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Management of Localized and Metastatic Gastric Cancer–Current and Emerging Treatments

Current treatment approach for localized and metastatic gastric cancer

Gastric cancer (GC) is the second most common cause of cancer-related deaths worldwide[1]

Geographical variations in its clinical features make it challenging to devise universally applicable treatment approaches[1]

Treatment approach[1,2]

Various therapeutic strategies have demonstrated improvements in the prognosis of GC

However, the locally aggressive nature of GC and low survival rates warrant a multimodal approach, including:

Surgical resection

Systemic chemotherapy

Radiotherapy

Immunotherapy

Targeted treatments

Surgical management approaches[1,2]

Surgical resection is crucial for the curative treatment of GC and its outcomes depend on several variables

- Extent of resection
- Scope of lymphadenectomy
- Tumor location, stage, and histological subtype
- Method of reconstruction
- Potential for a minimally invasive approach

Multiple endoscopic biopsies are needed for a definitive diagnosis

The type and extent of surgical resection depends on the histological subtype and Tumor-Node-Metastasis (TNM) stage of the tumor

Resection of the primary tumor

Endoscopic resection
- Early-stage non-ulcerated tumors
- Moderately differentiated tumors without invasion of the deep submucosa or lymphovascular invasion
- Size < 2 cm

Total or proximal gastrectomy
- Gastroesophageal junction (GEJ) adenocarcinoma
- Preserves gastric function and nutritional status
- May predispose patients to severe chronic reflux

Partial or total gastrectomy
- Diffuse and poorly-differentiated tumors
- Lymph node involvement
- Wide resections to obtain negative margins

Minimally invasive approaches—decreased postoperative morbidity and faster recovery
- Laparoscopic gastrectomy
- Robotic technologies
- Stapled anastomotic techniques

Reconstruction of the gastrointestinal tract can restore physiological function without compromising oncological outcomes
- Billroth I (gastroduodenostomy)
- Billroth II (loop gastrojejunostomy)
- Roux-en-Y gastrojejunostomy

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Management of localized GC[3,4,5]

Several clinical trials have demonstrated the efficacy of chemotherapeutic regimens in patients with locally advanced and resectable GC tumors, compared to surgery alone

- Improved patient survival
- Improved prognosis
- Reduced rate of recurrence

Treatment algorithm for localized gastric cancer[3]

Stage 1A → Endoscopic or surgical resection

Stage 1B – III → Preoperative chemotherapy → Radical gastrectomy → Postoperative chemotherapy

Perioperative chemotherapy	Trial	Experimental arm	Control arm
Epirubicin, cisplatin, and fluorouracil (ECF)	MAGIC	3 × ECF → Surgery → 3 × ECF	Surgery
Cisplatin and fluorouracil (CF)	FNCLCC & FFCD	2-3 × CF → Surgery → 3–4 × CF	Surgery
FLOT regimen - fluorouracil, leucovorin, oxaliplatin, and docetaxel	FLOT4-AIO	4 × FLOT → Surgery → 4 × FLOT	3 × ECF/ECX → Surgery → 3 × ECF/ECX
DOS regimen -Docetaxel, oxaliplatin, and S-1	PRODIGY	3 × DOS → Surgery → 8 × S-1	Surgery → S-1
S-1 plus oxaliplatin (SOX)	RESOLVE	3 × SOX → Surgery → 5 × SOX → 3 × S-1	Surgery → 8 × CAPOX
Adjuvant chemotherapy			
Capecitabine + oxaliplatin (CAPOX)	ACTS-GC	Surgery → S-1 for 1 year	Surgery
S-1 monotherapy	CLASSIC	Surgery → 8 × CAPOX	Surgery
SOX	RESOLVE	Surgery → 8 × SOX	Surgery → 8 × CAPOX
Docetaxel and S-1	JACCRO GC-07	Surgery → 1 × S-1 → 7 × Docetaxel plus S-1 → S-1 for 1 year	Surgery → S-1 for 1 year
Adjuvant chemoradiotherapy phase III INT-0116 trial, phase III ARTIST trial		Insufficient evidence supporting the efficacy of adjuvant radiotherapy in patients with resectable GC	
Novel targeted therapies			
First line – anti-HER2 therapies	HER-FLOT PETRARCA NEOHX	FLOT + trastuzumab	
	INNOVATION	FLOT + trastuzumab + pertuzumab CAPOX + trastuzumab FLOT/CAPOX/FOLFOX (fluorouracil + leucovorin and oxaliplatin)/XP + trastuzumab + pertuzumab	
Second line – anti-vascular endothelia growth factor (VEGF) therapies	ST03	ECX + bevacizumab	
	RAMSES/FLOT7	FLOT + ramucirumab	
Perioperative immunotherapy			
First line programmed death 1 (PD-1) inhibitors	Phase II DANTE trial	Atezolizumab + FLOT	
	Phase III	Nivolumab + CAPOX	
	ATTRACTION-5 KEYNOTE-585 , phase II INFINITY	Pembrolizumab + XP/FP/FLOT	

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Management of advanced unresectable and metastatic GC[3,4,5]

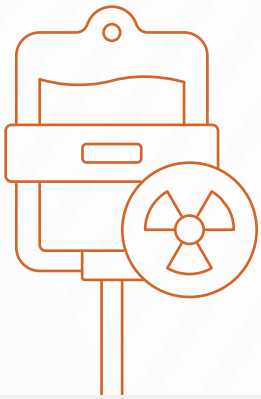
Locally advanced unresectable or metastatic gastric cancer is associated with poor prognosis and low survival rates

Surgical resection is not recommended for metastatic GC unless for palliative relief of symptoms

Treatment considerations[3,4]

- Patient performance status
- Extent of metastatic spread
- Medical comorbidities
- Toxicity profile of the treatment regime
- Treatment goals and palliative care

Treatment algorithm for first-line treatment of advanced/metastatic unresectable gastric cancer[3]



First line therapy - fluoropyrimidine, platinum, taxanes, and irinotecan
• HER2-positive tumors → trastuzumab • Anti-PD-L1 therapies – nivolumab/pembrolizumab

Second line therapy - ramucirumab–paclitaxel, docetaxel, or irinotecan

Third line therapy
• Oral - trifluridine-tipiracil (TAS-102) • Intravenous - taxane and irinotecan

Radical gastrectomy or surgical resection of metastases may be considered in selected cases

Immunotherapy[4,5]

Clinical trials for immunotherapeutic agents in the metastatic GC setting

First line (HER2-negative)	KEYNOTE-062	Pembrolizumab monotherapy/Pembrolizumab + PF or XP
	CheckMate-649	Nivolumab + XELOX/FOLFOX
	ATTRACTION-4	Nivolumab + XELOX/FOLFOX
	ORIENT-16	Nivolumab + SOX/ CAPOX
	RATIONALE-305	Sintilimab + CapeOX Tislelizumab + XELOX/PF
	KEYNOTE-859	Pembrolizumab + CAPOX/PF
	JAVELIN Gastric 100	Avelumab + FOLFOX
First line (HER2-positive)	KEYNOTE-811	Pembrolizumab + trastuzumab + XELOX/PF
Second line	KEYNOTE-061	Pembrolizumab
Third line	ATTRACTION-2	Nivolumab
	JAVELIN Gastric 300	Avelumab

Supportive care and nutrition[3]

Weight loss can be multifactorial in patients with advanced GC
• Obstruction of the gastrointestinal tract • Anorexia • Malabsorption • Dysphagia

Supportive care and nutritional support is crucial to improve the quality of life of patients with GC

Therapeutic options to relieve dysphagia and improve nutrition
• Radiotherapy • Single-dose brachytherapy • Metal stent placement • Pyloric stenting or bypass surgery
• Placement of feeding tube- nasojejunal, nasogastric, or percutaneous

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Importance of multidisciplinary treatment[3,6]

Multidisciplinary tumor board discussions (MDT), combining the expertise of various specialists can help streamline optimal treatment strategies and improve outcomes in patients with GC and GEJ

- Surgeons
- Radiologists
- Gastroenterologists
- Medical oncologists
- Nurse specialists
- Endoscopy specialists
- Pathologists
- Nutritionists
- Nuclear medicine and radiotherapy experts

Major determinants of patients' short-term and long-term outcomes[6]

- Patient factors – age, comorbidities, risk factors, and ethnicity
- Clinical TNM stage, histopathology, and disease biology
- Spatio-temporal intratumor heterogeneity
- MDT discussions and treatment decisions
- Perioperative therapy
- Tumor margins and quality of surgical resection
- Postoperative therapy and support

Treatment challenges[6]

- Limited precision of clinical staging
- Toxicity of standard of care: perioperative/adjuvant chemotherapy
- Molecular and histopathological heterogeneity
- Lack of subtype-specific appropriate treatment strategies
- Poor prognosis following perioperative chemotherapy plus surgery, particularly in metastatic settings

Future directions[4,6]

- Development and validation of biomarkers, including liquid biopsies
- Development of validated surrogate end-points for clinical trials
- Development of evidence-based treatment strategies for special populations, such as elderly patients or patients with comorbidities
- Accounting for geographical variations in the incidence and tumor biology of GC in international trial
- Improvement of surgical quality assurance, and standardization of multidisciplinary perioperative management and supportive care

Key message

A multidisciplinary approach including novel targeted therapies, which accounts for the intratumoral heterogeneity and geographical variations in the biology of GC, can help improve treatment outcomes

References:

1. Joshi, S. S., & Badgwell, B. D. (2021). Current treatment and recent progress in gastric cancer. *CA: A Cancer Journal for Clinicians, 71*(3), 264-279.
2. Ong, C. T., Schwarz, J. L., & Roggin, K. K. (2022). Surgical considerations and outcomes of minimally invasive approaches for gastric cancer resection. *Cancer, 128*(22), 3910-3918.
3. Lordick, F., Carneiro, F., Cascinu, S., Fleitas, T., Haustermans, K., Piessen, G., ... & Smyth, E. C. (2022). Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology, 33*(10), 1005-1020.
4. Guan, W. L., He, Y., & Xu, R. H. (2023). Gastric cancer treatment: recent progress and future perspectives. *Journal of Hematology & Oncology, 16*(1), 1-28.
5. Shah, M. A., Kennedy, E. B., Alarcon-Rozas, A. E., Alcindor, T., Bartley, A. N., Malowany, A. B., ... & Rajdev, L. (2023). Immunotherapy and targeted therapy for advanced gastroesophageal cancer: ASCO guideline. *Journal of Clinical Oncology, 41*(7), 1470-1491.
6. Wagner, A. D., Lordick, F., Grabsch, H. I., Terashima, M., Terada, M., Yoshikawa, T., ... & Moehler, M. H. (2020). Multidisciplinary management of stage II-III gastric and gastro-oesophageal junction cancer. *European Journal of Cancer, 124*, 67-76.

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