高 雄 榮 民 總 醫 院

口腔癌診療原則

2024年05月29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:2023/3/22

本共識與上一版的差異

上一版	新版
1. Subsite 處將anterior tongue 改成 oral tongue 2. Adverse features 改成 adverse pathologic features 3. T1-2術後 Positive Margin治療從 Re-resection or RT 改成 Re-resection + RT if negative margin 4. M1 ECOG PS 3 的病人治療選項加上 Single-agent systemic therapy 5. 在recurrent or persistent disease with distant metastases病人建議做NGS genomic profiling	1. 診斷後應screening HBV(業已列為本院guidline) 2. 所有tumor resectable的病患皆建議接受手術，除非患者拒絕或不適合接受手術(業已列為本院guidline) 3. 口腔癌第三期患者若MTR (margin/DOI<0.45)則可考慮輔助性CRT/RT 4. Inoperable ECOG PS 2 的病患建議優先考慮CRT 5. Oral UFUR(2#BID or 1#TID)可作為取代iv-formed 5-FU之替代藥物 6. Nutrition support應優先考慮腸道營養(NG, PEG)

Carcinoma of Oral Cavity

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WORK-UP

- History& PE (pack yr smoked)
- Biopsy & Pathology
- Image
  - MRI*or CT of H&N* or PET
  - Chest X-ray ± Chest CT
  - Bone scan* (if PET/CT not done)
  - Abd. Sono*
  - ± Neck Sono
  - ± PES
- Dental evaluation
  - Panorex ± teeth extraction
- Multidisciplinary consultation (± Fertility/reproductive, smoking cessation)

± Swallowing evaluation

- ± p16 status
- **Screening for HBV/HCV**

(* 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*
- [Oral cancer after surgery]
  詳見 Page 4
- [Inoperable status]
  詳見 Page 5
- [M1]
  詳見Page 6

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

±TSH, free T4*

As clinically indicated

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

(*if RT, every 6-12 months)

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Clinical T1-2, N0, M0

Primary treatment

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

→ Risk factor stratification (see page 4)

Pathological features | Adjuvant Treatment

Definitive RT*, 註1

→ Residual disease → Surgery

→ Complete clinical response → Follow-up

Depth of invasion ≧4 mm可考慮Elective ND (依腫瘤厚度、位置、SLN biopsy結果而定) 或close follow-up；T1-3, N0 mucosal lip cancer一般不考慮ND

* RT: external beam RT(EBRT) ± brachytherapy alone

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Clinical T3, N0; T1-3, N1-3; T4a-resectable T4b, any N; M0

Pathological features

Adjuvant treatment

Primary treatment

Resection of primary + ND, unil. or bil.# → Risk factor stratification (see page 4)

Induct. C/T註3

±RT/CRT

~~**RT/CRT**~~

Clinical trials

Therapeutic neck dissection level依cN status及腫瘤位置而定; T1-3, N0 mucosal lip cancer一般可不考慮ND

所有operable的病患皆建議接受手術，除非患者拒絕或不適合，inoperable cases(see page 10)

Carcinoma of Oral Cavity

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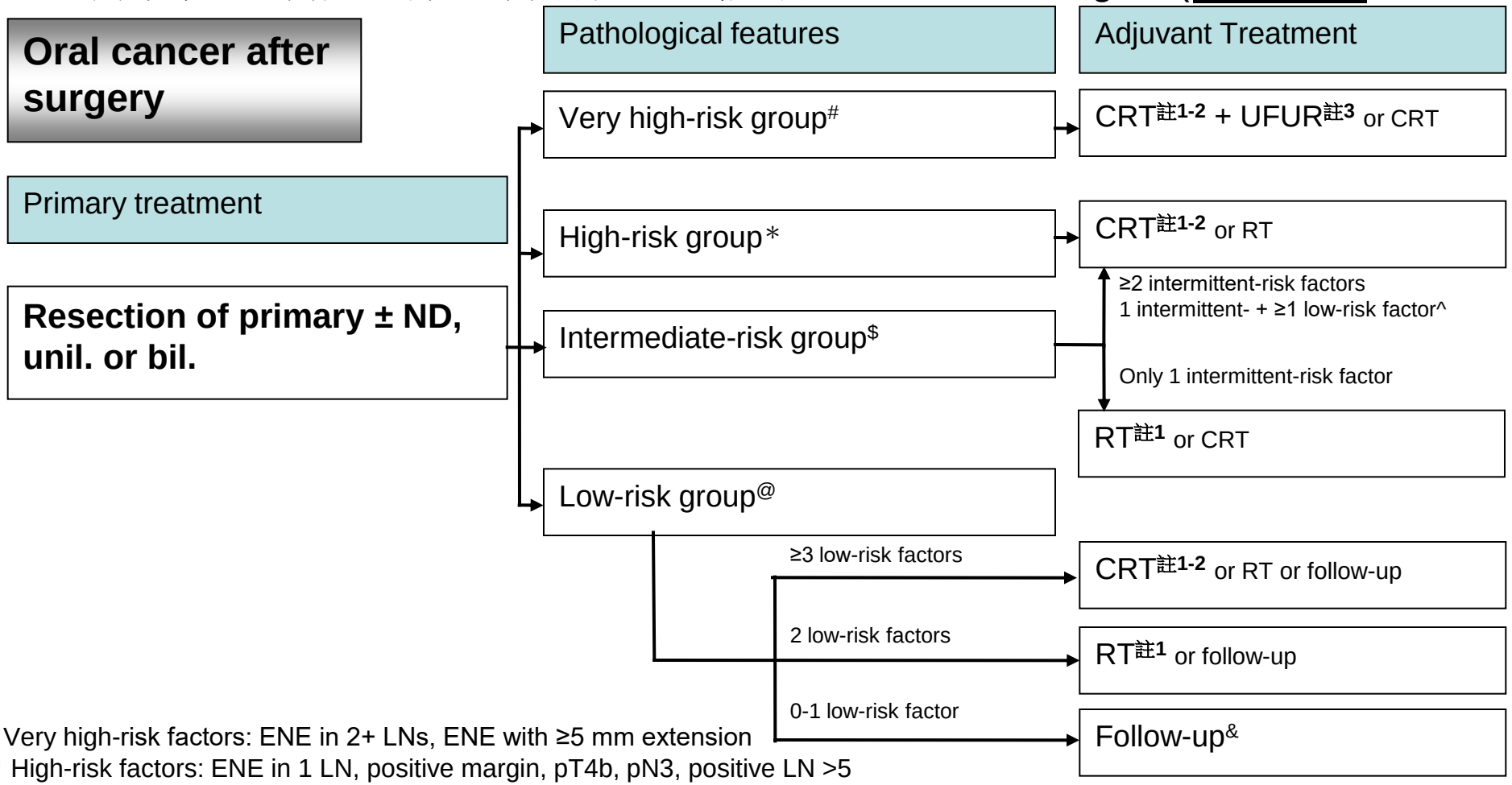

Very high-risk factors: ENE in 2+ LNs, ENE with ≥5 mm extension

* High-risk factors: ENE in 1 LN, positive margin, pT4b, pN3, positive LN >5

$ Intermediate-risk factors: pT3-4a, negative margin after re-resection for positive margin, tongue cancer with extrinsic muscle invasion, pN2 (positive LN ≤5), pN1 in lower neck, margin ≤2 mm (re-resection first), poorly differentiation + DOI ≥4 mm,口腔癌第三期患者若**MTR (margin/DOI<0.45)則可考慮輔助性CRT/RT,**pT1 shallow lesion margin ≤2 mm可以選擇OBS

@ Low-risk factors: pN1, perineural invasion, lymphovascular invasion, DOI ≥10 mm, poorly differentiation, margin 3-4 mm

^ Exception: pT3N1可以只做RT,

& 若只有一個low-risk factor但為perineural invasion且無接受過neck dissection，則建議RT0.

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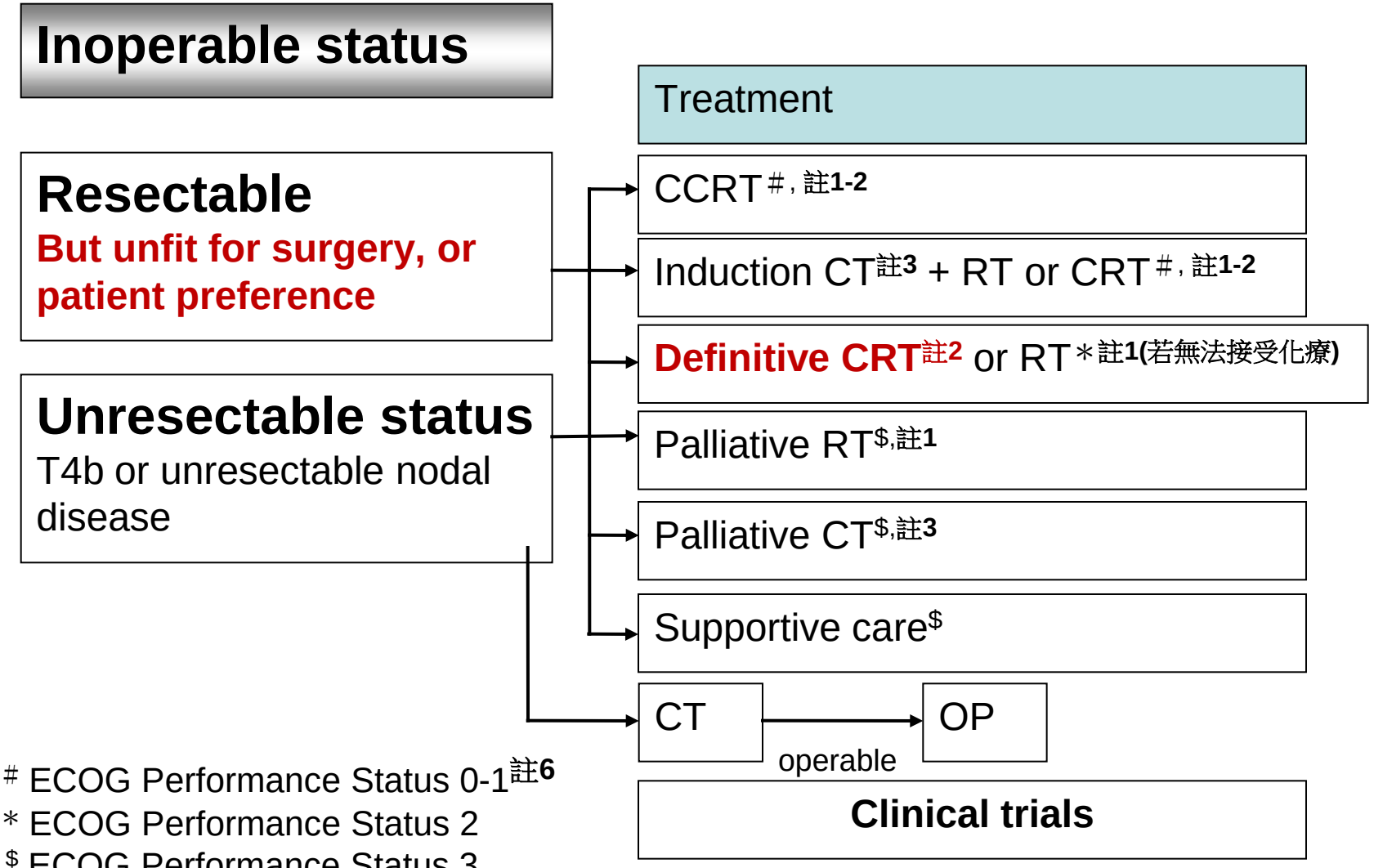

ECOG Performance Status 0-1註6

＊ ECOG Performance Status 2

$ ECOG Performance Status 3

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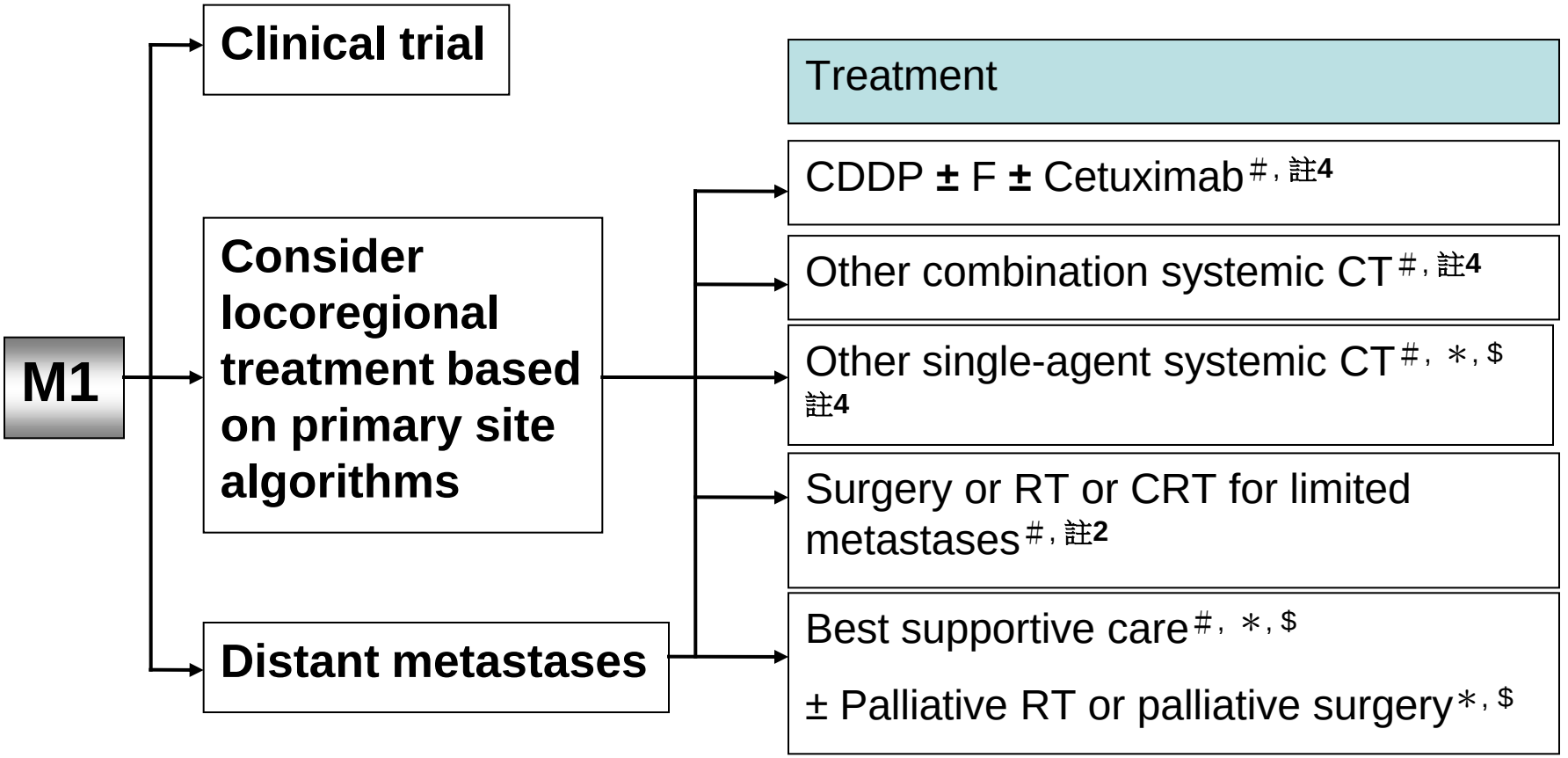

ECOG Performance Status 0-1 註6

* ECOG Performance Status 2

$ ECOG Performance Status 3

@ 在recurrent or persistent disease with distant metastases病人建議做NGS genomic profiling

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

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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

Regimen 7: Doxetaxel + RT
• Doxetaxel (60g/m^2) D1, if cisplatin not eligible

Carcinoma of Oral Cavity

Regimens of Chemotherapy

Induction or adjuvant, *建議2-3cycles*

Regimen 1 : q3-4 weeks T[註5] + P ± F (5-FU or UFUR) ± 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 or **UFUR**
- Cetuximab (400mg/ m^2) loading dose first week, then Cetuximab (250mg/ m^2) maintain dose

Regimen 2: q3-4 weeks Platinum ± F (5-FU or UFUR) ± 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) (1000mg/ m^2) D2-D5 or **UFUR**
- Cetuximab(400mg/ m^2) loading dose first week, then weekly Cetuximab (250mg/ m^2)

Regimen 3: weekly Cetuximab[註5]

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

Carcinoma of Oral Cavity

註3 高雄榮民總醫院 臨床診療指引 Ver.1 修訂於 2024.04.10 *Page 10 (**Ref. 15-20**)*

Regimens of Chemotherapy

Induction or adjuvant, *建議2-3cycles*

Regimen 4: oral Fluorouracil

- **Ufur cap (tegafur 100mg+uracil 224mg) 2# BID-TID**

(可作為取代iv-formed 5-FU之替代藥物)

Regimen 5: weekly Methotrexate

- Methotrexate (40-60mg/ m2)

Carcinoma of Oral Cavity

Regimens of Chemotherapy

Recurrent, unresectable, metastatic

Regimen 1 (First line): q3 weeks Pembrolizumab註5 ± Platinum ± F
- Pembrolizumab(200mg) D1
- 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)

Regimen 6: q3 weeks Pembrolizumab註5 + Platinum + Doxetacel
- Pembrolizumab(200mg) D1
- Cisplatin(80-100mg/ m^2) D1 or Cisplatin (20mg/ m^2) D1-D5 or Carboplatin (AUC x 5mg) D1
- Taxotere(60 mg/ m^2)

Carcinoma of Oral Cavity

註4 高雄榮民總醫院 臨床診療指引 Ver.1 修訂於 2024.04.10 *Page 12 (**Ref. 21-29**)*

Regimens of Chemotherapy

Recurrent, unresectable, metastatic

Regimen 6: 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)

Regimen 7: 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 8: 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 9: q2 weeks Bevacizumab
- Bevacizumab (200 mg/ m^2) D1

Regimen 10: weekly Gemcitabine
- Gemcitabine (1000 mg/m^2) 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，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 ＜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。 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 Oral Cavity

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 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	

Carcinoma of Oral Cavity

References

1. NCCN Clinical Practice Guidelines in Oncology – Head and Neck Cancers Version 1. 2024
2. Hsieh MC, Wang CC, Yang CC, Lien CF, Wang CC, Shih YC, Yeh SA, Hwang TZ. Tegafur-Uracil versus 5-Fluorouracil in Combination with Cisplatin and Cetuximab in Elderly Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: A Propensity Score Matching Analysis. Biology (Basel). 2021 Oct 8;10(10):1011. doi: 10.3390/biology10101011. PMID: 34681110; PMCID: PMC8533478.
3. Gregor Heiduschka, Sohaib A. Virk, Carsten E. Palme, Sydney Ch'ng, Michael Elliot, Ruta Gupta, Jonathan Clark, Margin to tumor thickness ratio – A predictor of local recurrence and survival in oral squamous cell carcinoma, Oral Oncology, Volume 55, 2016, Pages 49-54, ISSN 1368 8375, https://doi.org/10.1016/j.oraloncology.2016.01.010.
4. 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.
5. 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.
6. 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.
7. 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.
8. Lin CY, Fan KH, Lee LY, et al. Precision Adjuvant Therapy Based on Detailed Pathologic Risk Factors for Resected Oral Cavity Squamous Cell Carcinoma: Long-Term Outcome Comparison of CGMH and NCCN Guidelines. Int J Radiat Oncol Biol Phys. 2020;106(5):916-925.
9. Lee CC, Ho HC, Su YC, Yu CH, Yang CC. Modified Tumor Classification With Inclusion of Tumor Characteristics Improves Discrimination and Prediction Accuracy in Oral and Hypopharyngeal Cancer Patients Who Underwent Surgery. Medicine (Baltimore). 2015;94(27):e1114.
10. Yang CC, Kang BH, Liu WS, Yin CH, Lee CC. Postoperative radiotherapy is associated with improved survival in pT1-2N1 oral and oropharyngeal cancer without adequate neck dissection. Radiat Oncol. 2021;16(1):6.
11. Azzopardi S, Lowe D, Rogers S. Audit of the rates of re-excision for close or involved margins in the management of oral cancer. Br J Oral Maxillofac Surg. 2019;57(7):678-681.
12. Fan KH, Wang HM, Kang CJ, et al. Treatment results of postoperative radiotherapy on squamous cell carcinoma of the oral cavity: coexistence of multiple minor risk factors results in higher recurrence rates. Int J Radiat Oncol Biol Phys. 2010;77(4):1024-1029.
13. Bernier J, Vermorken JB, Koch WM. Adjuvant therapy in patients with resected poor-risk head and neck cancer. J Clin Oncol. 2006;24(17):2629-2635.
14. Huang TH, Li KY, Choi WS. Lymph node ratio as prognostic variable in oral squamous cell carcinomas: Systematic review and meta-analysis. Oral Oncol. 2019;89:133-143.
15. Brockstein, B, Vokes, EE. Concurrent chemoradiotherapy for head and neck cancer. Semin Oncol 2004; 31:786.
16. 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.
17. 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.

References

17. 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.
18. 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.
19. 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.
20. 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.
21. 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.
22. 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.
23. 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.
24. 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.
25. Price KA, Cohen EE. Current treatment options for metastatic head and neck cancer. Curr Treat Options Oncol 2012;13:35-46.
26. 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.
27. 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.
28. 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.
29. 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.
30. 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.
31. 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.
32. 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.