

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 → Surgery |
| Metastatic | M1 | Chemotherapy +/- Radiation |

Dyplasia

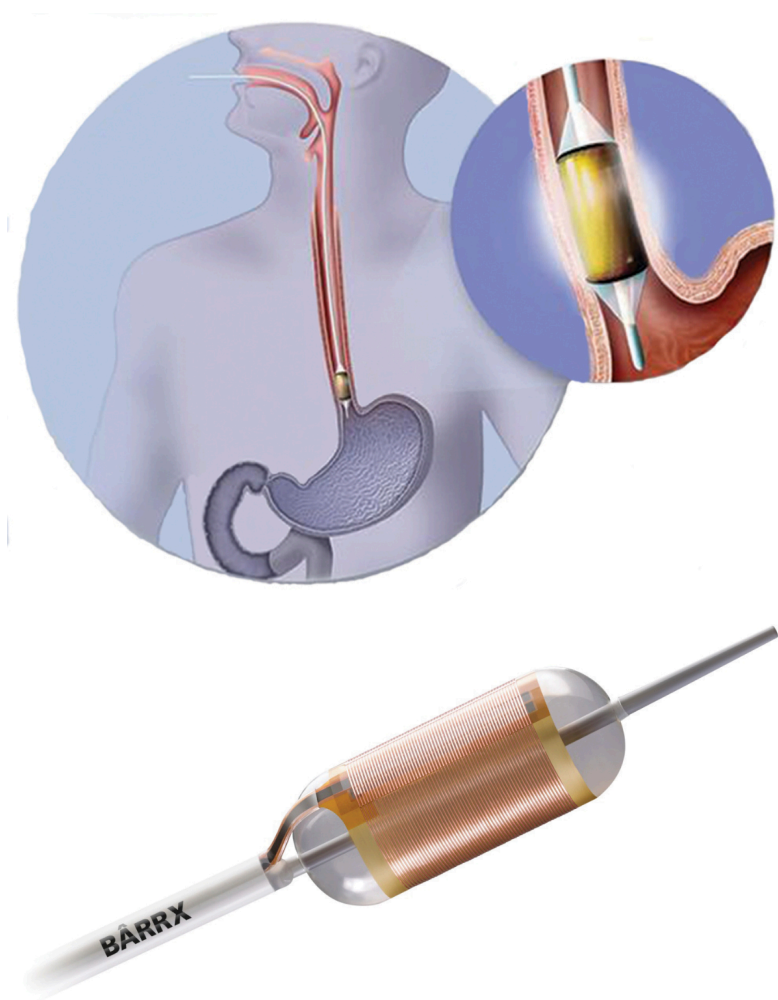
Radiofrequency Ablation for Dysplasia

127 patients with dysplasia randomized:

- Radio-frequency ablation
- Sham ablation

Low-grade dysplasia in 64

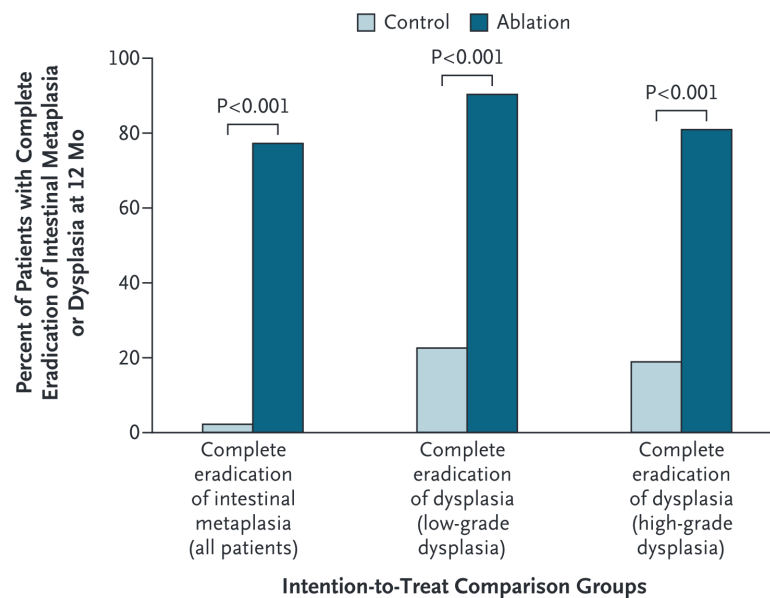
High-grade dysplasia in 63



(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 - 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 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): ECF¹→Surgery→ECF *vs* Surgery
- OEO2 Trial: (esophageal) Chemo→Surgery→ Chemo *vs* Surgery
- FLOT (gastric): FLOT²→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)

¹Epirubicin, Cisplatin, 5FU

²5FU, Leuovorin, Oxaliplatin, Decetaxol

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 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



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>.
- Hoeppe, Jens, Thomas Brunner, Claudia Schmoor, Peter Bronsert, Birte Kulemann, Rainer Claus, Stefan Utzolino, et al. 2025. "Perioperative Chemotherapy or Preoperative Chemoradiotherapy in Esophageal Cancer." *The New England Journal of Medicine* 392 (4): 323–35. <https://doi.org/10.1056/NEJMoa2409408>.
- 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. Hulschof, 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 Controlled 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).
- Stahl, Michael, Martin Stuschke, Nils Lehmann, Hans-Joachim Meyer, Martin K. Walz, Siegfried Seeber, Bodo Klump, et al. 2005. “Chemoradiation with and Without Surgery in Patients with Locally Advanced Squamous Cell Carcinoma of the Esophagus.” *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 23 (10): 2310–17. <https://doi.org/10.1200/JCO.2005.00.034>.