



ARRO*Case*

Stomach Cancer

Zain Siddiqui, MD, Ian Pereira MD
Faculty Advisor: Maria Kalyvas, MD, FRCPC

Kingston Health Sciences Center
Queen's University
September 2020

Objectives

To review key aspects of stomach cancer for radiation oncology trainees through a case vignette, contouring example, & epidemiology

1. Recognize the presentation of stomach cancer
2. Peer review a neoadjuvant radiation treatment plan
3. Apply epidemiology, classification systems, & prognosis
4. Justify a management framework

Outline

1. Stomach Cancer Case Presentation
2. Epidemiology
3. Classification Systems
4. Key Trials
5. Clinical Practice Guidelines
6. Treatment Planning

**denotes epidemiology relevant to our case throughout this deck*

Case

59yo male presents w/3-month h/o progressive heartburn. Also trouble swallowing, anorexia, & early satiety w/a 30lb weight loss.

ROS: independent of daily activities & active most of the day. No melena/hematochezia. Regular bowel movements

PMHx: treated for H. Pylori, GERD, & IDA. No upper scopes.

Sochx: ex-smoker (>20 pack-years).

Meds: ranitidine & Fe supplements.

FMHx: no h/o of gastric, breast, or ovary ca. No FAP/HNPCC.

Physical Exam: ++epigastric tenderness. No rebound or guarding. Abdomen tympanic. No jaundice, clinically palpable nodes, or hepatomegaly. Unremarkable DRE.

IDA = Iron Deficiency Anemia; FAP/HNPCC = Familial Adenomatous Polyposis/Hereditary Nonpolyposis Colorectal Cancer

Case

EGD: circumferential tumor at the EGJ ~ 30% of the lumen. Epicenter 4cm below the EGJ extending 7cm below. Diffuse linitis plastica appearance of stomach. Bx showed poorly differentiated adenocarcinoma, HER2-negative.

CT CAP/PET: thickened distal esophagus & gastric wall. Uptake in the primary (mSUV 8) & ~3 x enlarged right cardio-esophageal/lesser curve LNs (6.4cm, mSUV 6). No distant mets.

Bloodwork: within normal limits

Laparoscopy & washings: No peritoneal or diaphragmatic mets. Few atypical cells.

=>Stage IIA cT1/2 cN2 M0



Fig 1. Linitis plastica.

Source: Dr. Wiley Chung

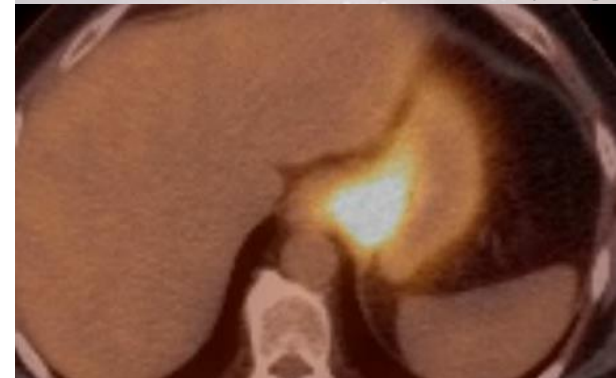


Fig 2. Intense PET uptake at the EGJ.

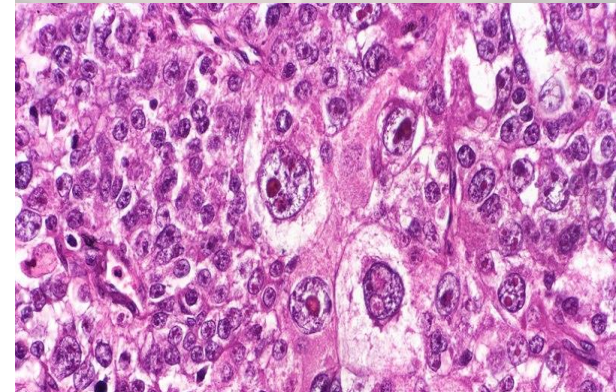
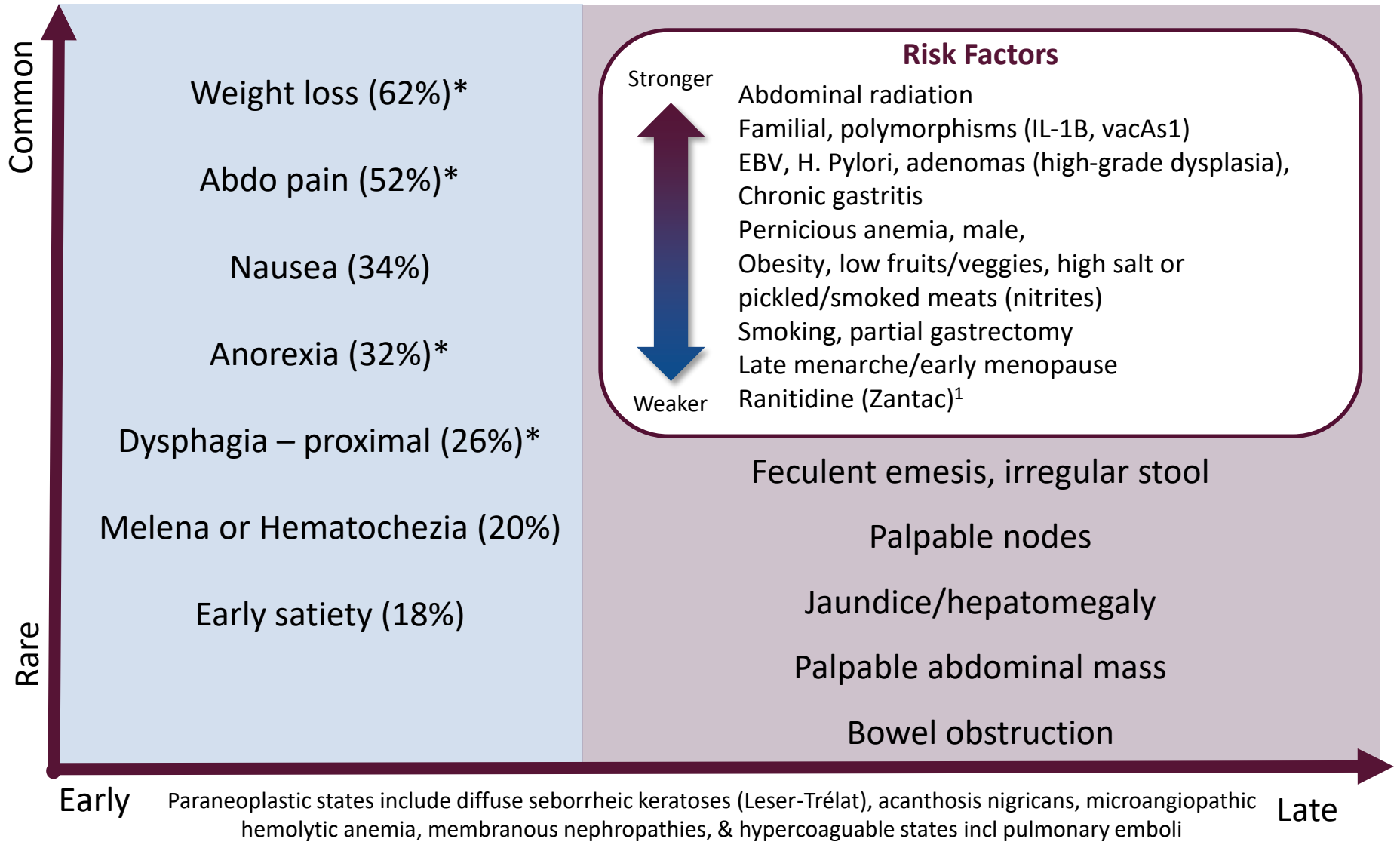


Fig 3. G3 Adenocarcinoma on H&E.

Source: CORUS13

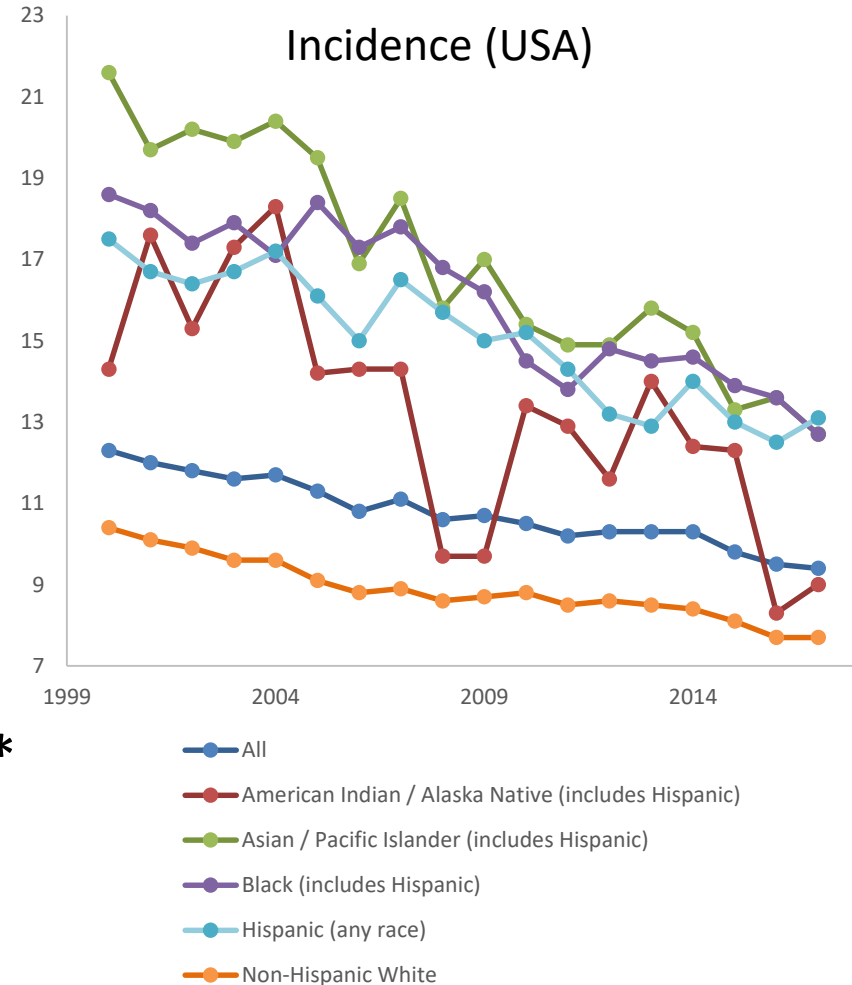
Clinical Presentations



Perez & Brady, 2019; Wanebo, 1993; ¹Appendix

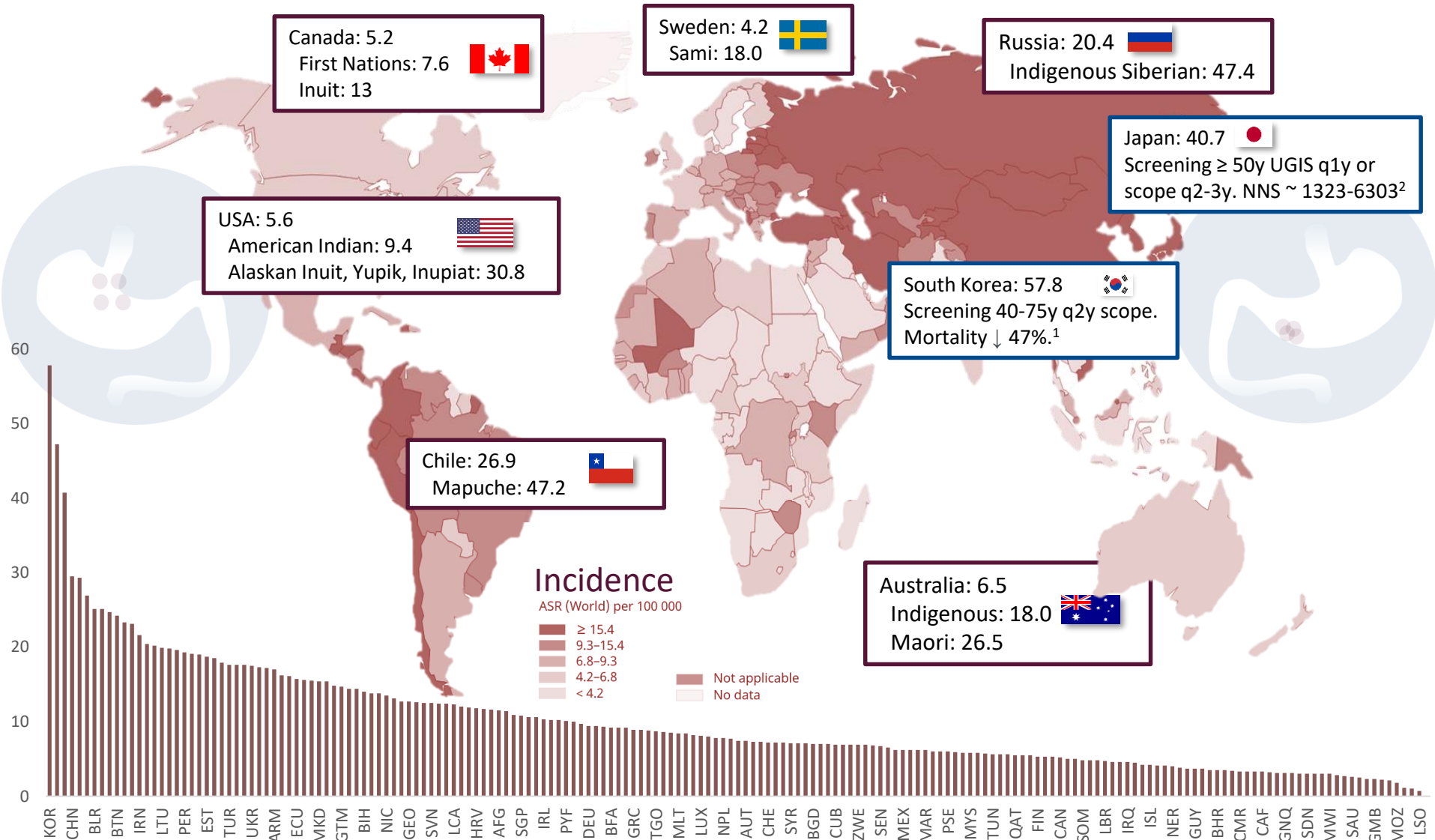
Stomach Cancer

- 27,510 cases & 11,140 deaths (USA)
- Median age 68
- Males 2:1 Females
- 3rd most common cause of death in males worldwide (13th in the USA)
- 95% adenocarcinoma (others: lymphoma, GIST, carcinoid, & SCC)
- ~80% present w/advanced disease
- Overall incidence is declining, but increasing for cardia tumors in men*
- All-comer 5-year OS 32% (USA)



GLOBOCAN, 2019; SEER, 2017

Disparities & Interventions



Canada: 5.2
First Nations: 7.6
Inuit: 13

Sweden: 4.2
Sami: 18.0

Russia: 20.4
Indigenous Siberian: 47.4

Japan: 40.7
Screening ≥ 50y UGIS q1y or
scope q2-3y. NNS ~ 1323-6303²

USA: 5.6
American Indian: 9.4
Alaskan Inuit, Yupik, Inupiat: 30.8

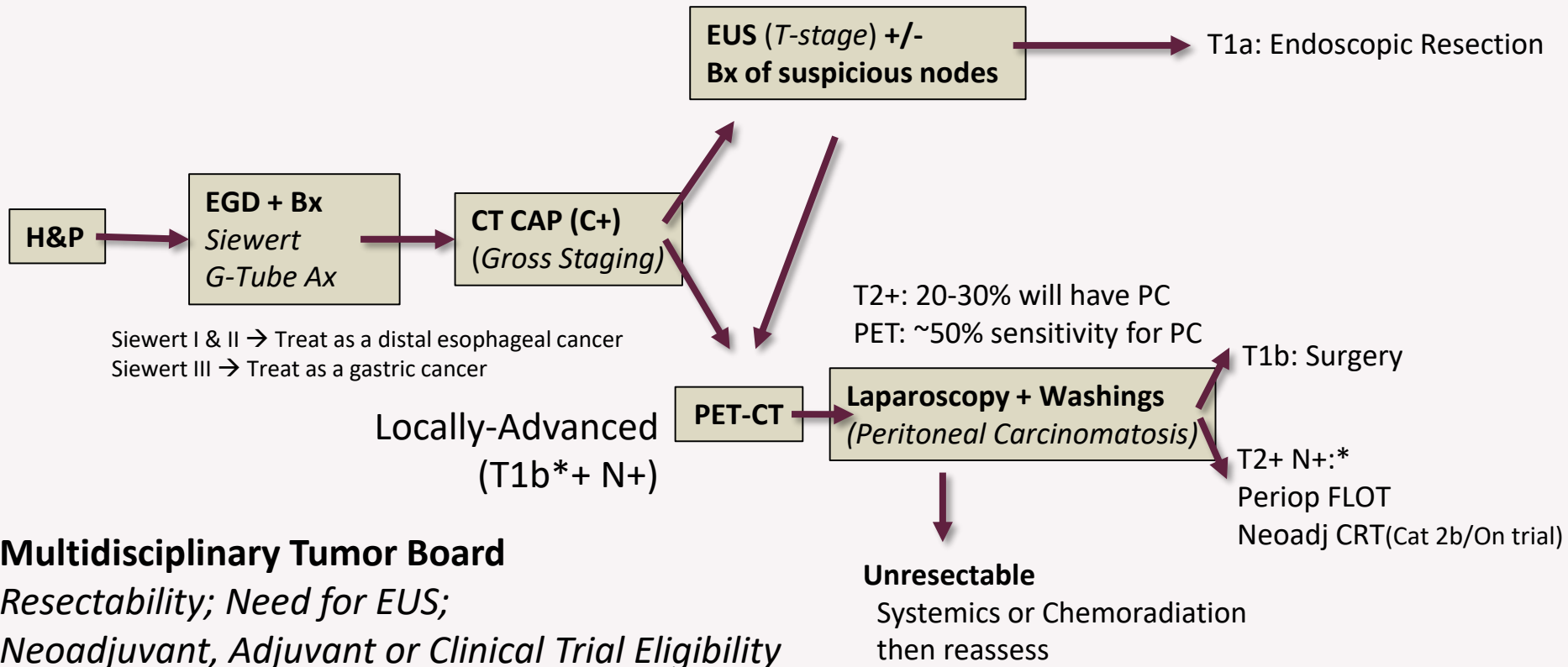
South Korea: 57.8
Screening 40-75y q2y scope.
Mortality ↓ 47%.¹

Chile: 26.9
Mapuche: 47.2

Australia: 6.5
Indigenous: 18.0
Maori: 26.5

Arnold 2014, Jun 2017¹, Hamashima 2018², GLOBOCAN 2019

Stomach Adenocarcinoma Initial Diagnostic Workup



Multidisciplinary Tumor Board

Resectability; Need for EUS;

Neoadjuvant, Adjuvant or Clinical Trial Eligibility

EGD = Upper GI endoscopy; Bx = Biopsy; CAP (C+) = Chest, Abdomen, & Pelvis w/Contrast; PC = Peritoneal Carcinomatosis;
CHT = chemotherapy; RT = radiation treatment

*There are differences on the extent of workup for T1b

Other Investigations: CBC, Renal/Liver Function

Anemia -> Fe supplementation or Transfusion

Kidney/Liver Disease -> Optimize prior to chemotherapy decision-making

NCCN 2020; ESMO 2016, UpToDate 2020

Siewert & AJCC

Used to guide therapeutic decision-making.

Siewert Class:

For esophagogastric junction (EGJ) tumors based on the tumor epicentre.

AJCC 8th Ed:

Esophagus: Siewert 1 o2

Stomach*: Siewert 3 involving the EGJ OR if tumor epicenter within 2cm of the EGJ without crossing it

Mainly for Clinical Trials.

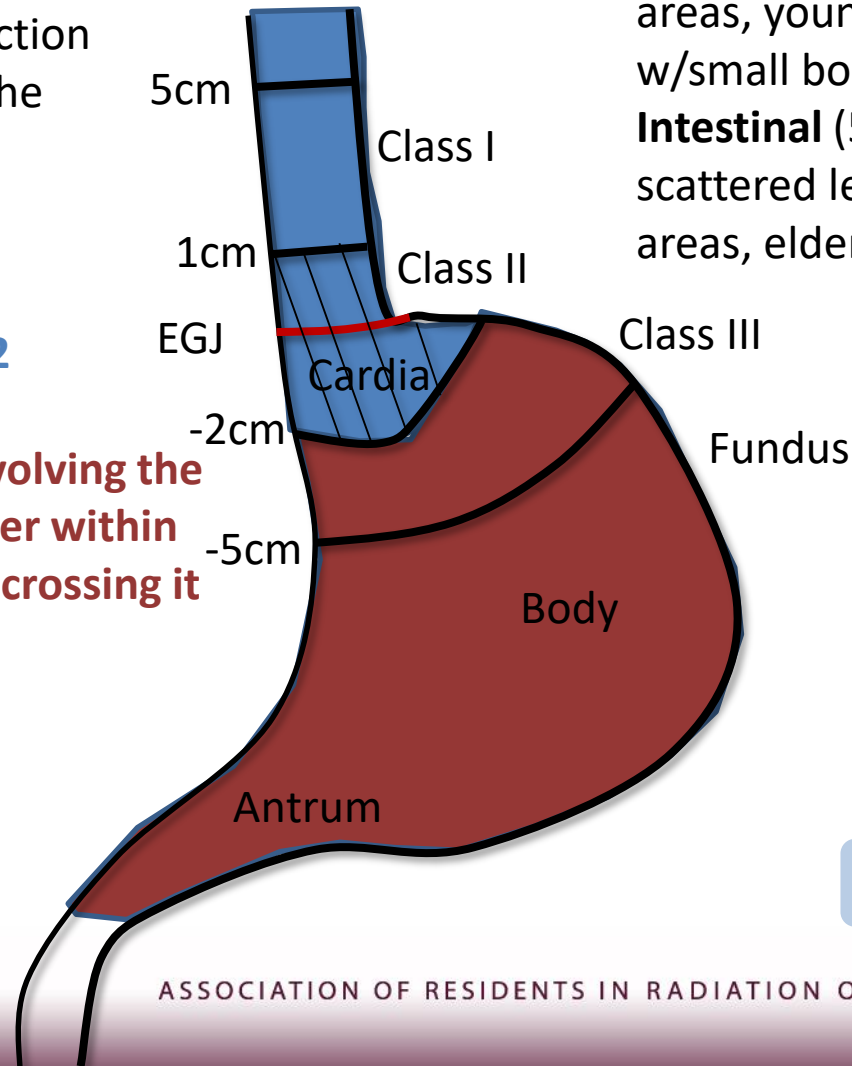
Lauren Classification:

Diffuse (32%): signet-cell, ↓ risk areas, young ♀, peritoneal mets w/small body primary, & ↓ prognosis

Intestinal (54%): H.Pylori, LVI, scattered lesions & antrum, ↑ risk areas, elderly ♂, & ↑ prognosis

WHO (2010):

22 AdenoCa subtypes



*AJCC 8th ed changed stomach cancer staging to include Siewert 3

AJCC 8th ed

		cN0	cN1	cN2	cN3a	cN3b
T1	a Lamina propria or muscularis mucosae	I	IIA			
	b Submucosa					
T2	Muscularis propria					
T3	Subserosal connective tissue	IIB	III			
T4	a Serosa (visceral peritoneum)					
	b Adjacent organs	IVA				
M1	Distant metastasis	IVB				

cN1 1-2 regional LNs; cN2 3-5 regional LNs; cN3a 7-15 regional LNs; cN3b is ≥ 16 regional LNs.

Good Prognostic Factors:

ECOG 0-2

Early-Stage

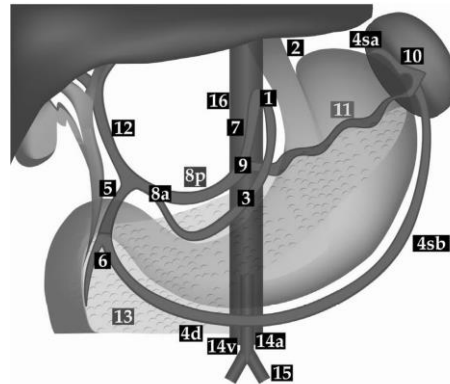
N0 > N+

R0 > R1 > R2

Intestinal > Diffuse Type

Regional LNs

Perigastric & 2nd tier



Distant LNs: include mediastinal, pancreatic, mesenteric, para-aortic

Rate of LN Mets:

80% present w/nodal mets

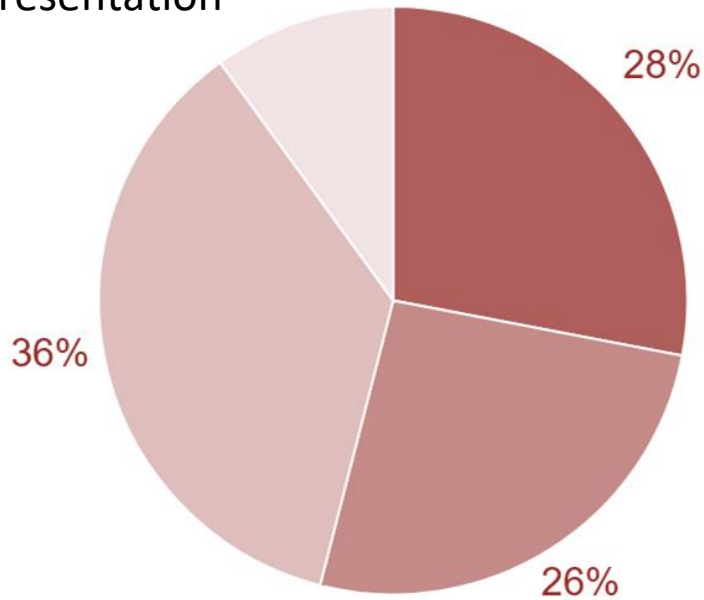
T1: 10-20%;* T2: 50%*;

T3: 65%; T4a: 75% ; T4b:

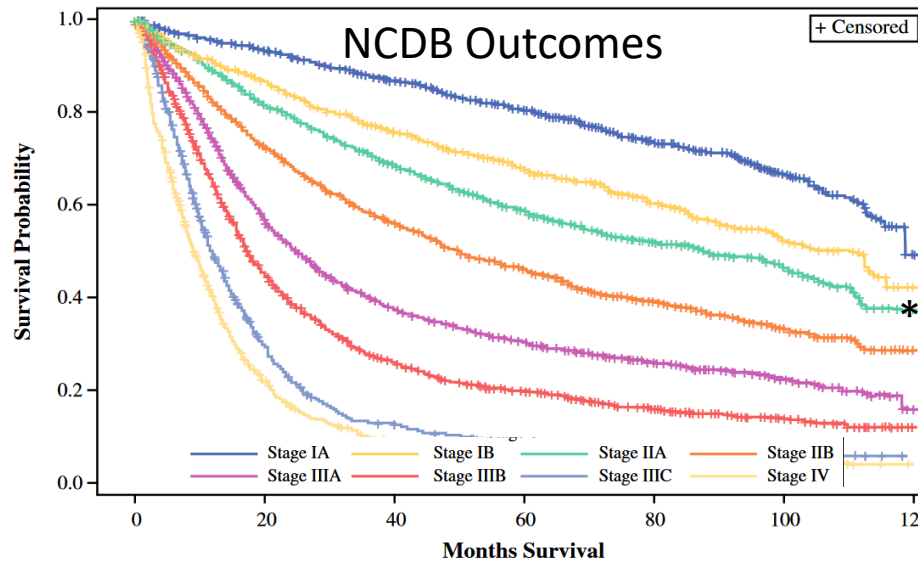
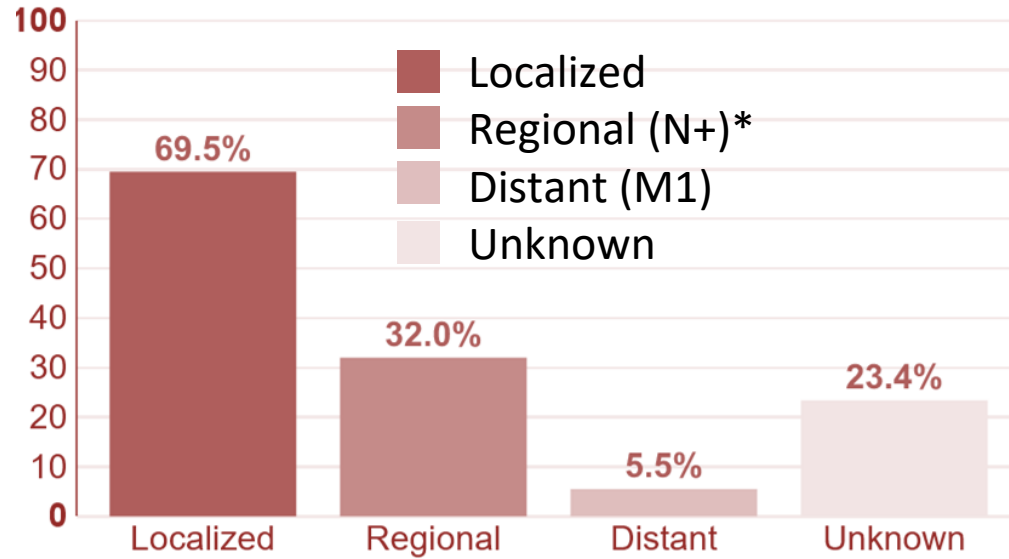
80%

Stage at Presentation & Outcomes

Presentation



5-Year OS



10y OS by Nodes
 N0: 92%; N1: 82%;
 N2: 73%;* N3: 27%

Treatment Planning

Enrolled onto TOP GEAR & Randomized to Neoadj CRT

Neoadjuvant FLOT x 3 Cycles: no issues

CT Simulation: With IV contrast. Immobilized with arms above his head, an arm board, & neck/knee rest. Directions given for similar stomach filling daily (following a light meal at a similar time each day or NPO 3 hours prior). Scanned from the whole thorax to the inferior kidneys w/2mm slices. Fused w/PET-CT & Diagnostic CT (w/small bowel contrast)

Technique/Rx: FLOT x 3 -> Neoadjuvant RT 45 Gy in 25 daily# to the PTV concurrent with systemic therapy (5-FU or Capecitabine per TOPGEAR) w/IMRT¹ (3DCRT & 4DCT are other options)

Imaging: Daily Cone Beam CT (bony match) & treatment verification at least weekly.

¹IMRT may spare dose to kidneys & other OARs.

Wieland et al. IMRT for postoperative treatment of gastric cancer: covering large target volumes in the upper abdomen. IJROBP 2004. PMID:[15234061](https://pubmed.ncbi.nlm.nih.gov/15234061/)

Treatment Planning

	TOP GEAR* ¹	EORTC-ROG ²
GTV	Primary + Involved Regional Nodes* [§]	GTVtumor = Primary; GTVnodal = Involved Regional Nodes [§]
CTVstomach	T1/2: Gastric Silhouette (GS)*	Proximal 1/3: GS excluding pylorus/antrum
	T3: GS + GTV + 0.5cm	Middle 1/3: GS (cardia to pylorus)
	T4: GS + GTV + 1cm	Distal 1/3: GS excluding cardia & fundus; if involving fundus then use a 3cm distal margin
	Superior margin is 1cm of proximal esophagus or 4cm if the tumor involves the cardia/GEJ/distal esophagus*	CTVtumor = GTVtumor + 1.5cm CTVnodal = GTVnodal + 0.5cm
	+1cm of the proximal duodenum; 4cm if tumor involves the pylorus	
CTV	CTVstomach + Regional Lymphatics [‡]	CTVgastric + CTVtumor + CTVnodal + CTVelective [†]
ITV	(not specified)	Siewert III: CTV + 1cm radial, 1.5cm distal, & 1cm proximal Gastric: CTV + 1.5cm
PTV	CTV + 1cm	ITV + 5mm

§Based on EGD, EUS, imaging, laparoscopy +/- discussion w/radiology & surgery

‡Regional Lymphatics include JRSGC 1-16, excluding 15 for Siewert III/Gastric Tumors (See Appendix)

†CTVelective for Siewert III tumors includes JRSGC 1-4,7,9-11, 19,20, 110,111; a 5mm margin around vessels; & a superior border 3cm above the tumor or the esophageal hiatus (whichever is higher)

†For Proximal 1/3 tumors: JRSGC 1-4,7,9-11,19

†For Middle 1/3 tumors: JRSGC 1-5,7-11,18,19

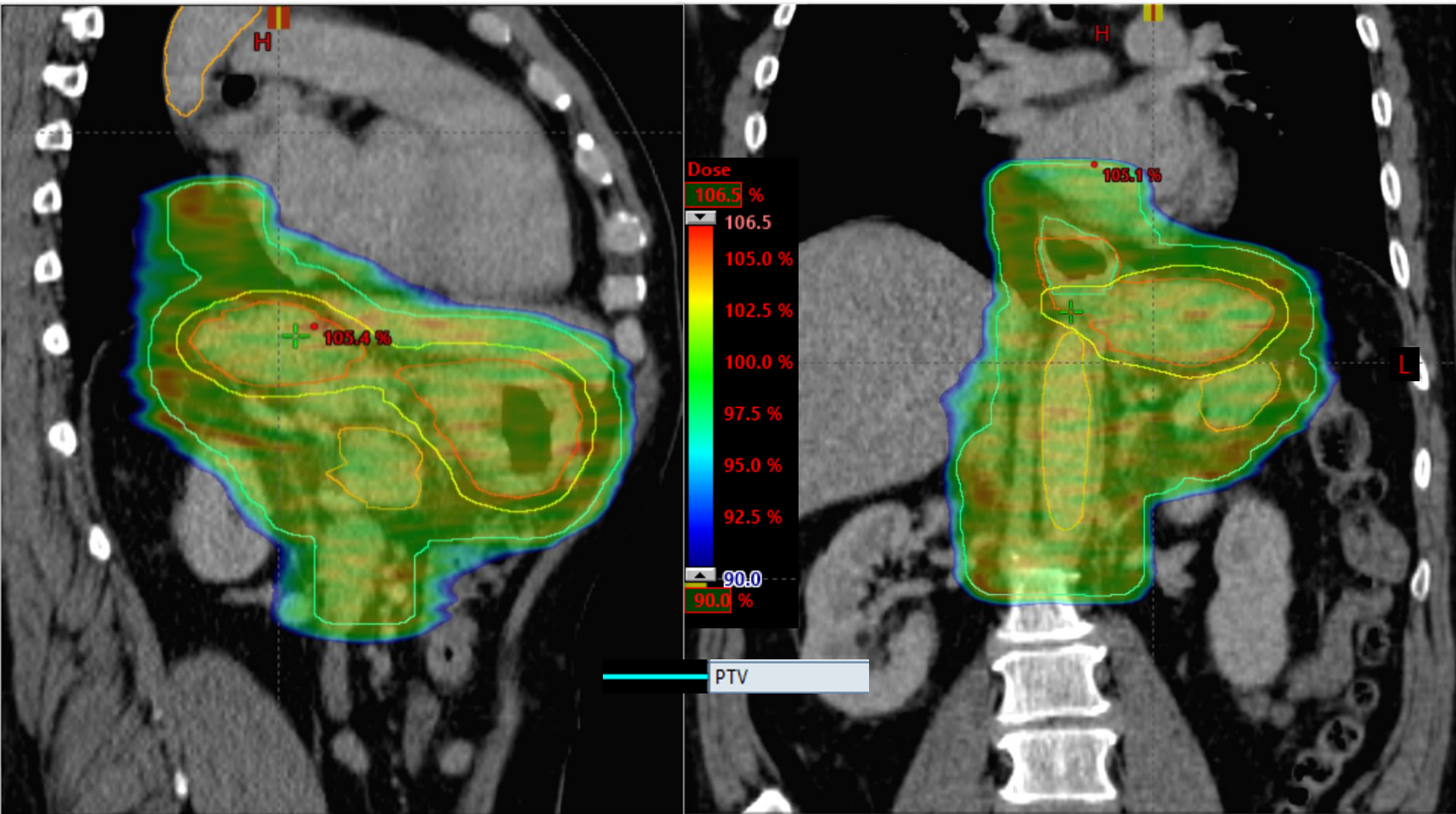
†For Distal 1/3 tumors: JRSGC 3-9,11-13,17,18

1 Leong T, Smithers BM, Haustermans K, et al. TOPGEAR: A Randomized, Phase III Trial of Perioperative ECF Chemotherapy with or Without Preoperative Chemoradiation for Resectable Gastric Cancer: Interim Results from an International, Intergroup Trial of the AGITG, TROG, EORTC and CCTG. *Ann Surg Oncol*. 2017;24(8):2252-2258. PMID: [28337660](#)

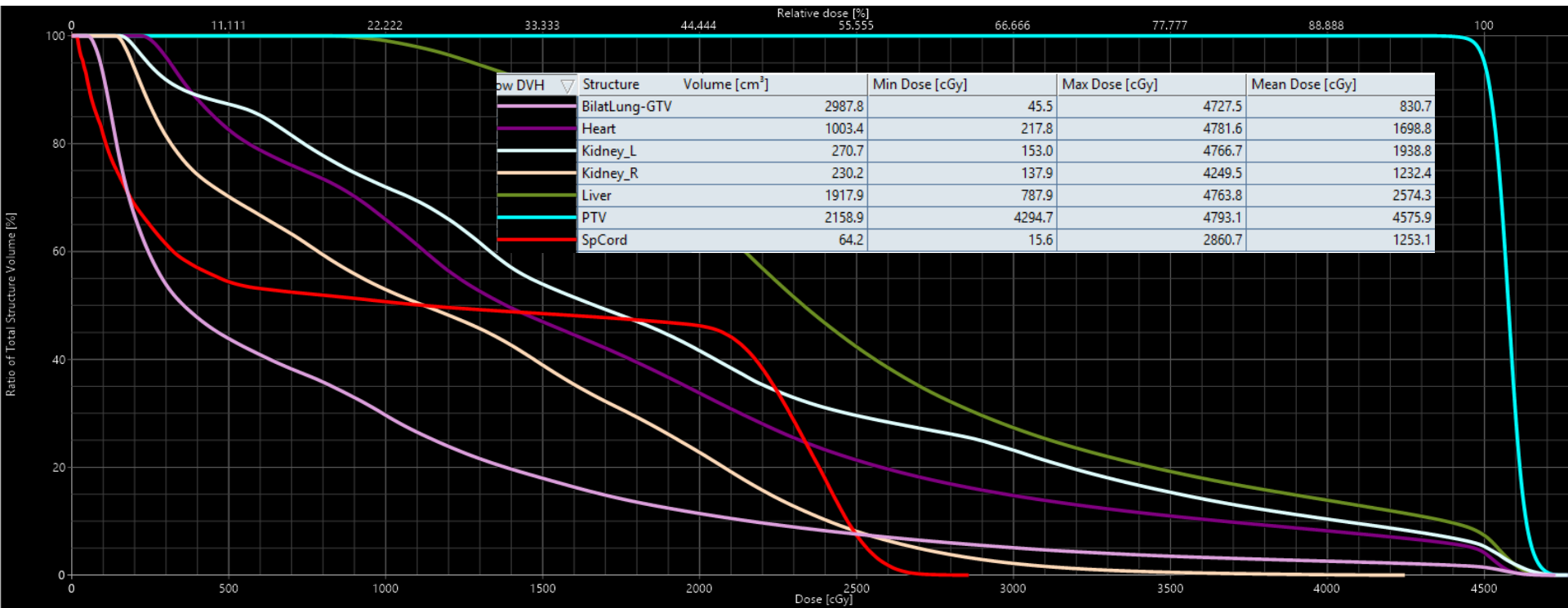
2 Matzinger, O., et al. (2009). "EORTC-ROG expert opinion: radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach." *Radiother Oncol* 92(2): 164-175. PMID: [19375186](#)

3. Wo et al. Gastric lymph node contouring atlas. PRO. 2013. PMID: [24674268](#)

Contours & Dose



Dose Volume Histograms



Spinal Cord	Dmax ≤ 45Gy	< 0.2% Myelopathy	PTV	D95 > 42.8Gy Mean & Median 44.5 to 45.9Gy Dmin > 40.5 Gy Dmax < 48.2 Gy
Liver	V _{1/3} ≤ 50Gy; V _{2/3} ≤ 35Gy; Mean Liver Dose ≤ 30Gy	TD < 5/5 < 5% Radiation Induced Liver Damage		
Kidneys	V _{1/3} (Single) ≤ 35Gy; V _{2/3} ≤ 20Gy; Mean Kidney Dose ≤ 23Gy	TD < 5/5 < 2 0% Symptomatic Radiation Nephropathy		
Heart	V40Gy ≤ 30%	Any pericarditis/pericardial effusion		
Lungs	V20Gy ≤ 30%, Mean Lung Dose ≤ 18 Gy	< 20% Symptomatic Pneumonitis		

c.t. NCCN Gastric Cancer v1.2020:

Mean Lung Dose ≤ 20Gy

Heart V30 ≤ 30% (20% preferred); Mean Heart Dose < 30Gy

Bowels V45Gy < 195cc

Liver V30Gy ≤ 33%, Mean Liver Dose < 25Gy

Emami 1991, Cassady 1995, QUANTEC 2010, TOPGEAR 2017

Follow-Up & Surveillance

- Neoadjuvant CRT: no any issues*
- Restaging CT ~3wks prior to surgery – no mets*
- Surgery: Unfortunately lost to follow-up...*
- Scheduled Perioperative Adjuvant FLOT:
 - FLOT q2w x 4 cycles
 - H&P, weight, PS, & bloodwork including tumor markers (CEA, CA19-9, CA125), lytes, creatinine, liver function tests, post-sx ax, & chemo/radiation toxicity ax prior to each cycle
- Scheduled Surveillance:
 - Y1: months 1,3,6,9,12 – Basics (H&P, wt, PS, sx/toxicity ax, and patient reported outcome ax), tumor markers, & CT CAP (months 6 & 12),
 - Y2: q3months x 1y – Basics & CT CAP (Y2 only)
 - Y3-5: q6months x 3y Basics

*c.t. NCCN Gastric Cancer v1.2020:
H&P q3-6mos x 1-2y; q6-12mos x 3-5y; then annually
CT CAP q 6-12mos x 2y than annually x 3y
BW & EGD prn; monitor for nutritional deficiency*

Randomized Trials Locally Advanced EGJ/Gastric

Trial	Accrual Dates	Trial Type	n	Criteria Population %EGJ	Arms	Outcomes	Conclusion
DUTCH D1D2	1989-1993 Bonenkampf, 2006	Sx	1078	Stomach, <85 Dutch 10% upper 1/3 stomach	D1 vs D2 Surgery	15yOS 21% D1 v 29% D2; cancer-related death 48% v 37%; LR 22% v 12%; higher mortality in D2 13 v 19%.	D2 resection improved survival & local recurrence at the expense of higher operative mortality
INT0116	1991-1998 Macdonald 2001 Smalley, 2012	Adj CRT	556	Stomach or EGJ, T3+ or N+ USA 7% Cardia, 8% body	Sx -> observation vs. CRT (45Gy + FL)	5-year OS 22% vs 42%, mOS 27 vs. 36mos (P=0.005).; 10% D2	Adjuvant CRT improves OS, but a limited resection
MAGIC	1994-2002 Cunningham, 2006	Periop CHT	503	Resectable T2+NxM0 esophagogastric UK 74% gastric including Siewert III	Sx alone vs. Periop ECF	5yOS 23 vs 36% (P=0.008); 42% D2	ECF decreases tumor size and improves survival, but a limited resection
FFCD	1995-2003 Ychou, 2011	Periop CHT	224	Esophagogastric France 11% Siewert I & 64% Siewert 2 or 3	Sx alone vs. Periop CF	5yOS 24 vs. 38% (p0.02), closed early due to low accrual.	Periop CF improves OS.
POET	2000-2005 Stahl, 2017	Neoadj CRT	119	EGJ Siewert 1-3, T3+NxM0 Germany 0% Siewert 3	Neoadj Cx (PLF) vs. Induction PLF + Neoadj CRT (30Gy + CE)	Closed early due to low accrual, 3yOS 27.7 vs 47.4%, 5yOS 24.4 v 39.5% p=0.07 . Improved pCR 2 v 15.6%,	Trends towards improved survival w/neoadjuvant CRT, but no gastric patients
ARTIST	2004-2008 Park, 2015	Adj CRT	458	Gastric, IB-IVA, D2 resection East Asia, majority stage I/II 4.8% proximal stomach	Adj XP vs. Adj CRT (45G + XP)	7yOS 73 v 75%; Trend for DFS in N+ or intestinal-type subsets	In pts receiving a D2 resection, a subset may have benefit.
CROSS	Hagen, 2012	Neoadj CRT	364	Esophageal/EGJ (I/II), T2+ or N+ M0 Dutch 24% Siewert II, 75% adenoCa	Sx Alone vs. Neoadj CRT (Carbo/Paclitaxel + 41.4Gy)	5yOS 34 vs. 37% p0.003, but less for adenoCa and N+ subgroups.	For esophageal cancer (incl Siewert II), CROSS is standard of care. Unclear how much Siewert III actually in the study.
CRITICS	2007-2015 Cats, 2018	Adj CRT	788	Stage IB-IVA, resectable, gastric or EGJ, At least D1+ Dutch 17% Siewert 2 or 3, 80% D1 & 14% D2	Periop CHT (ECX or EOX) vs. Periop CHT + Postop CRT (45Gy+ XP)	mOS 43 vs. 37mos (p0.9), surgical compliance 43 vs. 39% (p0.3); adjuvant compliance 59 vs. 62%.	No survival benefit for adj CRT, but poor surgical and adjuvant compliance in both arms.
FLOT4	2010-2015 Al-Batran, 2019	Periop CHT	716	>=cT2 or N+, EGJ/gastric, D2 resection 56% EGJ, 80% N+, Germany 32% Siewert 2 or 3	Periop CHT (ECF/ECX) vs. Periop CHT (FLOT)	5y OS 36% vs. 45%, mOS 35 v s. 50mos, similar complication rates (50 vs. 51%)	Periop FLOT improved OS w/similar tox.
ARTIST-2	2013-2018	Adj SOX, SOXRT	538	Stage II/III N+, D2 resection East Asia Unknown	Adj S1 vs. SOX vs. SOXRT (SOX -> S-1 + 45Gy -> SOX)	DFS S1/SOX vs. SOXRT HR 0.86 p0.40	Stopped early due to futility of S1 alone. Interim analysis suggested no difference in DFS for SOX vs. SOXRT.

CRT = chemoradiation; CHT = chemotherapy; F= 5-FU, C = Cisplatin, PLF = Cis + Leucovorin + 5-FU; CE = Cis + Etoposide; XP = Capecitabine + Cisplatin; FLOT = 5-FU + leucovorin + oxaliplatin + docetaxel; SOX = S-1 + Oxaloplatin. For the full chemotherapy regimens please see the appendix.

Summaries from East & West

West (North America, EU, & AUS/NZ) Stage II/III (T2+ or N+ M0)

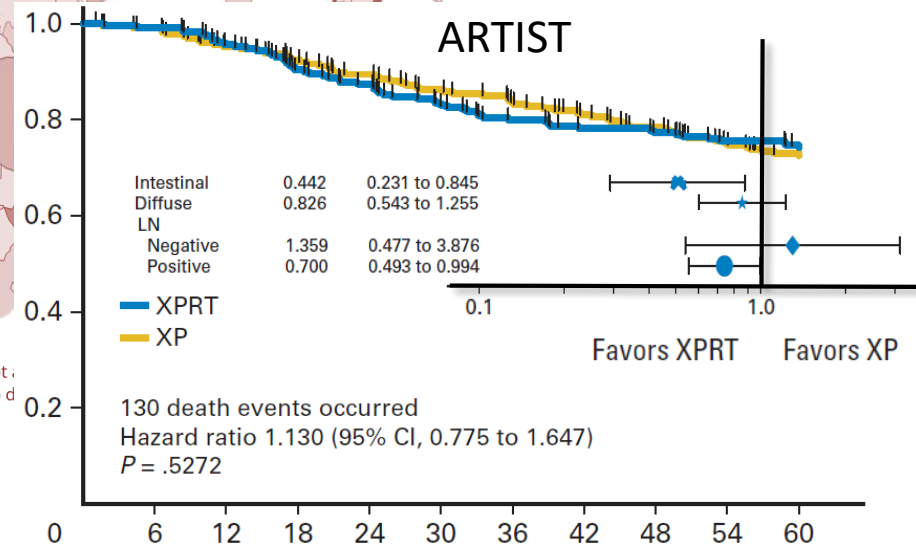
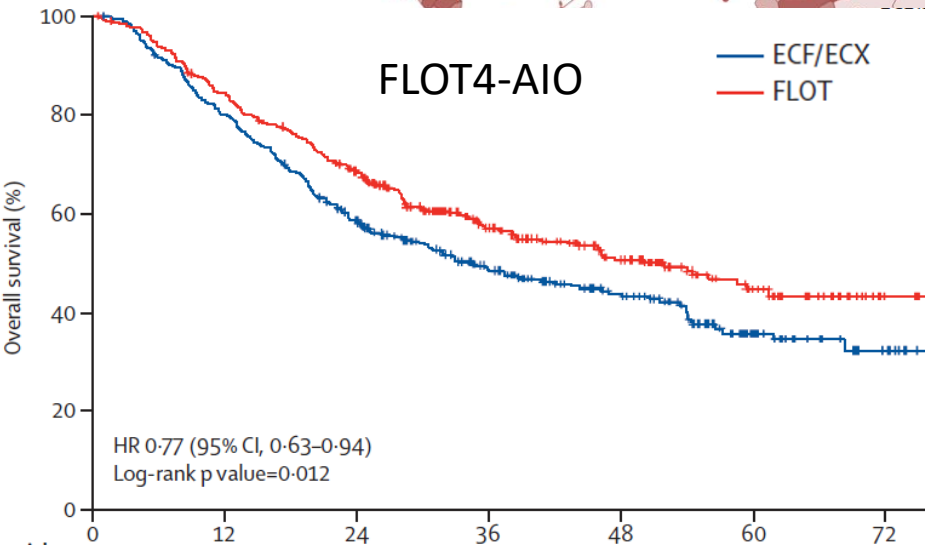
- Periop CHT (FLOT)
- FLOT4-AIO
- Neoadj CRT (on trial)
- TOPGEAR (Canada, EU, AUS/NZ)
- ESOPEC/NEO-AEGIS (EU)
- RACE? (USA)

Lower Incidence (<10)
No Screening
D2 largely in fit patients
5yO2 ~10-15%

East (Japan, South Korea, Taiwan, China) Stage II/III (T2+ or N+ M0)

- Sx -> Adj CHT
- ACTS-GC (S-1)¹: +10% 5yOS vs. Sx alone
- CLASSIC (Cape+Oxali)²: +9% 5yOS vs. Sx alone
- JACCRO GC-07 (S1+Docetaxel)³: +16% 3yOS vs. S1

Higher Incidence (>20)
National Gastric Cancer Screening Programs (Taiwan, S. Korea, Japan)
Diagnosed earlier (T1a) -> more endoscopic resection
Routine D2 dissection
5yO2 ~45-50%



Sakuramoto 2007¹ Bang 2012², Yoshida 2019³,

Open Trials – Locally Advanced EGJ/Gastric

Trial	Trial Type	Criteria Population	Arms	Endpoints	Conclusions
TOPGEAR*	Neoadj CRT	IB-IIIC, Siewert 2 & 3, gastric EU/Cdn 17% EGJ	Periop CHT (ECF or FLOT) vs. Periop CHT + Preop CRT (45Gy + F or X)	OS. Interim results - similar proportion of pts proceeding to surgery (90 vs 85%), but less completion of postop CHT (65 vs. 53%)	High compliance w/preop regimens, but lower compliance w/postop CRT arm. Est Completion: Dec 2020 NCT01924819
ESOPEC	Neoadj CRT	cT2+ or N+ M0 Esophageal/ EGJ (I-III) Germany	Periop FLOT vs. CROSS (Neoadj CRT Carbo/Pac + 41.4Gy)	OS	Est Completion: Jun 2024 NCT02509286
NEO-AEGIS	Neoadj CRT	cT2+NxM0 Esophageal/EGJ France-UK-Ireland	Periop FLOT or ECF vs. CROSS (Neoadj CRT)	OS	Est Completion: Jan 2024 NCT01726452
CRITICS-2	Neoadj CRT, no Adj		NeoAdj CHT (DOC x 4) vs. Neoadj CHT (DOC x 2) -> CRT (45Gy + carbo/pac) vs. Neoadj CRTalone	Event-free survival	Est Completion: Oct 2022
Swing & Berens	Phase II Neoadj CRT	cT3+ or N+ adeno Esophagus or EGJ Colorado	Periop FLOT + Neoadj CROSS	pCR	Est Completion: April 2025 NCT04028167

CRT = chemoradiation; CHT = chemotherapy; F= 5-FU, C = Cisplatin, PLF = Cis + Leucovorin + 5-FU; CE = Cis + Etoposide; XP = Capecitabine + Cisplatin; FLOT = 5-FU + leucovorin + oxaliplatin + docetaxel; SOX = S-1 + Oxaloplatin. X = Capecitabine. For the full chemotherapy regimens please see the appendix.

Conclusion

- For locally advanced cancer, outcomes are limited.
- Not discussed, for patients who did not have neoadjuvant treatment, indications for adjuvant treatment include N+ pathology (-> adj CHT) or R1/2 resection (-> adj CRT).¹
- Eastern patient populations have a lower incidence of advanced gastric cancers, perhaps due to established screening programs
- Perioperative (West – FLOT) or adjuvant (East – S-1 +/- Docetaxel) is an established standard of care. This may be driven both by more advanced presentation in the West to facilitate surgery, and more aggressive surgery (D2) in the East.
- The role of radiation is still unclear. It has shown a survival benefit in the setting of limited surgery (MAGIC, INT0116). It has not shown benefit in the adjuvant setting with older chemo (non-FLOT: CRITICS, ARTIST-2). However, in subsets of pts (ARTIST, POET) it has suggested promising trends in the neoadjuvant setting.
- Studies are currently underway to address the question of whether neoadjuvant CRT will have benefit in the Western societies (ESOPEC, CRITICS-2), with TOPGEAR results eagerly anticipated soon.
- However, with the recent shift of esophagogastric junction (EGJ) adenocarcinomas in AJCC 8th ed to Siewert I-II being classified as esophageal and Siewert III as gastric, and their limited inclusion in trials to date, it is unclear if this increasing Western disease will have the attention it requires, for now.
- Other areas of investigation include biomarkers including liquid biopsies, reducing toxicity or improving coverage with improved treatment techniques including QA/QI for radiation and surgery, and addressing disparities such as our neglected populations (under-represented minorities, the frail, and our elderly).

¹NCCN Gastric Cancer v1.2020



ARRO*Case* Stomach Cancer

References & Appendices

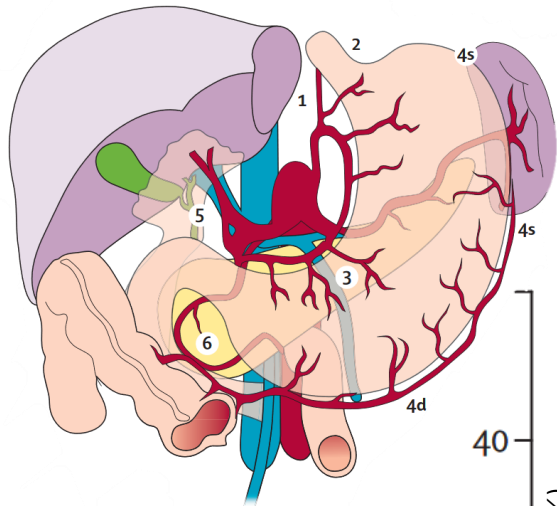
References

- National Comprehensive Cancer Network. Gastric Cancer (Version 1.2020). https://www.nccn.org/professionals/physician_gls/default.aspx#gastric. Accessed April 1st, 2020.
- Leong, T., Smithers, M., Michael, M., & Boussioutas, A. et al. TOP GEAR: Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma. A randomised phase II/III trial of preoperative chemoradiotherapy versus preoperative chemotherapy for resectable gastric cancer Protocol. TOP GEAR, 9.0, 1–94. July 13 2018.
- Wieland C, Hymmen U. Mega-volt therapy of malignant stomach neoplasms. *Strahlentherapie* 1970; 140: 20.
- Zhang Z., Gu X., Yin W. et al. Randomized Clinical Trial on the combination of preoperative irradiation and surgery in the treatment of adenocarcinoma of gastric cardia (AGC)- report on 370 patients. *Int. J. Radiation Oncology Biol. Phys.*,42:5 929-934.
- Macdonald J, Smalley S, et al. Chemoradiotherapy after surgery compared with surgery alone For Adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001; 345:725-730.
- Smalley, Benedetti et al. J Clin Oncol. 2012 Jul 1;30(19):2327-33. doi: 10.1200/JCO.2011.36.7136. Epub 2012 May 14.
- Cunningham D., Allum W, Stenning S et al. Preoperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. N Engl J Med 2006; 355:11-20 DOI: 10.1056/NEJMoa055531
- Sauer R, Becker H, Hohenberger W et al. Preoperative versus Postoperative Chemotherapy for Rectal Cancer. N Engl J Med 2004; 351:1731-1740. DOI: 10.1056/NEJMoa040694
- Leong T., Michael M., Lim Joon D., Jayamoham J, Spry N., Harvey J. et al.2 Adjuvant chemoradiation for gastric cancer using epirubicin, cisplatin, and 5-FU (ECF) before and after 3D-conformal radiotherapy with continuous infusional 5-FU: a multicentre study of the Trans-Tasman Radiation Oncology Group (TROG). *International Journal of Radiation Oncology, Biology, Physics* 2009. 79:3 690-695.
- Cats A., Jansen EPMB., van Grieken NCT., Sikorska K., Lind P., Nordmark M., et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol.* 2018 May;19(5):616-628. doi: 10.1016/S1470-2045(18)30132-3. Epub 2018 Apr 9.
- Slagter A., Jansen E., van Laarhoven H., et al. CRITICS-II: a multicentre randomised phase II trial of neo-adjuvant chemotherapy followed by surgery versus neo-adjuvant chemotherapy and subsequent chemoradiotherapy followed by surgery versus neoadjuvant chemoradiotherapy followed by surgery in resectable gastric cancer. *BMC Cancer* 2019. 18:87 7/
- Ajani, J. A., Winter, K., Okawara, G. S., Donohue, J. H., Pisters, P. W. T., Crane, C. H., Greskovich, J. F., Anne, P. R., Bradley, J. D., Willett, C., & Rich, T. A. (2006). Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): Quality of combined modality therapy and pathologic response. *Journal of Clinical Oncology*, 24(24), 3953-3958. <https://doi.org/10.1200/JCO.2006.06.4840>
- Halperin, E., Pérez, C., Wazer, D. and Brady, L., 2019. Principles And Practice Of Radiation Oncology. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

References

- Rosa F., Costamagna Guido., Et al. Classification of nodal stations in gastric cancer. *Transl Gastroenterol Hepatol* 2017;2:2.
- Sano T., Yasuhiro K. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011. 14:101-112.
- Siewert JR, Stein HJ. Classification of adencarcinoma of the oesophagogastric junction. *Br J Surg.* 1998;85(11):1457-1459.
- Rudiger SiewertJ, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. *Ann Surg.* 2000; 232 (3): 353-361.
- Surveillance, Epidemiology, and End Results (SEER) Program (<https://seer.cancer.gov/statfacts/html/stomach.html>). Accessed April 13 2020.
- Hamashima, C., 2018. Update version of the Japanese Guidelines for Gastric Cancer Screening. *Japanese Journal of Clinical Oncology.* doi:10.1093/jjco/hyy077
- Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965;64:31–49
- Ma J, Shen H, Kapesa L, Zeng S. Lauren classification and individualized chemotherapy in gastric cancer. *Oncol Lett.* 2016;11(5):2959-2964. doi:10.3892/ol.2016.4337
- Songun, I., Putter, H., Kranenbarg, E.M.-K., Sasako, M., Van De Velde, C.J., 2010. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *The Lancet Oncology.* doi:10.1016/s1470-2045(10)70070-x
- Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol.* 2009;27(6):851-856. doi:10.1200/JCO.2008.17.0506
- Al-Batran, et al. 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 ra. *The Lancet.* doi:10.1016/s0140-6736(18)32557-1

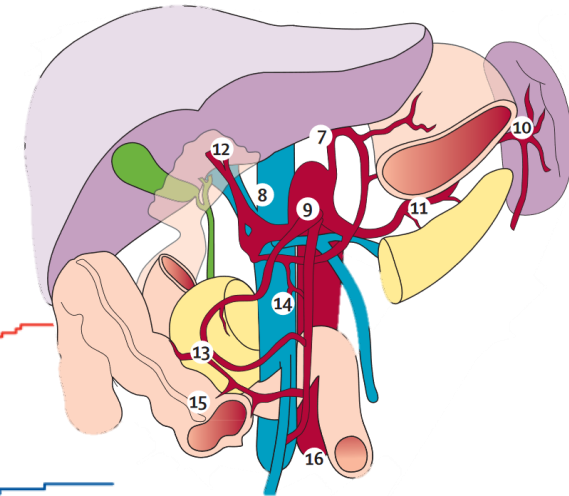
What Makes a Good Resection?



N1 Lymph nodes (perigastric)

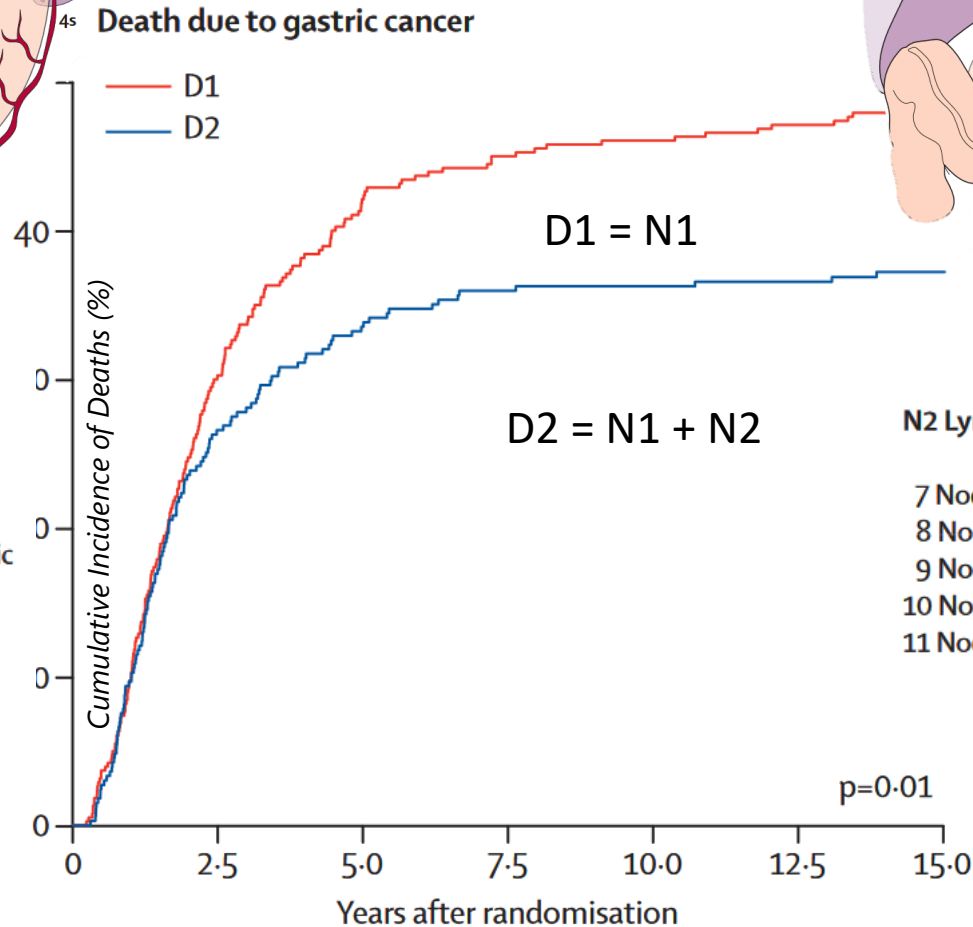
- 1 Right cardiac nodes
- 2 Left cardiac nodes
- 3 Nodes along the lesser curvature
- 4d Lymph nodes along the short gastric and the left gastroepiploic vessels
- 4s Lymph nodes along the right gastroepiploic vessels
- 5 Suprapyloric nodes
- 6 Infrapyloric nodes

The Dutch D1D2



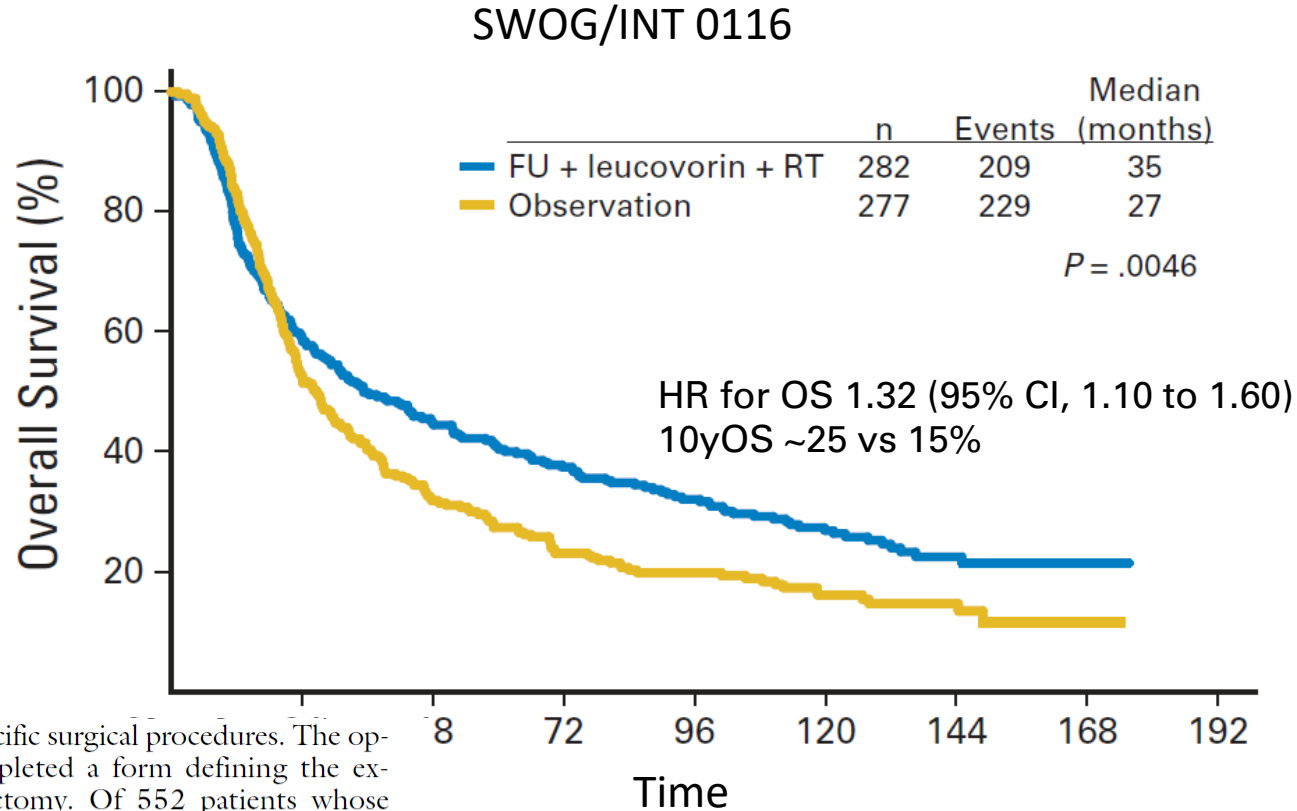
N2 Lymph nodes (branches coeliac axis)

- 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



Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol.* 2010;11(5):439-449.

What's Needed After a Limited Resection?

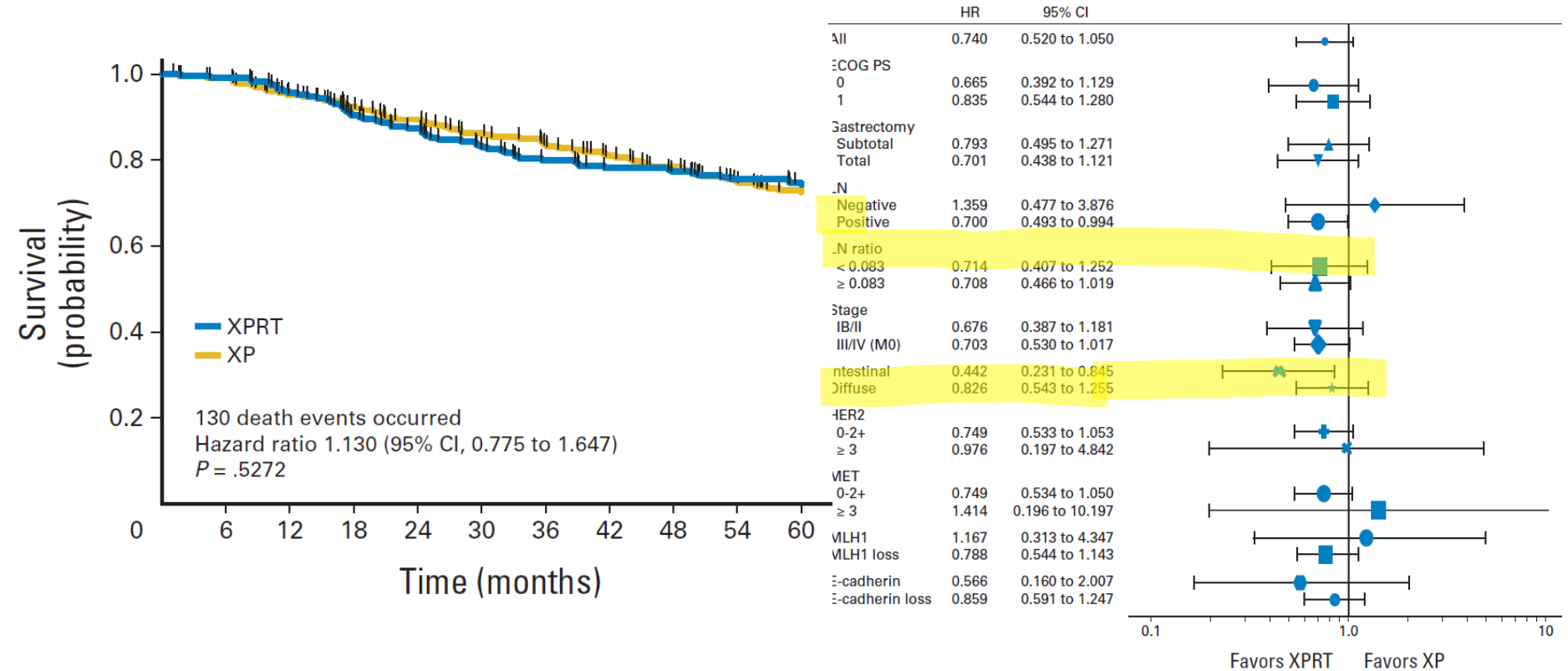


could not require specific surgical procedures. The operating surgeon completed a form defining the extent of lymphadenectomy. Of 552 patients whose surgical records were reviewed for completeness of resection, only 54 (10 percent) had undergone a formal D2 dissection. A D1 dissection (removal of all invaded [N1] lymph nodes) had been performed in 199 patients (36 percent), but most patients (54 percent) had undergone a D0 dissection, which is less than a complete dissection of the N1 nodes.

Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol. 2012;30(19):2327-2333.

Is there an art to chemoradiation?

ARTIST



Park SH, Sohn TS, Lee J, et al. Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses. *J Clin Oncol.* 2015;33(28):3130-3136.

Improved pCR

POET

pCR

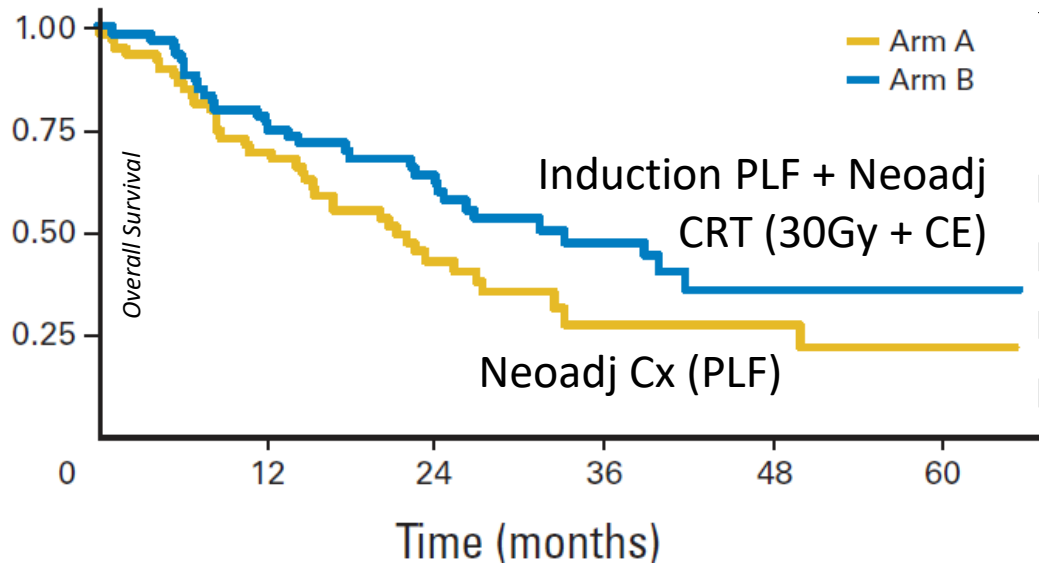


Table 3. Pathohistologic Results

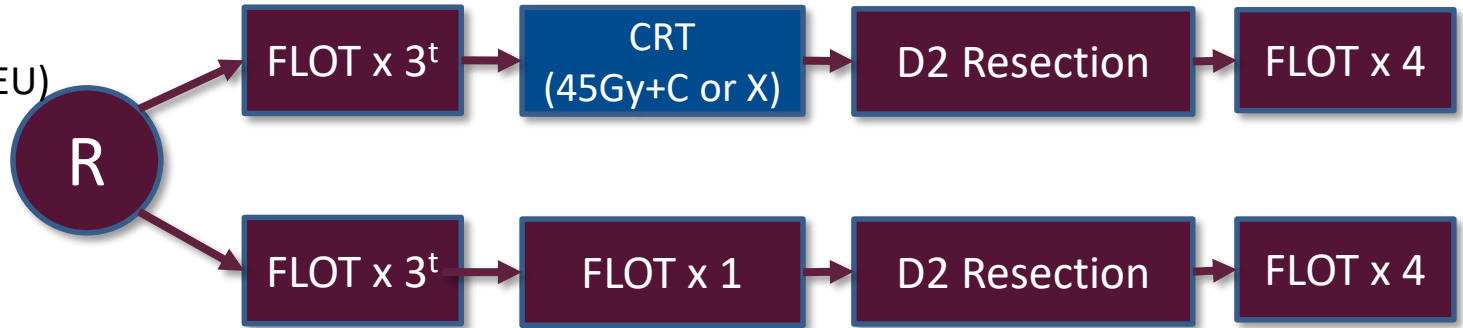
Treatment	Arm A		Arm B		P
	No.	%	No.	%	
Patients with resection	49	100.0	45	100.0	
pT0 N0 M0	1	2.0	7	15.6	.03*
pT1-4 N0 M0	17	34.7	22	48.9	
pT0-4 N0 M0†	18	36.7	29	64.4	.01*
pT0-4 N0 M0	18	36.7	29	64.4	.01*
pTall N+ M0	27	55.1	14	31.1	
pTall N+ M1	4	8.2	2	4.5	

Stahl M, Walz MK, Riera-Knorrenschild J, et al. Preoperative chemotherapy versus chemoradiotherapy in locally advanced adenocarcinomas of the oesophagogastric junction (POET): Long-term results of a controlled randomised trial. *Eur J Cancer*. 2017;81:183-190.

On the horizon...

TOP GEAR

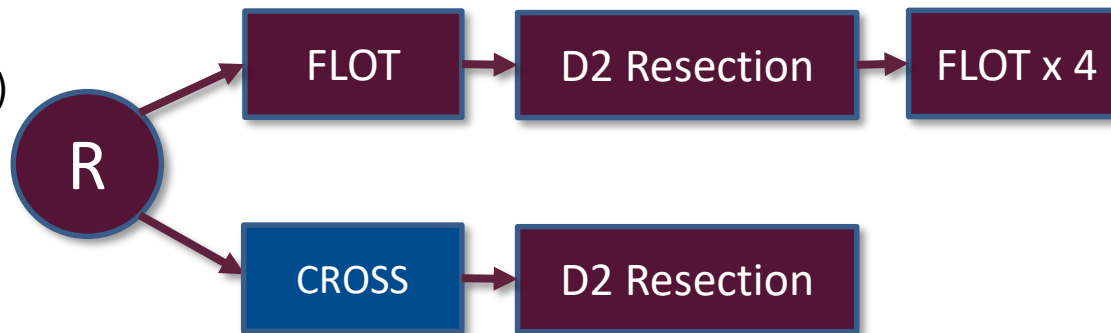
(AUS/NZ, Canada, EU)
EGJ (II-III)/Gastric
Ib - IVa



^tFLOT was a protocol addition from ECF (after FLOT4-AIO)

ESOPEC

(Germany)
Esophageal/EGJ (I-III)
AdenoCa
cT2+ or N+



Appendix

1. [Guides to defining CTV](#)
2. [CTV Contouring Atlas Glossary](#)
3. [CTV Contouring Atlas](#)
4. [Surgeries for Stomach Cancer](#)
5. [Follow-up Guidelines & Tumour Markers](#)
6. [Ranitidine- A Risk Factor for Esophageal and Stomach Cancer](#)

Chemotherapy Regimens

FL: Fluorouracil and Leucovorin

- start 1 month prior to RT, 2 cycles FL given 1 month after RT
- Fluorouracil given concurrently with RT

ECF: Epirubicin, Cisplatin, Fluorouracil

-3 cycles pre-op & 3 cycles post op

ECX: Epirubicin, Cisplatin, Capecitabine (**X**)

-3 cycles pre-op & 3 cycles post op.

- in CRT: Cisplatin and Capecitabine concurrent with RT

EOX: Epirubicin, Oxaliplatin, Capecitabine (**X**)

-3 cycles pre-op & 3 cycles post op.

- in CRT: Cisplatin and Capecitabine concurrent with RT

FLOT: Fluorouracil (2600mg/m² IV 24h infusion day 1, Leucovorin 200mg/m² IV D1, Oxaliplatin 85mg/m² IV D1, & Docetaxel 50mg/m² IV day 1)

S1: S-1 | **SOX:** S-1, Oxaliplatin | **SOX-RT:** S1, Oxaliplatin, RT

DOC: Docetaxel, Oxaliplatin, Capecitabine

PLF = Cisplatin + Leucovorin + 5-FU

CROSS: 41.4Gy/23 concurrently with Carboplatin and Paclitaxel

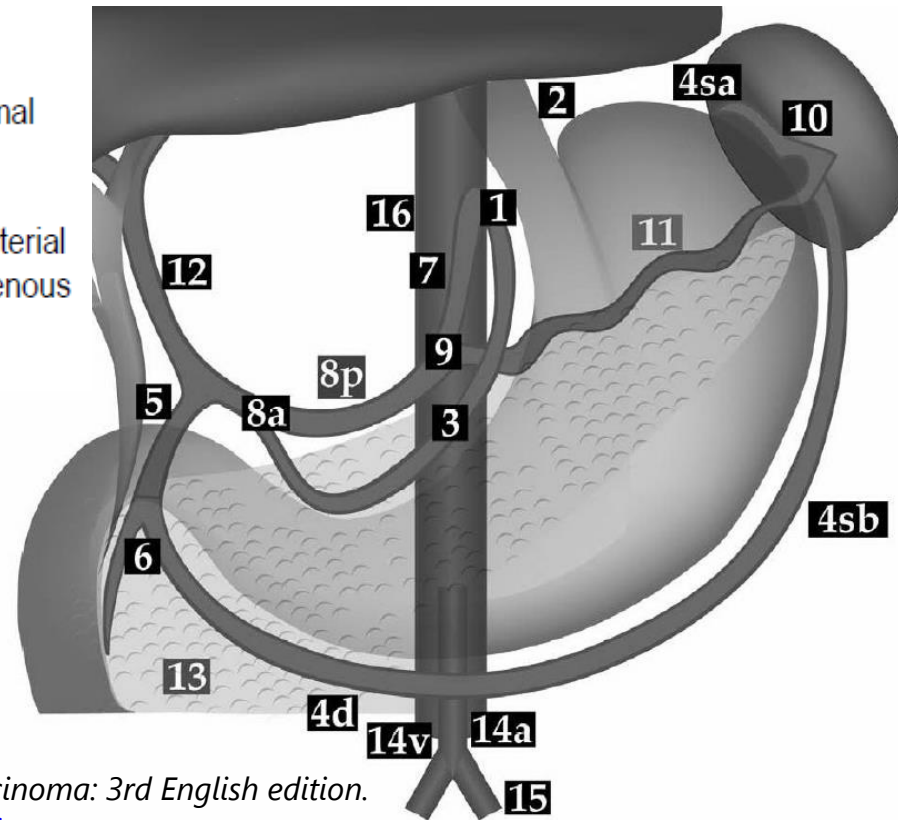
TOPGEAR Arm-CRT: Periop ECF x 2 (previously) or Periop FLOT x 3 & CRT - 45Gy/25# w/continuous 5-FU infusion (200 mg/m²/day, 7 days per week, throughout the entire period of RT) or capecitabine (825mg/m², bid, days 1 to 5 each week of RT)

Gastric Lymph Node Stations JRSGC 2010

CTV_{nodes} = Regional Lymphatics (Perigastrics & 2nd Tier Nodes)

Based on Japanese Research Society for Gastric Cancer surgical data. Identifying landmarks including the esophagus, stomach, proximal duodenum, hepatogastric ligament, porta hepatis, splenic hilum, pancreas, [celiac axis](#), SMA, fusion of diagnostic imaging, scopes, & discussions with surgery/radiology help with contouring target volumes.

- | | |
|--------------------------------|-----------------------------------|
| 1. Right cardio-esophageal | 10. Splenic hilum |
| 2. Left cardio-esophageal | 11d. Splenic arterial – distal |
| 3. Lesser curve | 11p. Splenic arterial - proximal |
| 4sa. Short gastric | 12. Hilar |
| 4sb. Left gastroepiploic | 13. Retropancreatic |
| 4d. Right gastroepiploic | 14a. Superior mesenteric arterial |
| 5. Suprapyloric | 14v. Superior mesenteric venous |
| 6. Infrapyloric | 15. Transverse mesocolon |
| 7. Left gastric | 16. Para-aortic |
| 8a. Common hepatic (anterior) | |
| 8p. Common hepatic (posterior) | |
| 9. Coeliac axis | |



1. *e-Contour Gastric Case (pending)*

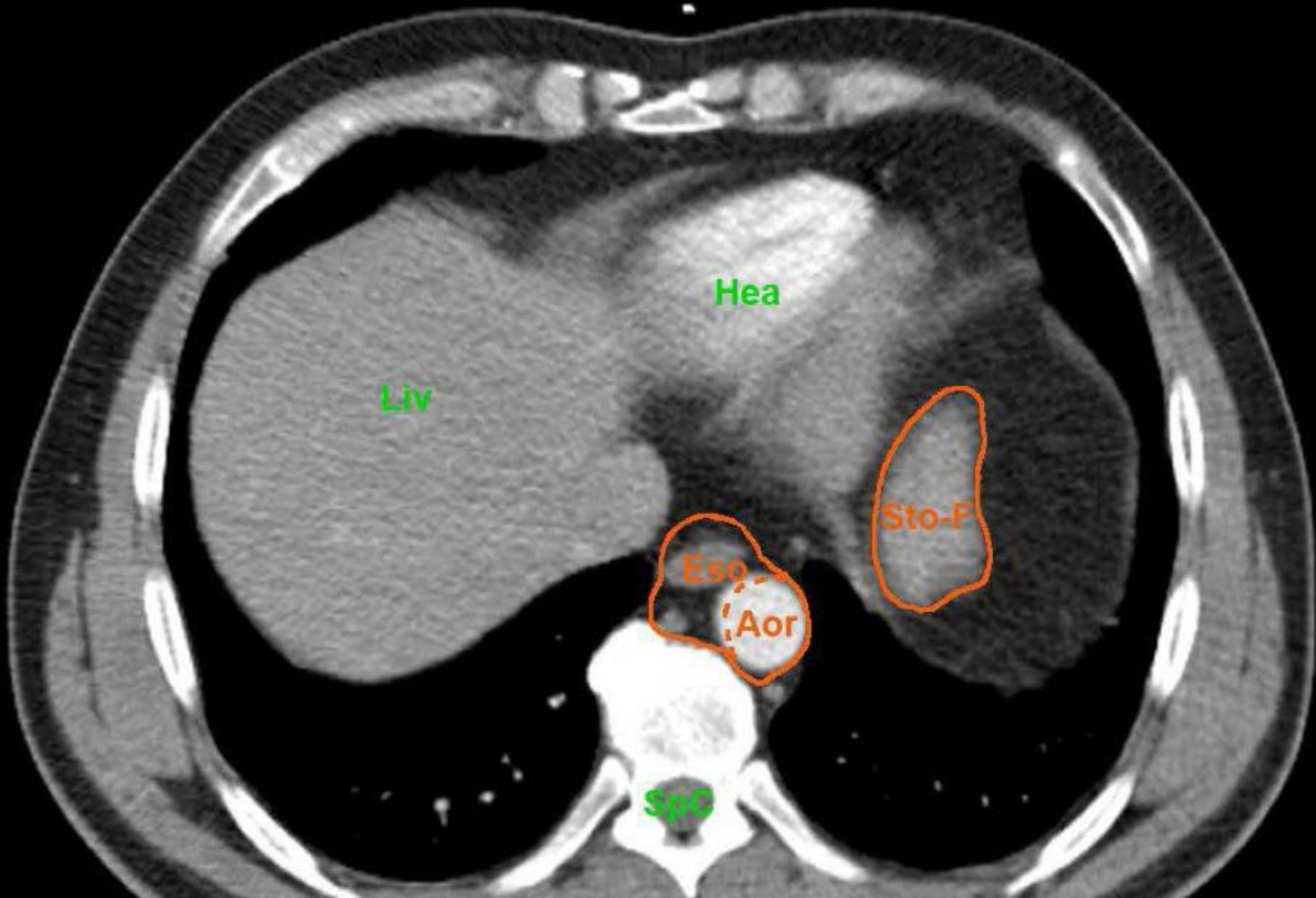
2. *Japanese Gastric Cancer A. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer. 2011;14(2):101-112. [10.1007/s10120-011-0040-6](https://doi.org/10.1007/s10120-011-0040-6).*

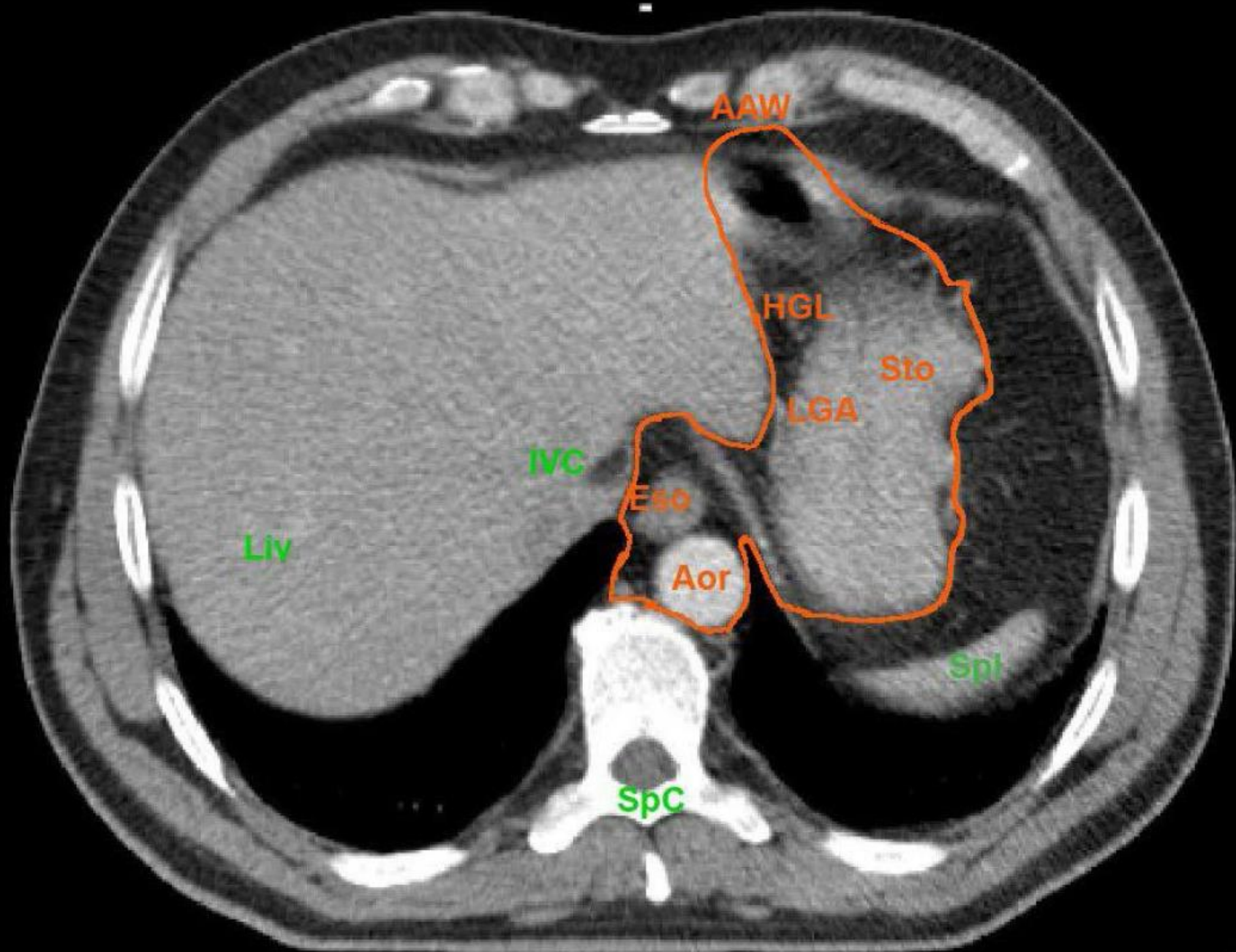
TOPGEAR 2017

Contour Acronyms

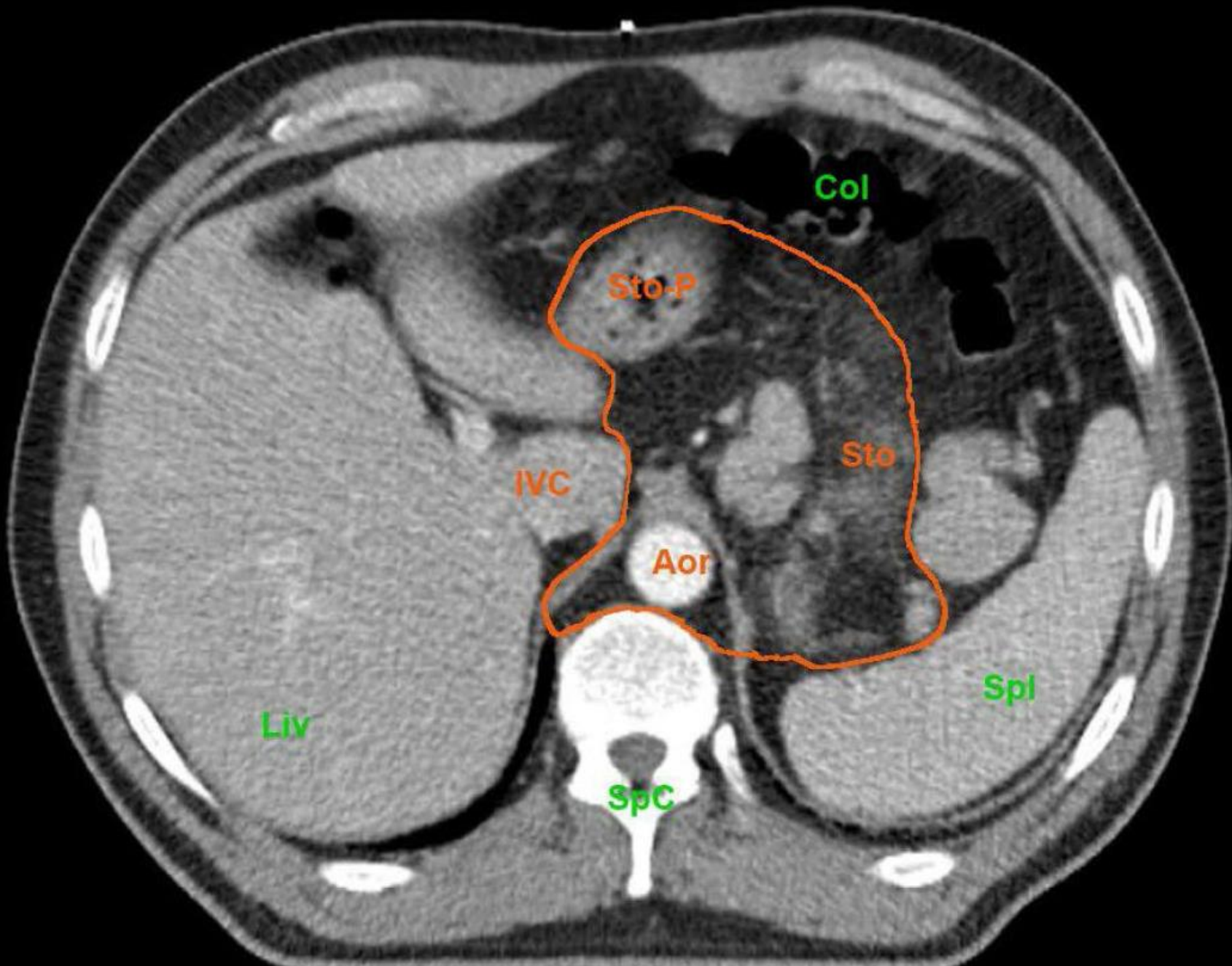
AAW	Anterior abdominal wall	Pan	Pancreas
Adr	adrenal	PoV	Portal vein
Aor	Aorta	ReA	Renal artery
CeA	Celiac artery	ReV	Renal vein
Col	Colon	SMA	Superior mesenteric artery
Duo	Duodenum	SMV	Superior mesenteric vein
Duo-3	Third part of duodenum	SpA	Splenic artery
Eso	Esophagus	SpC	Spinal cord
GaB	Gall bladder	SpF	Splenic flexure
Hea	Heart	SpH	Splenic Hilum
HeA	Hepatic Artery	Spl	Spleen
HGL	Hepatogastric ligament	SpV	Splenic Vein
IVC	Inferior Vena Cava	Sto	Stomach
Jej	Jejunum	Sto-A	Stomach antrum
Kid	Kidney	Sto-F	Stomach fundus
LGA	Left Gastric Artery	Sto-P	Stomach pylorus
Live	Liver		

Images reproduced from TOPGEAR protocol with approval of Dr. Trevor Leong









Liv

Col

Sto-P

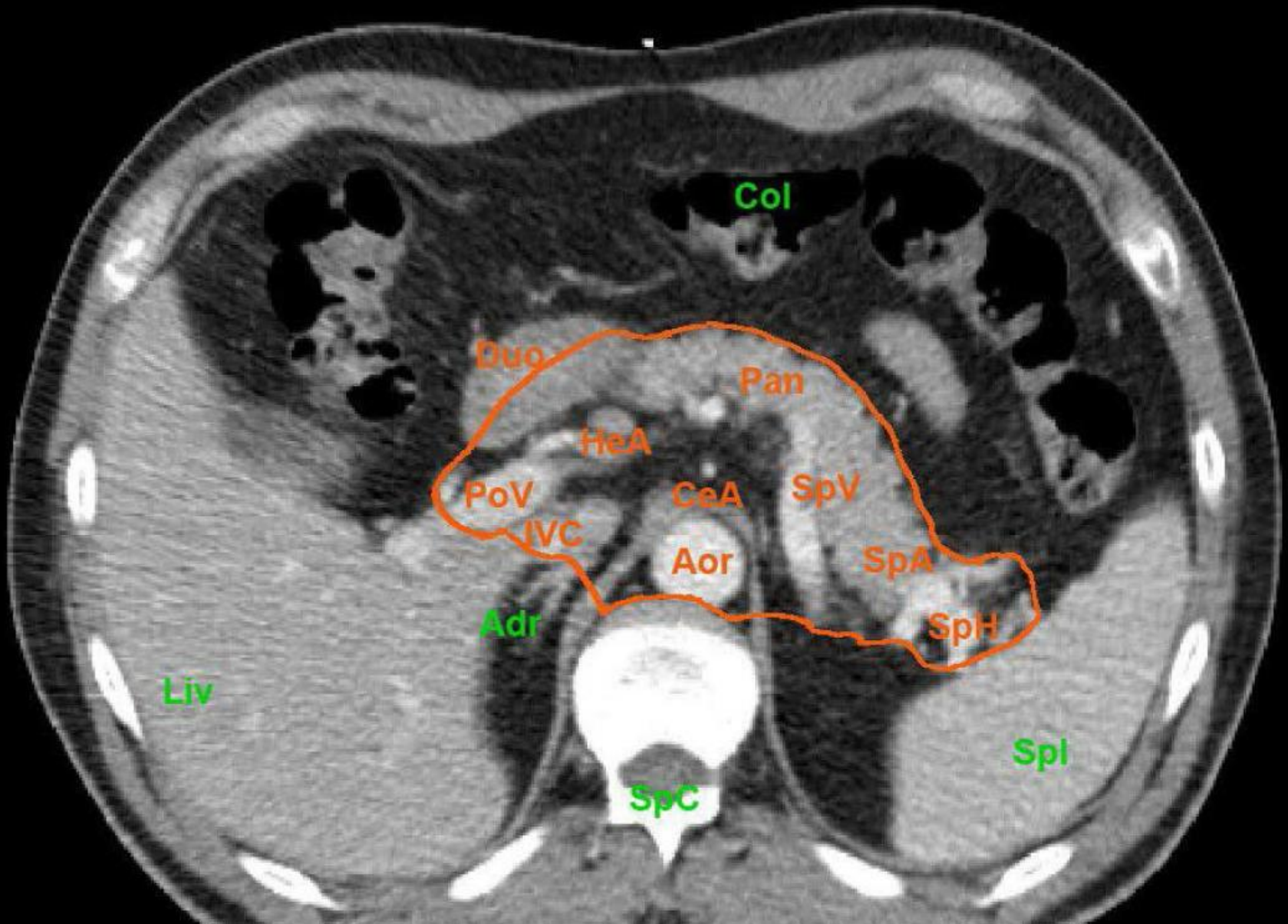
IVC

Aor

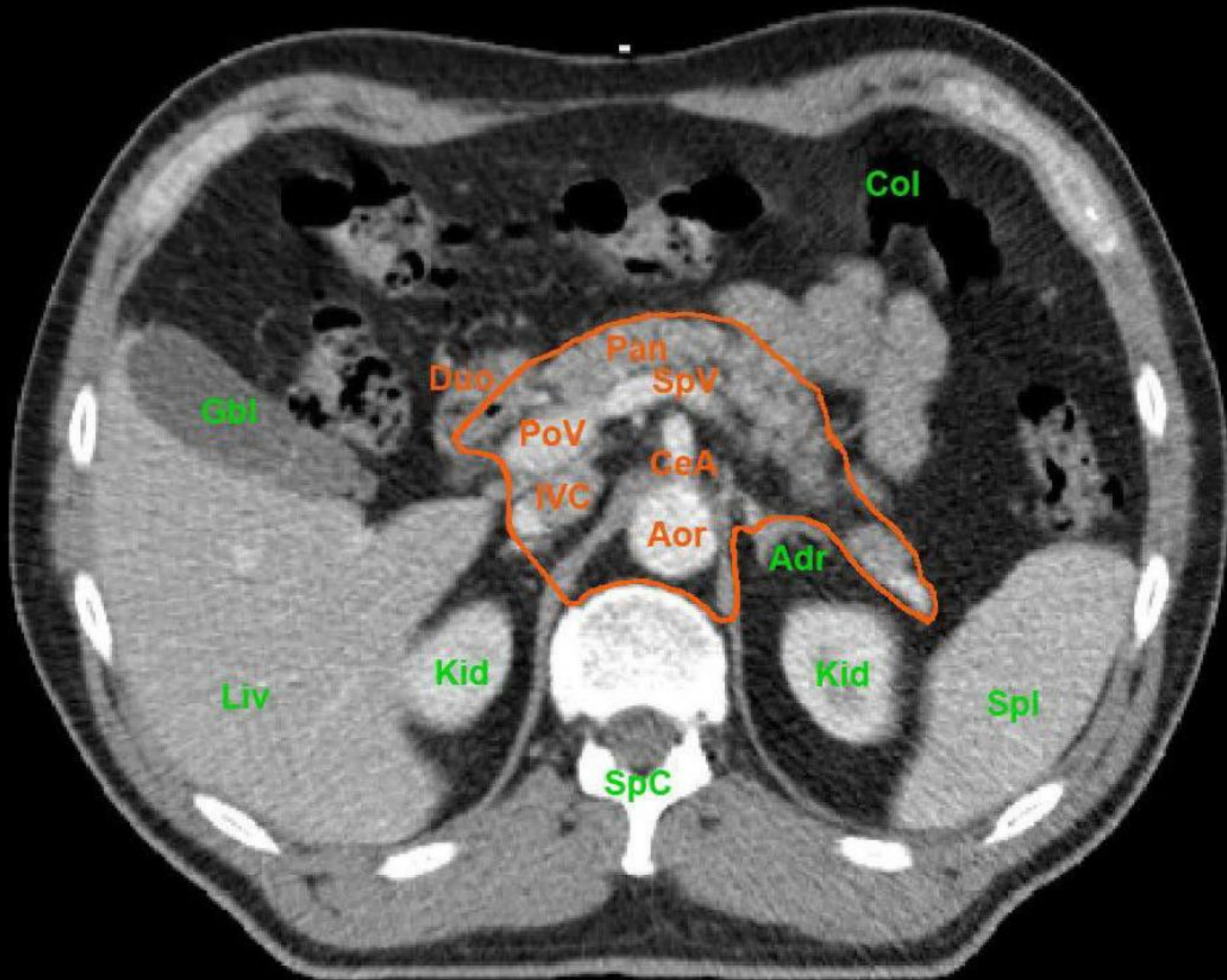
Sto

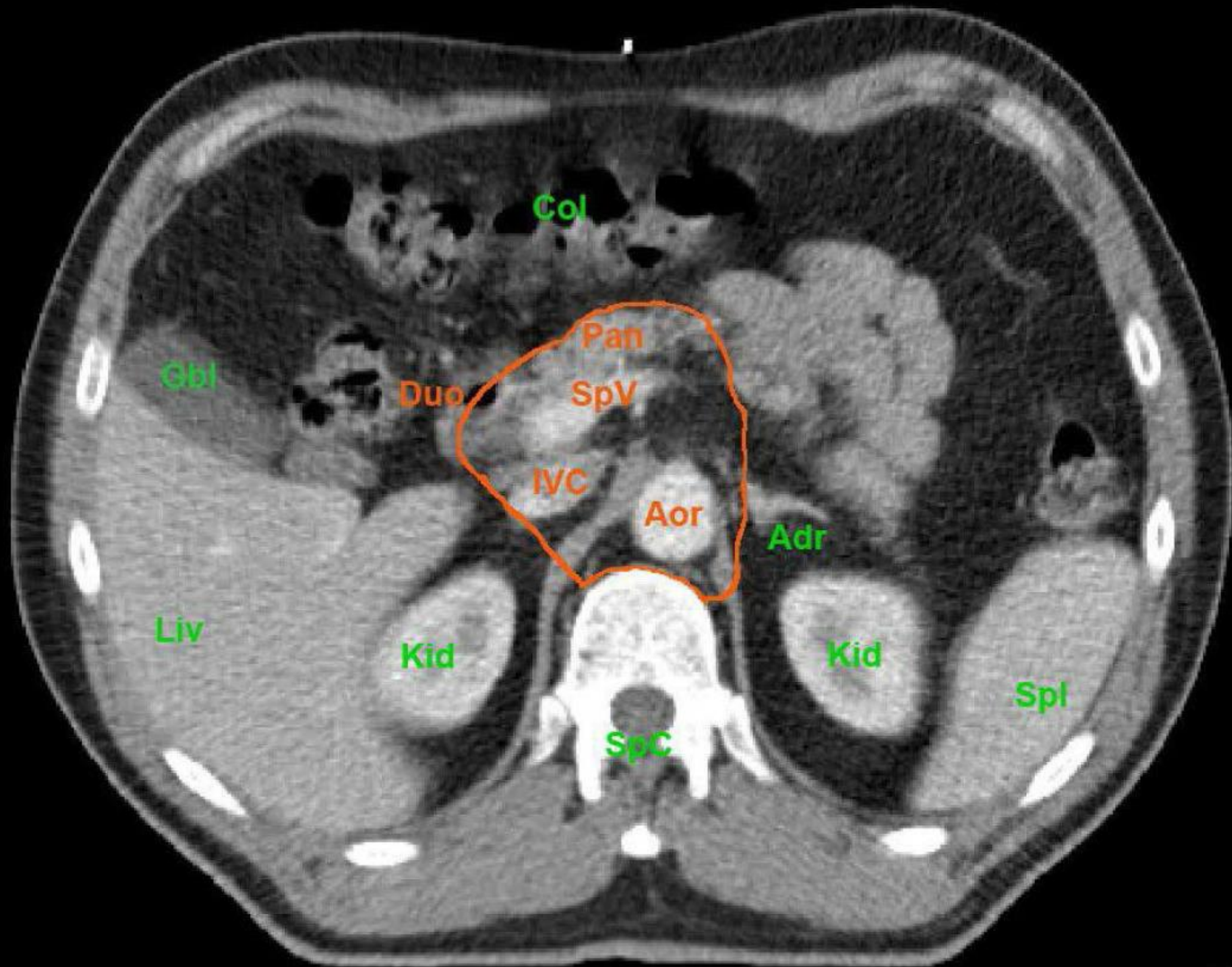
Spl

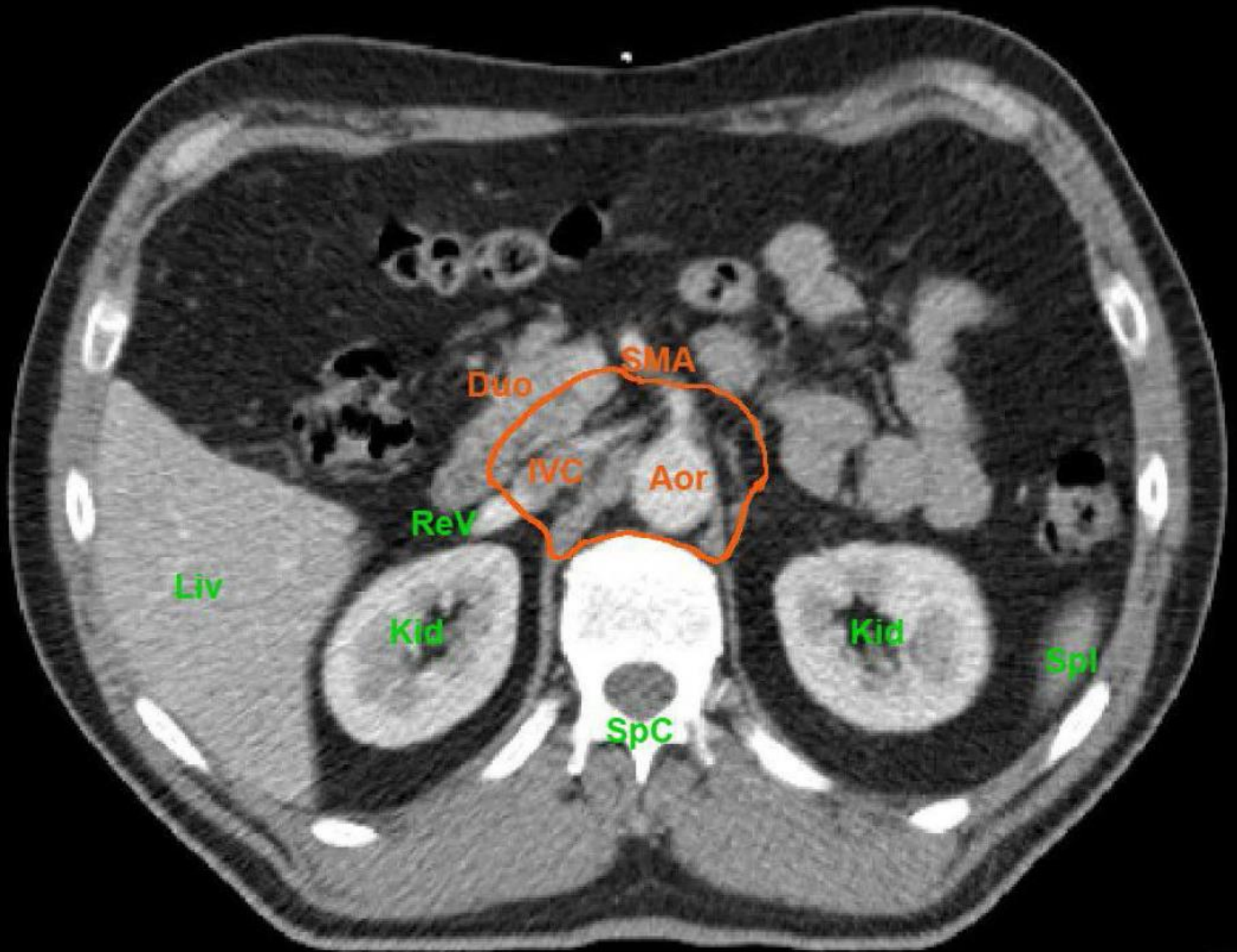
SpC

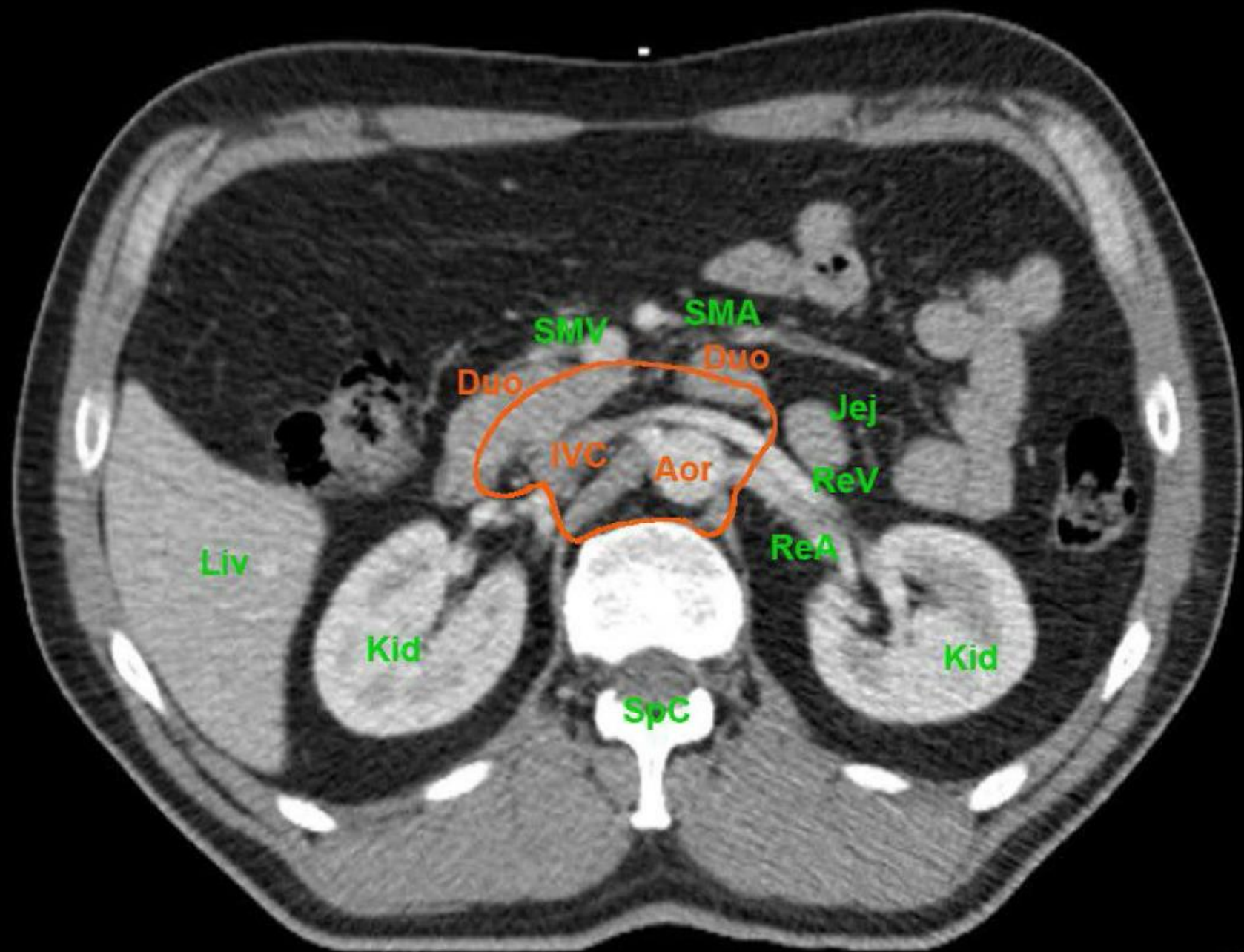


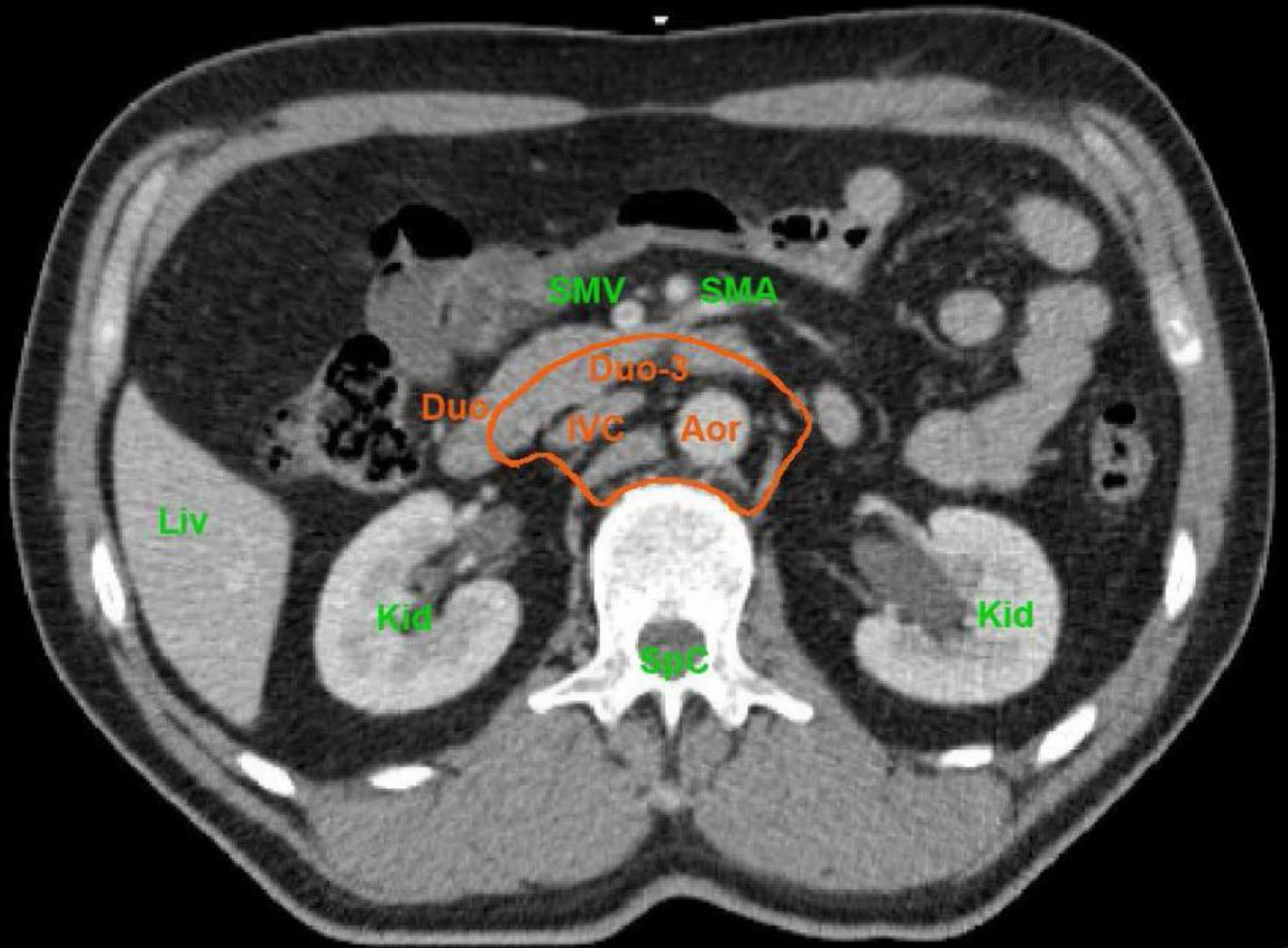
5 Celiac Axis (CeA): First branch arising from the front of the abdominal aorta, around T12











Ranitidine – A Risk Factor

- N-Nitrosodimethylamine (NDMA) is a probable carcinogen (EPA B2) especially for esophageal & gastric cancers
- Last year it was found in ranitidine
- Investigations showed that it was present in formulations from multiple manufacturers, increased over time, & increased when stored at higher temperatures resulting in unacceptable levels
- FDA, Health Canada, & other regulators worldwide have recalled the drug

If patients are on Ranitidine, switch to another H2 blocker or consider a PPI

FDA NEWS RELEASE

FDA Requests Removal of All Ranitidine Products (Zantac) from the Market

FDA Advises Consumers, Patients and Health Care Professionals After New FDA Studies Show Risk to Public Health

For Immediate Release: April 01, 2020

Thank you.