# **Esophageal Cancer Treatment**

# **Esophageal Cancer Treatment Categories**

Category	Stage	Treatment
Dyplasia	Tis	Radiofrequency Ablation
Superficial Tumors	T1a	Endoscopic Therapy
Localized Tumors	T1b T2	Surgery
Locally-advanced	$T3 \text{ or } N^+$	$\operatorname{ChemoRT} \to \operatorname{Surgery}$
Metastatic	M1	Chemotherapy +/- Radiation

# **Dyplasia**

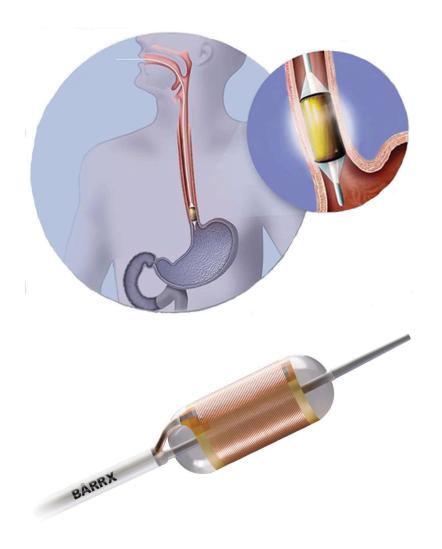
Radiofrequency Ablation for Dysplasia

127 patients with dysplasia randomized:

- Radio-frequency ablation
- Sham ablation

Low-grade dysplasia in 64

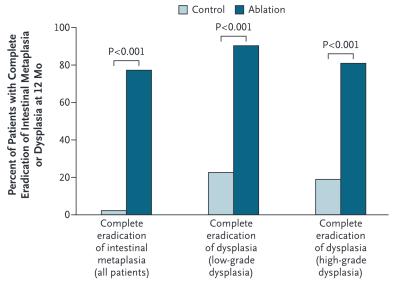
High-grade dysplasia in 63



(Shaheen et al. 2009)

# Radiofrequency Ablation for Dysplasia

Radiofrequency Ablation results in eradication of Barrett's in 75% at 1 year



Intention-to-Treat Comparison Groups

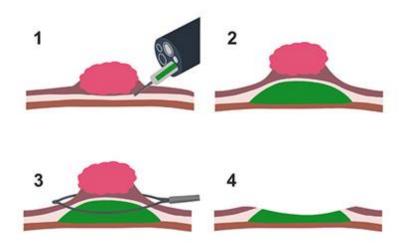
(Shaheen et al. 2009)

# **Superficial Tumors**

Workup of nodular Barretts:

- Endoscopic Ultrasound
- Endoscopic Mucosal Resection
  - Diagnostic (T staging)
  - May be the rapeutic for T1a tumors

# **Endoscopic Musocal Resection**



# **Endoscopic Submucosal Dissection**

Endoscopic resection uses needle-knife to dissect below submucosa

Maybe suitable for T1b lesions if lesion is completely resected Risk of perforation

### **Localized Tumors**

Patients staged as uT2 N0 are candidates for primary surgery. However:

- $\bullet~$  EUS has a 25% rate of understaging uT2 N0 tumors
- Understaged patients who undergo primary surgery would need chemo or chemoRT postop

## Asymptomatic Tumors (minimal dysphagia)

- EUS to distinguish T2 from T3 tumors
- If uT2 N0  $\rightarrow$  CT chest/abdomen/pelvis  $\rightarrow$  Esophagectomy
- If uT3 or N1  $\rightarrow$  PET  $\rightarrow$  neoadjuvant therapy

Patients with dysphagia almost always are T3 tumors (and don't need EUS)

### Symptomatic Tumors (dysphagia)

Patients with dysphagia to solids or weight loss or tumor length >3cm are unlikely to have T1-2 tumors and can be initially evaluated with PET Scan

- Disease confined to the esophagus and regional nodes  $\rightarrow$  Locally-advanced
- Metastatic disease  $\rightarrow$  Metastatic
- N3 → induction chemotherapy followed by chemoradiation and surgical evaluation.

### **EUS** in Patients with Dysphagia

Memorial Sloan Kettering patients with esophageal cancer:

- 61 with dysphagia, 54 (89%) were found on EUS to have uT3-4 tumors.
- 53 without dysphagia, 25 (47%) were uT1-2  $\rightarrow$  candidates for primary surgery.

EUS can be omitted for patients with dysphagia, but is useful in patients without dysphagia.

(Ripley et al. 2016)

### **PET Scan**

PET has more specificity and sensitivity than CT in detecting regional lymph node and distal metastasis

### Locally-advanced

For patients with locally-advanced esophageal cancer, improved survival with adjunctive therapy. There are two options:

- ChemoRT  $\rightarrow$  Surgery (CROSS Trial)
- Chemo  $\rightarrow$  Surgery  $\rightarrow$  Chemo ([EsoPEC Trial])

### **CROSS Trial**

- 368 esophageal cancer patients randomized:
  - Surgery alone
  - Chemo+RT  $\rightarrow$  Surgery
- 75% adenocarcinoma
- T3: 80%. T2: 17%
- age  $\tilde{x}$ =60
- longer survival with Chemo+RT  $\rightarrow$  Surgery

### CROSS Trial Details

Chemotherapy: Weekly carboplatin and paclitaxel Radiation: 4140 cGy in 23 fractions (180cGy/fraction)

(Shapiro et al. 2015)

### **CROSS**

The median time from randomization until resection was 24 days in the surgery group and 97 days in the chemoradiotherapy-surgery group. Of note, 13% of patients in the surgery only group were found to be unresectable at the time of operation versus 4% of the chemoradiotherapy-surgery group (p = 0.002). R0 resection was obtained in 92% of the chemoradiotherapy-surgery group versus 69% of the surgery alone group (p < 0.001). There were no significant differences in complications between the two groups, including in-hospital and 30-day mortality. Positive nodes were identified in 75% of the surgery alone group versus 31% of the chemoradiotherapy-surgery group (p < 0.001).

# **CROSS - Overall Survival**

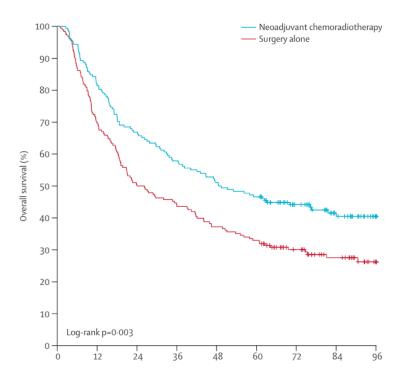


Figure 1: Surgery vs ChemoRT  $\rightarrow$  Surgery

(Shapiro et al. 2015)

# **CROSS** - Survival by Histology

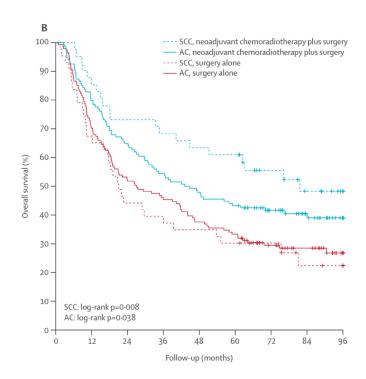


Figure 2: Surgery vs ChemoRT  $\rightarrow$  Surgery

### CROSS - Adenocarcinooma

(Shapiro et al. 2015)

Median survival 43mo v<br/>s $27\mathrm{mo}$ 

Pathologic complete response in 23%

# CROSS - Squamous cell carcinoma

Median survival 82mo vs 21mo

Pathologic complete response in 49%

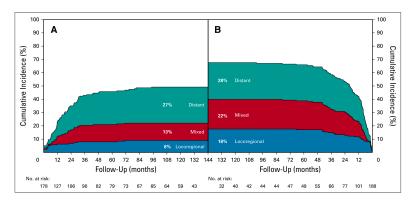
(Shapiro et al. 2015)

### **CROSS** - Sites of Failure

Sites of failure over time

 $ChemoRT + Surgery \ vs \ Surgery$ 

ChemoRT appears to reduce risk of local or local+distant failure, but not isolated distant failure



(Shapiro et al. 2015)

# Adjuvant Immunotherapy: Checkmate 577 Trial

Immunotherapy with nivolumab as adjuvant therapy after CROSS regimen for patients with residual disease

Stage II/II Esophageal or GE junction cancers Adenocarcinoma or squamous cell

ChemoRT  $\rightarrow$  Surgery with residual disease on pathology

Treatment Group: Nivolumab every 2 weeks x 4 months  $\rightarrow$  every month x 8 months

Control Group: No adjuvant therapy

Results: Better survival in group with adjuvant nivolumab

(Kelly et al. 2021)

### **Nivolumab**

PD-L1 agonist ligand

Interferes with tumor cell down-regulation of T cells

Active against stage IV esophageal cancer

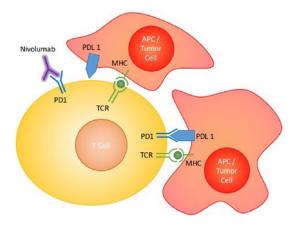


Figure 3: Nivolumab mechanism of action

### **Chekmate 577 Trial**

EsoCA patients who received ChemoRT $\rightarrow$  Surgery with residual disease (not pCR)

Randomized to one year of immunotherapy (nivolumab) vs Observation

Adjuvant nivolumab group had longer median survival: 22mo v<br/>s $11\mathrm{mo}$ 

(Kelly et al. 2021)

### Checkmate 577 Trial

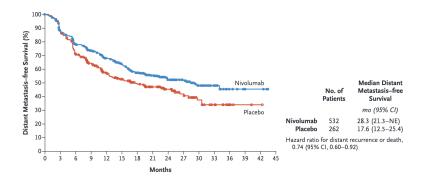


Figure 4: Adjuvant Nivolumab vs Observation

# Neoadjuvant Chemo for EsoCA

(Kelly et al. 2021)

- MAGIC trial (gastric):  $ECF^1 \rightarrow Surgery \rightarrow ECF \ vs \ Surgery$
- OEO2 Trial: (esophageal) Chemo $\rightarrow$ Surgery $\rightarrow$  Chemo vsSurgery
- FLOT (gastric): FLOT $^2 \rightarrow$ Surgery $\rightarrow$  FLOT vs ECF $\rightarrow$ Surgery $\rightarrow$ ECF
- EsoPEC: (esophageal):FLOT $\rightarrow$ Surgery $\rightarrow$ FLOT vs ChemoRT $\rightarrow$ Surgery (CROSS)

### **OEO2** Clinical Trial

- 802 Esophageal adenocarcinoma and squamous cell
- Randomized to Chemo  $\rightarrow$  Surgery  $\rightarrow$  Chemo vs Surgery alone
- Chemotherapy with ECF (Epirubicin, Cisplatin, 5FU)
- 5-year survival 23% for chemo+surgery vs 17% for surgery (HR 0.84 p=0.03)

(Allum et al. 2009)

<sup>&</sup>lt;sup>1</sup>Epirubicin, Cisplatin, 5FU

<sup>&</sup>lt;sup>2</sup>5FU, Leuvocorin, Oxaliplatin, Decetaxol

# Neo-Aegis Tral CROSS vs MAGIC/FLOT

- Adenocarcinoma T2-3 N0-3 M0 Tumor length <8cm
- ChemoRT arm: carboplatin + paclitaxel + 4140cGy
- Chemo arm: MAGIC (ECF) or FLOT (later in trial)
- No difference in overall survival
- R0 resection 96% with CROSS vs 82% with chemo
- pCR 12% with CROSS vs 4% with chemo

(reynolds1015?)

### **EsoPEC Trial CROSS vs FLOT**

- Adenocarcinoma esophagus T1 N+ or T2-4a M0. Median age =63. 89% men
- Randomized to CROSS (n=217) vs FLOT chemotherapy (n=221) = 438
- CROSS: carboplatin/paclitaxel +  $4140cGy \rightarrow Surgery$
- FLOT: FLOT  $\rightarrow$  Surgery  $\rightarrow$  FLOT
- Excluded: Squamous cell, gastric cancer, T1N0, T4b, M1

(Hoeppner et al. 2025)

### **EsoPEC: FLOT superior to CROSS**

- Surgery performed in 371/438 patients
- 90-day mortality 4.3% (3.2% in FLOT and 5.6% CROSS)
- Median survival 66mo in FLOT arm and 37mo in Cross arm
- 3-year overall survival 57% FLOT vs 51% CROSS
- 5-year overall survival 51% FLOT vs 29% CROSS
- pCR 17% for FLOT and 10% CROSS

(Hoeppner et al. 2025)

# Surgery for Squamous Cell Carcinoma

Squamous Cell Carcinoma of the esophagus

- responds well to chemo+RT
- more difficult to get a surgical margin on the airway
- additional benefit of surgery on top of chemoRT is uncertain

## FFCD 9102 2007 (Bedenne)

All patients received 4500cGy RT + 2 cycles of cisplatin +  $5\mathrm{FU}$ 

Patients with a clinical response were randomized:

- Surgery -> 2 year survival 34% Median 17.7mo
- 3 cycles of chemo + 2000 cGy RT -> 2 year survival 40% Median 19.3mo

No difference in overall survival

(Bedenne et al. 2007)

## German Trial (Stahl)

 $4000~\mathrm{cGY~RT} + \mathrm{Chemo} \rightarrow \mathrm{Surgery}.~64\%$ 2-year PFS. Mortality 12.8%

6500cGy RT + Chemo: 41% 2-year PFS. Mortality 3.5%

No difference in overall survival

(Stahl et al. 2005)

#### Metastatic

FOLFOX is first-line systemic therapy for metastatic GI cancers

• Dose-limiting toxicity is frequently peripheral neuropathy

### **Orientation Manual**



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