

# HUMANITAS

GAVAZZENI

## SEDE DEL CORSO

Sala Riunioni OMCeO Bergamo  
Via Giacomo Manzù 25 - Bergamo

**HUMANITAS**  
GAVAZZENI



Ordine dei Medici Chirurghi  
e Odontoiatri  
della provincia di Bergamo

MERCOLEDÌ 2 MARZO 2022

## DIAGNOSI E TERAPIA DEL CANCRO DELLO STOMACO: COSA FARE NEL 2022

### EDUCAZIONE CONTINUA IN MEDICINA

Corso gratuito e accreditato ECM (Educazione Continua in Medicina) della Regione Lombardia.

Corso accreditato ECM per Medici specialisti, Medici di Medicina Generale.

Per iscriversi, leggere la sezione "Modalità di partecipazione".

### SEGRETERIA ORGANIZZATIVA

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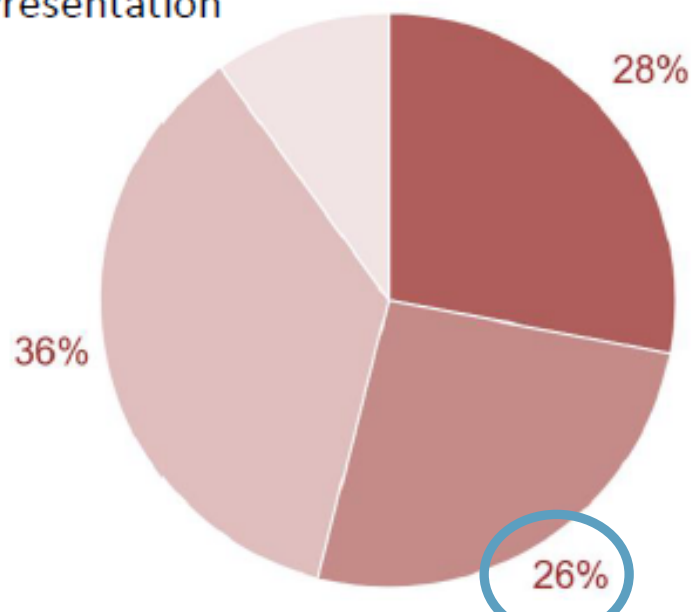
## Esiste un ruolo per la RT ?

Vittorio Vavassori  
UO Radioterapia  
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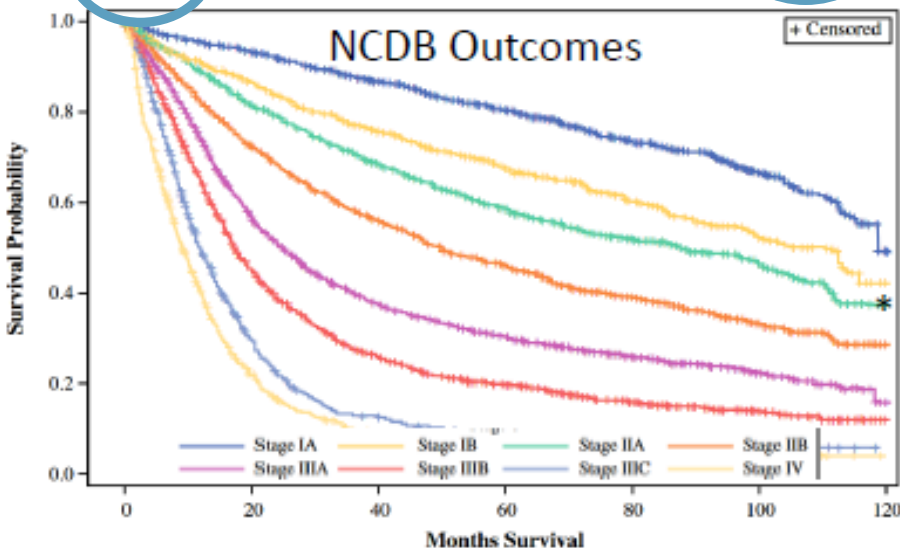
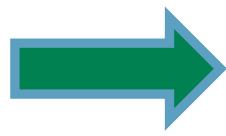
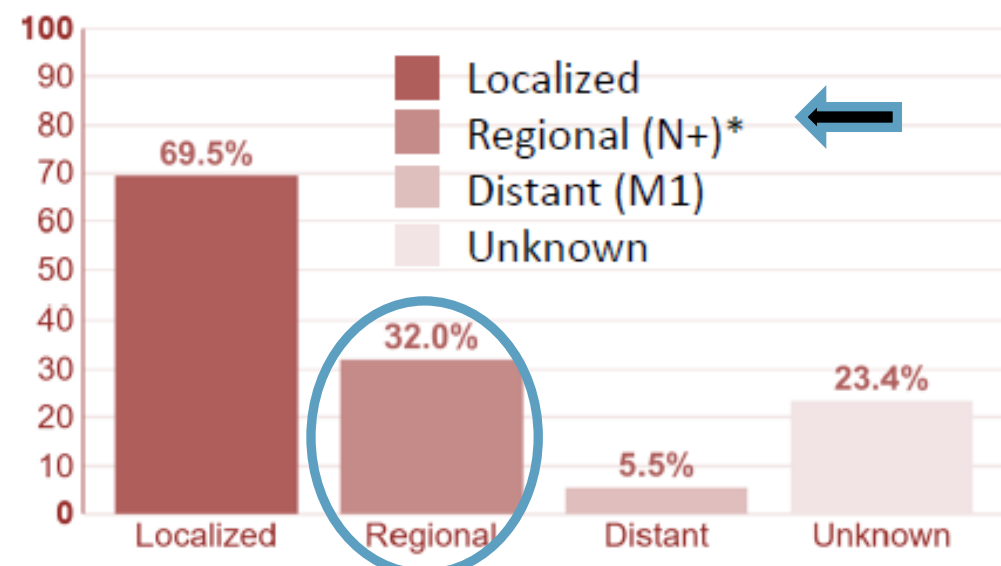


[www.humanitasedu.it](http://www.humanitasedu.it)

Presentation



5-Year OS



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

Ward 2018, A

| Trial      | Accrual Dates                                | Trial Type     | n    | Criteria   Population   %EGJ   | Arms   | Outcomes  | Conclusion  |
|------------|--|----------------|------|--|--|---|---|
| DUTCH D1D2 | 1989-1993<br>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<br>Macdonald 2001<br>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<br>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<br>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<br>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<br>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<br>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%.<br>5y OS 36% vs. 45%, | No survival benefit for adj CRT, but poor surgical and adjuvant compliance in both arms.                                |
| FLOT4      | 2010-2015<br>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)                     | 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.

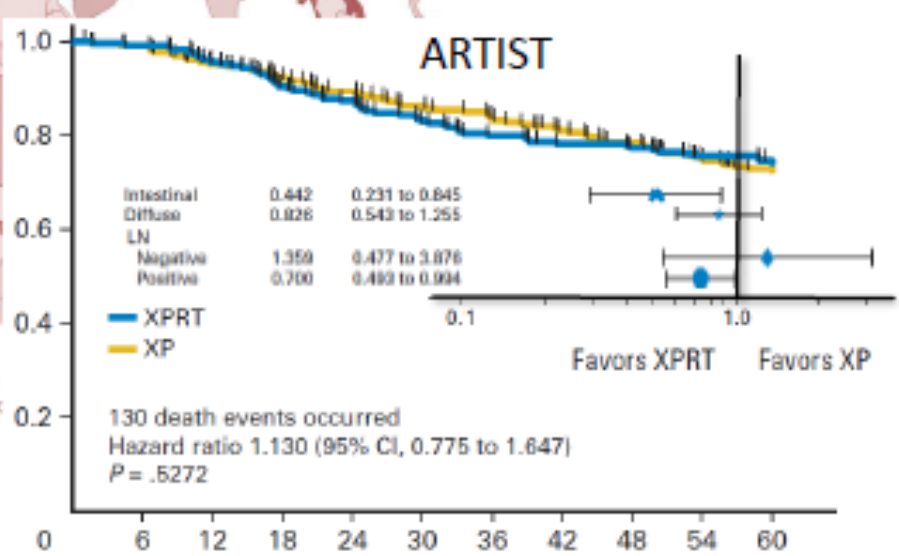
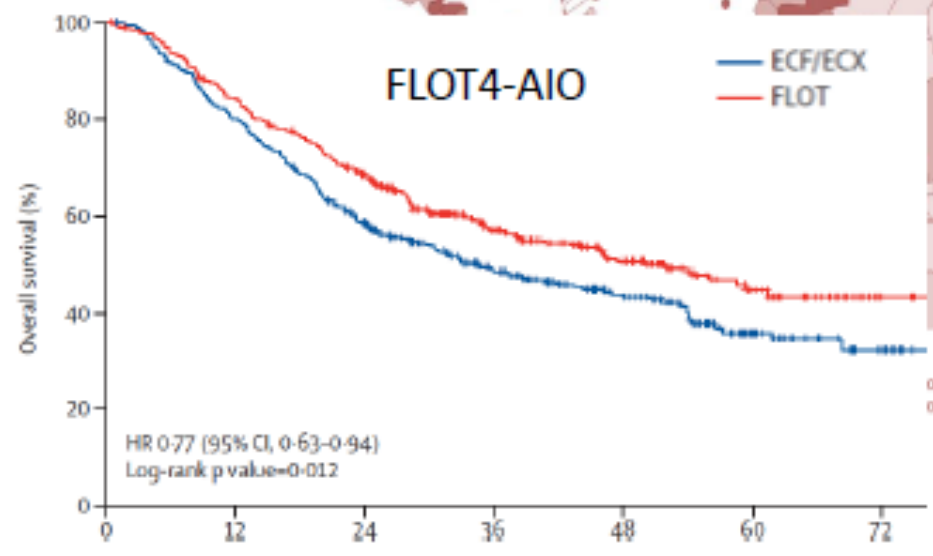
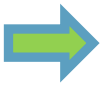
West ( North America, EU, & AUS/NZ)  
 Stage II/III (T2+ or N+ M0)  
 Periop CHT (FLOT)  
 FLOT4-AIO  
 Neoadj CRT (on trial)  
 TOPGEAR (Canada, EU, AUS/NZ)  
 ESOPEC/NEO-AEGIS (EU)  
 RACE? (USA)

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

*CT-RT, periop CT in USA,  
 periop CT in Europe*

East (Japan, South Korea, Taiwan, China)  
 Stage II/III (T2+ or N+ M0)  
 Sx > Adj CHT  
 ACTS GC (S-1)<sup>1</sup>: +10% 5yOS vs. Sx alone  
 CLASSIC (Cape+Oxali)<sup>2</sup>: +9% 5yOS vs. Sx alone  
 JACCRO GC-07 (S1+Docetaxel)<sup>3</sup>: +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 2007<sup>1</sup>, Bang 2012<sup>2</sup>, Yoshida 2019<sup>3</sup>

## TNM, prognosi

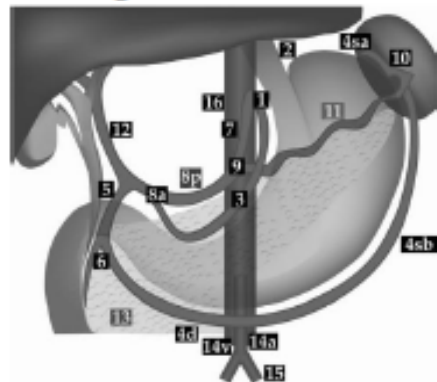
|   |  | cN0 | cN1 | cN2 | cN3a | cN3b |
|---|--|-----|-----|-----|------|------|
| T1  | a Lamina propria or muscularis mucosae | I   | IIA |     |      |      |
|   | b Submucosa                            |     |     |     |      |      |
| T2  | Muscularis propria                     |     |     |     |      |      |
| T3  | Subserosal connective tissue           | IIB | III |     |      |      |
| T4  | a Serosa (visceral peritoneum)         |     |     |     |      |      |
|   | b Adjacent organs                      | IVA |     |     |      |      |
| M1  | Distant metastasis                     | IVB |     |     |      |      |
| <i>cN1 1-2 regional LNs; cN2 3-5 regional LNs; cN3a 7-15 regional LNs; cN3b is ≥ 16 regional LNs.</i> |  |     |     |     |      |      |

### Good Prognostic Factors:

ECOG 0-2  
 Early-Stage  
 N0 > N+  
 R0 > R1 > R2  
 Intestinal > Diffuse Type

T.....recidiva locale, ILVS+,N+  
 N.....MTS

### Regional LNs Perigastric & 2<sup>nd</sup> tier



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

### Rate of LN Mets:

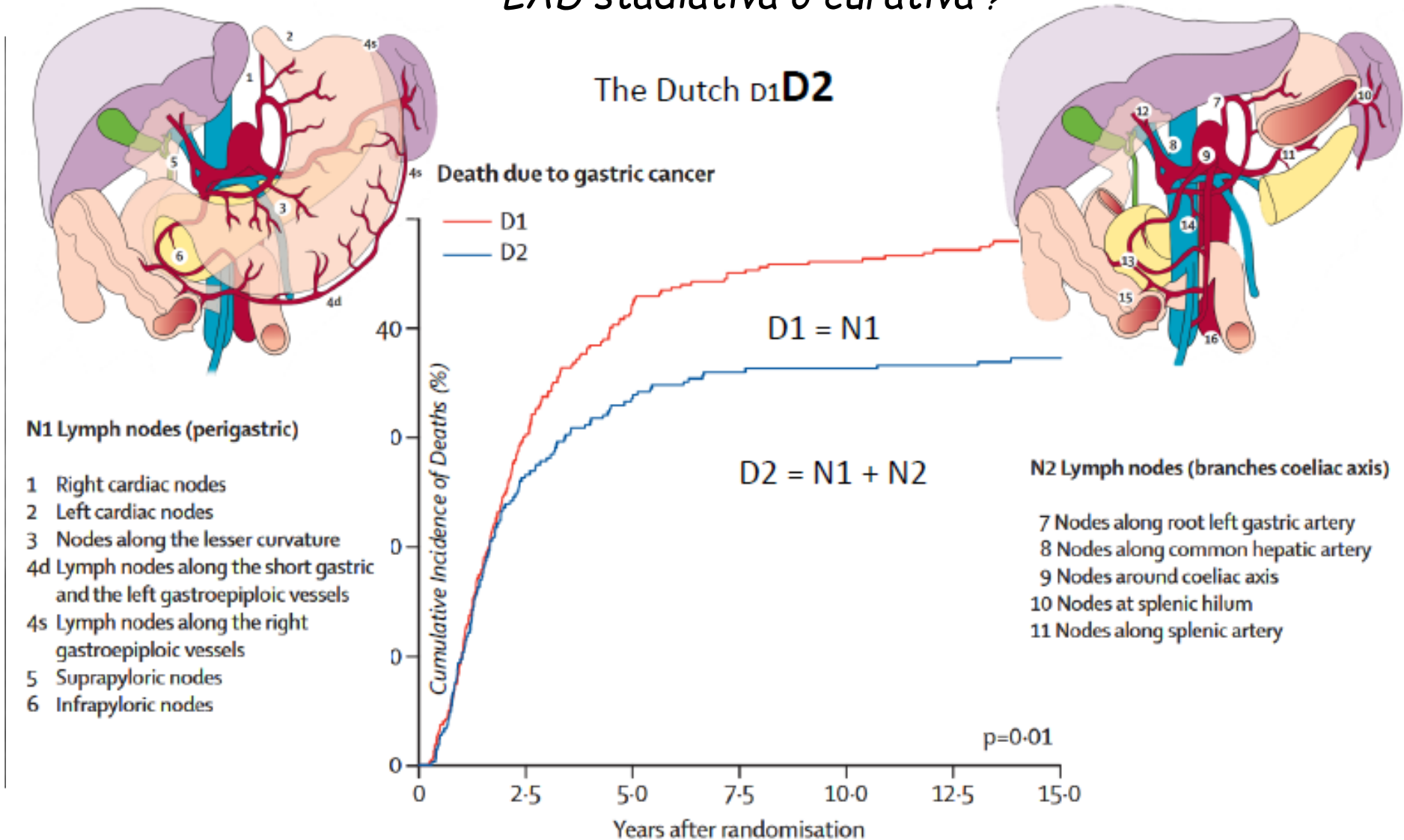
80% present w/nodal mets  
 T1: 10-20%;\* T2: 50%;\*  
 T3: 65%; T4a: 75% ; T4b:  
 80%

**SELEZIONE dei PAZIENTI**

Ward 2018, AJCC 8<sup>th</sup> ed 2017. TOPGEAR 2017

UICC raccomanda rimozione di almeno 16 LNF

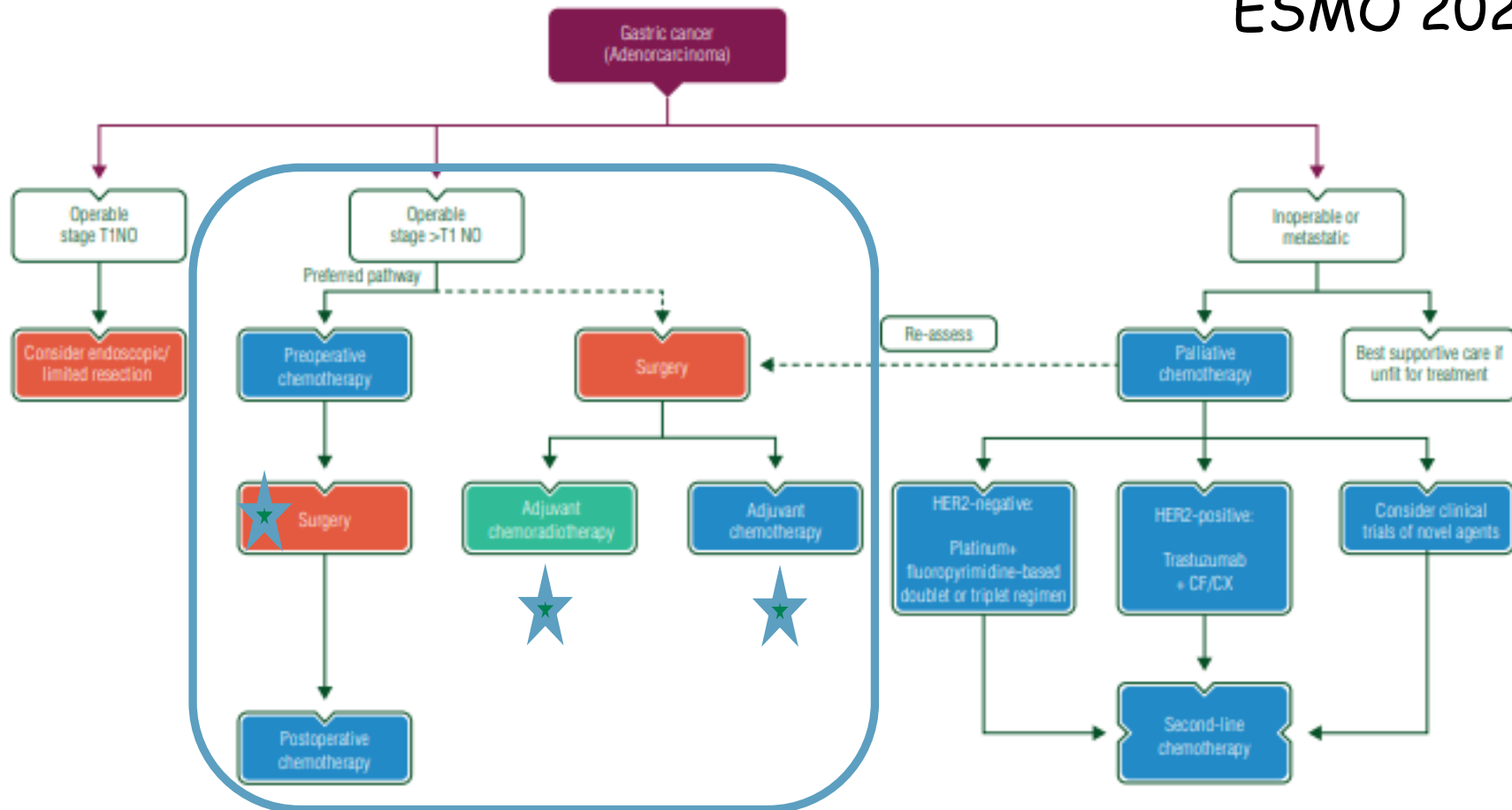
LAD stadiativa o curativa ?



\* Songun I, Putter H, Kranenborg 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.

## Fattori prognostici (oltre T e N)

- **T3-4N3**: prognosi simile a M+
- **LN RATIO ( N+/ N tot rimossi)**:  
ruolo prognostico anche in D2 oltre che se LAD inadeguata;  
LNR > 25% beneficio > da CT-RT v CT
- **Sottotipo istologico**: prognosi sottotipo intestinale > diffuso ;  
RT < efficace in diffuso
- **Grado di malignità**: correla con T3-4 e N+:  
ruolo per selezione pts per CT-RT?
- **LVSI correla con N+ e SM+ ; SM+ correla con PD e MTS**  
CT-RT > CT in R1; CT-RT in NO ma LVSI e/o R1?



**Figure 1.** Gastric cancer treatment algorithm.

HER2, human epidermal growth factor receptor 2; CF, cisplatin and 5-fluorouracil; CX, cisplatin and capecitabine

## Neoplasia resecabile- CT pre-op e CT-RT post-op ?

- **MAGIC**: (ECF perioperatorio vs obs) : considerato standard (<D2 in 85%)
  - **FLOT IV**: (docetaxel, oxaliplatino, 5-Fu, LV vs ECF o ECX), D2 , cT2+ o N+;  
> a ECF/ECX in OS e DFS a 5 yrs, non aumento tox, ( ma solo 46% pts completato tmt)
  - **CT-RT necessaria dopo CT neoadiuvante?**
  - **CRITICS** : CT pre (ECCape o EOCape) +CT/RT post-op (INT 0016) vs peri-op CT;  
IB-IVA, D1, 50% non ha terminato trtm ; non sottoanalisi per N+  
nessuna differenza in OS, OS mediana,LRC; < tox ematologica se RT.
- ESMO: pts che ricevono perioperative CT non dovrebbero ricevere CT-RT .
- **CT-RT post-op: Non di routine.**  
in T3-T4 e/o N+ e/o R1, specie se TRG 3 ( residuo esteso o non risposta) e buon PS ?

FOLFOX o FLOT o deGramont x2, RT 45 Gy+FU iv o Cape, ECF x2 o FOLFOX o deGramont x4

## Neoplasia resecabile-Chirurgia upfront

- **INT 0116:** CT-RT(45 Gy+ 5FU/LV)post-op vs obs : **90%<D2, D0 in 54%, 85%N+**  
10 yrs FU : CRT superiore in OS, RFS, LR,DM ; possibile strategia alternativa (USA)
- **ARTIST:**cape/cis vs cape/cis + RT+cape in post-op : **D2, R0, IB-IV**  
beneficio in DFS da RT in N+ e sottotipo intestinale, non differenza in OS  
LNR>25% predittivo per vantaggio da CRT in OS;
- **ARTIST 2:**S1 vs S1+ oxaliplatino vs S1+ oxaliplatino + 45 GyRT post-op, II-III,**D2, N+**  
nessuna differenza tra SOX e SOXRT, entrambi > S1 in DFS.

CT-RT non > CT in termini di OS, anche se > in termini di DFS, specie in D0- (D1?)

### A chi offrire CT-RT?

- T3-4 e/o N 1-N2 ( se LN ratio > 25%,< D2, LAD inadeguata )
- T2N0 e LVI+, <D2 o LAD inadeguata, specie in istotipo intestinale
- R1/R2

# Neoplasia resecabile- CT-RT preop ( + CT post-op) ?

- CT-RT pre-op in Ca esofago e EGJ

**POET:** pre-op CT-RT vs pre-op CT in EGJ tipo I-III;  
CT-RT migliora pCR e LR, trend per OS.

**NEO/AEGIS** : CROSS vs MAGIC/FLOT in esofago e EGJ; T2-3,N0-3  
CT-RT: > R0, > pCR, > pN0, OS non inferiorità della CT.

- Diversa patogenesi e biologia tra npl esofago e stomaco

- **RTOG 9904** ( fase II) : cis/5FUx2 + RT 45 Gy+5FU e taxolo settimanale pre-op  
pCR 26%, 1 yr OS 72 %, OS mediana 23 mesi, se pCR 1 yr OS 82 %.

- **TOPGEAR** ( ongoing) :- stomaco e GEJ

ECF x3 peri-op vs ECFx2 + CT-RT pre-op, ECFx3 post-op

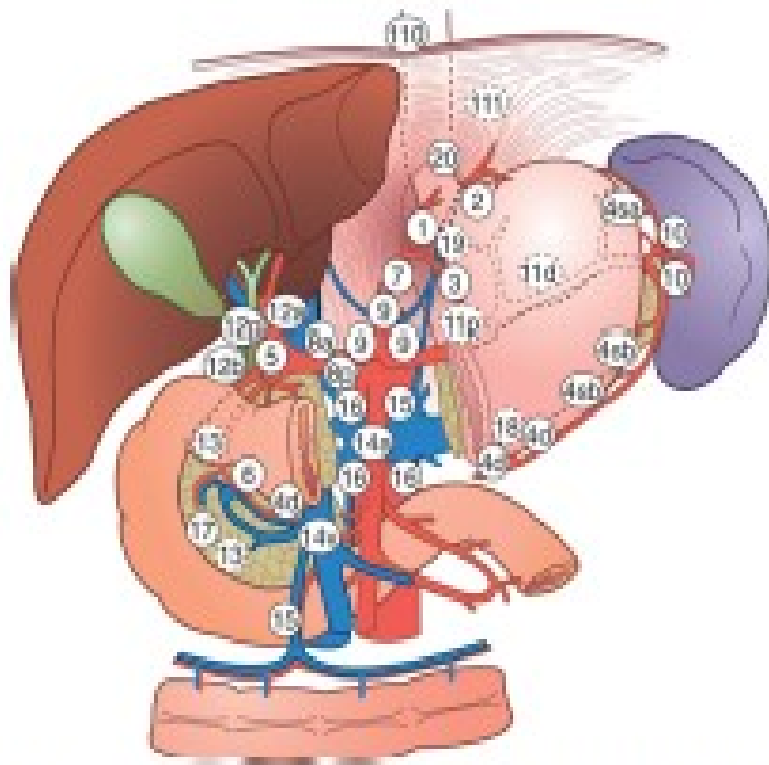
interim analysis: 65% vs 53% hanno terminato il trattamento, 98% ha terminato CT-RT

90 % vs 85 % ha effettuato chirurgia

non sostanziali differenze in complicanze post-chirurgiche (20%)

tox GI 3+ in circa il 30 % pts, simile nei 2 gruppi

tox ematologica 3+ in circa il 50% pts, simile nei 2 gruppi



**Fig. 1** Schematic diagram of lymph node station. 1N, lymph node; 1 right cardiac nodes; 2 left cardiac nodes; 3 nodes along the lesser curvature; 4 node along the greater curvature; 5 suprapyloric nodes; 6 infrapyloric nodes; 7 nodes along root left gastric artery; 8 nodes along common hepatic artery; 9 nodes around celiac axis; 10 nodes at splenic hilum; 11 lymph nodes along the proximal SA; 12 nodes at the hepatoduodenal ligament; 13 nodes on the posterior surface of the pancreatic head; 14 lymph nodes along the SMA or superior mesenteric vein; 15 nodes along the middle colic vein; 16a lymph nodes around the abdominal aorta for the upper margin of the celiac trunk to the lower margin of the LRV; 16b lymph nodes around the abdominal aorta from the upper margin of the LRV to the aortic bifurcation; 110 lymph nodes in the lower thoracic paroesophageal; 20 lymph nodes in the esophageal hiatus of the diaphragm [8].

**Table 4** Radiation range of lymph nodes after D2 dissection from Yoon

| Primary site                        | Radiation range             |
|-------------------------------------|-----------------------------|
| Proximal third stomach              | 9, 10, 13, and 16a/b        |
| Middle third stomach                | 12, 14, and 16a/b           |
| Distal third stomach                | 9, 11–14, and 16a/b         |
| More than two-thirds of the stomach | 2, 9, 11, 12, 14, and 16a/b |

**Table 5** Radiation range of lymph nodes after D2 dissection from the Chinese Academy of Medical Sciences

| Primary site           | Radiation range                         |
|------------------------|---|
| Proximal third stomach | 110, 20, 1–3, 7–11, and 16a/b           |
| Middle third stomach   | 1, 3, 5, 9, 11p, 12, 13, 14*, and 16a/b |
| Distal third stomach   | 3, 5, 9, 11p, 12, 13, 14*, and 16a/b    |

\*T4 or pancreas involved

Avanzamento tecnologico (IMRT/IGRT), definizione dei volumi in pre e post-op  
 > Accuratezza e precisione, < tossicità

# RT palliativa nel carcinoma gastrico

- Palliazione per sanguinamento, dolore, ostruzione/disfagia  
(anche in paziente con MTS)

da confrontare con stenting / chirurgia palliativa

-sanguinamento: basse dosi, minor durata (< effetti collaterali)  
effetto precoce, 80% RO

-ostruzione/disfagia: alte dosi, maggior durata (> effetti collaterali)  
effetto ritardato, 50% RO

- Paziente non operabile per controindicazioni mediche
- Paziente non resecabile (malattia avanzata)

CRT vs CT (CRT > CT?)

OS= 20-35 mesi

# RT e carcinoma gastrico: considerazioni (conclusive?)

- Paziente operabile :
- Perioperative CT standard terapeutico
- RT o CT-RT post-op dopo CT pre-op non di routine
- CT-RT dopo chirurgia possibile opzione:  
SELEZIONE dei pazienti in fx dei fattori di prognosi  
(T avanzato, N+, LN ratio, tipo linfadenectomia, R1, ILVS+)
- Nuova frontiera: CT-RT pre-op

MULTIDISCIPLINARIETA', ESPERIENZA, DOTAZIONE TECNOLOGICA

- Paziente non operabile :
- per controindicazioni mediche, paziente non resecabile (malattia avanzata)
- Palliazione: sanguinamento, dolore, ostruzione/disfagia.