



中山醫學大學附設醫院

食道癌診療指引

2025/12/11 Version17.0
 2024/12/12 Version16.0
 2023/12/14 Version15.0
 2022/12/08 Version14.0
 2021/12/09 Version13.0
 2021/01/10 Version12.0
 2019/12/12 Version11.0
 2018/11/15 Version10.0
 2017/12/21 Version9.0
 2016/12/15 Version8.0
 2015/12/01 Version7.0
 2014/12/26 Version6.0
 2013/12/27 Version5.0
 2012/12/28 Version4.0
 2011/12/02 Version3.0
 2010/12/31 Version2.0
 2009/12/17 Version1.0

本臨床指引參考台灣國家衛生研究院及美國NCCN版本

食道癌多專科醫療團隊編修

癌症委員會主任委員	癌症委員會執行長	癌症中心主任	抗癌藥物安全小組	團隊負責人

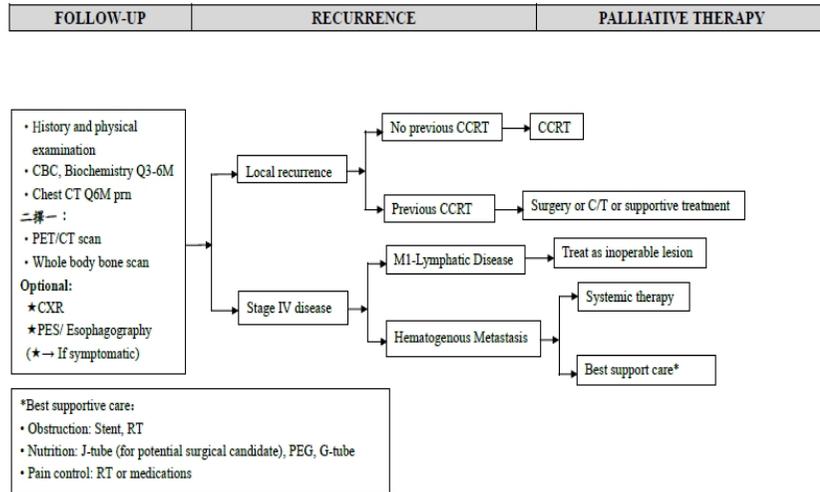


修訂內容

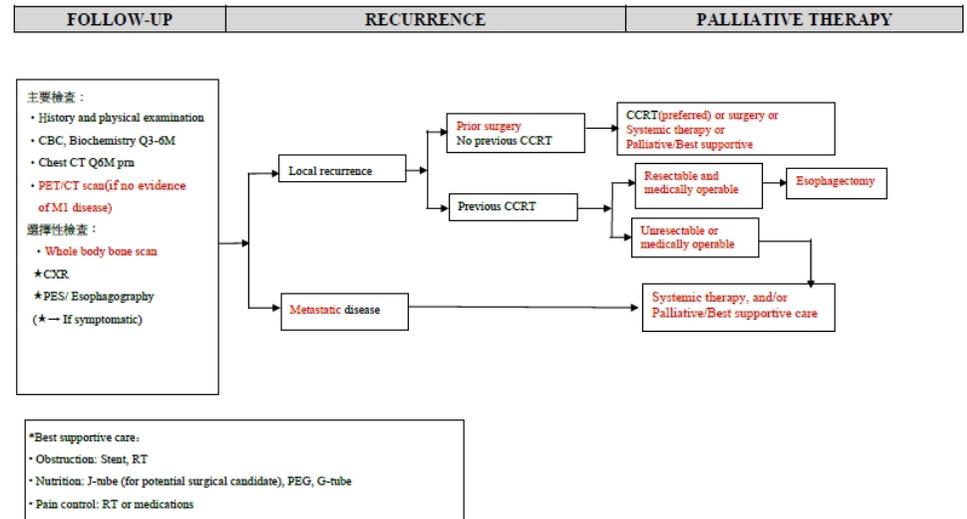
頁數	Version16.0	Version17.0												
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<ul style="list-style-type: none"> History and physical examination CBC and chemistry profile EGD and biopsy Chest or Abdominal CT / MRI Esophagography and/or upper GI series <p>二擇一：</p> <ul style="list-style-type: none"> PET/CT scan Whole body bone scan <p>Optional:</p> <ul style="list-style-type: none"> -PET/CT scan -EUS -Upper abdominal sonography -bronchoscopy: for cervix, upper and/or middle third -next-generation sequencing (NGS) 	<p>Tis and T1aN0 → Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD)</p> <p>Tis T1b-T2, N0 (low risk*) → Medically unfit and resectable or p't refuses surgery → CCRT</p> <p>Tis T1b-T2, N0 (low risk*) → Medically fit and resectable → Surgery → N(-) → pTis-pT1 → Observe and F/U</p> <p>Tis T1b-T2, N0 (low risk*) → Medically fit and resectable → Surgery → N(+), pT2, pT3, pT4a → CCRT</p> <p>T2 (high risk*) T1b-T2, N+ → Medically fit and resectable → Surgery → ypT0, N0 → C/T, if received perioperatively (category 1)</p> <p>T2 (high risk*) T1b-T2, N+ → Medically fit and resectable → Surgery → ypT+, N+ → Nivolumab (category 1)</p> <p>T2 (high risk*) T1b-T2, N+ → Neo-adjuvant CCRT (category 1) → Re-evaluation → R0 → Adjuvant CCRT/CT/RT</p> <p>T2 (high risk*) T1b-T2, N+ → Neo-adjuvant CCRT (category 1) → Re-evaluation → R1, R2 resection → Adjuvant CCRT/CT/RT</p> <p>T3-T4a, any N → CCRT</p> <p>T4, N+ or M1 → CCRT</p> <p>Inoperable, or refused surgery → Supportive care</p> <p>Inoperable, or refused surgery → Esophageal stent</p> <p>Inoperable, or refused surgery → Palliative Chemotherapy</p>	<p>*Low risk: <3cm, well differentiated.</p> <p>*High risk: ≥3cm, poorly differentiated.</p>												
WORK-UP	EVALUATION	TREATMENT												
<p>主要檢查：</p> <ul style="list-style-type: none"> History and physical examination CBC and chemistry profile EGD and biopsy Chest or Abdominal CT / MRI PET/CT scan (if no evidence of M1 disease) <p>選擇性檢查：</p> <ul style="list-style-type: none"> -EUS -Whole body bone scan -Esophagography and/or upper GI series -Upper abdominal sonography -bronchoscopy: for cervix, upper and/or middle third -next-generation sequencing (NGS) 	<p>pTis → Ablation</p> <p>pT1aN0 → Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) or Esophagectomy</p> <p>Superficial pT1b → Medically unfit and resectable or p't refuses surgery → CCRT</p> <p>cT1b-T2, N0 (low risk*) → Medically fit and resectable → Surgery → N(-) → pTis-pT1, 2 → Observe and F/U</p> <p>cT1b-T2, N0 (low risk*) → Medically fit and resectable → Surgery → N(+), pT3, pT4a → C/CCRT/Observe</p> <p>cT2 N0 (high risk*) cT1b-T2, N+ → Perioperative systemic therapy (preferred) → Surgery → N(-) → pT3, pT4a → C/CCRT/Observe</p> <p>cT2 N0 (high risk*) cT1b-T2, N+ → Perioperative systemic therapy (preferred) → Surgery → N(+), pT3, pT4a → C/CCRT/Observe</p> <p>cT2 N0 (high risk*) cT1b-T2, N+ → Neo-adjuvant CCRT → Re-evaluation → R0 → ypT0, N0 → Systemic therapy, if received perioperatively (category 1)</p> <p>cT2 N0 (high risk*) cT1b-T2, N+ → Neo-adjuvant CCRT → Re-evaluation → R0 → ypT+, N+ → Nivolumab if neo-CCRT received (category 1)</p> <p>cT3-T4a, any N → Neo-adjuvant or perioperative KI → Re-evaluation → R1, R2 resection → CCRT, if no previous CCRT Palliative management</p> <p>cT3-T4a, any N → Definitive CCRT → Inoperable, or refused surgery → Palliative management</p> <p>cT4b, N+ → unable to tolerate CCRT → Palliative RT</p> <p>cM1 → Systemic therapy, and/or Palliative/Best supportive care</p>	<p>*Low risk: <3cm, well differentiated.</p> <p>*High risk: ≥3cm, poorly differentiated, LVI(+)</p> <p>*cT4b: Consider chemotherapy alone in the setting of invasion of trachea, great vessels, vertebral body, or heart</p>												



第 11 頁



修改及新增



第 13 頁

PRINCIPLES OF SYSTEMIC THERAPY
Preoperative chemoradiation (Infusional Fluorouracil³ can be replaced with Capecitabine)
<u>Preferred Regimens</u>
• Paclitaxel and Carboplatin (category 1) ¹
• Fluorouracil and cisplatin (category 1) ^{5,6}
<u>Other Recommended Regimens</u>
• Fluorouracil ³ and Oxaliplatin (category 1) ²⁻⁴
• Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B) ⁵
Perioperative Chemotherapy
<u>Preferred Regimens</u>
• Fluorouracil and Cisplatin (category 1) ¹⁰
• Fluoropyrimidine and Oxaliplatin ^{b,c}
<u>Other Recommended Regimens</u>
• Fluorouracil, ^b Leucovorin, Oxaliplatin, and Docetaxel (FLOT) ⁹ (category 1) ²
Neoadjuvant or Perioperative Immunotherapy
<u>Useful in Certain Circumstances</u>
• MSI-H/dMMR tumors ^d
• Nivolumab and ipilimumab followed by nivolumab ^{a,11}
• Pembrolizumab ^{a,12,13}
• Tremelimumab and durvalumab for neoadjuvant therapy only ^{a,14,15}
Definitive Chemoradiation (Infusional fluorouracil can be replaced with capecitabine)
<u>Preferred Regimens</u>
• Paclitaxel and Carboplatin ¹
• Fluorouracil and Cisplatin (category 1) ¹⁶

修改及新增

PRINCIPLES OF SYSTEMIC THERAPY
Squamous Cell Carcinoma
Preoperative chemoradiation (Infusional Fluorouracil can be replaced with UFUR)
<u>Preferred Regimens</u>
• Paclitaxel and carboplatin (category 1) ⁴
• Fluorouracil and cisplatin (category 1) ^{8,9}
<u>Other Recommended Regimens</u>
• Fluorouracil and carboplatin (eGFR ≥ 60)
Neoadjuvant or Perioperative Immunotherapy
<u>Useful in Certain Circumstances</u>
• MSI-H/dMMR tumors ^a
• Nivolumab and ipilimumab followed by nivolumab ^{a,12}
• Pembrolizumab ^{b,13,14}
• Tremelimumab and durvalumab for neoadjuvant therapy only ^{b,15,16}
Definitive Chemoradiation (Infusional fluorouracil can be replaced with UFUR)
<u>Preferred Regimens</u>
• Paclitaxel and Carboplatin ⁴
• Fluorouracil and Cisplatin (category 1) ¹⁷
<u>Other Recommended Regimens</u>
• Cisplatin with Paclitaxel ^{18,20}
Postoperative Systemic Therapy
<u>Preferred Regimens</u>
• Nivolumab only after preoperative chemoradiation with R0 resection and residual disease (category 1) ^{a,21}
<u>Other Recommended Regimens</u>
for patient can't afford adjuvant ICI • may consider complete chemotherapy course (2-4 cycle)
Esophagogastric Junction adenocarcinoma
Perioperative Systemic Therapy (Infusional Fluorouracil³ can be replaced with Capecitabine or UFUR)
<u>Preferred Regimens</u>
• Fluorouracil, ³ leucovorin, oxaliplatin, and docetaxel (FLOT) ¹⁻² (category 1)



第 14 頁

<p>Other Recommended Regimens</p> <ul style="list-style-type: none"> Fluorouracil⁸ and Oxaliplatin (category 1)^{2,3} Cisplatin with Docetaxel or Paclitaxel¹⁷⁻¹⁹ <p>Postoperative Systemic Therapy</p> <p>Preferred Regimens</p> <ul style="list-style-type: none"> Nivolumab only after preoperative chemoradiation with R0 resection and residual disease (category 1)^{4,20} <p>Other Recommended Regimens</p> <ul style="list-style-type: none"> Fluoropyrimidine (infusional fluorouracil⁸ or capecitabine) Paclitaxel¹⁸ Capecitabine and oxaliplatin^{4,21} Fluorouracil⁸ and oxaliplatin <p>¹Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without Leucovorin. For important information regarding the Leucovorin shortage, please see the Discussion.</p> <p>²Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit.</p> <p>³The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.</p> <p>⁴See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.</p> <p>The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, nutritional status, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.</p>
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修改及新增

<ul style="list-style-type: none"> FLOT + durvalumab for PD-L1 CPS ≥ 1 or TAP $\geq 1\%$ (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma) <p>Other Recommended Regimens</p> <ul style="list-style-type: none"> Fluorouracil and cisplatin (category 1) Fluoropyrimidine and oxaliplatin <p>The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, nutritional status, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.</p>

第 16 頁

<p align="center">PRINCIPLES OF SYSTEMIC THERAPY</p> <p align="center">Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)</p> <p>First-Line Therapy</p> <ul style="list-style-type: none"> Oxaliplatin is generally preferred over Cisplatin due to lower toxicity. 但健保僅給付於腺癌。 <p>Preferred Regimens</p> <ul style="list-style-type: none"> HER2 overexpression positive adenocarcinoma⁴ <ul style="list-style-type: none"> Fluoropyrimidine (fluorouracil⁸ or capecitabine) and oxaliplatin and trastuzumab⁴ Fluoropyrimidine (fluorouracil⁸ or capecitabine) and cisplatin and trastuzumab (category 1)^{4,18} HER2 overexpression negative⁴ <ul style="list-style-type: none"> Fluoropyrimidine (fluorouracil⁸ or capecitabine), oxaliplatin, and nivolumab for adenocarcinoma (category 1 for PD-L1 CPS ≥ 5; category 2B for PD-L1 CPS < 5)^{4,19} Fluoropyrimidine (fluorouracil⁸ or capecitabine), oxaliplatin, and nivolumab for squamous cell carcinoma^{4,20} Fluoropyrimidine (fluorouracil⁸ or capecitabine), cisplatin, and nivolumab for squamous cell carcinoma^{4,20} Fluoropyrimidine (fluorouracil⁸ or capecitabine), oxaliplatin, and pembrolizumab (category 2A for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS < 10)^{4,21} Fluoropyrimidine (fluorouracil⁸ or capecitabine), cisplatin, and pembrolizumab (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS < 10)^{4,21} Fluoropyrimidine (fluorouracil⁸ or capecitabine) and oxaliplatin^{22,24} Fluoropyrimidine (fluorouracil⁸ or capecitabine) and cisplatin^{22,25-27} Nivolumab and ipilimumab for squamous cell carcinoma^{4,20} <p>Other Recommended Regimens (Trastuzumab⁴ should be added to first-line chemotherapy for HER2 overexpression positive adenocarcinoma)</p> <ul style="list-style-type: none"> HER2 overexpression positive adenocarcinoma⁴ <ul style="list-style-type: none"> Fluoropyrimidine (fluorouracil⁸ or capecitabine) and cisplatin and trastuzumab⁴ and pembrolizumab^{4,28} Fluoropyrimidine (fluorouracil⁸ or capecitabine) and oxaliplatin and trastuzumab⁴ and pembrolizumab^{4,28} Paclitaxel with or without cisplatin or carboplatin^{1,30-34} Docetaxel with or without cisplatin^{1,35-38} Fluoropyrimidine^{1,36,39,40} (fluorouracil⁸ or capecitabine) Docetaxel, cisplatin or oxaliplatin, and fluorouracil^{41,42} Docetaxel, carboplatin, and fluorouracil (category 2B)⁴³
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修改及新增

<p align="center">PRINCIPLES OF SYSTEMIC THERAPY</p> <p align="center">Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)</p> <p align="center">SQUAMOUS CELL CARCINOMA</p> <p>First-Line Therapy</p> <p>Preferred Regimens</p> <ul style="list-style-type: none"> Fluoropyrimidine (fluorouracil⁸ or capecitabine), cisplatin, and nivolumab for PD-L1 CPS ≥ 1 (category 1)^{4,60} Fluoropyrimidine (fluorouracil⁸ or capecitabine), cisplatin, and pembrolizumab for PD-L1 CPS ≥ 1 (category 1)^{4,61,62} Fluoropyrimidine (fluorouracil⁸ or capecitabine) and cisplatin^{35,36-38} Nivolumab and ipilimumab for PD-L1 CPS ≥ 1^{4,60} MSI-H/dMMR tumors (independent of PD-L1 status)⁶ <ul style="list-style-type: none"> Pembrolizumab^{6,39-41} Nivolumab and ipilimumab^{4,62} <p>Other Recommended Regimens</p> <ul style="list-style-type: none"> Fluorouracil⁸⁻⁹ and irinotecan⁴³ Paclitaxel with or without carboplatin or cisplatin⁴⁴⁻⁴⁸ Docetaxel with or without cisplatin⁴⁹⁻⁵² Fluoropyrimidine^{37,53,54} (fluorouracil) Docetaxel, cisplatin or carboplatin, and fluorouracil^{4,55,56} <p>Useful in Certain Circumstances</p> <ul style="list-style-type: none"> Entrectinib, larotrectinib, or repotrectinib for <i>NTRK</i> gene fusion-positive tumors (category 2B)⁵⁷⁻⁵⁹ <p align="center">PRINCIPLES OF SYSTEMIC THERAPY</p> <p align="center">Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)</p> <p align="center">ADENOCARCINOMA</p> <p>First-Line Therapy</p> <ul style="list-style-type: none"> Oxaliplatin is generally preferred over Cisplatin due to lower toxicity. <p>Preferred Regimens</p> <ul style="list-style-type: none"> HER2 overexpression positive <ul style="list-style-type: none"> Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and trastuzumab Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and pembrolizumab for PD-L1 CPS ≥ 1 (category 1) Fluoropyrimidine (fluorouracil or capecitabine), cisplatin, and trastuzumab (category 1) Fluoropyrimidine (fluorouracil or capecitabine), cisplatin, trastuzumab and pembrolizumab for PD-L1 CPS ≥ 1 (category 1) HER2 overexpression negative <ul style="list-style-type: none"> Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and nivolumab for PD-L1 CPS ≥ 1 (category 1 for PD-L1 CPS ≥ 5) Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and pembrolizumab for PD-L1 CPS ≥ 1 (category 1 for PD-L1 CPS ≥ 5) Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and zolbetuximab-clb for CLDN18.2 positive (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma) Fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin Fluoropyrimidine (fluorouracil or capecitabine), cisplatin, and pembrolizumab for PD-L1 CPS ≥ 1 (category 1 for PD-L1 CPS ≥ 5) Fluoropyrimidine (fluorouracil or capecitabine) and cisplatin MSI-H/dMMR tumors (independent of PD-L1 status) <ul style="list-style-type: none"> Pembrolizumab Nivolumab and ipilimumab Fluoropyrimidine (fluorouracil⁸ or capecitabine), oxaliplatin, and nivolumab Fluoropyrimidine (fluorouracil⁸ or capecitabine), oxaliplatin, and pembrolizumab <p>Other Recommended Regimens</p> <ul style="list-style-type: none"> Fluorouracil and irinotecan Paclitaxel with or without carboplatin or cisplatin Docetaxel with or without cisplatin Fluoropyrimidine (fluorouracil or capecitabine) Docetaxel, cisplatin or oxaliplatin, and fluorouracil <p>Useful in Certain Circumstances</p> <ul style="list-style-type: none"> Entrectinib, larotrectinib, or repotrectinib for <i>NTRK</i> gene fusion-positive tumors (category 2B)
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PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy
• Dependent on prior therapy and PS

Preferred Regimens:

- Nivolumab for esophageal squamous cell carcinoma (category 1)^{34,44}
- Pembrolizumab^{5,8}
 - For second-line therapy for esophageal squamous cell carcinoma with PD-L1 expression levels by CPS of ≥ 10 (category 1)⁴⁵
- Ramucicromab and paclitaxel for adenocarcinoma (category 1 for EGJ adenocarcinoma, category 2A for esophageal adenocarcinoma)⁴⁶
- Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma⁴⁷
- Docetaxel (category 1)^{37,38}
- Paclitaxel (category 1)^{37,34,48}
- Trifluridine and tipiracil for third-line or subsequent therapy for EGJ adenocarcinoma (category 1)⁴⁴

Other Recommended Regimens:

- Ramucicromab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)⁴⁵

Useful in Certain Circumstances:

- Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors^{60,61}
- Pembrolizumab^{5,8} for MSI-H or dMMR tumors^{62,64}
- Pembrolizumab^{5,8} for TMB high (≥ 10 mutations/megabase) tumors⁶⁵

³⁴An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
³⁷Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
³⁸See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
⁴⁴See Principles of Pathologic Review and Biomarker Testing (ES-OPH-B).
⁴⁵If no prior tumor progression while on therapy with a checkpoint inhibitor.
⁴⁷Trastuzumab should be added to first-line chemotherapy for HER2 overexpression positive adenocarcinoma. An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

修改及新增

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA

Second-Line or Subsequent Therapy
• Dependent on prior therapy and PS

Preferred Regimens:

- Nivolumab (category 1)
- Pembrolizumab for PD-L1 CPS ≥ 10 (category 1)
- Docetaxel (category 1)
- Paclitaxel (category 1)
- Irinotecan (category 1)
- Fluorouracil and irinotecan

Other Recommended Regimens:

- Irinotecan and cisplatin
- Docetaxel and irinotecan (category 2B)

Useful in Certain Circumstances:

- Entrectinib, larotrectinib, or repotrectinib for *NTRK* gene fusion-positive tumors
- Pembrolizumab for MSI-H/dMMR tumors
- Nivolumab and ipilimumab for MSI-H/dMMR tumors
- Pembrolizumab for TMB-high (TMB-H) (≥ 10 mutations/megabase) tumors
- Dabrafenib and trametinib for BRAF V600E-mutated tumors
- Selpercatinib for RET gene fusion-positive tumors

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

ADENOCARCINOMA

Second-Line or Subsequent Therapy
• Dependent on prior therapy and PS

Preferred Regimens:

- Ramucicromab and paclitaxel (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)
- Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive for adenocarcinoma
- Docetaxel (category 1)
- Paclitaxel (category 1)
- Irinotecan (category 1)
- Fluorouracil⁶⁴ and irinotecan
- Trifluridine and tipiracil for third-line or subsequent therapy for EGJ adenocarcinoma (category 1)

Other Recommended Regimens:

- Ramucicromab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)
- Irinotecan and cisplatin
- Fluorouracil and irinotecan + ramucicromab
- Irinotecan and ramucicromab
- Docetaxel and irinotecan (category 2B)

Useful in Certain Circumstances:

- Entrectinib, larotrectinib, or repotrectinib for *NTRK* gene fusion-positive tumors
- Pembrolizumab for MSI-H/dMMR tumors
- Nivolumab and ipilimumab for MSI-H/dMMR tumors
- Pembrolizumab for TMB-high (TMB-H) (≥ 10 mutations/megabase) tumors
- Dabrafenib and trametinib for BRAF V600E-mutated tumors
- Selpercatinib for RET gene fusion-positive tumors



NEOADJUVANT CHEMORADIATION
(followed by surgery for resectable cancer)

• Paclitaxel + Carboplatin

Paclitaxel	50 mg/m ²	IV	D1
Carboplatin	AUC 2	IV	D1

Weekly for 5 weeks
van Hagen P, Hulshof MC, van Lanschoot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-2084.

• Fluorouracil (5-FU) + Oxaliplatin (For ECJ adenocarcinoma)

Oxaliplatin	65 mg/m ²	IV	D1
(Leucovorin 400 mg/m ² on Day1; Fluorouracil 400 mg/m ² IV Push on Day 1)			
Fluorouracil (5-FU)	600 mg/m ²	IV	D1,29

IV continuous infusion over 24 hours daily on Days 1-2 Cycled every 14 days for 3 cycles with radiation.

1. van Hagen P, Hulshof MC, van Lanschoot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-2084.
2. Coaroy T, Galais MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGES/ACCORD17): final results of a randomised, phase 2/3 trial. *Lancet Oncol* 2014;15:305-314.

• PF

Cisplatin	60 - 80 mg/m ²	IV	D1
Fluorouracil (5-FU)	600 - 800 mg/m ²	civi	D1-4

Q4w x 2 cycles
Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer. *CALGB 9781. J Clin Oncol* 2008;26:1086-1092.

• Bi-weekly PF

Cisplatin	30 - 40 mg/m ²	IV	D1
Fluorouracil (5-FU)	1200 -1600 mg/m ² /day	civi	46-48 hours

Q2w x 3 cycles

• Cisplatin +/- Capecitabine (UFUR)

Cisplatin	25 - 30 mg/m ²	IV	D1
Capecitabine	800 mg/m ²	PO	BID
UFUR	200-250 mg/m ² /day	PO	BID

Qw x 12 cycles
Lee SS, Kim SB, Park SI, et al. Capecitabine and cisplatin chemotherapy (XP) alone or sequentially combined chemoradiotherapy containing XP regimens in patients with three different settings of stage IV esophageal cancer. *Jpn J Clin Oncol* 2007;37:829-835.

• Capecitabine + Oxaliplatin

Oxaliplatin	65 mg/m ²	IV	D1, 15, and 29 for 3 doses
Capecitabine	625 mg	PO	BID

D1-5 weekly for 5 weeks
Javie MM, Yang G, Nwogu CE, et al. Capecitabine, oxaliplatin and radiotherapy: a phase IB neoadjuvant study for esophageal cancer with gene expression analysis. *Cancer Invest* 2009;27:193-200.

• Capecitabine + Cisplatin

Cisplatin	30 mg/m ²	IV	D1
Capecitabine	625 mg	PO	BID

D1-5 weekly for 5 weeks

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trial: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

修改及新增

NEOADJUVANT CHEMORADIATION

PREFERRED REGIMENS

Paclitaxel + Carboplatin

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Paclitaxel	50 mg/m ²	IV	D1	Weekly for 5 weeks	
Carboplatin	AUC 2	IV	D1		
Ref.	van Hagen P, Hulshof MC, van Lanschoot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. <i>N Engl J Med</i> 2012;366:2074-2084.				

Fluorouracil and cisplatin

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin/or carboplatin (AUC 6)	60 - 80 mg/m ²	IV	D1	Cycled every 28 days for 2 cycles	
Fluorouracil (5-FU)	600 - 800 mg/m ² /day	IV	continuous infusion over 24 hours daily,D1-4		
or					
Cisplatin/or carboplatin (AUC 3)	30 - 40 mg/m ²	IV	D1	Cycled every 14 days for 3 cycles	
Fluorouracil (5-FU)	1200 -1600 mg/m ²	IV	drip 46-48 hours, D1-2		
Ref.	Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer. <i>CALGB 9781. J Clin Oncol</i> 2008;26:1086-1092.				

Cisplatin +UFUR

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin	25 - 30 mg/m ²	IV	D1	Weekly for 5 weeks	不願 24-48 小時注射或 不適合放置人工血管
UFUR	200-250 mg/m ² /day	PO	Bid,D1-5		
Ref.	Iwase, H., Shimada, M., Nakamura, M., Nakarai, K., Iyo, T., Katada, S., Indo, T., Kato, E., Horiuchi, Y., & Kusugami, K. (2003). Concurrent chemoradiotherapy for locally advanced and metastatic esophageal cancer: Long-term results of a phase II study of UFT/CDDP with radiotherapy. <i>International Journal of Clinical Oncology</i> , 8(3), 305-311.				

修改及新增

NEOADJUVANT OR PERIOPERATIVE IMMUNOTHERAPY

USEFUL IN CERTAIN CIRCUMSTANCES

(MSI-High/MMS tumors)

Nivolumab and ipilimumab followed by nivolumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Nivolumab	240mg	IV	D1	every 2 weeks	(preoperative for at least 12 total week), followed by surgery and adjuvant nivolumab 480 mg IV every 4 weeks for 9 cycles
Ipilimumab	1 mg/kg	IV	D1	every 6 weeks	
Ref.	Andre T, Tougeron D, Piesen G, et al. Neoadjuvant Nivolumab Plus Ipilimumab and Adjuvant Nivolumab in Localized Deficient Mismatch Repair/Microsatellite Instability-High Gastric or Esophagogastric Junction Adenocarcinoma: The GERCOR/NEONIGFA Phase II Study. <i>J Clin Oncol</i> 2023;41:255-265.				

Pembrolizumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Pembrolizumab	200 mg	IV	D1	every 3 weeks for at least 12 total weeks	followed by surgery and adjuvant pembrolizumab 200 mg IV every 3 weeks for 16 cycles ¹³
Ref.	Ludford K, Ho WJ, Thomas JT, et al. Neoadjuvant Pembrolizumab in Localized Microsatellite Instability-High/Deficient Mismatch Repair Solid Tumors. <i>J Clin Oncol</i> 2023;41:2181-2190.				



NEOADJUVANT CHEMORADIATION
(followed by surgery for resectable cancer)

• Paclitaxel + Carboplatin

Paclitaxel	50 mg/m ²	IV	D1
Carboplatin	AUC 2	IV	D1

Weekly for 5 weeks

van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-2084.

• Fluorouracil (5-FU) + Oxaliplatin (For ECJ adenocarcinoma)

Oxaliplatin	65 mg/m ²	IV	D1
(Leucovorin 400 mg/m ² on Day1; Fluorouracil 400 mg/m ² IV Push on Day 1)			
Fluorouracil (5-FU)	600 mg/m ²	IV	D1,29

IV continuous infusion over 24 hours daily on Days 1-2 Cycled every 14 days for 3 cycles with radiation.

1. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-2084.

2. Conroy T, Galaix MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE/ACCORD17): final results of a randomised, phase 2/3 trial. *Lancet Oncol* 2014;15:305-314.

• PF

Cisplatin	60 - 80 mg/m ²	IV	D1
Fluorouracil (5-FU)	600 - 800 mg/m ²	civi	D1-4

Q4w x 2 cycles

Tepper J, Krznai M, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer. *CALGB 9781. J Clin Oncol* 2008;26:1086-1092.

• Bi-weekly PF

Cisplatin	30 - 40 mg/m ²	IV	D1
Fluorouracil (5-FU)	1200 - 1600 mg/m ² /day	civi	46-48 hours D1

Q2w x 3 cycles

• Cisplatin +/- Capecitabine (UFUR)

Cisplatin	25 - 30 mg/m ²	IV	D1
Capecitabine	800 mg/m ²	PO	BID D1-5
UFUR	200-250 mg/m ² /day	PO	BID D1-5

Qw x 12 cycles

Lee SS, Kim SB, Park SI, et al. Capecitabine and cisplatin chemotherapy (XP) alone or sequentially combined chemoradiotherapy containing XP regimen in patients with three different settings of stage IV esophageal cancer. *Jpn J Clin Oncol* 2007;37:829-835.

• Capecitabine + Oxaliplatin

Oxaliplatin	65 mg/m ²	IV	D1, 15, and 29 for 3 doses
Capecitabine	625 mg	PO	BID D1-5 weekly for 5 weeks

Javle MM, Yang G, Nwogu CE, et al. Capecitabine, oxaliplatin and radiotherapy: a phase IB neoadjuvant study for esophageal cancer with gene expression analysis. *Cancer Invest* 2009;27:193-200.

NEOADJUVANT OR PERIOPERATIVE IMMUNOTHERAPY

USEFUL IN CERTAIN CIRCUMSTANCES

(MSI-H/dMMR tumors)

Tremelimumab and durvalumab (for neoadjuvant therapy only)

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Tremelimumab	300 mg	IV	D1	For 12 weeks preoperatively for 1 cycle only	
Durvalumab	1500mg	IV	D1, 29, and 57		

Ref.

Kelly RJ, Lee J, Bang YJ, et al. Safety and Efficacy of Durvalumab and Tremelimumab Alone or in Combination in Patients with Advanced Gastric and Gastroesophageal Junction Adenocarcinoma. *Clin Cancer Res* 2020;26:846-854.
Pietrantonio F, Raimondi A, Lonardi S, et al. INFIGHT: A multicentre, single-arm, multi-cohort, phase II trial of tremelimumab and durvalumab as neoadjuvant treatment of patients with microsatellite instability-high (MSI) resectable gastric or gastroesophageal junction adenocarcinoma (GAC/GEJAC). *Journal of Clinical Oncology* 2023;41:358-358.

修改及新增

DEFINITIVE CHEMORADIATION

Preferred Regimens

Paclitaxel + Carboplatin

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Paclitaxel	50 mg/m ²	IV	D1	Weekly for 5 weeks	
Carboplatin	AUC 2	IV	D1		

Ref.

van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-2084.

PF

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin/or carboplatin (AUC 6)	60 - 80 mg/m ²	IV	D1	Cycled every 28 days for total 4 cycles	2 cycles with radiation followed by 2 cycles without radiation
Fluorouracil (5-FU)	600 - 800 mg/m ² /day	IV	continuous infusion over 24 hours daily,D1-4		
or					
Cisplatin/or carboplatin (AUC3)	30 - 40 mg/m ²	IV	D1	Cycled every 14 days for 6-8 cycles	3-4 cycles with radiation followed by 3-4cycles without radiation
Fluorouracil (5-FU) + Leucovorin(200mg)	1200 - 1600 mg/m ²	IV	drip 46-48 hours, D1-2		

Ref.

Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002;20:1167-1174.

Preferred Regimens

Cisplatin +UFUR

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin	25 - 30 mg/m ²	IV	D1	Weekly for 5 weeks	不願 24-48 小時注射 或不適合放置人工血管
UFUR	200-250 mg/m ² /day	PO	Bid,D1-5		

Ref.

Iwase, H., Shimada, M., Nakamura, M., Nakarai, K., Iyo, T., Kaida, S., Indo, T., Kato, E., Horiuchi, Y., & Kusugami, K. (2003). Concurrent chemoradiotherapy for locally advanced and metastatic esophageal cancer: Long-term results of a phase II study of UFT/CDP with radiotherapy. *International Journal of Clinical Oncology*, 8(5), 305-311.

OTHER RECOMMENDED REGIMENS

Paclitaxel +cisplatin

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Paclitaxel	60 mg/m ²	IV	D1,8,15,22	1cycle	
cisplatin	75 mg/m ²	IV	D1		

Ref.

Urba SG, Orringer MB, Iannettoni M, et al. Concurrent cisplatin, paclitaxel, and radiotherapy as preoperative treatment for patients with locoregional esophageal carcinoma. *Cancer* 2003;93:2177-2183.



POSTOPERATIVE ADJUVANT THERAPY

• Nivolumab

Nivolumab	240 mg	IV	every 14 days for 16 weeks
followed by Nivolumab 480 mg every 28 days			
Maximum treatment duration of 1 year			
自費 3mg/kg IV			

Kelly R, Ajani J, Kuzdal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemotherapy: first results of the CheckMate 577 study. [abstract]. Presented at the Oral Presentation presented at the ESMO 2020 Annual Meeting, September 19-21, 2020; Virtual Meeting.

• or complete preoperative chemotherapy course

修改及新增

POSTOPERATIVE ADJUVANT THERAPY

PREFERRED REGIMEN

Nivolumab

	Dosage	Route of administration	Times	Frequency/Duration	Notes
Nivolumab	240 mg or 自費 3mg/kg	IV	D1	every 14 days for 16 weeks	followed by Nivolumab 480 mg every 28 days • Maximum treatment duration of 1 year
Ref.	Kelly R, Ajani J, Kuzdal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemotherapy: first results of the CheckMate 577 study. [abstract]. Presented at the Oral Presentation presented at the ESMO 2020 Annual Meeting; September 19-21, 2020; Virtual Meeting.				

Other Recommended Regimens

for patient can't afford adjuvant ICI • may consider complete chemotherapy course(2-4 cycle)

PERIOPERATIVE CHEMOTHERAPY

(Only for adenocarcinoma of the thoracic esophagus or EGJ)

• FOLFOX

Oxaliplatin	85 mg/m ²	IV	D1
Leucovorin	200 mg/m ²	Civi 46-48 hours	D1,2
Fluorouracil (5-FU)	2600 mg/m ²	civi 46-48 hours	D1,2

Q2w(4 cycles preoperative and 4 cycles postoperative)

Al-Batran S-E, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008;26:1435-1442.

• FLOT

Fluorouracil (5-FU)	2600 mg/m ²	civi	46-48 hours	D1,2
Leucovorin	200 mg/m ²	civi	46-48 hours	D1
Oxaliplatin	85 mg/m ²	IV	D1	
Docetaxel	30 mg/m ²	IV	D1	

Q2w (4 cycles preoperative and 4 cycles postoperative)

Al-Batran S-E, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastroesophageal junction adenocarcinoma (FLOG4): a randomised, phase 2/3 trial. Lancet 2019;393:1948-1957.

• Cisplatin + Fluorouracil (5-FU)

Cisplatin	80 mg/m ²	IV	D1
Fluorouracil (5-FU)	800 - 1000 mg/m ² /cl	civi	D1-4

Q4w total 6 cycles (2-3 cycles before operation)

修改及新增

PERIOPERATIVE SYSTEMIC THERAPY (Esophagogastric Junction adenocarcinoma)

Preferred Regimens

FLOT

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Fluorouracil (5-FU)	2600 mg/m ²	IV	drip 46-48 hours, D1-2	Cycled every 14days for total 8 cycles	4 cycles preoperative and 4 cycles postoperative
Leucovorin	200 mg/m ²	IV	drip 46-48 hours, D1-2		
Oxaliplatin	85 mg/m ²	IV	D1		
Docetaxel	30 mg/m ²	IV	D1		
Ref.	Al-Batran S-E, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastroesophageal junction adenocarcinoma (FLOG4): a randomised, phase 2/3 trial. Lancet 2019;393:1948-1957.				

FLOT +durvalumab

Drug Combination(durvalumab	Dosage	Route of administration	Times	Frequency/Duration	Notes
durvalumab	1500	IV	D1	Cycled every 28days for total 4cycles	2cycles preoperative and 2cycles postoperative followed by Durvalumab 1500 mg IV on Day 1 every 4 weeks for 10 additional cycles
Fluorouracil (5-FU)	2600 mg/m ²	IV	drip 46-48 hours, D1-2,15-16		
Leucovorin	200 mg/m ²	IV	drip 46-48 hours, D1-2,15-16		
Oxaliplatin	85 mg/m ²	IV	D1		
Docetaxel	30 mg/m ²	IV	D1		
Ref.	Janjigian YY, Al-Batran SE, Wainberg ZA, et al. Perioperative durvalumab in gastric and gastroesophageal junction cancer. N Engl J Med 2025;393:217-230.				

OTHER RECOMMENDED REGIMENS

Fluorouracil+Cisplatin

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin	50 mg/m ²	IV	D1	Cycled every 14days for total 8 cycles	4 cycles preoperative and 4 cycles postoperative
Fluorouracil (5-FU)	2000 mg/m ²	IV	drip 46-48 hours, D1-2		
Ref.	National Comprehensive Cancer Network. (2025). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Esophageal and Esophagogastric Junction Cancers (Version 4.2025).				

Fluoropyrimidine and oxaliplatin

Drug Combinatio	Dosage	Route of administration	Times	Frequency/Duration	Notes
Fluorouracil (5-FU)	1200mg/m ² /day	IV	continuous infusion over 24 hours daily, D1 and 2	Cycled every 14days for total 8 cycles	4 cycles preoperative and 4 cycles postoperative
Fluorouracil (5-FU)	400mg/m ²	IV push	D1		
Leucovorin	400mg/m ²	IV	D1		
Oxaliplatin	85 mg/m ²	IV	D1		
Ref.	Enzinger PC, Burness BA, Niedzwiecki D, et al. CALGB 80403 (Alliance)/E1206: a randomized phase II study of three chemotherapy regimens plus cetuximab in metastatic esophageal and gastroesophageal junction cancers. J Clin Oncol 2016;34:2736-2742.				

Fluoropyrimidine and oxaliplatin

Drug Combinatio	Dosage	Route of administration	Times	Frequency/Duration	Notes
Fluorouracil (5-FU)	2600 mg/m ²	IV	drip 46-48 hours, D1-2	Cycled every 14days for total 8 cycles	4 cycles preoperative and 4 cycles postoperative
Leucovorin	200 mg/m ²	IV	drip 46-48 hours, D1-2		
Oxaliplatin	85 mg/m ²	IV	D1		
Ref.	Al-Batran S-E, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008;26:1435-1442.				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated), 化療處方
修改及新增

Chemotherapy for stage IV cancer

• Cisplatin + Fluorouracil (5-FU)

Cisplatin	80 mg/m ²	IV	D1
Fluorouracil (5-FU)	800 - 1000 mg/m ² /d	civi	D1-4

Q4w total 3-6 cycles

Lorenzen S, Schuster T, Porschen R, et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. *Ann Oncol* 2009;20:1667-1673.

• PFL

Cisplatin	40 - 50 mg/m ²	IV	D1
Leucovorin	200 mg/m ²	civi	46-48 hours D1,2
Fluorouracil (5-FU)	1600-2000 mg/m ²	civi	46-48 hours D1,2

Q2W x 12 cycles

Hung TC et al. Weekly 24-hour infusional 5-fluorouracil as initial treatment for advanced gastric cancer with acute disseminated intravascular coagulation. *Anticancer Res* 2008;28:1293.

• Docetaxel

Docetaxel	30 - 35 mg/m ²	IV	D1, 8 Q3w
OR			
Docetaxel	22 - 25 mg/m ²	IV	D1, 8, 15 Q4w

Albertsson M et al. Phase II studies on docetaxel alone every third week, or weekly in combination with gemcitabine in patients with primary locally advanced, metastatic, or recurrent esophageal cancer. *Med Oncol* 2007;24:407.

• Paclitaxel

Paclitaxel	60 - 80 mg/m ²	IV	D1, 8, 15
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Q4w total 3-6 cycles

Iison DH et al. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. *Ann Oncol* 2007;18:898.

• Paclitaxel + Cisplatin

Paclitaxel	60 - 80 mg/m ²	IV	D1, 8, 15
Cisplatin	70 - 80 mg/m ²	IV	D1

Q4w x 3 -6 cycles

1. Komek, GV et al. Effective combination chemotherapy with paclitaxel and cisplatin with or without human granulocyte colony-stimulating factor and/or erythropoietin in patients with advanced gastric cancer. *Br J Cancer* 2002; 86:1858.

2. Iison DH et al. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. *Ann Oncol* 2007;18:898.

修改及新增

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)
SQUAMOUS CELL CARCINOMA(FIRST-LINE THERAPY)

PREFERRED REGIMENS

Cisplatin + Fluorouracil (5-FU)

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin/or carboplatin (AUC 6)	80 mg/m ²	IV	D1	every 28 days	
Fluorouracil (5-FU)	750 - 1000 mg/m ² /day	IV	continuous infusion over 24 hours daily, D1-4		
Ref.	Lorenzen S, Schuster T, Porschen R, et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. <i>Ann Oncol</i> 2009;20:1667-1673.				

PFL

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin/or carboplatin (AUC 2)	40 - 50 mg/m ²	IV	D1	every 14 days	
Leucovorin	200 mg/m ²	IV	drip 46-48 hours, D1-2		
Fluorouracil (5-FU)	1600-2000 mg/m ²	IV	drip 46-48 hours, D1-2		
Ref.	Hung TC et al. Weekly 24-hour infusional 5-fluorouracil as initial treatment for advanced gastric cancer with acute disseminated intravascular coagulation. <i>Anticancer Res</i> 2008;28:1293				

Cisplatin + Fluorouracil (5-FU) + nivolumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin/or carboplatin (AUC 6)	80 mg/m ²	IV	D1	every 28days	
Fluorouracil (5-FU)	800 mg/m ² /day	IV	continuous infusion over 24 hours daily, D1-5		
nivolumab	240mg	IV		every 14 days	per study maximum of 2
Ref.	Doki Y, Ajani JA, Kato K, et al. Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. <i>N Engl J Med</i> 2022;386:449-462.				

Cisplatin +Capecitabine + nivolumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin	80 mg/m ²	IV	D1	every 21days	
Capecitabine	850-1000mg	PO	Bid,D1-14		
nivolumab	360mg	IV	D1		
Ref.	Kang YK, Kang WK, Shin DB, et al. Capecitabine/ cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. <i>Ann Oncol</i> 2009;20:666-673.				

Cisplatin + Fluorouracil (5-FU) +Pembrolizumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin	80 mg/m ²	IV	D1	every 21days for up to 6cycles	
Fluorouracil (5-FU)	800 mg/m ² /day	IV	continuous infusion over 24 hours daily on Days 1-5		
Pembrolizumab	200mg	IV	D1	every 21 days	up to 2 years
Ref.	Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. <i>Lancet</i> 2021;398:759-771.				

Cisplatin +Capecitabine +Pembrolizumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin	80 mg/m ²	IV	D1	every 21 days for 6cycles(total of 18weeks)	
Capecitabine	850-1000mg	PO	Bid,D1-14		
Pembrolizumab	200mg	IV	D1		
Ref.	Rho SY, Oh DY, Yanez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. <i>Lancet Oncol</i> 2023;24:1181-1195.				



• S-1 (TS-1)

Tegafur/potassium oxonate/gimeracil	BSA < 1.25	40 mg	BID
	BSA 1.25 - 1.5	50 mg	BID
	BSA ≥ 1.5	60 mg	BID

4 weeks on, 2 weeks off (or 2 weeks on, 1 weeks off), 1 year

Sakuramoto S, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med*. 2007;357:1810. S-1 Monotherapy as Second- or Third-Line Chemotherapy for Unresectable and Recurrent Esophageal Squamous Cell Carcinoma Akutsu Y · Kono T · Uesato M · Hoshino I · Narushima K · Hanasaka T · Tochigi T · Semba Y · Qiu W · Matsubara H. Department of Frontier Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan

• Pembrolizumab

(for second-line therapy for esophageal squamous cell carcinoma, esophageal adenocarcinoma, and EGJ adenocarcinoma with PD-L1 expression levels by CPS of ≥10 or for third-line or subsequent therapy for esophageal and EGJ adenocarcinoma with PD-L1 expression levels by CPS of ≥1)

Pembrolizumab	200 mg	IV	D1
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Cycled every 21 days

1. Kojima T, Muro K, Francois E, et al. Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: phase III KEYNOTE-181 study. *J Clin Oncol* 2019;37:2.

2. Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. *JAMA Oncol* 2018;4:e180013.

• Nivolumab+ipilimumab (for squamous cell carcinoma)^{1,2}

Nivolumab	3 mg/kg	IV	every 2 weeks
Ipilimumab	1 mg/kg	IV	every 6 weeks

per study, maximum of 2 years

Doki Y, Ajani JA, Kato K, et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma *N Engl J Med* 2022;386:449-462.

Nivolumab+ipilimumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Nivolumab	3 mg/kg	IV	D1	every 2 weeks	(per study, maximum of 2 years)
Ipilimumab	1 mg/kg	IV	D1	every 6 weeks	
Ref.	Doki Y, Ajani JA, Kato K, et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. <i>N Engl J Med</i> 2022;386:449-462.				

OTHER RECOMMENDED REGIMENS

Fluorouracil and irinotecan

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	180 mg/m ²	IV	D1	Cycled every 14 days	
Leucovorin	400 mg/m ²	IV	on Day 1		
Fluorouracil	400 mg/m ²	IV Push	on Day 1		
Fluorouracil	1200 mg/m ² /days	IV	IV continuous infusion over 24 hours daily on Days 1 and 2		

Ref. Gumbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French Intergroup (Federation Francophone de Cancérologie Digestive, Federation Nationale des Centres de Lutte Contre le Cancer, and Groupe Cooperateur Multidisciplinaire en Oncologie) study. *J Clin Oncol* 2014;32:3520-3526.

OTHER RECOMMENDED REGIMENS

Paclitaxel with or without carboplatin or cisplatin

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Paclitaxel	175 mg/m ²	IV	on Day 1	Cycled every 21 days	
Carboplatin	AUC 5	IV	on Day 1		
or					
Paclitaxel	60-80 mg/m ²	IV	on D1,8,15	Cycled every 28 days	
Cisplatin	70-80 mg/m ²	IV	on Day 1		
or					
Paclitaxel	135-200mg/m ²	IV	on Day 1	Cycled every 21 days	
Cisplatin	75 mg/m ²	IV	on Day 1		
or					
Paclitaxel	90 mg/m ²	IV	on Day 1	Cycled every 14 days	
Cisplatin	50 mg/m ²	IV	on Day 1		
or					
Paclitaxel	132-250mg/m ²	IV	on Day 1	Cycled every 21 days	
or					
Paclitaxel	60-80 mg/m ²	IV	on D1,8,15	Cycled every 28 days	
or					
Ref.	1. Gadgeel SM, Shields AF, Hellron LK, et al. Phase II study of paclitaxel and carboplatin in patients with advanced gastric cancer. <i>Am J Clin Oncol</i> 2003;26:37-41. 2. Ison DH, Forastiere A, Arquette M, et al. A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. <i>Cancer J</i> 2000;6:316-323.				

OTHER RECOMMENDED REGIMENS

Ref.	3. Parnoch S, Wielt A, Retmacher A, et al. Chemotherapy with cisplatin and paclitaxel in patients with locally advanced, recurrent or metastatic oesophageal cancer. <i>Br J Cancer</i> 1998;78:511-514. 4. Ajani JA, Ison DH, Dougherty K, et al. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. <i>J Natl Cancer Inst</i> 1994;86:1086-1091. 5. Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: JCOG 4007 trial. <i>J Clin Oncol</i> 2013;31:4438-4444.				
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Docetaxel with or without cisplatin

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Docetaxel	70-85 mg/m ²	IV	D1	every 21 days	
Cisplatin	70-75 mg/m ²	IV	D1		
or					
Docetaxel	30-35 mg/m ²	IV	D1 - 8	every 21 days	
or					
Docetaxel	22-25 mg/m ²	IV	D1 - 8 - 15	every 28 days	
or					
Docetaxel	60-75mg/m ²	IV	D1	every 21 days	
or					

Ref. 1. Ajani JA, Fodor MB, Tykarski SA, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. *J Clin Oncol* 2005;23:5660-5667.
2. Kim JY, Do YR, Park KU, et al. A multi-center phase II study of docetaxel plus cisplatin as first-line therapy in patients with metastatic squamous cell esophageal cancer. *Cancer Chemother Pharmacol* 2010;66:31-36.



OTHER RECOMMENDED REGIMENS

Fluoropyrimidine

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Leucovorin	400 mg/m ²	IV	D1	Cycled every 14 days	
Fluorouracil	400 mg/m ²	IV Push	on Day 1		
Fluorouracil	1200 mg/m ² /days	IV	IV continuous infusion over 24 hours daily on Days 1 and 2	Cycled every 21 days	
Capecitabine	850-1000 mg/m ²	PO	BID, on D 1-14		
Fluorouracil	800mg/m ²	IV	IV continuous infusion over 24 hours daily on Days 1-5	Cycled every 28 days	
Ref.	1. Bosche O, Baroul JL, Bonnetain F, et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (L ² 3FU2), L ² 3FU2 plus epirubicin, or L ² 3FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancérologie Digestive Group Study-FPCD 9803. <i>J Clin Oncol</i> 2004;22:4319-4328. 2. Ohno A, Shimada Y, Shirao K, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus irinotecan and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). <i>J Clin Oncol</i> 2003;21:54-59. 3. Hoeg YS, Song SY, Lee SJ, et al. A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer. <i>Ann Oncol</i> 2004;15:1344-1347.				

OTHER RECOMMENDED REGIMENS

Docetaxel, cisplatin, and fluorouracil

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Docetaxel	40 mg/m ²	IV	on Day 1	Cycled every 14 days	
Leucovorin	400 mg/m ²	IV	on Day 1		
Fluorouracil	400 mg/m ²	IV	on Day 1	Cycled every 14 days	
Fluorouracil	1000 mg/m ² /day	IV	IV continuous infusion over 24 hours daily on Days 1 and 2		
Cisplatin	40 mg/m ²	IV	on Day 3		
Ref.	1. Shah MA, Jonghign YY, Stoller R, et al. Randomized multicenter phase II study of modified docetaxel, cisplatin, and fluorouracil (DCF) versus DCF plus growth factor support in patients with metastatic gastric adenocarcinoma: a study of the US Gastric Cancer Consortium. <i>J Clin Oncol</i> 2013;33:3874-3879. 2. Blum Murphy MA, Qiao W, Mesuda N, et al. A phase I/II study of docetaxel, oxaliplatin, and fluorouracil (D-FOX) chemotherapy in patients with unresected locally unresectable or metastatic adenocarcinoma of the stomach and gastroesophageal junction. <i>Am J Clin Oncol</i> 2018;41:321-325.				

S-1 (TS-1)

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Tegafur/potassium oxonate/gimeracil	40mg	PO	Bid	4 weeks on, 2 weeks off (or 2 weeks on, 1 weeks off), for 1 year	BSA \geq 1.25
Tegafur/potassium oxonate/gimeracil	50mg	PO	Bid		BSA 1.25 - 1.5

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA (FIRST-LINE THERAPY)

OTHER RECOMMENDED REGIMENS

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Tegafur/potassium oxonate/gimeracil	60mg	PO	Bid		BSA \geq 1.5
Ref.	Sakuramoto S, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. <i>N Engl J Med</i> . 2007;357:1810. S-1 Monotherapy as Second- or Third-Line Chemotherapy for Unresectable and Recurrent Esophageal Squamous Cell Carcinoma Akutsu Y · Kano T · Uekato M · Hashino I · Narushima K · Hanada T · Tochigi T · Senba Y · Qin W · Matsubara H. Department of Frontier Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan				

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

ADENOCARCINOMA (FIRST-LINE THERAPY)

HER2 overexpression-positive

Trastuzumab with chemotherapy (Fluoropyrimidine and oxaliplatin)

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Trastuzumab	8 mg/kg IV loading dose on Day 1 of cycle 1, then 6 mg/kg	IV	drip 90 mins, then 60 mins, day 1	every 21 days	HER2 overexpression-positive
Trastuzumab	6 mg/kg IV loading dose on Day 1 of cycle 1, then 4 mg/kg	IV	drip 90 mins, then 60 mins, day 1	every 14 days	
Ref.	Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. <i>Lancet</i> 2010;376:687-697.				
Oxaliplatin	85 mg/m ²	IV	on Day 1	Cycled every 14 days	
Leucovorin	200 mg/m ²	IV	continuous infusion over 24 hours on Day 1		
Fluorouracil	2600 mg/m ²	IV	continuous infusion over 24 hours on Day 1		
Capecitabine	850-1000 mg/m ²	PO	BID, On D 1-14	Cycled every 21 days	
Oxaliplatin	130 mg/m ²	IV	drip 120 mins, on Day 1		



	or		on D 1-14	Cycled every 21 days
Capecitabine	625 mg/m ² BID	PO	on Day 1	
Oxaliplatin	85 mg/m ²	IV	on Day 1	

1. Al-Batran S-E, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2008;26:1425-1442.
 2. Kruiger PC, Burmas RA, Miedwiecki D, et al. CALGB 80403 (Alliance)/E1206: a randomized phase II study of three chemotherapy regimens plus cetuximab in metastatic esophageal and gastroesophageal junction cancers. *J Clin Oncol* 2016;34:2736-2742.
 3. Kim GM, Jeung HC, Rha SY, et al. A randomized phase II trial of S-1-oxaliplatin versus capecitabine-oxaliplatin in advanced gastric cancer. *Eur J Cancer* 2012;48:318-326.
 4. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725-730.

Trastuzumab with chemotherapy (Fluoropyrimidine and cisplatin)					
Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Trastuzumab	8 mg/kg IV loading dose on Day 1 of cycle 1, then 6 mg/kg	IV	drip 90 mins, then 60 mins, day 1	every 21 days	HER2 overexpression-positive
Trastuzumab	6 mg/kg IV loading dose on Day 1 of cycle 1, then 4 mg/kg	IV	drip 90 mins, then 60 mins, day 1	every 14 days	
Ref.	Bang EJ, Van Cutsem E, Feyerherova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. <i>Lancet</i> 2010;376:687-697.				

+					
Cisplatin	75-100 mg/m ²	IV	on Day 1	continuous infusion over 24 hours daily on Days 1-4	Cycled every 28 days
Fluorouracil	750-1000 mg/m ² /day	IV			
or					
Cisplatin	50 mg/m ²	IV	on Day 1	IV continuous infusion over 24 hours daily on Day 1	Cycled every 14 days
Leucovorin	200 mg/m ²	IV			
Fluorouracil	2600 mg/m ²	IV			
or					
Cisplatin	80 mg/m ²	IV	daily on Day 1	Cycled every 21 days	
Capecitabine	850-1000 mg/m ²	PO	BID on D1-14		

+					
Cisplatin	80 mg/m ²	IV	daily on Day 1	Cycled every 21 days	
Capecitabine	850-1000 mg/m ²	PO	BID on D1-14		

1. Lorenzen S, Schuster T, Porschen K, et al. Capecitabine plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. *Ann Oncol* 2009;20:1667-1673.
 2. Al-Batran S-E, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2008;26:1425-1442.
 3. Bosche O, Raoul JL, Boucsein F, et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancérologie Digestive Group Study-FFCD 9803. *J Clin Oncol* 2004;22:4319-4328.
 4. Kang YK, Kang WK, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomized phase III noninferiority trial. *Ann Oncol* 2009;20:666-673.

Trastuzumab and pembrolizumab with fluoropyrimidine and oxaliplatin or fluoropyrimidine and cisplatin					
Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Trastuzumab	8 mg/kg loading dose on Day 1 of cycle 1, then 6 mg/kg	IV	drip 90 mins, then 60 mins, day 1	every 21 days	HER2 overexpression-positive
Pembrolizumab	200 mg	IV	on Day 1	Cycled every 3 weeks	
Ref.	1. Anjifan YY, Kawano A, Yano F, et al. Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analysis from the phase 3 KEYNOTE-811 randomized placebo-controlled trial. <i>Lancet</i> 2023;402:2197-2208. 2. Bang EJ, Van Cutsem E, Feyerherova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. <i>Lancet</i> 2010;376:687-697. 3. Anjifan YY, Kawano A, Yano F, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. <i>Nature</i> 2021;600:727-730.				
+					
Capecitabine	850-1000 mg/m ²	PO	BID, D1-14	Cycled every 21 days	
Oxaliplatin	130 mg/m ²	IV	drip 120 mins, on Day 1		
or					
Cisplatin	80 mg/m ²	IV	D 1	continuous infusion over 24 hours daily on Days 1-5	Cycled every 21 days
Fluorouracil	800 mg/m ² /day	IV			
or					
Cisplatin	80 mg/m ²	IV	D 1	Cycled every 21 days	
Capecitabine	850-1000 mg/m ²	PO	Bid, D1-14		

+					
Cisplatin	80 mg/m ²	IV	D 1	Cycled every 21 days	
Capecitabine	850-1000 mg/m ²	PO	Bid, D1-14		

1. Kim GM, Jeung HC, Rha SY, et al. A randomized phase II trial of S-1-oxaliplatin versus capecitabine-oxaliplatin in advanced gastric cancer. *Eur J Cancer* 2012;48:318-326.
 2. Anjifan YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet* 2021;398:27-40.
 3. Kang YK, Kang WK, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomized phase III noninferiority trial. *Ann Oncol* 2009;20:666-673.

Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and nivolumab					
Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Oxaliplatin	130 mg/m ²	IV	D 1	every 21 days	per study maximum of 2 years
Capecitabine	850-1000mg	PO	Bid, D1-14		
nivolumab	360mg	IV	D1		
Ref.	1. Anjifan YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. <i>Lancet</i> 2021;398:27-40. 2. Doki Y, Ajani JA, Kato K, et al. Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. <i>N Engl J Med</i> 2022;386:449-462.				



Oxaliplatin + Fluorouracil (5-FU) + Pembrolizumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Oxaliplatin	85mg/m ²	IV	D1	Cycled every 14 days for up to 9 cycles (total 18 weeks)	
Leucovorin	400mg	IV	continuous infusion over 24 hours daily on Days 1		
Fluorouracil	400mg	IV push	D1		
Fluorouracil	1200mg/m ² /day	IV	continuous infusion over 24 hours daily on Days 1 and 2		
Pembrolizumab	200mg	IV	D1		
Ref.	Rha SY, Oh DY, Yanez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. <i>Lancet Oncol</i> 2023;24:1181-1193.				

Oxaliplatin + Capecitabine + Pembrolizumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Oxaliplatin	130mg/m ²	IV	D1	every 21 days for 6cycles(total of 18weeks)	
Capecitabine	850-1000mg	PO	Bid,D1-14		
Pembrolizumab	200mg	IV	D1		
Ref.	Rha SY, Oh DY, Yanez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. <i>Lancet Oncol</i> 2023;24:1181-1193.				

Cisplatin + Fluorouracil (5-FU) + Pembrolizumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin	80 mg/m ²	IV	D1	every 21 days for 6cycles	
Fluorouracil (5-FU)	800 mg/m ² /day	IV	continuous infusion over 24 hours daily on Days 1-5		
Pembrolizumab	200mg	IV	D1		
Ref.	Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. <i>Lancet</i> 2021;398:759-771.				

Cisplatin + Capecitabine + Pembrolizumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin	80 mg/m ²	IV	D1	every 21 days for 6cycles(total of 18weeks)	
Capecitabine	850-1000mg	PO	Bid,D1-14		
Pembrolizumab	200mg	IV	D1		
Ref.	Rha SY, Oh DY, Yanez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. <i>Lancet Oncol</i> 2023;24:1181-1193.				

HER2 Overexpression Negative, CLDN18.2 Positive

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Zolbetuximab-clzb	800 mg/m ² first-dose only, subsequent doses 400 mg/m ²	IV	D1	Cycled every 14 days	
Oxaliplatin	85 mg/m ²	IV	on D 1 (per study maximum of 12 doses)		
Leucovorin	400mg	IV	D1		
Fluorouracil	400mg	IV push	continuous infusion over 24 hours daily on Days 1		
Fluorouracil	1200mg/m ² /day	IV	continuous infusion over 24 hours daily on Days 1 and 2		
		or			
Zolbetuximab-clzb	800 mg/m ² IV first-dose only, subsequent doses 600 mg/m ²	IV	on Day 1	Cycled every 21 days	
Oxaliplatin	130 mg/m ²	IV	on Day 1 (per study maximum of 8 doses)		
Capecitabine	850-1000 mg/m ² BID	PO	on Days 1-14		
Ref.	1. Shitara K, Lordick F, Bang YJ, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. <i>Lancet</i> 2023;401:1653-1668. 2. Shah MA, Shitara K, Ajani JA, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. <i>Nat Med</i> 2023;29:2133-2141.				

OTHER RECOMMENDED REGIMENS

Fluorouracil and irinotecan

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	180 mg/m ²	IV	D1	Cycled every 14 days	
Leucovorin	400 mg/m ²	IV	on Day 1		
Fluorouracil	400 mg/m ²	IV Push	on Day 1		
Fluorouracil	1200 mg/m ² /days	IV	IV continuous infusion over 24 hours daily on Days 1 and 2		
Ref.	Gimbleau R, Louvet C, Riet P, et al. Prospective, randomised, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French Intergroup (Federation Francophone de Cancerologie Digestive, Federation Nationale des Centres de Lutte Contre le Cancer, and Groupe Cooperateur Multidisciplinaire en Oncologie) study. <i>J Clin Oncol</i> 2014;32:3520-3526.				

Paclitaxel with or without carboplatin or cisplatin

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Paclitaxel	175 mg/m ²	IV	on Day 1	Cycled every 21 days	
Carboplatin	AUC 5	IV	on Day 1		
		or			
Paclitaxel	60-80 mg/m ²	IV	on D1,8,15	Cycled every 28 days	
Cisplatin	70-80 mg/m ²	IV	on Day 1		
		or			
Paclitaxel	135-200mg/m ²	IV	on Day 1	Cycled every 21 days	



Cisplatin	75 mg/m ²	IV	on Day 1	Cycled every 14 days
Paclitaxel	90 mg/m ²	IV	on Day 1	
Cisplatin	50 mg/m ²	IV	on Day 1	
Paclitaxel	132-150mg/m ²	IV	on Day 1	
			or	
Paclitaxel	60-80 mg/m ²	IV	on D1,8,15	Cycled every 28 days
Ref.	<p>1. Gadgeel SM, Shields AP, Hellman LK, et al. Phase II study of paclitaxel and carboplatin in patients with advanced gastric cancer. <i>Am J Clin Oncol</i> 2003;26:37-41.</p> <p>2. Ilson DH, Forastiere A, Arquette M, et al. A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. <i>Cancer J</i> 2000;6:316-323.</p> <p>3. Petrasch S, Weh A, Reitscher A, et al. Chemotherapy with cisplatin and paclitaxel in patients with locally advanced, recurrent or metastatic oesophageal cancer. <i>Br J Cancer</i> 1998;78:511-514.</p> <p>4. Ajani JA, Ilson DH, Daugherty K, et al. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. <i>J Natl Cancer Inst</i> 1994;86:1086-1091.</p> <p>5. Hirronaka S, Ueda S, Yazai H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. <i>J Clin Oncol</i> 2013;31:4438-4444.</p>			

Docetaxel with or without cisplatin

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Docetaxel	70-85 mg/m ²	IV	D1	every 21 days	
Cisplatin	70-75 mg/m ²	IV	D1		
			or		
Docetaxel	30 - 35 mg/m ²	IV	D1 - 8	every 21 days	
			or		
Docetaxel	22 - 25 mg/m ²	IV	D1 - 8 - 15	every 28 days	

Docetaxel	60-75mg/m ²	IV	D1	every 21 days	
Ref.	<p>1. Ajani JA, Fodor MB, Tjulandin SA, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. <i>J Clin Oncol</i> 2005;23:3660-3667.</p> <p>2. Kim JY, Do YR, Park KU, et al. A multi-center phase II study of docetaxel plus cisplatin as first-line therapy in patients with metastatic squamous cell esophageal cancer. <i>Cancer Chemother Pharmacol</i> 2010;66:31-36.</p>				

Fluoropyrimidine

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Leucovorin	400 mg/m ²	IV	D1	Cycled every 14 days	
Fluorouracil	400 mg/m ²	IV Push	on Day 1		
Fluorouracil	1200 mg/m ² /days	IV	IV continuous infusion over 24 hours daily on Days 1 and 2	Cycled every 21 days	
			or		
Capecitabine	850-1000 mg/m ²	PO	BID, on D 1-14	Cycled every 21 days	
			or		
Fluorouracil	800mg/m ²	IV	IV continuous infusion over 24 hours daily on Days 1-5	Cycled every 28 days	

Ref.	<p>1. Bosche O, Roussil JL, Bouvard M, et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LF2FU2), LF2FU2 plus cisplatin, or LF2FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study-FFCD 9803. <i>J Clin Oncol</i> 2004;22:4319-4328.</p> <p>2. Ohno A, Shinoda Y, Shirao K, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus irinotecan plus fluorouracil in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). <i>J Clin Oncol</i> 2003;21:34-39.</p> <p>3. Hong YS, Song SY, Lee SI, et al. A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer. <i>Ann Oncol</i> 2004;15:1344-1347.</p>				
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Docetaxel, cisplatin or oxaliplatin, and fluorouracil

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Docetaxel	40 mg/m ²	IV	on Day 1	Cycled every 14 days	
Leucovorin	400 mg/m ²	IV	on Day 1		
Fluorouracil	400 mg/m ²	IV	on Day 1		
Fluorouracil	1000 mg/m ² /day	IV	IV continuous infusion over 24 hours daily on Days 1 and 2	Cycled every 14 days	
Cisplatin	40 mg/m ²	IV	on Day 3		
			or		
Docetaxel	50 mg/m ²	IV	on Day 1	Cycled every 14 days	
Oxaliplatin	85 mg/m ²	IV	on Day 1		

Fluorouracil	1200 mg/m ² /day	IV	IV continuous infusion over 24 hours daily on Days 1 and 2	Cycled every 14 days	
Ref.	<p>1. Shah MA, Janjigian YY, Stotler R, et al. Randomized multicenter phase II study of modified docetaxel, cisplatin, and fluorouracil (DCF) versus DCF plus growth factor support in patients with metastatic gastric adenocarcinoma: a study of the US Gastric Cancer Consortium. <i>J Clin Oncol</i> 2015;33:3874-3879.</p> <p>2. Blum Murphy MA, Qiao W, Mevada N, et al. A phase III study of docetaxel, oxaliplatin, and fluorouracil (D-FOX) chemotherapy in patients with untreated locally unresectable or metastatic adenocarcinoma of the stomach and gastroesophageal junction. <i>Am J Clin Oncol</i> 2018;41:321-325.</p>				

Ref.	<p>1. 2019年12月20日 第1版</p> <p>2. 2020年12月20日 第2版</p> <p>3. 2021年12月20日 第3版</p> <p>4. 2022年12月20日 第4版</p> <p>5. 2023年12月20日 第5版</p> <p>6. 2024年12月20日 第6版</p> <p>7. 2025年12月20日 第7版</p> <p>8. 2026年12月20日 第8版</p>				
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ESOPHAGEAL CELL CARCINOMA (SECOND-LINE AND SUBSEQUENT THERAPY)					
MET-NEGATIVE tumors (independent of PD-L1 status)					
Pembrolizumab					
Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Pembrolizumab	200 mg	IV	D1	Cycled every 21 days	(up to 2 years)
Pembrolizumab	400 mg	IV	D1	Cycled every 6weeks	
Ref.	1. Kojima T, Shin MA, Moro K, et al. Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer. <i>J Clin Oncol</i> 2020;38:4138-4148. 2. Lala M, Li FR, de Abreu DP, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. <i>Eur J Cancer</i> 2020;131:68-75.				
Nivolumab and ipilimumab					
Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Nivolumab	240 mg	IV		every 2 weeks	For 16 weeks, followed by Nivolumab 240 mg IV every 2 weeks or Nivolumab 480 mg IV every 4 weeks (maximum of 2 years)
Ipilimumab	1 mg/kg	IV		every 6 weeks	
Ref.	Anagnostou YF, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. <i>Lancet</i> 2021;398:27-40.				
Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and nivolumab					
Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Nivolumab	360 mg	IV	on Day 1 (per study maximum of 2 years)	Cycled every 21 days	
Capecitabine	850-1000 mg/m ²	PO	BID on D 1-14		
Oxaliplatin	130 mg/m ²	IV	on Day 1		
or					
Nivolumab	240 mg	IV	on Day 1 (per study maximum of 2 years)	Cycled every 14 days	
Oxaliplatin	85 mg/m ²	IV	on Day 1		
Leucovorin	400mg	IV	continuous infusion over 24 hours daily on Days 1		
Fluorouracil	400mg	IV push	D1		
Fluorouracil	1200mg/m ² /day	IV	continuous infusion over 24 hours daily on Days 1 and 2		
Ref.	Anagnostou YF, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro oesophageal, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. <i>Lancet</i> 2021;398:27-40.				
Fluoropyrimidine, oxaliplatin, and pembrolizumab					
Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Pembrolizumab	200 mg	IV	every 21 days for up to 2 years	Cycled every 21 days for up to 6 cycles (total 18 weeks)	
Capecitabine	850-1000 mg/m ²	PO	BID, D1-14		
Oxaliplatin	130 mg/m ²	IV	drip 90-120 mins, on Day 1		
or					
Pembrolizumab	200 mg	IV	every 21 days for up to 2 years	Cycled every 14 days for up to 9 cycles (total 18 weeks)	
Oxaliplatin	85 mg/m ²	IV	on Day 1		
Leucovorin	400 mg/m ²	IV	on Day 1		
Fluorouracil	400 mg/m ²	IV Push	on Day 1		
Fluorouracil	1200 mg/m ²	IV	IV continuous infusion over 24 hours daily on Days 1 and 2		
Ref.	Rha SY, Oh DY, Yanez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. <i>Lancet Oncol</i> 2023;24:1181-1195.				
Systemic Therapy for Curable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)					
SQUAMOUS CELL CARCINOMA (SECOND-LINE AND SUBSEQUENT THERAPY)					
PREFERRED REGIMENS					
Nivolumab					
Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Nivolumab	240 mg/m ²	IV	D1	every 14days	(for second-line therapy for esophageal SCC)
nivolumab	480mg	IV	D1	every 28days	
Ref.	Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced esophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. <i>Lancet Oncol</i> 2019;20:1506-1517.				
Pembrolizumab					
Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Pembrolizumab	200mg/m ²	IV	D1	every 21days	(for second-line therapy for esophageal SCC with PD-L1 expression levels by CPS of ≥10)
Pembrolizumab	400mg	IV	D1	every 6 weeks	
Ref.	1. Kojima T, Shin MA, Moro K, et al. Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer. <i>J Clin Oncol</i> 2020;38:4138-4148. 2. Lala M, Li FR, de Abreu DP, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. <i>Eur J Cancer</i> 2020;131:68-75.				



Taxane

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Docetaxel	75-100mg/m ²	IV	D1	every 21days	
or					
Paclitaxel	135-250mg/m ²	IV	D1	every 21days	
or					
Paclitaxel	80mg/m ²	IV	D1	weekly	
or					
Paclitaxel	80mg/m ²	IV	D1,8,15	every 28days	
Ref.	<p>1. Albertsson M, Johansson B, Friesland S, et al. Phase II studies on docetaxel alone every third week, or weekly in combination with gemcitabine in patients with primary locally advanced, metastatic, or recurrent esophageal cancer. <i>Med Oncol</i> 2007;24:407-412.</p> <p>2. Ford ER, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. <i>Lancet Oncol</i> 2014;15:78-86.</p> <p>3. Ajani JA, Ison DH, Daugherty K, et al. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. <i>J Natl Cancer Inst</i> 1994;86:1086-1091.</p> <p>4. Ison DH, Wadleigh RG, Leichman LP, Kelsen DP. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. <i>Ann Oncol</i> 2007;18:898-902.</p> <p>5. Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. <i>J Clin Oncol</i> 2013;31:4438-4444.</p>				

Irinotecan

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	150-180mg/m ²	IV	D1	every 14days	
or					
Irinotecan	125mg/m ²	IV	D1,8	every 21days	
or					
Irinotecan	250-350mg/m ²	IV	D1	every 21days	
Ref.	<p>1. Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. <i>J Clin Oncol</i> 2013;31:4438-4444.</p> <p>2. Sym SI, Hong J, Park J, et al. A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. <i>Cancer Chemother Pharmacol</i> 2013;71:481-488.</p> <p>3. Fuchs CS, Moore MR, Harker G, et al. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. <i>J Clin Oncol</i> 2003;21:807-814.</p> <p>4. Dhaen-Pontenne PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer—a randomized phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). <i>Eur J Cancer</i> 2011;47:2306-2314.</p>				

Fluorouracil and irinotecan

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	180 mg/m ²	IV	D1	Cycled every 14 days	
Leucovorin	400 mg/m ²	IV	D1		
Fluorouracil	400 mg/m ²	IV Push	D1		
Fluorouracil	1200 mg/m ² /days	IV	IV continuous infusion over 24 hours daily on Days 1 and 2		
Ref.	Sym SI, Hong J, Park J, et al. A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. <i>Cancer Chemother Pharmacol</i> 2013;71:481-488.				

OTHER RECOMMENDED REGIMENS

Irinotecan and cisplatin

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	65mg/m ²	IV	D1,8	Cycled every 21 days	
cisplatin	25-30 mg/m ²	IV	D1,8		
Ref.	<p>1. Enzinger PC, Burness BA, Niedzwiecki D, et al. CALGB 80403 (Alliance)/E1206: a randomized phase II study of three chemotherapy regimens plus cetuximab in metastatic esophageal and gastroesophageal junction cancers. <i>J Clin Oncol</i> 2016;34:2736-2742.</p> <p>2. Ison DH. Phase II trial of weekly irinotecan/cisplatin in advanced esophageal cancer. <i>Oncology (Williston Park)</i> 2004;18:22-25.</p>				

Docetaxel and irinotecan

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	50mg/m ²	IV	D1,8	Cycled every 21 days	
Docetaxel	35 mg/m ²	IV	D1,8		
Ref.	Burness B, Gibson M, Egleston B, et al. Phase II trial of docetaxel-irinotecan combination in advanced esophageal cancer. <i>Ann Oncol</i> 2009;20:1242-1248.				



PREFERRED REGIMEN

Ramucirumab and paclitaxel

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Paclitaxel	80mg/m ²	IV	D1,S,15	Cycled every 28 days	
Ramucirumab	8mg/kg	IV	D1,15		
Ref.	White H, Maro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. <i>Lancet Oncol</i> 2014;15:1224-1235.				

Fam-trastuzumab deruxtecan-nxki

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Trastuzumab	6.4 mg/kg	IV	D1	every 21 days	(for HER2 overexpression-positive adenocarcinoma)
Ref.	Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. <i>N Engl J Med</i> 2020;382:2419-2430.				

Taxane

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Docetaxel	75-100mg/m ²	IV	D1	every 21 days	
		or			
Paclitaxel	135-210mg/m ²	IV	D1	every 21 days	
		or			
Paclitaxel	80mg/m ²	IV	D1	weekly	
		or			

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Paclitaxel	80mg/m ²	IV	D1,S,15	every 28days	
Ref.	<p>1. Albertson M, Johansson B, Friesland S, et al. Phase II studies on docetaxel alone every third week, or weekly in combination with gemcitabine in patients with primary locally advanced, metastatic, or recurrent esophageal cancer. <i>Med Oncol</i> 2007;24:407-412.</p> <p>2. Ford ER, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophago-gastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. <i>Lancet Oncol</i> 2014;15:78-86.</p> <p>3. Ajani JA, Ilson DH, Daugherty K, et al. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. <i>J Natl Cancer Inst</i> 1994;86:1086-1091.</p> <p>4. Ilson DH, Wadleigh RG, Leichman LP, Katsen DP. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. <i>Ann Oncol</i> 2007;18:898-902.</p> <p>5. Hironaka S, Ueda S, Yanai H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. <i>J Clin Oncol</i> 2013;31:4438-4444.</p>				

Irinotecan

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	150-180mg/m ²	IV	D1	every 14days	
		or			
Irinotecan	125mg/m ²	IV	D1,S	every 21 days	
Irinotecan	250-350mg/m ²	IV	D1	every 21 days	

Ref.	Notes
1. Hironaka S, Ueda S, Yanai H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. <i>J Clin Oncol</i> 2013;31:4438-4444.	
2. Sym SI, Hong J, Park J, et al. A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. <i>Cancer Chemother Pharmacol</i> 2013;71:481-488.	
3. Fuchs CS, Moore MR, Harker G, et al. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. <i>J Clin Oncol</i> 2003;21:807-814.	
4. Thuss-Patience FC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer—a randomized phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). <i>Eur J Cancer</i> 2011;47:2306-2314.	

Fluorouracil and irinotecan

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	180 mg/m ²	IV	D1	Cycled every 14 days	
Leucovorin	400 mg/m ²	IV	D1		
Fluorouracil	400 mg/m ²	IV Push	D1		
Fluorouracil	1200 mg/m ² /days	IV	IV continuous infusion over 24 hours daily on Days 1 and 2		
Ref.	Sym SI, Hong J, Park J, et al. A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. <i>Cancer Chemother Pharmacol</i> 2013;71:481-488.				

Trifluridine and tipiracil

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Trifluridine and tipiracil	35 mg/m ² up to a maximum dose of 80 mg per dose	PO	Bid, on Days 1-5 and 8-12	Cycled every 28 days	(for third-line or subsequent therapy for EGJ adenocarcinoma)
Ref.	Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomized, double-blind, placebo-controlled, phase 3 trial. <i>Lancet Oncol</i> 2018;19:1437-1448.				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)
ADENOCARCINOMA (SECOND-LINE AND SUBSEQUENT THERAPY)

OTHER RECOMMENDED REGIMENS

Ramucirumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Ramucirumab	8mg/kg	IV	D1	Cycled every 14 days	
Ref.	Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. <i>Lancet</i> 2014;383:31-39.				

Irinotecan and cisplatin

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	65mg/m ²	IV	D1,S	Cycled every 21 days	
cisplatin	25-30 mg/m ²	IV	D1,S		
Ref.	J. Estinger PC, Burrous BA, Niedzwiecki D, et al. CALGB 80403 (Alliance)E1206: a randomized phase II study of three chemotherapy regimens plus cetuximab in metastatic esophageal and gastroesophageal junction cancers. <i>J Clin Oncol</i> 2016;34:2736-2742. 2.Hoon DH. Phase II trial of weekly irinotecan/cisplatin in advanced esophageal cancer. <i>Oncology (Williston Park)</i> 2004;18:22-25.				

Fluorouracil and irinotecan + ramucirumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Ramucirumab	8mg/kg	IV	D1	Cycled every 14 days	(only for adenocarcinoma)
Irinotecan	180mg/m ²	IV	D1		
Fluorouracil	400 mg/m ²	IV Push	D1		

Useful in Certain Circumstances

For BRAF V600E-mutated tumors

Regimen	Dabrafenib and trametinib
藥名	Dabrafenib 150 mg PO twice daily Trametinib 2 mg PO daily
Ref.	Solomon ARS, JJ S, Macrae ER, et al. Dabrafenib and trametinib in patients with tumors with BRAF(V600E) mutations: Results of the NCI-MATCH trial subprotocol H. <i>J Clin Oncol</i> 2020;38:3893-3904.

For RET gene fusion-positive tumors

Regimen	Selpercatinib
藥名	Selpercatinib Patients >=50 kg: 160 mg PO twice daily Patients < 50 kg: 120 mg PO twice daily
Ref.	Solomon ARS, JJ S, Macrae ER, et al. Dabrafenib and trametinib in patients with tumors with BRAF(V600E) mutations: Results of the NCI-MATCH trial subprotocol H. <i>J Clin Oncol</i> 2020;38:3893-3904.

Drug Combination	Fluorouracil 1200 mg/m ² /days	IV	IV continuous infusion over 24 hours daily on Days 1 and 2		
Ref.	Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. <i>Lancet Oncol</i> 2015;16:499-508.				

irinotecan + ramucirumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Ramucirumab	8mg/kg	IV	D1	Cycled every 14 days	(only for adenocarcinoma)
Irinotecan	180mg/m ²	IV	D1		
Ref.	Sakai D, Boku N, Kodera Y, et al. An intergroup phase III trial of ramucirumab plus irinotecan in third or more line beyond progression after ramucirumab for advanced gastric cancer (BIND-2/RG trial). <i>J Clin Oncol</i> 2018;36:TP54138.				

Docetaxel and irinotecan

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	50mg/m ²	IV	D1,S	Cycled every 21 days	
Docetaxel	35 mg/m ²	IV	D1,S		
Ref.	Burtness B, Gillson M, Eggleston B, et al. Phase II trial of docetaxel-irinotecan combination in advanced esophageal cancer. <i>Ann Oncol</i> 2009;20:1242-1248.				

For NTRK gene fusion-positive tumors

Regimen	Entrectinib
藥名(藥名)	Entrectinib 600 mg PO once daily
Ref.	Dozile BC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: Integrated analysis of three phase 1-2 trials. <i>Lancet Oncol</i> 2020;21:271-282.

Regimen	Larotrectinib
藥名(藥名)	Larotrectinib 100 mg PO twice daily
Ref.	Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. <i>N Engl J Med</i> 2018;378:731-739.

Regimen	Repotrectinib
藥名(藥名)	Repotrectinib 160 mg PO Daily Days 1-14 of cycle 1 160 mg PO BID Days 15-28 of cycle 1 160 mg PO BID Days 1-28 of cycle 2 and beyond Cycled every 28 days
Ref.	Solomon BJ, Drilon A, Lin JJ, et al. 1772P Repotrectinib in patients (pts) with NTRK fusion-positive (NTRK+) advanced solid tumors, including NSCLC: Update from the phase III TRIDENT-1 trial. <i>Annals of Oncology</i> 2023;34:5787-5788.



<p>第 66 頁</p>	<p>八、放射治療原則</p> <p>Treatment Regimen</p> <p>CCRT : Definitive RT : Favor IMRT dose of 4500-6600 cGy. Neoadjuvant / Adjuvant RT : Favor IMRT dose of 4140 -5400 cGy.</p> <p>Chun, S. G., Skimmer, H. D., & Minsky, B. D. (2017). Radiation therapy for locally advanced esophageal cancer. <i>Surgical Oncology Clinics</i>, 26(2), 257-276.</p>	<p>修改</p> <p>八、放射治療原則</p> <p>Treatment Regimen</p> <p>CCRT : Definitive RT : Total dose of 45-66 Gy. Neoadjuvant / Adjuvant RT : Total dose of 41.4-54 Gy.</p> <p>Note : Radiotherapy should be delivered using intensity-modulated radiotherapy or more advanced techniques.</p> <p>Chun, S. G., Skimmer, H. D., & Minsky, B. D. (2017). Radiation therapy for locally advanced esophageal cancer. <i>Surgical Oncology Clinics</i>, 26(2), 257-276.</p>																																		
<p>第 73 頁</p>	<p>十二、食道癌完治定義</p> <table border="1"> <thead> <tr> <th>癌別</th> <th>期別</th> <th>治療方式</th> <th>完治定義</th> </tr> </thead> <tbody> <tr> <td rowspan="4">食道癌</td> <td>0 期 1 期</td> <td>OP</td> <td>EMR/ESD or OP : Margin free</td> </tr> <tr> <td>2 期</td> <td>OP or Neo-adjuvant CCRT+OP or Definitive CCRT</td> <td>1.術後 Margin free 2.Margin (+) → Adjuvant CCRT 結束日 3.Definitive CCRT 結束日</td> </tr> <tr> <td>3 期</td> <td>Neo-adjuvant CCRT+OP or Definitive CCRT</td> <td>1.術後 Margin free 2.Margin (+) → Adjuvant CCRT 結束日 3.Definitive CCRT 結束日</td> </tr> <tr> <td>4 期</td> <td>Definitive CCRT</td> <td>1.Definitive CCRT 結束日 2.Palliative C/T 達三個月(含口服化療 Ufur) 3.Palliative C/T 未達三個月，評估病患治療反應不佳，改二線藥持續治療，第一次治療就可算完治 4.治療中轉安寧</td> </tr> </tbody> </table>	癌別	期別	治療方式	完治定義	食道癌	0 期 1 期	OP	EMR/ESD or OP : Margin free	2 期	OP or Neo-adjuvant CCRT+OP or Definitive CCRT	1.術後 Margin free 2.Margin (+) → Adjuvant CCRT 結束日 3.Definitive CCRT 結束日	3 期	Neo-adjuvant CCRT+OP or Definitive CCRT	1.術後 Margin free 2.Margin (+) → Adjuvant CCRT 結束日 3.Definitive CCRT 結束日	4 期	Definitive CCRT	1.Definitive CCRT 結束日 2.Palliative C/T 達三個月(含口服化療 Ufur) 3.Palliative C/T 未達三個月，評估病患治療反應不佳，改二線藥持續治療，第一次治療就可算完治 4.治療中轉安寧	<p>修改及刪除</p> <p>十二、食道癌完治定義</p> <table border="1"> <thead> <tr> <th>癌別</th> <th>期別</th> <th>治療方式</th> <th>完治定義</th> </tr> </thead> <tbody> <tr> <td rowspan="4">食道癌</td> <td>0 期 1 期</td> <td>OP</td> <td>EMR/ESD or OP : Margin free</td> </tr> <tr> <td>2 期</td> <td>OP or Neo-adjuvant CCRT+OP or Definitive CCRT</td> <td>1.術後 Margin free 2.Margin (+) → Adjuvant CCRT 結束日 3.Definitive CCRT 結束日</td> </tr> <tr> <td>3 期</td> <td>Neo-adjuvant CCRT+OP or Definitive CCRT</td> <td>1.術後 Margin free 2.Margin (+) → Adjuvant CCRT 結束日 3.Definitive CCRT 結束日</td> </tr> <tr> <td>4 期</td> <td>Systemic therapy</td> <td>1.Definitive CCRT 結束日 2.Palliative C/T 達三個月(含口服化療 Ufur) 3.Palliative C/T 未達三個月，評估病患治療反應不佳，改二線藥持續治療，第一次治療就可算完治 4.治療中轉安寧</td> </tr> </tbody> </table>	癌別	期別	治療方式	完治定義	食道癌	0 期 1 期	OP	EMR/ESD or OP : Margin free	2 期	OP or Neo-adjuvant CCRT+OP or Definitive CCRT	1.術後 Margin free 2.Margin (+) → Adjuvant CCRT 結束日 3.Definitive CCRT 結束日	3 期	Neo-adjuvant CCRT+OP or Definitive CCRT	1.術後 Margin free 2.Margin (+) → Adjuvant CCRT 結束日 3.Definitive CCRT 結束日	4 期	Systemic therapy	1.Definitive CCRT 結束日 2.Palliative C/T 達三個月(含口服化療 Ufur) 3.Palliative C/T 未達三個月，評估病患治療反應不佳，改二線藥持續治療，第一次治療就可算完治 4.治療中轉安寧
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	2 期	OP or Neo-adjuvant CCRT+OP or Definitive CCRT	1.術後 Margin free 2.Margin (+) → Adjuvant CCRT 結束日 3.Definitive CCRT 結束日																																	
	3 期	Neo-adjuvant CCRT+OP or Definitive CCRT	1.術後 Margin free 2.Margin (+) → Adjuvant CCRT 結束日 3.Definitive CCRT 結束日																																	
	4 期	Systemic therapy	1.Definitive CCRT 結束日 2.Palliative C/T 達三個月(含口服化療 Ufur) 3.Palliative C/T 未達三個月，評估病患治療反應不佳，改二線藥持續治療，第一次治療就可算完治 4.治療中轉安寧																																	



目錄

一、 前言	1
二、 臨床症狀	2
三、 診斷檢查	3
四、 病理組織分類、食道癌分期	4
五、 巴瑞特氏食道治療指引	8
六、 食道癌治療指引	9
七、 化學治療原則	12
八、 放射線治療原則	66
九、 支持性治療(Supportive treatment)原則	66
十、 安寧緩和照護原則	67
十一、 參考文獻	68
十二、 食道癌完治定義	73



一、前言

根據統計，癌症為台灣十大死因首位，其中食道癌為十大癌症死因第九位。台灣地區九成食道癌屬鱗狀上皮細胞癌，其次為腺癌，好發於 50-70 歲人群，男性多於女性，致病原因和個人體質、生活習慣、飲食及環境皆有關聯。以喜歡吃刺激、醃製性或溫度較高食物者；或攝取蔬菜水果或維他命 A、C 不足者、微量元素如鋅的缺乏；此外高粱、玉米及茶葉中的鞣酸（Tan-nin），也被列為與食道癌有關的物質；飲水及食物中若含有過量的亞硝基氨（Nitrosamine），亦被證實會增加食道癌發生的風險。喝酒亦是食道癌的高危險因子，統計顯示喝酒引發食道癌是一般人的 2-4 倍，若合併菸、檳榔則罹癌風險高達 40 倍。胃食道逆流症或巴瑞特氏食道的患者，由於胃液反覆逆流到食道，長期刺激下，在食道下 1/3 段亦使黏膜受損造成食道癌，此類以腺癌占多數。曾患頭頸癌的患者，根據統計其發生的第二癌症，有 1/3 是在食道發生，兩者皆與吸菸有關。食道弛緩不能（食道擴約肌的運動能力降低）的患者，比一般人發生食道癌的機率高出 6-14%。曾有食道腐蝕性傷害，也較易引起食道癌的產生，其位置常見於食道中段。食道有豐富淋巴結及血流供應，多數患者因胃食道逆流、吞嚥困難及疼痛就診時，已是食道癌中晚期，且常併有體重減輕和營養不良等問題。



二、臨床症狀

1. 吞嚥困難：大多數患者，第一個症狀是在吃肉、麵包或粗糙的食物（如生蔬菜）時會覺得不易下嚥且不順暢的感覺，甚至會感到食物卡在胸骨的後方。隨著腫瘤生長，會使得食道漸漸變狹窄，先是不能吃乾飯，繼而連稀飯及液體也難以下嚥。
2. 體重減輕：由於食道阻塞造成患者吞嚥困難，身體的營養吸收不足，造成身體衰弱、體重減輕是必然的現象。
3. 呼吸有臭味：若食道被腫瘤完全阻塞後，食物會蓄積在腫瘤的上方，使得食物發酵而散發出惡臭。
4. 咳嗽：因唾液聚積在腫瘤上方，造成聚積的唾液或食物被吸入氣管而引起咳嗽，夜晚平躺時常會加重而使患者無法入睡。當腫瘤持續變大，可能穿出食道壁而產生食道氣管瘻管，此時進食將會引發吸入性肺炎及相關合併症。
5. 聲音嘶啞：因腫瘤壓迫到聲帶。
6. 胸痛：如果腫瘤擴展至胸腔後壁，進而侵犯到肋間神經時，患者常會有無法忍受的胸痛。
7. 大出血：若腫瘤侵犯到鄰近的大動脈時，會使大動脈破裂而產生大出血情形，是食道癌常見的致命原因之一。



三、診斷檢查

1. 胸部 X 光 (Chest X-ray)：由 X 光片中了解食道以及胸腔的形狀是否有異常。
2. 食道攝影 (Esophagography)：患者必須喝下鋇劑顯影劑，以觀察食物流經食道的方式，因鋇劑可附著在食道表面，透過 X 光而使病灶顯現出來。另外，本檢查可以評估食道癌所侵犯的長度範圍以及食道癌和其他相關構造的關係。若是出現食道癌，則會出現出連續不規則、模糊的連黏膜邊緣或管腔狹窄，而在阻塞處上方會有擴張的現象。但若懷疑有食道氣管瘻管，則不宜使用鋇劑顯影劑，須改用水溶性顯影劑。
3. 上消化道泛內視鏡檢查 (Upper G-I panendoscopy) 及內視鏡超音波檢查 (endoscopic ultrasound)：可詳細的觀察癌之表面與其浸潤的廣度，評估發生的位置以及食道內阻塞的情形。做此檢查時，喉嚨會先採局部噴霧麻醉，以減少不適及嘔吐的感覺。然後醫師會以內視鏡從口腔經喉嚨進入食道，透過食道鏡取下食道腫瘤的部份組織病理切片檢查。故上消化道泛內視鏡檢查及病理切片檢查是確立診斷的最重要檢查。
4. 胸部電腦斷層攝影 (Chest CT) 或腹部電腦斷層攝影 (Abdomen CT)：可得知腫瘤的厚度、長度、周圍組織的侵犯程度，及局部淋巴腺有無侵犯或有無其它器官轉移的情形。



5. 其他檢查：腹部超音波、正子放射斷層攝影（PET）、全身骨骼掃描（Whole body bone scan）等評估食道癌是否可能轉移。

四、病理組織分類、食道癌分期

食道癌分為鱗狀細胞癌（Squamous cell carcinoma）和腺癌（Adenocarcinoma）。目前有許多工具可用來做食道癌的分期，最常見的就是內視鏡超音波，依據內視鏡或上消化道攝影的發現，可獲得腫瘤的大小、位置、外觀等資訊。電腦斷層掃描也常用來分期，特別是腫瘤小於5公分時，用處更大。它可顯現癌細胞是否擴及附近的淋巴結或肺臟，腫瘤是否穿入氣管，或是有遠處轉移等。

在本院，則安排細徑（迷你）探頭式內視鏡超音波（Miniprobe Endoscopic Ultrasound；EUS），以了解腫瘤侵犯的深度。而侵犯深度是決定五年存活的重要因素，也是預測外科手術是否能介入的關鍵。



目前根據美國癌症聯合委員會（AJCC）第八版分期法，分期如下：

Primary Tumor(T)

- TX** Primary tumor can not be assessed
- T0** No evidence of primary tumor
- Tis** High-grade dysplasia, defined as malignant cells confined to the epithelium by the basement membrane
- T1** Tumor invades lamina propria, muscularis mucosae, or submucosa
 - T1a** Tumor invades lamina propria or muscularis mucosae
 - T1b** Tumor invades the submucosa
- T2** Tumor invades muscularis propria
- T3** Tumor invades adventitia
- T4** Tumor invades adjacent structures
 - T4a** Tumor invades pleura, pericardium, azygos vein, diaphragm, or peritoneum
 - T4b** Tumor invades other adjacent structures, such as aorta, vertebral body,-or airway

Regional Lymph Nodes(N)

- NX** Regional lymph nodes cannot be assessed
- N0** No regional lymph node metastasis
- N1** Metastasis in 1-2 regional lymph nodes
- N2** Metastasis in 3-6 regional lymph nodes
- N3** Metastasis in seven or more regional lymph nodes

Distant Metastasis(M)

- M0** No distant metastasis
- M1** Distant metastasis

Histologic Grade(G)

- GX** Grade cannot be assessed
- G1** Well differentiated
- G2** Moderately differentiated
- G3** Poorly differentiated, undifferentiated

Squamous Cell Carcinoma

Location	Location Criteria
X	Location unknown
Upper	Cervical esophagus to lower border of azygos vein
Middle	Lower border of azygos vein to lower border of inferior pulmonary vein
Lower	Lower border of inferior pulmonary vein to stomach, including gastroesophageal junction



Squamous Cell Carcinoma

Clinical Staging (cTNM)				Pathological (pTNM)						Postneoadjuvant Therapy (ypTNM)			
	cT	cN	M		pT	pN	M	G	Location		ypT	ypN	M
Stage 0	Tis	N0	M0	Stage 0	Tis	N0	M0	N/A	Any	Stage I	T0-2	N0	M0
Stage I	T1	N0-1	M0	Stage IA	T1a	N0	M0	G1/GX	Any	Stage II	T3	N0	M0
Stage II	T2	N0-1	M0	Stage IB	T1a	N0	M0	G2-3	Any	Stage IIIA	T0-2	N1	M0
	T3	N0	M0		T1b	N0	M0	G1-3/GX	Any		Stage IIIB	T3	N1
Stage III	T3	N1	M0		T2	N0	M0	G1	Any	T0-3		N2	M0
	T1-3	N2	M0	Stage IIA	T2	N0	M0	G2-3/GX	Any	T4a		N0	M0
Stage IVA	T4	N0-2	M0		T3	N0	M0	G1-3	lower	Stage IVA	T4a	N1-2/NX	M0
	Any T	N3	M0		T3	N0	M0	G1	upper/middle		T4b	N0-2	M0
Stage IVB	Any T	Any N	M1	Stage IIB	T3	N0	M0	G2-3	upper/middle	Stage IVB	Any T	N3	M0
					T3	N0	M0	GX	lower/upper/middle		Any T	Any N	M1
				T3	N0	M0	Any	Location X					
				T1	N1	M0	Any	Any					
				Stage IIIA	T1	N2	M0	Any		Any			
					T2	N1	M0	Any		Any			
				Stage IIIB	T2	N2	M0	Any		Any			
					T3	N1-2	M0	Any		Any			
					T4a	N0-1	M0	Any		Any			
				Stage IVA	T4a	N2	M0	Any		Any			
					T4b	N0-2	M0	Any		Any			
					Any T	N3	M0	Any		Any			
				Stage IVB	Any T	Any N	M1	Any		Any			

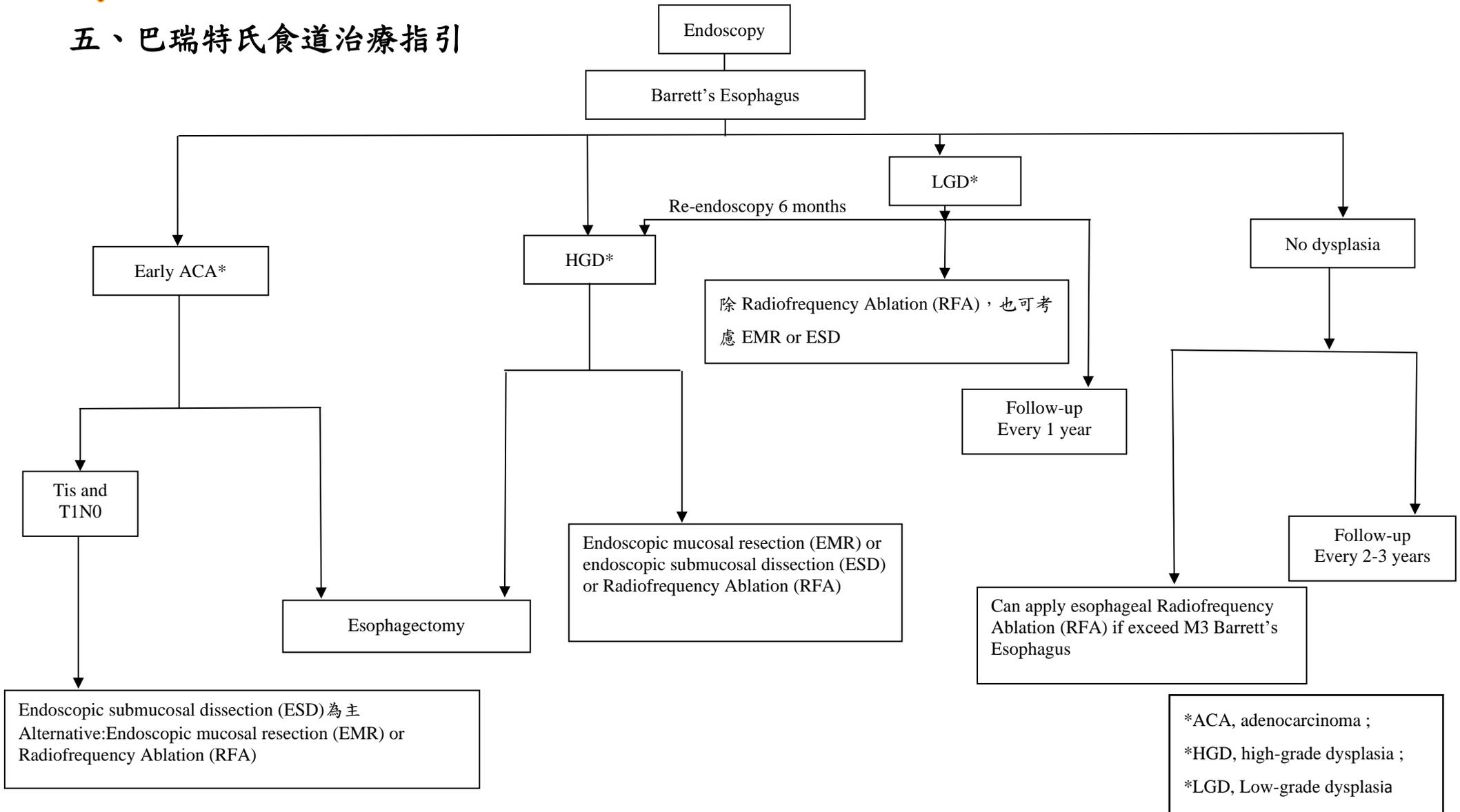


Adenocarcinoma

Clinical Staging (cTNM)				Pathological (pTNM)					Postneoadjuvant Therapy (ypTNM)			
	cT	cN	M		pT	pN	M	G		ypT	ypN	M
Stage 0	Tis	N0	M0	Stage 0	Tis	N0	M0	N/A	Stage I	T0-2	N0	M0
Stage I	T1	N0	M0	Stage IA	T1a	N0	M0	G1	Stage II	T3	N0	M0
Stage IIA	T1	N1	M0		T1a	N0	M0	GX	Stage IIIA	T0-2	N1	M0
Stage IIB	T2	N0	M0	Stage IB	T1a	N0	M0	G2	Stage IIIB	T3	N1	M0
Stage III	T2	N1	M0		T1b	N0	M0	G1-2		T0-3	N2	M0
	T3	N0-1	M0		T1b	N0	M0	GX		T4a	N0	M0
	T4a	N0-1	M0	Stage IC	T1	N0	M0	G3	Stage IVA	T4a	N1-2	M0
Stage IVA	T1-4a	N2	M0		T2	N0	M0	G1-2		T4a	NX	M0
	T4b	N0-2	M0	Stage IIA	T2	N0	M0	G3		T4b	N0-2	M0
	Any T	N3	M0		T2	N0	M0	GX	Any T	N3	M0	
Stage IVB	Any T	Any N	M1	Stage IIB	T1	N1	M0	Any	Stage IVB	Any T	Any N	M1
					T3	N0	M0	Any				
				Stage IIIA	T1	N2	M0	Any				
					T2	N1	M0	Any				
				Stage IIIB	T2	N2	M0	Any				
					T3	N1-2	M0	Any				
					T4a	N0-1	M0	Any				
				Stage IVA	T4a	N2	M0	Any				
					T4b	N0-2	M0	Any				
					Any T	N3	M0	Any				
				Stage IVB	Any T	Any N	M1	Any				



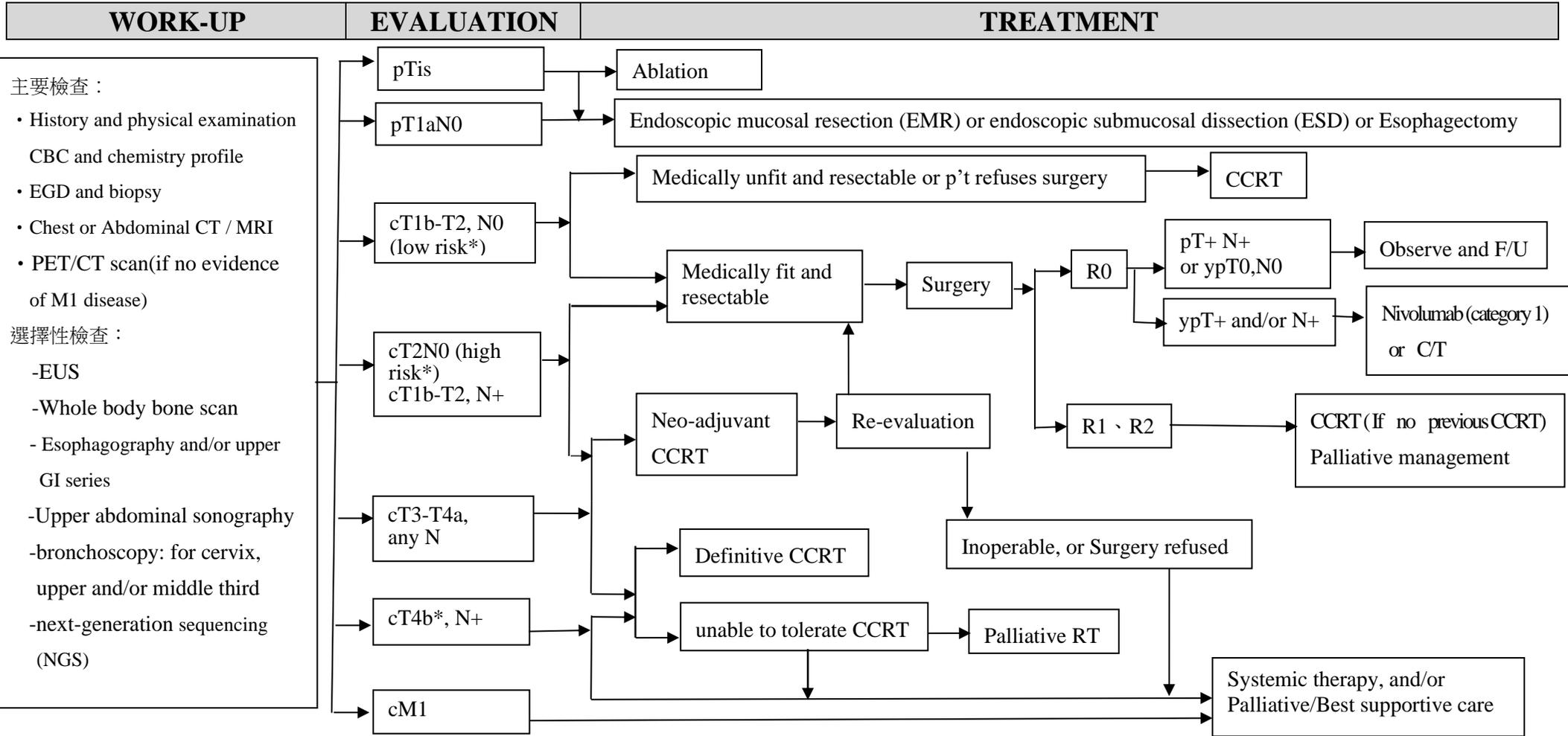
五、巴瑞特氏食道治療指引



8
 註 1：實際情況及手術與否需與胸腔外科/腫瘤內科及放射腫瘤科等多專科團隊討論
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



六、食道癌治療指引 (Squamous Cell Carcinoma)

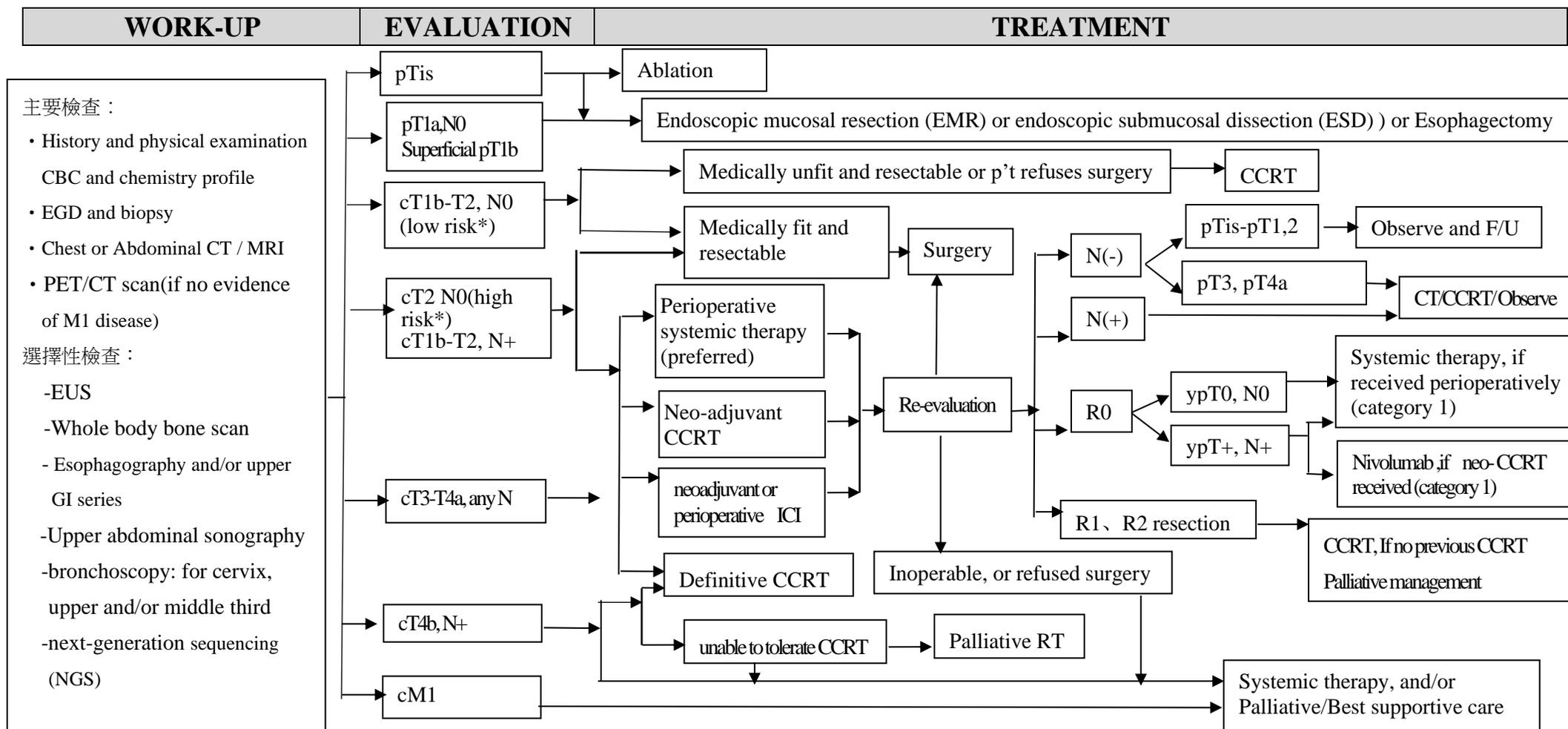


*Low risk: <3cm, well differentiated.
 *High risk: ≥3cm, poorly differentiated,LVI(+)
 *cT4b: Consider chemotherapy alone in the setting of invasion of trachea, great vessels, vertebral body, or heart

註 1：實際情況及手術與否需與胸腔外科/腫瘤內科及放射腫瘤科等多專科團隊討論
 Note: All recommendations are category 2A unless otherwise indicated.
 Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



食道癌治療指引 (Adenocarcinoma)



*Low risk: <3cm, well differentiated.
 *High risk: ≥3cm, poorly differentiated, LVI(+)
 *cT4b: Consider chemotherapy alone in the setting of invasion of trachea, great vessels, vertebral body, or heart

註 1：實際情況及手術與否需與胸腔外科/腫瘤內科及放射腫瘤科等多專科團隊討論

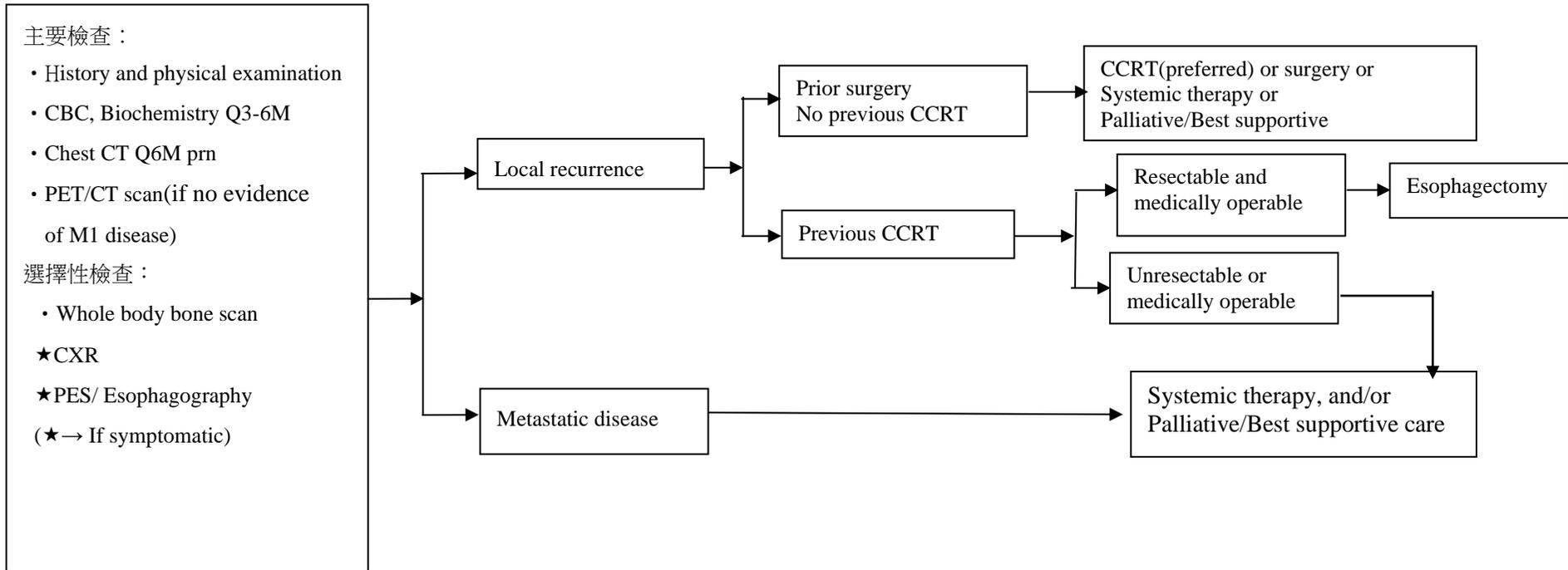
註 2：Adenocarcinoma of EJC 參考胃癌診療指引

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



FOLLOW-UP	RECURRENCE	PALLIATIVE THERAPY
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*Best supportive care:

- Obstruction: Stent, RT
- Nutrition: J-tube (for potential surgical candidate), PEG, G-tube
- Pain control: RT or medications

註 1：實際情況及手術與否需與胸腔外科/腫瘤內科及放射腫瘤科等多專科團隊討論
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

七、化學治療原則

(一) PRINCIPLES OF SYSTEMIC THERAPY

- 根據患者體能狀態、合併症和毒性反應選擇，對於晚期食道癌患者以三種藥物合併使用前，應確定患者的體能狀況良好（ECOG PS 0~1），並須定期進行毒性評估。
- 若有證據支持毒性更低且療效不受影響時，則優先選擇第 1 類（category 1）方案或使用第 2A、2B 類。
- 任何方案的劑量和用藥方案若不是來自第 1 類證據，則只能作為建議，應根據具體情況進行適當修改。
- 靜脈滴注 5-FU 和口服 capecitabine 可互換使用。與口服 capecitabine 相比，應優選靜脈持續滴注 5-FU。
- 完成化療後，應該評估療效和晚期併發症。

註 1：實際情況及手術與否需與胸腔外科/腫瘤內科及放射腫瘤科等多專科團隊討論

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



PRINCIPLES OF SYSTEMIC THERAPY

Squamous Cell Carcinoma

Preoperative chemoradiation (Infusional Fluorouracil can be replaced with UFUR)Preferred Regimens

- Paclitaxel and carboplatin (category 1)
- Fluorouracil and cisplatin (category 1)

Other Recommended Regimens

- Fluorouracil and carboplatin (eGFR≤60)

Neoadjuvant or Perioperative ImmunotherapyUseful in Certain Circumstances

- MSI-H/Dmmr tumors
- Nivolumab and ipilimumab followed by nivolumab
- Pembrolizumab
- Tremelimumab and durvalumab for neoadjuvant therapy only

Definitive Chemoradiation (Infusional fluorouracil can be replaced with UFUR)Preferred Regimens

- Paclitaxel and Carboplatin
- Fluorouracil and Cisplatin (category 1)

Other Recommended Regimens

- Cisplatin with Paclitaxel

Postoperative Systemic TherapyPreferred Regimens

- Nivolumab only after preoperative chemoradiation with R0 resection and residual disease (category 1)

Other Recommended Regimens

for patient can't afford adjuvant ICI , may consider complete chemotherapy course(2-4 cycle)

Esophagogastric Junction adenocarcinoma

Perioperative Systemic Therapy (Infusional Fluorouracil can be replaced with Capecitabine or UFUR)Preferred Regimens

- Fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) (category 1)

註 1：實際情況及手術與否需與胸腔外科/腫瘤內科及放射腫瘤科等多專科團隊討論

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



- FLOT + durvalumab for PD-L1 CPS ≥ 1 or TAP $\geq 1\%$ (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)

Other Recommended Regimens

- Fluorouracil and cisplatin (category 1)
- Fluoropyrimidine and oxaliplatin

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, nutritional status, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.



PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA

First-Line Therapy

Preferred Regimens

- Fluoropyrimidine (fluorouracil or capecitabine), cisplatin, and nivolumab for PD-L1 CPS ≥ 1 (category 1)
- Fluoropyrimidine (fluorouracil or capecitabine), cisplatin, and pembrolizumab for PD-L1 CPS ≥ 1 (category 1)
- Fluoropyrimidine (fluorouracil or capecitabine) and cisplatin
- Nivolumab and ipilimumab for PD-L1 CPS ≥ 1
- MSI-H/dMMR tumors (independent of PD-L1 status)
 - Pembrolizumab
 - Nivolumab and ipilimumab

Other Recommended Regimens

- Fluorouracil and irinotecan
- Paclitaxel with or without carboplatin or cisplatin
- Docetaxel with or without cisplatin
- Fluoropyrimidine (fluorouracil)
- Docetaxel, cisplatin or carboplatin, and fluorouracil

Useful in Certain Circumstances

- Entrectinib, larotrectinib, or repotrectinib for *NTRK* gene fusion-positive tumors (category 2B)



PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

ADENOCARCINOMA

First-Line Therapy

- Oxaliplatin is generally preferred over Cisplatin due to lower toxicity.

Preferred Regimens

- HER2 overexpression positive
 - Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and trastuzumab
 - Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, trastuzumab, and pembrolizumab for PD-L1 CPS ≥ 1 (category 1)
 - Fluoropyrimidine (fluorouracil or capecitabine), cisplatin, and trastuzumab (category 1)
 - Fluoropyrimidine (fluorouracil or capecitabine), cisplatin, trastuzumab and pembrolizumab for PD-L1 CPS ≥ 1 (category 1)
- HER2 overexpression negative
 - Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and nivolumab for PD-L1 CPS ≥ 1 (category 1 for PD-L1 CPS ≥ 5)
 - Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and pembrolizumab for PD-L1 CPS ≥ 1 (category 1 for PD-L1 CPS ≥ 5)
 - Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and zolbetuximab-clzb for CLDN18.2 positive (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)
 - Fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin
 - Fluoropyrimidine (fluorouracil or capecitabine), cisplatin, and pembrolizumab for PD-L1 CPS ≥ 1 (category 1 for PD-L1 CPS ≥ 5)
 - Fluoropyrimidine (fluorouracil or capecitabine) and cisplatin
- MSI-H/dMMR tumors (independent of PD-L1 status)
 - Pembrolizumab
 - Nivolumab and ipilimumab
 - Fluoropyrimidine (fluorouracil^a or capecitabine), oxaliplatin, and nivolumab
 - Fluoropyrimidine (fluorouracil^a or capecitabine), oxaliplatin, and pembrolizumab

Other Recommended Regimens

- Fluorouracil and irinotecan
 - Paclitaxel with or without carboplatin or cisplatin
 - Docetaxel with or without cisplatin
 - Fluoropyrimidine (fluorouracil or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil

Useful in Certain Circumstances

Entrectinib, larotrectinib, or repotrectinib for *NTRK* gene fusion-positive tumors (category 2B)

註 1：實際情況及手術與否需與胸腔外科/腫瘤內科及放射腫瘤科等多專科團隊討論

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA
Second-Line or Subsequent Therapy • Dependent on prior therapy and PS
<u>Preferred Regimens</u> • Nivolumab (category 1) • Pembrolizumab for PD-L1 CPS ≥ 10 (category 1) • Docetaxel (category 1) • Paclitaxel (category 1) • Irinotecan (category 1) • Fluorouracil and irinotecan
<u>Other Recommended Regimens</u> • Irinotecan and cisplatin • Docetaxel and irinotecan (category 2B)
<u>Useful in Certain Circumstances</u> • Entrectinib, larotrectinib, or repotrectinib for NTRK gene fusion-positive tumors • Pembrolizumab for MSI-H/dMMR tumors • Nivolumab and ipilimumab for MSI-H/dMMR tumors • Pembrolizumab for TMB-high (TMB-H) (≥ 10 mutations/megabase) tumors • Dabrafenib and trametinib for BRAF V600E-mutated tumors • Selpercatinib for RET gene fusion-positive tumors

註 1：實際情況及手術與否需與胸腔外科/腫瘤內科及放射腫瘤科等多專科團隊討論

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

ADENOCARCINOMA
Second-Line or Subsequent Therapy • Dependent on prior therapy and PS
<u>Preferred Regimens</u> • Ramucirumab and paclitaxel (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma) • Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive for adenocarcinoma • Docetaxel (category 1) • Paclitaxel (category 1) • Irinotecan (category 1) • Fluorouracil ^{a,g} and irinotecan • Trifluridine and tipiracil for third-line or subsequent therapy for EGJ adenocarcinoma (category 1)
<u>Other Recommended Regimens</u> • Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma) • Irinotecan and cisplatin • Fluorouracil and irinotecan + ramucirumab • Irinotecan and ramucirumab • Docetaxel and irinotecan (category 2B)
<u>Useful in Certain Circumstances</u> • Entrectinib, larotrectinib, or repotrectinib for NTRK gene fusion-positive tumors • Pembrolizumab for MSI-H/dMMR tumors • Nivolumab and ipilimumab for MSI-H/dMMR tumors • Pembrolizumab for TMB-high (TMB-H) (≥ 10 mutations/megabase) tumors • Dabrafenib and trametinib for BRAF V600E-mutated tumors • Selpercatinib for RET gene fusion-positive tumors

註 1：實際情況及手術與否需與胸腔外科/腫瘤內科及放射腫瘤科等多專科團隊討論

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NEOADJUVANT CHEMORADIATION

PREFERRED REGIMENS**Paclitaxel + Carboplatin**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Paclitaxel	50 mg/m ²	IV	D1	Weekly for 5 weeks	
Carboplatin	AUC 2	IV	D1		
Ref.	<i>van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-2084.</i>				

Fluorouracil and cisplatin

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin/or carboplatin (AUC 6)	60 - 80 mg/m ²	IV	D1	Cycled every 28 days for 2 cycles	
Fluorouracil (5-FU)	600 - 800 mg/m ² /day	IV	continuous infusion over 24 hours daily, D1-4		
or					
Cisplatin/or carboplatin (AUC 3)	30 - 40 mg/m ²	IV	D1	Cycled every 14 days for 3 cycles	
Fluorouracil (5-FU)	1200 -1600 mg/m ²	IV	drip 46-48 hours, D1-2		
Ref.	<i>Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 2008;26:1086-1092.</i>				



NEOADJUVANT CHEMORADIATION

Cisplatin +UFUR

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin	25 - 30 mg/m ²	IV	D1	Weekly for 5 weeks	不願 24-48 小時注射或 不適合放置人工血管
UFUR	200-250 mg/m ² /day	PO	Bid,D1-5		
Ref.	<i>Iwase, H., Shimada, M., Nakamura, M., Nakarai, K., Iyo, T., Kaida, S., Indo, T., Kato, E., Horiuchi, Y., & Kusugami, K. (2003). Concurrent chemoradiotherapy for locally advanced and metastatic esophageal cancer: Long-term results of a phase II study of UFT/CDDP with radiotherapy. International Journal of Clinical Oncology, 8(5), 305–311.</i>				



NEOADJUVANT OR PERIOPERATIVE IMMUNOTHERAPY

USEFUL IN CERTAIN CIRCUMSTANCES

(MSI-H/dMMR tumors)**Nivolumab and ipilimumab followed by nivolumab**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Nivolumab	240mg	IV	D1	every 2 weeks	(preoperative for at least 12 total weeks), followed by surgery and adjuvant nivolumab 480 mg IV every 4 weeks for 9 cycles
Ipilimumab	1 mg/kg	IV	D1	every 6 weeks	
Ref.	<i>Andre T, Tougeron D, Piessen G, et al. Neoadjuvant Nivolumab Plus Ipilimumab and Adjuvant Nivolumab in Localized Deficient Mismatch Repair/Microsatellite Instability-High Gastric or Esophagogastric Junction Adenocarcinoma: The GERCOR NEONIPIGA Phase II Study. J Clin Oncol 2023;41:255-265.</i>				

Pembrolizumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Pembrolizumab	200 mg	IV	D1	every 3 weeks for at least 12 total weeks	followed by surgery and adjuvant pembrolizumab 200 mg IV every 3 weeks for 16 cycles
Ref.	<i>Ludford K, Ho WJ, Thomas JV, et al. Neoadjuvant Pembrolizumab in Localized Microsatellite Instability High/Deficient Mismatch Repair Solid Tumors. J Clin Oncol 2023;41:2181-2190.</i>				



NEOADJUVANT OR PERIOPERATIVE IMMUNOTHERAPY

USEFUL IN CERTAIN CIRCUMSTANCES

(MSI-H/dMMR tumors)**Tremelimumab and durvalumab (for neoadjuvant therapy only)**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Tremelimumab	300 mg	IV	D1	For 12 weeks preoperatively for 1 cycle only	
Durvalumab	1500mg	IV	D1, 29, and 57		
Ref.	<p><i>Kelly RJ, Lee J, Bang YJ, et al. Safety and Efficacy of Durvalumab and Tremelimumab Alone or in Combination in Patients with Advanced Gastric and Gastroesophageal Junction Adenocarcinoma. Clin Cancer Res 2020;26:846-854.</i></p> <p><i>Pietrantonio F, Raimondi A, Lonardi S, et al. INFINITY: A multicentre, single-arm, multi-cohort, phase II trial of tremelimumab and durvalumab as neoadjuvant treatment of patients with microsatellite instability-high (MSI) resectable gastric or gastroesophageal junction adenocarcinoma (GAC/GEJAC). Journal of Clinical Oncology 2023;41:358- 358.</i></p>				



DEFINITIVE CHEMORADIATION

Preferred Regimens**Paclitaxel + Carboplatin**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Paclitaxel	50 mg/m ²	IV	D1	Weekly for 5 weeks	
Carboplatin	AUC 2	IV	D1		
Ref.	<i>van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-2084.</i>				

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Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin/or carboplatin (AUC 6)	60 - 80 mg/m ²	IV	D1	Cycled every 28 days for total 4 cycles	2 cycles with radiation followed by 2 cycles without radiation
Fluorouracil (5-FU)	600 - 800 mg/m ² /day	IV	continuous infusion over 24 hours daily, D1-4		
or					
Cisplatin/or carboplatin (AUC3)	30 - 40 mg/m ²	IV	D1	Cycled every 14 days for 6-8 cycles	3-4 cycles with radiation followed by 3-4cycles without radiation
Fluorouracil (5-FU) ± Leucovorin(200mg)	1200 -1600 mg/m ²	IV	drip 46-48 hours, D1-2		
Ref.	<i>Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combinedmodality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002;20:1167-1174.</i>				



DEFINITIVE CHEMORADIATION

Preferred Regimens**Cisplatin +UFUR**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin	25 - 30 mg/m ²	IV	D1	Weekly for 5 weeks	不願 24-48 小時注射 或不適合放置人工血管
UFUR	200-250 mg/m ² /day	PO	Bid,D1-5		
Ref.	<i>Iwase, H., Shimada, M., Nakamura, M., Nakarai, K., Iyo, T., Kaida, S., Indo, T., Kato, E., Horiuchi, Y., & Kusugami, K. (2003). Concurrent chemoradiotherapy for locally advanced and metastatic esophageal cancer: Long-term results of a phase II study of UFT/CDDP with radiotherapy. International Journal of Clinical Oncology, 8(5), 305–311.</i>				

OTHER RECOMMENDED REGIMENS**Paclitaxel +cisplatin**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Paclitaxel	60 mg/m ²	IV	D1,8,15,22	1cycle	
cisplatin	75 mg/m ²	IV	D1		
Ref.	<i>Urba SG, Orringer MB, Ianettonni M, et al. Concurrent cisplatin, paclitaxel, and radiotherapy as preoperative treatment for patients with locoregional esophageal carcinoma. Cancer 2003;98:2177-2183.</i>				



POSTOPERATIVE ADJUVANT THERAPY

PREFERRED REGIMEN**Nivolumab**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Nivolumab	240 mg or 自費 3mg/kg	IV	D1	every 14 days for 16 weeks	followed by Nivolumab 480 mg every 28 days · Maximum treatment duration of 1 year
Ref.	<i>Kelly R, Ajani J, Kuzdzal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiation therapy: first results of the CheckMate 577 study. [abstract]. Presented at the Oral Presentation presented at the ESMO 2020 Annual Meeting; September 19-21, 2020; Virtual Meeting.</i>				

Other Recommended Regimens

for patient can't afford adjuvant ICI , may consider complete chemotherapy course(2-4 cycle)



PERIOPERATIVE SYSTEMIC THERAPY (Esophagogastric Junction adenocarcinoma)

Preferred Regimens**FLOT**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Fluorouracil (5-FU)	2600 mg/m ²	IV	drip 46-48 hours, D1-2	Cycled every 14days for total 8 cycles	4 cycles preoperative and 4 cycles postoperative
Leucovorin	200 mg/m ²	IV	drip 46-48 hours, D1-2		
Oxaliplatin	85 mg/m ²	IV	D1		
Docetaxel	30 mg/m ²	IV	D1		
Ref.	<i>Al-Batran S-E, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastroesophageal junction adenocarcinoma (FLOG4): a randomised, phase 2/3 trial. Lancet 2019;393:1948-1957.</i>				

FLOT +durvalumab

Drug Combination(Dosage	Route of administration	Times	Frequency/Duration	Notes
durvalumab	1500	IV	D1	Cycled every 28days for total 4cycles	2cycles preoperative and 2cycles postoperative followed by Durvalumab 1500 mg IV on Day 1 every 4 weeks for 10 additional cycles
Fluorouracil (5-FU)	2600 mg/m ²	IV	drip 46-48 hours, D1-2,15-16		
Leucovorin	200 mg/m ²	IV	drip 46-48 hours, D1-2,15-16		
Oxaliplatin	85 mg/m ²	IV	D1		
Docetaxel	30 mg/m ²	IV	D1		
Ref.	<i>Janjigian YY, Al-Batran SE, Wainberg ZA, et al. Perioperative durvalumab in gastric and gastroesophageal junction cancer. N Engl J Med 2025;393:217-230.</i>				



PERIOPERATIVE SYSTEMIC THERAPY (Esophagogastric Junction adenocarcinoma)

OTHER RECOMMENDED REGIMENS**Fluorouracil+Cisplatin**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin	50 mg/m ²	IV	D1	Cycled every 14days for total 8 cycles	4 cycles preoperative and 4 cycles postoperative
Fluorouracil (5-FU)	2000 mg/m ²	IV	drip 46-48 hours, D1-2		
Ref.	<i>National Comprehensive Cancer Network. (2025). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Esophageal and Esophagogastric Junction Cancers (Version 4.2025).</i>				

Fluoropyrimidine and oxaliplatin

Drug Combinatio	Dosage	Route of administration	Times	Frequency/Duration	Notes
Fluorouracil (5-FU)	1200mg/m ² /day	IV	continuous infusion over 24 hours daily, D1 and 2	Cycled every 14days for total 8 cycles	4 cycles preoperative and 4 cycles postoperative
Fluorouracil (5-FU)	400mg/m ²	IV push	D1		
Leucovorin	400mg/m ²	IV	D1		
Oxaliplatin	85 mg/m ²	IV	D1		
Ref.	<i>Enzinger PC, Burtness BA, Niedzwiecki D, et al. CALGB 80403 (Alliance)/E1206: a randomized phase II study of three chemotherapy regimens plus cetuximab in metastatic esophageal and gastroesophageal junction cancers. J Clin Oncol 2016;34:2736-2742.</i>				



PERIOPERATIVE SYSTEMIC THERAPY (Esophagogastric Junction adenocarcinoma)

OTHER RECOMMENDED REGIMENS**Fluoropyrimidine and oxaliplatin**

Drug Combinatio	Dosage	Route of administration	Times	Frequency/Duration	Notes
Fluorouracil (5-FU)	2600 mg/m ²	IV	drip 46-48 hours, D1-2	Cycled every 14days for total 8 cycles	4 cycles preoperative and 4 cycles postoperative
Leucovorin	200 mg/m ²	IV	drip 46-48 hours, D1-2		
Oxaliplatin	85 mg/m ²	IV	D1		
Ref.	<i>Al-Batran S-E, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008;26:1435-1442.</i>				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA(FIRST-LINE THERAPY)

PREFERRED REGIMENS**Cisplatin + Fluorouracil (5-FU)**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin/or carboplatin (AUC 6)	80 mg/m ²	IV	D1	every 28 days	
Fluorouracil (5-FU)	750 – 1000 mg/m ² /day	IV	continuous infusion over 24 hours daily, D1-4		
Ref.	<i>Lorenzen S, Schuster T, Porschen R, et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2009;20:1667-1673.</i>				

PFL

Drug Combinatio	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin/or carboplatin (AUC2)	40 - 50 mg/m ²	IV	D1	every 14 days	
Leucovorin	200 mg/m ²	IV	drip 46-48 hours, D1-2		
Fluorouracil (5-FU)	1600-2000 mg/m ²	IV	drip 46-48 hours, D1-2		
Ref.	<i>Hung TC et al. Weekly 24-hour infusional 5-fluorouracil as initial treatment for advanced gastric cancer with acute disseminated intravascular coagulation. Anticancer Res 2008;28:1293</i>				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA(FIRST-LINE THERAPY)

PREFERRED REGIMENS**Cisplatin + Fluorouracil (5-FU) + nivolumab**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin/or carboplatin (AUC 6)	80 mg/m ²	IV	D1	every 28days	
Fluorouracil (5-FU)	800 mg/m ² /day	IV	continuous infusion over 24 hours daily,D1-5		
nivolumab	240mg	IV		every 14 days	per study maximum of 2 years
Ref.	<i>Doki Y, Ajani JA, Kato K, et al. Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. N Engl J Med 2022;386:449-462.</i>				

Cisplatin +Capecitabine + nivolumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin	80 mg/m ²	IV	D1	every 21days	per study maximum of 2 years
Capecitabine	850-1000mg	PO	Bid,D1-14		
nivolumab	360mg	IV	D1		
Ref.	<i>Kang YK, Kang WK, Shin DB, et al. Capecitabine/ cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol 2009;20:666-673.</i>				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA(FIRST-LINE THERAPY)

PREFERRED REGIMENS**Cisplatin + Fluorouracil (5-FU) +Pembrolizumab**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin	80 mg/m ²	IV	D1	every 21days for up to 6cycles	
Fluorouracil (5-FU)	800 mg/m ² /day	IV	continuous infusion over 24 hours daily on Days 1–5		
Pembrolizumab	200mg	IV	D1	every 21 days	up to 2 years
Ref.	<i>Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet 2021;398:759-771.</i>				

Cisplatin +Capecitabine +Pembrolizumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin	80 mg/m ²	IV	D1	every 21days for 6cycles(total of 18weeks)	
Capecitabine	850-1000mg	PO	Bid,D1-14		
Pembrolizumab	200mg	IV	D1	every 21 days	up to 2 years
Ref.	<i>Rha SY, Oh DY, Yanez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2023;24:1181- 1195.</i>				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA(FIRST-LINE THERAPY)

PREFERRED REGIMENS**Nivolumab+ipilimumab**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Nivolumab	3 mg/kg	IV	D1	every 2 weeks	(per study, maximum of 2 years)
Ipilimumab	1 mg/kg	IV	D1	every 6 weeks	
Ref.	<i>Doki Y, Ajani JA, Kato K, et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. N Engl J Med 2022;386:449-462.</i>				

OTHER RECOMMENDED REGIMENS**Fluorouracil and irinotecan**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	180 mg/m ²	IV	D1	Cycled every 14 days	
Leucovorin	400 mg/m ²	IV	on Day 1		
Fluorouracil	400 mg/m ²	IV Push	on Day 1		
Fluorouracil	1200 mg/m ² /days	IV	IV continuous infusion over 24 hours daily on Days 1 and 2		
Ref.	<i>Guimbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French Intergroup (Federation Francophone de Cancerologie Digestive, Federation Nationale des Centres de Lutte Contre le Cancer, and Groupe Cooperateur Multidisciplinaire en Oncologie) study. J Clin Oncol 2014;32:3520-3526.</i>				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA(FIRST-LINE THERAPY)

OTHER RECOMMENDED REGIMENS**Paclitaxel with or without carboplatin or cisplatin**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes	
Paclitaxel	175 mg/m ²	IV	on Day 1	Cycled every 21 days		
Carboplatin	AUC 5	IV	on Day 1			
or						
Paclitaxel	60-80 mg/m ²	IV	on D1,8,15	Cycled every 28 days		
Cisplatin	70-80 mg/m ²	IV	on Day 1			
or						
Paclitaxel	135–200mg/m ²	IV	on Day 1	Cycled every 21 days		
Cisplatin	75 mg/m ²	IV	on Day 1			
or						
Paclitaxel	90 mg/m ²	IV	on Day 1	Cycled every 14 days		
Cisplatin	50 mg/m ²	IV	on Day 1			
or						
Paclitaxel	135-250mg/m ²	IV	on Day 1	Cycled every 21 days		
or						
Paclitaxel	60-80 mg/m ²	IV	on D1,8,15	Cycled every 28 days		
Ref.	1. Gadgeel SM, Shields AF, Heilbrun LK, et al. Phase II study of paclitaxel and carboplatin in patients with advanced gastric cancer. <i>Am J Clin Oncol</i> 2003;26:37-41. 2. Ilson DH, Forastiere A, Arquette M, et al. A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. <i>Cancer J</i> 2000;6:316-323.					

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)



SQUAMOUS CELL CARCINOMA(FIRST-LINE THERAPY)

OTHER RECOMMENDED REGIMENS

Ref.	<p>3. Petrasch S, Welt A, Reinacher A, et al. Chemotherapy with cisplatin and paclitaxel in patients with locally advanced, recurrent or metastatic oesophageal cancer. <i>Br J Cancer</i> 1998;78:511-514.</p> <p>4. Ajani JA, Ilson DH, Daugherty K, et al. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. <i>J Natl Cancer Inst</i> 1994;86:1086-1091.</p> <p>5. Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. <i>J Clin Oncol</i> 2013;31:4438-4444.</p>
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Docetaxel with or without cisplatin

Drug Combinatio	Dosage	Route of administration	Times	Frequency/Duration	Notes	
Docetaxel	70-85 mg/m ²	IV	D1	every 21 days		
Cisplatin	70-75 mg/m ²	IV	D1			
or						
Docetaxel	30 - 35 mg/m ²	IV	D1、8	every 21 days		
or						
Docetaxel	22 - 25 mg/m ²	IV	D1、8、15	every 28 days		
or						
Docetaxel	60-75mg/m ²	IV	D1	every 21 days		
Ref.	<p>1. Ajani JA, Fodor MB, Tjulandin SA, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. <i>J Clin Oncol</i> 2005;23:5660-5667.</p> <p>2. Kim JY, Do YR, Park KU, et al. A multi-center phase II study of docetaxel plus cisplatin as first-line therapy in patients with metastatic squamous cell esophageal cancer. <i>Cancer Chemother Pharmacol</i> 2010;66:31-36.</p>					



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA(FIRST-LINE THERAPY)

OTHER RECOMMENDED REGIMENS**Fluoropyrimidine**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes	
Leucovorin	400 mg/m ²	IV	D1	Cycled every 14 days		
Fluorouracil	400 mg/m ²	IV Push	on Day 1			
Fluorouracil	1200 mg/m ² /days	IV	IV continuous infusion over 24 hours daily on Days 1 and 2			
or						
Capecitabine	850–1000 mg/m ²	PO	BID, on D 1–14	Cycled every 21 days		
or						
Fluorouracil	800mg/m ²	IV	IV continuous infusion over 24 hours daily on Days 1-5	Cycled every 28 days		
Ref.	<p>1. Bouche O, Raoul JL, Bonnetain F, et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study-FFCD 9803. <i>J Clin Oncol</i> 2004;22:4319-4328.</p> <p>2. Ohtsu A, Shimada Y, Shirao K, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). <i>J Clin Oncol</i> 2003;21:54-59.</p> <p>3. Hong YS, Song SY, Lee SI, et al. A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer. <i>Ann Oncol</i> 2004;15:1344-1347.</p>					



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA(FIRST-LINE THERAPY)

OTHER RECOMMENDED REGIMENS**Docetaxel, cisplatin, and fluorouracil**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Docetaxel	40 mg/m ²	IV	on Day 1	Cycled every 14 days	
Leucovorin	400 mg/m ²	IV	on Day 1		
Fluorouracil	400 mg/m ²	IV	on Day 1		
Fluorouracil	1000 mg/m ² /day	IV	IV continuous infusion over 24 hours daily on Days 1 and 2		
Cisplatin	40 mg/m ²	IV	on Day 3		
Ref.	<p>1. Shah MA, Janjigian YY, Stoller R, et al. Randomized multicenter phase II study of modified docetaxel, cisplatin, and fluorouracil (DCF) versus DCF plus growth factor support in patients with metastatic gastric adenocarcinoma: a study of the US Gastric Cancer Consortium. <i>J Clin Oncol</i> 2015;33:3874-3879.</p> <p>2. Blum Murphy MA, Qiao W, Mewada N, et al. A phase I/II study of docetaxel, oxaliplatin, and fluorouracil (D-FOX) chemotherapy in patients with untreated locally unresectable or metastatic adenocarcinoma of the stomach and gastroesophageal junction. <i>Am J Clin Oncol</i> 2018;41:321-325.</p>				

S-1 (TS-1)

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Tegafur/potassium oxonate/gimeracil	40mg	PO	Bid	4 weeks on, 2 weeks off (or 2 weeks on, 1 weeks off), for 1 year	BSA < 1.25
OR					
Tegafur/potassium oxonate/gimeracil	50mg	PO	Bid		BSA 1.25 - 1.5



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA(FIRST-LINE THERAPY)

OTHER RECOMMENDED REGIMENS

Tegafur/potassium oxonate/gimeracil	60mg	PO	Bid		BSA \geq 1.5
Ref.	<p><i>Sakuramoto S, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med. 2007;357:1810. S-1 Monotherapy as Second- or Third-Line Chemotherapy for Unresectable and Recurrent Esophageal Squamous Cell Carcinoma Akutsu Y. · Kono T. · Uesato M. · Hoshino I. · Narushima K. · Hanaoka T. · Tochigi T. · Semba Y. · Qin W. · Matsubara H. Department of Frontier Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan</i></p>				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

ADENOCARCINOMA (FIRST-LINE THERAPY)

HER2 overexpression-positive**Trastuzumab with chemotherapy(Fluoropyrimidine and oxaliplatin)**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes	
Trastuzumab	8 mg/kg IV loading dose on Day 1 of cycle 1, then 6 mg/kg	IV	drip 90 mins, then 60 mins, day 1	every 21 days	HER2 overexpression-positive	
or						
Trastuzumab	6 mg/kg IV loading dose on Day 1 of cycle 1, then 4 mg/kg	IV	drip 90 mins, then 60 mins, day 1	every 14 days		
Ref.	<i>Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2- positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, 38 randomized controlled trial. Lancet 2010;376:687- 697.</i>					
+						
Oxaliplatin	85 mg/m ²	IV	on Day 1	Cycled every 14 days		
Leucovorin	200 mg/m ²	IV	continuous infusion over 24 hours on Day 1			
Fluorouracil	2600 mg/m ²	IV	continuous infusion over 24 hours on Day 1			
or						
Capecitabine	850-1000 mg/m ²	PO	BID. On D 1–14	Cycled every 21 days		
Oxaliplatin	130 mg/m ²	IV	drip 120 mins, on Day 1			



or				
Capecitabine	625 mg/m ² BID	PO	on D 1–14	Cycled every 21 days
Oxaliplatin	85 mg/m ²	IV	on Day 1	
Ref.	<p>1 Al-Batran S-E, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. <i>J Clin Oncol</i> 2008;26:1435-1442.</p> <p>2 Enzinger PC, Burtness BA, Niedzwiecki D, et al. CALGB 80403 (Alliance)/E1206: a randomized phase II study of three chemotherapy regimens plus cetuximab in metastatic esophageal and gastroesophageal junction cancers. <i>J Clin Oncol</i> 2016;34:2736-2742.</p> <p>3 Kim GM, Jeung HC, Rha SY, et al. A randomized phase II trial of S-1-oxaliplatin versus capecitabine- oxaliplatin in advanced gastric cancer. <i>Eur J Cancer</i> 2012;48:518-526.</p> <p>4 Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. <i>N Engl J Med</i> 2001;345:725-730.</p>			

Trastuzumab with chemotherapy(Fluoropyrimidine and cisplatin)

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes	
Trastuzumab	8 mg/kg IV loading dose on Day 1 of cycle 1, then 6 mg/kg	IV	drip 90 mins, then 60 mins, day 1	every 21 days	HER2 overexpression-positive	
or						
Trastuzumab	6 mg/kg IV loading dose on Day 1 of cycle 1, then 4 mg/kg	IV	drip 90 mins, then 60 mins, day 1	every 14 days		
Ref.	Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2- positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, 39 randomized controlled trial. <i>Lancet</i> 2010;376:687- 697.					



+				
Cisplatin	75–100 mg/m ²	IV	on Day 1	Cycled every 28 days
Fluorouracil	750–1000 mg/m ² /day	IV	continuous infusion over 24 hours daily on Days 1–4	
or				
Cisplatin	50 mg/m ²	IV	on Day 1	Cycled every 14 days
Leucovorin	200 mg/m ²	IV	IV continuous infusion over 24 hours daily on Day 1	
Fluorouracil	2600 mg/m ²	IV	IV continuous infusion over 24 hours daily on Day 1	
or				
Cisplatin	80 mg/m ²	IV	daily on Day 1	Cycled every 21 days
Capecitabine	850–1000 mg/m ²	PO	BID, on D1–14	
Ref.	<p>1. Lorenzen S, Schuster T, Porschen R, et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. <i>Ann Oncol</i> 2009;20:1667-1673.</p> <p>2. Al-Batran S-E, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. <i>J Clin Oncol</i> 2008;26:1435-1442.</p> <p>Bouche O, Raoul JL, Bonnetain F, et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study-FFCD 9803. <i>J Clin Oncol</i> 2004;22:4319-4328.</p> <p>3. Kang YK, Kang WK, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomized phase III noninferiority trial. <i>Ann Oncol</i> 2009;20:666-673.</p>			

**Trastuzumab and pembrolizumab with fluoropyrimidine and oxaliplatin or fluoropyrimidine and cisplatin**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes	
Trastuzumab	8 mg/kg loading dose on Day 1 of cycle 1, then 6 mg/kg	IV	drip 90 mins, then 60 mins, day 1	every 21 days	HER2 overexpression-positive	
Pembrolizumab	200 mg	IV	on Day 1	Cycled every 3 weeks		
Ref.	<p>1. Janjigian YY, Kawazoe A, Bai Y, et al. Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial. <i>Lancet</i> 2023;402:2197-2208.</p> <p>2. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2- positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. <i>Lancet</i> 2010;376:687- 697.</p> <p>3. Janjigian YY, Kawazoe A, Yanez P, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. <i>Nature</i> 2021;600:727-730.</p>					
+						
Capecitabine	850–1000 mg/m ²	PO	BID,D1–14	Cycled every 21 days		
Oxaliplatin	130 mg/m ²	IV	drip 120 mins, on Day 1			
or						
Cisplatin	80 mg/m ²	IV	D 1	Cycled every 21 days		
Fluorouracil	800 mg/m ² /day	IV	continuous infusion over 24 hours daily on Days 1–5			
or						
Cisplatin	80 mg/m ²	IV	D 1	Cycled every 21 days		
Capecitabine	850–1000 mg/m ²	PO	Bid,D1–14			



Ref.

1. Kim GM, Jeung HC, Rha SY, et al. A randomized phase II trial of S-1-oxaliplatin versus capecitabine-oxaliplatin in advanced gastric cancer. *Eur J Cancer* 2012;48:518-526.
2. Janjigian YY, Kawazoe A, Yanez P, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. *Nature* 2021;600:727-730.
3. Kang YK, Kang WK, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Ann Oncol* 2009;20:666-673.

Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and nivolumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Oxaliplatin	130 mg/m ²	IV	D 1	every 21 days	per study maximum of 2 years
Capecitabine	850-1000mg	PO	Bid, D1-14		
nivolumab	360mg	IV	D1		
Ref.	<p>1. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. <i>Lancet</i> 2021;398:27-40.</p> <p>2. Doki Y, Ajani JA, Kato K, et al. Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. <i>N Engl J Med</i> 2022;386:449-462.</p>				

**Oxaliplatin + Fluorouracil (5-FU) + Pembrolizumab**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Oxaliplatin	85mg/m ²	IV	D1	Cycled every 14 days for up to 9 cycles (total 18 weeks)	
Leucovorin	400mg	IV	continuous infusion over 24 hours daily on Days 1		
Fluorouracil	400mg	IV push	D1		
Fluorouracil	1200mg/m ² /day	IV	continuous infusion over 24 hours daily on Days 1 and 2		
Pembrolizumab	200mg	IV	D1	every 21 days	up to 2 years
Ref.	<i>Rha SY, Oh DY, Yanez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2023;24:1181- 1195.</i>				

Oxaliplatin + Capecitabine + Pembrolizumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Oxaliplatin	130mg/m ²	IV	D1	every 21days for 6cycles(total of 18weeks)	
Capecitabine	850-1000mg	PO	Bid,D1-14		
Pembrolizumab	200mg	IV	D1	every 21 days	up to 2 years
Ref.	<i>Rha SY, Oh DY, Yanez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2023;24:1181- 1195.</i>				

**Cisplatin + Fluorouracil (5-FU) +Pembrolizumab**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin	80 mg/m ²	IV	D1	every 21days for 6cycles	
Fluorouracil (5-FU)	800 mg/m ² /day	IV	continuous infusion over 24 hours daily on Days 1–5		
Pembrolizumab	200mg	IV	D1	every 21 days	up to 2 years
Ref.	<i>Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet 2021;398:759-771.</i>				

Cisplatin +Capecitabine +Pembrolizumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Cisplatin	80 mg/m ²	IV	D1	every 21days for 6cycles(total of 18weeks)	
Capecitabine	850-1000mg	PO	Bid,D1-14		
Pembrolizumab	200mg	IV	D1	every 21 days	up to 2 years
Ref.	<i>Rha SY, Oh DY, Yanez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double- blind, phase 3 trial. Lancet Oncol 2023;24:1181- 1195.</i>				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

ADENOCARCINOMA (FIRST-LINE THERAPY)

HER2 Overexpression Negative, CLDN18.2 Positive

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes	
Zolbetuximab-clzb	800 mg/m ² first-dose only, subsequent doses 400 mg/m ²	IV	D1	Cycled every 14 days		
Oxaliplatin	85 mg/m ²	IV	on D 1 (per study maximum of 12 doses)			
Leucovorin	400mg	IV	D1			
Fluorouraci	400mg	IV push	continuous infusion over 24 hours daily on Days 1			
Fluorouraci	1200mg/m ² /day	IV	continuous infusion over 24 hours daily on Days 1 and 2			
or						
Zolbetuximab-clzb	800 mg/m ² IV first-dose only, subsequent doses 600 mg/m ²	IV	on Day 1	Cycled every 21 days		
Oxaliplatin	130 mg/m ²	IV	on Day 1 (per study maximum of 8 doses)			
Capecitabine	850–1000 mg/m ² BID	PO	on Days 1–14			
Ref.	<p>1. Shitara K, Lordick F, Bang YJ, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2- positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. <i>Lancet</i> 2023;401:1655-1668.</p> <p>2. Shah MA, Shitara K, Ajani JA, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. <i>Nat Med</i> 2023;29:2133-2141.</p>					



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

ADENOCARCINOMA (FIRST-LINE THERAPY)

OTHER RECOMMENDED REGIMENS**Fluorouracil and irinotecan**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	180 mg/m ²	IV	D1	Cycled every 14 days	
Leucovorin	400 mg/m ²	IV	on Day 1		
Fluorouracil	400 mg/m ²	IV Push	on Day 1		
Fluorouracil	1200 mg/m ² /days	IV	IV continuous infusion over 24 hours daily on Days 1 and 2		
Ref.	<i>Guimbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French Intergroup (Federation Francophone de Cancerologie Digestive, Federation Nationale des Centres de Lutte Contre le Cancer, and Groupe Cooperateur Multidisciplinaire en Oncologie) study. J Clin Oncol 2014;32:3520-3526.</i>				

Paclitaxel with or without carboplatin or cisplatin

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Paclitaxel	175 mg/m ²	IV	on Day 1	Cycled every 21 days	
Carboplatin	AUC 5	IV	on Day 1		
or					
Paclitaxel	60-80 mg/m ²	IV	on D1,8,15	Cycled every 28 days	
Cisplatin	70-80 mg/m ²	IV	on Day 1		
or					
Paclitaxel	135–200mg/m ²	IV	on Day 1	Cycled every 21 days	



Cisplatin	75 mg/m ²	IV	on Day 1	
or				
Paclitaxel	90 mg/m ²	IV	on Day 1	Cycled every 14 days
Cisplatin	50 mg/m ²	IV	on Day 1	
or				
Paclitaxel	135-250mg/m ²	IV	on Day 1	Cycled every 21 days
or				
Paclitaxel	60-80 mg/m ²	IV	on D1,8,15	Cycled every 28 days
Ref.	<p>1. Gadgeel SM, Shields AF, Heilbrun LK, et al. Phase II study of paclitaxel and carboplatin in patients with advanced gastric cancer. <i>Am J Clin Oncol</i> 2003;26:37-41.</p> <p>2. Ilson DH, Forastiere A, Arquette M, et al. A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. <i>Cancer J</i> 2000;6:316-323.</p> <p>3. Petrasch S, Welt A, Reinacher A, et al. Chemotherapy with cisplatin and paclitaxel in patients with locally advanced, recurrent or metastatic oesophageal cancer. <i>Br J Cancer</i> 1998;78:511-514.</p> <p>4. Ajani JA, Ilson DH, Daugherty K, et al. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. <i>J Natl Cancer Inst</i> 1994;86:1086-1091.</p> <p>5. Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. <i>J Clin Oncol</i> 2013;31:4438-4444.</p>			

Docetaxel with or without cisplatin

Drug Combinatio	Dosage	Route of administration	Times	Frequency/Duration	Notes
Docetaxel	70-85 mg/m ²	IV	D1	every 21 days	
Cisplatin	70-75 mg/m ²	IV	D1		
or					
Docetaxel	30 - 35 mg/m ²	IV	D1、8	every 21 days	
or					



Docetaxel	22 - 25 mg/m ²	IV	D1、8、15	every 28 days	
or					
Docetaxel	60-75mg/m ²	IV	D1	every 21 days	
Ref.	<p>1.Ajani JA, Fodor MB, Tjulandin SA, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. <i>J Clin Oncol</i> 2005;23:5660-5667.</p> <p>2.Kim JY, Do YR, Park KU, et al. A multi-center phase II study of docetaxel plus cisplatin as first-line therapy in patients with metastatic squamous cell esophageal cancer. <i>Cancer Chemother Pharmacol</i> 2010;66:31-36.</p>				

Fluoropyrimidine

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Leucovorin	400 mg/m ²	IV	D1	Cycled every 14 days	
Fluorouracil	400 mg/m ²	IV Push	on Day 1		
Fluorouracil	1200 mg/m ² /days	IV	IV continuous infusion over 24 hours daily on Days 1 and 2		
or					
Capecitabine	850–1000 mg/m ²	PO	BID,on D 1–14	Cycled every 21 days	
or					
Fluorouracil	800mg/m ²	IV	IV continuous infusion over 24 hours daily on Days 1-5	Cycled every 28 days	
Ref.	<p>1. Bouche O, Raoul JL, Bonnetain F, et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study-FFCD 9803. <i>J Clin Oncol</i> 2004;22:4319-4328.</p> <p>2. Ohtsu A, Shimada Y, Shirao K, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). <i>J Clin Oncol</i> 2003;21:54-59.</p>				



3. Hong YS, Song SY, Lee SI, et al. A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer. *Ann Oncol* 2004;15:1344-1347.

Docetaxel, cisplatin or oxaliplatin, and fluorouracil

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Docetaxel	40 mg/m ²	IV	on Day 1	Cycled every 14 days	
Leucovorin	400 mg/m ²	IV	on Day 1		
Fluorouracil	400 mg/m ²	IV	on Day 1		
Fluorouracil	1000 mg/m ² /day	IV	IV continuous infusion over 24 hours daily on Days 1 and 2		
Cisplatin	40 mg/m ²	IV	on Day 3		
or					
Docetaxel	50 mg/m ²	IV	on Day 1	Cycled every 14 days	
Oxaliplatin	85 mg/m ²	IV	on Day 1		
Fluorouracil	1200 mg/m ² /day	IV	IV continuous infusion over 24 hours daily on Days 1 and 2		
Ref.	<p>1. Shah MA, Janjigian YY, Stoller R, et al. Randomized multicenter phase II study of modified docetaxel, cisplatin, and fluorouracil (DCF) versus DCF plus growth factor support in patients with metastatic gastric adenocarcinoma: a study of the US Gastric Cancer Consortium. <i>J Clin Oncol</i> 2015;33:3874-3879.</p> <p>2. Blum Murphy MA, Qiao W, Mewada N, et al. A phase I/II study of docetaxel, oxaliplatin, and fluorouracil (D-FOX) chemotherapy in patients with untreated locally unresectable or metastatic adenocarcinoma of the stomach and gastroesophageal junction. <i>Am J Clin Oncol</i> 2018;41:321-325.</p>				



S-1 (TS-1)

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Tegafur/potassium oxonate/gimeracil	40mg	PO	Bid	4 weeks on, 2 weeks off (or 2 weeks on, 1 weeks off), for 1 year	BSA < 1.25
OR					
Tegafur/potassium oxonate/gimeracil	50mg	PO	Bid		BSA 1.25 - 1.5
Tegafur/potassium oxonate/gimeracil	60mg	PO	Bid		BSA ≥ 1.5
Ref.	<i>Sakuramoto S, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med. 2007;357:1810. S-1 Monotherapy as Second- or Third-Line Chemotherapy for Unresectable and Recurrent Esophageal Squamous Cell Carcinoma Akutsu Y. · Kono T. · Uesato M. · Hoshino I. · Narushima K. · Hanaoka T. · Tochigi T. · Semba Y. · Qin W. · Matsubara H. Department of Frontier Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan</i>				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

(SQUAMOUS CELL CARCINOMA AND ADENOCARCINOMA)

MSI-H/dMMR tumors (independent of PD-L1 status)

Pembrolizumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Pembrolizumab	200 mg	IV	D1	Cycled every 21 days	(up to 2 years)
or					
Pembrolizumab	400 mg	IV	D1	Cycled every 6weeks	
Ref.	<p>1. Kojima T, Shah MA, Muro K, et al. Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer. <i>J Clin Oncol</i> 2020;38:4138-4148.</p> <p>2. Lala M, Li TR, de Alwis DP, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. <i>Eur J Cancer</i> 2020;131:68-75.</p>				

Nivolumab and ipilimumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Nivolumab	240 mg	IV		every 2 weeks	For 16 weeks, followed by Nivolumab 240 mg IV every 2 weeks or Nivolumab 480 mg IV every 4 weeks (maximum of 2 years)
Ipilimumab	1 mg/kg	IV		every 6 weeks	
Ref.	<p>Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. <i>Lancet</i> 2021;398:27-40.</p>				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

(ADENOCARCINOMA)

MSI-H/dMMR tumors (independent of PD-L1 status)

Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and nivolumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes	
Nivolumab	360 mg	IV	on Day 1 (per study maximum of 2 years)	Cycled every 21 days		
Capecitabine	850–1000 mg/m ²	PO	BID.on D 1–14			
Oxaliplatin	130 mg/m ²	IV	on Day 1			
or						
Nivolumab	240 mg	IV	on Day 1 (per study maximum of 2 years)	Cycled every 14 days		
Oxaliplatin	85 mg/m ²	IV	on Day 1			
Leucovorin	400mg	IV	continuous infusion over 24 hours daily on Days 1			
Fluorouraci	400mg	IV push	D1			
Fluorouraci	1200mg/m ² /day	IV	continuous infusion over 24 hours daily on Days 1 and 2			
Ref.	<i>Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 2021;398:2740.</i>					



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

(ADENOCARCINOMA)

MSI-H/dMMR tumors (independent of PD-L1 status)

Fluoropyrimidine, oxaliplatin, and pembrolizumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Pembrolizumab	200 mg	IV	every 21 days for up to 2 years	Cycled every 21 days for up to 6 cycles (total 18 weeks)	
Capecitabine	850–1000 mg/m ²	PO	BID, D1–14		
Oxaliplatin	130 mg/m ²	IV	drip 90-120 mins, on Day 1		
or					
Pembrolizumab	200 mg	IV	every 21 days for up to 2 years	Cycled every 14 days for up to 9 cycles (total 18 weeks)	
Oxaliplatin	85 mg/m ²	IV	on Day 1		
Leucovorin	400 mg/m ²	IV	on Day 1		
Fluorouracil	400 mg/m ²	IV Push	on Day 1		
Fluorouracil	1200 mg/m ²	IV	IV continuous infusion over 24 hours daily on Days 1 and 2		
Ref.	<i>Rha SY, Oh DY, Yanez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2023;24:1181- 1195.</i>				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA(SECOND-LINE AND SUBSEQUENT THERAPY)

PREFERRED REGIMENS**Nivolumab**

Drug Combinatio	Dosage	Route of administration	Times	Frequency/Duration	Notes
Nivolumab	240 mg/m ²	IV	D1	every 14days	(for second-line therapy for esophageal SCC)
or					
nivolumab	480mg	IV	D1	every 28days	
Ref.	<i>Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy(ATTRACTION-3): a multicentre, randomised, open- label, phase 3 trial. Lancet Oncol 2019;20:1506- 1517.</i>				

Pembrolizumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Pembrolizumab	200mg/m ²	IV	D1	every 21days	(for second-line therapy for esophageal SCC with PD-L1 expression levels by CPS of >=10)
or					
Pembrolizumab	400mg	IV	D1	every 6 weeks	
Ref.	<p><i>1.Kojima T, Shah MA, Muro K, et al. Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer. J Clin Oncol 2020;38:4138-4148.</i></p> <p><i>2. Lala M, Li TR, de Alwis DP, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. Eur J Cancer 2020;131:68-75.</i></p>				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA(SECOND-LINE AND SUBSEQUENT THERAPY)

Taxane

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Docetaxe	75-100mg/m ²	IV	D1	every 21days	
or					
Paclitaxel	135-250mg/m ²	IV	D1	every 21days	
or					
Paclitaxel	80mg/m ²	IV	D1	weekly	
or					
Paclitaxel	80mg/m ²	IV	D1,8,15	every 28days	
Ref.	<p>1 Albertsson M, Johansson B, Friesland S, et al. Phase II studies on docetaxel alone every third week, or weekly in combination with gemcitabine in patients with primary locally advanced, metastatic, or recurrent esophageal cancer. <i>Med Oncol</i> 2007;24:407-412.</p> <p>2 Ford ER, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. <i>Lancet Oncol</i> 2014;15:78-86.</p> <p>3 Ajani JA, Ilson DH, Daugherty K, et al. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. <i>J Natl Cancer Inst</i> 1994;86:1086-1091.</p> <p>4 Ilson DH, Wadleigh RG, Leichman LP, Kelsen DP. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. <i>Ann Oncol</i> 2007;18:898-902.</p> <p>5 Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial <i>J Clin Oncol</i> 2013;31:4438-4444.</p>				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA(SECOND-LINE AND SUBSEQUENT THERAPY)

Irinotecan

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	150-180mg/m ²	IV	D1	every 14days	
or					
Irinotecan	125mg/m ²	IV	D1,8	every 21days	
or					
Irinotecan	250-350mg/m ²	IV	D1	every 21days	
Ref.	<p>1.Hironaka S, Ueda S, Yasui H, et al. Randomized,open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial J Clin Oncol 2013;31:4438-4444.</p> <p>2. Sym SJ, Hong J, Park J, et al. A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/ leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. Cancer Chemother Pharmacol 2013;71:481-488.</p> <p>3 Fuchs CS, Moore MR, Harker G, et al. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. J Clin Oncol 2003;21:807-814.</p> <p>4.Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 2011;47:2306-2314.</p>				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA(SECOND-LINE AND SUBSEQUENT THERAPY)

Fluorouracil and irinotecan

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	180 mg/m ²	IV	D1	Cycled every 14 days	
Leucovorin	400 mg/m ²	IV	D1		
Fluorouracil	400 mg/m ²	IV Push	D1		
Fluorouracil	1200 mg/m ² /days	IV	IV continuous infusion over 24 hours daily on Days 1 and 2		
Ref.	<i>Sym SJ, Hong J, Park J, et al. A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/ leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. Cancer Chemother Pharmacol 2013;71:481-488.</i>				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA(SECOND-LINE AND SUBSEQUENT THERAPY)

OTHER RECOMMENDED REGIMENS**Irinotecan and cisplatin**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	65mg/m ²	IV	D1,8	Cycled every 21 days	
cisplatin	25-30 mg/m ²	IV	D1,8		
Ref.	<p>1.Enzinger PC, Burtness BA, Niedzwiecki D, et al. CALGB 80403 (Alliance)/E1206: a randomized phase II study of three chemotherapy regimens plus cetuximab in metastatic esophageal and gastroesophageal junction cancers. <i>J Clin Oncol</i> 2016;34:2736-2742.</p> <p>2.Ilson DH. Phase II trial of weekly irinotecan/cisplatin in advanced esophageal cancer. <i>Oncology (Williston Park)</i> 2004;18:22-25.</p>				

Docetaxel and irinotecan

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	50mg/m ²	IV	D1,8	Cycled every 21 days	
Docetaxel	35 mg/m ²	IV	D1,8		
Ref.	<p>Burtness B, Gibson M, Egleston B, et al. Phase II trial of docetaxel-irinotecan combination in advanced esophageal cancer. <i>Ann Oncol</i> 2009;20:1242-1248.</p>				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

ADENOCARCINOMA (SECOND-LINE AND SUBSEQUENT THERAPY)

PREFERRED REGIMENS**Ramucirumab and paclitaxel**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Paclitaxel	80mg/m ²	IV	D1,8,15	Cycled every 28 days	
Ramucirumab	8mg/kg	IV	D1,15		
Ref.	<i>Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15:1224-1235.</i>				

Fam-trastuzumab deruxtecan-nxki

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Trastuzumab	6.4 mg/kg	IV	D1	every 21 days	(for HER2 overexpression-positive adenocarcinoma)
Ref.	<i>Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. N Engl J Med 2020;382:2419-2430</i>				

Taxane

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Docetaxe	75-100mg/m ²	IV	D1	every 21days	
or					
Paclitaxel	135-250mg/m ²	IV	D1	every 21days	
or					
Paclitaxel	80mg/m ²	IV	D1	weekly	
or					



Paclitaxel	80mg/m ²	IV	D1,8,15	every 28days	
Ref.	<p>1 Albertsson M, Johansson B, Friesland S, et al. Phase II studies on docetaxel alone every third week, or weekly in combination with gemcitabine in patients with primary locally advanced, metastatic, or recurrent esophageal cancer. <i>Med Oncol</i> 2007;24:407-412.</p> <p>2 Ford ER, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. <i>Lancet Oncol</i> 2014;15:78-86.</p> <p>3 Ajani JA, Ilson DH, Daugherty K, et al. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. <i>J Natl Cancer Inst</i> 1994;86:1086-1091.</p> <p>4 Ilson DH, Wadleigh RG, Leichman LP, Kelsen DP. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. <i>Ann Oncol</i> 2007;18:898-902.</p> <p>5 Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial <i>J Clin Oncol</i> 2013;31:4438-4444.</p>				

Irinotecan

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	150-180mg/m ²	IV	D1	every 14days	
or					
Irinotecan	125mg/m ²	IV	D1,8	every 21days	
or					
Irinotecan	250-350mg/m ²	IV	D1	every 21days	
Ref.	<p>1. Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial <i>J Clin Oncol</i> 2013;31:4438-4444.</p> <p>2. Sym SJ, Hong J, Park J, et al. A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/ leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. <i>Cancer Chemother Pharmacol</i> 2013;71:481-488.</p>				



	<p>3 Fuchs CS, Moore MR, Harker G, et al. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. <i>J Clin Oncol</i> 2003;21:807-814.</p> <p>4.Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). <i>Eur J Cancer</i> 2011;47:2306-2314.</p>
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Fluorouracil and irinotecan

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	180 mg/m ²	IV	D1	Cycled every 14 days	
Leucovorin	400 mg/m ²	IV	D1		
Fluorouracil	400 mg/m ²	IV Push	D1		
Fluorouracil	1200 mg/m ² /days	IV	IV continuous infusion over 24 hours daily on Days 1 and 2		
Ref.	Sym SJ, Hong J, Park J, et al. A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/ leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. <i>Cancer Chemother Pharmacol</i> 2013;71:481-488.				

Trifluridine and tipiracil

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Trifluridine and tipiracil	35 mg/m ² up to a maximum dose of 80 mg per dose	PO	Bid, on Days 1–5 and 8–12	Cycled every 28 days	(for third-line or subsequent therapy for EGJ adenocarcinoma)
Ref.	Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. <i>Lancet Oncol</i> 2018;19:1437-1448.				



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

ADENOCARCINOMA (SECOND-LINE AND SUBSEQUENT THERAPY)

OTHER RECOMMENDED REGIMENS**Ramucirumab**

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Ramucirumab	8mg/kg	IV	D1	Cycled every 14 days	
Ref.	<i>Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383:31-39.</i>				

Irinotecan and cisplatin

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	65mg/m ²	IV	D1,8	Cycled every 21 days	
cisplatin	25-30 mg/m ²	IV	D1,8		
Ref.	<i>1.Enzinger PC, Burtness BA, Niedzwiecki D, et al. CALGB 80403 (Alliance)/E1206: a randomized phase II study of three chemotherapy regimens plus cetuximab in metastatic esophageal and gastroesophageal junction cancers. J Clin Oncol 2016;34:2736-2742.</i> <i>2.Ilson DH. Phase II trial of weekly irinotecan/cisplatin in advanced esophageal cancer. Oncology (Williston Park) 2004;18:22-25.</i>				

Fluorouracil and irinotecan + ramucirumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Ramucirumab	8mg/kg	IV	D1	Cycled every 14 days	(only for adenocarcinoma)
Irinotecan	180mg/m ²	IV	D1		
Leucovorin	400 mg/m ²	IV	D1		
Fluorouracil	400 mg/m ²	IV Push	D1		



Fluorouracil	1200 mg/m ² /days	IV	IV continuous infusion over 24 hours daily on Days 1 and 2		
Ref.	<i>Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol 2015;16:499-508.</i>				

irinotecan + ramucirumab

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Ramucirumab	8mg/kg	IV	D1	Cycled every 14 days	(only for adenocarcinoma)
Irinotecan	180mg/m ²	IV	D1		
Ref.	<i>Sakai D, Boku N, Kodera Y, et al. An intergroup phase III trial of ramucirumab plus irinotecan in third or more line beyond progression after ramucirumab for advanced gastric cancer (RINDBeRG trial). J Clin Oncol 2018;36:TPS4138.</i>				

Docetaxel and irinotecan

Drug Combination	Dosage	Route of administration	Times	Frequency/Duration	Notes
Irinotecan	50mg/m ²	IV	D1,8	Cycled every 21 days	
Docetaxel	35 mg/m ²	IV	D1,8		
Ref.	<i>Burtness B, Gibson M, Egleston B, et al. Phase II trial of docetaxel-irinotecan combination in advanced esophageal cancer. Ann Oncol 2009;20:1242-1248.</i>				



**Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)
(SQUAMOUS CELL CARCINOMA AND ADENOCARCINOMA)**

Useful in Certain Circumstances

For NTRK gene fusion-positive tumors

Regimen	Entrectinib
藥名(學名)	Entrectinib 600 mg PO once daily
Ref.	<i>Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion- positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282.</i>

Regimen	Larotrectinib
藥名(學名)	Larotrectinib 100 mg PO twice daily
Ref.	<i>Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731-739.</i>

Regimen	Repotrectinib
藥名(學名)	Repotrectinib 160 mg PO Daily Days 1–14 of cycle 1 160 mg PO BID Days 15–28 of cycle 1 160 mg PO BID Days 1-28 of cycle 2 and beyond Cycled every 28 days
Ref.	<i>Solomon BJ, Drilon A, Lin JJ, et al. 1372P Repotrectinib in patients (pts) with NTRK fusion- positive (NTRK+) advanced solid tumors, including NSCLC: Update from the phase I/II TRIDENT-1 trial. Annals of Oncology 2023;34:S787-S788.</i>



Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

(SQUAMOUS CELL CARCINOMA AND ADENOCARCINOMA)

Useful in Certain Circumstances**For BRAF V600E-mutated tumors**

Regimen	Dabrafenib and trametinib
藥名	Dabrafenib 150 mg PO twice daily Trametinib 2 mg PO daily
Ref.	<i>Salama AKS, Li S, Macrae ER, et al. Dabrafenib and trametinib in patients with tumors with BRAF(V600E) mutations: Results of the NCI-MATCH trial subprotocol H. J Clin Oncol 2020;38:3895-3904.</i>

For RET gene fusion-positive tumors

Regimen	Selpercatinib
藥名	Selpercatinib Patients ≥ 50 kg: 160 mg PO twice daily Patients < 50 kg: 120 mg PO twice daily
Ref.	<i>Salama AKS, Li S, Macrae ER, et al. Dabrafenib and trametinib in patients with tumors with BRAF(V600E) mutations: Results of the NCI-MATCH trial subprotocol H. J Clin Oncol 2020;38:3895-3904.</i>



八、放射治療原則

Treatment Regimen

CCRT :

Definitive RT : Total dose of 45–66 Gy.

Neoadjuvant / Adjuvant RT : Total dose of 41.4–54 Gy.

Note : Radiotherapy should be delivered using intensity-modulated radiotherapy or more advanced techniques.

Chun, S. G., Skinner, H. D., & Minsky, B. D. (2017). Radiation therapy for locally advanced esophageal cancer. *Surgical Oncology Clinics*, 26(2), 257-276.

九、支持性治療(Supportive treatment)原則

- 避免因可控制的急性毒性而中斷治療或減少劑量。積極的監測及支持治療比中斷治療更好。
- 在放射治療過程中，至少每週檢查一次患者的狀態，記錄生命徵象、體重和全血球計數。
- 應在適當的時機以預防為基礎給予止吐藥。評估患者狀況後對症下藥，例如：開立制酸劑或止瀉藥。
- 熱量攝入<1500 kcal/天，應考慮腸內或靜脈輸液營養。視患者狀況，放置空腸造瘻或鼻胃管讓足夠的熱量攝入。
- 在整個放化療和恢復過程中，充分的腸內或靜脈輸液是必要的。



十、安寧緩和照護原則

若預期疾病難以治癒時，病人存活期小於6個月便適合安寧療護（Pomeranz & Brustman, 2005；Waldrop & Rinfrette, 2009）。若藉由症狀、檢驗數據、及確切的腫瘤診斷，證實臨床上該惡性腫瘤已經廣泛侵犯、或進展快速；功能分數（Palliative Performance Scale）低於70%；拒絕進一步腫瘤治癒性治療，或在治療之下仍持續惡化者，即可轉介緩和醫療團隊（彭等，2006）。



十一、參考文獻

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10. Shitara K, Lordick F, Bang YJ, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2- positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double- blind, phase 3 trial. *Lancet* 2023;401:1655-1668.
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84. 衛生福利部 (2025, 6 月 16 日) · 113 年國人死因統計結果。
<https://www.mohw.gov.tw/fp-16-82775-1.html>



十二、食道癌完治定義

癌別	期別	治療方式	完治定義
食道癌	治療期	0 期 1 期	OP EMR/ESD or OP : Margin free
		2 期	OP or Neo-adjuvant CCRT+OP or Definitive CCRT 1.術後 Margin free 2.Margin (+) → Adjuvant CCRT 結束日 3.Definitive CCRT 結束日
		3 期	Neo-adjuvant CCRT+OP or Definitive CCRT 1.術後 Margin free 2.Margin (+) → Adjuvant CCRT 結束日 3.Definitive CCRT 結束日
		4 期	Systemic therapy 1.Definitive CCRT 結束日 2.Palliative C/T 達三個月(含口服化療 Ufur) 3.Palliative C/T 未達三個月，評估病患治療反應不佳，改二線藥持續治療，第一次治療就可算完治 4.治療中轉安寧