高 雄 榮 民 總 醫 院
生殖細胞瘤診療原則

2020年02月27日 第一版

兒童癌症醫療團隊擬訂

注意事項：這個診療原則主要作為醫師和其他保健專家診療癌症病人參考之用。假如你是一個癌症病人，直接引用這個診療原則並不恰當，只有你的醫師才能決定給你最恰當的治療。

修訂指引

- 本共識依下列參考資料制定版本
  - 台灣兒童癌症研究群(TPOG)
    MaGCT 2017 Protocol V1 (2017-07)

會議討論

上次會議：2019/02/26

本共識與上一版的差異

上一版	新版
1. 依據TPOG MaGCT-2017版本修訂生殖細胞瘤診療指引。	1. TPOG MaGCT-2017無新增或修改Potocol，故今年僅審視未修。

兒癌-生殖細胞瘤

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臨床診療指引　2020年第一版

◎前言

兒童顱外惡性生殖細胞瘤過去35年來因使用platinum-為基礎的化療療方治癒率有顯著進步。但即使平均治癒率達90%，仍有些病童發生在特殊部位，如前縱膈腔處，或有特殊病理組織情況，治癒率較低。platinum-為基礎的化療療方固然有效，但也產生了許多短期或長期的後遺症。兒童顱外惡性生殖細胞瘤的治療方案包括化療及外科治療，目前最新治療為根據3個風險等級(依據年紀、臨床分期、病理分型做分級)而有不同的治療方案。[1] 在台灣，需考慮我們國情和歐美國家不同，以及台灣本土的治療經驗，治療方案須調整，和歐美不完全一樣。

◎Patient Eligibility

All previously untreated patients < 18 years of age, diagnosed with extracranial malignant germ cell tumor (MaGCT) including immature teratoma, embryonal carcinoma, yolk-sac tumor, choriocarcinoma, dysgerminoma, and mixed germ cell tumor will be eligible.

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◎Pretreatment Evaluation

-Laboratory and Image evaluation

1. History, physical examination
2. Complete blood counts, blood group, PT/APTT
3. Biochemistry: GOT, GPT, albumin, Bilrubin (direct/total), BUN, creatinine, LDH, uric acid, P, alkaline phosphate, Na, K, Cl, Ca, glucose
4. Tumor markers: α-fetoprotein (AFP), β-human chorionic gonadotropin (β-HCG), CA-125
5. Chest x-ray, abdominal sonogram, brain CT scan, chest CT scan, abdominal CT scan, MRI, bone survey, whole body bone scan
6. Cytogenetic study for patient with mediastinal GCT (To rule out the Klinefelter's syndrome, which comprise 22% of mediastinal GCT)

◎Staging

Testis, Ovarian, and Extragonadal Children's Oncology Group (COG) Staging

A: Testis

Staging Criteria for testicular MaGCT

Stage	
I	Tumor confined to testis, complete resection: high inguinal or high ligation scrotal orchiectomy and negative nodes
II	Trans-scrotal biopsy, microscopic disease in scrotum or cord, or failure of tumor markers to normalize
III	Retroperitoneal lymph node involvement, but no visceral or extra-abdominal involvement
IV	Distant metastases, including liver

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◎Staging

Testis, Ovarian, and Extragonadal Children's Oncology Group (COG) Staging

B: Ovary

Staging Criteria for ovarian MaGCT

Stage	
I	Tumor confined to ovary (peritoneal evaluation should be negative), no clinical, histological, or radiographic evidence of disease outside ovary*
II	Microscopic residual, peritoneal evaluation negative, failure of serum tumor markers to normalize
III	Lymph node involvement, metastatic nodule, gross residual disease or biopsy only, contiguous visceral involvement (omentum, intestine, and bladder), peritoneal evaluation positive for malignancy
IV	Distant metastases, including liver

* The presence of gliomatosis peritonei does not result in a stage change.

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◎Staging

Testis, Ovarian, and Extragonadal Children's Oncology Group (COG) Staging

C: Extragonadal

Staging Criteria for extragonadal MaGCT

Stage	
I	Tumor confined to organ/site of origin, complete resection at any site with negative margins or coccygectomy for sacrococcygeal teratoma
II	Microscopic residual, with lymph nodes negative
III	Lymph node involvement, gross residual disease, or biopsy only
IV	Distant metastases, including liver

◎ Histopathologic Subtypes of Extracranial MaGCT

Subtype	Pathogenesis and histologic definitions
Immature teratoma	Display somatic differentiation. **Major histologic findings:** Usually neurogenic elements; mesodermal elements common; some tumors derived primarily of esophageal, liver and intestinal structures(endodermal) Norris grading system: based on proportion of tissue containing immature neuroepithelium G1: less than one lower power field (LPF) of immature neuroepithelium; LPF defined field at 4X magnification. G2: 1-3 LPFs G3: more than 3 LPFs **Immunohistochemistry:** Positive for Neuron-specific enolase (NSE), neuron-specific B tubulin, and synaptophysin

◎ Histopathologic Subtypes of Extracranial MaGCT

Subtype	Pathogenesis and histologic definitions
Embryonal carcinoma	Display embrionic differentiation. **Major histologic findings**: Sheets and nests of large primitive cells, occasional papillae and abortive glands. Syncytiotrophoblast-like tumor cells seen. **Immunohistochemistry:** Typically positive for placental alkaline phosphatase (PLAP), c-kit (CD117), keratins, CD30, NANOG, SOX2, and OCT3/4. Negative for AFP.

◎ Histopathologic Subtypes of Extracranial MaGCT

Subtype	Pathogenesis and histologic definitions
Yolk-sac tumor (YST)	Display extra-embrionic differentiation. **Major histologic findings**: Schiller-Duval body is pathognomonic - central blood vessel enveloped by germ cells within a space similarly lined by germ cells, resembles glomerulus. Hyaline droplets present. Mostly present as reticular/microcystic or polyvesicular vitelline patterns. **Immunohistochemistry**: positive for AFP, cytokeratin, and vimentin can be positive in spindle cell patterns. Approximately 40-80% of YSTs are positive for PLAP.

◎ Histopathologic Subtypes of Extracranial MaGCT

Subtype	Pathogenesis and histologic definitions
Choriocarcinoma	Display extra-embrionic trophoblastic differentiation. **Major histologic findings:** Composed of cytotrophoblast, intermediate trophopblast and multinucleated syncytiotrophoblast around periphery of blood channels. Cytotrophoblasts have clearly defined cytoplasmic borders, are mononucleated with vesicular nuclei and distinct nucleolus. Syncytiotrophoblasts contain basophilic to amphophilic cytoplasm with multiple nuclei. **Immunohistochemistry**: Syncytiotrophoblasts are positive for hCG, human placental lactogen (HPL), pregnancy-specific beta-1 glycoprotein (SP1), inhibin. Low–molecular-weight keratins such as Cam 5.2 are positive in both syncytiotrophoblasts and cytotrophoblasts. PLAP is positive in about 50% of choriocarcinomas, whereas CEA is positive in about 25%

◎ Histopathologic Subtypes of Extracranial MaGCT

Subtype	Pathogenesis and histologic definitions
Dysgerminoma (ovary)	Undifferentiated tumours that maintain pluripotency. **Major histologic findings**: Nests of tumor cells separated by fibrous stroma with T lymphocytes. Large vesicular cells with well defined cell borders, cleared cytoplasm containing glycogen and central nuclei. **Immunohistochemistry**: Positive for PLAP, c-kit (CD117), OCT 3/4, SALL4, and, variably, cytokeratin. Negative for epithelial membrane antigen (EMA), S100 protein, CD45 (LCA), or AFP.

◎ Histopathologic Subtypes of Extracranial MaGCT

Mixed	Pathogenesis and histologic definitions
Mixed germ cell tumor	Includes patients who had two of following histologies : teratoma, YST, embryonal carcinoma, or choriocarcinoma

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◎ Risk Groups Assignment

Risk		Age (yr)	Locations	Stage
Low	a	**<11**	**Testis**	**I**
	b	**≥ 11**	**Testis**	**I**
		Any	Ovary, extragonadal	I
Intermediate	a	**Any**	**Any**	**II**
	b	**<11**	**Testis, ovary**	**III, IV**
		≥ 11	Testis, ovary	III
		<11	Extragonadal	III
Poor		**≥ 11**	**Testis, ovary**	**IV**
		Any	Extragonadal	III, IV

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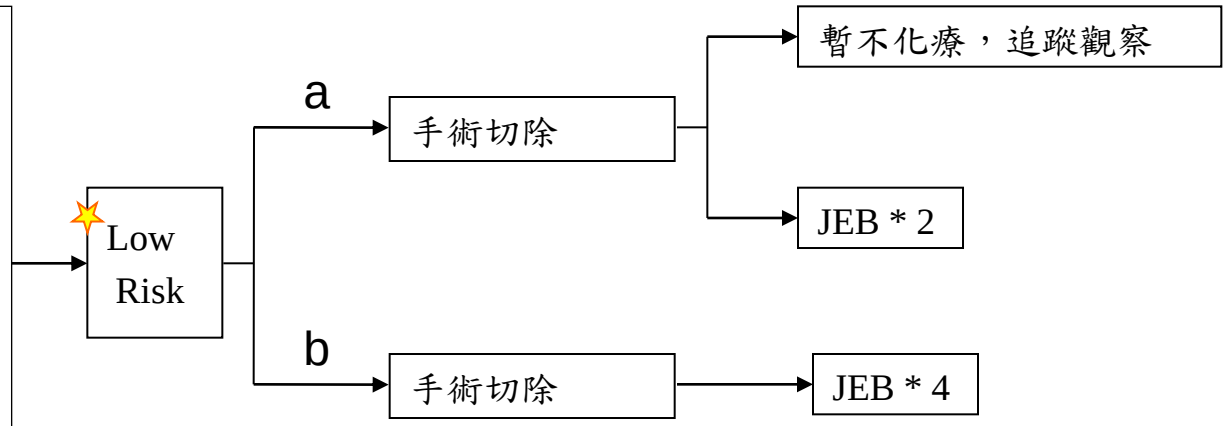
評估	診斷	治療	追蹤

•病史，理學檢查
•營養及日常體能狀態
•身高體重，體表面積
•血液常規
•電解質及肝腎功能
•凝血功能
•心臟/腹部超音波
•聽力檢查
•尿液檢查(24小時CCr)
•腫瘤指數AFP, β-HCG, CA-125
•腫瘤病理種類*
•骨頭掃描*
•腦部電腦斷層(CT)*
•胸部電腦斷層(CT)#
•腹部電腦斷層攝影(CT)* or 核磁共振檢查(MRI)*(擇一)
•染色體檢測(縱膈腔GCT需要)

*與癌症期別相關之主要檢查
#與癌症期別相關之次要檢查



詳見Risk groups assignment

※AFP, β-HCG(若為卵巢腫瘤加驗CA-125) Q1M*12 then Q3M*4 then Q6M
※ CBC, U/R, electrolytes Ca, Mg, IP, liver/renal function Q6M*4 then annually
※ WBBS Q3M*8 then Q6M*4 then annually
※ Sono/CT/MRI of original site Q3M*6 then Q6M*2 then annually

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評估	診斷	治療	追蹤

評估

- 病史，理學檢查
- 營養及日常體能狀態
- 身高體重，體表面積
- 血液常規
- 電解質及肝腎功能
- 凝血功能
- 心臟/腹部超音波
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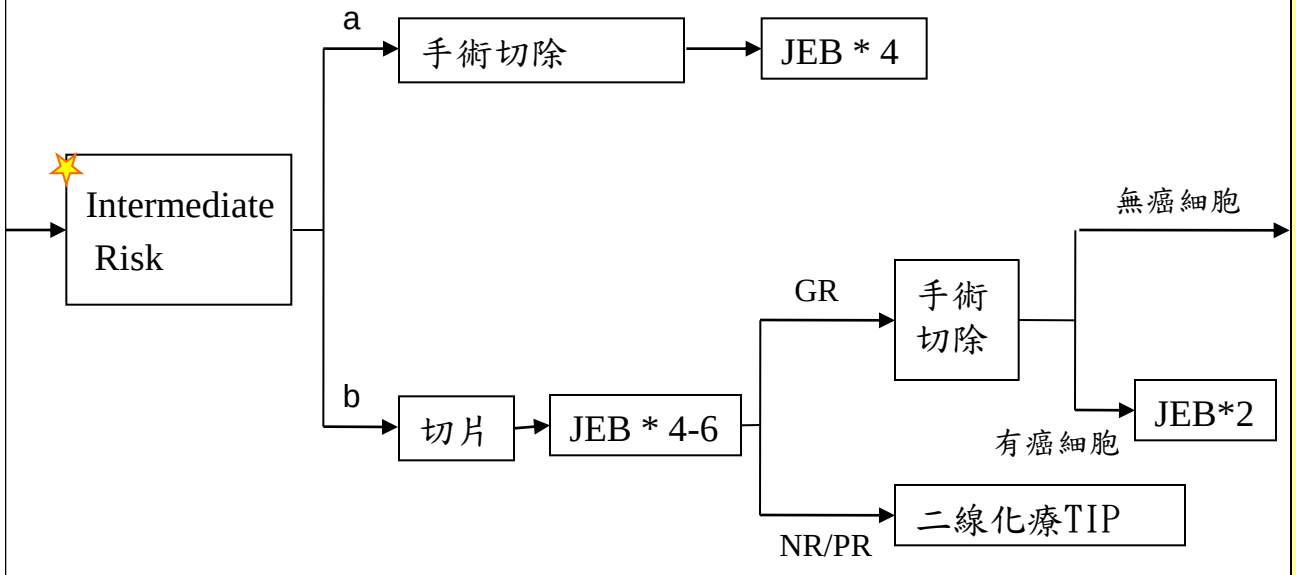
- 尿液檢查(24小時CCr)
- 腫瘤指數AFP, β-HCG, CA-125
- 腫瘤病理種類*
- 骨頭掃描*
- 腦部電腦斷層(CT)*
- 胸部電腦斷層(CT)#
- 腹部電腦斷層攝影(CT)* or 核磁共振檢查(MRI)*(擇一)
- 染色體檢測(縱膈腔GCT需要)

*與癌症期別相關之主要檢查
#與癌症期別相關之次要檢查

診斷 / 治療



詳見Risk groups assignment

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評估	診斷	治療	追蹤

- 病史，理學檢查
- 營養及日常體能狀態
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*與癌症期別相關之主要檢查
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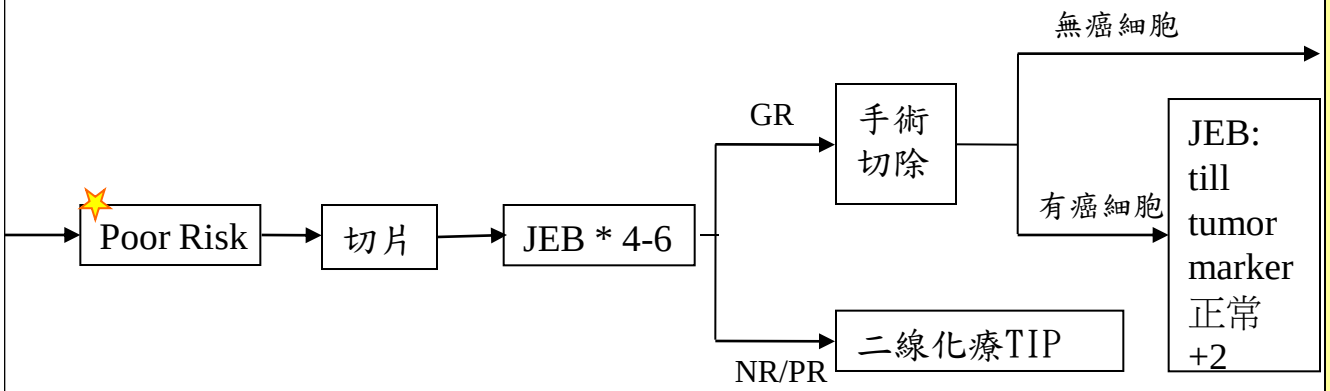

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◎ Surgery Principles for MaGCT

對於手術治療的原則，第1及第2期病童以手術完全切除為原則。第3及第4期病童，因腫瘤大或已擴散出去，若預期第1次手術時腫瘤不易完全切除，則應先以切片為主，先診斷，其後給予化學治療，待腫瘤縮小至容易完全切除後才予第2次手術。而primary vaginal, cervix, uterus 之MaGCT手術原則，需考量若將此處腫瘤完全切除，未來病童即喪失生育功能。因此，診斷時採切片方式，其後給予足夠的化療療程，待腫瘤標記降至正常值，影像追蹤剩殘餘腫瘤時，給予第2次手術。手術同樣採切片方式，意即second-look surgery，針對懷疑有殘餘腫瘤處採樣即可。而primary urinary及prostate MaGCT也盡可能採用相同手術及化療原則治療。目的為保護及維持病童重要器官功能，同時降低手術危險度，提高治癒率外能保有長期好的life quality。

◎ Treatment Programs

兒童顱外惡性生殖細胞瘤對JEB化療反應大多相當好，即使是第3期腫瘤，腫瘤標記在4-6次化療後多降低到正常範圍。同時，病童對JEB化療耐受性一般皆好，無cisplatin治療造成的短期或長期副作用。[7,12] 唯已經開始有月經的青少女在第一次化療前應開始每個月Leuprorelin的治療至化療完成止，以保護卵巢。所以，第3或4期腫瘤以化療先減少腫瘤體積，讓外科醫師在其後的手術較為容易，既可以減少手術風險同時提高治癒率。對於primary vaginal, cervix, uterus, urinary bladder, prostate MaGCT治療設計也是我們的特點，診斷及化療後的評估皆採切片，以減少大手術傷害到重要的生殖泌尿器官功能，同時必須給予足夠療程化療，確保好的治癒率。TPOG MaGCT 2017 protocol詳見以下治療方案說明。

◎ Treatment Programs

- Frontline chemotherapy: JEB

TPOG MaGCT-2017 JEB Protocol

1. **Carboplatin: 600 mg/m2, iv infusion >1 hour, day 2**
2. **Etoposide: 120 mg/m2, iv infusion >2 hours, days 1, 2, 3**
3. **Bleomycin: 15 mg/m2, iv infusion 15 minutes, day 3**

Cycle: every 3 weeks

Cumulative dosage of JEB

Cumulative Dosage of JEB (mg/m2)			
Courses	Carboplatin	VP-16	Bleomycin
4	2,400	1,440	60
6	3600	2160	90
8	4800	2880	120

◎ Treatment Programs :Frontline chemotherapy: JEB

Notes:

-Hb >8 g/dL, ANC >1,000/ mm3, platelet >75,000/ mm3, and renal function is normal, chemotherapy will be started.

-G-CSF administer for hematopoietic recovery.

-IV fluid: 2,000cc/m2 during chemotherapy.

-Etoposide should be diluted in D5W prior to administration, and solutions with a final concentration of 0.4mg/ml are stable at room temperature for 24 hours. Avoid rapid infusions to prevent hypotension and anaphylaxis reactions.

-Acetaminophen for 1-2 days to prevent high fever induced by bleomycin; the 1st dose of acetaminophen will be started before bleomycin.

- For age < 1yr, dosage will be given according to body weight: carboplatin: 20mg/kg on D2, etoposide: 4 mg/kg on D1-3, bleomycin 0.5mg/kg on D3.

-The maximum BSA will be 2 m2

-Enough antiemetic during chemotherapy

-Leuprorelin injection will be recommended for girls have had menstrual cycle and started before the first JEB course and then monthly till completion of chemotherapy

◎ Treatment Programs

兒童immature teratoma一般使用化療效果不佳。但若腫瘤標記高者，則仍有可能為mixed MaGCT。[10] 所以，對於診斷為第3期GCT，腫瘤初切片為grade II or III immature teratoma且腫瘤標記高者，若預期能完全切除腫瘤則盡可能先手術切除，其後給予4次化療即完成治療；若腫瘤無法一次完全切除，或手術前評估手術時有很高的風險，則仍可考慮先化療，待2-4次化療後才評估完全切除手術。術後腫瘤標記持續下降，再給予2次化療即完成治療。至於第3期 grade I immature teratoma及第3期 grade II or III immature teratoma且腫瘤標記不高者，原則上不化療，以手術治療為主。

◎ Treatment Programs

化學治療成績以英國UKCCSG發表：使用JEB (Carboplatin, etoposide, bleomycin) protocol治療，5年治癒率為90.9%最佳。 其他如美國POG及CCG發表使用PEB protocol，法國TGM85及90 protocols，德國MAKEI protocols，5年治癒率約80-90%。使用JEB protocol治療的孩童，化療中病童的合併症較少，治癒率更高。因此， TPOG MaGCT 2017 protocol 採用JEB protocol為第一線化學治療。

對於refractory或relapse的個案，近來美國COG以TIGER作為relapse個案salvage治療。[1]此一以platinum-為基礎的化療療方，加入病童過去未曾使用過的paclitaxel 及ifosphamide治療，對於不易治療的族群，文獻的報告2年PFS也有65%。[8]因此，TPOG MaGCT 2017 protocol 採用TIP protocol為第二線化學治療，治療refractory或relapse的個案。

◎ Treatment Programs

- Second-line chemotherapy: VIP

Cisplatin 20mg/m^2, IV infusion over 2 hours (for age < 1yr, 0.66mg/kg)	Day 1, 2, 3, 4, 5
Etoposide 75mg/m^2, IV infusion over 4 hours (for age < 1yr, 2.5mg/kg)	Day 1, 2, 3, 4, 5
Ifosphamide 1.2g/m^2, IV continue infusion 24 hours (for age < 1yr, 40mg/kg)	Day 1, 2, 3, 4, 5

Cycle: every 3 weeks

◎ Treatment Programs

- Second-line chemotherapy: TIP

TPOG MaGCT-2017 TIP Protocol

1. **Paclitaxel 250 mg/m2, administered by 24-hour continuous infusion on day 1**
2. **Ifosfamide 1,500 mg/m2, iv infusion >1hour, days 2, 3, 4, 5**
3. **Cisplatin 25 mg/m2, iv infusion > 30minutes, days 2, 3, 4, 5**

Cycle: every 3 weeks

Cumulative dosage of TIP

Cumulative Dosage of TIP (mg/m2)			
Courses	Paclitaxel	Ifosphamide	Cisplatin
2	500	12,000	200
3	750	18,000	300
4	1000	24,000	400

◎ Treatment Programs : Second-line chemotherapy:TIP

Notes:

-Hb >8 g/dL, ANC >1,000/ mm3, platelet >75,000/ mm3, and renal function is normal, chemotherapy will be started.

-G-CSF administer for hematopoietic recovery.

-Hydration with IV fluid: 2,400cc/m2 during chemotherapy.

-Dexamethasone, 14 and 7 hours, and diphenhydramine, 1 hour, intravenously before paclitaxel as pretreatment therapy for a total 5 days to avoid acute allergic reactions.

-To reduce neurotoxicity, vit B6 and gabapentin administer orally before paclitaxel.

- Mesna 500 mg/m2 is administered before the ifosfamide and at 4 and 8 hours after ifosfamide daily, for a total daily dose of mesna of 1,500 mg/m2

- For age < 1yr, dosage will be given according to body weight: paclitaxel: 8.33mg/kg administered by 24-hour continuous infusion on day 1, ifosphamide: 50 mg/kg on D2-5, cisplatin 0.833mg/kg on D2-5.

-The maximum BSA will be 2 m2

-Enough antiemetic during chemotherapy

-Leuprorelin injection will be recommended for girls have had menstrual cycle and started before the first JEB course and then monthly till completion of chemotherapy

兒癌- 生殖細胞瘤

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◎ Stratification of Treatment by MaGCT risk groups

Risk		Steps of treatment, including courses of chemotherapy and surgery principles
Low	a	1.Complete excision of primary tumor 2.No chemotherapy v.s. chemotherapy (JEB×2)
	b	1.Complete excision of primary tumor 2.Chemotherapy with JEB×4

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◎ Stratification of Treatment by MaGCT risk groups

Risk		Steps of treatment, including courses of chemotherapy and surgery principles
Intermediate	**a**	**1.**Complete excision of primary tumor **2.**Chemotherapy with JEB×4
	b	**1.** Biopsy for diagnosis **2.** Chemotherapy with JEB×4-6 till primary tumor can be complete resection + tumor makers continuing drop and near normalization *Patient with no response (NR) or progressive disease (PD) will receive second-line chemotherapy: TIP **Patients have very good response, esp. tumor makers return to normal , after JEB×3 can receive interval debulking surgery after 3 courses of chemotherapy **3.**Interval debulking surgery with complete excision of residual tumor **4.**Post-surgery chemotherapy: based on the pathologic results **a.**No malignancy, courses of chemotherapy: till tumor markers normalization +2 courses (Max: 2 courses) **b.**Malignancy present: 2 courses of chemotherapy

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◎ Stratification of Treatment by MaGCT risk groups

Risk	Steps of treatment, including courses of chemotherapy and surgery principles
Notes:	For primary vaginal, cervix, uterus, urinary bladder, prostate MaGCT **1.** Biopsy for diagnosis **2.** Chemotherapy with JEB×4-6 till only minimal suspected residual tumor left in the site of primary tumor and tumor makers return to normal *Patients have very good response, esp. tumor makers return to normal , after JEB×3 can receive second-look surgery (with biopsy) after 3 courses of chemotherapy **3.** Second-look surgery (with biopsy) of suspected residues **4.** Post-surgery chemotherapy: based on the pathologic results **a.** No malignancy, courses of chemotherapy: till tumor markers normalization +2 courses (Max: 2 courses) **b.** Malignancy present: 2 courses of chemotherapy

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◎ Stratification of Treatment by MaGCT risk groups

Risk	Steps of treatment, including courses of chemotherapy and surgery principles
Poor	**1.** Biopsy for diagnosis **2.** Chemotherapy with JEB×4-6 till primary tumor can be complete resection + tumor makers continuing drop and near normalization *Patient with no response (NR) or progressive disease (PD) will receive second-line chemotherapy: TIP **3.** Interval debulking surgery with complete excision of residual tumor **4.** Post-surgery chemotherapy: based on the pathologic results and image evaluation of metastases tumor **a.** No malignancy, courses of chemotherapy: till tumor markers normalization +2 courses (Max: 2 courses) **b.** Malignancy present, courses of chemotherapy: till tumor markers normalization +2 courses **c.** Surgical excision for metastases tumor if continuing image (+)

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◎ Surgery Principles for MaGCT

Stage	Sites	Principles
I, II	Any	Completely surgical excision after initial diagnosis.
I, II	Testis	Radical inguinal orchidectomy with high ligation of the spermatic cord. Avoid trans-scrotal biopsy and surgery.
I, II	Ovary	Peritoneal evaluation should be negative.
Any	Sacrococcygeal	Coccygectomy should be performed.
II, III	Any	Regional lymph nodes should be evaluated during operation.
III, IV	Any	1. For primary tumor, **biopsy only for diagnosis** and interval debulking surgery after chemotherapy to prevent major morbidity. 2. For residual tumor after chemotherapy, an interval debulking surgery **with complete resection** will be recommended.
Any	Special*	1. For primary tumor, **biopsy only for diagnosis** and a second-look surgery after chemotherapy to prevent major morbidity 2. For minimal suspected residues after chemotherapy and tumor makers return to normal, a second-look surgery **with biopsy** will be recommend.

*: Primary vaginal, cervix, uterus, urinary bladder, prostate sites

◎ Special Consideration For Treatment

-Immature Teratoma

1. Patients with pure immature teratoma without elevation of tumor makers will receive complete excision as possible as.
2. Patients with pure grade I immature teratoma with elevation of tumor makers will receive complete excision as possible as. Chemotherapy will not be administered after surgery.
3. Patients with grade II or III immature teratoma with elevated tumor makers will receive the following strategy:
   a.For stage I, complete excision of tumor only
   b.For stage II, complete excision of tumor and then post-surgery chemotherapy with JEB×2 cycles.
   c. For stage III, complete excision without major morbidity can be performed, surgery first and post-surgery chemotherapy with JEB×2-4 cycles (till tumor markers normalization +2 cycles).
   d.For stage III with bulky primary tumor, complete excision without major morbidity can not be performed, patients will receive initial biopsy following 2-4 cycles of JEB chemotherapy. Interval debulking surgery (with complete excision) will be offered once partial response is achieved. Post-surgery JEB cycles: tumor markers normalization +2 cycles.

◎ Special Consideration For Treatment

- Pulmonary and Hepatic Metastases at Diagnosis

1. Patients with pulmonary or hepatic metastases will receive chemotherapy first.
2. Give Chest or abdominal CT scan evaluation after tumor makers return to normal.
3. If pulmonary or hepatic metastases disappeared after chemotherapy, no further surgery is needed
4. Patients with pulmonary or hepatic metastases that do not respond to chemotherapy entirely will receive surgically removable of metastases tumors.

- Treatment Plans for Refractory Disease or Relapse

1.Patients with refractory or relapsed MaGCT will receive chemotherapy with TIP.
2.Patients continue to have no response or progressive disease after TIP, high-dose chemotherapy and stem-cell rescue might be considered.[13,14]

◎ Evaluation of Treatment Response

-Tumor makers and imaging evaluation

(1) Tumor makers weekly
(2) Abdominal sonogram or chest X ray according to primary site of tumor, monthly
(3) CT scan (chest or abdomen according to primary site of tumor) will be arranged prior to the interval debulking or second-look surgery (3D reconstruction before for surgery is recommended)

-Definition of treatment response:

(1)Complete remission (CR): normalization of tumor markers and resolution of all imaging abnormalities
(2)Partial response (PR): residual imaging abnormalities (> 50% decrease) at either the primary or metastatic sites and/or declining markers
(3)No response (NR): < 50% decrease in size on imaging studies and unchanged or persistent marker elevation
(4)Progressive disease (PD): > 25% increase in size, new lesions, or increasing tumor markers

◎Drop off criteria

1. Incorrect diagnosis
2. Patient and/or parents refuse to allow additional therapy
3. A patient who, in the judgment of the Principal Investigator, could not or did not follow the assigned treatment, may be removed from study
4. Patients who fail to meet all eligibility requirements of protocol (i.e., ineligible) will be taken off study, e.g., using other protocols, or not newly diagnosed patients

◎癌症藥物停藥準則

影像學檢查，腫瘤有復發或變大情況，應停止或改變治療方式。

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