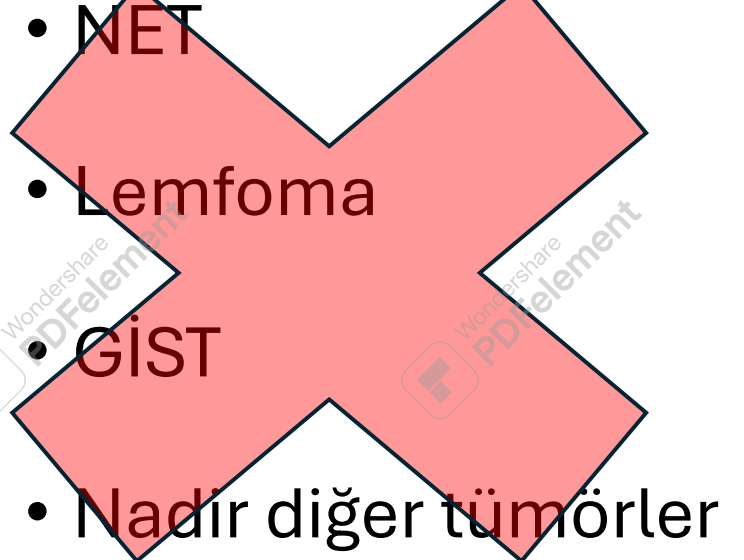


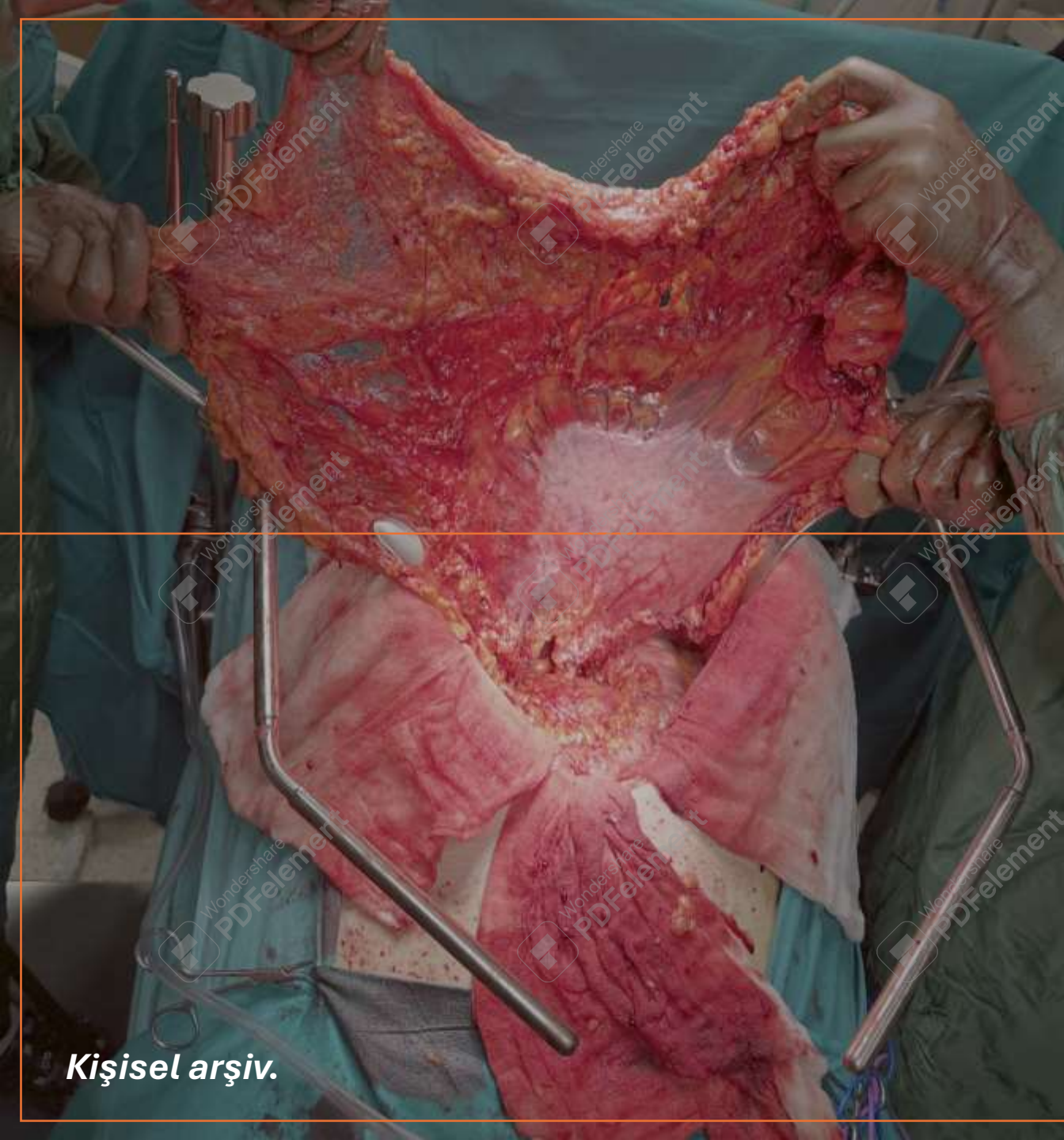
Mide Kanserlerinde Uluslararası Kılavuzlar Eşliğinde Güncel Tedavi

Dr. Abdullah Kut

Sunum planı

- Genel bilgiler
- Sınıflama/evreleme
- Japonya, Avrupa, Amerika klavuzları
- Özet/sonuç
- +/- Neoadjuvan tedavi
- Kaynaklar

- 
- NET
 - Lemfoma
 - GİST
 - Nadir diğer tümörler



Mide Kanseri

Kişisel arşiv.

Sıklık

Risk faktörleri

Tarama programı

Tanı

Neoadjuvan tedavi

Cerrahi

Sağ kalım

5.en sık kanser

Kanserler içinde 3. en sık ölüm nedeni

Gençlerde (<45 yaş) ve gelecekte



%70 gelişmekte olan ülkelerde

%50 si doğu Asya' da

E/K: 2/1

Genetik Mide Kanseri?

%10 Ailesel aggregasyon

%1-3 Germline mutasyon

Hereditör mide kanserleri

- OD
- 1- HDGC, <%1, %30-40 CDH1 Testi ile tarama, **%70 belirsiz**
- 2- Familiyal intestinal gastrik kanser
- 3- Gastrik adenokarsinom, proksimal mide polipozisiyle birlikte

Risk faktörleri

H.pylori infeksiyonu

- Nonkardiya tümörleri için en iyi tanımlanmış

Yüksek tuz kullanımı

İleri yaş

Meyve ve sebzeden az beslenme

Düşük sosyoekonomik durum

- Sigara
- Alkol
- Aile öyküsü
- Pernisyöz anemi
- Yüksek riskli toplumda yaşamak

**Yüksek tuz +
H.Pylori**

**Genetik+Çevresel
etkenler**

- Mide mukozasında kronik infeksiyon
- Atrofik gastrit
- İntestinal metaplazi

H.Pylori eradikasyonu ?

- Pangastrit
- Korpus predominant gastrit
- 1. derece akrabasında mide kanseri öyküsü
- Gastrik neoplazi öyküsü

Tedavi

- Erken evre → Endoskopik rezeksiyon
- Erken evre olmayan operabl → Cerrahi rezeksiyon + D2 diseksiyon
- ≥Evre 1b → Perioperativ yada adjuvan KT sağkalımı artırır
- İleri evre → Platin ve floropirimidin birlikte ilk seçenek **KT (ortalama survi < 1 yıl)**
- **Hedefe yönelik tedavi**
 - *HER2+ ise Transtuzumab ilk seçilecek tedavi (%20 olguda+)*
 - *Ramucirumab, anti anjiyojenik ikinci basamak*
 - *Nivolumab veya pembrolizumab, anti-PD-1 3.basamak*

- H.Pylori eradikasyonu

- Endoskopi

Sıklığı ve mortalite



Erken evre mide kanserinde

Histolojik sınıflama – Makroskopik

Paris sınıflaması

Protrude → Tip1

Süperfisyel → Tip2

- 1-Eleve
- 2-Flat
- 3-Deprese

Ekskave → Tip3

İlerlemiş erken evre mide kanserinde

Histolojik sınıflama - Makroskopik

- Borrmann sınıflaması
- Prognostik önemi var –Tip 4 en kötüsü
 - Tip1 → Geniş zemin ve ülserasyon olmadan polipoid tip
 - Tip2 → Eleve ve keskin sınırlı ülserasyon alanı
 - Tip3 → Zemini diffüz infiltrasyon gösteren ülsere tip
 - Tip4 → Duvarı kalınlaşmaya neden olan diffüz infiltrasyon

Diğer sınıflamalar?

- **Nakamura sınıflaması**

- Erken evre mide kanserinde endoskopik rezeksiyon kriterleri

- **Lauren**

- İntestinal tip
- Diffüz tip
- İndetermine
- Sınıflanamayan

- **WHO**

- Adenokarsinom alt tipleri
- Tubuler, pariyeteal hücre, papiler, mikropapiller, mukoepidermoid, müsinöz, poorly cohesive, taşlı yüzük hücreli, medüller karsinom- lenfoid stroma, hepatoid ve Paneth hücreli)

Genomik sınıflama sistemi

- Rutin klinik kullanımı henüz yok
- The Cancer Genome Atlas
 1. EBV+
 2. MSI (Mikrosatellit instabil)
 3. Genomik olarak stabil
 4. CIN(Kromozomal instabil)
- Mismatch repair gen eksikliği ve HER2 rutinde bakılması önerilir.
 - Transtuzumab ve diğer ilaç seçimi için

8th Edition of the AJCC Gastric Cancer Staging System

T category definitions, gastric cancer

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria

T1 Tumor invades lamina propria, muscularis mucosae, or submucosa

T1a Tumor invades lamina propria or muscularis mucosae

T1b Tumor invades submucosa

T2 Tumor invades muscularis propria

T3 Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures. T3 tumors also include those extending into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures

T4 Tumor invades serosa (visceral peritoneum) or adjacent structures

T4a Tumor invades serosa (visceral peritoneum)

Tumor invades adjacent structures such as spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum

T4b Tumor invades adjacent structures such as spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum

N category definitions, gastric cancer

NX Regional lymph node(s) cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in 1 to 2 regional lymph nodes

N2 Metastasis in 3 to 6 regional lymph nodes

N3 Metastasis in 7 or more regional lymph nodes

M category definitions, gastric cancer

M0 No distant metastasis

M1 Distant metastasis

Anatomic stage/prognostic groups, gastric cancer

Stage I	T1, T2,	N0	M0
---------	---------	----	----

Stage IIA	T1, T2	N1, N2, N3	M0
-----------	--------	------------	----

Stage IIB	T3, T4a	N0	M0
-----------	---------	----	----

Stage III	T3, T4a	N1, N2, N3	M0
-----------	---------	------------	----

Stage IV	T4b	Any N	M0
----------	-----	-------	----

Stage IV	Any T	Any N	Any M1
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NCCN Guidelines Version 3.2025 Gastric Cancer

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American Joint Committee on Cancer (AJCC) TNM Staging Classification for Carcinoma of the Stomach (8th ed., 2017)

Table 1. Definitions for T, N, M

T	Primary Tumor	N	Regional Lymph Nodes
TX	Primary tumor cannot be assessed	NX	Regional lymph node(s) cannot be assessed
T0	No evidence of primary tumor	N0	No regional lymph node metastasis
Tis	Carcinoma <i>in situ</i> : intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia	N1	Metastasis in one or two regional lymph nodes
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa	N2	Metastasis in three to six regional lymph nodes
T1a	Tumor invades the lamina propria or muscularis mucosae	N3	Metastasis in seven or more regional lymph nodes
T1b	Tumor invades the submucosa	N3a	Metastasis in seven to 15 regional lymph nodes
T2	Tumor invades the muscularis propria*	N3b	Metastasis in 16 or more regional lymph nodes
T3	Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures**,**	M	Distant Metastasis
T4	Tumor invades the serosa (visceral peritoneum) or adjacent structures**,**	M0	No distant metastasis
T4a	Tumor invades the serosa (visceral peritoneum)	M1	Distant metastasis
T4b	Tumor invades adjacent structures/organs		

*A tumor may penetrate the muscularis propria with extension into the gastroduodenal or gastrophrenic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified as T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified as T4.

**The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

***Intramural extension to the duodenum or esophagus is not considered invasion of an adjacent structure, but is classified using the depth of the greatest invasion in any of these sites.

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

[Continued](#)

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NCCN Guidelines Version 3.2025

Gastric Cancer

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Carcinoma of the Stomach (8th ed., 2017)

Table 2. AJCC Prognostic Stage Groups
Clinical Staging (cTNM)

	cT	cN	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage IIA	T1	N1, N2, N3	M0
	T2	N1, N2, N3	M0
Stage IIB	T3	N0	M0
	T4a	N0	M0
Stage III	T3	N1, N2, N3	M0
	T4a	N1, N2, N3	M0
Stage IVA	T4b	Any N	M0
Stage IVB	Any T	Any N	M1

Pathological Staging (pTNM)

	pT	pN	M
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2	N0	M0
Stage IIA	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIB	T1	N3a	M0
	T2	N2	M0
	T3	N1	M0
	T4a	N0	M0
Stage IIIA	T2	N3a	M0
	T3	N2	M0
	T4a	N1 or N2	M0
	T4b	N0	M0
Stage IIIB	T1	N3b	M0
	T2	N3b	M0
	T3	N3a	M0
	T4a	N3a	M0
	T4b	N1 or N2	M0
Stage IIIC	T3	N3b	M0
	T4a	N3b	M0
	T4b	N3a or N3b	M0
Stage IV	Any T	Any N	M1

Post-Neoadjuvant Therapy (ypTNM)

	ypT	ypN	M
Stage I	T1	N0	M0
	T2	N0	M0
	T1	N1	M0
Stage II	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage III	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

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JGCA 2021 6. Baskı
ESMO 2024
NCCN 2025

JGCA 2021 Kılavuzu - Genel Bakış & Yenilikler

- 32 adet Klinik Soru ile kanıta dayalı tıp
- **Başlıca Yenilikler:**
 - Özofagogastrik bileşke kanseri için cerrahi yaklaşım ve lenf nodu diseksiyonu algoritması (JGCA-Japan Esophageal Society ortak çalışması).
 - Laparoskopik ve robotik cerrahide güncel kanıtların entegrasyonu
 - İleri evre/rekürren mide kanserinde immün kontrol noktası inhibitörlerinin (nivolumab, pembrolizumab) tedavi algoritmasına eklenmesi.
 - Kemoterapi rejimleri "Önerilen Rejimler" ve "Koşullu Önerilen Rejimler" olarak sınıflandırıldı.

Evreleme ve Tedavi Algoritması (Genel Prensip)

Evreleme: Japanese Classification of Gastric Carcinoma 15. Baskı / UICC TNM 8. Baskı.

Tedavi Seçimi Temel Algoritması:

Erken Evre (T1a, bazı T1b, N0): Endoskopik rezeksiyon (EMR/ESD) öncelikli.

Küratif Cerrahi Adayı Lokalize Hastalık (T1b-T4a, N+/-, M0): Cerrahi rezeksiyon + uygun lenf nodu diseksiyonu (D1/D2) ± adjuvan kemoterapi.

İleri/ Metastatik Hastalık (M1): Sistemik kemoterapi ± hedefe yönelik tedaviler ± palyatif cerrahi.

Cerrahi Tedavi - Rezeksiyon Sınırı & Gastrektomi Türleri

Rezeksiyon Sınırı:

- T2+ tümörler: Diffüz patern için ≥ 3 cm, infiltratif patern için ≥ 5 cm.
- T1 tümörler: Makroskopik olarak ≥ 2 cm.

Gastrektomi Türleri:

- **Distal Gastrektomi:** Distal yerleşimli tümörler.
- **Total Gastrektomi:** Proksimal yerleşim, yetersiz proksimal sınır, pankreas invazyonu.
- **Pilor Koruyucu Gastrektomi (PPG):** Orta 1/3'teki erken evre tümörler (CQ4).
- **Proksimal Gastrektomi:** Proksimal erken evre tümörler (CQ5, CQ14).

Cerrahi sonrası rekonstrüksiyon?

1. Total gastrectomy

- Roux-en-Y esophagojejunostomy.
- Jejunal interposition.
- Double-tract method.

2. Distal gastrectomy

- Billroth I gastroduodenostomy.
- Billroth II gastrojejunostomy.
- Roux-en-Y gastrojejunostomy.
- Jejunal interposition.

3. Pylorus-preserving gastrectomy

- Gastro-gastrostomy.

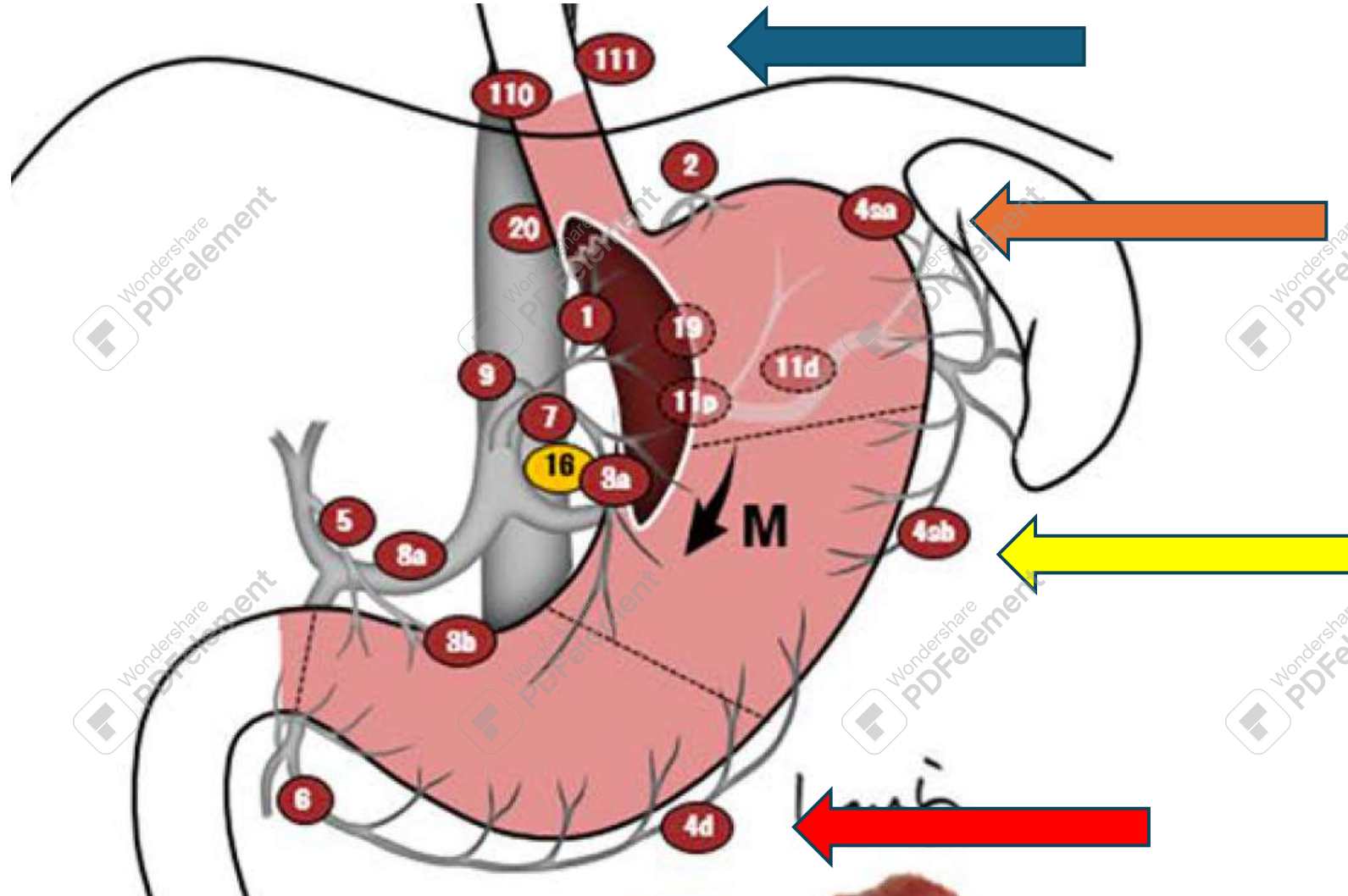
4. Proximal gastrectomy

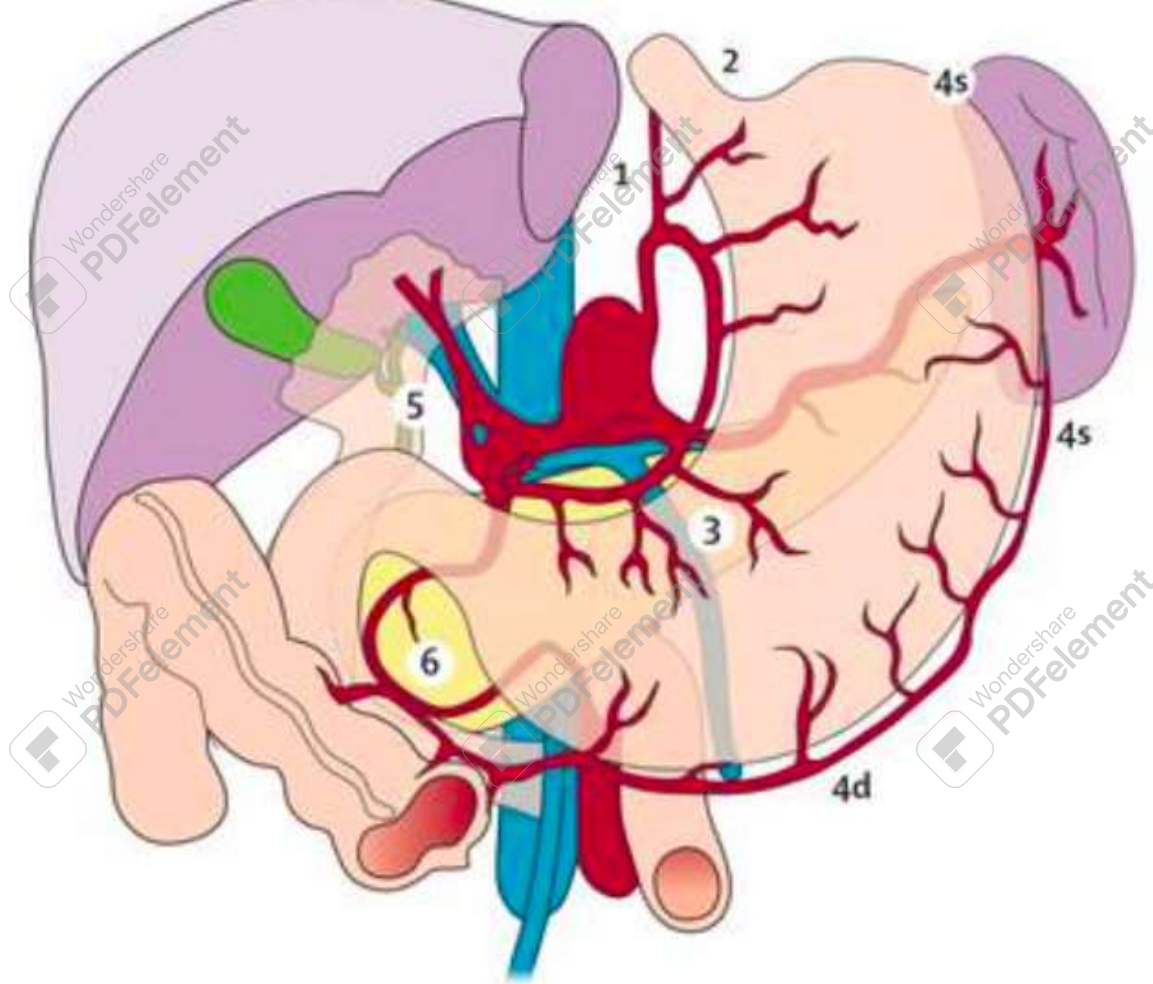
- Esophagogastrostomy.
- Jejunal interposition.
- Double-tract method.

Cerrahi Tedavi - Lenf Nodu Diseksiyonu (D Seviyeleri)

- **Standart:** D2 lenf nodu diseksiyonu (küratif cerrahide altın standart).
- **D Seviyeleri:** Gastrektomi tipine göre tanımlanır (Total, Distal, Proksimal, PPG).
- **Özofagus invazyonu:** Özofagus invazyonu varlığında mediastinal lenf nodları (No. 19, 20, 110) D2'ye eklenir.
- **Omentektomi:** T3+ tümörlerde standart, T1/T2'de omentumun bir kısmı korunabilir (CQ6).
- **Bursektomi:** Serozayı penetre posterior duvar tümörlerinde sağkalım faydası kanıtlanmamıştır (JCOG1001).

Abdominal lenf nodu diseksiyonu



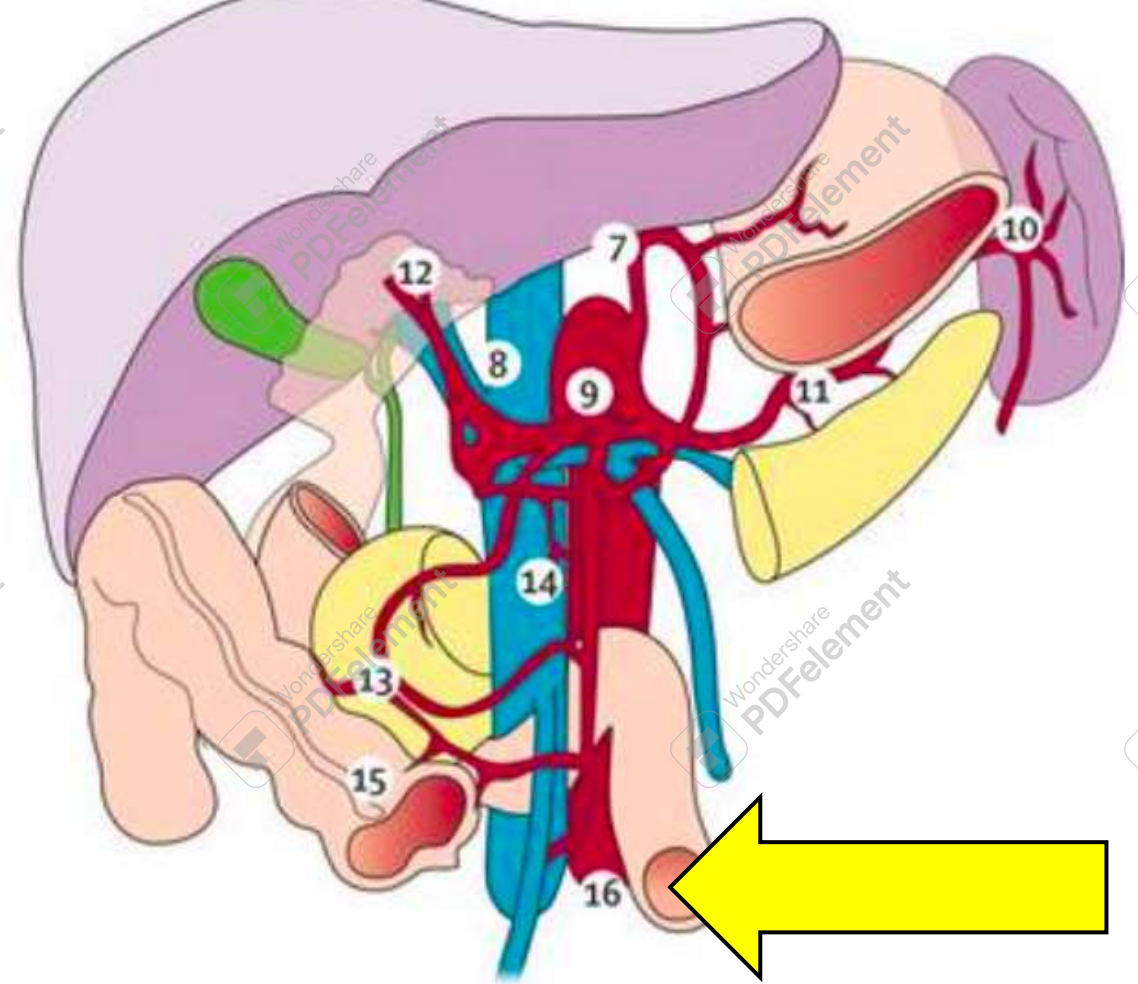


N1 Lymph nodes (perigastric)

- 1 Right cardiac nodes
- 2 Left cardiac nodes
- 3 Nodes along the lesser curvature
- 4d Lymph nodes along the short gastric and the left gastroepiploic vessels
- 4s Lymph nodes along the right gastroepiploic vessels
- 5 Suprapyloric nodes
- 6 Infrapyloric nodes

N2 Lymph nodes (branches coeliac axis)

- 7 Nodes along root left gastric artery
- 8 Nodes along common hepatic artery
- 9 Nodes around coeliac axis
- 10 Nodes at splenic hilum
- 11 Nodes along splenic artery



N3 Lymph nodes

- 12 Nodes at the hepatoduodenal ligament
- 13 Retropancreatic (periduodenal) nodes
- 14 Nodes at the root of the mesentery

N4 Lymph nodes

- 15 Nodes along the middle colic vein
- 16 Para-aortic nodes

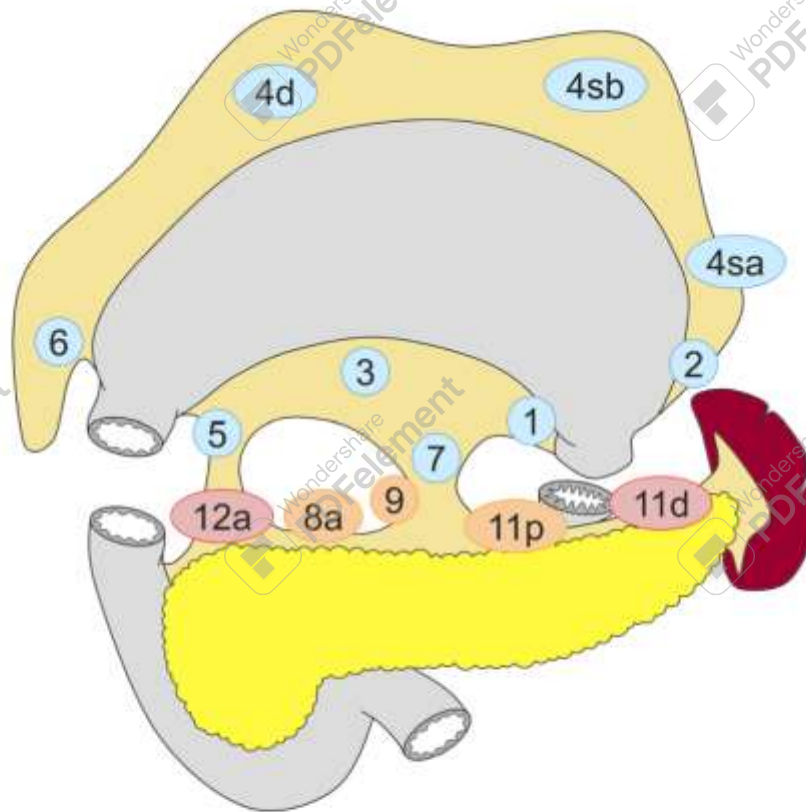


Fig. 2 Lymph node dissection in total gastrectomy. Lymph node stations in blue need to be dissected in D1 dissection. In addition, lymph node stations in orange need to be dissected in D1 +dissection and lymph node stations in red as well in D2 dissection

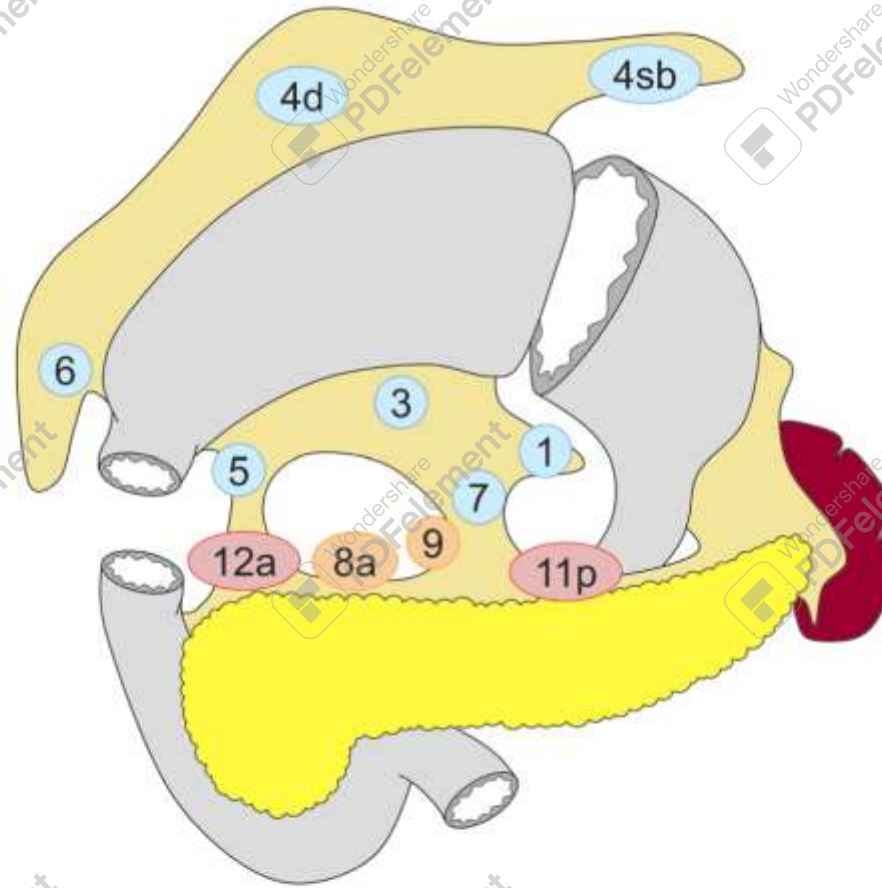


Fig. 3 Lymph node dissection in distal gastrectomy. Lymph node stations in blue need to be dissected in D1 dissection. In addition, lymph node stations in orange need to be dissected in D1+dissection and lymph node stations in red as well in D2 dissection

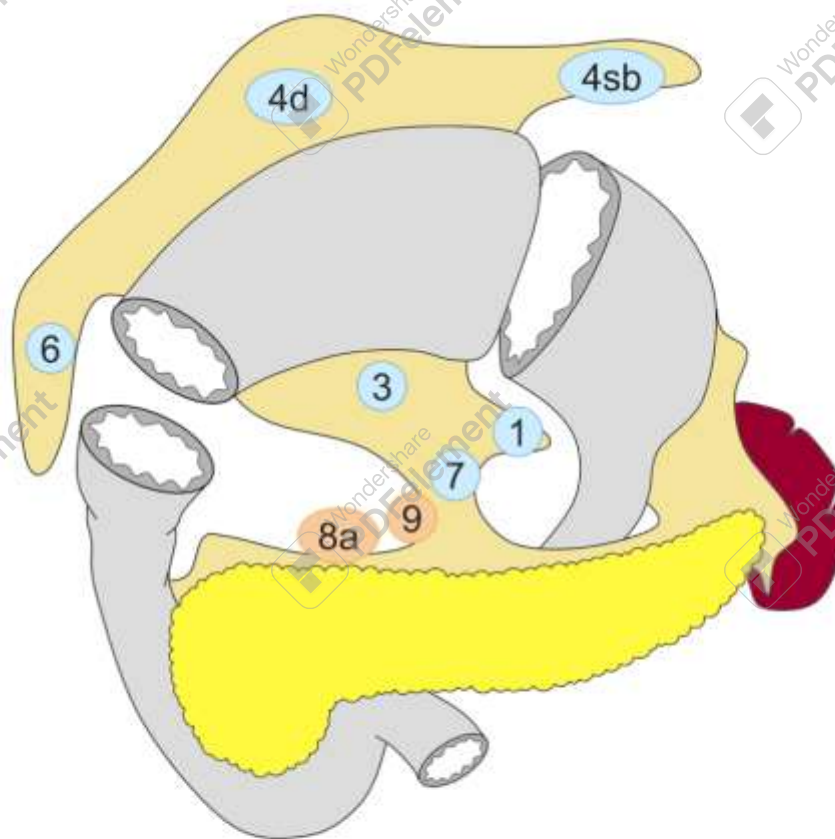


Fig.4 Lymph node dissection in pylorus-preserving gastrectomy. Lymph node stations in blue need to be dissected in D1 dissection. In addition, lymph node stations in orange need to be dissected in D1+ dissection

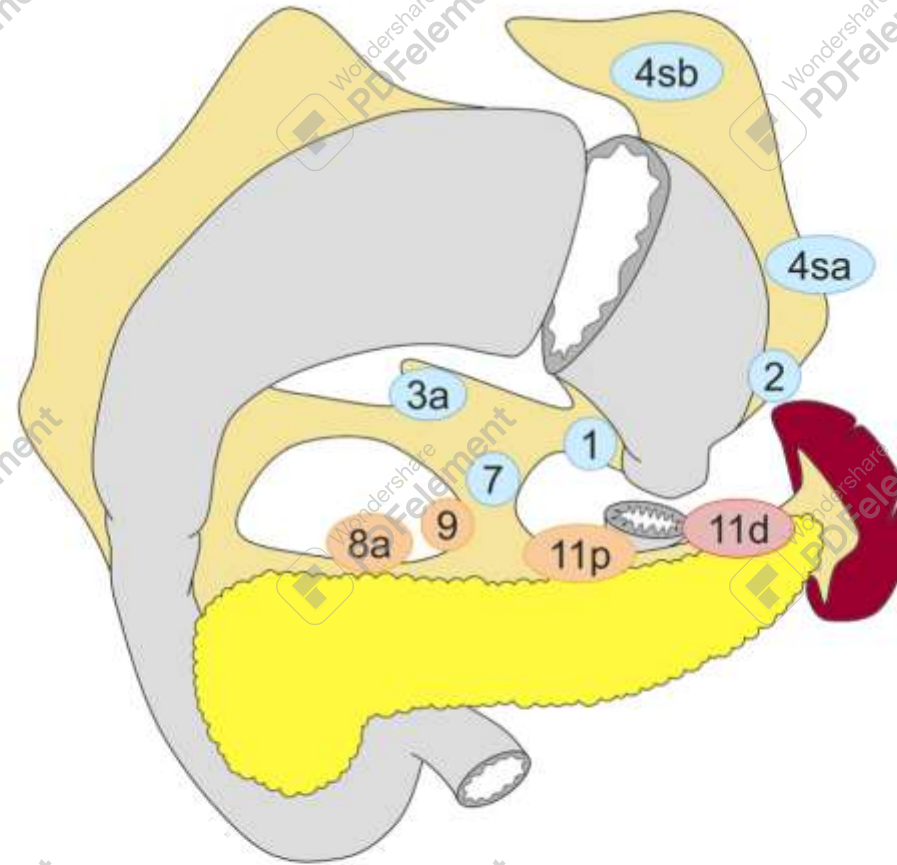
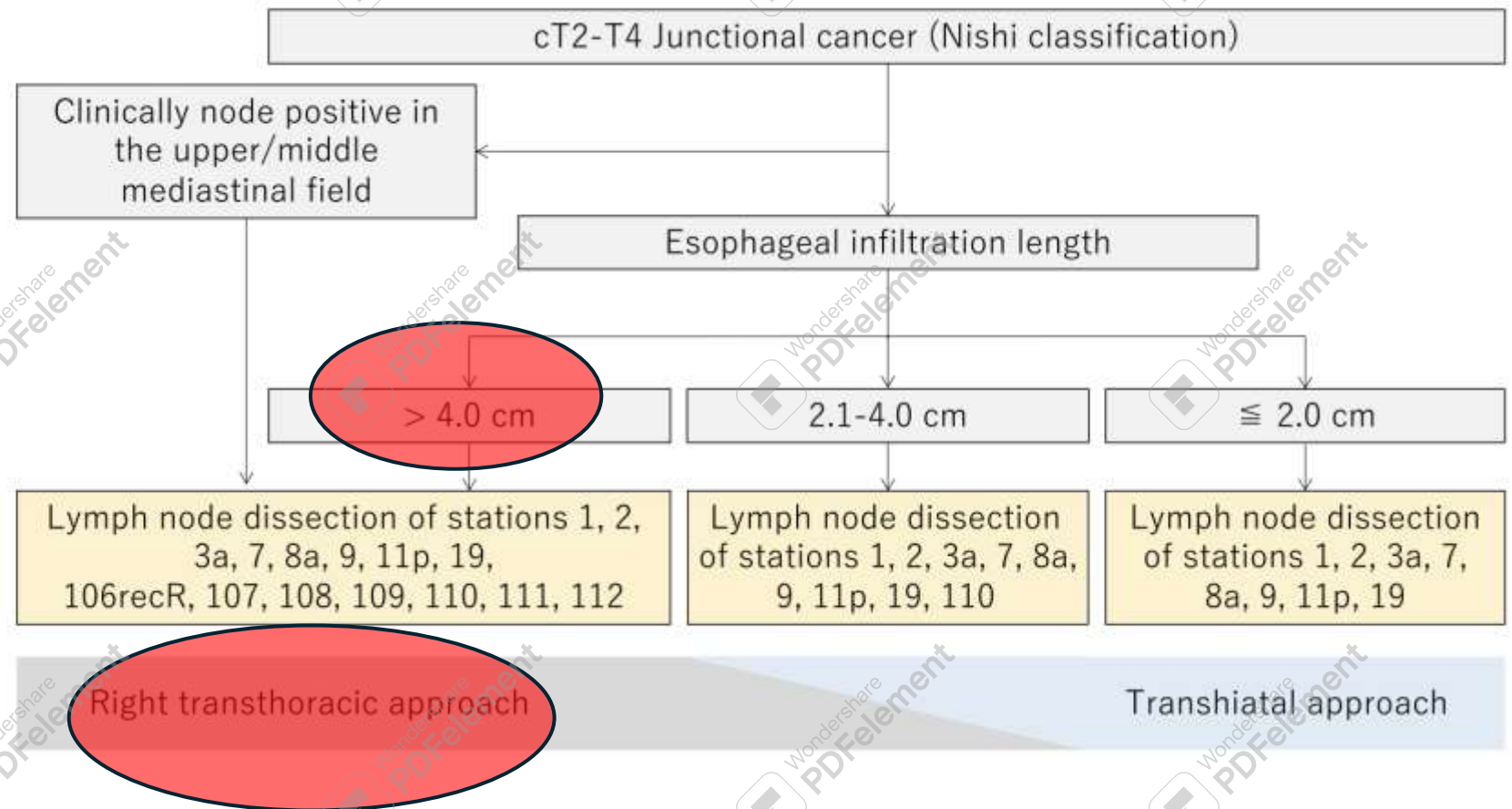


Fig. 5 Lymph node dissection in proximal gastrectomy. Lymph node stations in blue need to be dissected in D1 dissection. In addition, lymph node stations in orange need to be dissected in D1+dissection and lymph node stations in red as well in D2 dissection

Özofagogastrik Bileşke (OGB) Kanseri - Cerrahi Yaklaşım

- **Özofagus İnvazyon Uzunluğuna Göre Algoritma (CQ12):**
 - **≤ 2.0 cm:** Abdominal transhiatal yaklaşım. Alt mediastinal lenf nodu diseksiyonu (No. 19, 110).
 - **2-4 cm:** Abdominal transhiatal yaklaşım. Alt mediastinal lenf nodu diseksiyonu (No. 19, 110).
 - **> 4.0 cm:** Sağ transtorasik yaklaşım. Üst/Orta/Alt mediastinal lenf nodu diseksiyonu.
- **Cerrahi Yöntem:** Proksimal gastrektomi veya total gastrektomi ± alt özofagus rezeksiyonu (CQ14).

Fig. 6 Algorithm of the surgical approach and lymph node dissection for esophagogastric junctional carcinoma



Minimal İnvaziv Cerrahi - Laparoskopik & Robotik

- **Laparoskopik Distal Gastrektomi:**

- **Evre I:** Açık cerrahiye eşdeğer, **kuvvetle önerilir** (JCOG0912, KLASS-01).
- **Evre II/III:** Güvenlik verileri mevcut, ancak uzun dönem sağkalım sonuçları netleşmek üzere (KLASS-02, CLASS-01). Net öneri yok (CQ2).

- **Laparoskopik Total/Proksimal Gastrektomi:**

- Evre I için **zayıf öneri** (CQ1).

- **Robotik Cerrahi:**

- Evre I için **zayıf öneri**. Komplikasyonları azaltma potansiyeli var, ancak üstünlük kanıtı için randomize çalışmalar (JCOG1907) devam ediyor (CQ3)

Endoskopik Rezeksiyon (EMR/ESD) - Endikasyonlar

- **Amaç:** Lenf nodu metastaz riski <%1 olan erken evre tümörlerde kür sağlamak.
- **Absolute Endikasyon (ESD):**
 - Diff. tip, UL(ülserasyon)0, T1a, çap >2 cm.
 - Diff. tip, UL1, T1a, çap ≤3 cm.
 - Undiff. tip, UL0, T1a, çap ≤2 cm.
- **Genişletilmiş Endikasyon:** Belirli T1b-SM1 (<500µm) lezyonlar.
- **Küratif Değerlendirme (eCura Sistemi):**
 - **eCura A/B:** Takip.
 - **eCura C-1:** Tekrar ESD, cerrahi veya yakın takip.
 - **eCura C-2:** Cerrahi (lenf nodu diseksiyonu ile gastrektomi) **kuvvetle önerilir.**

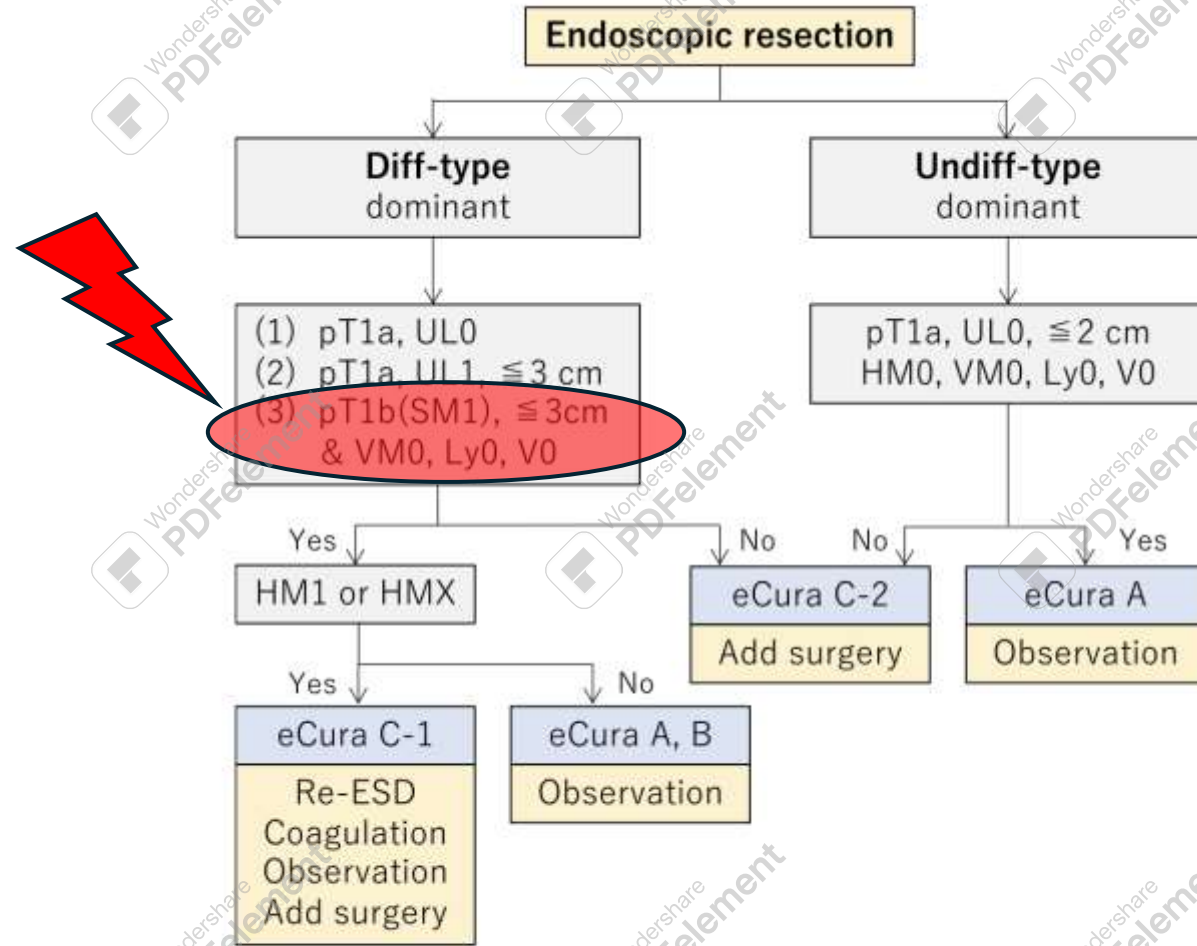


Fig.7 Algorithm showing curability decision and additional treatments for patients who have undergone endoscopic resection

Table 2 Incidence of nodal metastasis in various categories of early gastric cancer observed from surgically resected specimens operated at National Cancer Center Hospital and Cancer Institute Hospital [34]

Depth	Ulceration	Differentiated type		Undifferentiated type	
M	UL0	Tumor diameter	≤ 2cm	≤ 2cm	> 2cm
		Incidence of nodal metastasis	0% (0/437)	0% (0/310)	2.8% (6/214)
		95% confidence interval	0~0.7%	0~0.96%	1.0~6.0%
	UL1	Tumor diameter	≤ 3cm	≤ 2cm	> 2cm
		Incidence of nodal metastasis	0% (0/488)	2.9% (8/271)	5.9% (44/743)
		95% confidence interval	0~0.6%	1.2~5.7%	4.3~7.9%
SM1		Tumor diameter	≤ 3cm	> 3cm	Any diameter
		Incidence of nodal metastasis	0% (0/145)	2.6% (2/78)	10.6% (9/85)
		95% confidence interval	0~2.6%	0.3~9.0%	5.0~19.2%

Green zone indicates absolute indication for endoscopic resection, yellow zone indicates expanded indication and red zone indicates relative indication

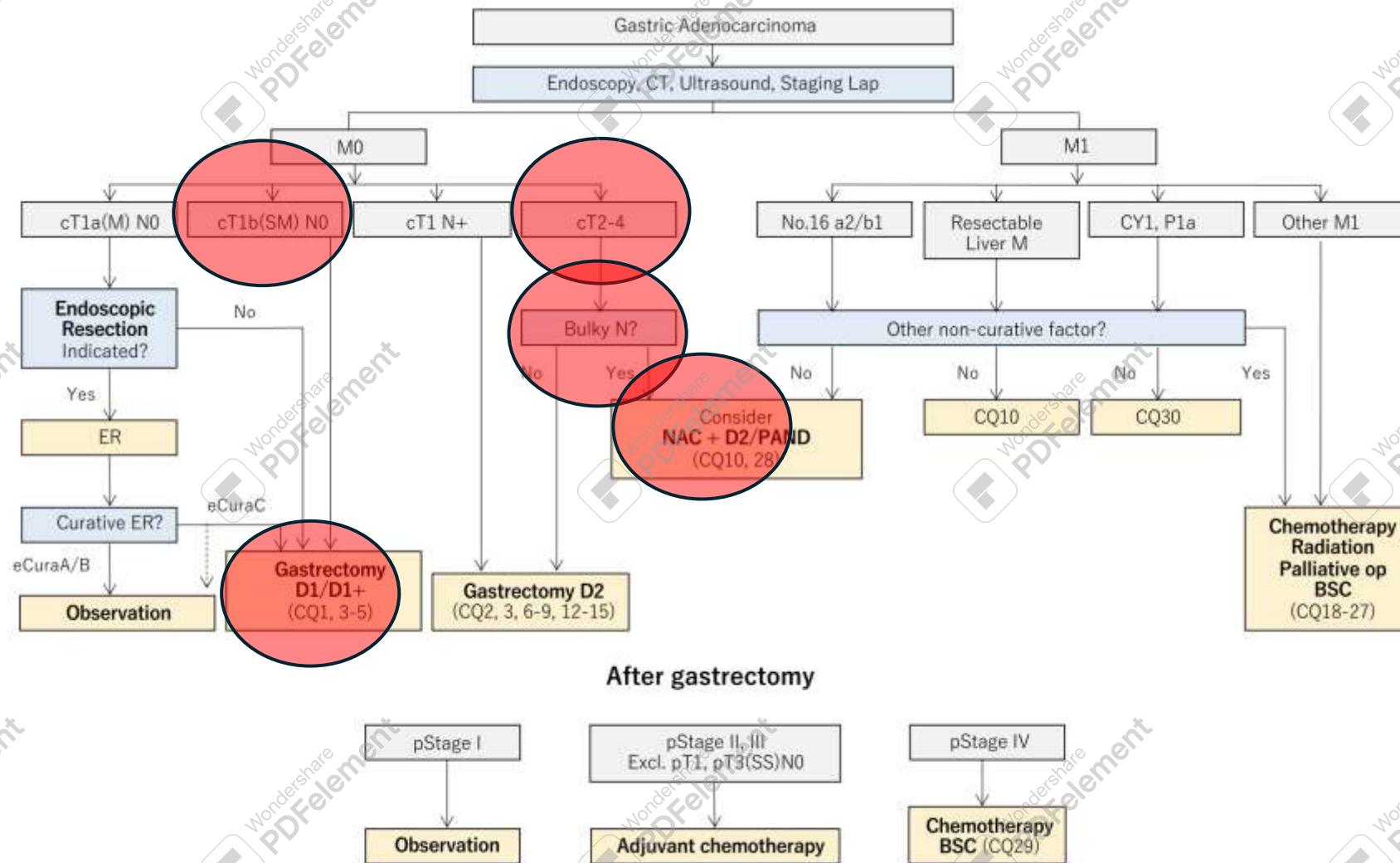


Fig. 1 Algorithm of standard treatments. T/N/M and Stage are used in conjunction with the Japanese Classification of Gastric Carcinoma 15th edition [1] and TNM classification 8th edition [2]

İleri Evre/Metastatik Mide Kanseri (AGC) - 1. Basamak Tedavi

- **HER2-Negatif:**

- **Önerilen:** Fluoropirimidin (S-1/Cape/5-FU) + Platin (Cisplatin/Oxaliplatin) ± **Nivolumab**.
- *Not: Nivolumab eklenmesi, özellikle PD-L1 CPS ≥ 5 olan hastalarda sağkalım avantajı gösterdi (CheckMate 649). CPS < 5 için risk/yarar dengesi hasta bazında değerlendirilmeli.*
- MSI-High: Pembrolizumab (2. basamak ve sonrası).

- **HER2-Pozitif (IHC 3+ veya FISH+):**

- **Önerilen:** Trastuzumab + Fluoropirimidin + Platin (XP/SP/CapeOX/SOX + Trastuzumab).

İleri Evre/Metastatik Mide Kanseri (AGC) - 2. ve 3. Basamak Tedavi

2. Basamak:

Önerilen: Ramucirumab + Paklitaksel (RAINBOW çalışması).

Koşullu Önerilen: İrinotekan, Doksetaksel, Ramucirumab (mono), Nab-paklitaksel ± Ramucirumab.

MSI-High: Pembrolizumab.

3. Basamak ve Sonrası:

Önerilen: Nivolumab, İrinotekan, Trifluridin/Tipirasil (FTD/TPI).

HER2-Pozitif: Trastuzumab Deruxtecan (T-DXd) (DESTINY-Gastric01).

Adjuvan ve Neoadjuvan Kemoterapi

- **Adjuvan Kemoterapi (R0 Rezeksiyon Sonrası):**
 - **Evre II:** S-1 (1 yıl) önerilir.
 - **Evre III:** S-1 + Docetaxel veya CapeOx kombinasyonları önerilir (JACCRO GC-07, CLASSIC). SOX de ARTIST2 çalışması ile etkin bulunmuştur.
- **Neoadjuvan Kemoterapi:**
 - "Bulky N" veya lokal ileri hastalıkta (özellikle Batı ve Asya çalışmalarında) etkinlik gösterilmiştir.
 - Ancak, Japonya'da rutin uygulama için **net bir öneri yoktur** (CQ28). Preoperatif evreleme hatası riski ve cerrahi morbidite artışı endişeleri vardır.

Palyatif Bakım ve Destek Tedavileri

- Palyatif bakım, yaşam kalitesini artırmak için tanı anından itibaren entegre edilmelidir.
- **Özel Uygulamalar (JGCA):**
 - **CQ26:** Gastrik çıkış obstrüksiyonunda gastrointestinal stent veya gastrojejunostomy.
 - **CQ27:** Asit için hücresiz konsantre asit reinfüzyon tedavisi (CART) – net öneri yok, hasta/fonksiyon bazında değerlendirme.
- ERAS (Enhanced Recovery After Surgery) protokolleri **kuvvetle önerilir** (CQ16).

CLINICAL PRACTICE GUIDELINES

An ESMO Product

Gastric Cancer

ESMO Living Guideline, v1.4 September 2024

Initially prepared by F Lordick, L Candia Montero, L Castelo-Branco, G Pentheroudakis, C Sessa and E Smyth, on behalf of the Clinical Practice Guideline author group.
v1.4 was prepared by F Lordick and E Smyth.

For details of author affiliations, correspondence and versions, please see the full version at <https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-gastrointestinal-cancers/clinical-practice-guideline-gastric-cancer>



CLINICAL PRACTICE GUIDELINES

ESMO Gastric Cancer Living Guideline
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Staging

Diagnostic and Staging
Investigations
in Gastric Cancer

Procedure	Purpose
FBC	Assess for iron deficiency anaemia
Renal and liver function	Assess renal and liver function to determine appropriate therapeutic options
Endoscopy and biopsy	Obtain tissue for diagnosis, histological classification and molecular biomarkers, e.g. HER2 status
CT of thorax + abdomen ± pelvis	Staging of tumour – to detect local/distant lymphadenopathy and metastatic disease or ascites
EUS	Accurate assessment of T and N stage in potentially operable tumours Determine the proximal and distal extent of tumour
Laparoscopy + washings	Exclude occult metastatic disease involving peritoneum/diaphragm
PET, if available	May improve detection of occult metastatic disease in some cases. Often negative in diffuse-type gastric cancer
Assessment of nutritional status	May detect relevant dietary and nutritional deficiencies in both localised and advanced disease settings

CLINICAL PRACTICE GUIDELINES

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Localised Gastric Cancer

*Endoscopic resection indicated if: (i) confined to mucosa; (ii) well-differentiated G1-2; (iii) ≤ 2 cm; (iv) non-ulcerated. Endoscopic resection is to be considered if no more than two expanded criteria are met

*Lymph node dissection for T1 tumours may be confined to perigastric lymph nodes and include local N2 nodes (D1+ lymphadenectomy, with variation in nodal groups dissected according to site of cancer)

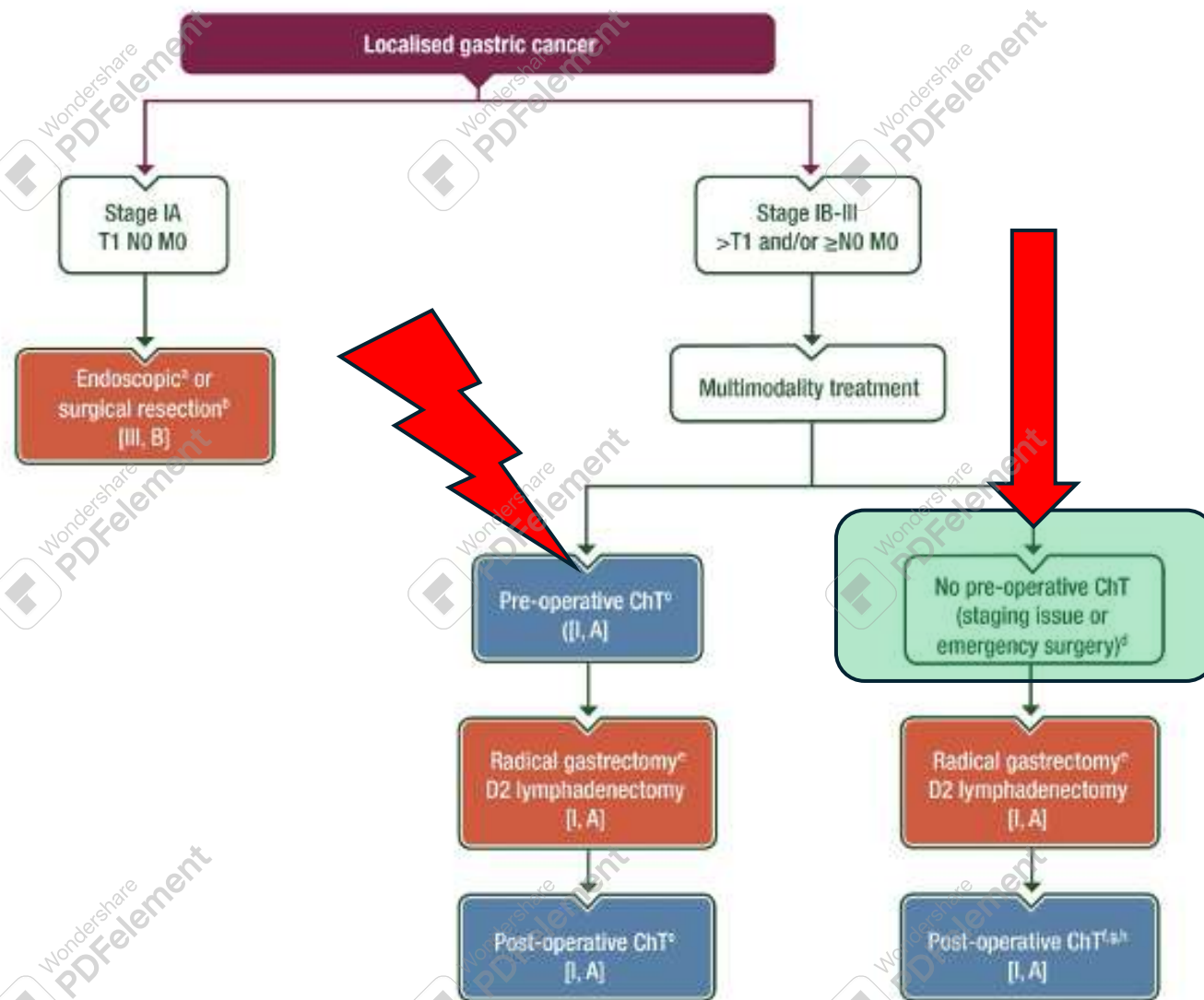
*A triple ChT regimen including a fluoropyrimidine, a platinum compound and docetaxel should be given when possible. Recommended treatment duration is 2-3 months pre- and post-operatively
*For patients with stage $\geq$ IB gastric cancer who have undergone surgery without administration of preoperative ChT. However, a peri-operative approach is preferred as adjuvant ChT is less well tolerated than neoadjuvant ChT and neoadjuvant therapy leads to tumour downsizing, allowing for more curative resections

*Subtotal gastrectomy may be carried out if a macroscopic proximal margin of ≥ 3 cm can be achieved. For cancers of the poorly cohesive/diffuse subtype, a margin of ≥ 5 cm is advocated

*A doublet ChT for a total duration of 6 months containing a fluoropyrimidine plus oxaliplatin or docetaxel is recommended

*For patients with an R1 resection, adjuvant RT or ChT might be considered as an individual recommendation but is not standard

*For patients with MSI-H gastric cancers who have undergone surgery, adjuvant ChT cannot be recommended



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Localised Gastric Cancer

Summary of recommendations	LoE, GoR
Multidisciplinary treatment planning before any treatment decision is mandatory	IV, B
Endoscopic or surgical resection alone is appropriate for selected very early tumours (stage IA)	III, B
For stage IB-III gastric cancer, peri-operative therapy and radical gastrectomy is recommended	I, A
Patients should undergo D2 resection in a high-volume surgical centre	II, B



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Peri-operative ChT

Summary of recommendations	LoE, GoR
Peri-operative (pre- and post-operative) ChT is recommended for patients with stage >IB resectable gastric cancer	I, A
A triplet ChT regimen including a fluoropyrimidine, a platinum compound and docetaxel should be given when possible [ESMO-MCBS v2.0 score: A (PT)]	I, A
Peri-operative use of FLOT is standard of care for patients who are able to tolerate a triple cytotoxic drug regimen [ESMO-MCBS v2.0 score: A (AT, PT)]	I, A
For patients unfit for triplet ChT, a combination of a fluoropyrimidine with cisplatin or oxaliplatin is recommended	II, B

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Adjuvant Treatment

Summary of recommendations	LoE, GoR
For patients with stage $\geq$ IB gastric cancer who have undergone surgery without administration of preoperative ChT, adjuvant ChT is recommended	I, A
For patients who have undergone surgery with clear margins (R0), post-operative RT has no added benefit and should not be given	I, D
For patients undergoing peri- or post-operative ChT, the addition of post-operative RT has no added benefit and should not be given	I, E
For patients who have not received preoperative ChT and have not undergone an appropriate D2 lymphadenectomy, adjuvant CRT can be considered	I, C
For patients who have undergone surgery with involved margins (R1), adjuvant RT or CRT might be considered as an individual recommendation, but is not standard	IV, C
For patients with MSI-H gastric cancer who have undergone curative surgery, adjuvant ChT cannot be recommended, but if a response is required to downstage a tumour before surgery, FLOT is recommended	IV, D

CLINICAL PRACTICE GUIDELINES

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Metastatic Disease

Advanced/Metastatic Unresectable Oesophageal, Oesophagogastric Junction and Gastric Adenocarcinoma: First-line Therapy (HER2-positive)

*HER2 IHC 3+ or IHC 2+ and FISH ≥2

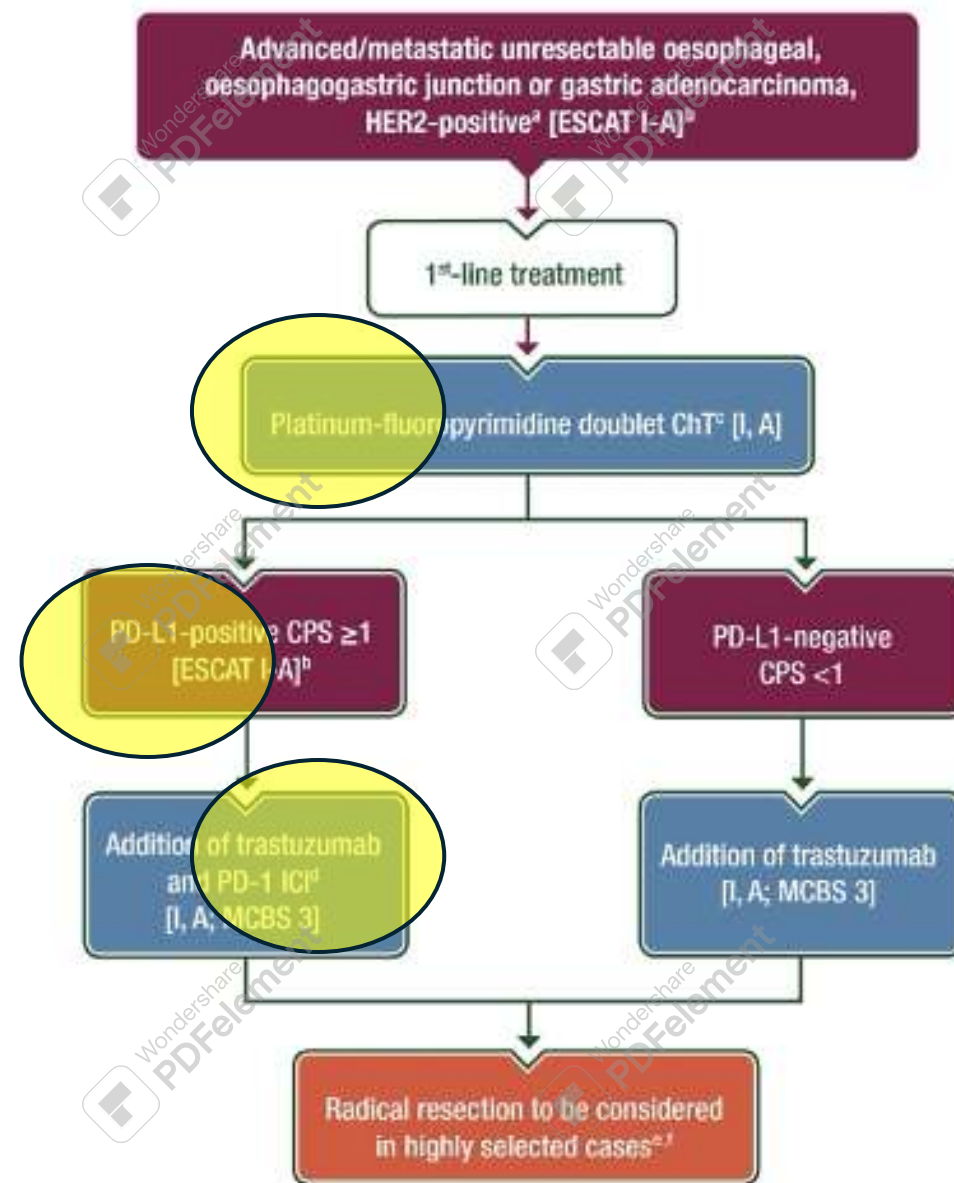
^aESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group (Mateo, 2018)

^bRecommended platinum compounds are oxaliplatin or cisplatin. Oxaliplatin is preferred, especially for older patients. Recommended fluoropyrimidines are intravenous 5-FU, oral capecitabine or oral S-1. Irinotecan-5-FU can be considered an alternative option for patients who do not tolerate platinum compounds or for patients who have progressed shortly after adjuvant platinum-based therapy.

^cPembrolizumab-trastuzumab-ChT, in combination with fluoropyrimidine and platinum-containing ChT, is recommended for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥1. EMA and FDA approved. Results from the randomised AIO Intega study suggest safety and activity for the combination of nivolumab-trastuzumab-FOLFOX (Stein, 2022), not EMA and not FDA approved for this indication.

^dGastrectomy is not recommended in metastatic gastric cancer unless required for palliation of symptoms.

^eResection of metastases and cytoreductive surgery in case of peritoneal metastases cannot be recommended in general but might be considered as an individual approach in highly selected cases with oligometastatic disease and response to ChT. Resection of metastases in addition to systemic ChT was not shown to improve survival in the Renaissance trial. Cytoreductive surgery for peritoneal metastases may even be detrimental. The standard of care is systemic therapy with an established and recommended regimen for stage IV disease. Surgery cannot be recommended outside the context of a clinical trial or in very selected cases, after a sufficiently long period of systemic treatment (standard of care) and after critical discussion in a multidisciplinary tumour board at a high-volume tertiary referral centre.



CLINICAL PRACTICE GUIDELINES

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Metastatic Disease

First-line Therapy

Summary of recommendations

LoE, GoR

First-line ChT with a platinum and fluoropyrimidine is recommended. Oxaliplatin is preferred, especially for older patients. S-1 is commonly used in Asian patients

I, A

Due to higher levels of toxicity and uncertain survival benefit over recommended doublet regimens, first-line taxane-based triplet ChT is not recommended as a standard approach

I, C

Irinotecan–5-FU can be considered an alternative option for patients who do not tolerate platinum compounds

II, B

Claudin-18.2-positive

LoE, GoR

The addition of zolbetuximab [ESMO-MCBS v2.0 score: 2] to ChT is recommended for patients with HER2-negative and PD-L1-negative tumours in the first-line metastatic disease setting

I, A

Zolbetuximab is a potential option for some patients with claudin-18.2-positive, HER2-negative and PD-L1-positive tumours. However, the addition of one of the approved immune checkpoint inhibitors for this indication is a valid alternative

I, C

CLINICAL PRACTICE GUIDELINES

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Metastatic Disease

First-line Therapy – PD-L1-positive
and HER2-positive

Summary of recommendations	
PD-L1-positive	
Nivolumab–ChT is recommended for advanced, untreated AC of gastric, OGJ and oesophageal cancer with a PD-L1 CPS ≥ 5 , based on the results of CheckMate 649 [ESMO-MCBS v2.0 score: 4]	I, A
Pembrolizumab–ChT is recommended for AC of stomach and OGJ with PD-L1 ≥ 1 , based on the results of KEYNOTE-859 [ESMO-MCBS v2.0 score: 4]	I, B
Pembrolizumab–ChT should be considered for AC of the oesophagus with PD-L1 ≥ 10 , based on the results of KEYNOTE-590 [ESMO-MCBS v2.0 score: 4]	II, C
HER2-positive	
Trastuzumab–ChT is recommended in patients with HER2-positive tumours [ESMO-MCBS v2.0 score: 3; ESCAT score: I-A]	I, A
Pembrolizumab–trastuzumab–ChT is recommended in patients with HER2-positive tumours and PD-L1 CPS ≥ 1 [ESMO-MCBS v2.0 score: 2; ESCAT score: I-A]	I, A

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Metastatic Disease

Surgery for Metastatic Gastric Cancer

Summary of recommendations

LoE, GoR

Gastrectomy is not recommended in metastatic gastric cancer unless required for palliation of symptoms

I, D

Resection of metastases cannot be recommended in general, but might be considered as an individual approach in highly selected cases with oligometastatic disease and response to ChT

V, C

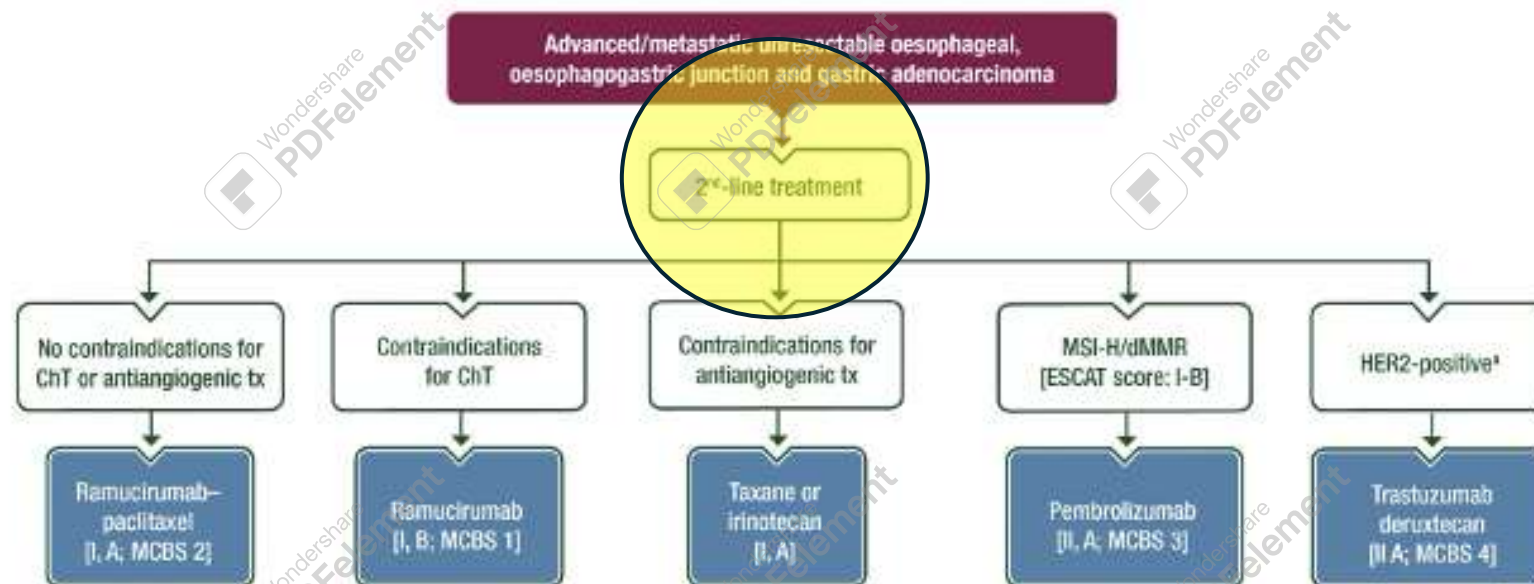
CLINICAL PRACTICE GUIDELINES

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Metastatic Disease

Advanced/Metastatic Unresectable Oesophageal, Oesophagogastric Junction and Gastric Adenocarcinoma: Second-line Therapy

*HER2 IHC 3+ or IHC 2+ and FISH ≥2



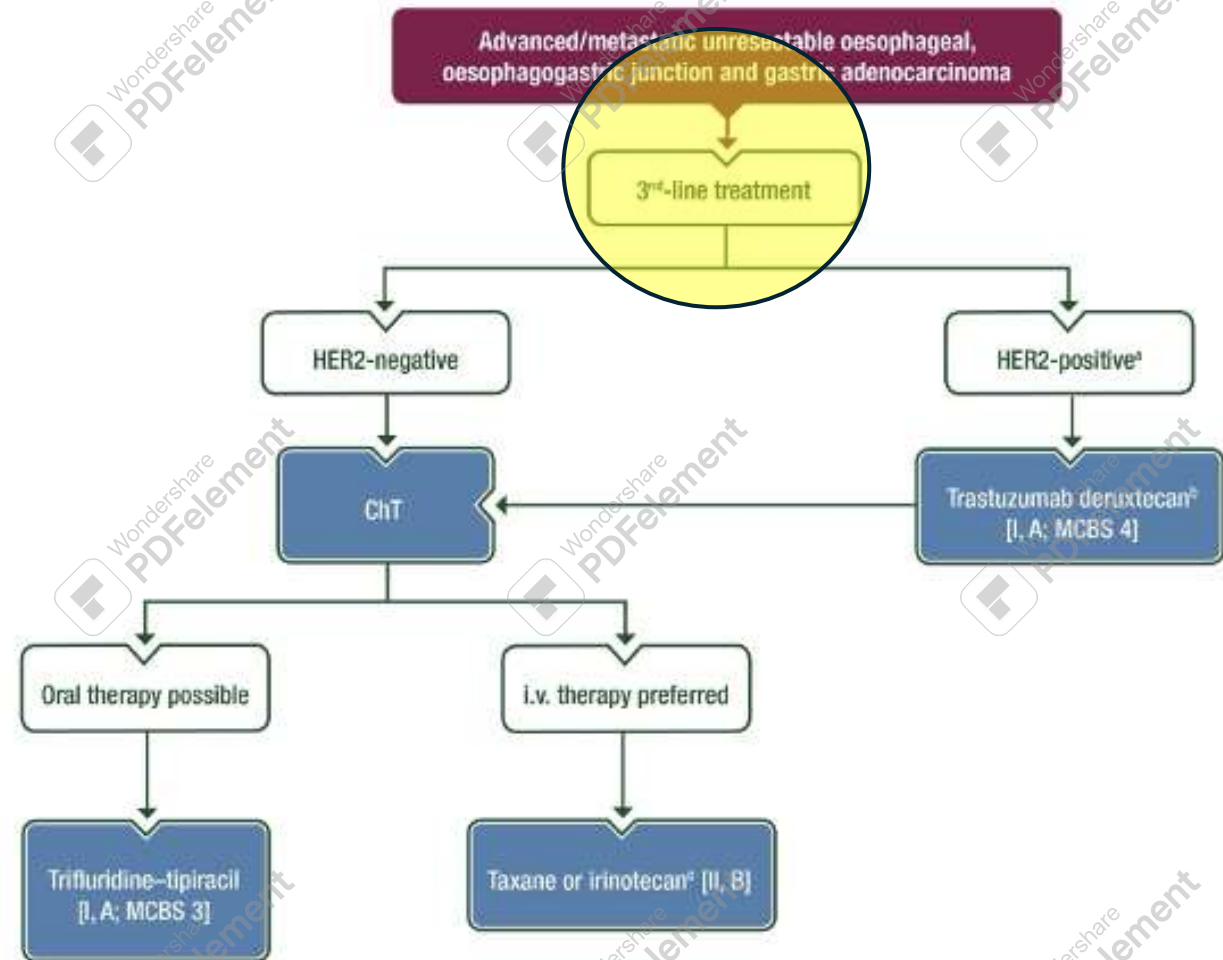
CLINICAL PRACTICE GUIDELINES

ESMO Gastric Cancer Living Guideline
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Metastatic Disease

Advanced/Metastatic Unresectable Oesophageal,
Oesophagogastric Junction and Gastric
Adenocarcinoma: Third-line Therapy

*HER2 IHC 3+ or IHC 2+ and FISH ≥2
†If not administered in second line
‡Not given previously for advanced/metastatic disease



CLINICAL PRACTICE GUIDELINES

ESMO Gastric Cancer Living Guideline
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Metastatic Disease

Second-, Third- and Later-line Treatment



Summary of recommendations	LoE, GoR
Ramucirumab–paclitaxel is recommended for second-line treatment of gastric cancer [ESMO-MCBS v2.0 score: 2]	I, A
Ramucirumab monotherapy is also an option [ESMO-MCBS v2.0 score: 1]	I, B
Where ramucirumab is not available, paclitaxel, docetaxel or irinotecan monotherapy [I, A] or FOLFIRI [II, B] are recommended	I, A / II, B
For patients previously treated with two lines of therapy, trifluridine–tipiracil is recommended [I, A; ESMO-MCBS v2.0 score: 3]. Alternative treatments include a taxane or irinotecan [II, B]	I, A / II, B
MSI-H	LoE, GoR
Pembrolizumab is recommended for second-line treatment of patients with MSI-H/dMMR gastric cancer [ESMO-MCBS v2.0 score: 2; ESCAT score: I-B]	II, A
HER2-positive	LoE, GoR
Treatment with trastuzumab is not recommended after first-line therapy in HER2-positive advanced gastric cancer	I, D
Trastuzumab deruxtecan is recommended for patients with HER2-positive advanced gastric cancer who have received a prior trastuzumab-based regimen [ESMO-MCBS v2.0 score: 4]	I, A
Re-biopsy is recommended when possible	

CLINICAL PRACTICE GUIDELINES

ESMO Gastric Cancer Living Guideline
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Metastatic Disease

Surgery

Surgery for metastatic gastric cancer	LoE, GoR
Gastrectomy is not recommended in metastatic gastric cancer unless required for palliation of symptoms	I, D
Resection of metastases cannot be recommended in general, but might be considered as an individual approach in highly selected cases with oligometastatic disease and response to ChT	V, C

CLINICAL PRACTICE GUIDELINES

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Supportive Care and Nutrition

Summary of recommendations	LoE, GoR
Care for patients with gastric cancer should include an early palliative care referral and nutritional support	I, A
Low-dose olanzapine with dietary support should be considered to improve appetite and weight gain	I, B

CLINICAL PRACTICE GUIDELINES

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Follow-up, Long-term Implications and Survivorship

Summary of recommendations	LoE, GoR
Regular follow-up is recommended for investigation and treatment of symptoms, psychological support and early detection of recurrence	III, B
Follow-up should be tailored to the individual patient and stage of disease	V, B
Dietary support is recommended with attention to vitamin and mineral deficiencies	V, B
In the advanced disease setting, regular follow-up is recommended to detect symptoms of disease progression before significant clinical deterioration	IV, B
Radiological investigations, specifically CT of the thorax and abdomen, should be carried out every 6-12 weeks in patients who are candidates for further cancer specific therapies	IV, B



National Comprehensive
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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Gastric Cancer

Version 3.2025 — August 22, 2025

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**NCCN recognizes the importance of clinical trials and encourages participation when applicable and available.
Trials should be designed to maximize inclusiveness and broad representative enrollment.**

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Gastric Cancer

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WORKUP

- History and physical (H&P)
- Esophagogastroduodenoscopy (EGD) and biopsy^a
- Chest/abdomen/pelvis CT with oral and IV contrast
- FDG-PET/CT evaluation (skull base to mid-thigh) for locally advanced or metastatic disease^b or if clinically indicated
- CBC and comprehensive chemistry profile
- Endoscopic ultrasound (EUS) is recommended if early-stage disease suspected or if early versus locally advanced disease needs to be determined (preferred)
- Endoscopic resection (ER) is essential for the accurate staging of early-stage cancers (T1a or T1b).^c Early-stage cancers can best be diagnosed by ER.
- Biopsy of metastatic disease as clinically indicated
- Universal testing for microsatellite instability (MSI) by PCR/next-generation sequencing (NGS) or MMR by IHC is recommended in all newly diagnosed patients^d
- Universal testing for programmed death ligand 1 (PD-L1) is recommended in all newly diagnosed patients^d
- HER2 testing if advanced/metastatic disease is documented/suspected^{d,e}
- CLDN18.2 testing if advanced/metastatic disease is documented/suspected^d
- NGS should be considered^d
- Assess Siewert category^f
- Nutritional assessment and counseling
- Smoking cessation advice, counseling, and pharmacotherapy as indicated^g
- Screen for family history^h
- Test for *H. pylori* infection and eradicate in all patients with early gastric cancer if positive. Conduct genetic testing as needed and recommend *H. pylori* testing of close family membersⁱ

CLINICAL STAGE

ADDITIONAL EVALUATION

cTis
or
cT1a

Medically fit^k

Non-surgical candidate^l

Locoregional
(cM0, Any N)

Medically fit,^{f,k}
potentially
resectable

Recommend
laparoscopy
with
cytology^m

Medically fit,^{f,k}
surgically
unresectable

Consider
laparoscopy
with
cytology^m

Stage IV
(cM1)

Multidisciplinary
review preferredⁿ → [GAST-2](#)

Palliative
Management
([GAST-9](#))

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

[Footnotes on GAST-1A](#)



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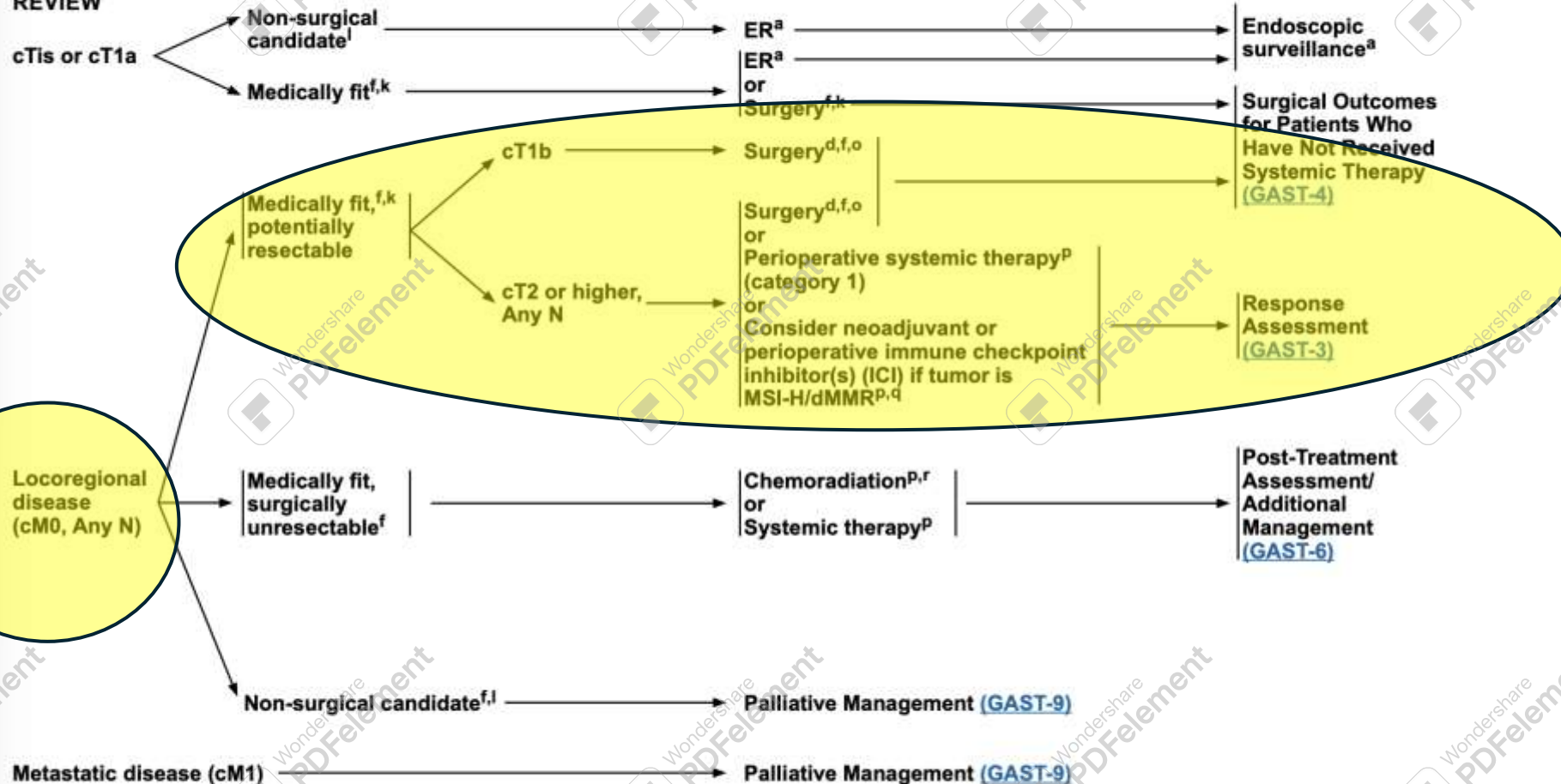
Gastric Cancer

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CONCLUSIONS OF MULTIDISCIPLINARY REVIEW

FINAL STAGE¹

PRIMARY TREATMENT



[Footnotes on GAST-2A](#)

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



**PRIMARY TREATMENT
FOR PATIENTS WHO
ARE MEDICALLY FIT**

RESPONSE ASSESSMENT

OUTCOME

ADDITIONAL MANAGEMENT

Perioperative
systemic
therapy^p
(category 1)

- Chest/abdomen/
pelvis CT with oral
and IV contrast
- FDG-PET/CT as
clinically indicated

Resectable
disease

Surgery^{d,f,o}
(preferred)
or
Palliative Management
([GAST-9](#))

Surgical Outcomes
for Patients Who Have
Received Systemic
Therapy ([GAST-5](#))

Unresectable
or
Metastatic disease

Palliative Management ([GAST-9](#))

No evidence
of disease^{q,u}

Observation
or
Surgery^{d,f,v}

Follow-up ([GAST-7](#))

Surgical Outcomes
for Patients Who Have
Received Systemic
Therapy ([GAST-5](#))

Persistent local
disease^q

Surgery
(preferred)^{d,f,v}
or
Palliative Management
([GAST-9](#))

New metastatic
disease

Palliative Management ([GAST-9](#))

Neoadjuvant or
perioperative
ICI if tumor is
microsatellite
instability-high
(MSI-H)/mismatch
repair deficient
(dMMR)^{p,q}

- FDG-PET/CT as clinically
indicated^s
- Chest/abdomen CT with
oral and IV contrast
(not required if FDG-PET/
CT is done)^t
- EGD and biopsy^u

^d [Principles of Pathologic Review and Biomarker Testing \(GAST-B\)](#).

^f [Principles of Surgery \(GAST-C\)](#).

^o Surgery as primary therapy is appropriate for $\geq T1b$ cancer or actively bleeding cancer, or when postoperative therapy is preferred.

^p [Principles of Systemic Therapy \(GAST-F\)](#).

^q In patients with an MSI-H/dMMR tumor, perioperative immunotherapy should be considered in consultation with a multidisciplinary team. The role of surgery after biopsy proven and radiologic/metabolic complete response on neoadjuvant immunotherapy is unclear.

^s Assessment ≥ 5 to 8 weeks after completion of preoperative therapy.

^t Pelvis CT if clinically indicated.

^u See Post-Treatment Surveillance in [Principles of Endoscopic Staging and Therapy \(GAST-A 3 of 4\)](#).

^v Feeding jejunostomy for postoperative nutritional support, generally preferred.

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



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Gastric Cancer

**SURGICAL OUTCOMES/CLINICAL
PATHOLOGIC FINDINGS**
(Patients Have Not Received
Systemic Therapy)

**TUMOR
CLASSIFICATION^f**

POSTOPERATIVE MANAGEMENT

R0 resection^w

pTis or
pT1, N0

Observation

pT2, N0

Observation
or

Fluoropyrimidine (fluorouracil or capecitabine)^{p,x}
then fluoropyrimidine-based chemoradiation,^{p,r,x}
then fluoropyrimidine (fluorouracil or capecitabine)^{p,x} for
selected patients^y

pT3, pT4, Any N
or Any pT, N+

Fluoropyrimidine (fluorouracil or capecitabine)^{p,x}
then fluoropyrimidine-based chemoradiation,^{p,r,x}
then fluoropyrimidine (fluorouracil or capecitabine)^{p,x}
if less than a D2 dissection (category 1)
or
Chemotherapy for patients who have undergone primary D2
lymph node dissection^{f,p} (category 1)

R1 resection^w

Chemoradiation^{p,r} (fluoropyrimidine-based)

R2 resection^w

Chemoradiation^{p,r} (fluoropyrimidine-based)
or
[Palliative Management \(GAST-9\)](#), as clinically indicated

pM1

Follow-up
[\(GAST-7\)](#)

[Palliative
Management
\(GAST-9\)](#)

^f [Principles of Surgery \(GAST-C\)](#).
^j See [Staging \(ST-1\)](#) for tumor classification.
^p [Principles of Systemic Therapy \(GAST-F\)](#).
^r [Principles of Radiation Therapy \(GAST-G\)](#).

^w R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1.

^x Smalley SR, et al. J Clin Oncol 2012;30:2327-2333. See [Principles of Systemic Therapy \(GAST-F\)](#).

^y High-risk features include poorly differentiated or higher grade cancer, lymphovascular invasion (LVI), neural invasion, or <50 years of age or patients who did not undergo D2 lymph node dissection.

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



**SURGICAL OUTCOMES/CLINICAL
PATHOLOGIC FINDINGS**
(Patients Have Received Systemic
Therapy)

**TUMOR
CLASSIFICATION^J**

POSTOPERATIVE MANAGEMENT

R0 resection^W

Systemic therapy,^P (category 1)

R1 resection^W

Chemoradiation^{P,†} (fluoropyrimidine-based)
or
Consider re-resection

R2 resection^W

Chemoradiation^{P,†} (fluoropyrimidine-based)
or
Palliative Management ([GAST-9](#)), as clinically indicated

ypM1^z

Follow-up
([GAST-7](#))

Palliative
Management
([GAST-9](#))

^J See [Staging \(ST-1\)](#) for tumor classification.

^P [Principles of Systemic Therapy \(GAST-F\)](#).

[†] [Principles of Radiation Therapy \(GAST-G\)](#).

^W R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1.

^z The yp prefix is used to indicate cases in which staging is performed following preoperative therapy.

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

FOLLOW-UP/SURVEILLANCE^{cc}

Tis
(successfully
treated by
ER)^{bb}

- H&P every 3–6 months for 1–2 years, then every 6–12 months for 3–5 years
- CBC and chemistry profile as clinically indicated
- Upper gastrointestinal (GI) endoscopy (EGD) every 6 months for 1 year, then annually for 3 years
- Routine imaging (CT chest/abdomen/pelvis with oral and IV contrast) as clinically indicated based on symptoms and concern for recurrence

p stage I
(T1a,T1b,
N0 treated
by surgical
resection or
T1a treated
by ER)^{bb}

- H&P every 3–6 months for 1–2 years, then every 6–12 months for 3–5 years
- CBC and chemistry profile as clinically indicated
- For patients treated by ER, EGD every 6 months for 1 year, then annually for up to 5 years
- Thereafter, as needed based on symptoms and/or radiographic findings
- For patients treated by surgical resection, EGD as clinically indicated
- CT chest/abdomen/pelvis with oral and IV contrast as clinically indicated^{dd,ee}
- Monitor for nutritional deficiency in patients who have undergone surgical resection (especially after total gastrectomy) and treat as indicated^{ff}

p stage II/III or
yp stage I–III
(treated with
neoadjuvant
± adjuvant
therapy)^{bb}

- H&P every 3–6 months for 1–2 years, then every 6–12 months for 3–5 years
- CBC and chemistry profile as clinically indicated
- For patients who had partial or subtotal gastrectomy, EGD as clinically indicated
- CT chest/abdomen/pelvis with oral and IV contrast every 6 months for first 2 years, then annually for up to 5 years^{dd,ee}
- Monitor for nutritional deficiency in patients who have undergone surgical resection (especially after total gastrectomy) and treat as indicated^{ff}

Recurrence
(GAST-8)
or
Survivorship^{gg}

^{bb} For patients undergoing total gastrectomy for curative intent, surveillance should follow these recommendations except for endoscopy. Endoscopy as clinically indicated for routine surveillance for total gastrectomy unless patients are symptomatic.

^{cc} [Principles of Surveillance \(GAST-H\)](#).

^{dd} After 5 years, additional follow-up may be considered based on risk factors and comorbidities.

^{ee} CT scan preferred. For patients who cannot undergo CT scan, alternative imaging such as PET/CT or MRI as clinically indicated.

^{ff} Follow-up with appropriate practitioners or specialists should be established for lifelong monitoring and management of potential nutritional sequelae of gastrectomy, which may include, but are not limited to, vitamin B₁₂, iron, zinc, calcium, and vitamin D deficiencies. Consider routine supplementation with a daily multivitamin/mineral complex, vitamin B₁₂, calcium, and vitamin D. See [Principles of Survivorship \(GAST-I 2 of 4\)](#).

^{gg} [Principles of Survivorship \(GAST-I\)](#).

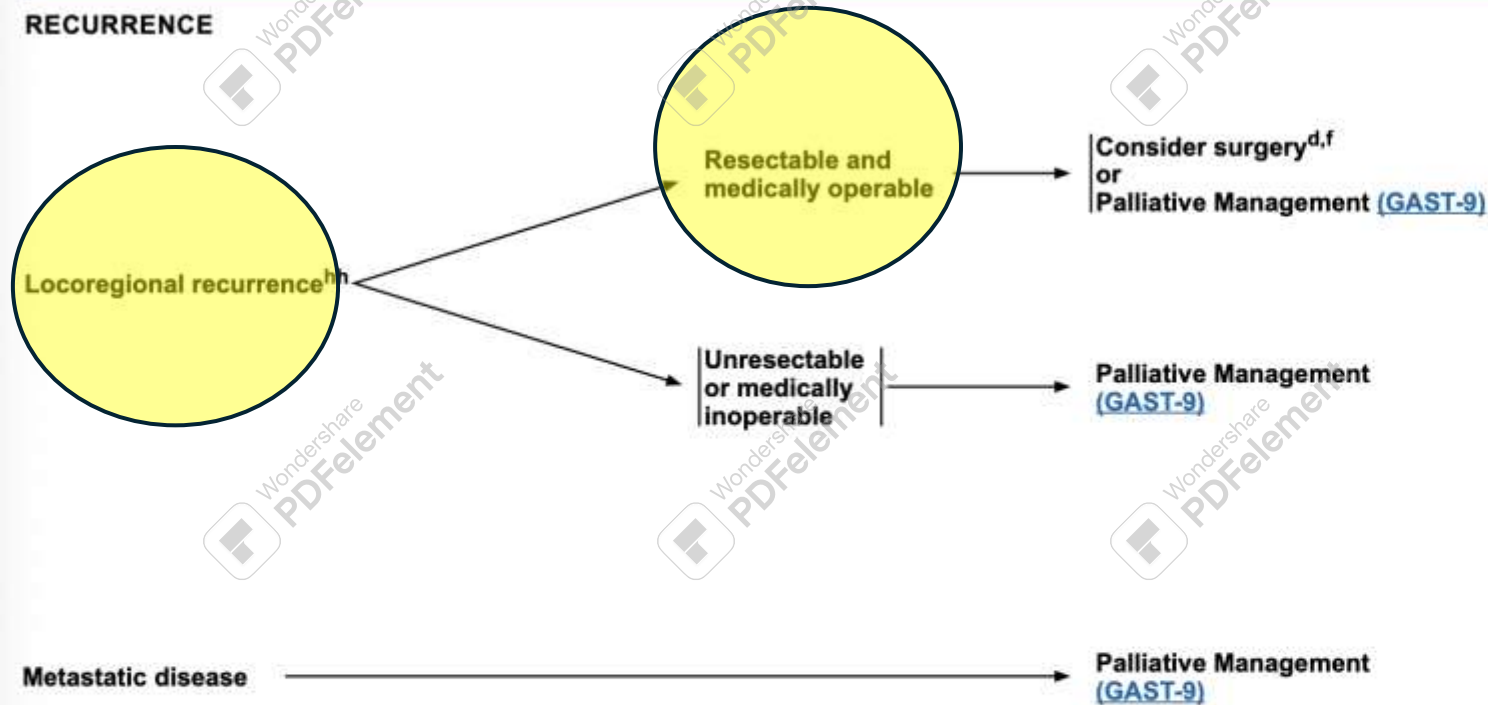
Note: All recommendations are category 2A unless otherwise indicated.



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Gastric Cancer

RECURRENCE



^d [Principles of Pathologic Review and Biomarker Testing \(GAST-B\)](#).

^f [Principles of Surgery \(GAST-C\)](#).

^{hh} Review if surgery is appropriate for patients with isolated local recurrences. Surgery should be considered as an option for locoregional recurrence in patients who are medically fit.

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



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Gastric Cancer

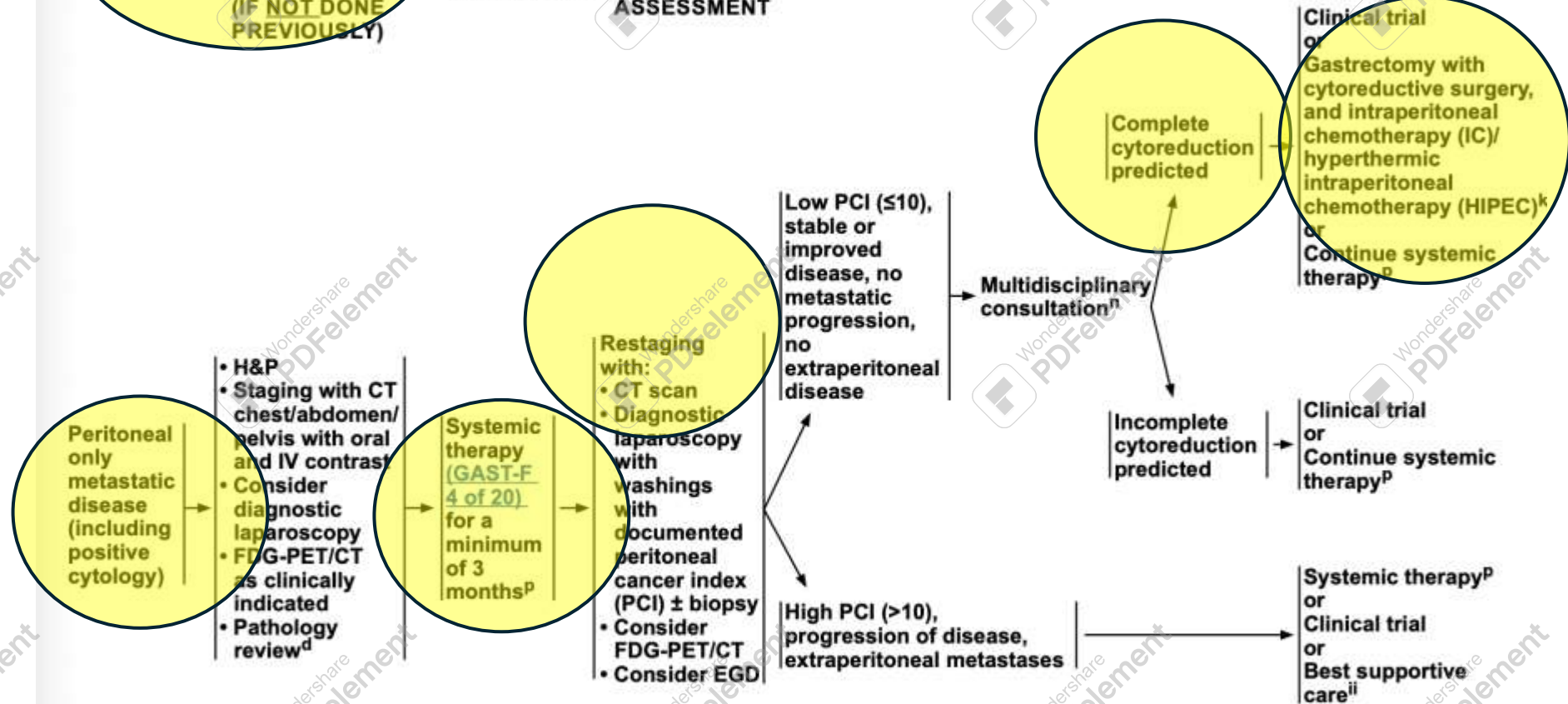
PERITONEAL CARCINOMA AS ONLY DISEASE^{jj}

WORKUP
(IF NOT DONE
PREVIOUSLY)

TREATMENT

RESPONSE
ASSESSMENT

ADDITIONAL
TREATMENT



^d [Principles of Pathologic Review and Biomarker Testing \(GAST-B\)](#).

ⁿ [Principles of Multidisciplinary Team Approach \(GAST-E\)](#).

^p [Principles of Systemic Therapy \(GAST-F\)](#).

ⁱⁱ [Principles of Palliative Care/Best Supportive Care \(GAST-J\)](#).

^{jj} Chicago Consensus Working Group. Ann Surg Oncol 2020;27:1768-1773.

^{kk} [Principles of Surgery \(GAST-C 3 of 5\)](#).

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



PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Next-Generation Sequencing (NGS):

At present, several targeted therapeutic agents (GAST-F) have been approved by the FDA for use in gastric cancer. IHC/ISH/targeted PCR is the preferred approach to assess biomarkers, initially. However, NGS testing through a CLIA-approved laboratory may be considered later in the clinical course of patients with sufficient tumor tissue available for testing. The list of targeted biomarkers includes:

- ▶ HER2 overexpression/amplification
- ▶ PD-L1 expression
- ▶ MSI
- ▶ CLDN18.2
- ▶ TMB
- ▶ NTRK gene fusion
- ▶ RET gene fusion
- ▶ BRAF V600E mutation

Liquid Biopsy^{12,13}

The genomic alterations of solid cancers may be identified by evaluating circulating tumor DNA (ctDNA) in the blood, hence a form of "liquid biopsy." The detection of mutations/alterations or fusions in DNA shed from gastric carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. Therefore, when limited tissue is available or for patients who have metastatic or advanced gastric cancer who are not able to undergo a traditional biopsy, testing using a validated NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered. A negative result should be interpreted with caution, as this does not exclude the presence of tumor.

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

References



PRINCIPLES OF SURGERY

N Category Determination

- Determine extent of disease by CT scan (chest, abdomen, and pelvis) ± EUS (if no metastatic disease seen on CT).
- In patients being considered for surgical resection without preoperative therapy, laparoscopy¹ may be useful in detecting radiographically occult metastatic disease in patients with cT3 and/or cN+ disease seen on preoperative imaging. If laparoscopy is planned as a separate procedure, peritoneal washings with cytology should be performed as well.
- In patients receiving preoperative therapy, a baseline laparoscopy along with peritoneal washings should be considered.
- Positive peritoneal cytology (performed in the absence of visible peritoneal implants) is associated with poor prognosis and is defined as pM1 disease.²

Siewert Classification

- Siewert tumor type should be assessed in all patients with adenocarcinomas involving the EGJ.^{3,4}
 - › Siewert Type I: adenocarcinoma of the lower esophagus (often associated with Barrett esophagus) with the epicenter located within 1 cm to 5 cm above the anatomic EGJ.
 - › Siewert Type II: true carcinoma of the cardia at the EGJ with the tumor epicenter within 1 cm above and 2 cm below the EGJ.
 - › Siewert Type III: subcardial carcinoma with the tumor epicenter between 2 cm and 5 cm below the EGJ, which infiltrates the EGJ and lower esophagus from below.
- The treatment of Siewert types I and II is as described in the [NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers](#).
- Siewert type III lesions are considered gastric cancers, and thus should be treated as described in the NCCN Guidelines for Gastric Cancer. In some cases additional esophageal resection may be needed in order to obtain adequate margins.^{3,5,6}

Criteria of Unresectability for Cure

- Locoregionally advanced
 - › Disease infiltration of the root of the mesentery or para-aortic lymph node highly suspicious on imaging or confirmed by biopsy
 - › Invasion or encasement of major vascular structures (excluding the splenic vessels)
- Distant metastasis or peritoneal seeding (including positive peritoneal cytology)

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

[Continued](#)
[References](#)

GAST-C
1 OF 5



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Gastric Cancer

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PRINCIPLES OF SURGERY

Resectable Tumors

- Tis or T1⁷ tumors limited to mucosa (T1a) may be candidates for EMR or ESD if they meet appropriate criteria (in experienced centers).⁸
- T1b–T3⁹: Adequate gastric resection to achieve negative microscopic margins along with lymphadenectomy.
 - Distal gastrectomy
 - Subtotal gastrectomy
 - Total gastrectomy
- T4b tumors require en bloc resection of involved structures.
- Gastric resection should include the regional lymphatics—perigastric lymph nodes (D1) and those along the named vessels of the celiac axis (D2), with a goal of examining ≥16 lymph nodes.^{10–12}
 - Definition of D1 and D2 lymph node dissections
 - ◊ D1 dissection entails gastrectomy and the resection of both the greater and lesser omenta (which would include the lymph nodes along the right and left cardiac, lesser and greater curvature, suprapyloric along the right gastric artery, and infrapyloric area);
 - ◊ D2 dissection is a D1 plus all the nodes along the left gastric artery, common hepatic artery, celiac artery, and splenic artery.
- Routine splenectomy is not indicated unless the spleen is involved or extensive hilar adenopathy is noted.¹³
- Consider placing feeding tube in select patients undergoing total gastrectomy (especially if postoperative chemoradiation appears a likely recommendation).
- Minimally invasive surgical approaches may be considered for selected cases based on the following criteria:
 - The surgeon has experience performing laparoscopic or robotic foregut procedures and has experience in lymphadenectomy.
 - Both early and locally advanced gastric cancers can be considered for laparoscopic or robotic gastrectomy given evidence that supports equivalent oncologic outcomes from the East and West.^{14–17}
 - Minimally invasive approaches are generally not recommended for T4b or N2 bulky gastric cancer.

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

[Continued](#)
[References](#)

GAST-C
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Gastric Cancer

PRINCIPLES OF SURGERY

Resectable Tumors—Continued

• IC/HIPEC/Pressurized Intraperitoneal Aerosolized Chemotherapy (PIPAC)¹⁸⁻²¹

- ▶ The evidence for the use of IC/HIPEC/PIPAC is limited. There are no randomized trials to demonstrate efficacy, and results are limited to case reports and small series. However, IC/HIPEC may be effective in selected patients with low burden of tumor. The decision to pursue IC/HIPEC should be made only after multidisciplinary discussion.
- ▶ PIPAC is investigational and should only be done in the context of a clinical trial.
- ▶ IC/HIPEC may be a therapeutic alternative for carefully selected patients with peritoneal carcinoma as only disease.
 - ◊ Patients who are being considered for IC/HIPEC should undergo pre-treatment evaluation with a chest/abdomen/pelvis CT, diagnostic laparoscopy with washings to assess for PCI and/or cytology-positive disease, and consider a PET scan to rule out distant metastatic disease. Patients with documented peritoneal metastatic disease should begin with systemic therapy given for a minimum of 3 months. Then patients should undergo re-staging and demonstrate stable or improving disease to be considered for further therapy. Treatment decisions should be made in the context of a multidisciplinary tumor board. In this setting:
 - ◊ IC/HIPEC can be used in conjunction with cytoreductive surgery^a for patients with low PCI (≤ 10) who are candidates to undergo complete cytoreduction.
 - In patients with a higher burden of peritoneal disease (PCI > 10), IC/HIPEC may be considered in the setting of a clinical trial.
 - The role of prophylactic IC/HIPEC/PIPAC is currently investigational for patients with non-metastatic cancers and should only be performed in the setting of a clinical trial.

^a Cytoreduction of all visible nodules/plaques.

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



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Gastric Cancer

PRINCIPLES OF SURGERY

Palliative Procedures

- **Gastric resections** should be reserved for the palliation of symptoms (eg, obstruction or uncontrollable bleeding) in patients with incurable disease when non-surgical options are not feasible such as endoscopic or interventional radiology procedures (ie, endoscopic stenting).
- Lymph node dissection is not required.
- In patients fit for surgery and who have a reasonable prognosis, gastrojejunostomy (open or laparoscopic) or endoluminal stenting are options. Except for rare cases that may have slow growth, endoluminal stenting is preferred in patients with gastric outlet obstruction/disease and very minimal metastatic disease, in the liver or other area not affecting the GI tract. If longer term palliation is needed, surgical bypass may be considered.^{22,23}
- Venting gastrostomy and/or feeding tube may be considered.

[References](#)

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



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PRINCIPLES OF SYSTEMIC THERAPY

Perioperative Systemic Therapy

Preferred Regimens

- Fluorouracil,^a leucovorin, oxaliplatin, and docetaxel (FLOT)^b (category 1)¹
- FLOT^a + durvalumab^c for PD-L1 CPS ≥1 or TAP ≥1%^b (category 1)^{d,*}
- Fluoropyrimidine and oxaliplatin^{a,e}

Other Recommended Regimens

- Fluorouracil and cisplatin (category 1)²

Neoadjuvant or Perioperative Immunotherapy

Useful in Certain Circumstances

- MSI-H/dMMR tumors^b
 - ▶ Nivolumab and ipilimumab followed by nivolumab^{c,3}
 - ▶ Pembrolizumab^{c,4,5}
 - ▶ Tremelimumab and durvalumab for neoadjuvant therapy only^{c,6,7}

Postoperative Chemoradiation

(For patients who received less than a D2 lymph node dissection [[Principles of Surgery \(GAST-C\)](#)])

- Fluoropyrimidine (infusional fluorouracil^a or capecitabine) before and after fluoropyrimidine-based chemoradiation⁸

Postoperative Chemotherapy

(For patients who have undergone primary D2 lymph node dissection [[Principles of Surgery \(GAST-C\)](#)])

Preferred Regimens

- Capecitabine and oxaliplatin (category 1)⁹
- Fluorouracil^a and oxaliplatin

Chemoradiation for Unresectable Disease

(Infusional fluorouracil^a can be replaced with capecitabine)

Preferred Regimens

- Fluorouracil^a and oxaliplatin^{10,11}
- Fluorouracil and cisplatin^{12,13}

Other Recommended Regimens

- Fluoropyrimidine (fluorouracil or capecitabine) and paclitaxel (category 2B)¹⁴

^a Leucovorin 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 [Discussion](#).

^b [Principles of Pathologic Review and Biomarker Testing \(GAST-B\)](#).

^c [NCCN Guidelines for Management of Immunotherapy-Related Toxicities](#).

^d In the MATTERHORN trial, diffuse type gastric or EGJ adenocarcinoma showed no EFS advantage when durvalumab was added to FLOT.

^e The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.

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

[Continued
References](#)

**GAST-F
3 OF 20**

JGCA/ESMO/NCCN Temel Benzerlikler ve Farklılıklar (Özet)

- **Cerrahi (D2 Diseksiyon):** Uç kılavuz da küratif cerrahide D2 diseksiyonu altın standart olarak kabul eder.
- **Adjuvan Kemoterapi:** JGCA ve ESMO/NCCN, Evre II/III için floropirimidin bazlı adjuvan kemoterapiyi önerir. Kombinasyon seçimleri (S-1 bazlı vs. FLOT/XELOX) bölgesel farklılıklar gösterir.
- **1. Basamak AGC, HER2-Negatif:**
 - **JGCA:** Fluoropirimidin + Platin ± Nivolumab (CPS≥5 vurgusu).
 - **ESMO/NCCN:** Fluoropirimidin + Platin + Nivolumab (CPS≥5 için 1. sıra). *Not: ESMO/NCCN, CPS bakılmaksızın nivolumab+kemoterapiyi daha geniş bir şekilde onaylamış/önerebilir.*
- **1. Basamak AGC, HER2-Pozitif:**
 - **Hepsi:** Trastuzumab + Kemoterapi standarttır.
 - **NCCN/ESMO:** İleri evrede immünoterapi (örneğin, pembrolizumab) onayı/önerisi daha geniş olabilir.
- **2. Basamak AGC:**
 - **Hepsi:** Ramucirumab + Paklitaksel önemli bir seçenektir.
- **Neoadjuvan Kemoterapi:**
 - **ESMO/NCCN:** Lokal ileri hastalıkta (özellikle FLOT protokolü ile) daha güçlü ve yaygın bir şekilde önerilir.
 - **JGCA:** Daha temkinli yaklaşır, net öneri sunmaz.

Sonuç

JGCA 2021 kılavuzu, mide kanseri tedavisinde kapsamlı, kanıta dayalı ve güncel bir rehberdir.

Tedavi kararı; hassas evreleme, histopatolojik/moleküler alt tip belirleme (HER2, MSI, PD-L1) ve hasta performansına dayanmalıdır.

Minimal invaziv cerrahi erken evrelerde standart hale gelmiştir.

İmmüno-onkoloji (nivolumab, pembrolizumab) ve hedefe yönelik tedaviler (T-DXd, ramucirumab), ileri evre hastalıkta tedavi şemasını kökten değiştirmiştir.

ESMO ve NCCN kılavuzları ile genel prensipler benzer olsa da, immünoterapi kullanımında ve neoadjuvan kemoterapi yaklaşımında bölgesel farklılıklar bulunmaktadır.

Multidisipliner yaklaşım (cerrahi, medikal onkoloji, gastroenteroloji, radyasyon onkolojisi, palyatif bakım) optimal sonuçlar için esastır.

Neoadjuvan tedavi

- R0 rezeksiyon oraları artar
- Uzak metastaz ve nüks azalır
- Tümör evresi geriler

- Optimum rejim ?
- Optimum siklus ?
- Histolojik alt tiplerin cevabı ?
- Sağ kalıma katkı ?

**Kim hangi
hastaya, nasıl bir
neoadjuvan
tedavi vermekte?**

Amerika,
NCCN $\rightarrow \geq$
T2N0-3M0

Avrupa $\rightarrow$
> T2N0
tüm
rezektabl
kanserler

- ESMO guidelines
- MAGIC ve
FNCLCC/FFCD
çalışmaları

Japonya →

- Erken tanı oranı çok
- D2 diseksiyon ile başarı yüksek
- 2018 JGCA 5. baskı rehberinde neoadjuvan tedavi çıkarıldı
- **Mart 2019’da D2 lenfadenektomi düşünüldüğünde rezektabl mide kanserinde neoadjuvan tedavinin bir seçenek olmadığına karar verildi.**

Kore → Japonya ile benzer

Çin → T3 - T4N1 – 3M0 lokal ileri kanserler

- Faz III çalışmalar yetersiz

Current clinical indications of neoadjuvant chemotherapy and chemoradiotherapy for gastric cancer.

Guidelines	Neo-chemotherapy			Neo-chemoradiotherapy		
	Stage	Regimen	Evidence	Stage	Regimen	Evidence
NCCN (2018.V2)	≥cT2, Nany	TX, TC, PFL, XELOX, FOLFOX, FLOT	1	≥cT2, Nany	TX, TC, PFL, FOLFOX, XELOX, CRT – 45 Gy	2B
JGCA Guideline (5th edition)	Tany, Bulky N	—	—	—	—	—
ESMO (2016)	>T1N0	5-FU and platinum-based	1A	—	—	—
CSCO (2019)	Stage III (T2N3M0, T3N2-3M0, T4aN1-3M0)	ECF (2A), PF (2A), XELOX (2A)	2A	EGJ Stage III (T2N3M0, T3N2-3M0, T4aN1-3M0)	CRT 45–50 Gy (5-FU/platinum-based/Taxol)	1
Korean Practice Guideline (2018)	Not considered for resectable GC	—	Not considered for resectable GC			

NCCN: National Comprehensive Cancer Network; JGCA: Japanese Gastric Cancer Association; ESMO: European Society for Medical Oncology; CSCO: Chinese Society of Clinical Oncology; TX: Taxol+ capecitabine; TC: Taxol, cisplatin; PFL: cisplatin, fluorouracil, leucovorin; ECF: epirubicin, cisplatin, fluorouracil; PF: cisplatin, fluorouracil; XELOX: capecitabine, oxaliplatin; FOLFOX: fluorouracil, oxaliplatin. FLOT: docetaxel, oxaliplatin, fluorouracil; EGJ: esophagogastric junction; CRT: Chemoradiotherapy; GC: gastric cancer.

Neoadjuvan Kemoterapi

>1990 lokal ileri mide kanserinde başladı.

2006 dönüm noktası → MAGIC çalışması

- En büyük randomize Faz III çalışma
- 9 Amerikan hastanesi + birçok farklı ülke
- 503 hasta
- Sadece cerrahi & Cerrahi + perioperatif KT (ECF 3 + 3 siklus)

MAGIC

R0 rezeksiyon oranı arttı % 79 & % 70

Tümör çapı geriledi T1/T2 % 52 & % 37

Lenf nodu metastazı azaldı N0/N1 % 84 & % 71

5 yıllık sağ kalım arttı % 36 & % 23

Progresyonsuz sağ kalım arttı

Fransız FFCD9703

224 hasta NAK & Cerrahi

5-FU + Sisplatin 2 veya 3 siklus

R0 rezeksiyon oranı arttı %84 & %73

5 yıllık hastalıksız sağ kalım arttı %34 & %19

Bu iki çalışmada limitasyon neydi?

01

Sadece alt
özofageal
adenokanserler ve
özofagogastrik
bileşke tümörleri

02

D2 diseksiyon
sadece
öneriliyordu.
Standart
uygulanmadı.

03

D2 diseksiyon oranı
az

Avrupa kanser araştırma grubu

- EORTC 40954 ve FLOT

- ECF veya ECX & FLOT

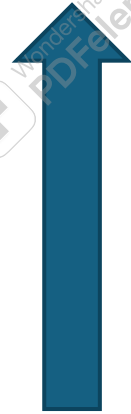
- R0 rezeksiyon

- Sağ kalım

- Hastalıksız sağ kalım

- Mide ve özofagogastrik bileşke tümörları için standart tedavi

→ FLOT



2014, Japonya → COMPASS

4 Kür S-1/sisplatin veya
Paklitaksel/sisplatin
neoadjuvan tedavi →
%10 Patolojik tam
yanıt

ilaç toksisitesi
yaşanmadı

Japonya → JCOG 0405

53 hastanın 5 yıllık sonuçları

2 Kür S-1+Sisplatin neoadjuvan →
D2 gastrektomi + Paraaortik LND

R0 rezeksiyon %82

3 yıllık sağ kalım % 59

5 yıllık sağ kalım % 53

Summary of clinical trials investigating the impact of neoadjuvant chemotherapy for locally advanced gastric cancer.

Author	Studies	Year	Inclusion criteria	Group	Patients	R0 rate (%)	CR rate (%)	OS or median survival time
Ajani et al ⁵⁰		1991	Resectable gastric M0 + EGJ cancer	EFP × 2 + surgery + EFP × 3	25	72	0	15 months
Ajani et al ⁵¹		1993	Resectable gastric M0 cancer	EAP × 3 + surgery + EAP × 2	48	90	0	16 months
Rougier et al ⁵²		1994	Locally advanced gastric cancer M0 + EGJ	FP × 6 + surgery	30	78	0	16 months
Songun et al ¹⁴		1999	T2–4M0	1.FAMTX × 3 + surgery/2.surgery	27/29	75/75	NS	18/30 months
Schuhmacher et al ⁵³		2001	Locally advanced gastric cancer III–IV (M0) + EGJ	EAP + surgery	42	86	0	19 months
D'Ugo et al ⁵⁴		2006	T3–4 Nx M0 or T ≤ 2N + M0	EEP × 3/ ECF × 3 + surgery + EEP × 3/ ECF × 3	34	82	3	>28 months
Cunningham et al ⁴	MAGIC	2006	Resectable gastric + EGJ cancer	1. ECF × 3 + surgery + ECF × 3/2. surgery	250/253	74/68	NS	5 years, 36.3% vs. 23.0%, P = 0.009
Tsuburaya et al ¹⁶	JCOG0405	2007	Bulky N2/3	S-1/CDDP × 2 –3 + surgery + D2 + PAND	53	82.4	NS	5 years, 53%
Ychou et al ⁵	FNLCC and FFGD	2011	Resectable gastric + EGJ cancer	1. FP × 2–3 + surgery + FP × 3–4/ 2. surgery	113/111	84/73	NS	5 years 38% vs. 24%, P = 0.02
Schuhmacher et al ⁶	EORTC	2010	T3–4NxM0	1. PFL × 2/2. surgery	72/72	81.9/66.7	NS	64.62/52.53 months
Kinoshita et al ⁵⁵		2009	T2–3/N+ or T4aN0	S-1 × 2 + surgery	55	80.8	0	NS
Biffi et al ⁵⁶		2010	T3–4 Nx or Tx N1–3 M0 + EGJ	1. TCF × 4 + surgery/2. surgery	34/35	85	11.7/-	NS
Iwasaki et al ⁵⁷	JCOG0210	2013	Resectable gastric cancer	SC × 2 + surgery	36	73.5	NS	17.3 months, 3 years, 24.5%
Yoshikawa et al ¹⁵	COMPASS	2014	T2–3/N+ or T4aN0 + EGJ	1. SC × 2 + surgery/2. SC × 4 + surgery	21/20	NS	NS	NS
Cunningham et al ²⁹	ST03	2017	Resectable gastric + EGJ + esophageal cancer	1. Bevacizumab + ECX + surgery/2. ECX + surgery	530/533	64/61	NS	33.97 vs. 34.46 months, 3 years, 48.9% vs. 47.6%

Author	Studies	Year	Inclusion criteria	Group	Patients	R0 rate (%)	CR rate (%)	OS or median survival time
Katayama et al ⁵⁴	JCOG1002	2013	Bulky N2/3	CDDP/S-1 × 2 -3 + surgery + D2 + PAND	53	84.6	NS	5 years, 55%
Al-Batran et al ⁵⁵	FLOT-AIO	2017	cT2-4/cN-any/cM0 or cT-any/cN+/cM0	1. ECF/ECX + surgery/2. FLOT + surgery	360/356	78/85	NS	35/50 months, <i>P</i> = 0.012
Terashima et al ⁶⁰	JCOG0501	2019	Resectable gastric cancer	1. Surgery + S1/2. SC × 2 + surgery + S-1	149/151	NS	NS	3 years, 62.4% vs.
	PRODIGY	Ongoing	cT2-3/N(+), T4/N(+/-)	DOS + surgery + S-1 vs. surgery + S-1				60.9%, <i>P</i> = 0.916

CR: complete response; OS: overall survival; EGJ: esophagogastric junction; EFP: etoposide, fluorouracil, cisplatin; PFL: cisplatin, fluorouracil, leucovorin; SC: S-1, cisplatin; TCF: Taxol, cisplatin, fluorouracil; EEP: etoposide, epirubicin, cisplatin; EAP: etoposide, adriamycin, cisplatin; FP: fluorouracil and cisplatin; F: fluorouracil; ECX: epirubicin, cisplatin, capecitabine; TC: Taxol, cisplatin; SC: Systemic chemotherapy; FAMTX: fluorouracil-adriamycin-methotrexate; DOS: docetaxel, oxaliplatin, S-1; CDDP: cisplatin; ECF: epirubicin, cisplatin, fluorouracil; PAND: para-aortic nodes dissection; NS: Not Sure.

SONUÇTA NAK

Evreyi düşürdü

R0 rezeksiyon oranlarını
artırdı

5 yıllık sağ kalımı artırdı

Postop komplikasyon,
mortalite, hastanede
kalış süresini etkilemedi.

Özofagogastrik bileşke
tümörleri daha fazla
yararlandı

2- 4 siklus önerilse de

- Patolojik tam yanıt oranı verilen ilaçtan bağımsız olarak 4 siklus olanlarda daha fazla
- 4 siklusda nutrisyonel risk arttı!!

NAK + RT?

INT0116 çalışması

- FU + 45 Gy/5 hafta à % 83 Patolojik tam yanıt

Alman POET

- NAK & NAKRT
- NAKRT 3 yıllık sağ kalım arttı %47 & % 27
- Patolojik tam yanıt %15

2006

2001

2009

Ajani çalışmaları inceledi

- 5-FU + 35-37,5 Gy/4-5 hafta alan lokal ileri mide kanserleri
- Sadece RT ye göre surviyi artırdığını buldu

MD Anderson Cancer Center – RTOG 9904

- NAKRT R0 rezeksiyon ve patolojik tam yanıt yanında tümör evresini de düşürdüğünü kanıtladı
- %77 R0
- %27 Patolojik tam yanıt

NAKRT' de limitasyon?

- Yapılan çalışmalar gastroözofageal bileşke tümörleriyle sınırlı
- Distal mide tümörleri için veriler ?
- Japon ve Çin rehberlerinde yeterli NAKRT çalışması yok
 - Asya ülkelerinde daha çok distal mide tümörleri görülmekte

Summary of clinical trials investigating impact of neoadjuvant chemoradiotherapy for locally advanced gastric cancer.

Author	Studies	Year	Inclusion criteria	Group	Patients	R0 rate (%)	CR rate (%)	OS or median survival time
Shchepotin et al ⁶¹		1994	Resectable gastric cancer	1. Surgery/ 2. 20 Gy EBRT/ 3. 20 Gy EBRT + Hy	98/100/95	NS	NS	5 years, 21% vs. NS vs. NS
Safran et al ⁶²	INT0116	1997	Unresectable gastric cancer	45 Gy EBRT + paclitaxel	27	NS	11	2 years, 35% vs. NS
Lowy et al ¹⁹		2001	T > 2, N±, M0	45 Gy EBRT, 5-FU	24	75	11	NS
Ajani et al ²²		2004	T > 2, N±	5-FU, LV, P + 45 Gy EBRT, 5-FU	33	70	30	34 months
Ajani et al ²⁰		2005	Resectable gastric + EGJ cancer	FP, paclitaxel + 45 Gy EBRT	41	78	20	>36 months
Allal et al ⁶³	POET trial	2005	T3-T4, N+	FP, LV + 31.2–45.6 Gy EBRT	19*	NS	5	NS
Stahl et al ⁷		2009	EGJ	1. PFL × 3 + 30 Gy + cisplatin/surgery/ 2. PFL × 2 + surgery	62/64	72/69	15.6/2	33.1/21.1 months
Van Hagen et al ⁸	CROSS trial	2012	Esophageal cancer + EGJ cancer	1. Paclitaxel + carboplatin + 41.1 Gy + surgery/ 2. surgery	178/188	92/69	NS	49.9/24 months
Cats A et al ²⁵	TOPGEAR	2018	Resectable gastric cancer	ECF + surgery vs. ECF + 45 Gy + surgery	393/395	80/82	6	43/37 months, <i>P</i> = 0.9; 5 years, 42% vs. 40%
	Neo-Aegis	Ongoing	Esophageal cancer + EGJ cancer	ECF × 3 + surgery vs. Paclitaxel + carboplatin + 41.1 Gy	620			
	CRITICS-2	Ongoing	Resectable gastric + EGJ cancer	DOS × 3 weeks (45 Gy in 1.8 Gy + surgery vs. DOS × 3 + surgery	540			
	NEO-CRAG	Ongoing	Resectable gastric + EGJ cancer	RT (45 Gy) + XELOX × 3 + surgery + XELOX × 3 vs. XELOX × 3 + surgery + XELOX	632			
	PREACT	Ongoing	Resectable gastric + EGJ cancer	SOX × 1 + CRT (45 Gy/ S1) + SOX × 1 + surgery + SOX × 3 vs. SOX × 3 + surgery + SOX × 3				

CR: complete response; OS: overall survival; EBRT: external beam radiotherapy; IORT: intraoperative radiation therapy; CRT: Chemoradiotherapy; Hy: hyperthermia; FP: fluorouracil and cisplatin; PFL: cisplatin, fluorouracil, leucovorin; LV: leucovorin; DOS: docetaxel, oxaliplatin, S-1; ECF: epirubicin, cisplatin, fluorouracil; XELOX: capecitabine and oxaliplatin; SOX: S-1 and Oxaliplatin; NS: Not Sure.

Hedefe yönelik neoadjuvan tedaviler?

HER-2 + lokal ileri tümörler

Transtuzumab, Ramucirumab ve apatinib
(anti-vasküler endoteliyal büyüme faktörü 2)

Cetuximab (anti-epidermal büyüme faktör
reseptörü)

miRNAs

2014 - Alman HER-FLOT

- 4 kür , R0 %93, Patolojik tam yanıt %23

2015 – İspanya NEOHX

- Transtuzumab+Xelox, rezektabl mide kanseri veya gastroözofageal bileşke tümörleri objektif yanıt oranı %39, patolojik tam yanıt %8

2017 – ST03

- 1063 hasta → ECX + Bevacizumab & ECX
- Fark yok

JCOG 1301

Summary of clinical trials investigating targeted drugs of neoadjuvant chemotherapy for locally advanced gastric cancer.

Studies	Year	Inclusion criteria	Group	Patients	R0 rate (%)	CR rate (%)	OS or median survival time
HER-FLOT	2014	uT2–4,N+,M0	HER-FLOT	52	NS	23%	NS
NEOHX	2015	T1–2N + M0 or T3–4NxM0	XELOX-T	36	NS	8	NS
STO-0801 ⁶⁴	2017	Locally advanced gastric cancer + EGJ	Panitumumab + ECX 3 vs. ECX 3	83/80	84%/82%	NS	10.3 vs. 9.6, HR = 1.17, $P = 0.43$
ST03 ⁶⁵	2017	Resectable lower esophageal, EGJ, or gastric cancer	ECX 3 vs. bevacizumab + ECX 3	530/533	64/61	NS	33.97 vs. 34.46, HR = 1.067, $P = 0.4784$ 3 years, 48.9% vs. 47.6%
FLOT6	Ongoing	T 2–4 any N, M0 OR any T N + M0	FLOT vs. FLOT + pertuzumab + trastuzumab				
INNOVATION	Ongoing	HER2 + resectable gastric and GEJ cancer	Chemotherapy vs chemotherapy + trastuzumab				
PERIHER	Ongoing	T2N2–3, T3/T4aN+, T4bN any, M0	XELOX vs. XELOX + trastuzumab				
Trigger	Ongoing	Extensive lymph node metastasis	SP vs. SP + trastuzumab				
NCT03229096	Ongoing	T3–4 N any M0	SOX vs. SOX + trastuzumab				
NCT03192735	Ongoing	Locally advanced gastric cancer	Apatinib plus XELOX				
NCT03599778	Ongoing	Locally advanced gastric adenocarcinoma	Apatinib				
NCT03355612	Ongoing	Locally advanced gastric signet ring carcinoma	Apatinib vs. XELOX				
NCT03878472	Ongoing	Resectable gastric cancer	Camrelizumab vs. apatinib vs. S1				

ECX: epirubicin, cisplatin, capecitabine; XELOX: capecitabine and oxaliplatin, FLOT: docetaxel, oxaliplatin, fluorouracil; SP: S-1, cisplatin; SOX: S-1 and Oxaliplatin; NS: not sure.

Güncel problemler ve gelecekte beklenenler

Asya & Avrupa, Amerika’ da tedaviler farklı

- Erken evre, tarama, distal tümörler & özofagogastrik bileşke tümörleri

S-1 güvenli ve efektif tedavi iken batıda kullanımı pek yok

- CYP2A6 gen polimorfizmi

Özofagogastrik bileşke tümörleri neoadjuvan tedaviden daha çok yararlanmakta

Kemosensitif olmayan hastalarda cerrahi gecikebilir

- Kim kemosenstif?
Tahmin edemiyoruz.

Immun checkpoint inhibitors – PD-1/PD-L1 ve CTLA-4 → Progresyon gösteren hastalıkta etkili

2017, İlk immunoterapi ajanı pembrolizumab işe yaramadı ve mide kanseri tedavisinden çekildi

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Teşekkürler