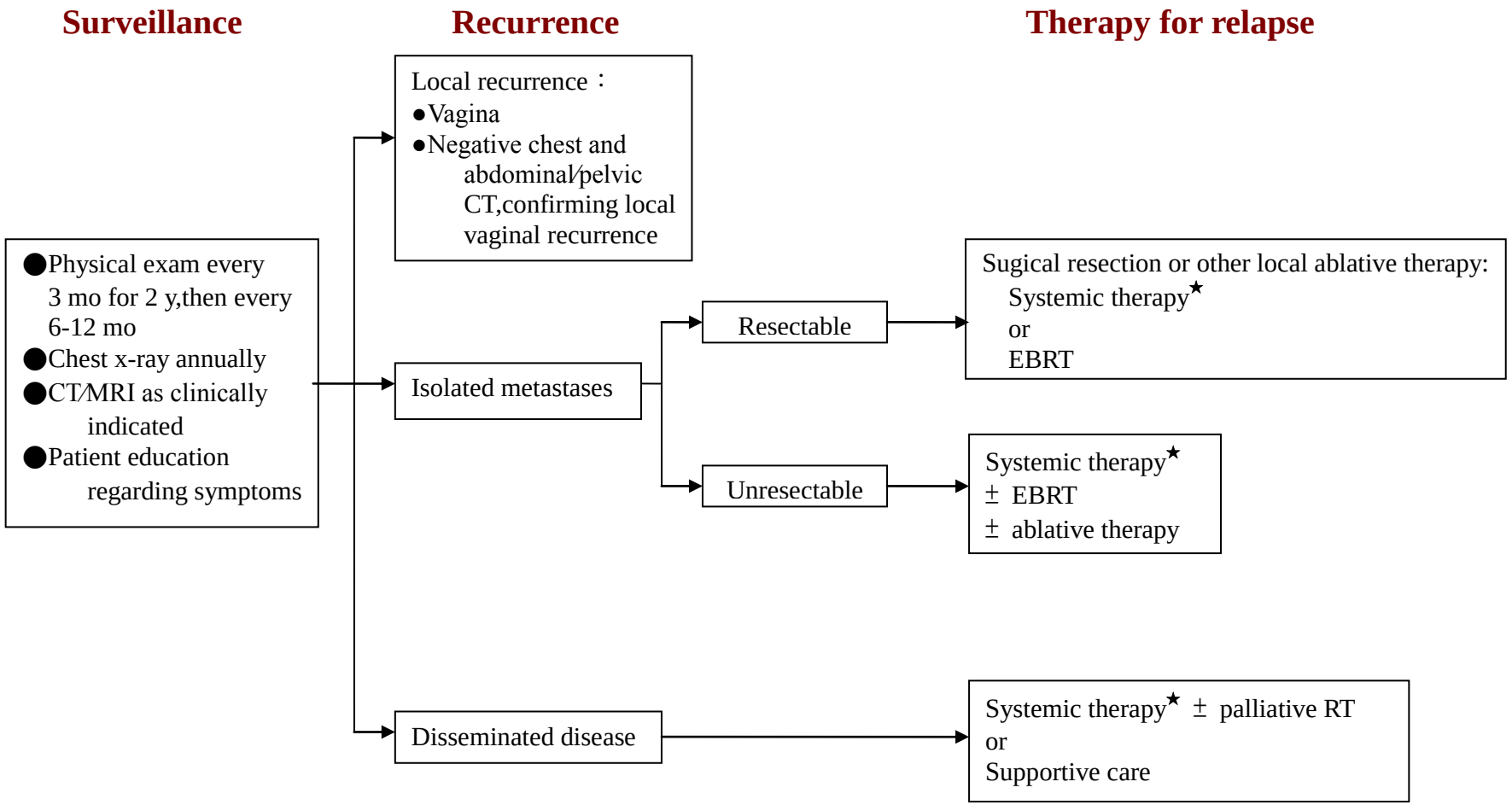
★Systemic therapy：意為化學治療或荷爾蒙治療或標靶治療或免疫療法(詳見 P.31)


Pathologic findings /Histologic grade
Adjuvant treatment
Low-grade Endometrial Stromal sarcoma (ESS)
Stage I
Observe or Hormone therapy
StageII、III
Hormone therapy ± EBRT
Stage IVA
Stage IVB
Hormone therapy ± palliative EBRT



★Systemic therapy：意為化學治療或荷爾蒙治療或標靶治療或免疫療法(詳見 P.31)

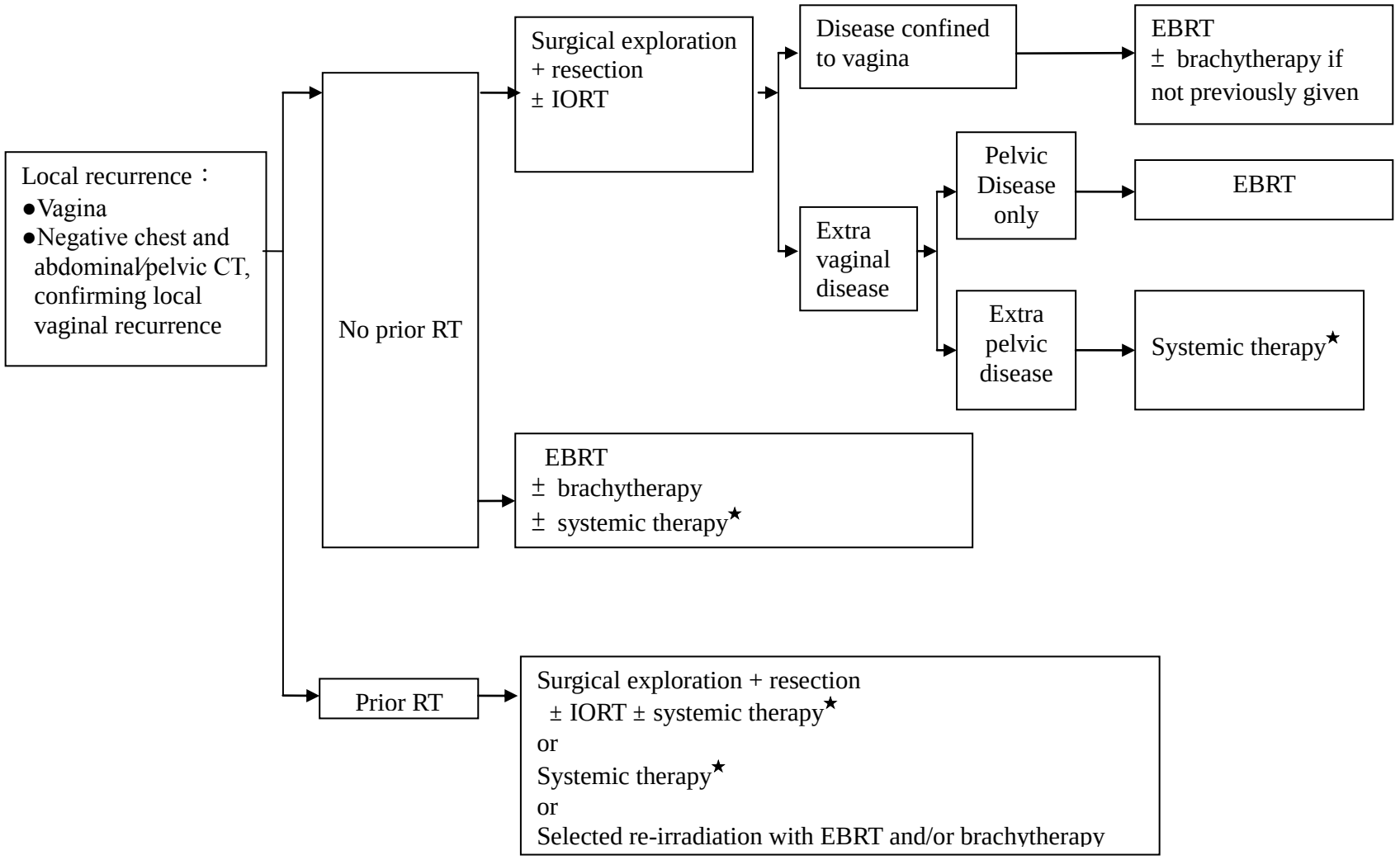
2-3.子宮惡性肉瘤之復發處置



★Systemic therapy：意為化學治療或荷爾蒙治療或標靶治療或免疫療法(詳見 P.31)

Recurrence

Therapy for relapse



★Systemic therapy：意為化學治療或荷爾蒙治療或標靶治療或免疫療法(詳見 P.31)

2-4.子宮惡性肉瘤之全身性治療

SYSTEMIC THERAPY FOR UTERINE SARCOMA
(Clinical trials strongly recommended)

<table>
<tr>
<td>Combination regimens:
★ Docetaxel/gemcitabine (preferred for leiomyosarcoma)
★ Doxorubicin/ifosfamide
★ Doxorubicin/dacarbazine
★ Gemcitabine/dacarbazine
★ Gemcitabine/vinorelbine</td>
<td rowspan="2">Single-agent options:
★ Dacarbazine
★ Doxorubicin
★ Epirubicin
★ Eribulin (category 2B)
★ Gemcitabine
★ Ifosfamide
★ Liposomal doxorubicin
★ Pazopanib
★ Temozolomide
★ Trabectedin
★ Vinorelbine (category 2B)
★ Docetaxel (category 3)</td>
</tr>
<tr>
<td>HORMONE THERAPY
(For Low-grade ESS or Hormone Receptor Positive (ER/PR) uLMS2):
★ Medroxyprogesterone acetate
(category 2B for ER/PR positive uLMS)
★ Megestrol acetate (category 2B for ER/PR positive uLMS)
★ Aromatase inhibitors
★ GnRH analogs (category 2B for low-grade ESS and
★ ER/PR positive uLMS)</td>
</tr>
</table>

Adjuvant chemotherapy

Epirubicin+Cisplatin

Epirubicin	60mg/m2	iv	d1
Cisplatin	60mg/m2	iv	d1
q3w x 6wks cycles			

Lissoni1, A. Gabriele1, G. Gorga2, et al. Cisplatin-, epirubicin- and aclitaxel-containing chemotherapy in uterine adenocarcinoma.*Ann Oncol* (1997) 8 (10): 969-972

Epirubicin+Carboplatin

Epirubicin	60mg/m2	iv	d1
Carboplatin	AUC (4-6)	iv	d1
q3w x 6wks cycles			

F. Calero, E. Asins-Codoñerb, J. Jimenoc,et al. Epirubicin in advanced endometrial adenocarcinoma: a phase II study of the grupo ginecologico Español para el tratamiento oncologico (GGETO).European Journal of Cancer and Clinical Oncology, Volume 27, Issue 7, July 1991, Pages 864–866

Paclitaxel+Cisplatin

Paclitaxel	(135/175)mg/m2	iv	d1
Cisplatin	75mg/m2	iv	d1
q3w x 6wks cycles			

Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A Gynecologic Oncology Group study. Gynecol Oncol 2009;112:543-552.

Paclitaxel+Carboplatin

Paclitaxel	(135/175)mg/m2	iv	d1
Carboplatin	AUC (4-6)	iv	d1
q3w x 6wks cycles			

Miller D, Filiaci V, Fleming G, et al. Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: a Gynecologic Oncology Group study [abstract]. Gynecol Oncol 2012;125:771.

Doxorubicin +Cisplatin

Doxorubicin	50mg/m^2 iv	d1
Cisplatin	75mg/m^2 iv	d1
q3w x 6 cycles		

Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A Gynecologic Oncology Group study. Gynecol Oncol 2009;112:543-552.

Doxorubicin +Carboplatin

Doxorubicin	50mg/m^2 iv	d1
Carboplatin	AUC (4-6) iv	d1
q3w x 6 cycles		

Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A Gynecologic Oncology Group study. Gynecol Oncol 2009;112:543-552.

Cisplatin+Ifosfamide

Cisplatin	50-100mg/m^2 iv	d1
Ifosfamide	3-5g/m^2 iv	d1
q3w x 6 cycles		

Howard D. Homesley, Virginia Filiaci, Maurie Markman, et al. Phase III Trial of Ifosfamide With or Without Paclitaxel in Advanced Uterine Carcinosarcoma: A Gynecologic Oncology Group Study.JCO February 10, 2007 vol. 25 no. 5 526-531

carboplatin+Ifosfamide

Carboplatin	AUC (4-6) iv	d1
Ifosfamide	3-5g/m^2 iv	d1
q3w x 6 cycles		

A. Pawinski1, a, e, S. Tumolob, G. Hoeselc, A. Cervantesd, et al. Cyclophosphamide or ifosfamide in patients with advanced and/or recurrent endometrial carcinoma: a randomized phase II study of the EORTC Gynecological Cancer Cooperative Group.European Journal of Obstetrics & Gynecology and Reproductive Biology Volume 86, Issue 2, October 1999, Pages 179–183

Doxorubicin (Adriamycin)

Doxorubicin 75mg/m^2 iv bolus.	d1
Repeat cycle every 31 days OR	
60mg/m^2–70mg/m^2 iv typically dosed every 3 weeks.	

1.NCCN Clinical Practice Guidelines in Oncology™. Uterine Neoplasms.v 2.2012. Available at: http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed February 24, 2012.
2. Sarcoma Meta-analysis Collaboration (SMAC). Cochrane Database Syst Rev. 2000;4:CD001419.

Gemcitabine (Gemzar) +docetaxel (Taxotere) + granulocyte-colony-stimulating factor (G-CSF)

Gemcitabine 900mg/m2 iv over 90 min(自費),	d1
Docetaxel 100mg/m2 iv over 60 min,	d8
G-CSF 150mcg/m2 SC(自費)	d9-15
OR Pegfilgrastim 6mg SC.	d9 or d10
Repeat cycle every 3 weeks until disease progression or toxicity occurs.	
NOTE: Patients with prior pelvic irradiation received Gemcitabine 675mg/m2 iv and Docetaxel 75mg/m2 iv	

1.NCCN Clinical Practice Guidelines in Oncology™. Uterine Neoplasms.v 2.2012. Available at: http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed February 24, 2012.
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Gemcitabine

Gemcitabine 1,000mg/m2 iv. (自費)	d1,8,15
Repeat cycle every 4 weeks.	

1.NCCN Clinical Practice Guidelines in Oncology™. Uterine Neoplasms.v 2.2012. Available at: http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed February 24, 2012.
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三、妊娠組織瘤

1. Definition

Complete hydatidiform mole. It arises from the fertilisation of an empty ovum lacking maternal genes. [1] The sperm then duplicates, making a diploid number of chromosomes which are therefore entirely male in origin and thus no embryonic tissue is present. [1] The overgrowth of the placenta is benign but can metastasise if left untreated. [2,3]
Partial hydatidiform moles differ in that the ovum retains its maternal genes, which results in a triploid chromosomal pattern after the addition of duplicated sperm to the normal ovum. [1] In this case a foetus may be present but survival after 8 weeks is unlikely due to its abnormal genetic make-up. [2]

Invasive moles occur as a result of local invasion of the myometrium by a complete or partial mole. [2] In the spectrum of malignant potential they are intermediate between hydatidiform moles and choriocarcinomas. [4]

Choriocarcinoma is a rare and overtly malignant condition both clinically and histologically. [2] It occurs when chorionic cells become malignant and metastasise to other parts of the body. [2] A choriocarcinoma can therefore arise subsequent to a molar pregnancy, or follow an otherwise normal pregnancy or miscarriage. [1,2]

PSTT are the least common form of GTD, comprising less than 2% of all cases. [2,5] They arise from the non-villous trophoblast and are diploid in nature. [2] In contrast to the other GTDs, it is characterised by a late presentation (months to years) of symptoms caused by a prior pregnancy, miscarriage or hydatidiform mole. [2]
The secretion of human Chorionic Gonadotrophin (hCG) is characteristic of all GTDs and is therefore used as part of their diagnosis, treatment and follow up. [2]

2. Treatment and follow-up:

2.1.Partial and complete mole

For complete and partial molar pregnancies suction evacuation (with dilation) is recommended. [2] An ultrasound scan should be performed prior to evacuation, to confirm the diagnosis, assess for the possible presence of a foetus and ensure absence of theca lutein cysts. [2,4] Other preoperative evaluations include complete history, examination, measurement of baselines serum hCG level, chest x-ray, full blood count, coagulation profile and liver, renal and thyroid function tests. [2,6] If excessive bleeding occurs after a complete evacuation, a single dose of oxytocin can be administered. [2]

Surveillance with serial serum hCG determinations commences within 48 hours following evacuation to obtain a baseline serum hCG level. [2] Thereafter this is performed weekly until the hCG level returns to normal. [2]

If the serum hCG level returns to normal within 8 weeks post-evacuation, monitoring of serum hCG levels can be stopped at 6 months. [2] However, if they do not monitoring stops 6 months after the first normal value following normalisation. [2,4] After normalisation of the serum hCG levels, monitoring continues through urine hCG measurements monthly. [2,4]

Following a molar evacuation, patients should avoid pregnancy until after the completion of the surveillance period. [2] Pregnancy naturally increases serum hCG levels, which could be perceived as abnormal and ultimately means that the hCG levels can no longer be used to monitor the patient. [2] Although, the oral contraceptive pill (and Hormone Replacement therapy) cannot be used until normal hCG values are obtained, thus other methods of contraception should be in place. [2,7]

Complete mole frequently proceeds to invasive disease with 8-20% of patients requiring chemotherapy, whereas Partial mole rarely becomes malignant, with only 0.5% of patients requiring chemotherapy. [2,3] A rise in the hCG level during surveillance can be used to detect this and patients should be treated with the appropriate chemotherapy as outlined below. [2]

2.2.Indications for chemotherapy

The treatment of women with GTD is undertaken in conjunction with Charing Cross Hospital. Chemotherapy cycles are administered by them and therefore the assessment of whether or not a patient requires chemotherapy is decided using their guidelines [2].

1. Brain, liver, GI mets or lung mets >2cm on CXR
2. Histological evidence of choriocarcinoma
3. Heavy PV bleeding or GI/intraperitoneal bleeding
4. Pulmonary, vulval or vaginal mets unless the hCG level is falling
5. Rising hCG in two consecutive serum samples
6. hCG > 20,000 IU/L more than 4 weeks after evacuation
7. hCG plateau in 3 consecutive serum samples
8. Raised hCG level 6 months after evacuation (even if falling)

Any one of these findings would be considered an indication for chemotherapy, however further assessments are carried out by Charing Cross Hospital.

2.3.FIGO Indications for chemotherapy treatment [2,7]

1. hCG plateau of 4 values +/- 10% over a 3 week period
2. hCG increase of >10% of three values over a 2 week period
3. Persistence of hCG for more than 6 months after molar evacuation.

4. Staging for chemotherapy

Human chorionic gonadotrophin (hCG) is a hormone that is predominantly produced by syncytiotrophoblast cells. [1,2] The measurement of hCG allows for an estimation of the number of proliferating cells. [2] This forms the basis of disease risk assessment in patients with GTD, and allows for the monitoring of subsequent responses to treatment. [2]

There is now a revised 2000 FIGO prognostic score table [2,7] which has parameters that allow clinicians to determine the risk category of individual patients. [2]

Scores	0	1	2	4
Age	＜40	≧40	.	.
Antecedent pregnancy	Mole	Abortion	Term	.
Months from index pregnancy	＜4	4-6	7-13	＞13
Pre-Treatment hCG	＜1,000	1,000-10,000	10,000-100,000	＞100,000
Largest Tumour Size	.	3-5cm	≧5cm	.
Site of mets	Lung	Spleen, kidney	Gastro-Intestinal	Brain, Liver
Number of Mets	.	1-4	5-8	＞8
Previous chemotherapy	.	.	Single agent	Two or more drug

According to FIGO 2002, if the patient scores between 0-6 they are considered to be in the low risk category and initial treatment will involve a single chemotherapeutic agent. [2,8] However if their score is greater than 7, then the treatment regime will involve multi-agent combinations of chemotherapy. [2,8]

5. Treatment

5.1.Low risk disease management

The standard treatment of low risk GTD is Methotrexate administered intra-muscularly, with oral Folinic Acid rescue. [2,9] The first course of treatment is administered in hospital to minimise complications which may arise due to the rapid shrinkage of the tumour. [2] Cycles subsequent to this are administered at home. [2]
The treatment is generally well tolerated without major toxicity. [2] Common side effects include pleural inflammation, mucositis, and asymptomatic elevation of liver function tests. [2,9] Alopecia, nausea and myelosuppression are possible but extremely rare. [2,9]
To minimise the risk of development of CNS disease in patients with lung metastasis, CNS prophylaxis with intra-thecal Methotrexate (12.5mg) is also added, and administered at 2 week intervals on 3 occasions. [2,9]
Treatment is continued for 6 weeks after the normalisation of hCG levels. [2,9] However, if patients have an inadequate response to Methotrexate therapy (as shown by an hCG plateau or rise), the treatment is switched to second line therapy using single agent Actinomycin D or EMA/CO combination chemotherapy (consisting of Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide and Vincristine), if the hCG level is above 300iu/L. [2,9]

5.2.High risk disease management

EMA/CO chemotherapy has shown a cure rate of 86% for high risk patients. [2,10] This intense treatment combines 5 chemotherapy agents delivered in 2 cycles one week apart (see appendix 8.2 for full details). [2,10] This appears to be the most effective approach to this rapidly proliferating malignancy. [2] In patients with cerebral metastasis at the time of diagnosis of GTD (4%), treatment may also include surgical resection if the disease is superficial, and higher doses of chemotherapy may be implemented to enhance penetration into the CNS. [2,11]
G-CSF (Granylocyte-Colony Stimulating Factor) support is frequently helpful as these drugs can be fairly myelosuppressive. [2,11] Life threatening toxicity is rare and the majority of patients tolerate treatment without any major problems. [2]

Treatment is continued for 6 weeks after the normalisation of hCG levels, although the dose of Etoposide may be reduced after the hCG levels normalise to minimise the risk of developing secondary malignancies. If patients develop resistance to the EMA/CO treatment regime (17%), a change to a second line drug treatment is required. The general replacement is EP/EMA (consisting of Etoposide-Cisplatin and Etoposide-Methotrexate-Actinomycin D) which, combined with surgery to defined drug resistant areas of the uterus, produces a cure rate of 90% in this minority of patients.

5.3.Management of PSTT

Prognosis for these patients is dependent upon the time of presentation after the antecedent pregnancy, but data from Charing Cross hospital showed a 100% cure rate for those presenting within 4 years of the antecedent pregnancy (later presentation carries a poorer prognosis). [2,12]

These tumours are characterised by resistance to the conventional chemotherapy used in the treatment of GTD, so a hysterectomy should be considered early in the course of treatment as a curative measure. [2,4] For patients with disseminated disease, EP/EMA chemotherapy is recommended, which can be stopped 6-8 weeks after normalisation of the hCG levels. [2,] Following this, hysterectomy is still also recommended. [2]

6. Follow-up

6.1.Post-chemotherapy follow up

Patients are reviewed 6 weeks after the completion of chemotherapy and the following inquiries should be undertaken, as stated by Charing Cross Hospital [2]:

- Recheck the sites of original disease
- Doppler US of pelvis
- CXR or CT/MRI if abnormal at presentation
- Advise on the need for contraception for 12 months
- Advise re avoidance of excess sunlight exposure
- Outline the risk of relapse

All patients have routine hCG marker follow-up for life. [2]

6.2.Post treatment hCG follow-up as stated by Charing Cross Hospital [2]

Year 1	→	2-weekly serum and urine hCG for 1 – 6 months
		2 weekly urine hCG for 7-12 months
Year 2	→	4 weekly urine hCG
Year 3	→	8 weekly urine hCG
Year 4	→	3-monthly urine hCG
Year 5	→	4-monthly urine hCG
Year 6 – life	→	6-monthly urine hCG

Note: hCG levels should also be taken 6 weeks after the delivery of any future pregnancy. [2\]

Women should be advised not to conceive until the hCG level has been normal for six months. (level C).

GTD Chemotherapy Protocol【Primary】

GTD-Low risk Methotrexate-FA

MTX	1mg/kg IM	d 1,3,5,7
Folinic acid	0.1mg/kg IM	d 2,4,6,8
qow		

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GTD-Low risk Actinomycin-D

Actinomycin-D	1.25 mg/m2 iv	d1
q2w		

Newlands ES, Bagshawe KD, Begent RH, Rustin GJ, Holden L. Results with the EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) regimen in high risk gestational trophoblastic tumours, 1979 to 1989. Br J Obstet Gynaecol. 1991 Jun;98(6):550-7.

GTD-High EMA/CO

Etoposide	100 mg/m2	d1
Actinomycin-D	0.5 mg	d1
MTX	100mg/m2 iv push	d1
MTX	200mg/m2 iv 12hrs	d1
Etoposide	100 mg/m2	d2
Actinomycin-D	0.5 mg	d2
Folinic acid	15 mg P.O q12h*4	d2
Cyclophophamide	60	d8

Newlands ES, Bagshawe KD, Begent RH, Rustin GJ, Holden L. Results with the EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) regimen in high risk gestational trophoblastic tumours, 1979 to 1989. Br J Obstet Gynaecol. 1991 Jun;98(6):550-7.

GTD Chemotherapy Protocol【Resistant】

GTD-Resistant EMA/PE

Etoposide	100 mg/m2	d1
Actinomycin-D	0.5 mg	d1
MTX	100mg/m2 iv push	d1
MTX	200mg/m2 iv 12hrs	d1
Etoposide	100 mg/m2	d2
Actinomycin-D	0.5 mg	d2
Folinic acid	15 mg P.O q12h*4	d2
Cisplatin	75~80 mg	d8

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四、安寧緩和照護原則

若預期疾病難以治癒時,病人存活期小於 6 個月便適合安寧療護(Pomeranz & Brustman, 2005；Waldrop & Rinfrette, 2009) 。若藉由症狀、檢驗數據、及確切的腫瘤診斷，證實臨床上該惡性腫瘤已經廣泛侵犯、或進展快速；功能分數（Palliative Performance Scale）低於 70%；拒絕進一步腫瘤治癒性治療，或者在治療之下仍持續惡化者，即可轉介緩和醫療團隊（彭等，2006）。

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