IS THERE A ROLE FOR RADIOTHERAPY IN CA GE JUNCTION

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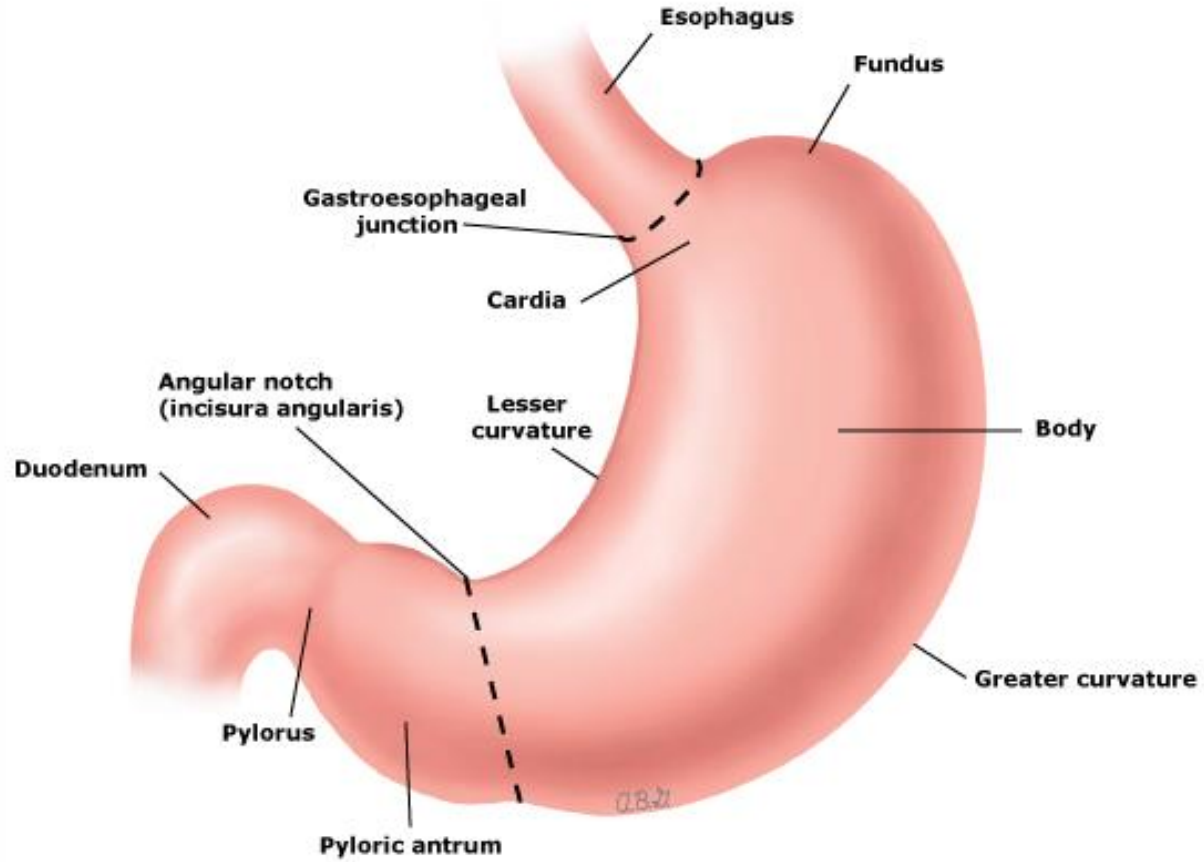
Parts of the stomach



This drawing shows the parts of the anterior surface of the stomach. The body of the stomach is separated from the pyloric part by an oblique line that extends from the angular notch (incisura angularis) on the lesser curvature to the greater curvature.

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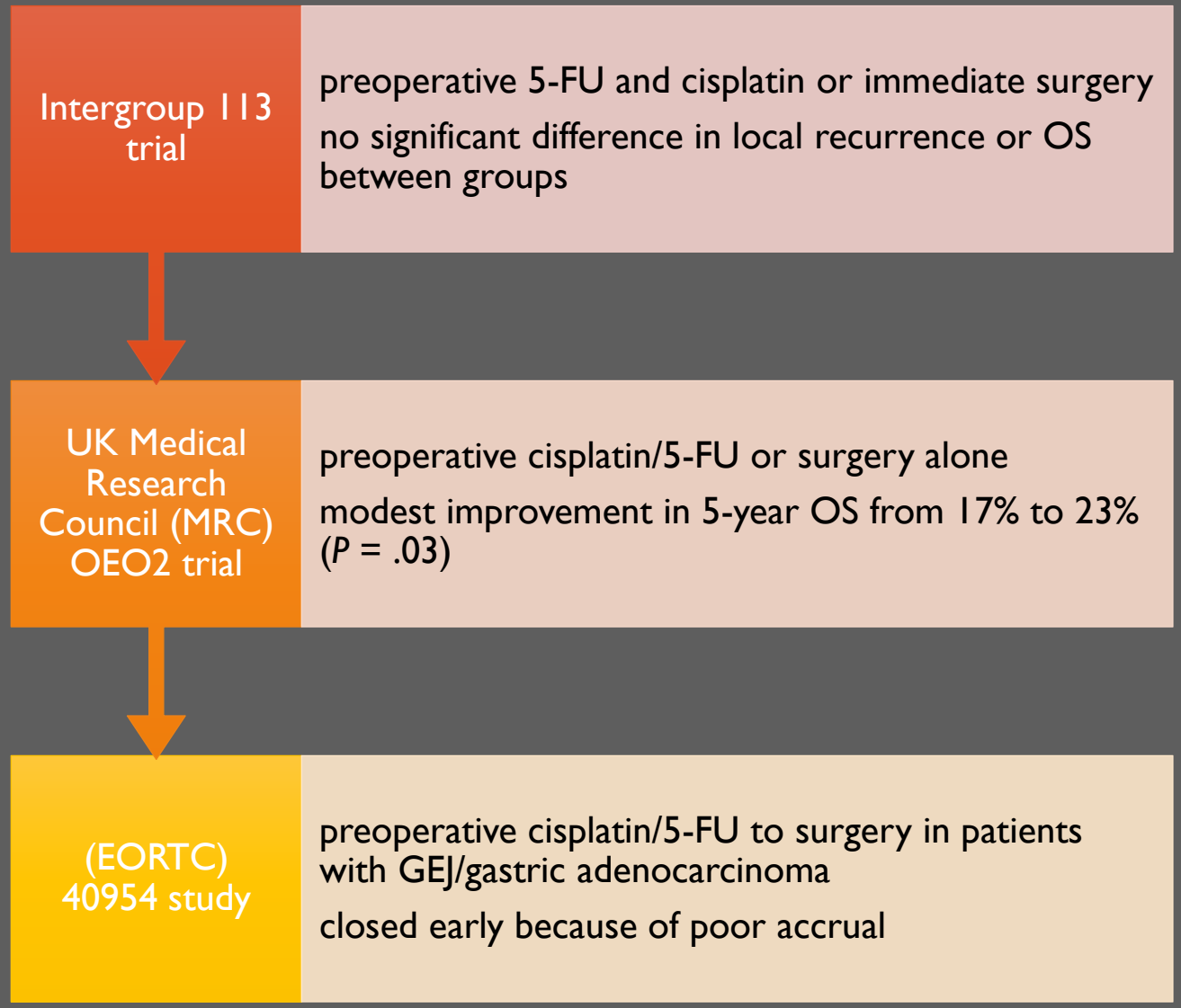
GE JUNCTION – DISEASE EXTENT

- Early stage
- Locally Advanced

PREOPERATIVE & PERIOPERATIVE CHEMOTHERAPY



NEWER TRIALS

- phase 3 MAGIC trial
  - 3 cycles each of epirubicin, cisplatin, and 5-FU (ECF) before and after surgery versus surgery alone
  - 15% GEJ
  - Perioperative chemotherapy significantly improved 5-year OS (36% vs 23%; *P* = .009)

ANTHRACYCLINE NOT BENEFICIAL??

FFCD 9703 trial

6 cycles of perioperative 5-FU and cisplatin with surgery versus surgery alone

64% GEJ tumors

5-year OS (38% vs 24%; *P* = .02)

magnitude of OS benefit was similar between the FFCD and MAGIC studies. (Cautious interpretation)

ANTHRACYCLINE NOT BENEFICIAL??

UK MRC OEO-5

6 weeks of preoperative cisplatin/5-FU or
12 weeks of epirubicin, cisplatin, and capecitabine (ECX)

pCR7% vs 1% with ECX

No significant difference in OS between groups

ANTHRACYCLINE NOT BENEFICIAL??

FLOT4-AIO phase 3 trial - perioperative FLOT or ECF/ECX.

716 patients with resectable gastric/GEJ adenocarcinoma

56% GEJ tumors

FLOT was superior to ECF/ECX in all efficacy endpoints,

complete resection (R0) rate (85% vs 78%; *P* = .016),

progression-free survival (PFS), and

OS (median OS, 50 vs 35 months; 3-year OS, 57% vs 48%; hazard ratio [HR], 0.77; *P* = .012).

Only one-half of patients completed all planned chemotherapy, similar to completion rates in the MAGIC and FFCD studies,

difficulty in administering adjuvant therapy and suggesting that patients benefit from short durations of chemotherapy

PREOPERATIVE CHEMORADIATION

- phase 3 Dutch CROSS
- Preoperative radiation (41.4 Gy) with weekly carboplatin and paclitaxel for 5 weeks
- 366 patients with mostly locally advanced esophageal tumors; 75% of patients had adenocarcinoma, and 24% had GEJ tumors.
- Higher R0 resection and pCR rates (29%: adenocarcinoma, 23%; SCC, 49%), and
- Improved 5-year OS (47% vs 33%; HR, 0.067).
- No increased postoperative mortality associated with chemoradiation.
- Long-term follow-up reported a 9% reduction in distant metastases in the chemoradiation arm

IS CARBOPLATIN AND PACLITAXEL THE OPTIMAL REGIMEN

- (CALGB) 80803
- 257 patients with esophageal/GEJ adenocarcinoma (57% had GEJ)
- Induction 5-FU, leucovorin, and oxaliplatin (FOLFOX6) or carboplatin and paclitaxel followed by a (^{18}F)2-fluoro-deoxy-D-glucose–positron emission tomography (FDG-PET) scan.
- PET responders continued with the same regimen during concurrent chemoradiation, and nonresponders crossed to the alternate chemotherapy with radiation before surgery.
- pCR rate in patients who were PET responders to induction FOLFOX and continued that regimen during radiation was 37.5%, compared with 12.5% in PET responders to induction carboplatin and paclitaxel who received this regimen with radiation.
- Both treatments were well tolerated.
- A 4-year OS of 52.7% was seen in PET responders to FOLFOX versus 44.7% in PET responders to carboplatin and paclitaxel.
- study was not powered to evaluate survival differences between regimens, these results are hypothesis-generating

IS CARBOPLATIN AND PACLITAXEL THE OPTIMAL REGIMEN

- phase 2 NEOSCOPE study
- induction capecitabine and oxaliplatin
- then underwent randomization to capecitabine and oxaliplatin or carboplatin and paclitaxel with radiation.
- Carboplatin and paclitaxel was associated with higher pCR rates (29.3% vs 11.1%),
- the study was not designed to detect a difference in this endpoint.

- German POET study
- enrolled 119 patients with GEJ adenocarcinoma to preoperative chemotherapy with 5-FU, leucovorin, and cisplatin or 5-FU, leucovorin, and cisplatin followed by chemoradiation with cisplatin and etoposide before surgery.21 The study's power to detect a difference between groups was restricted by the small numbers accrued. Patients who received chemoradiation had a higher pCR rate (15.6% vs 2%; *P* = .03) and lymph node–negative status, and a trend toward improved local control and 5-year OS was observed

ONGOING TRIAL

- PROTECT study (NCT02359968) is comparing chemoradiation with carboplatin and paclitaxel versus chemoradiation with FOLFOX

PERIOPERATIVE CHEMOTHERAPY VS PREOP CHEMORADIATION - ESOPEC

- 438 patients with locally advanced (cT1, N1-3, M0 or cT2-4a, N0-3, M0) adenocarcinoma of the esophagus, including Siewert type I GEJ tumors
- eight cycles of perioperative chemotherapy with FLOT or neoadjuvant CRT (41.4 Gy of RT with concurrent carboplatin plus paclitaxel) followed by surgery
- median follow-up of 55 months,
- perioperative FLOT improved OS (median 66 versus 37 months; five-year OS 51 versus 39 % HR 0.70, 95% CI 0.53-0.92)
- PFS; median 38 versus 16 months, five-year PFS 44 vs 31 % HR 0.66, 95% CI 0.51-0.85).

Clinical OS benefit for perioperative FLOT was seen in all clinically relevant subgroups, including sex, age, ECOG PS, clinical tumor (T) stage, and clinical node (N) stage.

PERIOPERATIVE CHEMOTHERAPY VS PREOP CHEMORADIATION - ESOPEC

- 371 patients who underwent surgery, relative to neoadjuvant CRT, perioperative FLOT demonstrated
  - similar rates of R0 resection (94 versus 95 percent) and R1 resection (5 versus 4 percent); similar
  - postoperative nodal stage (ypN0 51 versus 54 percent)
  - higher pathologic complete remission rate (ypT0 ypN0; 17 versus 10 percent).
- Toxicity:
- Perioperative FLOT and neoadjuvant CRT demonstrated grade ≥3 toxicity rates of 58 and 50
- FLOT resulted in higher rates of grade ≥3 neutropenia (20 vs 2 %),
- diarrhea (7 % vs 0), nausea (4 versus 0 percent), vomiting (3 versus <1 percent), pulmonary embolism (4 versus 1 percent), and polyneuropathy (3 versus 0 percent), whereas CRT resulted in higher rates of grade ≥3 leukopenia (10 versus 6 percent) and pneumonia (9 versus 6 percent).

CHECKMATE 577

- 794 patients with esophageal (60 percent) or GEJ (40 percent) adenocarcinoma (71 percent) or SCC (29 percent) who had received neoadjuvant CRT and had residual pathologic disease at the time of surgery
- were randomly assigned to adjuvant nivolumab (240 mg IV) or placebo every 2 weeks for 16 weeks followed by nivolumab 480 mg IV or placebo every 4 weeks;
- the maximum treatment duration was one year

CHECKMATE 577

- At a median follow-up of 24 months, adjuvant nivolumab improved DFS (median 22 versus 11 months, HR 0.69, 95% CI 0.56-0.86).
- In preliminary results, with extended follow-up (median follow-up of five years), adjuvant nivolumab continued to improve DFS (median DFS 22 versus 11 months; five-year DFS 37 versus 29 percent, HR 0.76, 95% CI 0.63-0.91) .
- •In preliminary results, adjuvant nivolumab demonstrated a nonstatistically significant trend towards higher OS compared with placebo, (median OS 52 versus 35 months, five-year OS 46 versus 41 percent, HR 0.85, 95% CI 0.70-1.04)
- •Grade 3 to 4 toxicity rates were similar between the treatment arms (34 versus 32 percent).
- Only 9 percent of patients discontinued adjuvant nivolumab because of adverse effects
- Adjuvant nivolumab did not cause any significant decline in patient-reported health-related quality-of-life over the year treatment.

PERIOPERATIVE CHEMOTHERAPY VS PREOP CHEMORADIATION – TOPGEAR

- 574 patients with resectable adenocarcinoma of the stomach or GEJ
- neoadjuvant CRT (45 Gy in 25 fractions plus FU infusion) plus perioperative chemotherapy (either ECF or FLOT) or perioperative chemotherapy alone
- At a median follow-up of 67 months, the addition of neoadjuvant CRT to perioperative chemotherapy improved the pCR rate (17 versus 8 percent)
- failed to improve OS (median 46 versus 49 months, HR 1.05, 95% CI 0.83-1.31)
- The rates of grade ≥3 toxicity (66 versus 61 percent) and surgical complications (18 versus 16 percent) were similar between the two treatment arms.

PERIOPERATIVE CHEMOTHERAPY VS PREOP CHEMORADIATION NEO-AEGIS

- open-label phase III trial (neo-AEGIS)
- 362 patients with cT2-3, N0-N3, M0 adenocarcinoma of the esophagus or GEJ
- neoadjuvant CRT with concurrent carboplatin plus paclitaxel was compared with perioperative chemotherapy (three preoperative and three postoperative cycles of modified ECF, or four preoperative and four postoperative cycles of FLOT)
- median FU 39 months,
- NACTRT increased the rate of R0 resection (96 versus 82 percent)
- pCR rates for the primary tumor (14 versus 4 percent) and the lymph nodes (60 versus 44 percent) but
- No improvement OS (median OS 49 versus 48 months; three-year OS 57 versus 55 percent, HR 1.03, 95% CI 0.77-1.38)

ADJUVANT CHEMORADIATION **INT-0116**

556 patients

Post curative resection of gastric or esophagogastric junction (EGJ) cancer (T1-4N0-1),

observation vs adjuvant CRT (one cycle of FU/LV bolus chemotherapy followed by CRT and then two more cycles of chemotherapy)

T3/T4 (68 and 69 percent of the treated and control groups, respectively), and 85 percent had nodal metastases

ADJUVANT CHEMORADIATION **INT-0116**

Three-year DFS (48 vs31 %)

OS rates (50 vs 41 %) were significantly better with combined modality therapy, and median survival was significantly longer (36 versus 27 months).

Benefits were maintained with longer follow-up (five-year OS 43 versus 28 percent, HR for survival 1.32, 95% CI 1.10-1.60)

In the CRT group, grade 3 and 4 acute toxic effects occurred in 41 and 32 percent of patients, respectively, while three patients (1 percent) died from treatment-related toxicity [42]. The most frequent grade 3 or worse adverse effects were hematologic (54 percent), gastrointestinal (33 percent), infectious (6 percent), and neurologic (4 percent).

Pattern of failure - similar frequency of distant metastasis (16 vs18 %)

Less local (2 vs 8 %) and regional (22 vs 39 % recurrences with CRT

The initial report of this study changed the standard of care in the United States following potentially curative resection of gastric cancer from observation alone to surgery followed by adjuvant combined CRT and FU/LV chemotherapy.

CALGB 80101

compared the INT 0116 protocol regimen with postoperative ECF before and after concurrent FU-based CRT

Both arms received continuous infusion FU during the CRT part of the adjuvant regimen.

22 % GEJ tumors.

Patients receiving ECF had lower rates of diarrhea, mucositis, and grade 4 or worse neutropenia.

OS, the primary endpoint, was not significantly better with ECF (at 5 yrs, 44 % in both groups).

The trial was not adequately powered to assess noninferiority.

Escalating adjuvant systemic therapy from FU plus leucovorin to ECF (epirubicin, cisplatin, and FU) did not confer additional OS benefit

ADJUVANT CHEMOTHERAPY VS CHEMORT - ARTIST

- 458 patients with completely resected gastric cancer and a D2 lymph node dissection
- 6 cycles of postoperative capecitabine plus cisplatin or two courses of postoperative capecitabine plus cisplatin followed by CRT (45 Gy RT with concurrent daily capecitabine [825 mg/m^2 twice daily]) and two additional courses of capecitabine plus cisplatin
- median follow-up of 84 months, three-year DFS (the primary endpoint) was not significantly better in patients who received combined modality therapy (HR 0.74, 95% CI 0.52-1.05),
- unplanned subset analysis did indicate a significantly better DFS with CRT in those with node-positive disease (three-year DFS 76 versus 72 percent)
- OS, a secondary endpoint, was also not significantly different (HR 1.13, 95% CI 0.775-1.647). Notably, even though the ARTIST trial met its accrual goal,

Fewer events than expected resulting in the study being underpowered for the planned endpoints.

ADJUVANT CHEMOTHERAPY VS CHEMORT - **ARTIST 2**

- 900 Korean patients with pathologically staged II or III, node-positive, D2-resected gastric cancer
- adjuvant S-1 for one year, S-1 plus oxaliplatin (SOX) for six months, or SOX chemotherapy plus CRT (two months of SOX followed by 45 Gy RT plus S-1 and then four additional months of SOX)
- In an analysis of the first 546 enrolled patients, with a median follow-up of 47 months, there was no significant benefit for the addition of RT to SOX in terms of DFS, the primary endpoint (at 3 years, 73 versus 74 percent, HR 0.971).

Fewer events than anticipated

INDUCTION CHEMO → CHEMO VS CHEMORADIATION

- CRITIC I
- 788 patients with stage IB to IV
- induction chemotherapy (three courses of ECX/EOX) followed by surgery and randomization to postoperative chemotherapy (three cycles of the same regimen) or CRT (45 Gy in 25 fractions with weekly cisplatin and daily capecitabine)
- All patients were to have a D1 or better lymphadenectomy with at least 15 nodes in the resection specimen.
- Median FU of 61 months, there were no significant differences in five-year OS