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# LOCALLY ADVANCED GASTRIC CANCER

**Dr. Sebastian Stintzing**

Charité Universitätsmedizin Berlin  
Germany

**Dr. Samuel Klempner**

Harvard Medical School, USA

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# STAGING IS CRITICAL TO GUIDE THERAPY



- ASCO and ESMO endorse multidisciplinary discussion for new locally advanced gastric cancer
- Key modalities include EGD/EUS, computed tomography to include chest, abdomen, and pelvis
- Consideration for baseline PET imaging where available

# STAGING LAPAROSCOPY IS UNDERUTILISED IN GASTRIC CANCER

- Gastric cancers have a predilection toward peritoneal spread, particularly diffuse type gastric cancers
- The sensitivity of EUS is decreased in diffuse type disease and earlier T-stage cancers<sup>1</sup>
- CT and PET-CT have significant false negative rates for identifying peritoneal involvement<sup>2</sup>
- Up to 17-30% of patients with clinical T2 or greater gastric cancer and negative CT imaging will have occult peritoneal involvement at diagnosis<sup>1-2</sup>

# LOCALLY ADVANCED GASTRIC CANCER APPROACHES IN EUROPE AND THE UNITED STATES

- **Surgery alone** – no longer considered adequate in Europe and the United States for locally advanced gastric cancer despite being considered the only curative approach
- **Neo-adjuvant therapy:** aim to reduce the tumoral extension and the biological potential of tumor cells.
- **Perioperative therapy:** Administration of chemotherapy before surgery and post-operative chemotherapy with interval surgery. Used approach in Europe
- **Adjuvant therapy:** Adjuvant chemotherapy after radical surgery. Standard approach in most of the world

# PERIOPERATIVE TRIALS IN GASTRIC/ESOPHAGEAL CANCER

Trial	Region	Type of Surgery	Treatment Arms	Study Pop Notes	Pathologic Complete Response	OS and DFS
<b>MAGIC</b> (Cunningham D. et al., NEJM 2006)	United Kingdom	Curative Intent	Periop: ECF → Surgery → ECF (n=250) vs. Surgery alone (n=253)	74% stomach, 11% GEJ, 15% lower esophagus  ~40% D2	Periop = 1% Surgery alone = 0%	OS (p = 0.009, HR 0.75) 5yr survival rate: Periop = 36.3% Surgery alone = 23.0%
<b>FNCLCC/FFCD</b> (Ychou M, et al. JCO 2011)	France	Curative Intent, D2 recommended	Periop: Cisplatin/5FU → Surgery → Csiplatin/5FU (n=113) vs. Surgery alone (n=111)	25% stomach, 64% GEJ, 11% lower esophagus  R0 = 87% periop vs 74% surgery alone	Periop = 3% Surgery alone = 0%	5yr OS (p = 0.02, HR 0.69) Periop = 38% Surgery alone = 24% 5yr DFS (p = 0.003, HR 0.65) Periop = 34% Surgery alone = 19%
<b>OE05</b> (Alderson D, et al. Lancet Oncol 2017)	United Kingdom	Two-phase esophagectomy	ECX: ECX → Surgery → ECX (n=446) vs. CF: CF → Surgery → CF (n=451)	Esophageal/GEJ only 58% siewert 1, 22% Siewert 2, 17% mid-esophageal and 3% missing  R0 = 59% CF vs 66% ECX, R1 = 36% CF vs 31% ECX	ECX = 7% CF = 1%	mOS (p = 0.19, HR 0.9) ECX = 26.1 months CF = 23.4 months mDFS (p = 0.051, HR = 0.86) ECX = 14.4 months CF = 11.6 months
<b>FLOT4</b> (Al Batran SE, et al. Lancet 2019)	Germany	D2	Periop ECF/ECX (n=360) vs. Periop FLOT (n=356)	44% stomach, 24% Siewert 1, 33% Siewert 2-3,  R0 = 78% ECF/ECX vs 85% FLOT	FLOT = 16% ECF/ECX = 6%	mOS (p = 0.012, HR 0.77) ECF/ECX = 35 months FLOT = 50 months mDFS (p = 0.0036, HR 0.75) ECF/ECX = 18 months FLOT = 30 months

# ADJUVANT TRIALS IN GASTRIC CANCER

Trial	Region	Type of Surgery	Key I/E	Adjuvant Treatments	Study Pop Notes	3 and/or 5yr DFS/RFS <sup>ED</sup>
<b>INT-0116</b> (Macdonald JS, et al. NEJM 2001)	US	10% = D2 36% = D1 54% < D1	Only R0	CRT (n = 281) vs. Surgery only (n = 275)	20% proximal 16% N0	3yr RFS CRT = 48% Surgery only = 31% (HR 1.52, p<0.001)
<b>ARTIST</b> (Lee J, et al. JCO 2012)	Asia (Korea)	D2	Only R0	XP (n = 228) vs. XP→XRT→XP (n = 230)	11.1% N0 Almost no proximal tumors 60% DGC	3yr DFS (p = 0.0862) XP = 74.2% XP/CRT/XP = 78.2%
<b>CLASSIC</b> (Bang YJ, et al. Lancet 2012)	Asia (Korea, China, Taiwan)	D2	Only R0	CAPOX (n = 520) vs. Surgery alone (n = 515)	10% N0 1% T4 Almost no proximal tumors	3yr DFS CAPOX = 74% Surgery alone = 59% (HR 0.56, p<0.0001)
<b>ACTS</b> (Sakuramoto S, et al. NEJM 2007)	Asia (Japan)	D2	Only R0	S-1 (n = 529) vs. Surgery alone (n = 530)	Only ~2% T4 No N3 pts, 10% N0 Almost no proximal tumors	3yr RFS S-1 = 72.2% Surgery alone = 59.6% (HR 0.62, p< 0.001)
<b>CALBG 80101</b> (Fuchs CS, et al. JCO 2017)	US	En-bloc resection, not specified	Only R0	5FU/LV + Radiation (n = 280) vs. ECF + Radiation (n = 266)	24% GEJ, 15% N0, ~40% distal gastric, 4% T4	5yr DFS 5FU/LV + RT = 39% ECF + RT = 37% (HR 0.96, p = 0.94)
<b>ARTIST 2</b> (Park SH, et al. ASCO 2019, Abstract 4001)	Asia (Korea)	D2	LN+ (stage II-III)  +final margin excluded	S-1 (n = 180) vs. SOX (n = 180) vs. SOX/RT: SOX → S-1/RT → SOX (n = 178)	~35% pT4 Median 5+ LN	3yr DFS S-1 = 65% SOX = 78% SOX/RT = 73%

5-FU, 5-fluorouracil; CAPOX, oxaliplatin and capecitabine; CRT, chemoradiation; DFS, disease-free survival; DGC, diffuse gastric cancer; ECF, cisplatin, epirubicin and continuous infusion 5-fluorouracil ; GEJ, gastro oesophageal junction; HR, hazard ratio; I/E, inclusion and exclusion criteria; LV, leucovorin; RFS, relapse-free survival; RT, radiotherapy; SOX, S-1 plus oxaliplatin; XP, cisplatin and capecitabine; XRT, XP and radiotherapy with capecitabine



# CONCLUSIONS

- Complete clinical staging is critical to the management of locally advanced gastric cancers
- Consider laparoscopy in all T2 or greater or LN+ gastric cancers<sup>1</sup>
- Multidisciplinary management is supported by outcomes data
- FLOT is the emerging standard for perioperative therapy in locally advanced gastric cancer in Europe and the United States

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1. NCCN Clinical Practice Guidelines in Oncology, Version 2, June 2019.

FLOT, Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin; LN; lymph node; T2, primary tumor stage 2

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Email  
[antoine.lacombe@cor2ed.com](mailto:antoine.lacombe@cor2ed.com)



GI CONNECT  
Bodenackerstrasse 17  
4103 Bottmingen  
SWITZERLAND

Dr. Antoine Lacombe  
Pharm D, MBA  
Phone: +41 79 529 42 79  
[antoine.lacombe@cor2ed.com](mailto:antoine.lacombe@cor2ed.com)

Dr. Froukje Sosef  
MD  
Phone: +31 6 2324 3636  
[froukje.sosef@cor2ed.com](mailto:froukje.sosef@cor2ed.com)

