PHILIPPINE SOCIETY OF MEDICAL ONCOLOGY (PSMO)
CONSENSUS RECOMMENDATIONS IN THE MANAGEMENT OF GASTRIC CANCER DURING COVID-19 PANDEMIC IN THE CORONAVIRUS DISEASE 2019 (COVID-19) ERA

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I. Background and Rationale

- COVID-19 is a global public health emergency and the Philippines is not spared from it. Our country currently has over 24,000 confirmed cases and still with an increasing trend in new infections.[1] Most people infected with it will only manifest with mild symptoms. However, those with an underlying medical condition, such as cancer, are at risk to develop serious illness.[2] Since our patients belong to a high risk population, the benefit/risk ratio of the aspects of our medical care should be reconsidered.

II. Objective

- These recommendations aim to offer local guidance in the management of gastric cancer patients in the COVID era.

III. Target Users

- These recommendations are meant for the use of medical oncologists practicing in the Philippines.

IV. Related Guidelines

- The ESMO guidelines on gastric cancer was used as a reference in drafting the recommendation. It was adapted to suit the local setting.

Key Clinical Issues

V. General Recommendations

- Prioritization

  Q: How do we prioritize patients presenting with gastric mass/gastric cancer during the COVID-19 pandemic?

  A: The tiered approach of ESMO during the COVID-19 pandemic is designed across three levels of priorities, namely: tier 1 (high priority intervention), tier 2 (medium priority) and tier 3 (low priority) and is defined as follows:

  - High Priority: Patient's condition is immediately life-threatening, clinically unstable, and/or the magnitude of benefit qualifies the intervention as high priority (e.g. significant overall survival [OS] gain and/or substantial improvement in quality of life [QoL]);
  - Medium Priority: Patient's condition is non-critical but delay beyond 6 weeks could potentially impact overall outcome and/or the magnitude of benefit qualifies for intermediate priority;
  - Low Priority: Patient's condition is stable enough that services can be delayed for the duration of the COVID-19 pandemic and/or the intervention is non-priority based on the magnitude

of benefit (e.g. no survival gain with no changed nor reduced QoL).[3]

- COVID-19 Screening
  Q: Among patients with gastric cancer, what is the recommendation for screening for COVID-19?

  A: In a resource-limited setting, RT-PCR SARS-Cov-2 testing is proposed to all patients with suggestive symptoms of COVID-19 infection.[3]

- Outpatient Visits
  Q: Among patients with gastric cancer, who are the patients we prioritize for out patient visits?

  A: Patients who are potentially unstable (with severe dysphagia, bleeding or weight loss), those who are newly diagnosed, those undergoing perioperative chemotherapy and chemoradiotherapy and patients with metastatic disease who are currently in active treatment are considered high priority. Medium priority patients, on the other hand, are either post-operative or post-definitive chemoradiotherapy who have no complications and those receiving oral therapies that are well-tolerated. Surveillance in patients with low-to-moderate risk of relapse and survivorship visits are deemed low priority.[4]
- Telemedicine
  Q: Among gastric cancer patients, who are the ones that can be offered telemedicine?

  A: The following patients may be offered telemedicine consults: Established patients with no new complaints, patients on surveillance, and those who need psychosocial support without an acute medical need.[4]

VI. Specific Recommendations

- **Diagnosis and Staging**
  Q: Among patients with signs and symptoms of gastric cancer, who should we prioritize for endoscopic procedure?

  A: The following patients are high priority: Those with cT1N0, consider endoscopic resection according to guidelines, those with high suspicion for gastric cancer diagnosis and unstable (bleeding, severe dysphagia, weight loss, symptomatic anemia and other upper GI-related symptoms), and patients susceptible to clear benefit from a stent or endoscopic gastrostomy for feeding tube. Medium priority is recommended for EUS for staging.[4]

  Q: Among patients with gastric mass/gastric cancer, what is the minimum metastatic workup that should be performed?

A: A CT scan of the chest and whole abdomen with contrast for initial staging has an overall accuracy of 72%-82% in determining the TNM status in gastric cancer. It should be done especially in high priority in patients who are symptomatic, when used for initial staging, for preop evaluation and re-evaluation after pre-op treatment, and for evaluation of patients under active treatment or patients on follow-up with clinical suspicion of progression.[5]

Q: What is the role of endoscopic ultrasound in initial staging of gastric cancer patients?

A: In centers with capability to perform such, it is recommended as medium priority for staging.2 It has a sensitivity of 85% and specificity of 90% in distinguishing T1-T2 vs T3-T4 gastric tumors.[6]

Q: What is the role of staging laparoscopy in gastric cancer?

A: It is a medium priority in this COVID era2 and should be considered if performing so will alter management.[7]

Q: What are the minimum biomarker tests that can be done in advanced gastric cancer patients?

A: Minimum biomarker testing for MSI and Her2, if feasible, can be done based on the availability of immunotherapy directed towards these molecules. [29]

- **Locoregional Gastric Cancer**
  a. Surgery

  Q: Among patients with resectable gastric cancer, who are at high priority to undergo gastric resection?

  A: It is highly recommended and encouraged that all patients be presented in a multidisciplinary meeting for treatment planning[8]. During the COVID-19 pandemic, the following patients are considered high priority for surgery: patients with ongoing perioperative chemotherapy, obstructing or perforating gastric cancers, and with active bleeding. [4]

  The following table may aid in risk-stratification and decision-making for the surgical management of gastric cancer patients.

Table 1. Modified Guide on Triage of Non-Emergent Procedure [10]

Tier 1a	Tier 1b	Tier 2a	Tier 2b	Tier 3a	Tier 3b
Low acuity surgery/healthy patient *Outpatient surgery* *Not life-threatening illness*	**Low acuity surgery/unhealthy patient**	**Intermediate acuity surgery/healthy patient** *Not life threatening but potential for future morbidity and mortality.* *Requires in hospital stay*	**Intermediate acuity surgery/unhealthy patient**	**High acuity surgery/healthy patient**	**High acuity surgery/unhealthy patient**

- **Tier 3a or 3b (ESAS):** All patients in this Tier should undergo appropriate procedures to remedy their urgent or emergent condition.
- **Tier 2a or 2b (ESAS):** The majority of cancer patients will fall in Tier 2. The guiding principle here is that these patients will require multidisciplinary input (done virtually as needed), and also that the surgeon carefully assess all variables listed above. Patients falling in the high-risk category, i.e. personal high-risk features or high-risk due to environment and resource issues (as outlined by the considerations above), should preferentially be offered non-operative alternative measures in-lieu of surgery. If surgery cannot be avoided, measures to reduce inpatient LOS are recommended.
- **Tier 1a or 1b (ESAS):** All patients in this Tier are considered elective and should be delayed until pandemic is stabilized, resources are rebalanced, and risk is returning to baseline levels.

Q: Is there a preferred surgical approach?

A: Open or laparoscopic / minimally invasive surgical approaches are appropriate. The benefits of laparoscopic / minimally invasive approach with reduced hospital stay should be considered in the surgical planning during this pandemic. The likelihood need for postoperative ICU stay should also be considered. [10]

b. Perioperative Chemotherapy

Q: Among patients with resectable gastric, who should undergo perioperative chemotherapy?

A: Perioperative chemotherapy for patients with Stage II or higher gastric cancer without evidence of distant metastasis has been shown to improve survival [11,12].

During the COVID-19 era, it is recommended that all patients with Stage II or higher gastric carcinoma without evidence of distant metastasis, good performance status, and with stable medical conditions should be considered for perioperative chemotherapy.[10] Treatment

should be individualized depending on the patient's condition and capacity to manage toxicities.

Q: Among patients who are candidates for perioperative chemotherapy, what choice of regimens should be given to the patients?

A: Chemotherapy regimen options should be tailored to each patient. The choice for chemotherapy regimens will be considered in the light of its toxicity profile and the clinical condition of the patients. In general, triplet regimens have a higher risk of adverse events than doublet regimens. [11,12,13]

c. Adjuvant Chemotherapy / Chemoradiotherapy

Q: Which patients are at high priority to undergo adjuvant chemotherapy or chemoradiation?

A: Continuation of ongoing treatment in patients are considered high priority. Consider clinical benefit for patients commencing treatment. [1]

- **Advanced and metastatic gastric cancer**

a. Systemic therapy

Q: Who are considered high priority among patients receiving systemic therapy for advanced or metastatic gastric cancer?

A: Patients receiving first line chemotherapy and patients receiving maintenance therapy who continue to show benefit to treatment are considered high priority while second line treatment and beyond are considered medium priority **[15]**.

Q: Among patients with advanced or metastatic gastric cancer, what are the recommended treatment options?

A: Patients with inoperable locally advanced or stage IV disease should be considered for systemic treatment, which has shown improved survival and quality of life **[16-18]**. Patient factors (co-morbidities, organ function and performance status) must be considered **II, B**.

Doublet chemotherapy combinations are preferred over triplet combination due to a lower toxicity profile **[19-23]**. Consider giving dose reductions to select patients (i.e. elderly, frail) to reduce risk of toxicities **[25-29]**.

REFERENCES

1. Department of Health, Philippines. Updates on COVID-19. https://covid19.healthypilipinas.ph/updates-covid. Publication Date June 12, 2020. Accessed June 13, 2020.
2. World Health Organization. Overview on coronavirus. https://www.who.int/health-topics/coronavirus#tab=tab_1. Accessed June 13, 2020.
3. European Society of Medical Oncology. Cancer Patient Management During the COVID-19 Pandemic. Cancer patient prioritization. https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic
4. European Society of Medical Oncology. https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/gastrointestinal-cancers-gastro-oesophageal-tumours-in-the-covid-19-era
5. Seevaratnam R, Cardoso R, et al. How useful is preop imaging for TNM Staging of Gastric Cancer? *The International Gastric Cancer Association and The Japanese Gastric Cancer Association 2011;* S3-S18.doi:10.1007/s10120-011-0069-6.
6. Mocellin, S., & Pasquali, S. (2015). Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer. *The Cochrane database of systematic reviews*, *2015*(2), CD009944. https://doi.org/10.1002/14651858.CD009944.pub2
7. Pierre-Anthony L, Cardoso R, et al. : A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer. ? *The International Gastric Cancer Association and The Japanese Gastric Cancer Association 2012;* S38-S47.DOI:10.1007/s10120-011-0047-z.
8. Basta, Y. L., Bolle, S., Fockens, P., & Tytgat, K. (2017). The Value of Multidisciplinary Team Meetings for Patients with Gastrointestinal Malignancies: A Systematic Review. Annals of surgical oncology, 24(9), 2669–2678. https://doi.org/10.1245/s10434-017-5833-3
9. Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Recommendations Regarding Surgical Management of Gastric Cancer Patients During The Response to the COVID-19 Crisis
10. Ychou M, Boige V, Pignon JP, et al. (2011). Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29(13):1715-1721. doi:10.1200/JCO.2010.33.0597
11. Cunningham D, Allum WH, Stenning SP, et al. (2006). Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med.355(1):11-20. doi:10.1056/NEJMoa055531
12. Mary F, Zaanan A, Boige V, et al. Perioperative chemotherapy with FOLFOX in resectable gastroesophageal adenocarcinoma in real life practice: An AGEO multicenter retrospective study. Dig Liver Dis. 2016;48(12):1498-1502. doi:10.1016/j.dld.2016.07.022
13. Al-Batran, S. E., Homann, N., Pauligk, C., Goetze, T. O., Meiler, J., Kasper, S., Kopp, H. G., Mayer, F., Haag, G. M., Luley, K., Lindig, U., Schmiegel, W., Pohl,

M., Stoehlmacher, J., Folprecht, G., Probst, S., Prasnikar, N., Fischbach, W., Mahlberg, R., Trojan, J., … FLOT4-AIO Investigators (2019). Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet (London, England)*, *393*(10184), 1948–1957. https://doi.org/10.1016/S0140-6736(18)32557-1

14. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†E. C. Smyth1, M. Verheij2, W. Allum3, D. Cunningham4, A. Cervantes5 & D. Arnold6 on behalf of the ESMO Guidelines Committee* Annals of Oncology 27 (Supplement 5): v38–v49, 2016 doi:10.1093/annonc/mdw350
15. Wagner AD, Unverzagt S, Grothe W et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2010; 3: CD004064.
16. Glimelius B, Ekström K, Hoffman K et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol 1997; 8: 163–168.
17. Bouché 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. J Clin Oncol 2004; 22: 4319–4328.
18. Okines AF, Norman AR, McCloud P et al. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Ann Oncol 2009; 20: 1529–1534.
19. Dank M, Zaluski J, Barone C et al. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol 2008; 19: 1450–1457.
20. Van Cutsem E, Moiseyenko VM, Tjulandin S et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006; 24: 4991–4997.
21. 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. J Clin Oncol 2015; 33: 3874–3879.
22. Van Cutsem E, Boni C, Tabernero J et al. Docetaxel plus oxaliplatin with or without fluorouracil or capecitabine in metastatic or locally recurrent gastric cancer: a randomized phase II study. Ann Oncol 2015; 26: 149–156.
23. 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 (Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) Study. J Clin Oncol 2014; 32: 3520–3526.

24. Xiang XJ, Zhang L, Qiu F et al. A phase II study of capecitabine plus oxaliplatin as f irst-line chemotherapy in elderly patients with advanced gastric cancer. Chemotherapy 2012; 58: 1–7. 67. Lee JL, Kang YK, Kang HJ et al. A randomised multicentre phase II trial of capecitabine vs S-1 as first-line treatment in elderly patients with metastatic or recurrent unresectable gastric cancer. Br J Cancer 2008; 99: 584–590.
25. 26. Catalano V, Bisonni R, Graziano F et al. A phase II study of modified FOLFOX as f irst-line chemotherapy for metastatic gastric cancer in elderly patients with associated diseases. Gastric Cancer 2013; 16: 411–419.
26. Rivera F, Massutí B, Salcedo M et al. Phase II trial of miniDOX (reduced dose docetaxel-oxaliplatin-capecitabine) in 'suboptimal' patients with advanced gastric cancer (AGC). TTD 08-02. Cancer Chemother Pharmacol 2015; 75: 319–324.
27. Trumper M, Ross PJ, Cunningham D et al. Efficacy and tolerability of chemotherapy in elderly patients with advanced oesophago-gastric cancer: a pooled analysis of three clinical trials. Eur J Cancer 2006; 42: 827–834.
28. Al-Batran SE, Pauligk C, Homann N et al. The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: a randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65 +). Eur J Cancer 2013; 49: 835–842.
29. Bartley AN, Washington MK, Ventura CB, et al. HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline From the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology. *Am J Clin Pathol*. 2016;146(6):647-669. doi:10.1093/ajcp/aqw206

APPENDIX A

STUDY TITLE: How useful is preoperative imaging for TNM Staging of Gastric Cancer?
DATE PUBLISHED: 2012

P	N = 40 articles involving 7,758 patients
I	Investigation of preop TNM staging performance of abdominal ultrasound, CT scan, MRI and PET in newly diagnosed patients with histopathology- confirmed gastric cancer.
C	Preoperative TNM staging by imaging was compared with postoperative pathological staging.
O	• T staging - MRI had the best overall performance with overall accuracy of 83% and stage-specific accuracy of 77%-87% • N staging – accuracy was not significantly different between modalities. PET had the worst sensitivity and highest specificity • M staging – did not differ significantly by modality
M	Meta-analysis of prospective and retrospective cohorts.

Level of Recommendation: Category IIA
CITATION: Seevaratnam R, Cardoso R, et al. How useful is preop imaging for TNM Staging of Gastric Cancer? *The International Gastric Cancer Association and The Japanese Gastric Cancer Association 2011;* S3-S18.doi:10.1007/s10120-011-0069-6.

APPENDIX B

STUDY TITLE: Diagnostic Accuracy of EUS for the preoperative locoregional staging of primary gastric cancer.
DATE PUBLISHED: 2015

P	N = 66 articles involving 7747 patients
I	A minimum sample size of 10 patients with histologically proven primary carcinoma of the stomach. Use of endoscopic ultrasound for T and N staging in initial work up.
C	Pathologic evaluation of samples in terms of primary tumor (T stage) and regional lymph nodes (N stage)

O	• In discriminating T1-T2 vs T3-T4 gastric carcinoma:
	  • Sensitivity 0.86 (95% CI 0.81-0.90)
	  • Specificity 0.90 (95% CI 0.87-0.93)
	• T1 vs T2
	  • Sensitivity 0.85 (95% CI 0.78-0.91)
	  • Specificity 0.90 (95% CI 0.85-0.93)
	• T1a vs T1b
	  • Sensitivity 0.87 (95% CI 0.81-0.92)
	  • Specificity 0.75 (95% CI 0.62-0.84)
	• N stage
	  • Sensitivity 0.83 (95% CI 0.79-0.87)
	  • Specificity 0.67 (95% CI 0.61-0.72)

M	Meta-analysis

Level of Recommendation: Category IIA

CITATION: Mocellin, S., & Pasquali, S. (2015). Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer. *The Cochrane database of systematic reviews*, *2015*(2), CD009944. https://doi.org/10.1002/14651858.CD009944.pub2

APPENDIX C

STUDY TITLE: A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer.
DATE PUBLISHED: 2012

P	N = 21 articles
I	• Studies that provided data on the role of diagnostic laparoscopy in changing management or avoiding laparotomy • Minimum of 30 patients with confirmed biopsy of gastric adenocarcinoma
C	The correlation of laparoscopy with final histopathology with respect to tumor size, N and M.
O	• ACCURACY T staging – moderate to substantial agreement of laparoscopy and surgery N staging - fair agreement of laparoscopy and surgery M staging – accuracy 93.4%-100% • Sensitivity 73.7%-100% • Specificity 83%-100% • Change in management – 8.5-59.6% cases • Avoided laparotomy – 8.5-43.8% cases
M	Systematic review of retrospective and prospective cohort

Level of Recommendation: Category IIA
CITATION: Pierre-Anthony L, Cardoso R, et al. : A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer.? *The International Gastric Cancer Association and The Japanese Gastric Cancer Association 2012;* S38-S47.DOI:10.1007/s10120-011-0047-z.

APPENDIX D

STUDY TITLE: Perioperative Chemotherapy vs. Surgery Alone for Resectable

P	Patients with resectable gastric cancer
	Perioperative Chemotherapy with EF (3 cycles preop/3 cycles postop)
C	Observation
O	Median follow-up: 49 months vs. 47 months PFS: HR 0.66 p< 0.001 5 year OS: 36.3% vs. 23% (HR 0.74, p=0.008)
M	Randomized Controlled Trial

Gastroesophageal Carcinoma (MAGIC)
DATE PUBLISHED: 2006
Level of Recommendation: Category IA

CITATION: Cunningham D, Allum WH, Stenning SP, et al. (2006). Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med.355(1):11-20. doi:10.1056/NEJMoa055531

APPENDIX E

STUDY TITLE: Perioperative Chemotherapy Compared with Surgery Alone for Resectable Gastroesophageal Cancer Adenocarcinoma: FNCLCC/FFCD Multicenter P III Trial/ ACCORD 07I

P	Patients with resectable gastric cancer
	Perioperative Chemotherapy with Cis-5FU 2-3 cycles preop/3-4 cycles postop
C	Observation
O	Median follow up: 5.7 years 5year OS: 38% vs. 24% (HR 0.69, p=0.02) 5 year DFS: 34% vs. 19% (HR 0.65, p=0.03)
M	Randomized Controlled Trial

Level of Recommendation: Category IA

CITATION: Ychou M, Boige V, Pignon JP, et al. (2011). Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29(13):1715-1721. doi:10.1200/JCO.2010.33.0597

APPENDIX F

STUDY TITLE: Perioperative Chemotherapy with FOLFOX in resectable GE Adenocarcinoma (AGEO Multicenter Retrospective

P	Patients with resectable gastric cancer
I	Preoperative Chemotherapy with FOLFOX
C	None
O	Median RFS: 41.5 months 3 year RFS: 54% Median OS: 41.9 months 3 year OS: 58.2%
M	Feasibility Study

Level of Recommenation: Category IVA

CITATION: Mary F, Zaanan A, Boige V, et al. Perioperative chemotherapy with FOLFOX in resectable gastroesophageal adenocarcinoma in real life practice: An AGEO multicenter retrospective study. Dig Liver Dis. 2016;48(12):1498-1502. doi:10.1016/j.dld.2016.07.022

APPENDIX G

Study Title: Perioperative Chemotherapy With Fluorouracil Plus Leucovorin, Oxaliplatin, and Docetaxel Versus Fluorouracil or Capecitabine Plus Cisplatin and Epirubicin for Locally Advanced, Resectable Gastric or Gastro-Oesophageal Junction Adenocarcinoma (FLOT4): A Randomised Trial

P	Patients with resectable gastric cancer
I	Perioperative Chemotherapy with FLOT 4 cyles preop and 4 cycles postop
C	Perioperative Chemotherapy with ECF 3 cycles preop and 3 cycles postop
O	Median Follow-up: 43 months DFS: 30 vs. 18 months (HR 0.75 p=0.0036) OS: 50 months vs. 35 months (HR 0.76 p= 0.0093)
M	Randomized Controlled Trial

Level of Recommenation: Category IA

CITATION: Al-Batran, S. E., Homann, N., Pauligk, C., Goetze, T. O., Meiler, J., Kasper, S., Kopp, H. G., Mayer, F., Haag, G. M., Luley, K., Lindig, U., Schmiegel, W., Pohl, M., Stoehlmacher, J., Folprecht, G., Probst, S., Prasnikar, N., Fischbach, W., Mahlberg, R., Trojan, J., … FLOT4-AIO Investigators (2019). Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet (London, England)*, *393*(10184), 1948–1957. https://doi.org/10.1016/S0140-6736(18)32557-1

APPENDIX H

STUDY TITLE: 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

DATE PUBLISH:November 2006 to June 2010

P	P: N=85 evaluable patients were enrolled. (male, n=61; female, n=24; median age, 58 years; Karnofsky performance status 90%, (GEJ, n=28; gastric n=57).
I	I:mDCF (fluorouracil 2,000 mg/m2 intravenously [IV] over 48 hours, docetaxel 40 mg/m2 IV on day 1, cisplatin 40 mg/m2 IV on day 3, every 2 weeks)
C	C: DCF (docetaxel 75 mg/m , cisplatin 75 mg/m , and fluorouracil 750 mg/m IV over 5 days with granulocyte colony-stimulating factor, every 3 weeks).
O	O: Six-month PFS: mDCF:63% (95% CI, 48% to 75%) DCF: 53% (95% CI, 34% to 69%) Median overall survival: improved for mDCF (18.8 v 12.6 months; P =.007).
M	M: Randomized Multicenter Phase II study

CONCLUSION: mDCF is less toxic than parent DCF, even when supported with growth factors, and is associated with improved efficacy. mDCF should be considered a standard first-line option for patients with metastatic gastric or GEJ adenocarcinoma.
Level of Recommendation: Category IIA
CITATION:Manish A. Shah, Yelena Y. Janjigian, Ronald Stoller, Stephen Shibata,† Margaret Kemeny,Smitha Krishnamurthi, Yungpo Bernard Su, Allyson Ocean, Marinela Capanu, Bhoomi Mehrotra, Paul Ritch, Charles Henderson, and David P. Kelsen.

APPENDIX I

STUDY TITLE: A modified DCF regimen as primary treatment for patients with metastatic gastric cancer
DATE PUBLISH: 2011

P	P: N= 89 (median age 59 years(31-79)MGC KPS >80, normal renal, liver & cardiac function.
I	I: mDCF included folinic acid 400 mg/m2 (day 1) + 5-fluorouracil (5-FU) 400 mg/m2 i.v. bolus (day 1) + 5-FU 2400 mg/m2 46-h infusion (days 1 and 2) + docetaxel 60 mg/m2 (day 1) + cisplatin 50 mg/m2 (day 1) and was administered once every two weeks in MGC patient
C	C: N/A
O	O: Median number of course: 6. Median follow-up: 8.6 mos Median PFS rate: 7 months (95% CI 5.7-8.2). Median OS rate: 11 months (95% CI 9.7-12.2). ORR: 67.4 % CR :3 (3.3%), PR : 21 (23.6%), SD: 36 (40.4%)
M	M: Retrospective Study to assess the efficacy and toxicity of mDCF

CONCLUSION: mDCF with reduced doses, given every two weeks, is rather efficient regimen for MGC patients.
Level of Recommendation: Category IIA
CITATION: D. Koca1, E. Dogan1, H. Yardim2, O. Duzen2, S. Karaca3. 1Department of Internal Diseases, Division of Medical Oncology, 2Department of Internal Diseases, 3Department of Radiology, Van Yuzuncu Yil University, Regional Training and Research Hospital, Van, Turkey.

APPENDIX J

STUDY TITLE: Phase III Study of Docetaxel and Cisplatin Plus Fluorouracil Compared With Cisplatin and Fluorouracil As First-Line Therapy for Advanced Gastric Cancer: A Report of the V325 Study Group
DATE PUBLISH: Nov. 1999 to Jan. 2003

P	N= 445 (DCF : 221; CF: 224), Advanced gastric cancer patients
I	Docetaxel 75 mg/m2 and cisplatin 75 mg/m2 (day 1) plus fluorouracil 750 mg/m2/d (days 1 to 5) every 3 weeks
C	Cisplatin 100 mg/m2 (day 1) plus fluorouracil 1,000 mg/m2/d (days 1 to 5) every 4 weeks
O	TTP was longer with DCF versus CF (32% risk reduction; log-rank P=.001).

	OS was longer with DCF versus CF (23% risk reduction; log-rank P=.02). Two-year survival rate was 18% with DCF and 9% with CF. Overall response rate was higher with DCF (P=.01).
M	Randomized, multinational phase II/III trial (V325)

CONCLUSION: Adding docetaxel to CF significantly improved TTP, survival, and response rate in gastric cancer patients, but resulted in some increase in toxicity. Incorporation of docetaxel, as in DCF or with other active drug(s), is a new therapy option for patients with untreated advanced gastric cancer.
Level of Recommendation: Category IIA
CITATION: Eric Van Cutsem, Vladimir M. Moiseyenko, Sergei Tjulandin, Alejandro Majlis, Manuel Constenla, Corrado Boni, Adriano Rodrigues, Miguel Fodor, Yee Chao, Edouard Voznyi, Marie-Laure Risse, and Jaffer A. Ajani.

APPENDIX K

STUDY TITLE: Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer.
DATE PUBLISH: June 2000 to May 2005

P	N=1002,18 years or older, adenocarcinoma, squamous-cell carcinoma, or undifferentiated carcinoma of EGJ,or locally advanced/metastatic gastric ca, measurable disease, ECOG performance status of 0 to 2 and adequate renal, hepatic, and hematologic function.
I	ECX,EOF, EOX
C	ECF
O	Median OS: ECF: 9.9 mos, ECX:9.9 mos, EOF: 9.3 mos,and EOX: 11.2 mos Survival rates at 1 year were 37.7%, 40.8%, 40.4%, and 46.8%, respectively. Secondary analysis: OS: longer EOX than ECF ,HR 0.80 EOX group (95% CI, 0.66 to 0.97; P = 0.02). PFS & RR: did not differ significantly among the regimens.
M	Randomized, Phase 3 study of triplet cytotoxic therapy, two-by-two design.

CONCLUSION: Capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin, respectively, in patients with previously untreated esophagogastric cancer.
CITATION: David Cunngham et al

APPENDIX L

STUDY TITLE: Her2 Testing and clinical Decision making Gastroesophageal carcinoma: Guide for CAP, ASCP and ASCO
DATE PUBLISHED: 2017

P	This review included the studies with the following: • Human studies • Invasive GEA • Pubished in English

	• Compared prospectively or retrospectively laboratory testing methodologies or potential testing algorithm for Her2 testing • The study included measurable data • The study addressed one of the key questions
O	Recommendations for clinicians are the following: • In patients with advanced GEA who are potential candidates for Her2-targeted therapy, the treating physician should request for Her2 testing on the tumor tissue. • Treating physicians should request Her2 testing on tumor tissue in the biopsy or resection specimens preferably before the initiation of trastuzumab therapy. • Treating clinician should offer combination chemotherapy and anti-Her2n therapy as the initial treatment for appropriate patients with Her2 positive tumors who have advanced GEA.
M	Systematic Review

Level of Recommendation: Category IIA

CITATION: Bartley AN, Washington MK, Ventura CB, et al. HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline From the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology. *Am J Clin Pathol*. 2016;146(6):647-669. doi:10.1093/ajcp/aqw206

APPENDIX M

Level of Evidence		Grades of Recommendation	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well- conducted randomised trials without heterogeneity	A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity	B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
III	Prospective cohort studies	C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
IV	Retrospective cohort studies or case-control studies	D	Moderate evidence against efficacy or for adverse outcome, generally not recommended

V	Studies without control group, case reports, expert opinions	E	Strong evidence against efficacy or for adverse outcome, never recommended

Source: Infectious Diseases Society of America- US Public Health Service Grading System