高雄榮民總醫院
喉癌診療原則

2023年04月19日 2023第一版

喉癌醫療團隊擬訂

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

上次會議日期:2022/5/11

本共識與上一版的差異

上一版	新版
1. NCCN 在Tumor survey的檢查項chest CT scan原本的備注建議advanced nodal disease to screen distant metastasis and for select patients who smoke to screen for lung cancer已刪除。 2. 在metastatic disease(M1)治療中，ECOG PS:0-1項目治療後仍惡化的病人，新增Palliative RT；PS:2項目治療後仍惡化的病人，新增Alternative single agent systemic therapy or palliative RT 。 3. 將high PS、multiple comorbidity or decline surgery之T4a病人歸類在優先CCRT及Induction chemotherapy。 4. 新增induction chemotherapy後primary tumor partial response + neck nodes progression or stable disease之治療選項。 5. Induction chemotherapy 改1-4 cycles。	1. Multidisciplinary team adjunctive service增加pain management。Supportive service增加Physical therapy (lymphedema management)。 2. 術後adjuvant治療，將pN1 without other risk features，考慮加上RT。 3. Adverse pathologic feature項目中新增subglottic extension。 4. T3N0-1的手術治療不再區分N0或N1決定是否做Lateral ND，而是統一都做單側或雙側ND。 5. pT4aN0-3手術治療不再將N0獨立標示出±單側或雙側ND，改成不論N0-3皆需單側或雙側ND。 6. 針對T4a拒絕手術的病人，將2022-2版當中的Clinical trial for function-preserving surgical or nonsurgical management，改成Clinical trial for function-preserving surgical or RT management。 7. 針對Initial M1且PS3，新增single-agent systemic therapy。 8. 針對Recurrent or persistent disease with M1，建議NGS。 9. CCRT/RT後有response，且8-12wks後Imaging positive，可做PET(≧12wk)，或者ND(if confirmed residual/persistent/progression)。

Carcinoma of the Glottis Larynx

WORK-UP

- History(pack yr smoked) & PE; fiberoptic exam
- Biopsy of primary site or FNA of the neck
- Contrast and thin angled cuts CT of larynx * and/or MRI with contrast of primary and neck *
- Bone scan* (若有PET，可不做此項檢查)
- Abd. Sono*
- 臨床需求時安排以下檢查

✓Chest CT (with or without contrast)
✓Consider FDG PET/CT
✓Preanesthesia studies
✓Pulmonary function evaluation for conservation surgery candidates
✓Consider videostroboscopy for select patients
✓EUA with endoscopy
✓Neck Sono
✓Panendoscopy
✓Dental evaluation
- ☐ Panorex ± teeth extraction

✓Nutrition, Speech and Swallowing evaluation/therapy
✓Audiogram
✓Smoking cessation couseling
✓Fertility/reproductvie couseling
(* 期別之相關之主要檢查)

STAGING & TREATMENT

- [Tis, N0]
  詳見 *Page 2*
- [T1-2, N0; select T3, N0]
  詳見 *Page 3*
- [T3 requiring total laryngectomy, N0-1]
  詳見 *Page 4*
- [T3 requiring total laryngectomy, N2-3]
  詳見 *Page 6*
- [T4a]
  詳見 *Page 7*
- [T4b, N0-3; Unresectable N; Unfit for surgery]
  詳見 Page 8
- [M1]
  詳見Page 9

FOLLOW-UP

(base on risk of relapse, second primaries. Treatment sequelae, and toxicities)

- [Post-Tx within 1 year]

→ Every 1-3 months: complete head and neck exam + fiberoptic examination
→ Baseline CT or MRI
→ ± Neck Sono

- [1-2 years after Tx]

→ Every 2-6 months: complete head and neck exam + fiberoptic examination
→ Clinical indicated every 1 year: Larynx CT or MRI, CxR, Bone scan & Abd. Sono ± Neck Sono ±TSH, free T4*

- [3-5 years after Tx]

→ Every 4-8 months: complete head and neck exam + fiberoptic examination

- [5 years later after Tx]

→ Every 12 months: complete head and neck exam + fiberoptic examination
(*if RT, every 6-12 months)

Carcinoma of the Glottis Larynx

Carcinoma in situ

Primary treatment	Pathological features	Adjuvant Treatment
Endoscopic resection (Preferred)		Follow-up
RT$, 註1		Follow-up

$RT: Either IMRT or 3D conformal RT is recommended

Carcinoma of the Glottis Larynx

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Amenable to larynx preserving (conservation) surgery

(T1-2, N0 or select T3, N0) @

Primary treatment	Pathological features	Adjuvant Treatment
RT$, 註1		Follow-up
Partial laryngectomy /endoscopic or open resection as indicated and ND as indicated	Adverse features*(-)	Follow-up
	Adverse features*(+) → Positive margin	Re-resection, if feasible or RT註1
	Adverse features*(+) → ENE(Extranodal extension)	CRT註1-2
	Adverse features*(+) → Other adverse features(+)	RT註1
	pN1 without other risk features	Consider RT註1

@Nodal disease in such glottis tumors is rare

*Adverse features: extranodal extension, positive or close margins, pT4 primary, pN2 or pN3 nodal disease, perineural invasion, vascular invasion, lymphatic invasion, subglottic extension

$RT: Either IMRT or 3D conformal RT is recommended

Carcinoma of the Glottis Larynx

T3 requiring(amenable to) total laryngectomy, N0-1, M0

Primary treatment	Pathological features	Adjuvant treatment

Concurrent CRT or RT if patient not candidate for CRT註1-2 → Follow-up, clinical assessment after 4-8 week as appropriate

Surgery, including ipsilateral or bilateral neck dissection; consider thyroidectomy to clear central compartment nodes

- pN0 without other risk features → Follow-up
- pN1 without other risk features → Consider RT註1
- Adverse features＊(+)
  - Extranodal extension and/or positive margin → CRT 註1-2
  - Other adverse features(+) → RT or consider CRT註1-2

Induction Chemotherapy註3 → CT or MRI (with contrast) of primary and neck → See Response Assessment (Page 5)

Clinical trials

＊Adverse features： extranodal extension, positive margins, close margins, pT4 primary, pN2 or pN3 nodal disease, perineural invasion, vascular invasion, lymphatic invasion, subglottic extension

Carcinoma of the Glottis Larynx

Response assessment | Pathological features | Adjuvant treatment

Response after induction chemotherapy

Primary site and neck nodes：CR+ → RT註1 → Follow-up, clinical assessment after 4-8 week as appropriate

Primary site and neck nodes: PR+ → Surgery@ → Follow-up, clinical assessment after 4-8 week as appropriate

Primary site and neck nodes: PR+ → CCRT or RT註1-2 → Follow-up, clinical assessment after 4-8 week as appropriate

Primary site: PR+ and neck nodes: SD or PD → Upfront ND → Follow-up, clinical assessment after 4-8 week as appropriate

Primary site：SD or PD → @Laryngectomy with thyroidectomy as indicated, with ipsilateral or bilateral neck dissection as indicated, and pretracheal and ipsilateral paratracheal lymph node dissection

- Adverse features＊(-) → RT註1
- Extranodal extension and/or positive margin → CRT註1-2
- Other adverse features(+) → RT or CRT註1-2

Unresectable Nodal disease → See Page 8

\+ Primary site evaluated by CT or MRI(with contrast) of primary head and neck

＊Adverse features： extranodal extension, positive margins, close margins, pT4 primary, pN2 or pN3 nodal disease, perineural invasion, vascular invasion, lymphatic invasion, subglottic extension

Carcinoma of the Glottis Larynx

T3 requiring (amenable to) total laryngectomy (N2-3)

Primary treatment	Pathological features	Adjuvant treatment

Concurrent CRT註1-2 → Follow-up, clinical assessment after 4-8 week as appropriate

Laryngectomy with thyroidectomy as indicated, ipsilateral or bilateral neck dissection, and pretracheal and ipsilateral paratracheal lymph node dissection

- Adverse features＊(-) → Follow-up
- Adverse features＊(+)
  - Extranodal extension and/or positive margin → CRT 註1-2
  - Other adverse features(+) → RT or consider CRT註1-2
- pN1 without other risk features → Consider RT註1

Induction Chemotherapy註3 → CT or MRI (with contrast) of primary and neck → See Response Assessment (Page 5)

Clinical trials

＊Adverse features： extranodal extension, positive margins, close margins, pT4 primary, pN2 or pN3 nodal disease, perineural invasion, vascular invasion, lymphatic invasion, subglottic extension

Carcinoma of the Glottis Larynx

Primary treatment	Pathological features	Adjuvant treatment

T4a, N0-3

Surgery, including ipsilateral or bilateral neck dissection; thyroidectomy to clear central Compartment nodes, especially when there is thyroid cartilage with gross invasion of the thyroid gland and significant subglottic extension

- Adverse features*(-) → Follow-up
- Adverse features*(+)
  - Extranodal extension and/or positive margin → CRT 註1-2
  - Other adverse features(+) → RT or consider CRT 註1-2
- pN1 without other risk features → Consider RT 註1

Select T4a patients (high PS, multiple comorbidity or decline surgery)

Consider CRT 註1-2 → Follow-up, clinical assessment after 4-8 week as appropriate

Clinical trial for function-preserving surgical or RT management

Induction Chemotherapy 註3 → CT or MRI (with contrast) of primary and neck → See Response Assessment (Page 5)

*Adverse features： extranodal extension, positive margins, close margins, pT4 primary, pN2 or pN3 nodal disease, perineural invasion, vascular invasion, lymphatic invasion, subglottic extension

Carcinoma of the Glottis Larynx

Newly diagnosed (M0)T4b, N0-3;
Unresectable nodal disease;
Unfit for surgery

Treatment

Clinical trial preferred

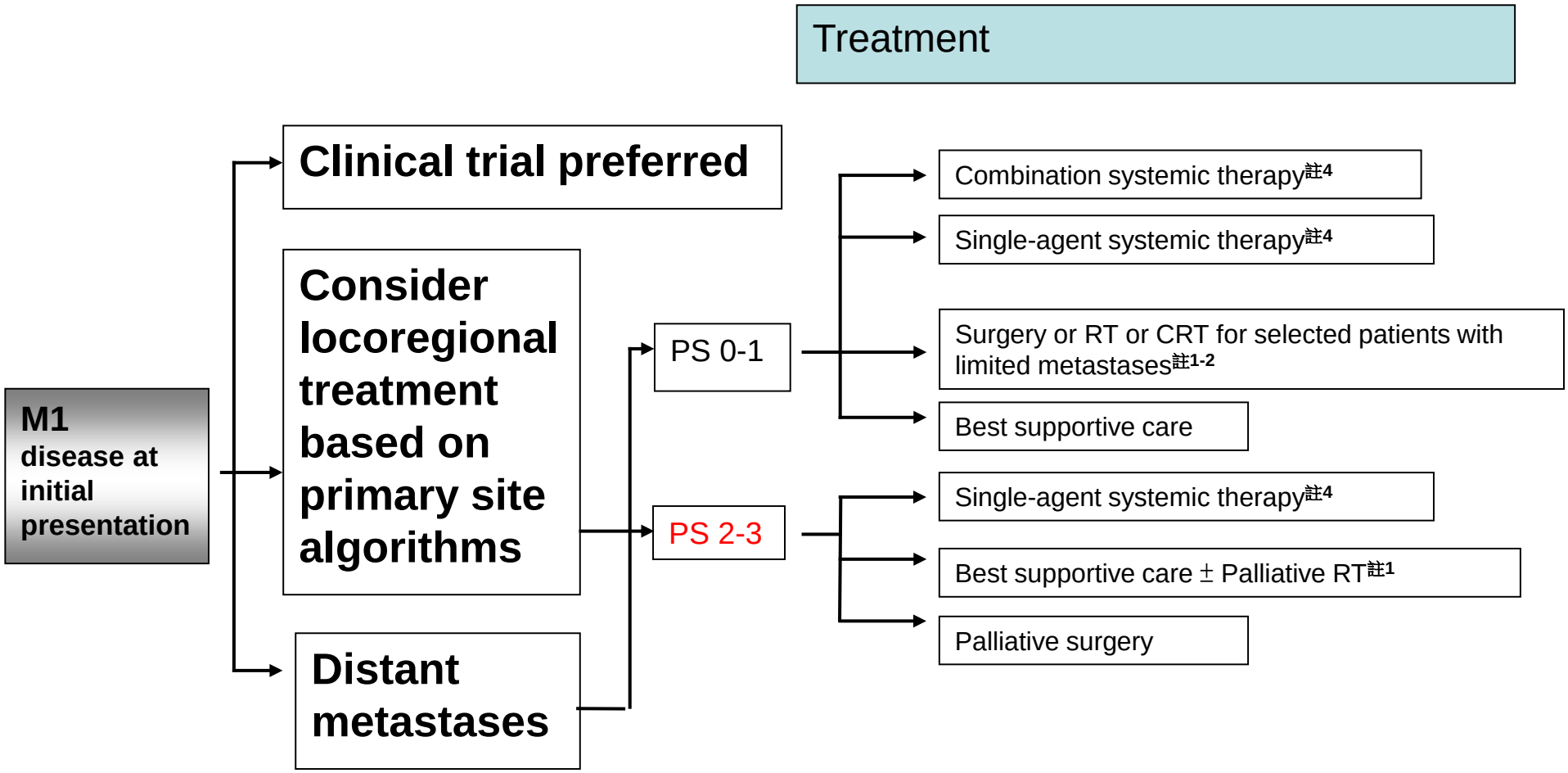
PS 0-1#
- Concurrent CRT註1-2
- Induction C/T註3 as indicated followed by RT or CRT註1,3

PS 2*
- RT註1
- Concurrent CRT註1-2

PS 3$
- Palliative RT註1
- Single-agent systemic therapy註4
- Best supportive care

ECOG Performance Status 0-1註6
* ECOG Performance Status 2
$ ECOG Performance Status 3

Carcinoma of the Glottis Larynx



1. PS 0-1若治療無效，除 best supportive care 外可再考慮systemic therapy, clinical trial or palliative RT
2. PS 2-3 single agent systemic therapy 若治療無效，除 best supportive care 外可再考慮 alternate single agent systemic therapy or palliative RT

Carcinoma of the Glottis Larynx

註1 高雄榮民總醫院 臨床診療指引Ver.1.2023 *Page 10 (**Ref. 21)***

Principles of Radiotherapy

Definitive (RT alone)

- Tis, N0：60.75 - 66 Gy (2.0-2.25 Gy/fraction)
- T1, N0：63 - 66 Gy (2.0-2.25 Gy/fraction) or 50 - 52 Gy (3.28-3.12 Gy/fraction)
- T2, N0：65.25 - 70 Gy (2.0-2.25 Gy/fraction)
- >=T2, N1 ：
  - ✓ **High risk**：Primary tumor and involved lymph nodes
    - ➢ 66 - 70 Gy (2.0-2.2 Gy/fraction) ；daily Monday-Friday in 6-7 weeks
    - ➢ Concomitant boost accelerated RT
      - ◆ 72 Gy /6 weeks (1.8 Gy/fraction, large field；1.5Gy boost as second daily fraction during last 12 treatment days)
      - ◆ 66–70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)
    - ➢ Hyperfractionation ：79.2 – 81.6 Gy /7 weeks (1.2 Gy/fraction, twice daily)
  - ✓ **Low to intermittent risk**：Sites of suspected subclinical spread

Postoperative (RT or Concurrent CRT)

- Preferred interval between resection and postoperative RT is ≤6 weeks
- High risk: Adverse features such as positive margins
  - ✓ 60–66 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 6–6.5 weeks
- Low to intermediate risk: sites of suspected subclinical spread
  - ✓ 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

Concurrent CRT

- High-risk: typically 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 7 weeks
- Low to intermediate risk: 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)

Carcinoma of the Glottis Larynx

Principles of Chemotherapy

Concurrent with RT

Regimen 1 : q3w CDDP ± Cetuximab[註5] + RT
•Cisplatin (80-100mg/ m^2) q3w during R/T
•Cetuximab(400mg/ m^2) loading dose first week, then Cetuximab(250mg/ m^2) maintain dose D1 + Cisplatin (80-100mg/ m^2) q3w D2 during R/T

Regimen 2: Weekly CDDP ± Cetuximab[註5] + RT
•Cisplatin (30-40mg/ m^2) weekly during R/T
•Cetuximab(400mg/ m^2) loading dose first week, and then Cisplatin (30-40mg/ m^2) weekly D1 + Cetuximab(250mg/ m^2) 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/ m^2) loading dose first week, then Cetuximab(250mg/ m^2) maintain dose D1 + Carboplatin (AUC x 5mg) q3w D2 during R/T

Regimen 4: Weekly Cetuximab[註5] + RT
•Cetuximab(400mg/ m^2) loading dose first week, then Cetuximab(250mg/ m^2) maintain dose during RT

Regimen5 : Carboplatin + 5-FU + Hydroxyurea (CCr < 60) + RT
•Carboplatin (AUC x 1.25mg) D1-D4
•Fluorouracil (5-FU) (850mg/m^2) D1-D4
•Hydroxyurea 1CAP BID D1-D5

Regimen6 : Cisplatin + 5-FU + Hydroxyurea + RT
•Cisplatin(20mg/ m^2) D1-D4
•Fluorouracil (5-FU) (850mg/m^2) D1-D4
•Hydroxyurea 1CAP BID D1-D5

Carcinoma of the Glottis Larynx

註3 高雄榮民總醫院 臨床診療指引 Ver.1.2023 *Page 12 (**Ref. 22-27**)*

Regimens of Chemotherapy

Induction, adjuvant, *建議1-4cycles*

Regimen 1 : q3-4 weeks T[註5] + P ± F ± weekly Cetuximab[註5]

- Taxotere(60 mg/ m^2) D1
- Cisplatin(60-75 mg/ m^2) D1
- Fluorouracil (5-FU) (600-750mg/m^2) D2-D5
- Cetuximab (400mg/ m^2) loading dose first week, then Cetuximab (250mg/ m^2) 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/m^2) D2-D5
- Cetuximab(400mg/m^2) loading dose first week, then weekly Cetuximab (250mg/ m^2)

Carcinoma of the Glottis Larynx

註3 高雄榮民總醫院 臨床診療指引 Ver.1.2023 *Page 13 (**Ref. 22-27)***

Regimens of Chemotherapy

Induction, adjuvant, *建議1-4cycles*

Regimen 3: weekly Cetuximab[註5]

•Cetuximab (400mg/ m^2) loading dose first week, then Cetuximab (250mg/ m^2) 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/ m^2)

Carcinoma of the Glottis Larynx

註4 高雄榮民總醫院 臨床診療指引 Ver.1.2023 *Page 14* (***Ref. 22-27***)

Regimens of Chemotherapy

Recurrent, unresectable, metastatic *

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

- Pembrolizumab(200mg) D1 (if CPS≧1)
- Cisplatin(80-100mg/m^2) D1 or Cisplatin (20mg/ m^2) D1-D5 or Carboplatin (AUC x 5mg) D1
- Fluorouracil (5-FU) (600-1000 mg/m^2) D2-D5

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

- Pembrolizumab(200mg) D1 (if CPS≧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/ m^2) D1 or Cisplatin (20mg/ m^2) D1-D5 or Carboplatin (AUC x 5mg) D1
- Fluorouracil (5-FU) (600-1000 mg/m^2) D2-D5
- Cetuximab(400mg/ m^2) loading dose first week, then weekly Cetuximab (250mg/ m^2)

*針對Recurrent or persistent disease with M1，建議NGS

Carcinoma of the Glottis Larynx

註4 高雄榮民總醫院 臨床診療指引 Ver.1.2023 *Page 15 (**Ref. 22-27**)*

Regimens of Chemotherapy

Recurrent, unresectable, metastatic *

Regimen 6: q3-4 weeks T ± Platinum ± weekly Cetuximab[註5]

- Taxotere(60 mg/ m^2) D1
- Cisplatin(60-75 mg/ m^2) D1 or Carboplatin (AUC x 5mg) D1
- Cetuximab(400mg/ m^2) loading dose first week, then weekly Cetuximab (250mg/ m^2)

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

- Cisplatin (60 mg/ m^2) D1
- Epirubicin (50 mg/ m^2) D1
- Fluorouracil (5-FU) (2000 mg/m2) D1

Regimen 8: q2 weeks Bevacizumab

- Bevacizumab (200 mg/ m^2) D1

Regimen 9: weekly Gemcitabine

- Gemcitabine (1000 mg/m2) D1

*針對Recurrent or persistent disease with M1，建議NGS

Carcinoma of the Glottis Larynx

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。

符合下列條件之一：

1.年齡 ≧ 70 歲

2.Ccr ＜50ml/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。需經事前審查核准後使用，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。 (106/4/1)

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 the Glottis Larynx

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≦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≧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≦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 the Glottis Larynx

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 the Glottis Larynx

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