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 or N^+	ChemoRT $\rightarrow$ Surgery
Metastatic	M1	Chemotherapy +/- Radiation

Dyplasia

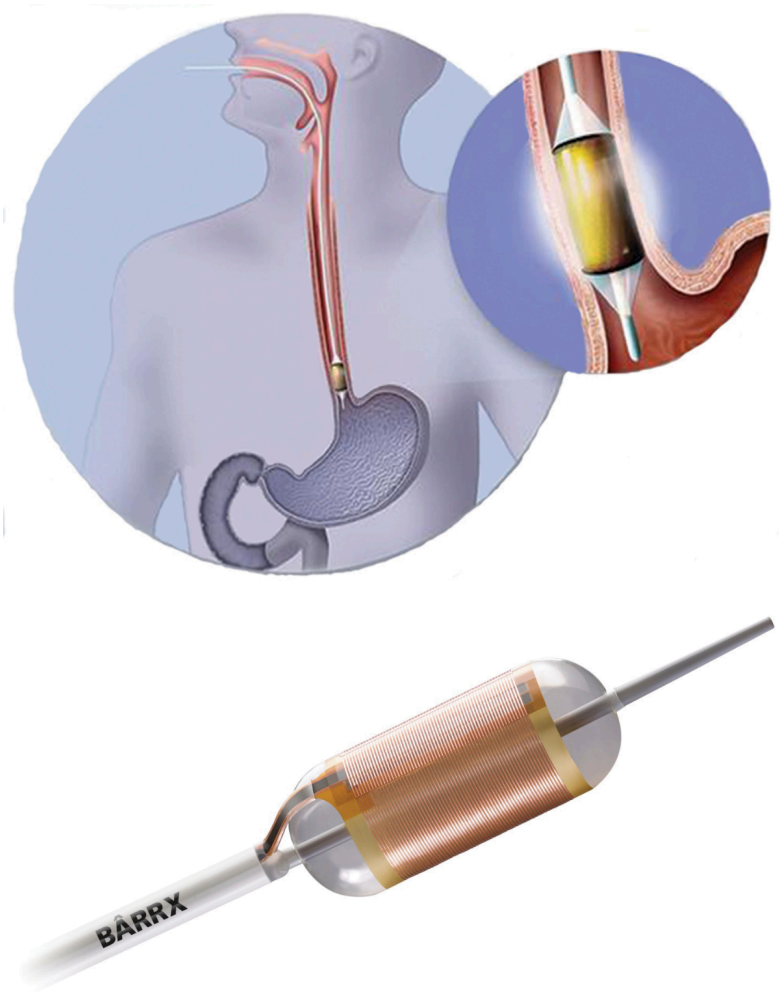
Radiofrequency Ablation for Dysplasia

127 patients with dysplasia randomized:

- Radio-frequency ablation
- Sham ablation

Low-grade dysplasia in 64

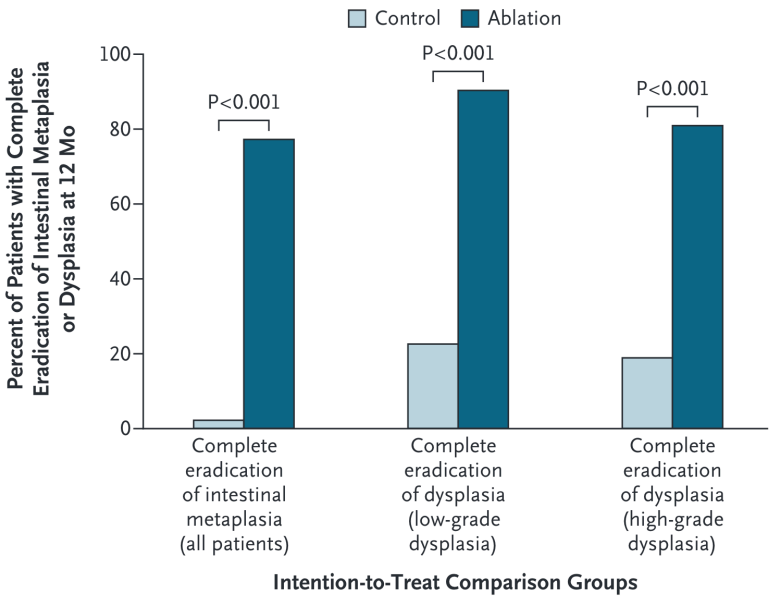
High-grade dysplasia in 63



(Shaheen et al. 2009)

Radiofrequency Ablation for Dysplasia

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



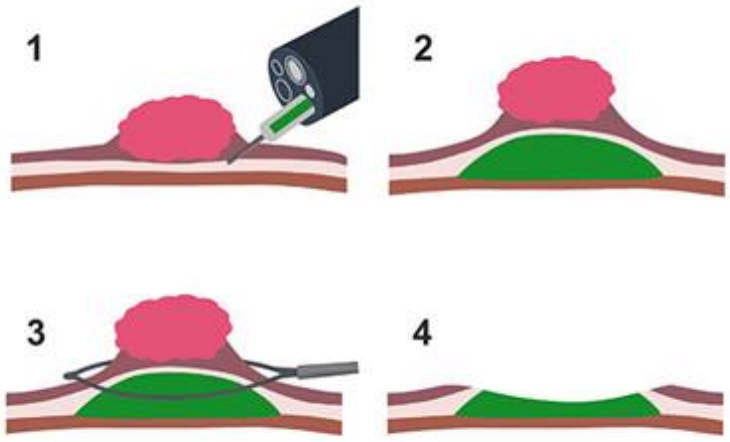
(Shaheen et al. 2009)

Superficial Tumors

Workup of nodular Barretts:

- Endoscopic Ultrasound
- Endoscopic Mucosal Resection
  - Diagnostic (T staging)
  - May be therapeutic 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:*

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

Small Tumors (minimal dysphagia)

- EUS to distinguish T2 from T3 tumors
- If uT2 N0 → CT chest/abdomen/pelvis → Esophagectomy
- If uT3 or N1 → PET → 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 → Locally-advanced
- Metastatic disease → 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 → 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

(**gotze1?**)

Locally-advanced

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

- ChemoRT → Surgery (CROSS Trial)
- Chemo → Surgery → Chemo ([EsoPEC Trial])

CROSS Trial

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

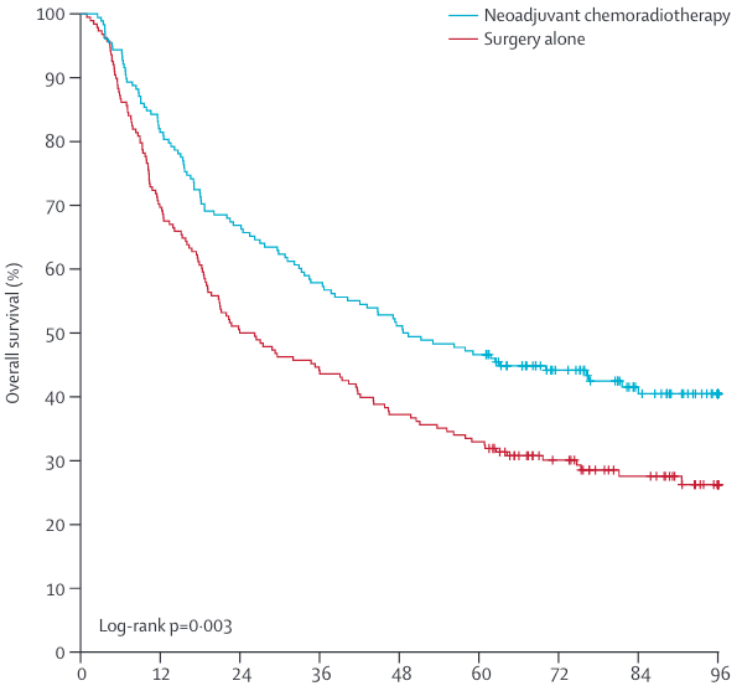


Figure 1: Surgery vs ChemoRT → Surgery

(Shapiro et al. 2015)

CROSS - Survival by Histology

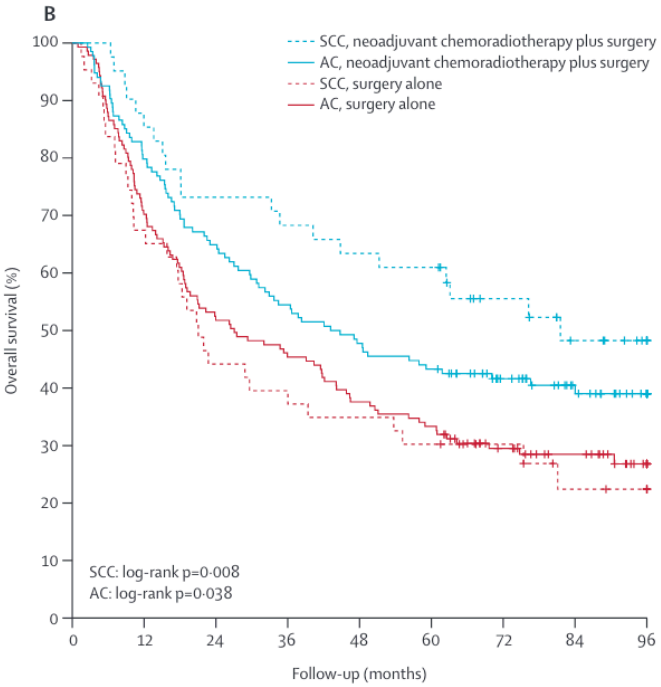


Figure 2: Surgery vs ChemoRT → Surgery

CROSS - Adenocarcinooma

(Shapiro et al. 2015)

Median survival 43mo vs 27mo

Pathologic complete response in 23%

CROSS - Squamous cell carcinoma

Median survival 82mo vs 21mo

Pathologic complete response in 49%

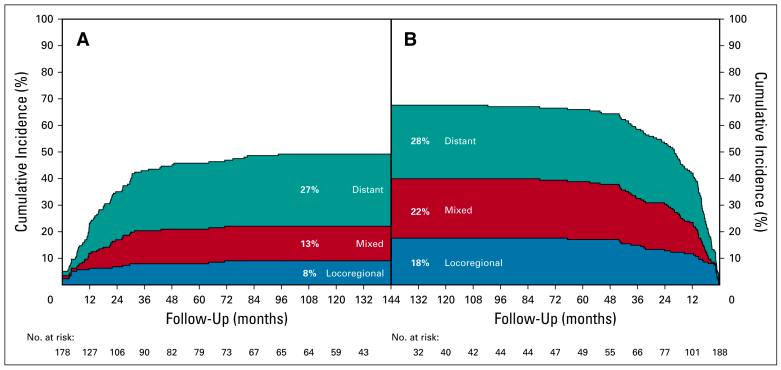
(Shapiro et al. 2015)

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 → Surgery *with residual disease on pathology*

Treatment Group: Nivolumab every 2 weeks x 4 months → 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

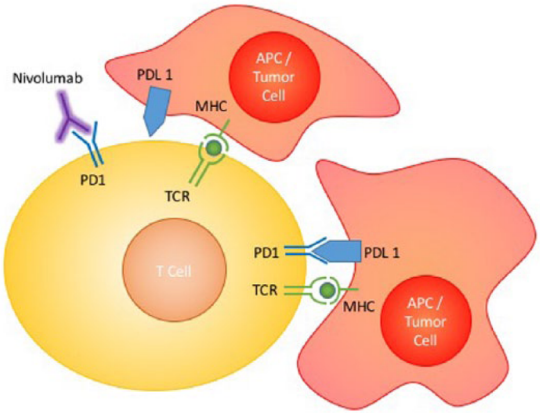


Figure 3: Nivolumab mechanism of action

Chekmate 577 Trial

EsoCA patients who received ChemoRT→ Surgery with residual disease (not pCR)

Randomized to one year of immunotherapy (nivolumab) vs Observation

Adjuvant nivolumab group had longer median survival: 22mo vs 11mo

(Kelly et al. 2021)

Checkmate 577 Trial

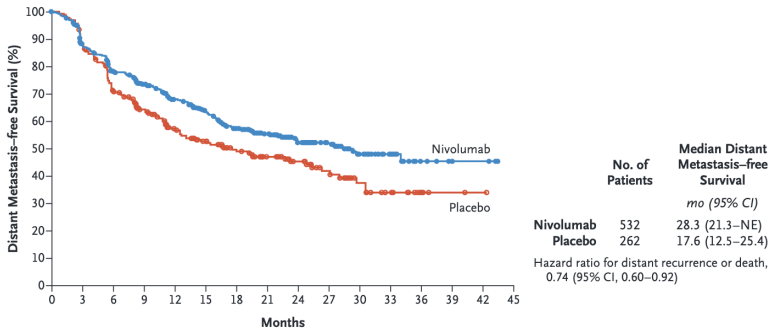


Figure 4: Adjuvant Nivolumab vs Observation

Neoadjuvant Chemo for EsoCA

(Kelly et al. 2021)

- MAGIC trial (gastric): ECF[1]→Surgery→ECF *vs* Surgery
- OEO2 Trial: (esophageal) Chemo→Surgery→ Chemo *vs* Surgery
- FLOT (gastric): FLOT[2]→Surgery→ FLOT *vs* ECF→Surgery→ECF
- EsoPEC: (esophageal):FLOT→Surgery→FLOT *vs* ChemoRT→Surgery (CROSS)

OEO2 Clinical Trial

- 802 Esophageal adenocarcinoma and squamous cell
- Randomized to Chemo → Surgery → 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)

[1]Epirubicin, Cisplatin, 5FU
[2]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 → Surgery
- FLOT: FLOT → Surgery → 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 + 5FU

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

(**bedene1160?**)

German Trial (Stahl)

4000 cGY RT + Chemo → 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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