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The Before and The After: *Can chemotherapy revise the trajectory of gastric and esophageal cancers?*

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Disclosures

- **None**

- *All of my conflicts are internal…..*

Objectives: At the end of this session, the attendee will:

- Be able to identify situations where chemotherapy should be considered either before or after surgery for gastric and esophageal cancers

- Be able to select which patients with gastric and esophageal cancer should be referred to consider chemotherapy in the metastatic setting

Objectives: At the end of this session, the attendee will:

- Understand which chemotherapy regimens are used in the above settings
- Remember the prognosis for treated gastric and esophageal cancers.

So you have confirmed a patient has **GASTRIC** cancer on histology….

No evidence of spread! ***So what next?***

- A: “To Cut is to Cure”: immediate referral for surgical resection
- B: Neoadjuvant Chemotherapy
- C: Induction Chemotherapy
- D: Chemotherapy does not work in gastric cancer, so cut it out
- E: Go to Hawaii because gastric cancer is a bad one
- F: None of the above

Answer: Perioperative Chemotherapy

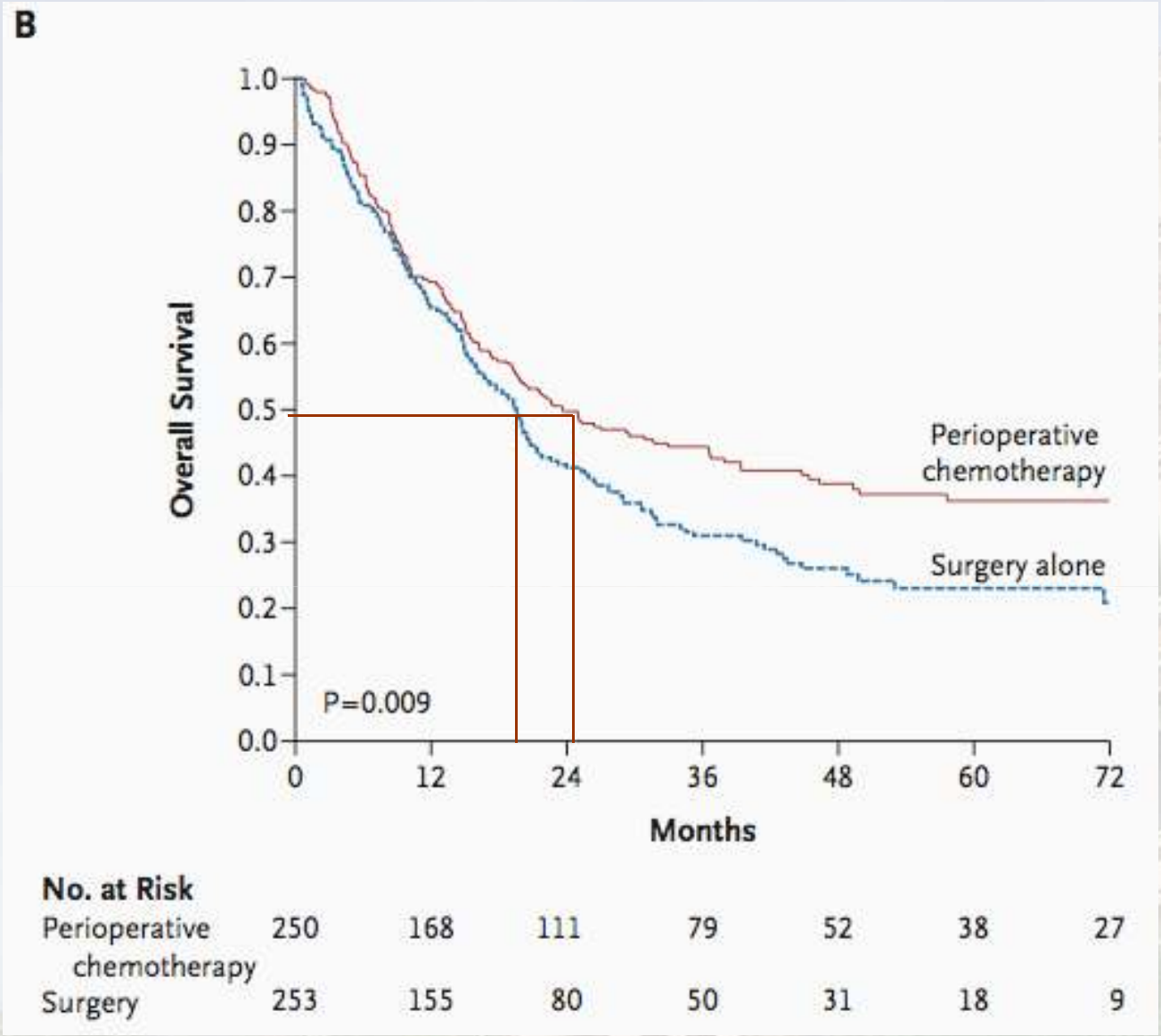
- Phase III randomized "MAGIC" trial[1]
- Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer (began accrual before INT 116 reported)
- 503 patients randomized with resectable adenocarcinoma of the stomach (74%), *Esophagastric junction (10%), and Lower Esophagus (15%)*; T1-4, N0-3
- Control arm: Surgery alone
- Experimental arm: 3 cycles of chemotherapy before surgery and 3 cycles postoperatively
- 1° Endpoint: Overall Survival

Chemotherapy Protocol: ECF

- IV epirubicin 50mg/m^2 Day 1
  - MUGA scan needed at baseline and follow-up to assess heart function
- IV cisplatin 60mg/m^2 Day 1
- Continuous ambulatory infusional fluorouracil 200mg/m^2/day D1-21
  - Less than 5% chance of “MI” in patients with CAD

Results

- Patients well balanced
- 41.6% of experimental arm got all of prescribed therapy
- Pre-operative chemotherapy did down stage the tumors
- Overall Survival @ 5 years:
  - 36.3 % chemo + S
  - 23.0 % Sx alone (significant difference)
  - corresponding to a a 25% reduction in the risk of death with perioperative chemotherapy


B
Overall Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
P=0.009
Perioperative chemotherapy
Surgery alone
0
12
24
36
48
60
72
Months
No. at Risk
Perioperative chemotherapy 250 168 111 79 52 38 27
Surgery 253 155 80 50 31 18 9

Surgeon: "The patient was bleeding at presentation of their stage 3 disease, so we proceeded directly to surgery.
It is all cut out!!!!!"

Med Onc/Rad Onc: "Don't worry, we have it covered."

Adjuvant Therapy for fully resected gastric cancer…..

CT + RT after Surgery compared with Surgery alone for Adenocarcinoma of Stomach & GE Junction

- INT 0116 - Macdonald et al – NEJM 2001[2]

- 556 pts with adenocarcinoma of stomach and GE junction (IB – IVA)
- Control arm: Surgery alone
- Study arm: Surgery → Adjuvant RT + CT

- CT: 5FU 425 mg per square meter per day D1→ D5
- Leucovorin 20 mg per square meter per day D1→ D5

- RT: 4500 cGy in 25 fractions over 5 weeks
- Modified doses of 5FU and leucovorin on the first four days and the last three days of RT

- One month after completion of RT, two five day cycles of same CT regimen given one month apart

Results

- 556 patients randomized
- Two group balanced
- Overall survival at 3 years
  - Surgery alone group: 40%
  - Adjuvant chemoradiotherapy: 50%
- Median survival
  - Surgery alone group: 27 months
  - Adjuvant chemoradiotherapy: 36 months

MAGIC vs INT 0116

- Both are Level 1 evidence
- Can you compare the two?
- INT has longer follow-up
- They look at two distinct clinical patient groups
  - Pre-op vs. post op
- INT patients more like our own
  - Less D2 resections
    - Local RT can “make up” for less than adequate surgery and therefore higher rates of local recurrence
- Message to surgeons has really been to send patients pre-op to be assessed at CCMB

Advanced Gastric Disease: Chemotherapy

- Old School: FAMTX (1980s)
  - 5-FU, Adriamycin, Methotrexate
- New School: ECF (1990s)
- 274 patients head to head with GE junction tumors[3]
- **ECF**
  - RR: 45%; Median Survival: 8.9 months
- FAMTX
- ECF vs. EOF vs. ECX vs. EOX: comparable[4]
  - RR: 21%; Median Survival: 5.7 months

Second line chemotherapy: no level 1 evidence

- Standard is sequential active agents
  - Irinotecan (FOLFIRI in combination)
  - Taxanes
  - Gemcitabine
- Biologic Therapies: not prime time in Canada
  - HER 2: most compelling
  - EGFR
  - VEGF
  - VEGFR2: ramucirumab (latest FDA)

Trastuzumab

- HER-2 is over expressed in ~20% of gastric cancers
- Phase 3 trial adding trastuzumab to cisplatin and 5-FU
- 594 patients randomized with incurable disease
- 80% gastric, 20% GE junction
- Median follow-up ~ 18 months

Results

- Median survival
  - 13.8 vs 11.1 months, advantage trastuzumab
- Most common toxicities are neutropenia (30%) and anemia (10%)
- Not yet used commonly in Winnipeg because there are challenges getting HER2 testing completed in time

Prognosis: *Silver Medal*

- ***Only surpassed by lung cancer in 1980s as biggest world cancer killer***
- Prognosis related to tumor extent (depth) and nodal status
- Superficial T1 cancers
  - 78% survival at 5 years
- In North America, only 10-20% of cases are at an early stage
- 7-15 nodes positive
  - 12 % survival at 5 years
- Metastatic disease
  - Median survival around 6 months

Now what about esophageal cancer?

A Case

- 55 year old man presents to your office with dysphagia and 20 lbs weight loss
- PMHx: 40 pk yr smoker, GERD
- Nothing on exam
- You take Dr. Moffat's suggestions on work-up

- Biopsy during scope shows cancer in the ***distal*** esophagus

So, your patient has esophageal cancer…

- 1st Question – are there distant metastases?
  - If yes, refer to medical or radiation oncology
  - If no, go to Question 2

- Question 2 – is the local/regional disease resectable?
  - If yes, consider preop chemoradiotherapy (ChemoRT) or perioperative chemotherapy
  - If no and **Squamous Cell Carcinoma (SCC)**, consider definitive ChemoRT (usually not distal tumors)

Metastatic Disease

- Accounts for almost 40% of cases[5]
- Median survival without chemo – 6 months
- Benefit of chemo not consistently seen in trials, but many show median survival 9-11 mo.[6]

Metastatic Disease

- In young, fit patients with adenocarcinoma can try EOX (minority)[4]
  - Epirubicin, Oxaliplatin, Capecitabine
  - RR 47.9%, OS 11.2 mo
  - Most common AE – neutropenia, alopecia, fatigue, diarrhea
- Others, consider CF, other doublets, or palliation
- Second line chemo same as for gastric cancer

- SCC: 5-FU and Cisplatin the standard, but little evidence for improved survival

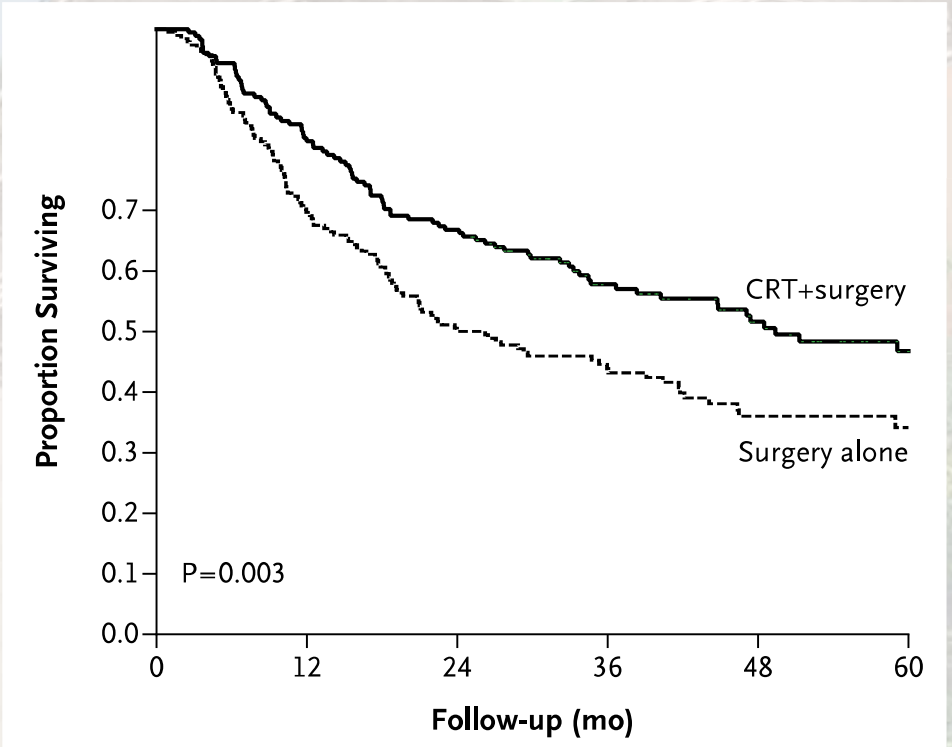
Resectable Disease

- Two options:
- 1) MAGIC protocol as discussed for gastric cancer
- 2) Neoadjuvant chemotherapy + Radiation (RT)
  - Older protocol with cisplatin + 5-FU
    - Cisplatin 75 mg/m^2 Day 1 and 29
    - 5-fluorouracil continuous infusion Day 1-4 and 29-32
    - Concurrent RT
  - Newer (CROSS) protocol
    - Carboplatin AUC 2 and Paclitaxel 50 mg/m^2 weekly
    - Concurrent RT
    - This is increasingly the preferred regimen due to less toxicity

CROSS Protocol[7]

- 368 patients randomized to surgery or surgery and neoadjuvant weekly chemo + RT
- 75% adenocarcinoma, ECOG 0-1, T1N1 or T2-3N0-1

- Median OS 49.4 v 24 mo
  - both histologies benefit
- 5-year survival
  - Surgery + CRT – 47%
  - Surgery alone – 34%



Side Effects

Events of any grade during chemoradiotherapy — no. of patients (%)	
Alopecia	25 (15)
Diarrhea	30 (18)
Esophagitis	32 (19)
Fatigue	115 (67)
Nausea	91 (53)
Neurotoxic effects	25 (15)
Vomiting	43 (25)
Leukopenia	103 (60)
Neutropenia	16 (9)
Thrombocytopenia	92 (54)

Definitive chemo + RT

- Almost exclusively for squamous cell carcinoma and only if surgery is not feasible

- Exception – standard for upper esophageal SCC
- Regimen from RTOG 85-01[8]
  - Cisplatin 75 mg/m^2 Day 1 and 29 plus 5-fluorouracil continuous infusion Day 1-4 and 29-32 along with radiotherapy
  - Followed by 2 more cycles of chemo afterwards

RTOG 85-01

- 121 patients, 90% SCC, T1-3N0-1
- 50% middle, 30% lower esophagus

difficult to evaluate. However, the available data suggest that combined therapy resulted in better control of local tumors and fewer distant metastases, as well as improved survival. Because the dose of radiation was lower in the combined-therapy group, the results are compatible with the concept of radiosensitization as described by Byfield.[23] He suggests that chemotherapy may not only enhance the local effects of radiation and thus decrease the likelihood of spread from the primary tumor, but also reduce or eliminate micrometastases.

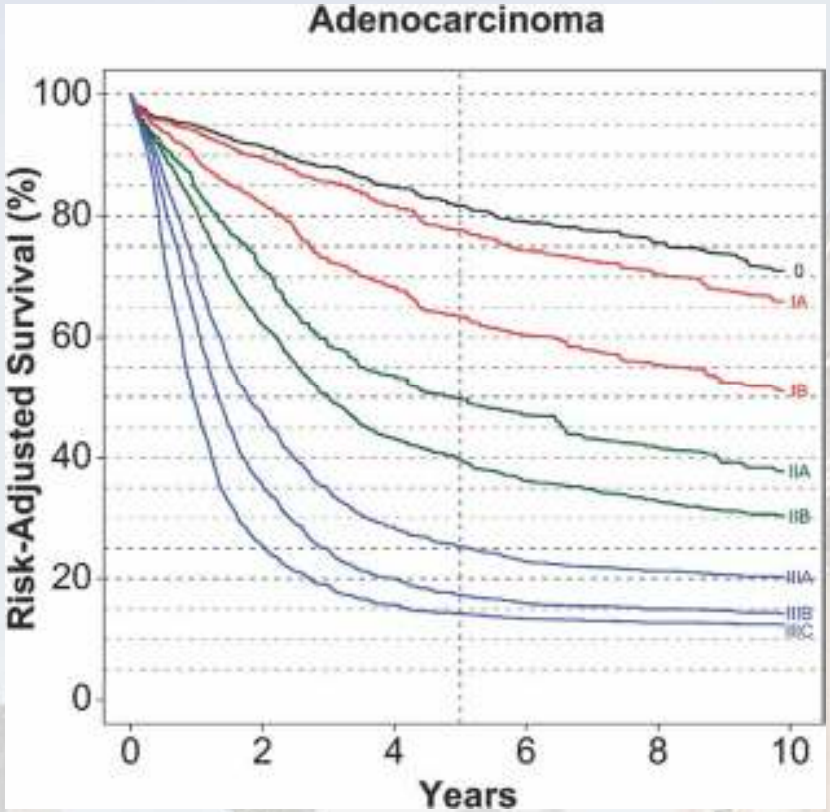
Improved control of local tumors could lengthen survival and at the same time result in an increased frequency of metastases. No such increase has been found, which was surprising because distant metasta-

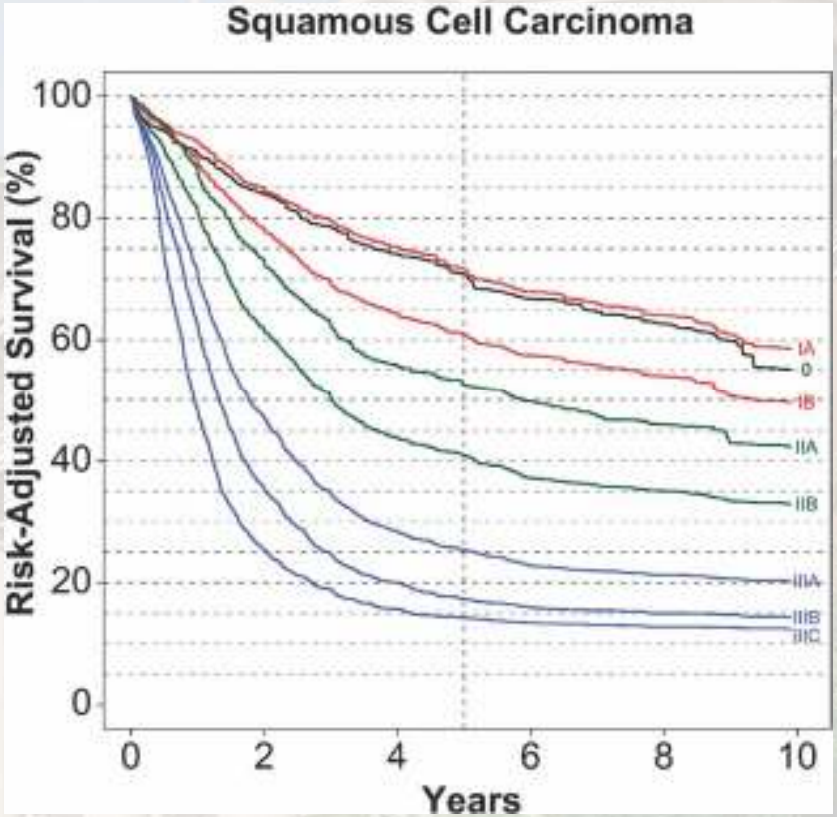
tistical signifi
terms of recu
would benefit
compliance w
the treatmen
more comple
ation therapy
has its own
higher and
group, and th
they often in
these side effe
life remaining
patients deci
of the magn

RTOG 85-01- survival

13 of the 33 had biopsies (11 of which were positive for cancer). Because the chief end point of the study was survival, the use of invasive procedures in patients with poor performance may be inappropriate; consequently, the information about sites of recurrence is partially clinical. The sites of first recurrences are described in Table 2 on the basis of the information available. Forty percent of the patients who received radiation therapy had persistent disease, and an additional 24 percent had local recurrences (Fig. 2), as compared with 27 percent and 16 percent, respective-

Prognosis


Adenocarcinoma
Risk-Adjusted Survival (%)
100
80
60
40
20
0
0
2
4
6
8
10
Years
0
IA
IB
IIA
IIB
IIIA
IIIB
IIIC


Squamous Cell Carcinoma
Risk-Adjusted Survival (%)
100
80
60
40
20
0
0
2
4
6
8
10
Years
IA
0
IB
IIA
IIB
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Take Home Messages

- Resectable disease
  - Increasing and important focus of treatment PRIOR to surgery
  - Adding chemotherapy and radiotherapy improves survival
- Unresectable disease
  - Prognosis remains poor BUT
  - Chemo can help and some early reason for optimism about targeted therapies

References:

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QUESTIONS?