

高雄榮民總醫院

下咽癌診療原則

2021年04月28日第一版

頭頸癌醫療團隊擬訂

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。

會議討論

上次會議： 2020/04/29

本共識與上一版的差異

上一版	新版
<ol style="list-style-type: none">1. Survey時可加上panendoscopy、Chest CT及戒菸。2. 後續追蹤時加驗TSH、free T4。3. Chemoselection的病患，若complete response後續RT(category 1) or CRT。4. 在Recurrent, unresectable, metastatic的化療Regimen提升immunotherapy順序，並加入合併使用化療的選項。	<ol style="list-style-type: none">1. Workup中的Multidisciplinary consultation 加上會診項目Fertility/reproductive, smoking cessation2. Workup增加± Pulmonary function if conservation surgery3. Follow-up的every year，增加PES4. [Recurrent, unresectable, metastatic]化療 regimen，把immunotherapy順序往前調升，將EXTREME Regimen順序後移。5. M1的部分，PS 2、PS 3增加Palliative RT 或palliative surgery。

Hypopharyngeal cancer

Clinical staging AJCC 8th

Hypopharyngeal cancer TNM clinical staging AJCC UICC 2017

Primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
Tis	Carcinoma <i>in situ</i>
T1	Tumor limited to one subsite of hypopharynx and/or 2 cm or smaller in greatest dimension
T2	Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures larger than 2 cm but not larger than 4 cm in greatest dimension without fixation of hemilarynx
T3	Tumor larger than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus
T4	Moderately advanced and very advanced local disease
T4a	Moderately advanced local disease. Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue.*
T4b	Very advanced local disease. Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures.
* NOTE: Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.	
Regional lymph nodes (N)	
Clinical N (cN) – Oropharynx (p16–) and hypopharynx	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); or Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); or In bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); or Metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-)
N3b	Metastasis in any node(s) and clinically overt ENE(+)
NOTE: A designation of "U" or "L" may be used for any N category to indicate metastasis above	

the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(-) or ENE(+).			
Distant metastasis (M)			
Oropharynx (p16–) and hypopharynx			
M category	M criteria		
M0	No distant metastasis		
M1	Distant metastasis		
Prognostic stage groups			
When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1, T2, T3	N1	M0	III
T4a	N0, N1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; ENE: extranodal extension.

Hypopharyngeal cancer

Pathological staging AJCC 8th

Hypopharyngeal cancer TNM pathologic staging AJCC UICC 2017

Primary tumor (T)	
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T4	Moderately advanced and very advanced local disease
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N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); or Larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); or Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); or In bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-)
N2a	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); or A single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2c	Metastasis in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); or In a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or

N3a	Multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+); or A single contralateral node 3 cm or smaller and ENE(+)		
N3b	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); or Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or Multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+); or A single contralateral node 3 cm or smaller and ENE(+)		
NOTE: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(-) or ENE(+).			
Distant metastasis (M)			
Oropharynx (p16–) and hypopharynx			
M category	M criteria		
M0	No distant metastasis		
M1	Distant metastasis		
Prognostic stage groups			
When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1, T2, T3	N1	M0	III
T4a	N0, N1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; ENE: extranodal extension.

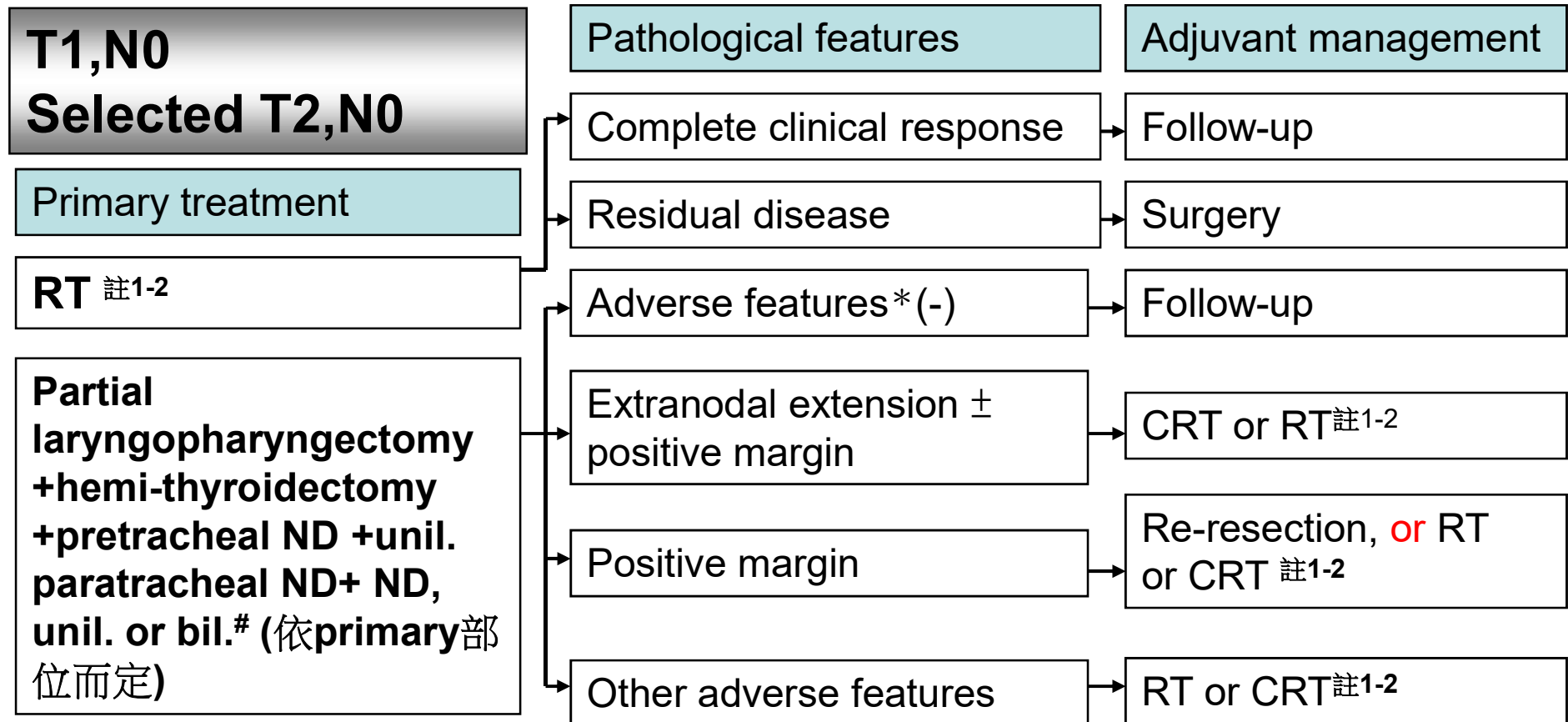
Carcinoma of Hypopharynx

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WORK-UP	STAGING & TREATMENT	FOLLOW-UP
<ul style="list-style-type: none">• History & PE• Biopsy & Pathology• Image<ul style="list-style-type: none">→ MRI*or CT of H&N* or PET→ WBBS* (if PET/CT not done)/ Abd.Sono*/CXR*→ PES→ ± Chest CT(upper med.) (*if PET/CT not done)→ ± Neck sono• Dental evaluation<ul style="list-style-type: none">→ Panorex ± teeth extraction• Multidisciplinary consultation (Fertility/reproductive, smoking cessation)± Swallowing/speech• ± p16 status• ± Pulmonary function if conservation surgery <p>(* 期別之相關之主要檢查)</p>	<ul style="list-style-type: none">• <u>[T1, N0 or Selected T2, N0, M0]</u> 詳見 Page 2• <u>[T2-3, any N; T1, N1-3, M0]</u> 詳見 Page 3• <u>[T4a, any N, M0]</u> 詳見 Page 4• <u>[T4b, any N, M0 or Inoperable status]</u> 詳見 Page 5• <u>M1</u> 詳見 Page 6	<ul style="list-style-type: none">• <u>[Post-Tx within 3-6 months]</u><ul style="list-style-type: none">→ Baseline MRI or CT (PET)→ Every 1-2 months: PE• <u>[2nd year after Tx]</u><ul style="list-style-type: none">→ Every 2-3 months: PE• <u>[3-5 years after Tx]</u><ul style="list-style-type: none">→ Every 4-8 months: PE• <u>[5 years after Tx]</u><ul style="list-style-type: none">→ Every 12 months: PE• Every year: H & N MRI or CT, CxR, Bone scan & Abd. Sono, Neck Sono, PES, TSH, free T4(if RT, 6-12 months) As clinically indicated

Carcinoma of Hypopharynx

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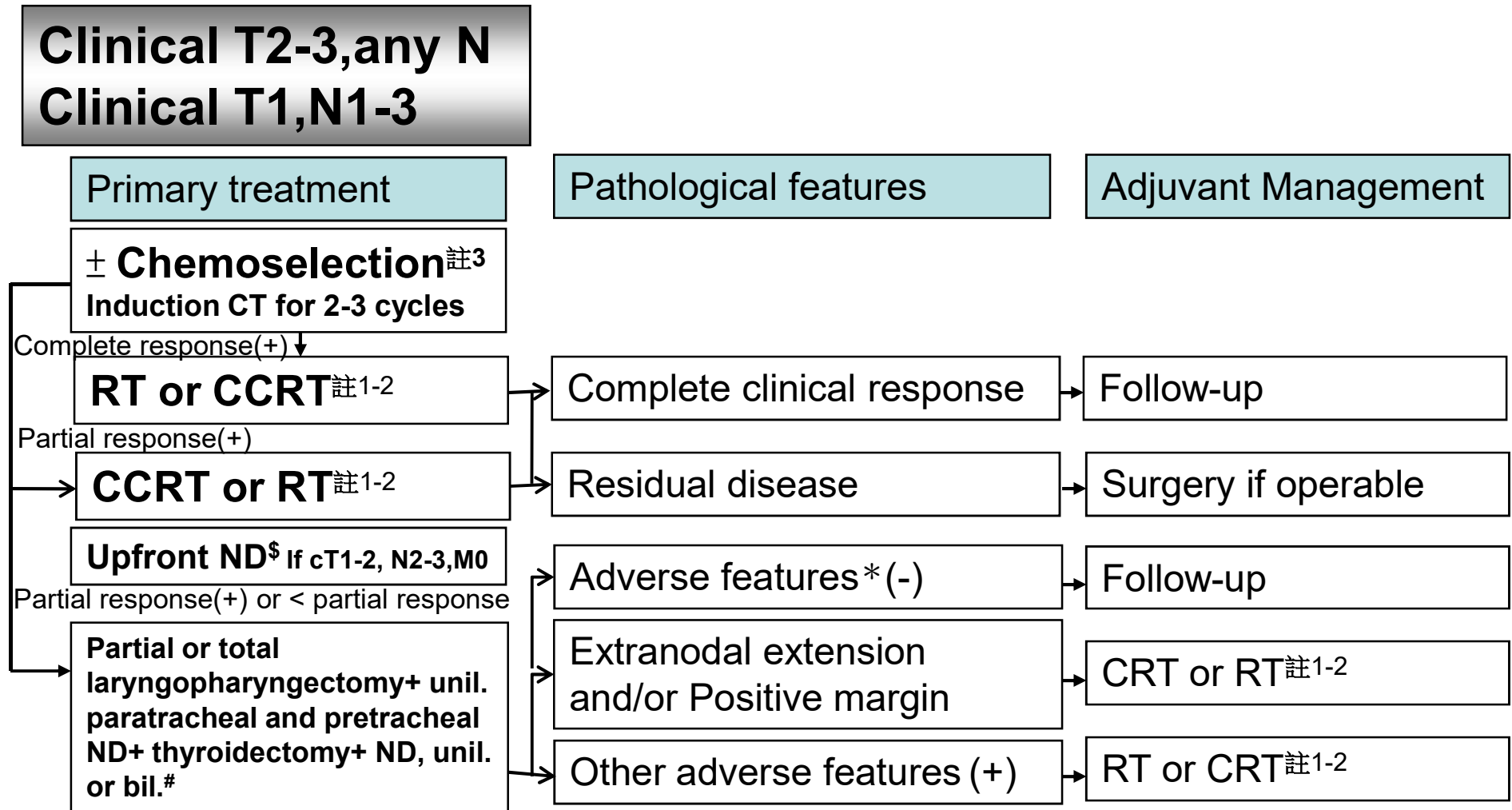


Bilateral ND was suggested if the primary site is the posterior pharyngeal wall or the postcricoid area.

* Adverse features : Extranodal extension, positive or close margins, pT3 or pT4 primary, pN2 or pN3 nodal disease, perineural invasion, lymphovascular invasion

Carcinoma of Hypopharynx

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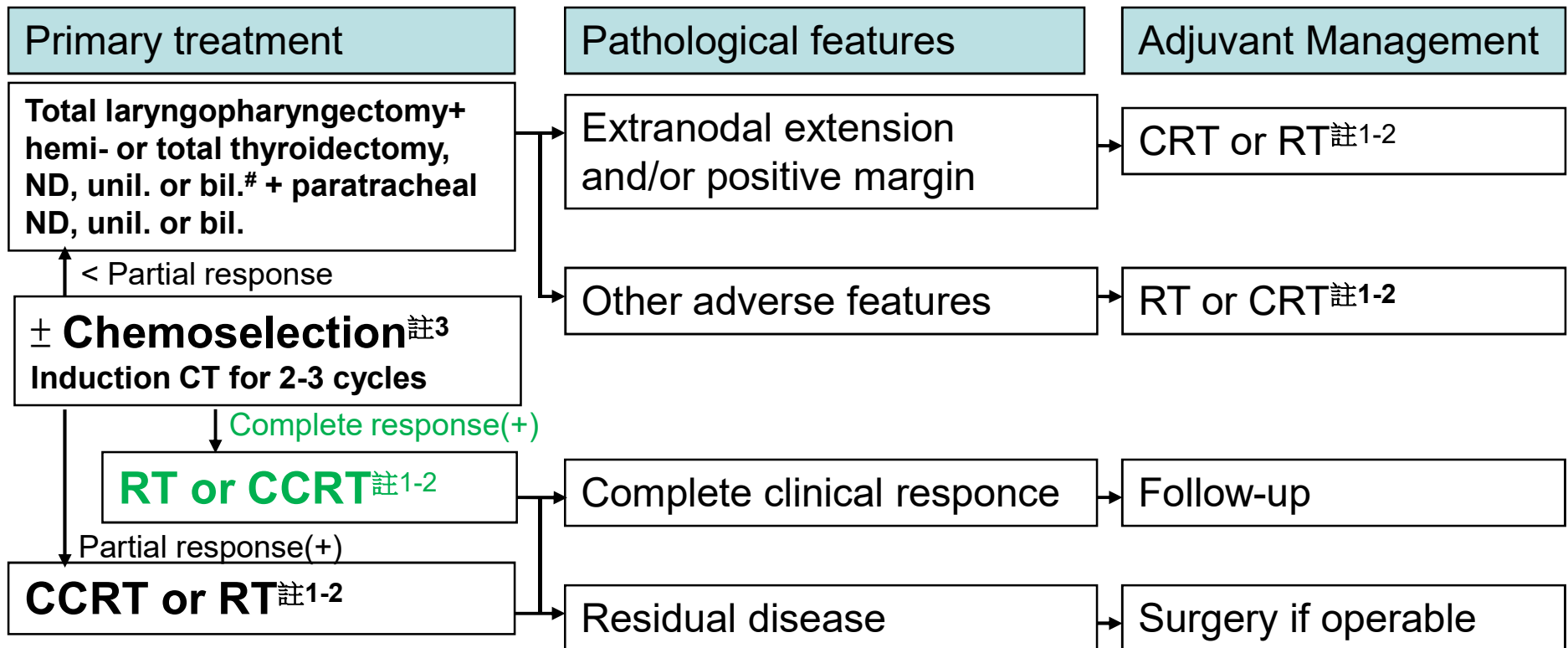
Bilateral ND was suggested if the primary site is the posterior pharyngeal wall or the postcricoid area.

* Adverse features : Extranodal extension, positive or close margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, lymphovascular invasion

Carcinoma of Hypopharynx

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Clinical T4a, any N
Resectable T4b, any N

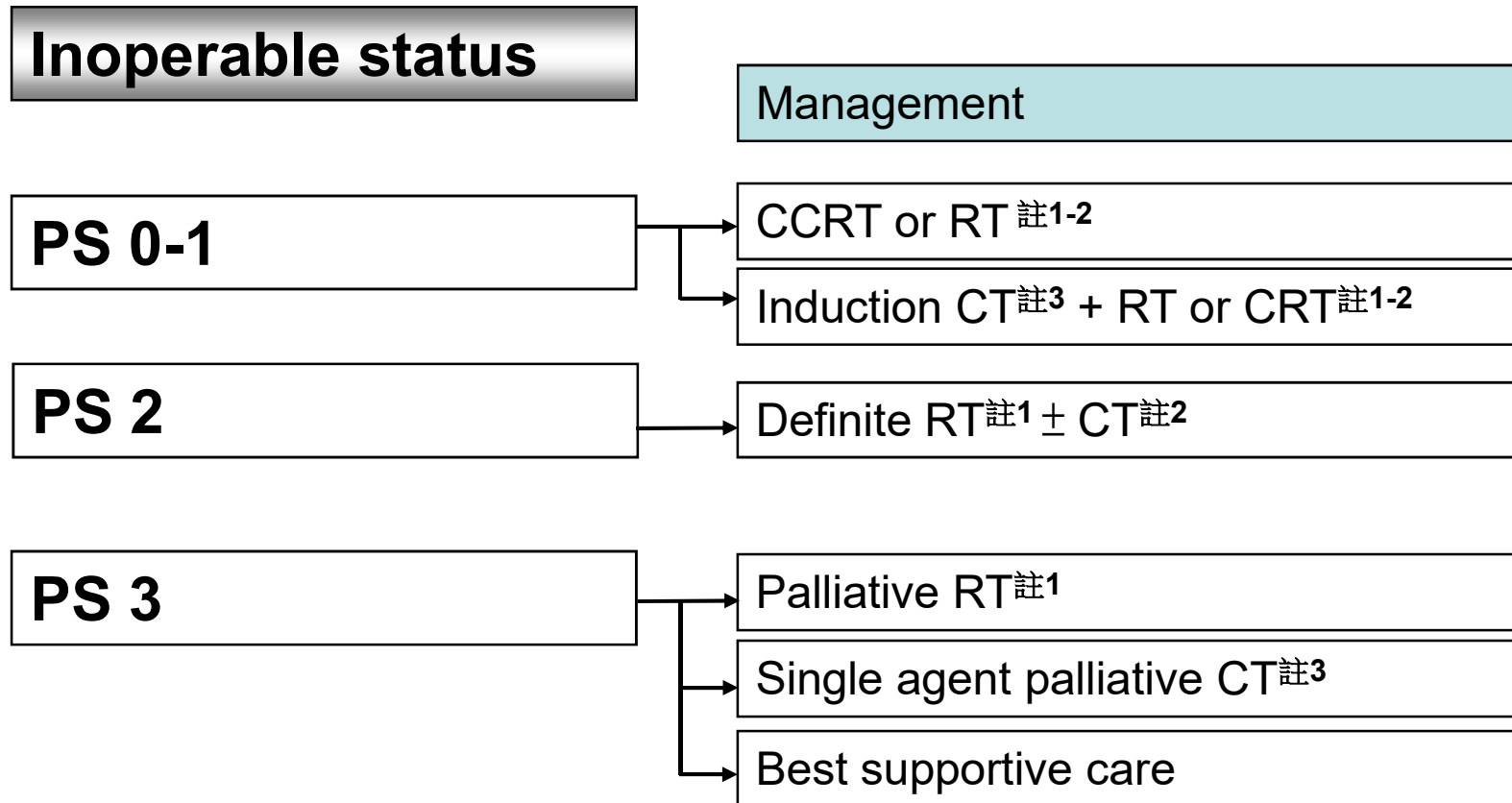


Neck dissection level 依primary部位及cN status而定。

* Adverse features : Extranodal extension, positive or close margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, lymphovascular invasion

Carcinoma of Hypopharynx

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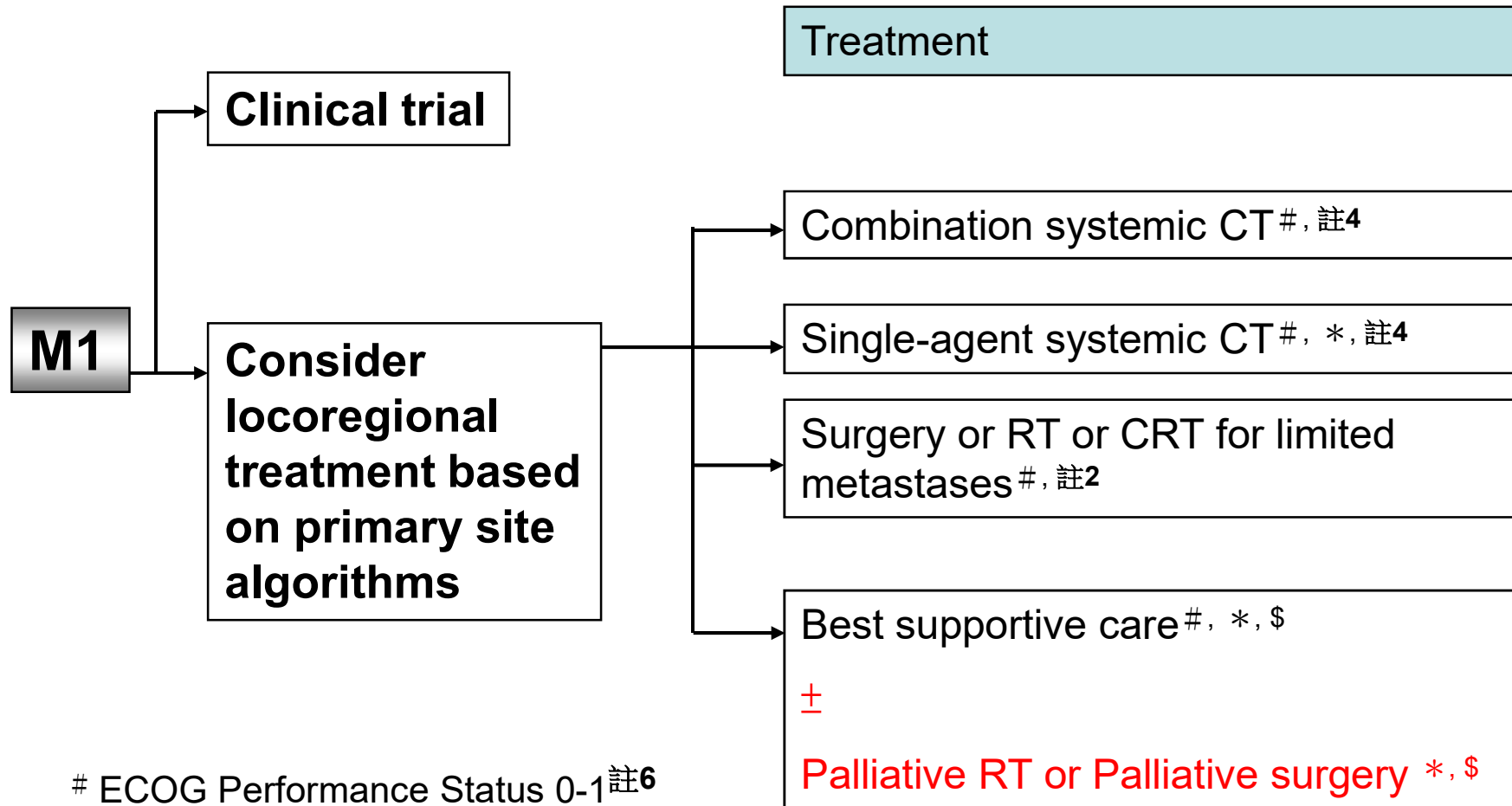
ECOG Performance Status 0-1^{註6}

ECOG Performance Status 2

ECOG Performance Status 3

Carcinoma of Hypopharynx

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ECOG Performance Status 0-1 註6

* ECOG Performance Status 2

\$ ECOG Performance Status 3

Carcinoma of Hypopharynx

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註1

Principles of Radiotherapy

Definitive Radiotherapy

- Primary and gross adenopathy : 66 - 74Gy (2.0-2.2 Gy/fraction)
- Low to intermediate risk : 44 - 64 Gy (2.0 Gy/fractions) in 3D RT, 54- 63 Gy (1.6-1.8 Gy/fractions)

Postoperative Radiotherapy

- Preferred interval between operation and radiotherapy is ≤ 6 weeks.
- High risk(adverse feature) : 60 - 66 Gy (2.0 Gy/fraction)
- Low to intermediate risk : 44 - 64 Gy (2.0 Gy/fractions) in 3D RT, 54- 63 Gy (1.6-1.8 Gy/fractions)

CCRT or RT

- RT alone if old age, impaired renal function, poor condition or refused chemotherapy

Palliative RT

- Indicated in : relieve local symptoms, prevent debilitation such as spinal cord compression and pathological fracture, achieve durable locoregional control.

Carcinoma of Hypopharynx

註2 高雄榮民總醫院 臨床診療指引 Ver.1 修訂於 2021.04.28 Page 8 (Ref. 6-10)

Principles of Chemotherapy

Concurrent with RT

Regimen 1 : q3w CDDP ± Cetuximab^{註5} + RT

- Cisplatin (80-100mg/ m²) q3w during R/T
- Cetuximab(400mg/ m²) loading dose first week, then Cetuximab(250mg/ m²) maintain dose D1 + Cisplatin (80-100mg/ m²) q3w D2 during R/T

Regimen 2: Weekly CDDP ± Cetuximab^{註5} + RT

- Cisplatin (30-40mg/ m²) weekly during R/T
- Cetuximab(400mg/ m²) loading dose first week, and then Cisplatin (30-40mg/ m²) weekly D1 + Cetuximab(250mg/ m²) maintain dose D2 during R/T

Regimen 3: q3w Carboplatin^{註5} ± Cetuximab^{註5} + RT

- Carboplatin (AUC x 5mg) q3w during R/T
- Cetuximab(400mg/ m²) loading dose first week, then Cetuximab(250mg/ m²) maintain dose D1 + Carboplatin (AUC x 5mg) q3w D2 during R/T

Regimen 4: Weekly Cetuximab^{註5} + RT

- Cetuximab(400mg/ m²) loading dose first week, then Cetuximab(250mg/ m²) maintain dose during RT

Regimen5 : Carboplatin + 5-FU + Hydroxyurea (CCr < 60) + RT

- Carboplatin (AUC x 1.25mg) D1-D4
- Fluorouracil (5-FU) (850mg/m²) D1-D4
- Hydroxyurea 1CAP BID D1-D5

Regimen6 : Cisplatin + 5-FU + Hydroxyurea + RT

- Cisplatin(20mg/ m²) D1-D4
- Fluorouracil (5-FU) (850mg/m²) D1-D4
- Hydroxyurea 1CAP BID D1-D5

Carcinoma of Hypopharynx

註3

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Regimens of Chemotherapy

Induction, adjuvant, 建議2-3cycles

Regimen 1 : q3-4 weeks T^{註5} + P ± F ± weekly Cetuximab^{註5}

- Taxotere(60 mg/ m²) D1
- Cisplatin(60-75 mg/ m²) D1
- Fluorouracil (5-FU) (600-750mg/m²) D2-D5
- Cetuximab (400mg/ m²) loading dose first week, then Cetuximab (250mg/ m²) maintain dose

Regimen 2: q3-4 weeks Platinum ± F ± weekly Cetuximab^{註5}

- Cisplatin(80-100mg/ m²) D1 or Cisplatin (20mg/ m²) D1-D5 or Carboplatin (AUC x 5mg) D1
- Fluorouracil (5-FU) (600-1000mg/m²) D2-D5
- Cetuximab(400mg/m²) loading dose first week, then weekly Cetuximab (250mg/ m²)

Carcinoma of Hypopharynx

註3

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Regimens of Chemotherapy

Induction, adjuvant, 建議2-3cycles

Regimen 3: weekly Cetuximab^{註5}

- Cetuximab (400mg/ m²) loading dose first week, then Cetuximab (250mg/ m²) maintain dose

Regimen 4: oral Fluorouracil

- Ufur cap (tegafur 100mg+uracil 224mg) 2# BID-TID
(Salvage or palliative CT中作為取代iv-formed 5-FU之替代藥物)

Regimen 5: weekly Methotrexate

- Methotrexate (40-60mg/ m²)

Carcinoma of Hypopharynx

註4

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Regimens of Chemotherapy

Recurrent, unresectable, metastatic

Regimen 1 (First line): q3 weeks Pembrolizumab^{註5} ± Platinum ± F

- Pembrolizumab(200mg) D1 (if CPS \geq 1)
- Cisplatin(80-100mg/m²) D1 or Cisplatin (20mg/ m²) D1-D5 or Carboplatin (AUC x 5mg) D1
- Fluorouracil (5-FU) (600-1000 mg/m²) D2-D5

Regimen 2 (First line): q3 weeks Pembrolizumab^{註5}

- Pembrolizumab(200mg) D1 (if CPS \geq 1)

Regimen 3 (Subsequent line): q2 weeks Nivolumab^{註5}

- Nivolumab(3mg/kg) D1

Regimen 4 (Subsequent line): q3 weeks Pembrolizumab^{註5}

- Pembrolizumab(200mg) D1 (if disease progression on or after platinum therapy)

Regimen 5: q3-4 weeks Platinum ± F ± weekly Cetuximab^{註5}

- Cisplatin(80-100mg/ m²) D1 or Cisplatin (20mg/ m²) D1-D5 or Carboplatin (AUC x 5mg) D1
- Fluorouracil (5-FU) (600-1000 mg/m²) D2-D5
- Cetuximab(400mg/ m²) loading dose first week, then weekly Cetuximab (250mg/ m²)

Carcinoma of Hypopharynx

註4 高雄榮民總醫院 臨床診療指引 Ver.1 修訂於 2021.04.28 Page 12 (Ref. 16,17)

Regimens of Chemotherapy

Recurrent, unresectable, metastatic

Regimen 6: q3-4 weeks T ± Platinum ± weekly Cetuximab^{註5}

- Taxotere(60 mg/ m²) D1
- Cisplatin(60-75 mg/ m²) D1 or Carboplatin (AUC x 5mg) D1
- Cetuximab(400mg/ m²) loading dose first week, then weekly Cetuximab (250mg/ m²)

Regimen 7: cisplatin+ epirubicin+ 5-FU+ Leucovorin

- Cisplatin (60 mg/ m²) D1
- Epirubicin (50 mg/ m²) D1
- Fluorouracil (5-FU) (2000 mg/m²) D1

Regimen 8: q2 weeks Bevacizumab

- Bevacizumab (200 mg/ m²) D1

Regimen 9: weekly Gemcitabine

- Gemcitabine (1000 mg/m²) D1

Carcinoma of Hypopharynx

註5

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特殊用藥健保給付規定

Taxotere

- 頭頸部癌，限局部晚期且無遠端轉移之頭頸部鱗狀細胞癌且無法手術切除者。
- 與Cisplatin 及5-FU 併用，作為放射治療前的引導治療，限使用四個療程。

Cetuximab

- 限與放射線療法合併使用於局部晚期之口咽癌、下咽癌及喉癌患者，使用總療程以接受8次輸注為上限，需經事前審查核准後使用，且符合下列條件之一：
 - 1.年齡 ≥ 70 歲
 - 2.Ccr < 50 ml/min
 - 3.聽力障礙者 (聽力障礙定義為500Hz、1000Hz、2000Hz 平均聽力損失大於25 分貝)
 - 4.無法耐受platinum-based 化學治療
- 限無法接受局部治療之復發及/或轉移性頭頸部鱗狀細胞癌，且未曾申報 cetuximab 之病患使用。使用總療程以18週為限，每9週申請一次，需無疾病惡化情形方得繼續使用。

Carboplatin

- 限腎功能不佳 (CCr < 60) 或曾作單側或以上腎切除之惡性腫瘤患者使用。

Carcinoma of Hypopharynx

註5

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特殊用藥健保給付規定

Pembrolizumab、Nivolumab

• 先前已使用過 platinum 類化學治療失敗後，又有疾病惡化的復發或轉移性頭頸部鱗狀細胞癌成人患者。本類藥品與 cetuximab 僅能擇一使用，且治療失敗時不可互換。

• 符合下列條件：

1. 病人身體狀況良好(ECOG \leq 1)
2. NYHA (the New York Heart Association) Functional Class I 或 II
3. GOT $<$ 60U/L及GPT $<$ 60U/L，且T-bilirubin $<$ 1.5mg/dL；Creatinine $<$ 1.5mg/dL，且 eGFR $>$ 60mL/min/1.73m²
4. PD-L1 表現量 TPS \geq 50%

• 初次申請以12 週為限，申請時需檢附以下資料：病理或細胞檢查報告、生物標記(PD-L1)表現量檢測報告、病人身體狀況良好(ECOG \leq 1)及心肺與肝腎功能之評估資料、符合 i-RECIST 定義之影像檢查及報告(上述影像檢查之給付範圍不包括PET)、先前已接受過之治療與完整用藥資料、使用免疫檢查點抑制劑之治療計畫(treatment protocol)。

• 用藥後每 12 週評估一次，以 i-RECIST 或 mRECIST 標準評定反應，依下列原則給付：

- I. 有療效反應者(PR 及 CR)得繼續使用；
- II. 出現疾病惡化(PD)或出現中、重度或危及生命之藥物不良反應時，應停止使用；
- III. 疾病呈穩定狀態者(SD)，可持續再用藥 4 週，並於 4 週後再次評估，經再次評估若為 PR、CR 者，得再繼續使用 12 週。若仍為 SD 或已 PD 者，應停止使用。

Carcinoma of Hypopharynx

註6

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Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description	Suggestion
0	Normal activity fully ambulatory (無症狀)	按照標準化療評估及療程。
1	Symptoms, but nearly fully ambulatory (有症狀，完全步行，但對生活無影響)	按照標準化療評估及療程。
2	Some bed time, but needs to be in bed less than 50% of normal daytime (躺在床上的時間<50%)	按照標準化療評估及療程。
3	Needs to be in bed more than 50% of normal daytime (躺在床上的時間>50%)	可視情況考慮停止化學治療。
4	Unable to get out of bed (長期完全臥床)	建議停止化學治療。
5	Dead	

Carcinoma of Hypopharynx

References

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