NEOADJUVANT THERAPY IN CARCINOMA STOMACH

Dr Jyotirup Goswami
Consultant Radiation Oncologist
Narayana Superspeciality Hospital, Howrah

NEOADJUVANT THERAPY?!

Few believers

Limited evidence

Many surgeons do not have access to colleagues in Radiation Oncology & Medical Oncology before surgery

Patients are either operable (undergo resection) or inoperable (undergo feeding stoma +/- palliative chemotherapy)

Neoadjuvant therapy can benefit a small but significant number of patients in the intermediate stage: can cause tumor downsizing→R0 resection→ improved local control→ reduced chance of distant metastases→ improved overall survival

PROBLEMS UNIQUE TO GASTRIC CANCER

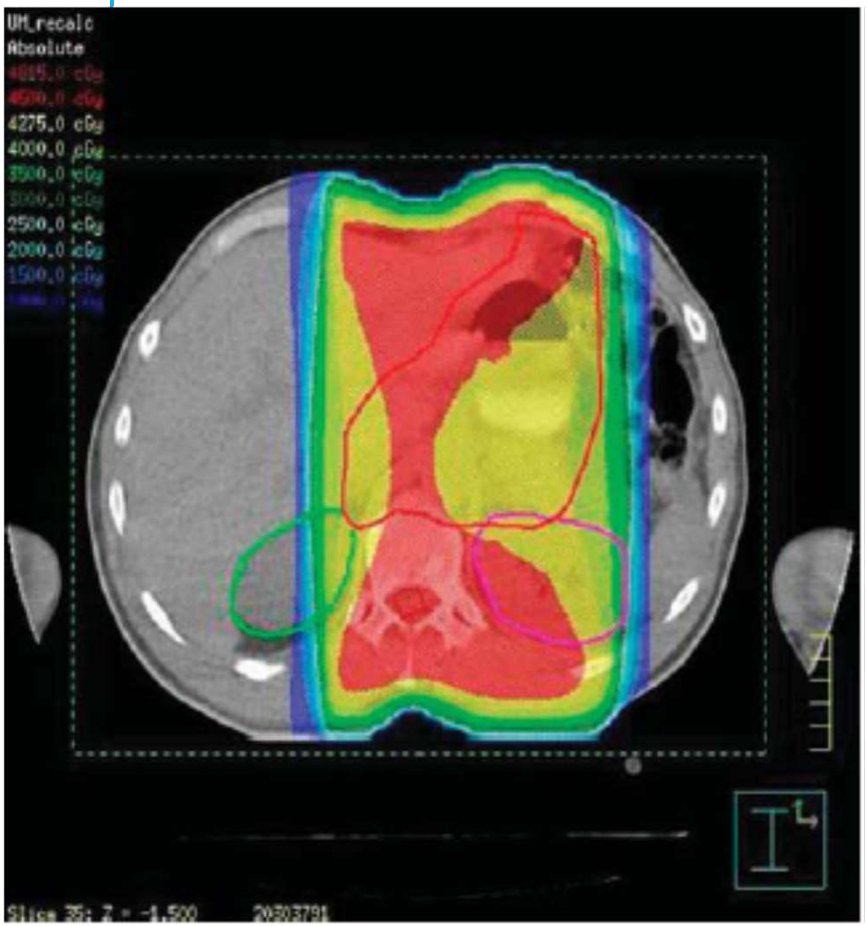
Symptoms mimic peptic ulcer disease

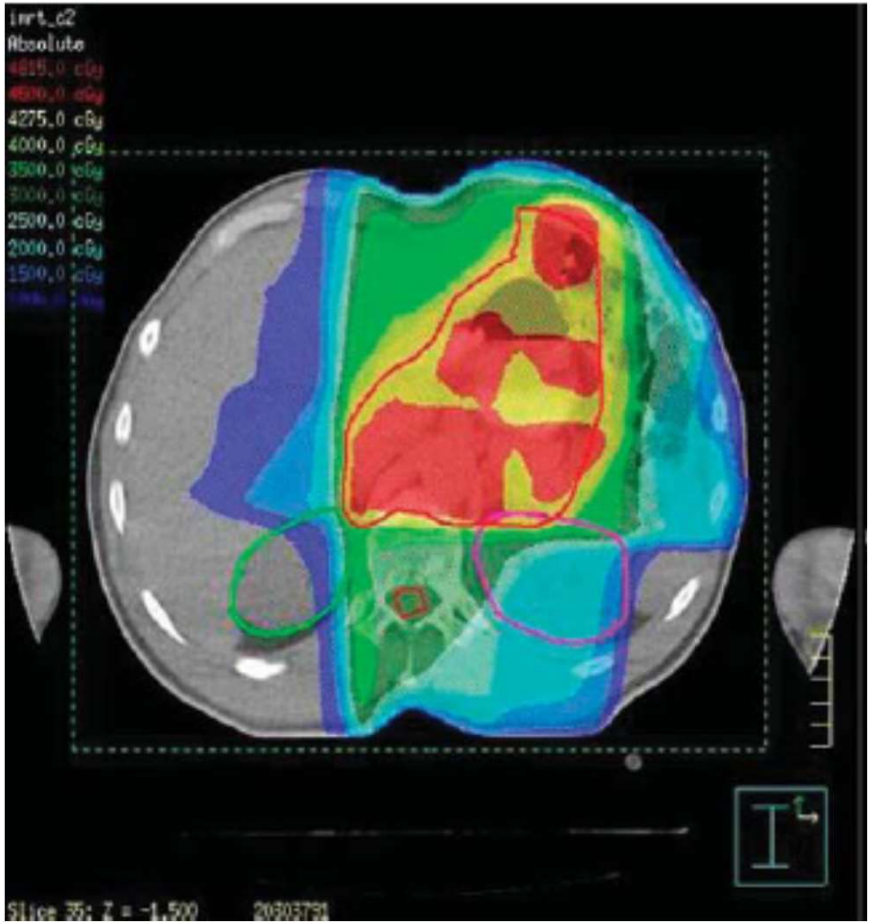
Diagnosis is almost always delayed

Patients may already have distant metastases or be too weak to undergo pre-operative chemotherapy/radiotherapy

Radiotherapy to upper abdomen to any significant dose, with/without chemotherapy used to be quite toxic in the era of conventional telecobalt therapy: significant emesis, neutropenia & thrombocytopenia (splenic radiation), renal failure (kidney radiation)

THE OLD & THE NEW





LESSONS FROM OESOPHAGEAL & JUNCTIONAL CANCERS

The MAGIC trial of perioperative ECF chemotherapy created the standard of care in management of GE junctional tumors

[Cunningham et al. NEJM 2006;355:11-20]

The CROSS trial has created a new paradigm for management of oesophageal and junctional cancers [van Hagen et al. NEJM 2012;366:2074-84]

Moderate dose radiotherapy, delivered conformally, with low dose chemotherapy concurrently, is safe and effective

LESSONS FROM RECTAL CANCER

Short course RT/long course CTRT are both equally effective

Pre-op therapy is better than post-op in terms of tolerability and local control

Pre-op therapy is effective in downstaging advanced tumors involving CRM; around 25% patients even achieve a complete response

ISSUES WITH PRE-OPERATIVE THERAPY

Moderate dose

Conformal delivery (sparing kidneys & other OARs)

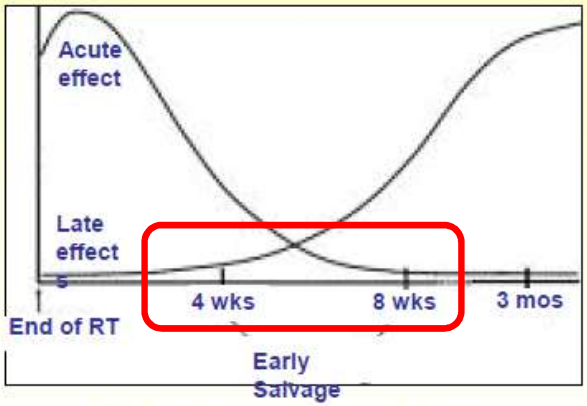
Better tolerated (smaller volumes can be delineated as primary disease is in-situ)

More effective (well-vascularised tissues)

Wound healing may be a problem post-operatively

Timing of surgery needs to be immediately following CTRT/ after settling down of initial acute inflammation and before development of significant fibrosis

LESSON FROM HEAD-NECK CANCERS



Window for response evaluation,

when acute inflammatory reactions subside and before long-term soft tissue damage is maximal

ADJUVANT THERAPY IN GASTRIC CANCERS

Landmark trials:

INT-0116 (MacDonald et al) [NEJM 2001;345:725-30]

ARTIST (Lee et al) [JCO 2011;30:268-73]

Radiotherapy and Oncology 92 (2009) 176–183

Systematic review

Survival after radiotherapy in gastric cancer: Systematic review and meta-analysis

Vincenzo Valentini [a,*], Francesco Cellini [b], Bruce D. Minsky [c], Gian Carlo Mattiucci [a], Mario Balducci [a], Giuseppe D'Agostino [a], Elisa D'Angelo [d], Nicola Dinapoli [a], Nicola Nicolotti [e], Chiara Valentini [a], Giuseppe La Torre [f]

Results: Radiotherapy had a significant impact on 5-year survival. Using an intent to treat (ITT) and a Per Protocol (PP) analysis, the overall 5-year RR was 1.26 (95% CI: 1.08–1.48; NNT = 17) and 1.31 (95% CI: 1.04–1.66; NNT = 13), respectively. Although the quality of the studies was variable, the data were consistent and no clear publication bias was found.

Conclusion: This meta-analysis showed a statistically significant 5-year survival benefit with the addition of radiotherapy in patients with resectable gastric cancer. Radiotherapy remains a standard component in the treatment of resectable gastric cancer and new RCTs need to address the impact of new conformal radiotherapy technologies.

9 studies
N=2025

Significant criticism of the RT trials:

Quality of surgery often ***sub-optimal***

The results of intention to treat method analysis.

	RR	95% CI	NNT
Intention to treat (ITT)			
Overall at 3 years of follow-up	1.12	(0.99–1.27)	24.52
Higher quality	1.04	(0.69–1.57)	23.82
Lower quality	1.11	(0.93–1.32)	22.57
Overall at 5 years of follow-up	**1.26**	**(1.08–1.48)**	**17.12**
Higher quality	1.3	(0.99–1.71)	21.47
Lower quality	**1.24**	**(1.02–1.50)**	**12.35**
Sensitivity analysis – 3 years			
$LQED_2 \geqslant 40$ Gy	1.13	(0.95–1.34)	23.85
$LQED_2 < 40$ Gy	1.11	(0.93–1.32)	22.57
Preoperative-RT	1.18	(0.76–1.81)	14.68
Postoperative-RT	1.01	(0.73–1.41)	29.58
IORT – yes	0.97	(0.79–1.19)	46.1
IORT – no	**1.17**	**(1.01–1.36)**	**17.44**
Before 1990	0.9	(0.74–1.09)	19.04
After 1990	**1.28**	**(1.09–1.51)**	**8.93**
Sensitivity analysis – 5 years			
$LQED_2 \geqslant 40$ Gy	1.18	(0.97–1.44)	27.93
$LQED_2 < 40$ Gy	**1.4**	**(1.08–1.82)**	**10.79**
Preoperative-RT	**1.39**	**(1.13–1.73)**	**10.05**
Postoperative-RT	1.53	(0.19–12.15)	93.00
IORT – yes	1.09	(0.88–1.34)	29.24
IORT – no	**1.41**	**(1.12–1.77)**	**15.06**
Before 1990	1.08	(0.86–1.36)	6265.7
After 1990	**1.39**	**(1.13–1.73)**	**10.05**

In bold type are reported statistically significant results.

EORTC-ROG expert opinion: Radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach

Oscar Matzinger [a,b,*], Erich Gerber [c], Zvi Bernstein [d], Philippe Maingon [e], Karin Haustermans [f], Jean François Bosset [g], Akos Gulyban [a], Philip Poortmans [h], Laurence Collette [a], Abraham Kuten [d]

Radiotherapy and Oncology 92 (2009) 164–175

RECOMMENDATIONS

Dose=45Gy/25#/5 weeks

Max duration=37 days

Planning CECT scan mandatory; no oral contrast recommended

Technique:3DCRT/IMRT

Beam energy:6MV/15MV

Single-phase plan

VOLUMES

GTV=gross disease

CTV=GTV+1.5cm (primary)/0.5cm (nodes); all draining LN stations to be included

ITV=CTV+1 cm (1.5cm distally) [for GEJ]/CTV+1.5cm [for stomach]

PTV=ITV+0.5cm

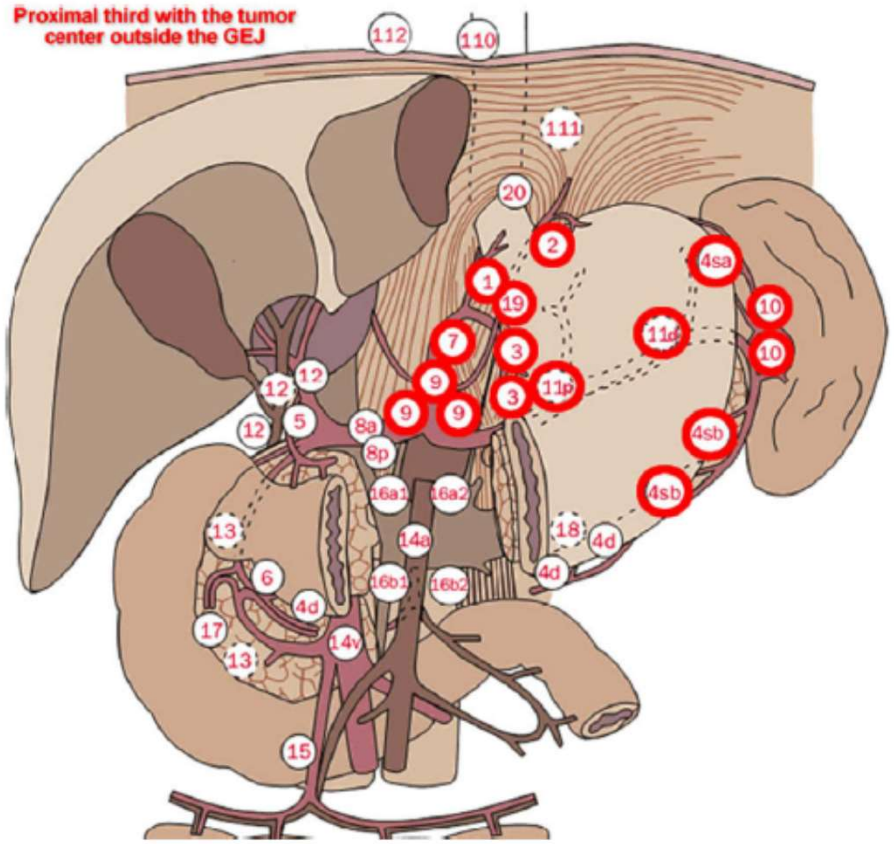
DELINEATION

CECT scans vital for delineation of gross disease

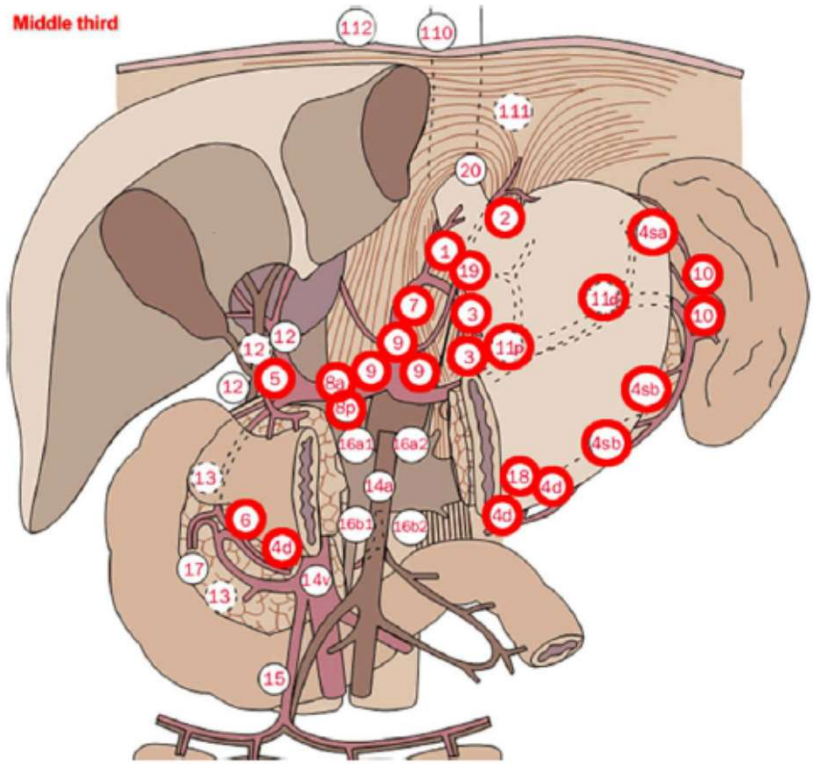
EUS difficult to use directly for delineation

PET-CT not essential; less sensitive; should not be used to exclude LN in the draining areas but can be used to include involved LN outside usual elective volume.

Proximal 1/3
with tumor centre
outside GEJ



Middle 1/3


Middle third
112
110
111
20
2
4sa
1
19
10
11s
7
3
10
12
9
11p
12
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9
9
4sb
8p
16a1
16a2
4sb
13
14a
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16b1
16b2
4d
4d
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14v
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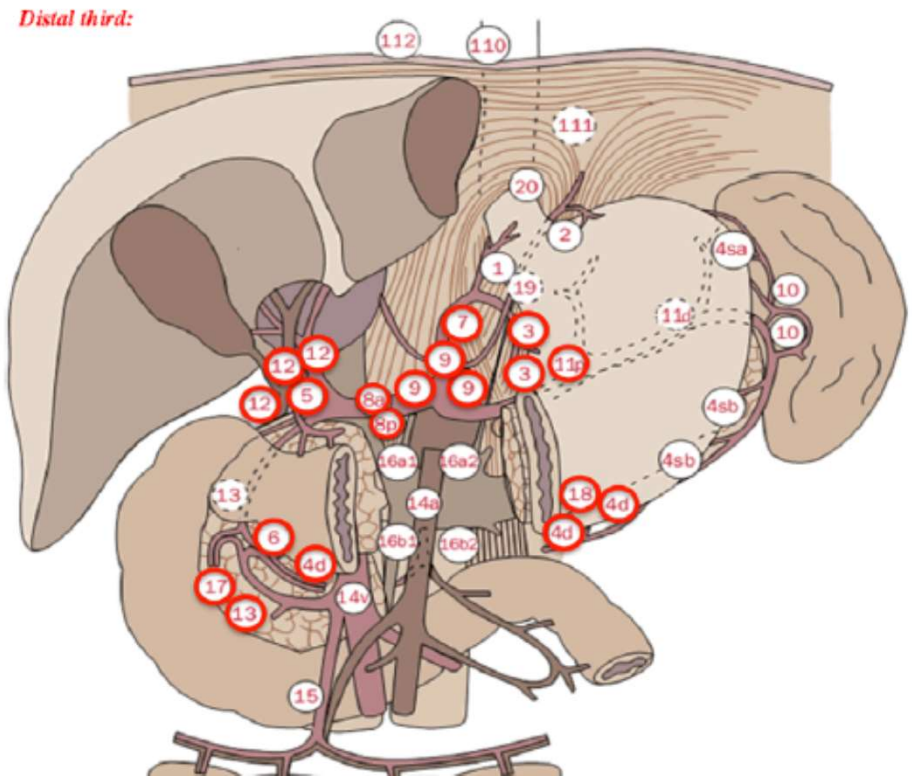
Distal 1/3


Distal third:
112
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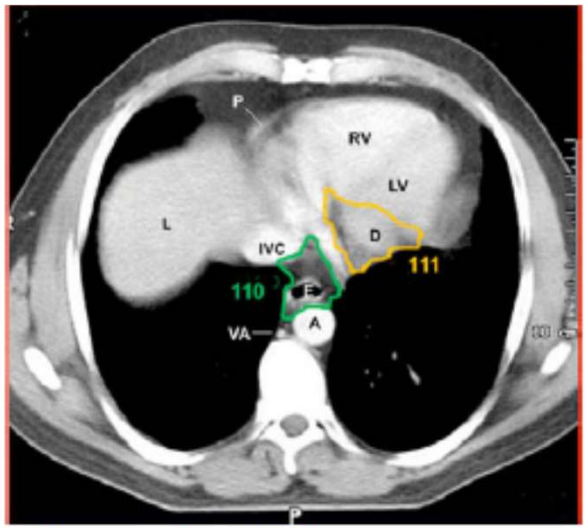
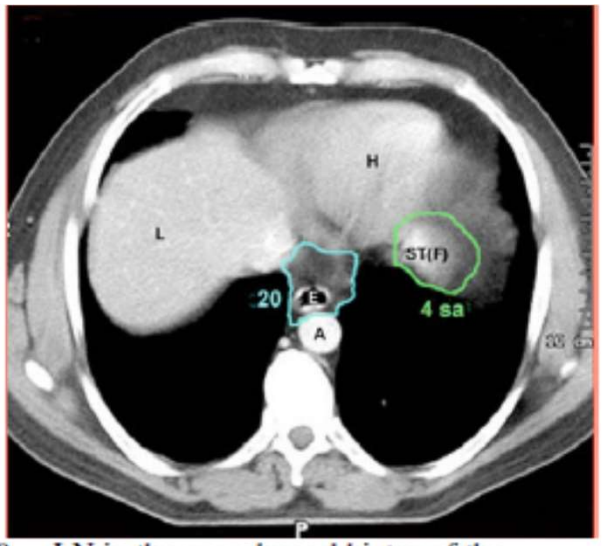
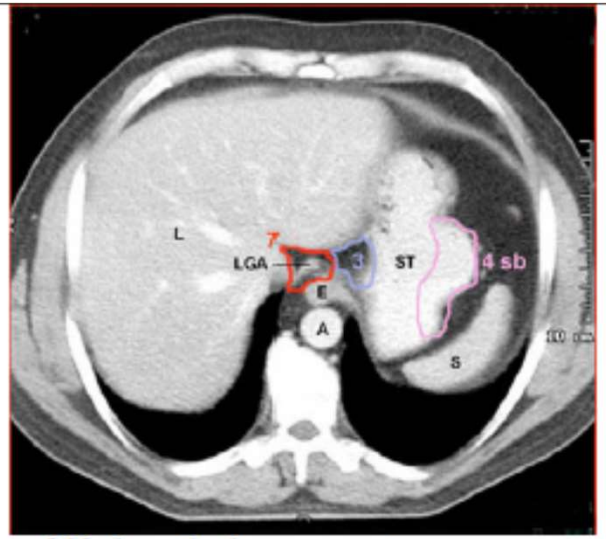


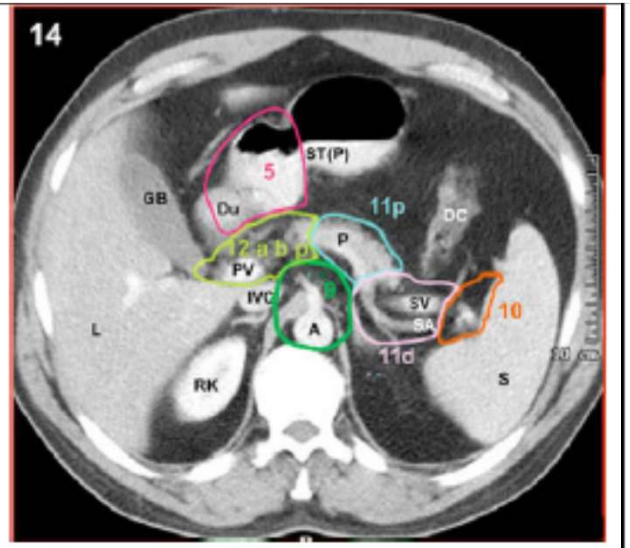
110 - Paraoesophageal LN
111 - Supradiaphragmatic LN



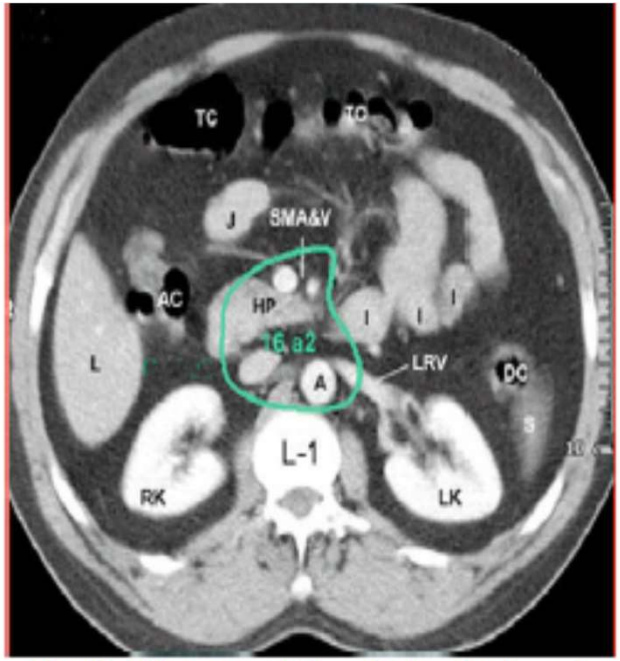
20 - LN in the oesophageal hiatus of the diaphragm
4sa - LN along the short gastric vessels



3 - LN along the lesser curvature
4sb - LN along the left gastroepiploic vessels
7 - LN along the left gastric artery



5 - Suprapyloric LN,
9 - LN around the celiac artery
10 - LN at the splenic hilum
11p - LN along the proximal splenic artery
11d - LN along the distal splenic artery
12 a, b, p - LN in the hepatoduodenal ligament



16 a2 LN around the abdominal aorta

CONSTRAINTS

Spinal cord max=45Gy

Bilateral lungs V20<20%

Heart D40<30%

Kidneys V20<70%

Liver V30<30%

IMAGE GUIDANCE

Portal imaging at least once weekly compulsory for treatment verification

Daily cone-beam CT (IGRT) should be used wherever possible for accurate treatment delivery

Motion management techniques like gating should be used if available ; can reduce margins for tumor motion.

ONGOING TRIALS

TOP-GEAR (Australia-NZ): MAGIC protocol vs pre-op ECFx3→XRT 45Gy+Capecitabine→S→post-op ECFx3. Resectable gastric/ GEJ tumors.

Chinese trial: XRT 45Gy+ S-1→ Surgery→ SOX x 4 cycles vs SOX x3→Surgery→SOX x 3

ELANCe trial (TMH Mumbai): MAGIC protocol in both arms, comparing D2 vs D3 lymnphadenectomy in resectable gastric tumors

SIOG-STO-1 (South India Oncology Group): NACT x 2 cycles→ Surgery→ ACT x 4 cycles vs Surgery→ACT x 6 cycles

NEO-ADJUVANT BIOTHERAPY

Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial

*Florian Lordick, Yoon-Koo Kang, Hyun-Cheol Chung, Pamela Salman, Sang Cheul Oh, György Bodoky, Galina Kurteva, Constantin Volovat, Vladimir M Moiseyenko, Vera Gorbunova, Joon Oh Park, Akira Sawaki, Ilhan Celik, Heiko Götte, Helena Melezínková, Markus Moehler, on behalf of the Arbeitsgemeinschaft Internistische Onkologie (AIO) and EXPAND Investigators**

N=904

Unresectable (4%) or metastatic (96%) carcinoma stomach

Randomised to either neoadjuvant XP or XP+weekly Cetuximab

Primary endpoint was PFS

PFS was 4.4 vs 5.6 months (p=NS)

Thus, addition of Cetuximab does not provide any advantage over chemotherapy alone in 1st line treatment of advanced carcinoma stomach

Lancet Oncol 2013; 14: 490–99

Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial

Yung-Jue Bang, Eric Van Cutsem,* Andrea Feyereislova, Hyun C Chung, Lin Shen, Akira Sawaki, Florian Lordick, Atsushi Ohtsu, Yasushi Omuro, Taroh Satoh, Giuseppe Aprile, Evgeny Kulikov, Julie Hill, Michaela Lehle, Josef Rüschoff, Yoon-Koo Kang, for the ToGA Trial Investigators†*

Lancet 2010; 376: 687–97

Included patients with unresectable/recurrent/metastatic adenocarcinoma of stomach/GEJ with HER-2+(IHC 3+/FISH+)
N=584
Chemotherapy + H (N=294) vs chemotherapy alone (N=290)
Median OS was 13.8 vs 11.1 months (p=0.0046)
Trastuzumab in combination with chemotherapy can be thus considered a new standard of care for advanced HER-2 + gastric/ GEJ cancers

DO ALL PATIENTS BENEFIT FROM SURGERY

Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial

Kazumasa Fujitani, Han-Kwang Yang*, Junki Mizusawa, Young-Woo Kim, Masanori Terashima, Sang-Uk Han, Yoshiaki Iwasaki, Woo Jin Hyung, Akinori Takagane, Do Joong Park, Takaki Yoshikawa, Seokyung Hahn, Kenichi Nakamura, Cho Hyun Park, Yukinori Kurokawa, Yung-Jue Bang, Byung Joo Park, Mitsuru Sasako, Toshimasa Tsujinaka, for the REGATTA study investigators†*

Lancet Oncol 2016

Non-curable factors were hepatic metastases (2-4,>1cm, =<5cm) OR peritoneal metastases (diaphragm or peritoneum caudal to transverse colon) OR para-aortic LN metastases (above coeliac axis and /or below inferior mesenteric artery)

Randomised to either chemotherapy (S-1+CDDP) [N=86] or D1-gastrectomy followed by chemotherapy [N=89]

Primary endpoint was OS. Median OS was 16.6 vs 14.3 months (p=0.7)

Hence, in absence of OS benefit, gastrectomy cannot be justified in advanced gastric cancer with a single non-curable factor

FUTURE DIRECTIONS

Better case –selection criteria, including molecular pathology

EBRT dose unlikely to escalate, but likely to utilize more image-guidance & motion management techniques

Concurrent systemic therapy based on Capecitabine; doublets with platinum agents may also become standard

Use of biotherapies likely to move beyond metastatic setting into the 1st line perioperative setting

Optimisation of scheduling of systemic chemotherapy in combination with chemoradiation and surgery

THANK YOU

Phase III Trial Comparing Capecitabine Plus Cisplatin Versus Capecitabine Plus Cisplatin With Concurrent Capecitabine Radiotherapy in Completely Resected Gastric Cancer With D2 Lymph Node Dissection: The ARTIST Trial

Jeeyun Lee, Do Hoon Lim, Sung Kim, Se Hoon Park, Joon Oh Park, Young Suk Park, Ho Yeong Lim, Min Gew Choi, Tae Sung Sohn, Jae Hyung Noh, Jae Moon Bae, Yong Chan Ahn, Insuk Sohn, Sin Ho Jung, Cheol Keun Park, Kyoung-Mee Kim, and Won Ki Kang

J Clin Oncol 30:268-273.

Korean trial

N=485

All patients had curatively resected adenocarcinoma of stomach; patients had all undergone R0 resection and D2 gastrectomy

Patients were randomised to two arms:

Arm A (N=228): 6 cycles of adjuvant XP

Arm B (N=230): 2 cycles of XP→ XRT 45Gy+ X→ 2 cycles of XP

- DFS was not improved overall with XRT, but only for N+ patients
- Being an unplanned subgroup analysis, this is a less than robust finding

DEMOGRAPHICS

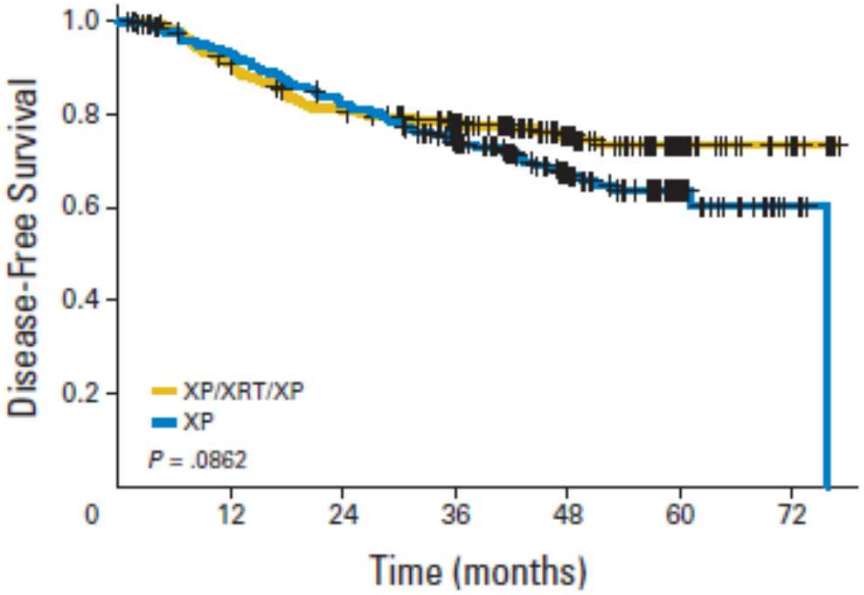
Median age=56 years

Most patients had body/ antral disease (around 40% each)

62% patients were male

>80% patients had N+ disease

DFS (overall)



DFS FOR N+