Which Patients with Esophageal Cancer Should Undergo Chemoradiotherapy without Surgery

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Introduction and Overview

Esophageal cancer is a challenging disease with multiple treatment options.

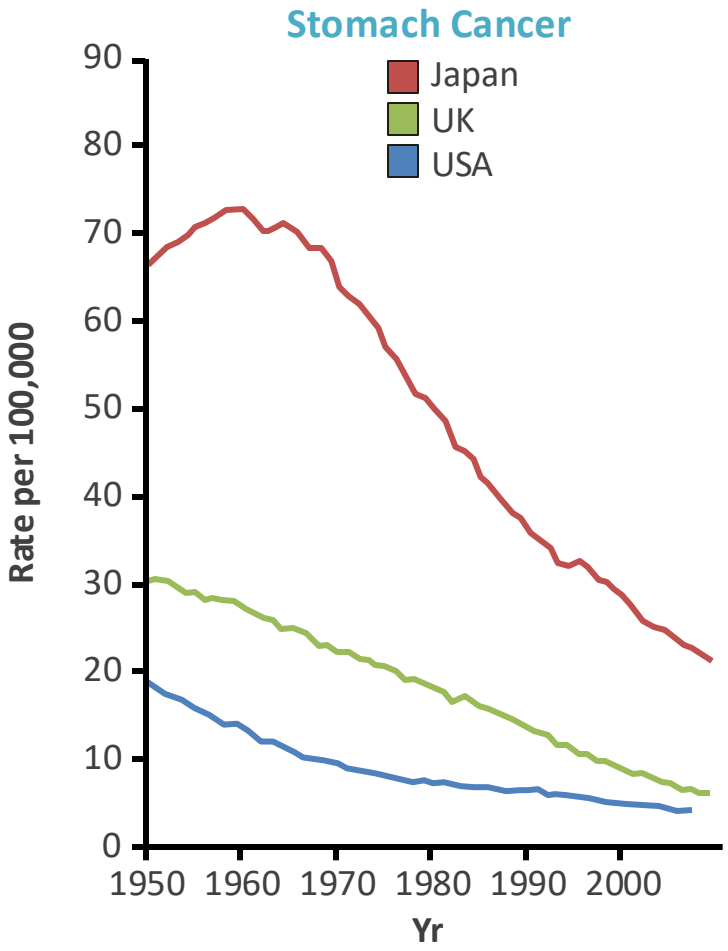
Standard treatments include surgery, chemotherapy, and radiotherapy.

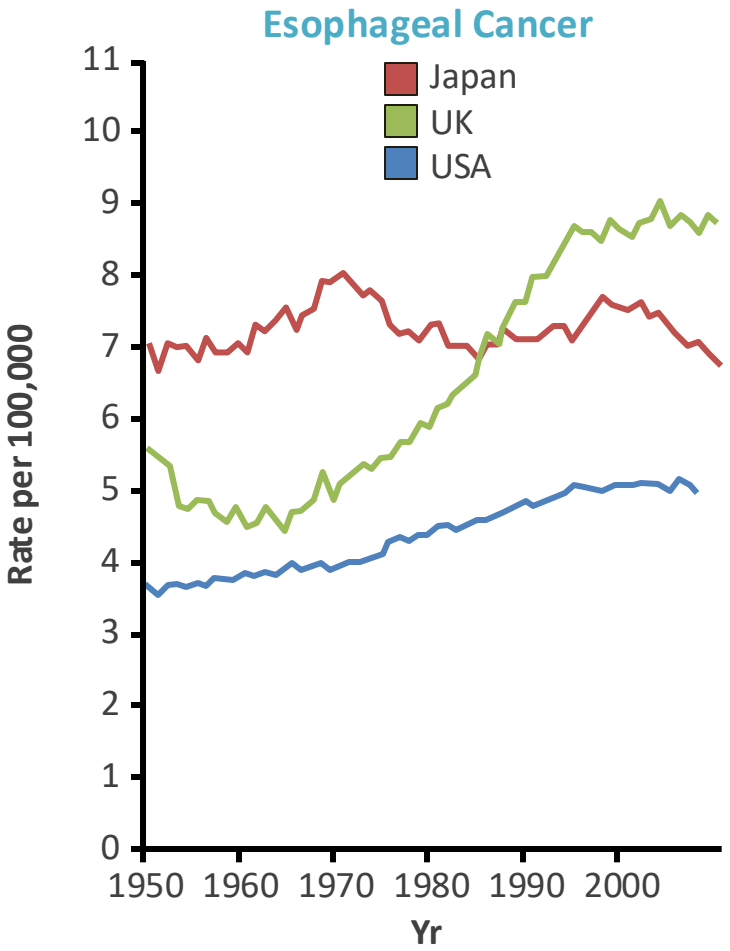
Definitive chemoradiotherapy (CRT) is an alternative for selected patients.

Epidemiology

- Esophageal cancer is the 7th leading cause of cancer deaths
- 1% of all malignancy and 6% of all GI malignancy
- Most common in China, Iran, South Africa, India and former soviet union
- Incidence rises with age, reaching a peak in the 6th to 7th decade of life
- Male: female 3.5:1
- In the US African-American males: white males=5:1

Age-Standardized Mortality Trends: Males





World Health Organization. Mortality database.

PRINCIPLES OF SYSTEMIC THERAPY

Perioperative Chemotherapy

Preferred Regimen
- Fluorouracil,[a] leucovorin, oxaliplatin, and docetaxel (FLOT)[1,2] (category 1)

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)[3]
- Fluoropyrimidine and oxaliplatin[a,b]

Preoperative Chemoradiation
(Infusional fluorouracil[a] can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin (category 1)[4]
- Fluorouracil[a] and oxaliplatin (category 1)[5-7]

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)[8-9]
- Irinotecan and cisplatin (category 2B)[10]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[11]

Neoadjuvant or Perioperative Immunotherapy

Useful in Certain Circumstances
- MSI-H/dMMR tumors[c]
  - Nivolumab and ipilimumab followed by nivolumab[d,12]
  - Pembrolizumab[d,13,14]
  - Tremelimumab and durvalumab for neoadjuvant therapy only[d,15,16]

Definitive Chemoradiation
(Infusional fluorouracil can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin[4]
- Fluorouracil[a] and oxaliplatin (category 1)[5,6]

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)[17]
- Cisplatin with docetaxel or paclitaxel[18-20]
- Irinotecan and cisplatin (category 2B)[10]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[11]

Postoperative Systemic Therapy

Preferred Regimens
- Nivolumab only after preoperative chemoradiation with R0 resection and residual disease (category 1)[d,21]

Other Recommended Regimens
- Capecitabine and oxaliplatin[22]
- Fluorouracil[a] and oxaliplatin
- Fluoropyrimidine (infusional fluorouracil[a] or capecitabine) before and after fluoropyrimidine-based chemoradiation[23]

[a] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[b] The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.
[c] Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

Continued

Non Operative Management of Esophageal Cancer

- **RTOG 85-01: 5-FU, Cisplatin and RT standard non operative management of esophageal cancer**
  - Trial of mainly squamous cancer
  - Local recurrence/persistence 46%
  - 5 yr OS 26%
  - Adenocarcinoma: 13% 5 yr OS
- **Phase II Trials of Taxane, Platinum, RT in esophageal cancer**
  - Comparable rates of response and survival to 5-FU/Cis

NRG ONCOLOGY™

Cooper et al JAMA 281: 1623; 1999 Constantinou et al Cancer Invest 21: 887; 2003

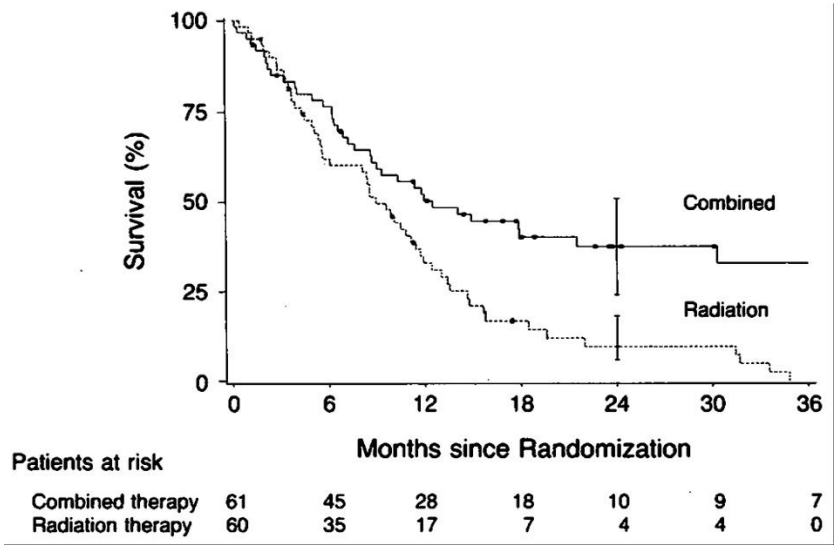
RTOG 85-01

Examined the hypothesis that chemoradiotherapy is better than radiation alone.

Cisplatin 75 mg/m2 given first day of Wk 1, 5, 8 and 11

Fluorouracil infusion (1000 mg/m2), IVCI over 24 hours daily x 4 days, Wk 1-4

EBRT – 50Gy over 25 fractions to the tumor including 5cm proximal and distal margin



Herskovic A. NEJM 1992

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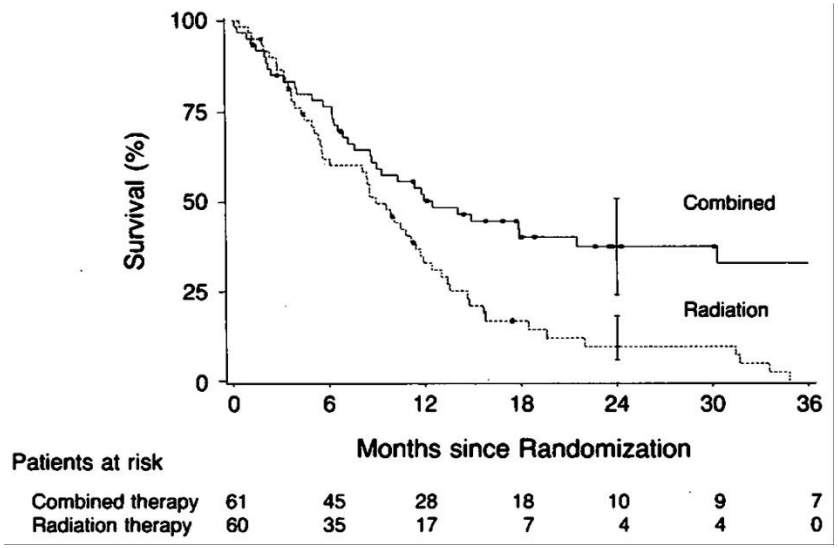

Definitive CRT is an option for patients who are not surgical candidates

Herskovic A. NEJM 1992

Definitive Chemoradiotherapy vs. Surgery

- Studies suggest definitive CRT may be

Randomized Controlled Trial > J Clin Oncol. 2007 Apr 1;25(10):1160-8.
doi: 10.1200/JCO.2005.04.7118.

Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102

Laurent **Bedenne** [1], Pierre Michel, Olivier Bouché, Chantal Milan, Christophe Mariette,

Patients with T3N0-1M0 esophageal cancer received chemo/RT.

Patients with response to therapy were randomized to surgery or completion RT (i.e. +15Gy)

Definitive Chemoradiotherapy vs. Surgery

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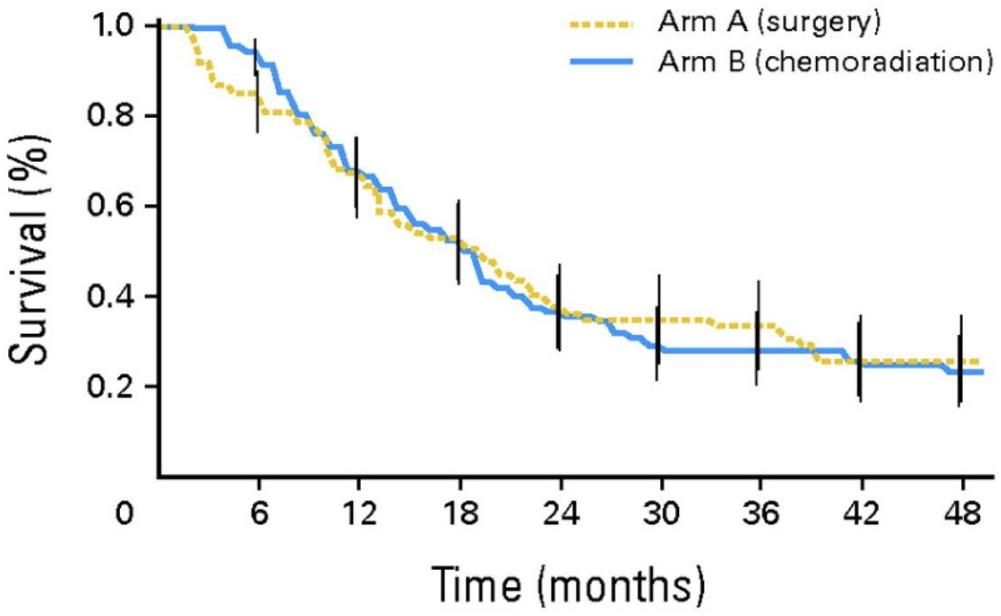
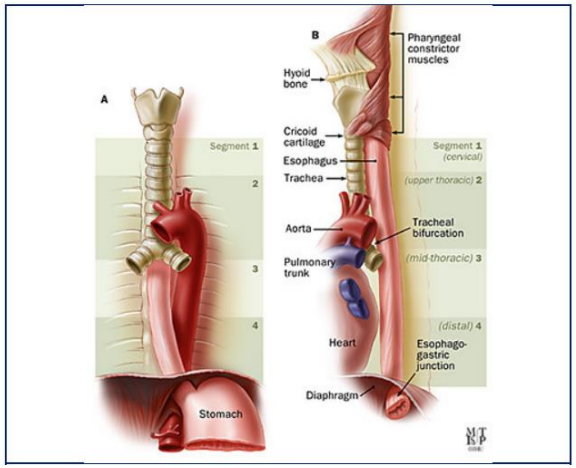
Randomized Controlled Trial > J Clin Oncol. **2007** Apr 1;25(10):1160-8.
doi: 10.1200/JCO.2005.04.7118.

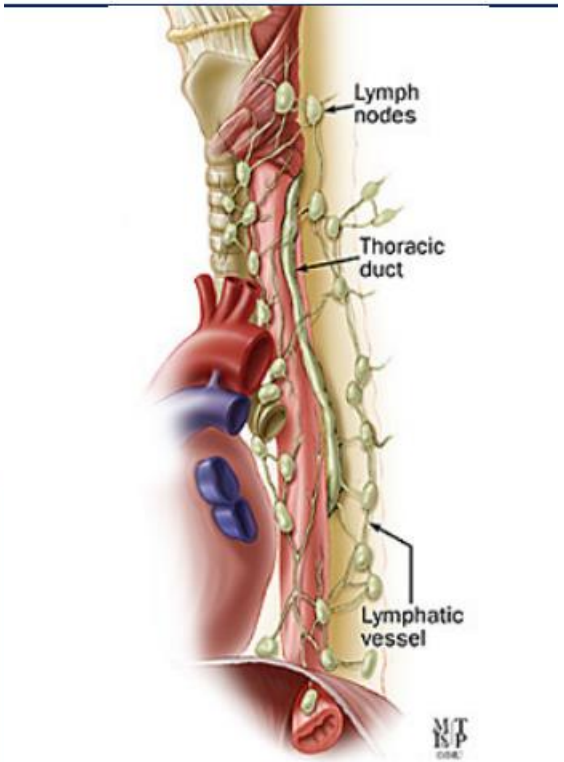


Median OS
Surgery – 17.7 mo
CRT – 19.3 mo

In responding patients, dCRT seems quite reasonable!

Adenocarcinoma v. Squamous Cell Cancer?





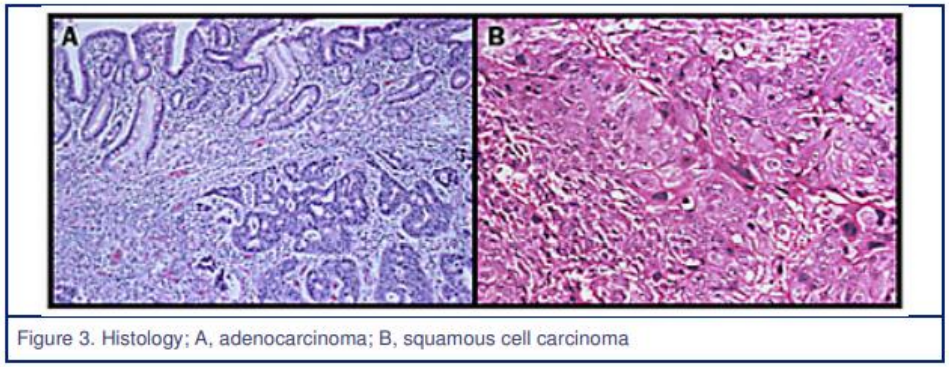
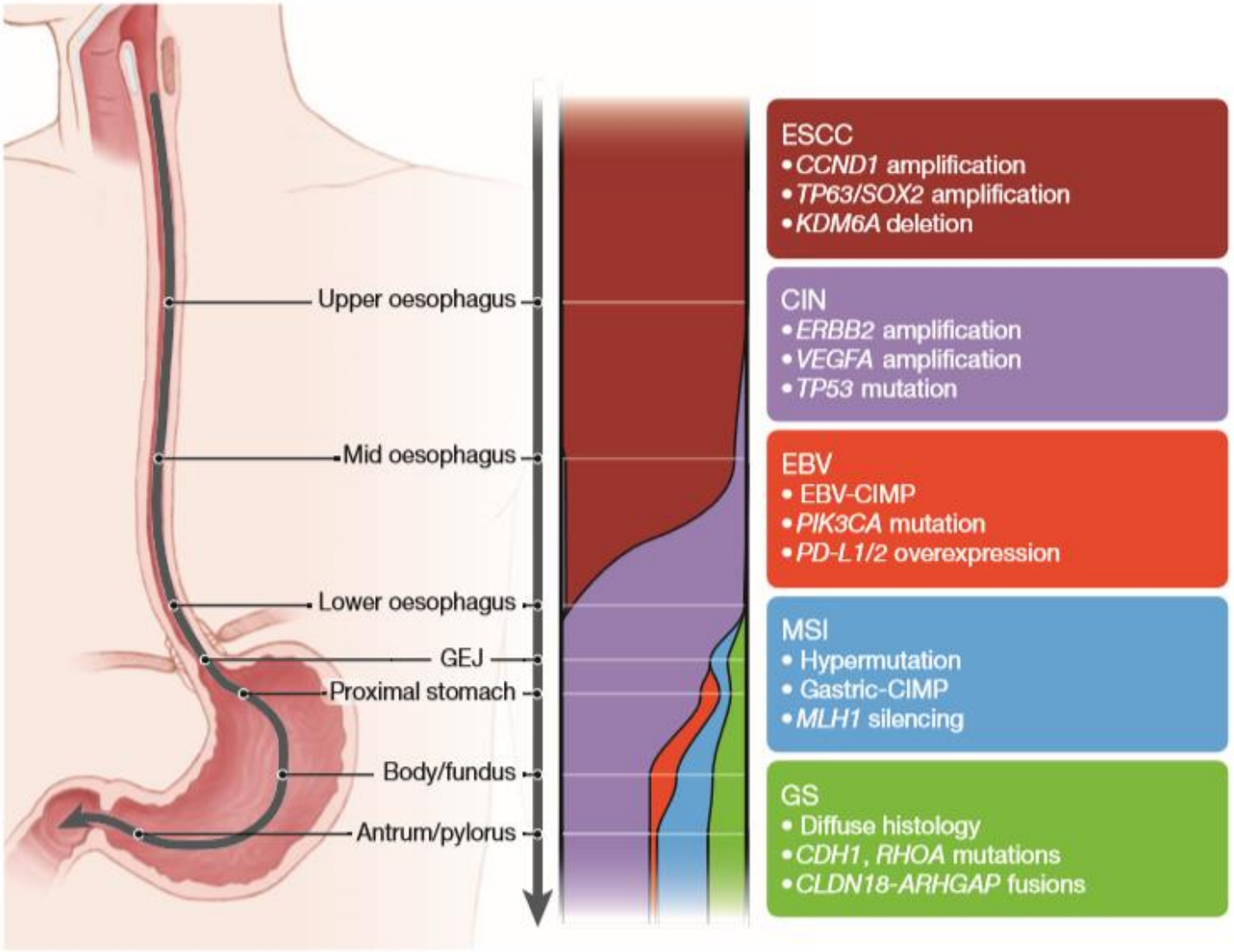


Figure 3. Histology; A, adenocarcinoma; B, squamous cell carcinoma

Esophageal Cancer can present as Squamous Cell Carcinoma (SCC) or Adenocarcinoma

Esophago-gastric cancer subclasses

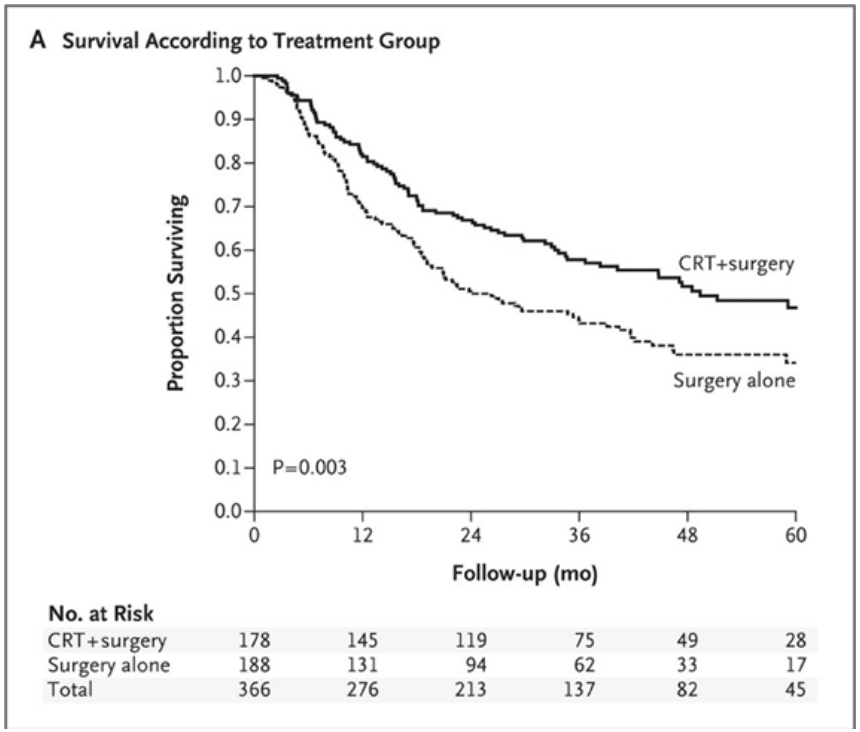


The Cancer Genome Atlas Research Network. *Nature.* 2017;541:169-175

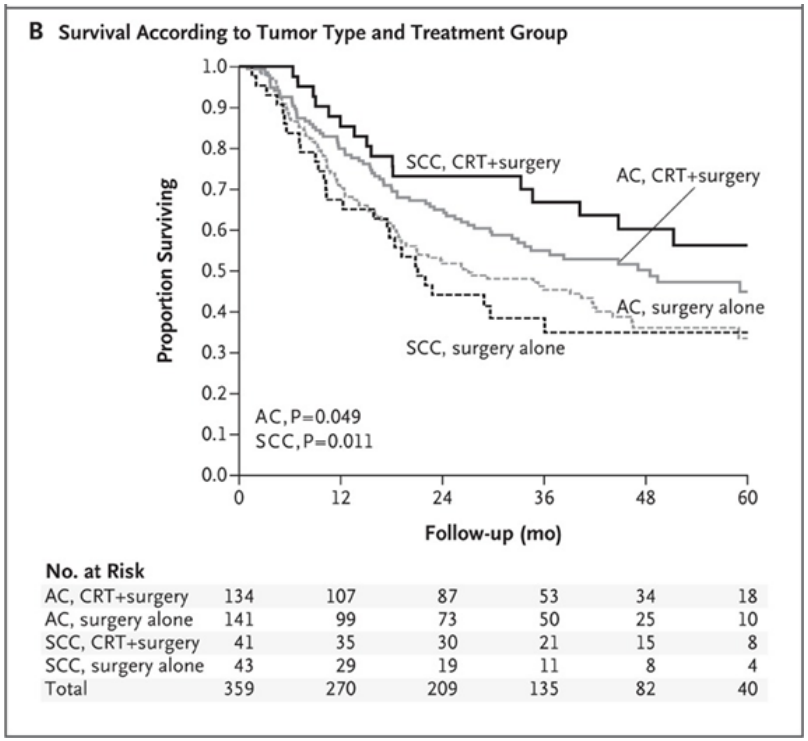
Adenocarcinoma v. Squamous Cell Cancer?

CROSS

- 366 patients with resectable esophageal or GEJ tumors
- Chemoradiotherapy (41.4 Gy+ carboplatin+ paclitaxel) followed by surgery vs surgery alone
- Median OS of 49.4 months vs 24.0 months



No. at Risk						
CRT+surgery	178	145	119	75	49	28
Surgery alone	188	131	94	62	33	17
Total	366	276	213	137	82	45



No. at Risk						
AC, CRT+surgery	134	107	87	53	34	18
AC, surgery alone	141	99	73	50	25	10
SCC, CRT+surgery	41	35	30	21	15	8
SCC, surgery alone	43	29	19	11	8	4
Total	359	270	209	135	82	40

Adenocarcinoma v. Squamous Cell Cancer?

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- 366 patients with resectable esophageal or GEJ tumors
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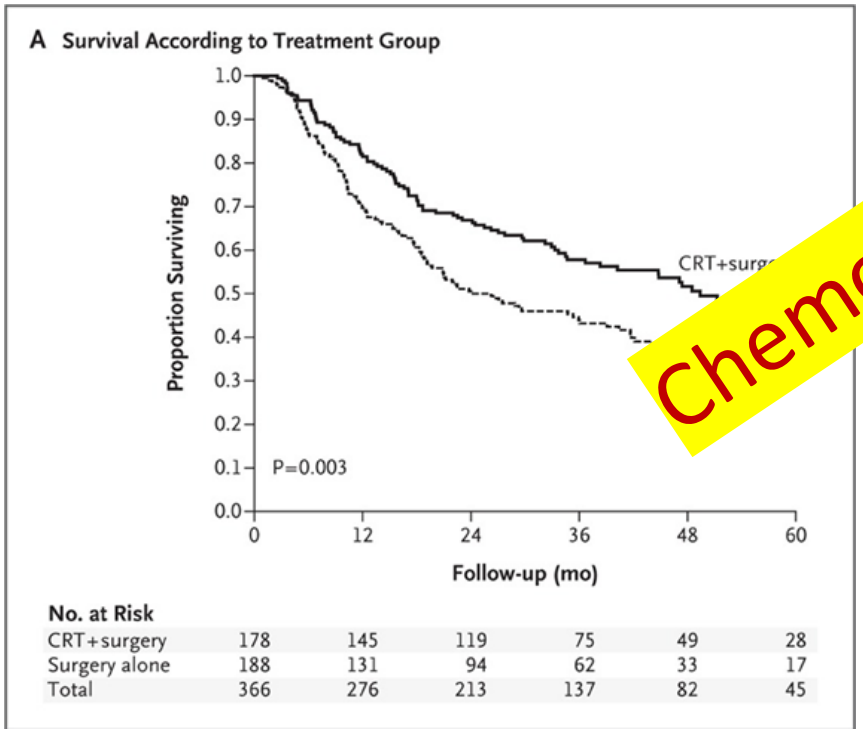
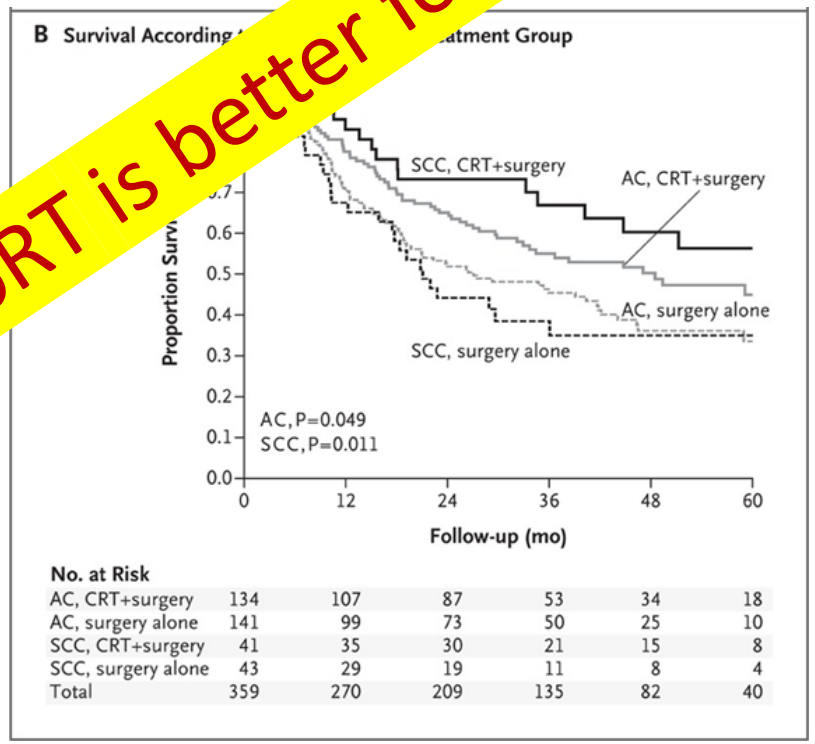
ChemoRT is better for SCC





Watch and Wait Approach

- • Some patients with local progression post-CRT may benefit from close surveillance instead of immediate surgery.
- • Swisher et al. (2017) discuss salvage surgery options when necessary.
- • A non-operative approach can be considered for those with minimal residual disease.

SANO-Trial (surgery v active surveillance)

MADRID 2023 ESMO congress

Neoadjuvant chemoradiotherapy followed by surgery versus active surveillance for oesophageal cancer (SANO-trial): a phase-III stepped-wedge cluster randomised trial

Berend van der Wilk, MD, PhD
On behalf of the SANO study group

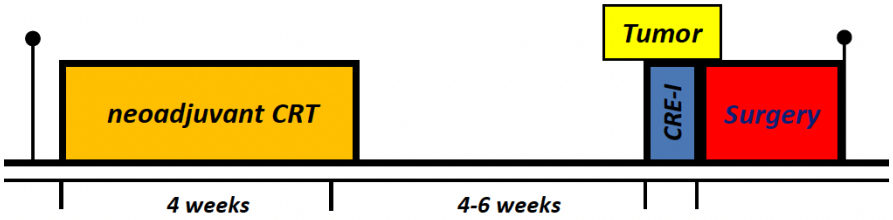
Project leader: prof. dr. J.J.B. van Lanschot

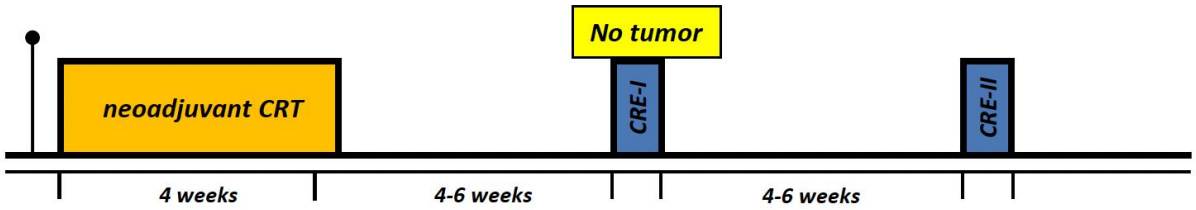
Department of surgery
Erasmus MC – University Medical Centre
Rotterdam, the Netherlands

Erasmus MC
Universitair Medisch Centrum Rotterdam

Active surveillance

- Frequent clinical response evaluations (CREs) using diagnostics
- Surgery only after proven residual tumor (without distant metastases)





CRE-III, CRE-IV etc.

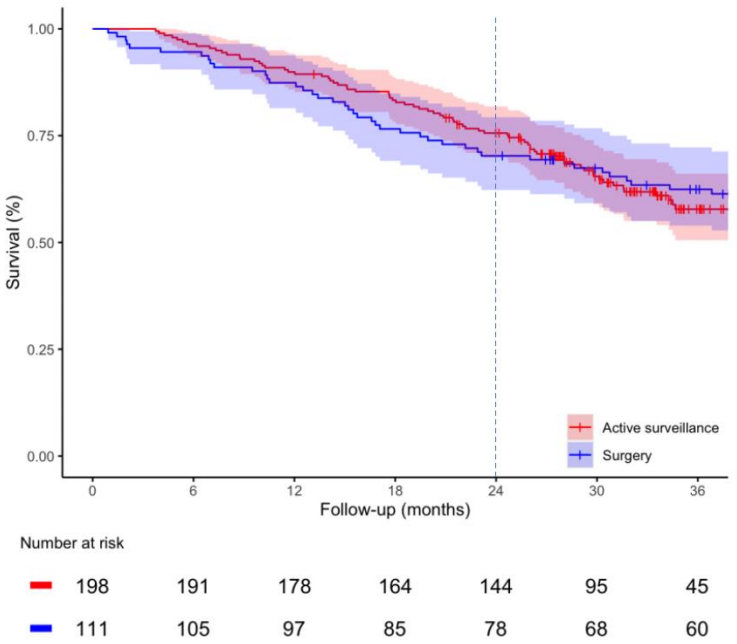
- Potential pitfalls of active surveillance:
  - Development irresectable regrowths
  - Increased distant dissemination

SANO-Trial (surgery v active surveillance)

Baseline Characteristics

	Active surveillance n= 198	Standard surgery n=111
Median age	69	68
Male sex	79%	77%
Adenocarcinoma	74%	76%
WHO-0	66%	61%

Overall Survival



HR 1.14, 95%CI 0.74-1.78, p=0.55

SANO-Trial (surgery v active surveillance)

Baseline Characteristics

	Active surveillance n= 198	Standard surgery n=111
Median age	69	68
Male sex	79%	77%
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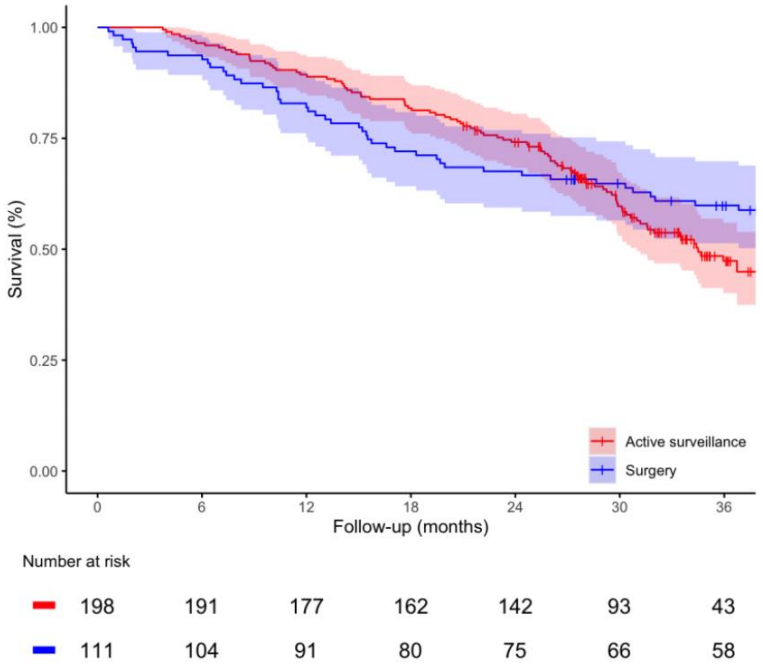
Disease-free Survival



HR 1.35, 95%CI 0.89-2.03, p=0.15

Toxicity and Side Effects of CRT

- Common side effects include esophagitis, fatigue, and hematologic toxicity.
- Long-term risks: strictures, pulmonary complications, and second malignancies.
- Careful patient selection is crucial to minimize adverse effects.

Definitive Chemoradiotherapy

- Definitive CRT is an option
  - Particularly for patients who are responding
- Local-recurrence still occurs in ~50%
- Can we improve on local response

INT0123 Chemoradiotherapy at 2 dose levels

- US study of 236 nonmetastatic esophageal SCC or adenocarcinoma
- FU and Cisplatin per RTOG 85-01 but randomized to 50.4 Gy vs 64.8 Gy
- Higher doses not associated with median (13 vs 18 months) or 2 year survival (31% vs 40%) or incidence of locoregional persistent or recurrent disease (56% vs 52%)
- High dose RT was more toxic

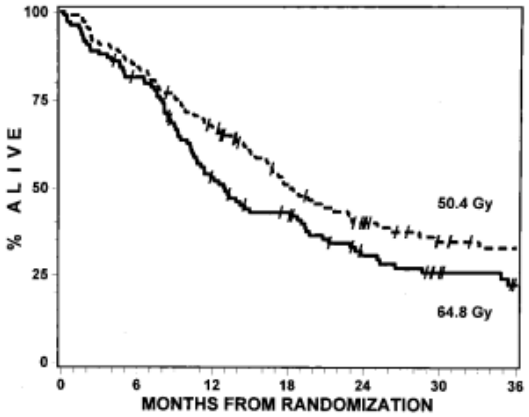


Fig 2. Overall survival according to the assigned treatment. No significant difference was observed between the two treatments.

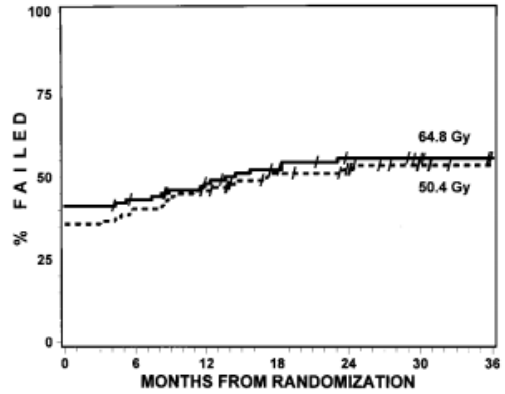


Fig 4. Time to first failure (local or regional failure and persistence) for all patients. No significant difference was observed between the two treatments.

Table 3. Overall Maximum Toxicity Per Patient

	Acute Toxicity				Late Toxicity			
	High Dose (64.8 Gy) (n = 109)		Standard Dose (50.4 Gy) (n = 109)		High Dose (64.8 Gy) (n = 95)		Standard Dose (50.4 Gy) (n = 99)	
Grade	No.	%	No.	%	No.	%	No.	%
1	2	2	1	1	9	9	19	20
2	21	19	28	26	28	29	22	22
3	50	46	47	43	32	34	24	24
4	23	21	28	26	10	11	13	13
5	10	9	2	2	1	1	0	

J Clin Oncol. 2002 Mar 1; 20(5):1167-74

PRODIGE(5)/ACCORD17: DCRT+ FOLFOX vs DCRT+FP

- France: 267 patients randomized between DCRT + FOLFOX vs DCRT+FP with localized esophageal cancer
- No difference in PFS or OS between FOLFOX and FP group
- Both treatments appear to be reasonable options to combine with DCRT
- Did not compare to carboplatin+paclitaxel

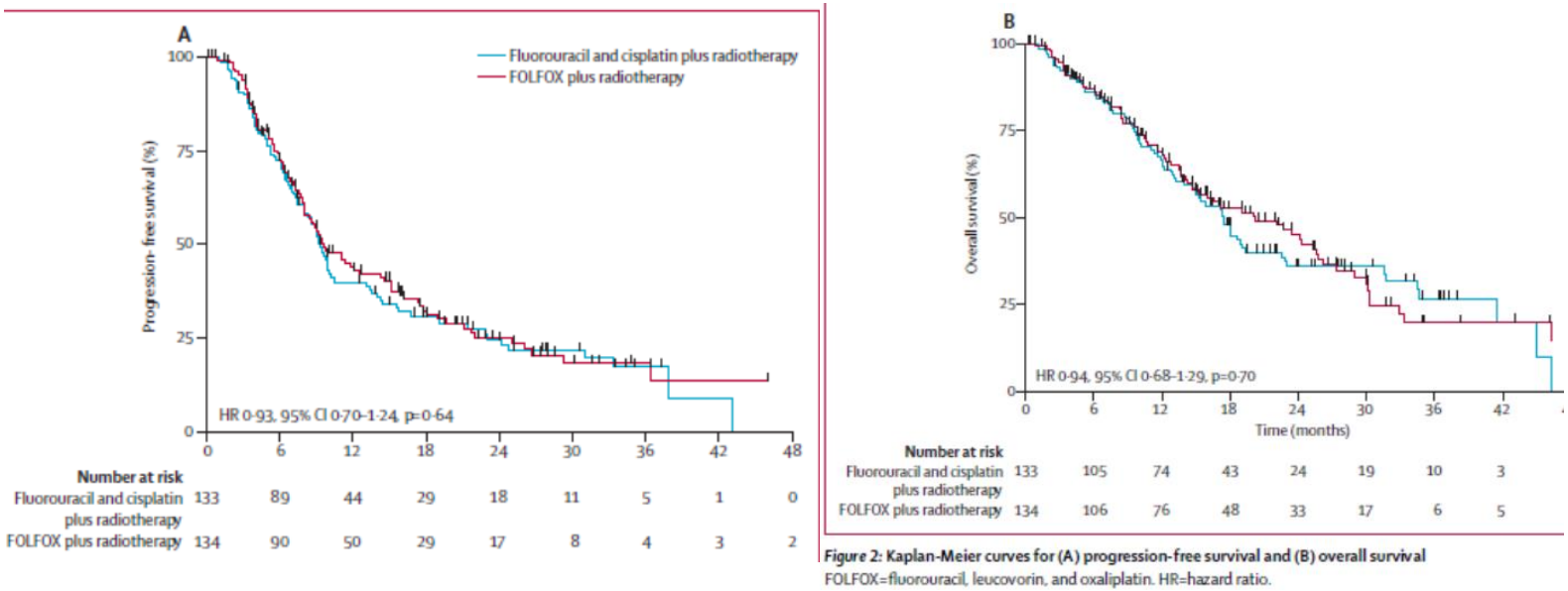


Figure 2: **Kaplan-Meier curves for (A) progression-free survival and (B) overall survival**
FOLFOX=fluorouracil, leucovorin, and oxaliplatin. HR=hazard ratio.

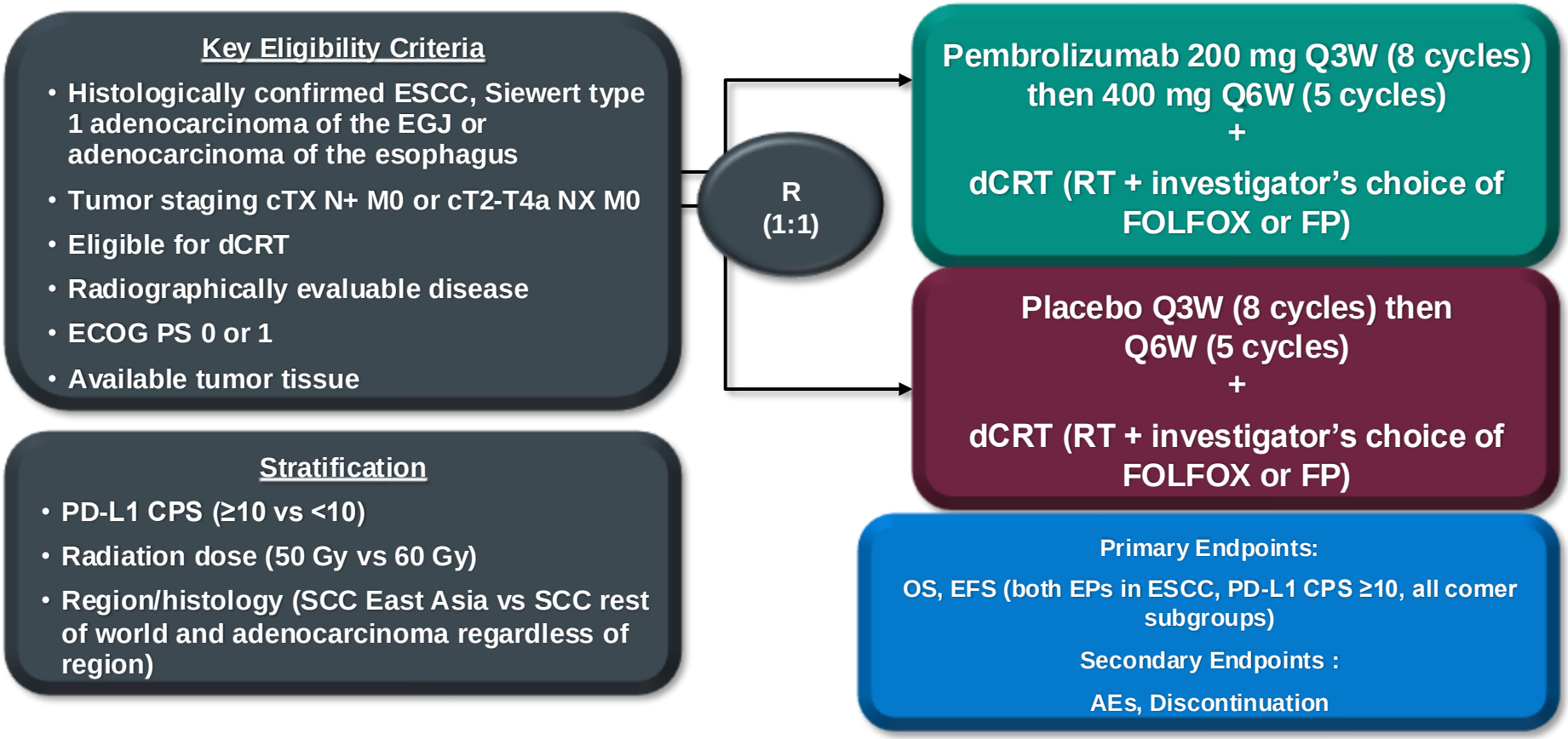
Lancet Oncol 2014; 15:305-14

Definitive Chemoradiotherapy

- Definitive CRT is an option
  - Particularly for patients who are responding
- Local-recurrence still occurs in ~50%
- Can we improve on local response
  - Higher doses of RT = NO (INT-0123)
  - Oxaliplatin $\tilde{=}$ Cisplatin (Prodige 5)
- Immunotherapy?

KEYNOTE-975: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial of Pembrolizumab Versus Placebo in Participants With Esophageal Carcinoma Receiving Concurrent Definitive Chemoradiotherapy

KEYNOTE-975: Study Design (NCT04210115)



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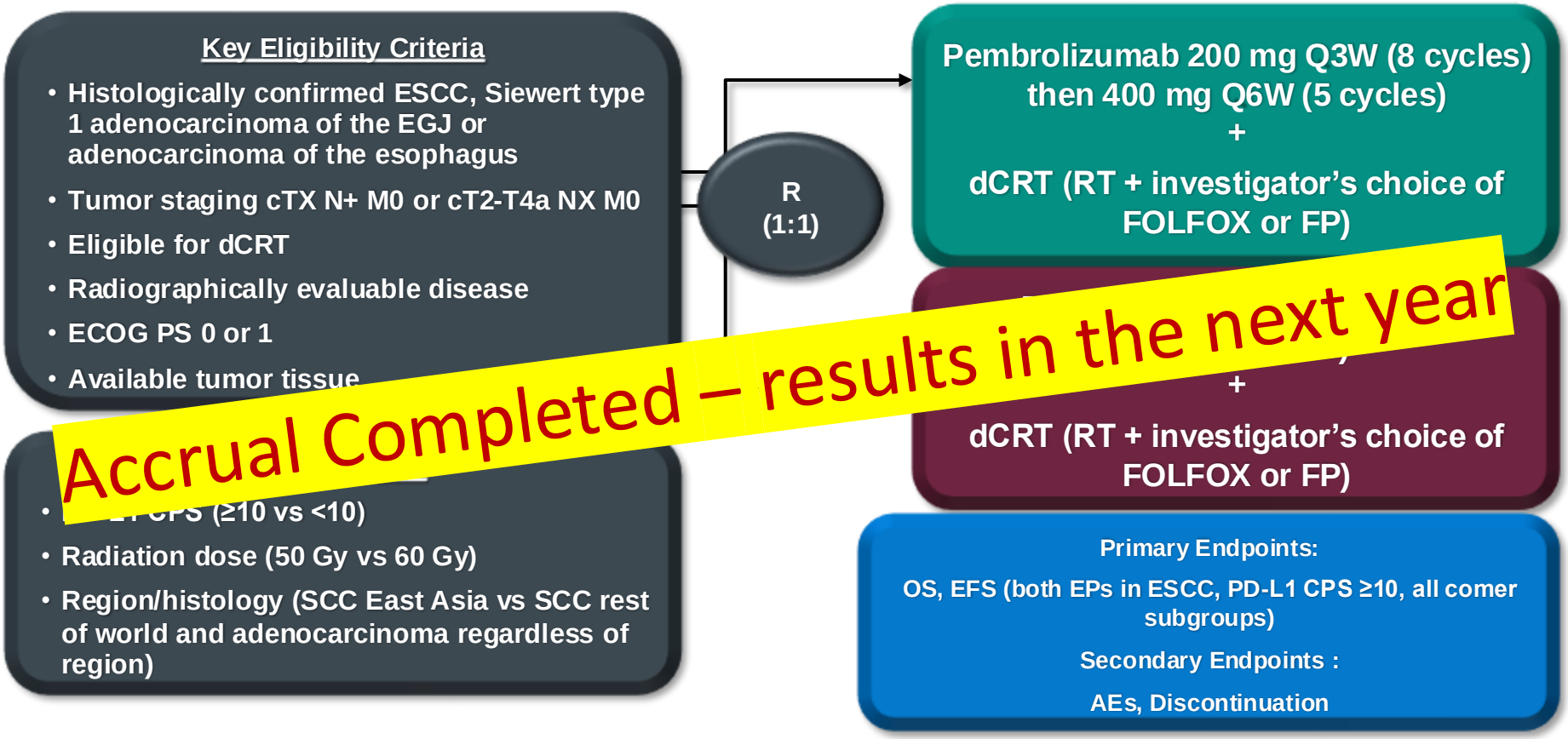

Accrual Completed – results in the next year

Who Receives Definitive Chemoradiotherapy?

Approximately 10-20% of esophageal cancer patients are considered for definitive CRT.

Typically chosen for patients who are inoperable or refuse surgery.

Patients must have localized disease without distant metastases.

Conclusions

- Definitive CRT is a viable option for selected esophageal cancer patients.
- Survival outcomes can be comparable to surgery. Improving response will obviate the need for surgery
- The Watch and Wait approach may be appropriate for certain cases. – awaiting the results
- Future research – integrate immunotherapy and modalities to identify residual disease