

# 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 <sup>+</sup>	ChemoRT → 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



## 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<sup>1</sup> 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.

## PET Scan

PET has more specificity and sensitivity than CT in detecting regional lymph node and distal metastasis <sup>2</sup>

## 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](#)])

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<sup>1</sup>Ripley et al. (2016)

<sup>2</sup>Block et al. (1997)

## 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 - Overall Survival



Figure 1: Surgery vs ChemoRT → Surgery

## CROSS - Survival by Histology

(Shapiro et al. 2015)



Figure 2: Surgery vs ChemoRT → Surgery

## CROSS - Adenocarcinoma

(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 40%

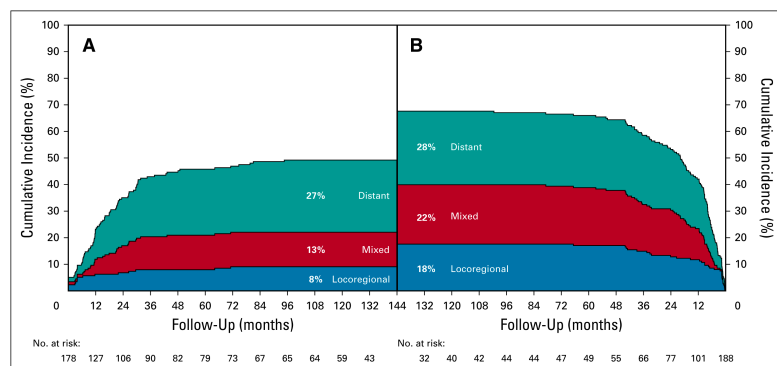
(Shapiro et al. 2015)

## 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)

## Neoadjuvant Chemo for EsoCA

- MAGIC trial (gastric): ECF<sup>3</sup>→Surgery→ECF *vs* Surgery
- OEO2 Trial: (esophageal) Chemo→Surgery→ Chemo *vs* Surgery
- FLOT (gastric): FLOT<sup>4</sup>→Surgery→ FLOT *vs* ECF→Surgery→ECF
- EsoPEC: (esophageal):FLOT→Surgery→FLOT *vs* ChemoRT→Surgery (CROSS)

## OEO2 Clinical Trial

- 802 Esophageal adenocarcinoma and squamous cell

<sup>3</sup>Epirubicin, Cisplatin, 5FU

<sup>4</sup>5FU, Leuovorin, Oxaliplatin, Decetaxol



- 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)

### **Neo-Aegis Trial 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 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

## **EsoPEC Trial Results**

- 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

## **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 4-16 weeks prior Residual pathologic disease

Treatment Group: Nivolumab every 2 weeks x 4 months → every month x 8 months

(Kelly et al. 2021)

## **Nivolumab**

PD-L1 agonist ligand

Interferes with tumor cell down-regulation of T cells

Active against stage IV esophageal cancer

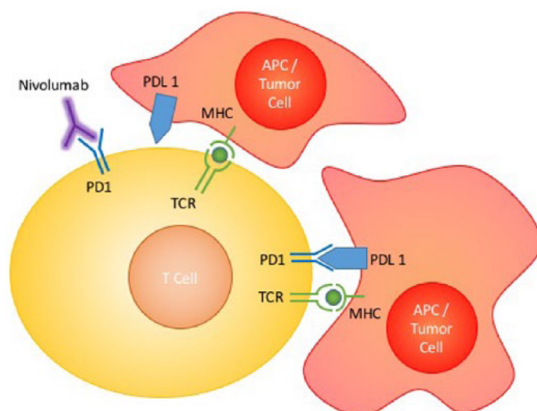


Figure 3: Nivolumab mechanism of action

### Checkmate 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

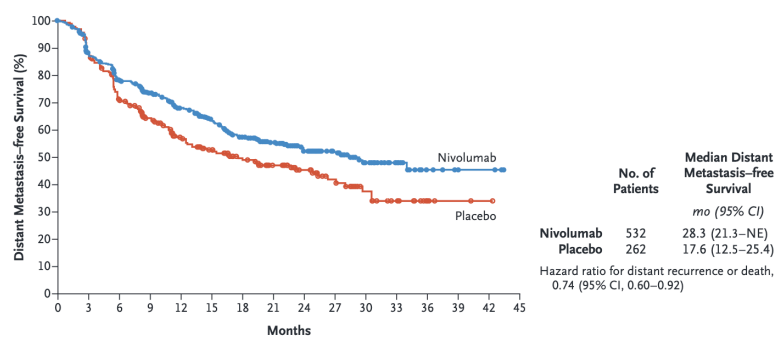


Figure 4: Adjuvant Nivolumab vs Observation

## FFCD 9102 2007 (Bedenne)

(Kelly et al. 2021)

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

Randomized:

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## German Trial (Stahl)

4000 cGy RT + PE → Surgery. 64% 2-year PFS. Mortality 12.8%

6500cGy RT + PE 41% PFS.Mortality 3.5%

## Metastatic

FOLFOX is first-line systemic therapy for metastatic GI cancers

- Dose-limiting toxicity is frequently peripheral neuropathy

## Orientation Manual



## References

- Allum, William H., Sally P. Stenning, John Bancewicz, Peter I. Clark, and Ruth E. Langley. 2009. "Long-Term Results of a Randomized Trial of Surgery with or Without Preoperative Chemotherapy in Esophageal Cancer." *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 27 (30): 5062–67. <https://doi.org/10.1200/JCO.2009.22.2083>.
- Block, M. I., G. A. Patterson, R. S. Sundaresan, M. S. Bailey, F. L. Flanagan, F. Dehdashti, B. A. Siegel, and J. D. Cooper. 1997. "Improvement in Staging of Esophageal Cancer with the Addition of Positron Emission Tomography." *The Annals of Thoracic Surgery* 64 (3): 770–776; discussion 776–777. [https://doi.org/10.1016/s0003-4975\(97\)00619-x](https://doi.org/10.1016/s0003-4975(97)00619-x).
- Kelly, Ronan J., Jaffer A. Ajani, Jaroslaw Kuzdzal, Thomas Zander, Eric Van Cutsem, Guillaume Piessen, Guillermo Mendez, et al. 2021. "Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer." *The New England Journal of Medicine* 384 (13): 1191–1203. <https://doi.org/10.1056/NEJMoa2032125>.
- Ripley, R. Taylor, Inderpal S. Sarkaria, Rachel Grosser, Camelia S. Sima, Manjit S. Bains, David R. Jones, Prasad S. Adusumilli, et al. 2016. "Pretreatment Dysphagia in Esophageal Cancer Patients May Eliminate the Need for Staging by Endoscopic Ultrasonography." *The Annals of Thoracic Surgery* 101 (1): 226–30. <https://doi.org/10.1016/j.athoracsur.2015.06.062>.
- Shaheen, Nicholas J., Prateek Sharma, Bergein F. Overholt, Herbert C. Wolfsen, Richard E. Sampliner, Kenneth K. Wang, Joseph A. Galanko, et al. 2009. "Radiofrequency Ablation in Barrett's Esophagus with Dysplasia." *The New England Journal of Medicine* 360 (22): 2277–88. <https://doi.org/10.1056/NEJMoa0808145>.
- Shapiro, Joel, J. Jan B. van Lanschot, Maarten C. C. M. Hulshof, Pieter van Hagen, Mark I. van Berge Henegouwen, Bas P. L. Wijnhoven, Hanneke W. M. van Laarhoven, et al. 2015. "Neoadjuvant Chemoradiotherapy Plus Surgery Versus Surgery Alone for Oesophageal or Junctional Cancer (CROSS): Long-Term Results of a Randomised Con-

trolled Trial.” *The Lancet. Oncology* 16 (9): 1090–98. [https://doi.org/10.1016/S1470-2045\(15\)00040-6](https://doi.org/10.1016/S1470-2045(15)00040-6).