高 雄 榮 民 總 醫 院
口腔癌診療原則

2019年03月06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：2018/05/23

本共識與上一版的差異

上一版	新版
1. WBBS為必要檢查項目。 2. 依據cN決定頸部淋巴結廓清。 3. 無Clinical trials。	1. 若安排PET/CT檢查，無須排WBBS(p1)。 2. 維持cN，不依據SNL biopsy病理報告決定做頸部淋巴結廓清(p2)。 3. 新增Clinical trials(p3)。 4. 核對線上化藥處方集與診療指引化藥處方集一致性，未列出者將補齊。 Regimen1 : Carboplatin + 5-FU + Hydroxyurea (CCr < 60) + RT Carboplatin (AUC x 1.25mg) D1-D4 Regimen2 : Cisplatin + 5-FU + Hydroxyurea + RT Regimen3 : cisplatin+epirubicin+ 5-FU+ Leucovorin Regimen4 : q2 weeks Bevacizumab Regimen5 : weekly Gemcitabine

Carcinoma of Oral Cavity

高雄榮民總醫院 臨床診療指引 Ver.1 修訂2019.03.06 *Page 1 (**Ref. 1**)*

WORK-UP

- History & PE
- Biopsy & Pathology
- Image
  - → MRI*or CT of H&N* or PET
  - → Chest X-ray*
  - → Bone scan*

(若有PET，可不做此項檢查)

  - → Abd. Sono*
  - → ± Neck Sono
- Dental evaluation
  - → Panorex
  - → ± teeth extraction
- Multidisciplinary consultation

± Swallowing evaluation

•± p16 status

(* 期別之相關之主要檢查)

STAGING & TREATMENT

- [T1-2, N0, M0]

  詳見 *Page 2*
- [T3, N0; T1-3, N1-3; T4a-resectable T4b, any N, M0]

  詳見 *Page 3*
- [Inoperable status]

  詳見 Page 4
- [M1]

  詳見Page 5

FOLLOW-UP

- [Post-Tx within 6 months]
  - → Every 1-2 months: PE
  - → Baseline MRI or CT
  - → ± Neck Sono
- [0.5-3 years after Tx]
  - → Every 2-3 months: PE
  - → Every 1 year:

H & N MRI or CT, CxR, Bone scan & Abd. Sono ± Neck Sono

As clinically indicated

- [3-5 years after Tx]
  - → Every 4-6 months: PE
- [5 years later after Tx]
  - → Every 6-12 months:

    Physical exam

Carcinoma of Oral Cavity

高雄榮民總醫院 臨床診療指引 Ver.1 修訂2019.03.06 *Page 2 (**Ref. 1-5**)*

Clinical T1-2, N0, M0

Primary treatment

Resection of primary ± ND, unil. or bil.#

Pathological features	Adjuvant Treatment
Adverse features*(-), N0	Follow-up
Positive margin	Re-resection, RT or CRT註1-2 (T2 only)
Adverse features(-), N1	RT註1 or follow-up
ENE(Extranodal extension)	CRT or RT註1-2 or follow-up
Other adverse features(+)	RT or CRT註1-2 or follow-up

Definite RT$, 註1

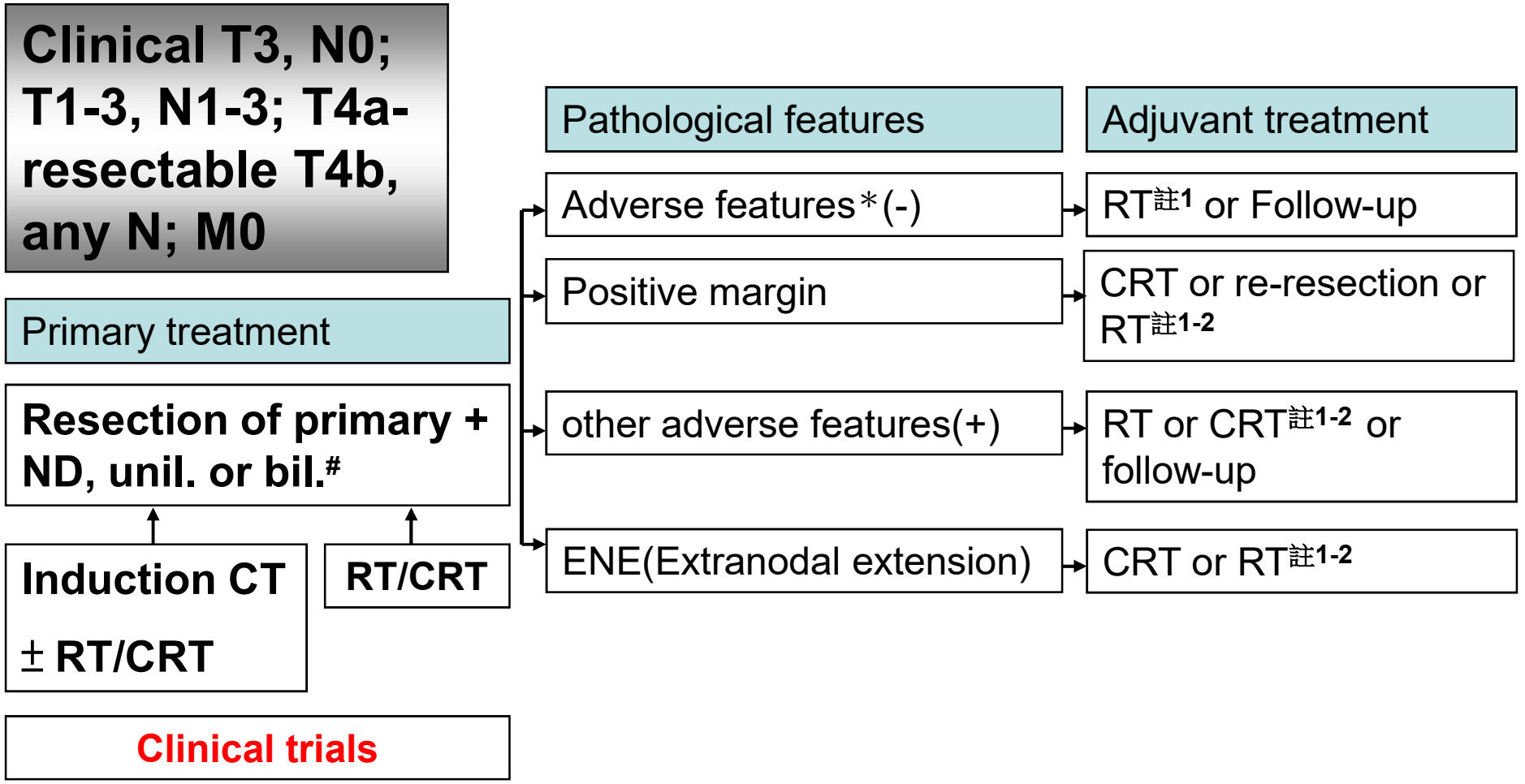
Residual disease	Surgery
Complete clinical response	Follow-up

#Depth of invasion ≥ 4mm 可考慮Elective neck dissection (依~~cN status~~、腫瘤厚度、位置、SLN biopsy結果而定) 或close follow-up

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

$ RT: external beam RT(EBRT) ± brachytherapy or brachytherapy alone

Carcinoma of Oral Cavity

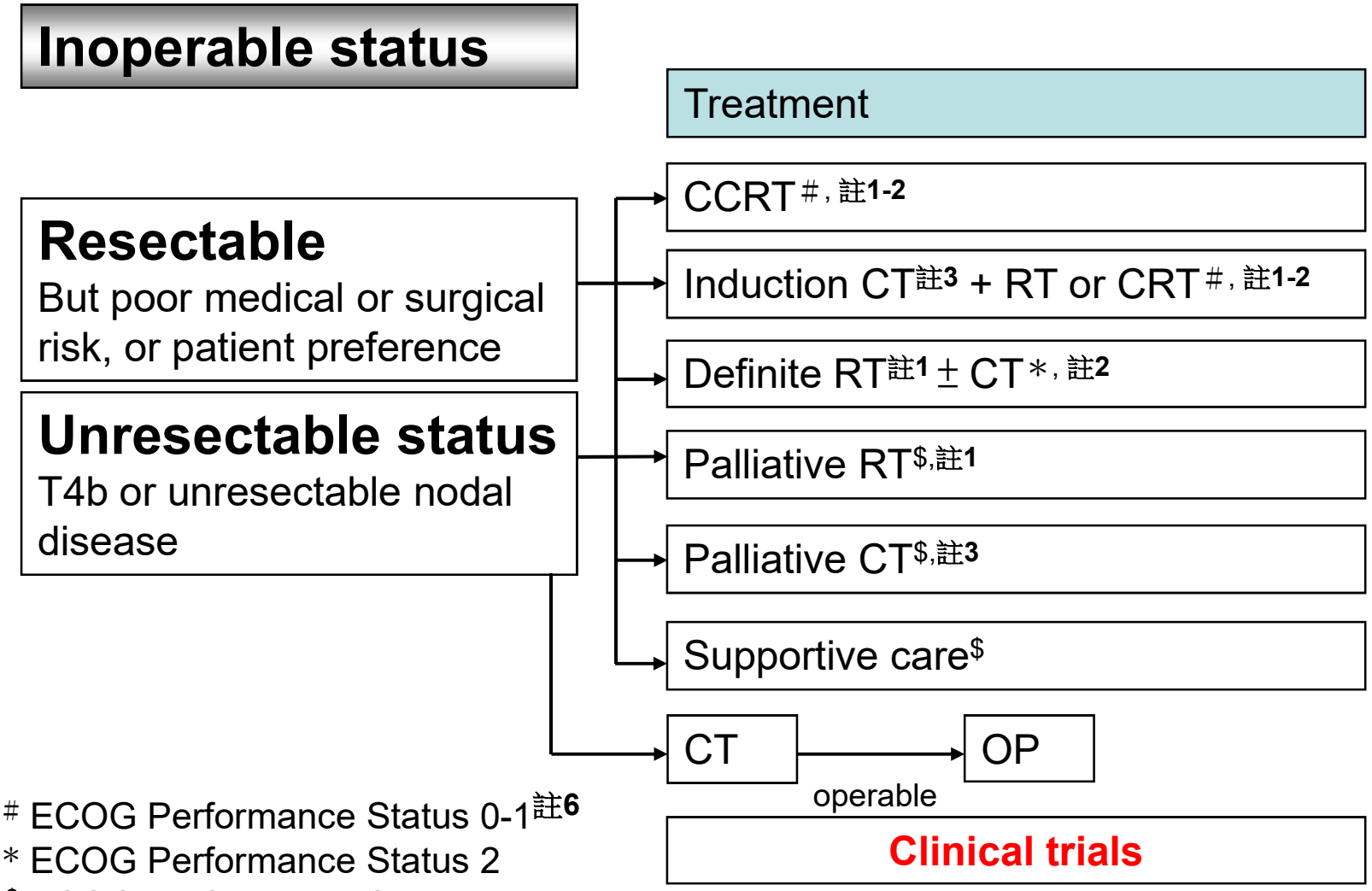


＃Therapeutic neck dissection, level依cN status及腫瘤位置而定

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

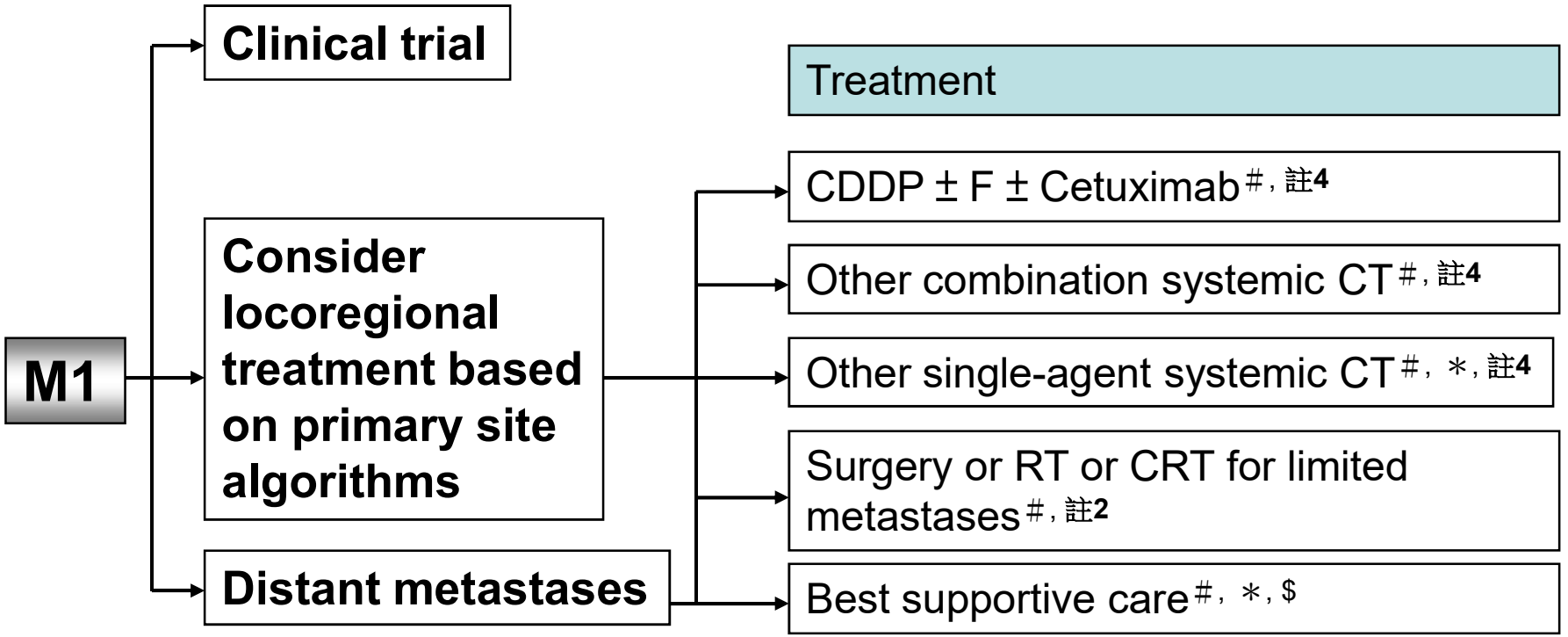
Carcinoma of Oral Cavity

高雄榮民總醫院 臨床診療指引 Ver.1 修訂2019.03.06 *Page 4 (**Ref. 1,8**)*



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

Carcinoma of Oral Cavity



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

Carcinoma of Oral Cavity

註1

Principles of Radiotherapy

Definitive Radiotherapy

- Primary and gross adenopathy：66 - 74 Gy (1.8-2.0 Gy/fraction)
- Neck uninvolved nodal stations：44 - 64 Gy (1.6-2.0 Gy/fractions)

Postoperative Radiotherapy

- Preferred interval between operation and radiotherapy is ≤ 6 weeks.
- Primary：60-66 Gy (1.8-2.0 Gy/fraction)
- Neck involved nodal stations：60 - 66 Gy (1.8-2.0 Gy/fraction)
- Neck uninvolved nodal stations：44 - 64 Gy (1.6-2.0 Gy/fraction)

Palliative RT

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

CCRT or RT

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

Carcinoma of Oral Cavity

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 Oral Cavity

Regimens of Chemotherapy

***Induction or adjuvant,** 建議2-3cycles*

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: P ± F q3-4 weeks ± weekly Cetuximab[註5]

- Cisplatin(80-100mg/ m^2) D1
- Fluorouracil (5-FU) (1000mg/ m^2) D2-D5
- Cetuximab(400mg/ m^2) loading dose first week, then weekly Cetuximab (250mg/ m^2)

Regimen 3: q3-4 weeks CDDP ± F ± weekly Cetuximab[註5]

- Cisplatin (20mg/ m^2) D1-D5
- Fluorouracil (5-FU) (1000mg/m^2) D1-D5
- Cetuximab(400mg/ m^2) loading dose first week, then weekly Cetuximab (250mg/ m^2)

Carcinoma of Oral Cavity

Regimens of Chemotherapy

***Induction or adjuvant,** 建議2-3cycles*

Regimen 4: q3-4 weeks Carboplatin[註5] ± F ± weekly Cetuximab[註5]

- Carboplatin (AUC x 5mg) D1
- Fluorouracil (5-FU) (1000mg/ m^2) D2-D5
- Cetuximab(400mg/ m^2) loading dose first week, then weekly Cetuximab (250mg/ m^2)

Regimen 5: weekly Cetuximab[註5]

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

Regimen 6: 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 7: weekly Methotrexate

- Methotrexate (40-60mg/ m2)

Carcinoma of Oral Cavity

Regimens of Chemotherapy

Recurrent, unresectable, metastatic

Regimen 1: q3-4 weeks CDDP ± F ± weekly Cetuximab[註5]

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

Regimen 2: q3-4 weeks Carboplatin ± F ± weekly Cetuximab[註5]

- Carboplatin (AUC x 5mg) D1
- Fluorouracil (5-FU) (1000mg/ m^2) D2-D5
- Cetuximab(400mg/ m^2) loading dose first week, then weekly Cetuximab (250mg/ m^2)

Regimen 3: q3-4 weeks T ± P ± weekly Cetuximab[註5]

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

Carcinoma of Oral Cavity

Regimens of Chemotherapy *Recurrent, unresectable, metastatic*

Regimen 4: q3-4 weeks T ± Carboplatin ± weekly Cetuximab註5
- Taxotere(60 mg/ m^2) D1
- Carboplatin (AUC x 5mg) D1
- Cetuximab(400mg/ m^2) loading dose first week, then weekly Cetuximab (250mg/ m^2)

Regimen 5: q3 weeks Pembrolizumab
- Pembrolizumab(200mg) D1

Regimen 6: q2 weeks Nivolumab
- Nivolumab(3mg/kg) D1

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

Carcinoma of Oral Cavity

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，且符合下列條件之一：

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。

- 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。

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 Oral Cavity

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	

References

1. NCCN Clinical Practice Guidelines in Oncology – Head and Neck Cancers Version 2. 2017
2. AJCC (American Joint Committee on Cancer) Manual for Staging of Cancer, 8th ed, Amin M, Edge S, Greene F, et al. (Eds), Springer-Verlag, New York 2017.
3. Chen, YK, Huang, HC, Lin, LM, Lin, CC. Primary oral squamous cell carcinoma: an analysis of 703 cases in southern Taiwan. Oral Oncol 1999; 35:173.
4. Iro, H, Waldfahrer, F. Evaluation of the newly updated TNM classification of head and neck carcinoma with data from 3247 patients. Cancer 1998; 83:2201.
5. Bradley, PJ, MacLennan, K, Brakenhoff, RH, Leemans, CR. Status of primary tumour surgical margins in squamous head and neck cancer: prognostic implications. Curr Opin Otolaryngol Head Neck Surg 2007; 15:74.
6. Brockstein, B, Vokes, EE. Concurrent chemoradiotherapy for head and neck cancer. Semin Oncol 2004; 31:786.
7. Nair, MK, Sankaranarayanan, R, Padmanabhan, TK. Evaluation of the role of radiotherapy in the management of carcinoma of the buccal mucosa. Cancer 1988; 61:1326.
8. Hong, WK, Bromer, RH, Amato, DA, et al. Patterns of relapse in locally advanced head and neck cancer patients who achieved complete remission after combined modality therapy. Cancer 1985; 56:1242.
9. Forastiere, AA, Metch, B, Schuller, DE, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: A Southwest Oncology Group study. J Clin Oncol 1992; 10:1245.
10. Jacobs, C,Lyman, G,Velez-Garcia, E, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. J Clin Oncol 1992; 10:257.
11. Rowland KM, Taylor SG, O'Donnell MR et al. Cisplatin and 5-FU infusion chemotherapy in advanced recurrent cancer of the head and neck: An Eastern Cooperative Oncology Group pilot study. Cancer Treat Rep 1986; 70: 461-464.
12. Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, Stewart JS, Jelic S, Betka J, Preiss JH, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med. 2007 Oct 25; 357(17):1695-704
13. Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, Tjulandin S, Shin DM, Cullen K, Ervin TJ, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med. 2007 Oct 25; 357(17):1705-1
14. Vermorken JB, Mesia, R , Rivera F, Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer N Engl J Med. 2008 Sep 11; 359:1116-27
15. Guigay J, Fayette J, Dillies A-F, et al. Cetuximab, docetaxel, and cisplatin (TPEx) as first-line treatment in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): Final results of phase II trial GORTEC 2008-03 [abstract]. J Clin Oncol 2012;30(Suppl 15):Abstract 5505.

References

16. Samlowski WE, Moon J, Kuebler JP, et al. Evaluation of the combination of docetaxel/carboplatin in patients with metastatic or recurrent squamous cell carcinoma of the head and neck (SCCHN): a Southwest Oncology Group Phase II study. Cancer Invest 2007;25:182-188.
17. Gibson MK, Li Y, Murphy B, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): An Intergroup Trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2005;23:3562-3567.
18. Price KA, Cohen EE. Current treatment options for metastatic head and neck cancer. Curr Treat Options Oncol 2012;13:35-46.
19. Herbst RS, Arquette M, Shin DM, et al. Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. J Clin Oncol 2005;23:5578-5587.
20. Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol 2016;17:956-965.
21. Chow LQ, Haddad R, Gupta S, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort. J Clin Oncol 2016.
22. Ferris R, Blumenschein G, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016;375:1856-1867.
23. Raguse JD, Gath HJ, Bier J, et al. Gemcitabine in the treatment of advanced head and neck cancer. Clin Oncol (R Coll Radiol). 2005;17(6):425-9.
24. Lee NY, Zhang Q, Pfister DG, et al. Phase II Study of the Addition of Bevacizumab to Standard Chemoradiation for Loco-regionally Advanced Nasopharyngeal Carcinoma: Radiation Therapy Oncology Group (RTOG) Trial 0615. Lancet Oncol. 2012; 13(2): 172–180.
25. Garden AS, Harris J, Vokes EE, et al. Preliminary results of Radiation Therapy Oncology Group 97-03: a randomized phase ii trial of concurrent radiation and chemotherapy for advanced squamous cell carcinomas of the head and neck. J Clin Oncol. 2004 Jul 15;22(14):2856-64.