

Esophageal Cancer Cases

Case 1

62M with longstanding reflux has first EGD.

Reflux got worse during training for a triathalon



Case 1

Pathology shows Barrett's metaplasia without dysplasia

What is appropriate follow up?

Biopsy strategy?

Case 1 Barrett's metaplasia without dysplasia

What is appropriate follow up?

AGA Guidelines

- No dysplasia: 3-5 years
- Low grade dysplasia: 6-12 months
- High grade dysplasia 3 months
 - (in the absence of ablation)

Case 1 Barrett's metaplasia without dysplasia

Biopsy strategy?

AGA Guidelines

- White light endoscopy
- 4-quadrant biopsy every 2cm
- Mucosal irregularity biopsied separately
- 4-quadrant biopsy every 1cm if dysplasia)

Case 2

Pathology shows high-grade dysplasia

Treatment Options:

- [Observation](#)
- [Esophagectomy](#)
- [Cryotherapy]
- [Irreversible Electroporation]
- [Radio-frequency Ablation](#)

Observation

You receive a hand-written note from the family
inviting you to the funeral of the patient
who passed after a heroic battle with esophageal cancer

[Case 2](#)

Esophagectomy

Correct answer, wrong century (not the 20th)

[Case 2](#)

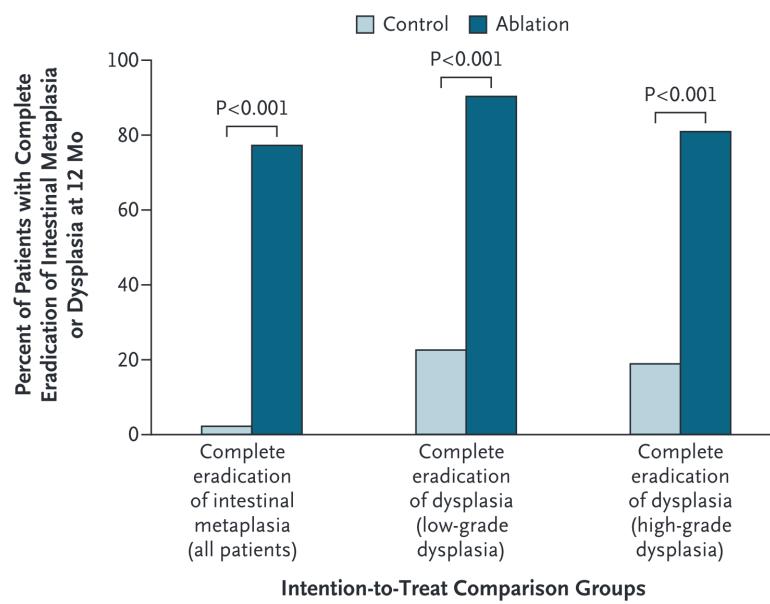
Cyrotherapy

Correct answer, wrong century (not the 22nd)

[Case 2](#)

Radio-frequency Ablation

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



Case 3

(Shaheen et al. 2009)

Case 3

EGD shows a nodule in the Barrett's esophagus

Treatment Options:

- [Surveillance]
- **Minimally Invasive Esophagectomy**
- Endoscopic Mucosal Resection
- Radio-frequency Ablation Barxx

Surveillance

You receive a hand-written note from the family
inviting you the patient's 70th birthday
after being treated at a competing medical center
for esophageal cancer

Case 3

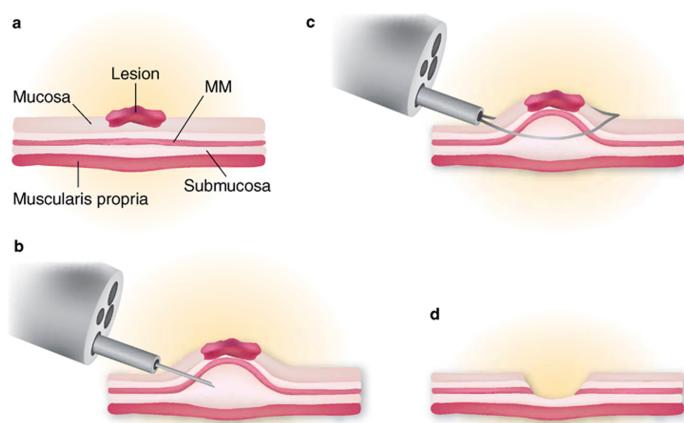
Minimally Invasive Esophagectomy

Correct answer, wrong patient

Case 3

Endoscopic Mucosal Resection

Endoscopic procedure to remove a superficial tumor from the inner layer of the esophagus



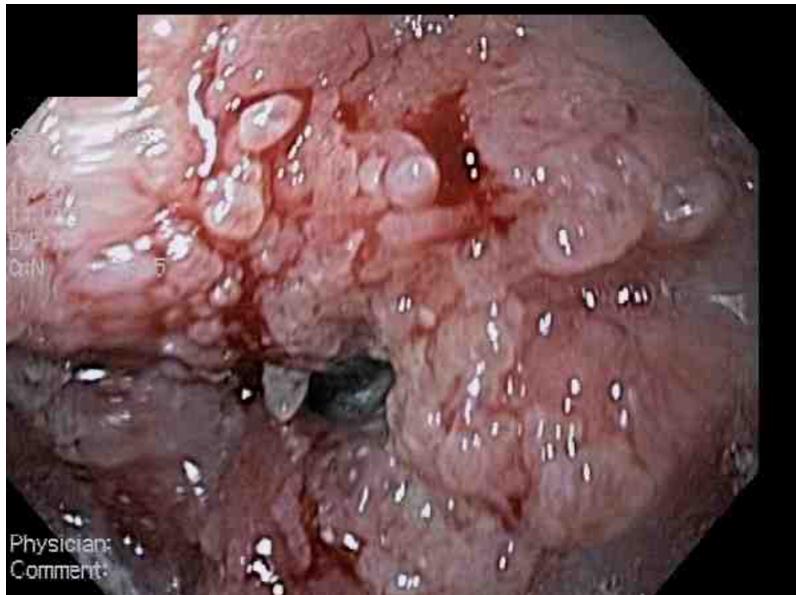
[Case 4]

Radio-frequency Ablation Barxx

Correct answer, wrong question

Case 5

Your patient from Case 2 returns with dysphagia and weight loss



Physician:
Comment:

Case 5

Pathology shows adenocarcinoma

Workup?

Case 5 adenocarcinoma

Workup?

[Barium Swallow Endoscopic Ultrasound CT Chest/Abdomen/Pelvis](#)

Barium Swallow

Correct answer, wrong century

Endoscopic Ultrasound

You receive a hand-written note from the family
inviting you the patient's 70th birthday
after they died from an esophageal perforation
which occurred during EUS

Autopsy showed T3 adenocarcinoma

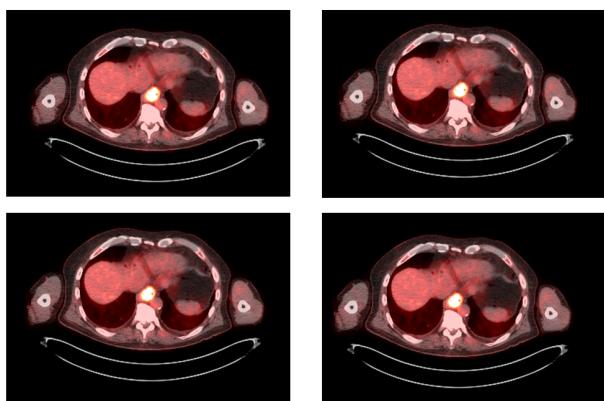
Case 5

CT Chest/Abdomen/Pelvis

What test do you order next?

PET scan

A PET scan is similar to a CT scan, and uses a small amount of tracer to light up areas of cancer.



T3 N0 M0 adenocarcinoma

Treatment Options - First Treatment Course

[Esophagectomy](#) [Chemo + Radiation] [Chemotherapy]

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

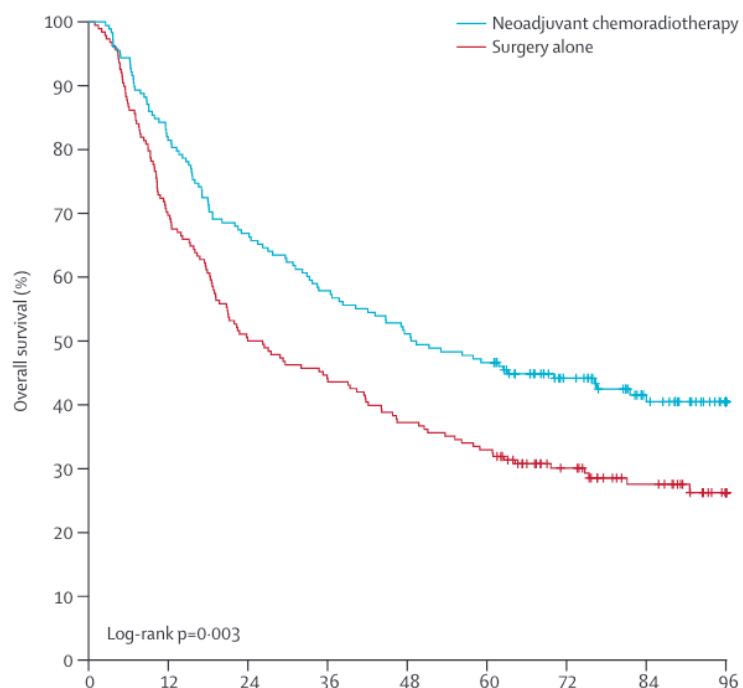


Figure 1: Surgery vs ChemoRT → Surgery

(Shapiro et al. 2015)

CROSS - Survival by Histology

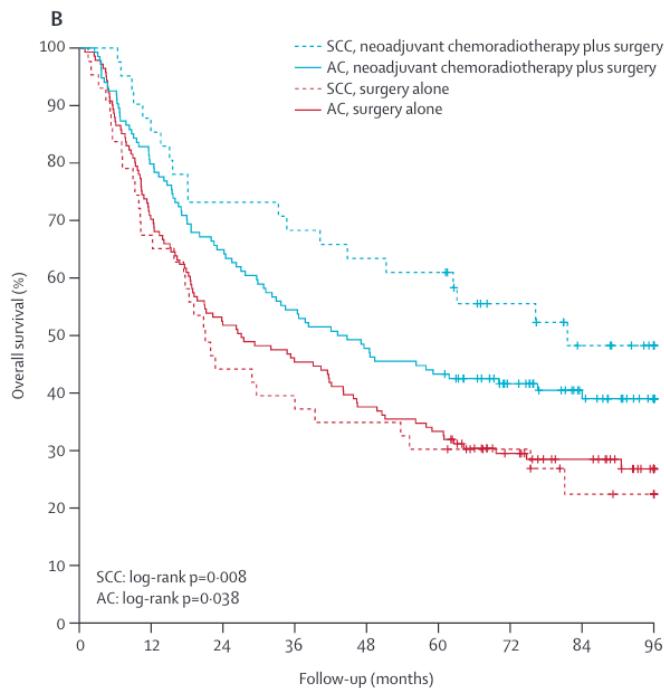


Figure 2: Surgery vs ChemoRT → Surgery

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 40%

(Shapiro et al. 2015)

T3 N0 M0 adenocarcinoma

Family asks if there is a better treatment option than CROSS

EsoPEC Trial

- 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

Case 7

Patient returns after FLOT chemotherapy

What are surgical options?

Esophageal Cancer Treatment Categories

| Category | Stage | Treatment |
|--------------------|----------------------|----------------------------|
| Dysplasia | Tis | Radiofrequency Ablation |
| Superficial Tumors | T1a | Endoscopic Therapy |
| Localized Tumors | T1b T2 | Surgery |
| Locally-advanced | T3 or N ⁺ | Chemo or ChemoRT → Surgery |
| Metastatic | M1 | Chemotherapy +/- Radiation |

| Category | Stage | Treatment |
|----------|-------|-----------|
|----------|-------|-----------|

Dyplasia

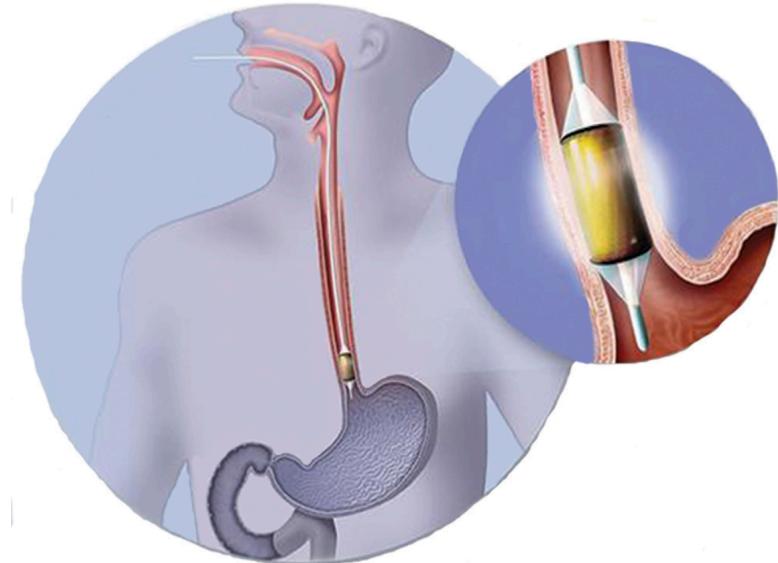
Radiofrequency Ablation for Dysplasia

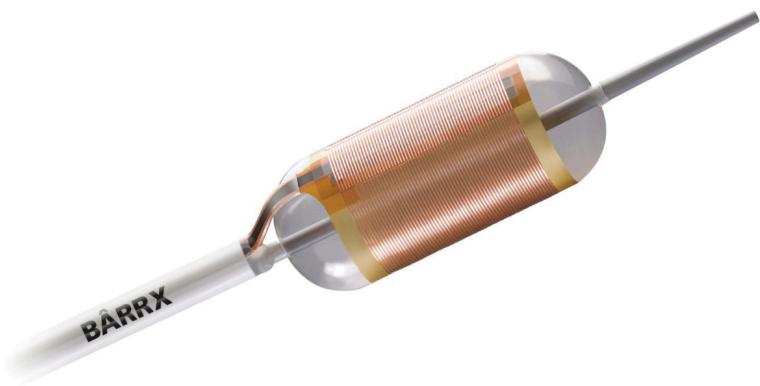
127 patients with dysplasia randomized:

- Radio-frequency ablation
- Sham ablation

Low-grade dysplasia in 64

High-grade dysplasia in 63

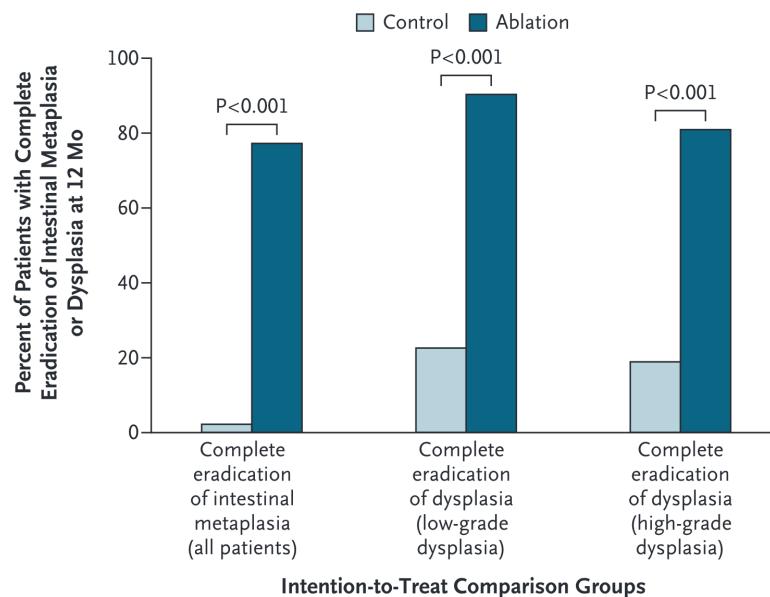




(Shaheen et al. 2009)

Radiofrequency Ablation for Dysplasia

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



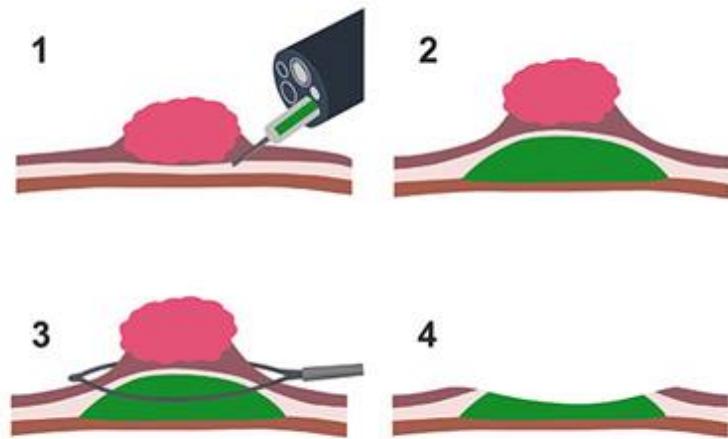
(Shaheen et al. 2009)

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 Kettering¹ 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 ²

¹Ripley et al. (2016)

²Block et al. (1997)

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 - Overall Survival

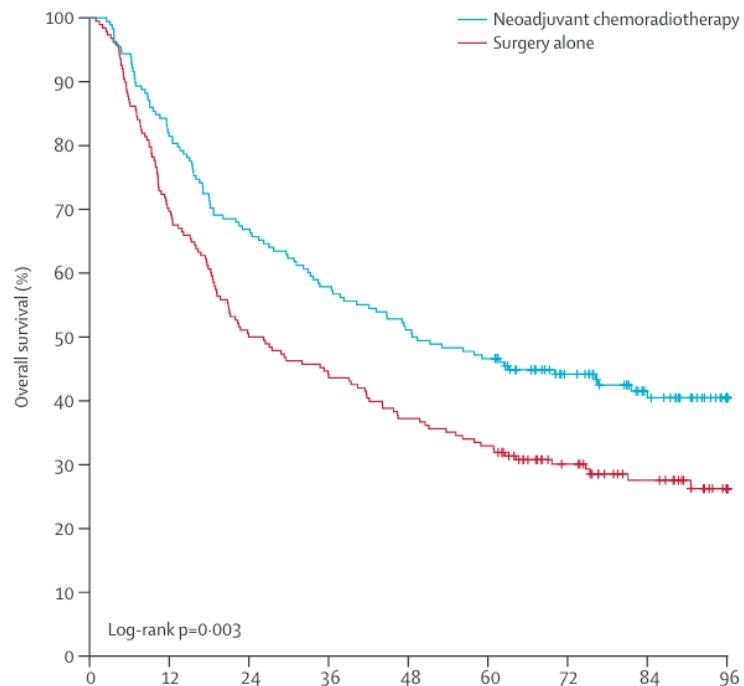


Figure 3: Surgery vs ChemoRT → Surgery

(Shapiro et al. 2015)

CROSS - Survival by Histology

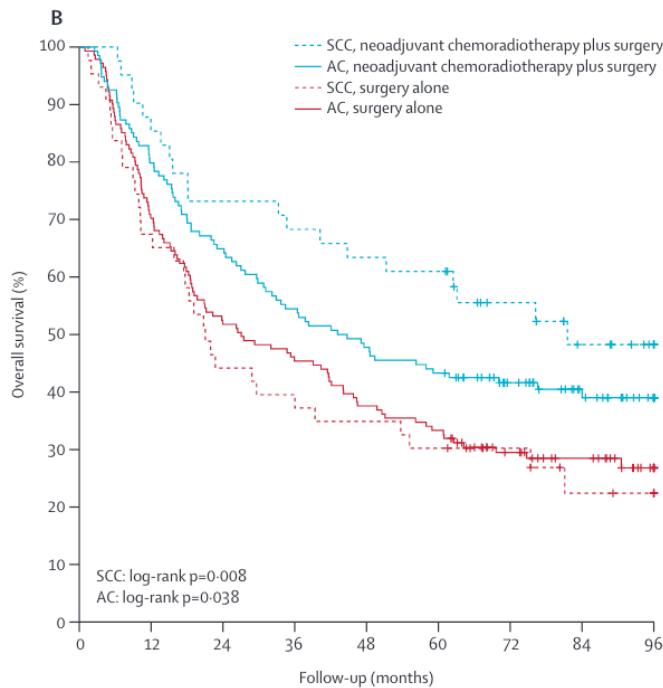


Figure 4: Surgery vs ChemoRT → Surgery

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%

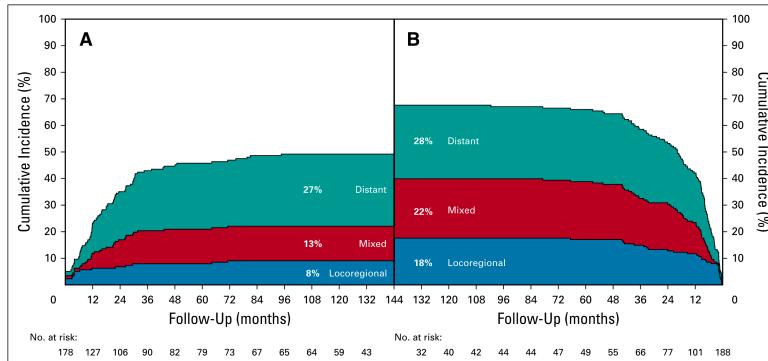
(Shapiro et al. 2015)

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): ECF³→Surgery→ECF *vs* Surgery
- OEO2 Trial: (esophageal) Chemo→Surgery→ Chemo *vs* Surgery
- FLOT (gastric): FLOT⁴→Surgery→ FLOT *vs* ECF→Surgery→ECF
- EsoPEC: (esophageal):FLOT→Surgery→FLOT *vs* ChemoRT→Surgery (CROSS)

OEO2 Clinical Trial

- 802 Esophageal adenocarcinoma and squamous cell

³Epirubicin, Cisplatin, 5FU

⁴5FU, Leuvocorin, 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 Trial

- 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 *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

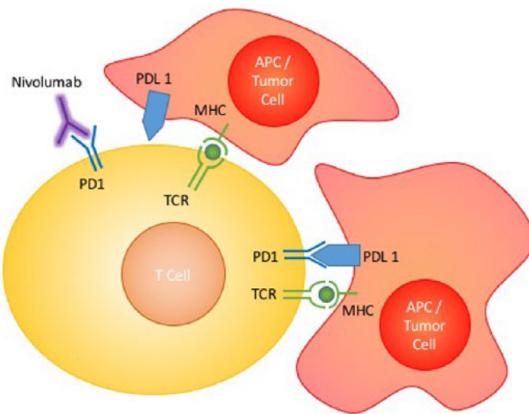


Figure 5: Nivolumab mechanism of action

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

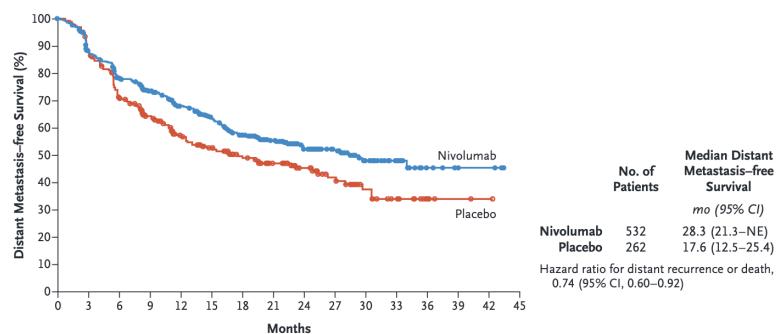


Figure 6: Adjuvant Nivolumab vs Observation

Surgery for Squamous Cell Carcinoma

(Kelly et al. 2021)

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

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

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 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).