RADIO-CHEMIOTERAPIA NEOADIUVANTE, CONCOMITANTE NEL CARCINOMA DELL'ESOFAGO

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Background

- The management of local-regional cancer of the esophagus and esophagogastric junction (EGJ) has undergone a major evolution over the past 15 years

- The majority of patients now undergo some forms of combined modality therapy. However, the optimal management of these patients remains controversial

- There are two major histologies of esophageal cancer: squamous cell cancer (SCC) and adenocarcinoma (ADK)

- They differ in terms of their pathogenesis, epidemiology, tumor biology, and prognosis

Engel et al. J Natl Cancer Inst 2003

Treatment Modalities for Esophageal Cancer

1. Surgery

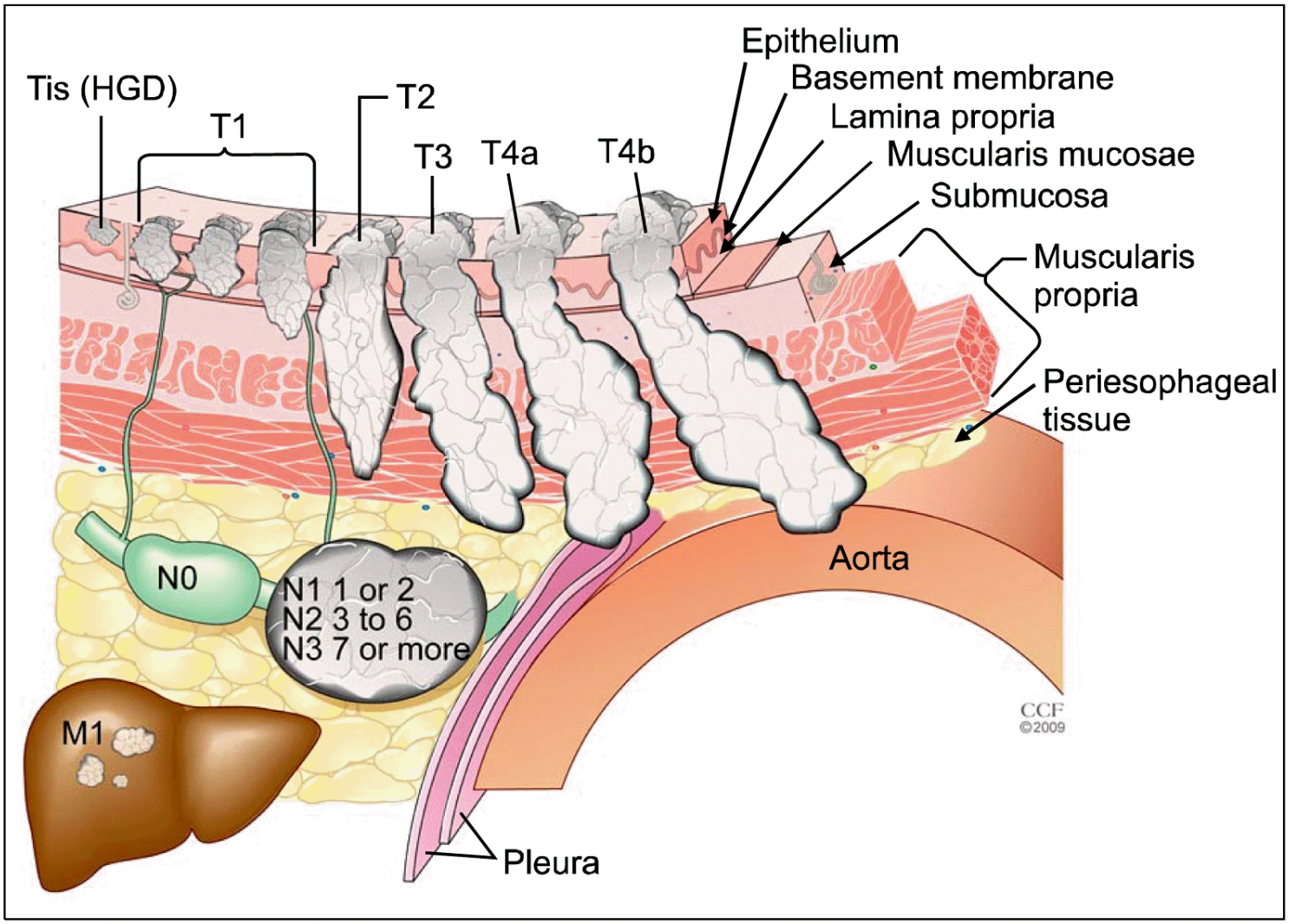
2. Radiation Therapy

3. Chemotherapy

-Multimodality Management

-**Surgical resection** remains the cornerstone of treatment for resectable esophageal cancer

TNM staging for esophageal cancer – AJCC/UICC 7th-2010



Treatment Modalities for Esophageal Cancer

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- The difference **in tumor location** also has implications for the **choice of therapy**

- Some suggest that induction CT alone may suffice for **ADK**, while results are superior with RT-CT for **SCC** because of the greater need for tumor downsizing to achieve a complete radical resection

Semin Radiat Oncol. 2007 Jan;17(1):38-44.

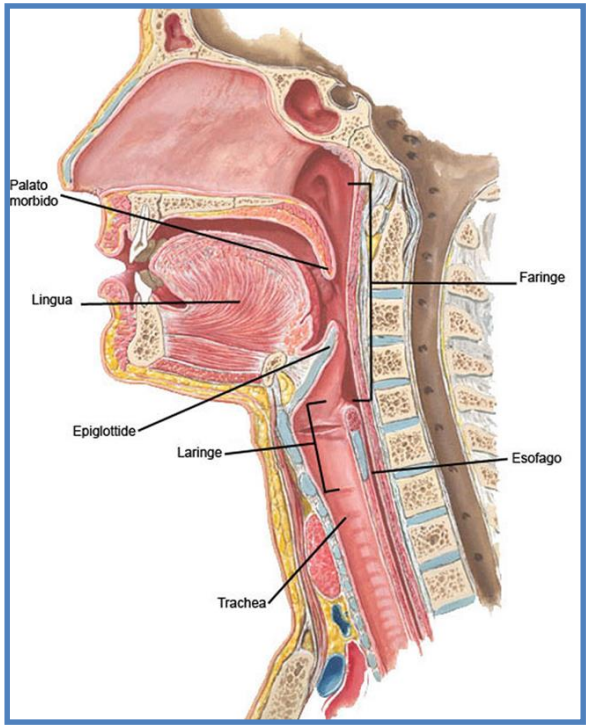
Cervical Esophagus Tumors

✓ SCC of the cervical esophagus presents a unique management situation

✓ if Surgery is performed…removal of portions of the pharynx, the larynx, the thyroid gland, and portions of the proximal esophagus

✓ the management is more closely related to SCC of the head and neck

✓ **RT-CT is preferred** over surgery for proximal esophageal cancers where laryngectomy would be necessary for a good cancer operation…since **survival appears to be comparable** and major morbidity is avoided in most cases



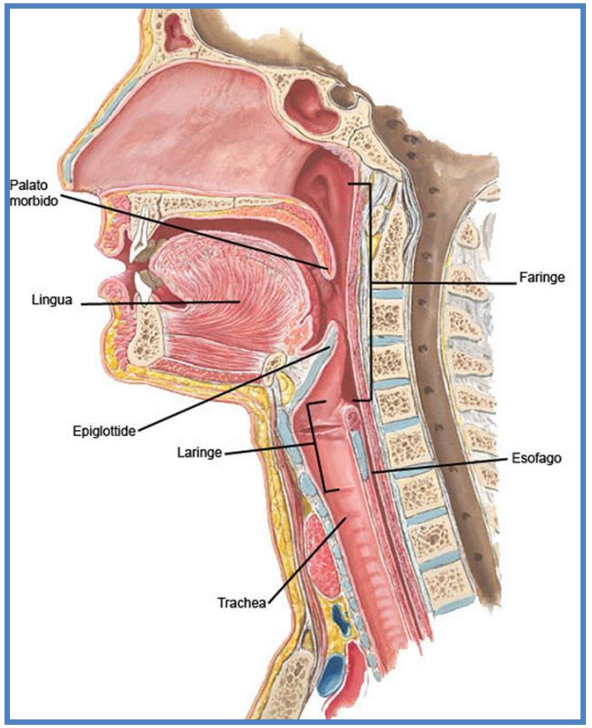
Zhang et al. Radiother Oncol 2015; 116:257

Cervical Esophagus Tumors

✓ Which RT doses?

50-50.4 Gy + boost **10-16 Gy** (to tumor volume)

+ concomitant **chemotherapy (CDDP and 5-FU).**



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Thoracic Esophagus Tumors & GEJ

Treatment of Loco-regionally Advanced Resectable Disease

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(T2 – T3 – T4 or Node positive – M0)

1. Surgery → Adjuvant (Postoperative) Radiotherapy + Chemotherapy

2. Neoadjuvant (Preoperative) Chemotherapy → Surgery → Chemotherapy

(Adenocarcinoma of distal esophagus and GEJ)

3. Neoadjuvant (Preoperative) Chemotherapy+Radiotherapy → Surgery

(Adenocarcinoma and Squamous Carcinoma of Esophagus and GEJ)

Treatment of Loco-regionally Advanced Resectable Disease

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(T2 – T3 – T4 or Node positive – M0)

-556 patients with locally advanced adenocarcinoma of stomach (80%) and GEJ (20%) were randomized to **surgery alone** or **surgery** → **adjuvant CT+RT**

-CT used 2 cycles of 5FU/LV + **RT 4500 cGy** in 25 fractions over 5 weeks, followed by additional 2 cycles of 5FU/LV

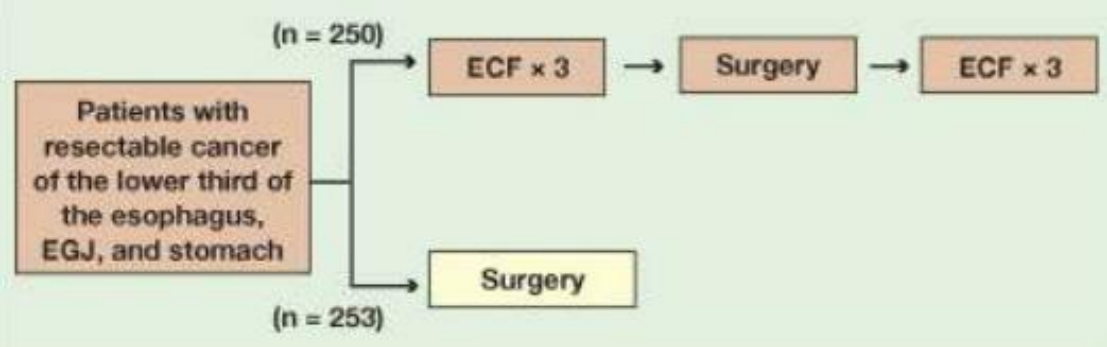
-Median survival: 36 months versus 27 months in favor of **Surgery** → **CT+RT** arm (p = 0.005)

-3-year OS: 50% versus 40% in **Surgery** → **CT+RT** versus surgery alone arms

(~10% absolute survival benefit)

McDonald et al – Intergroup Trial 0116 – NEJM – 2001

Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer



Randomized 503 patients with adenocarcinoma of stomach (75%), GEJ (10%), or distal esophagus (15%) to **surgery alone** or **surgery with perioperative chemotherapy**

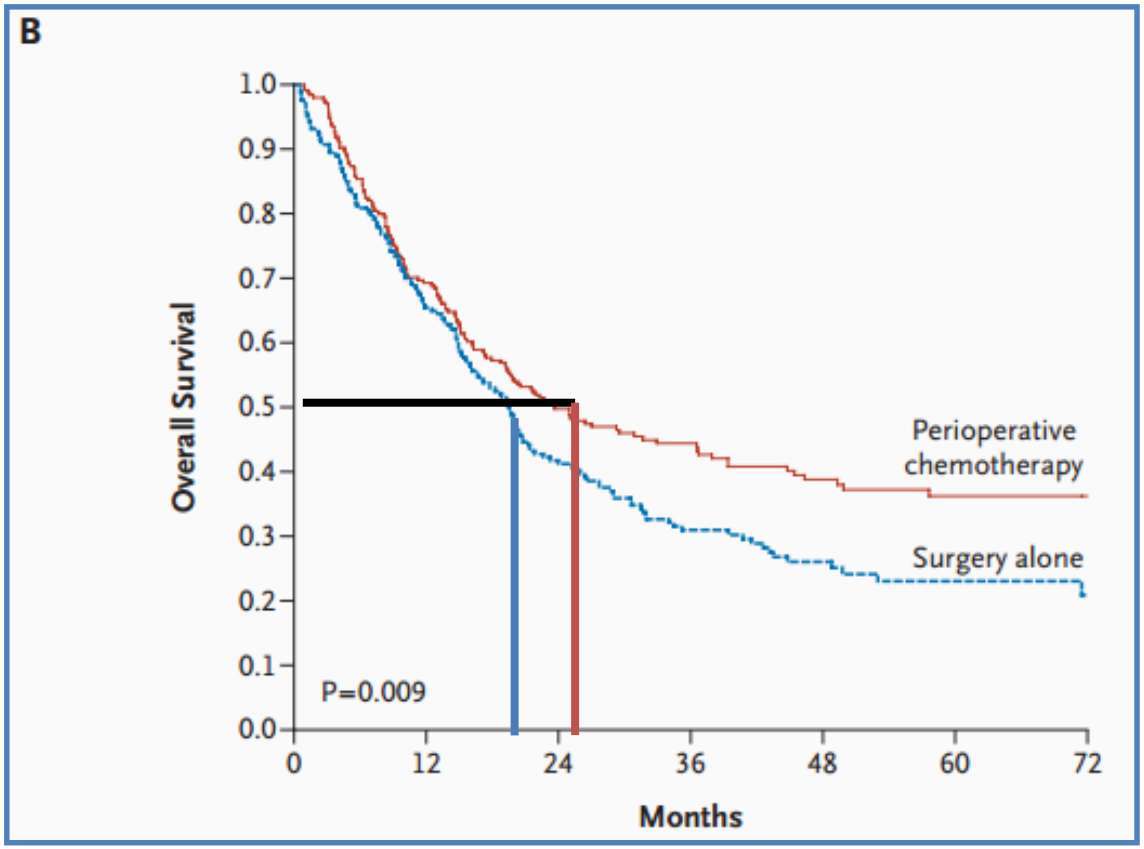
-CT regimen included epirubicin, cisplatin, and 5-FU (ECF)

-Improved survival in CT arm: 5-year OS, 36% versus 23% ($p < 0.009$)

-Perioperative ECF chemotherapy **improved overall survival and progression-free survival** among patients with resectable adenocarcinoma of the stomach, GEJ, and distal esophagus, as compared with surgery alone

Cunningham et al – MRC MAGIC Trial – NEJM July 2006

Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer



Median OS: 26 months perioperative CT
18 months surgery alone

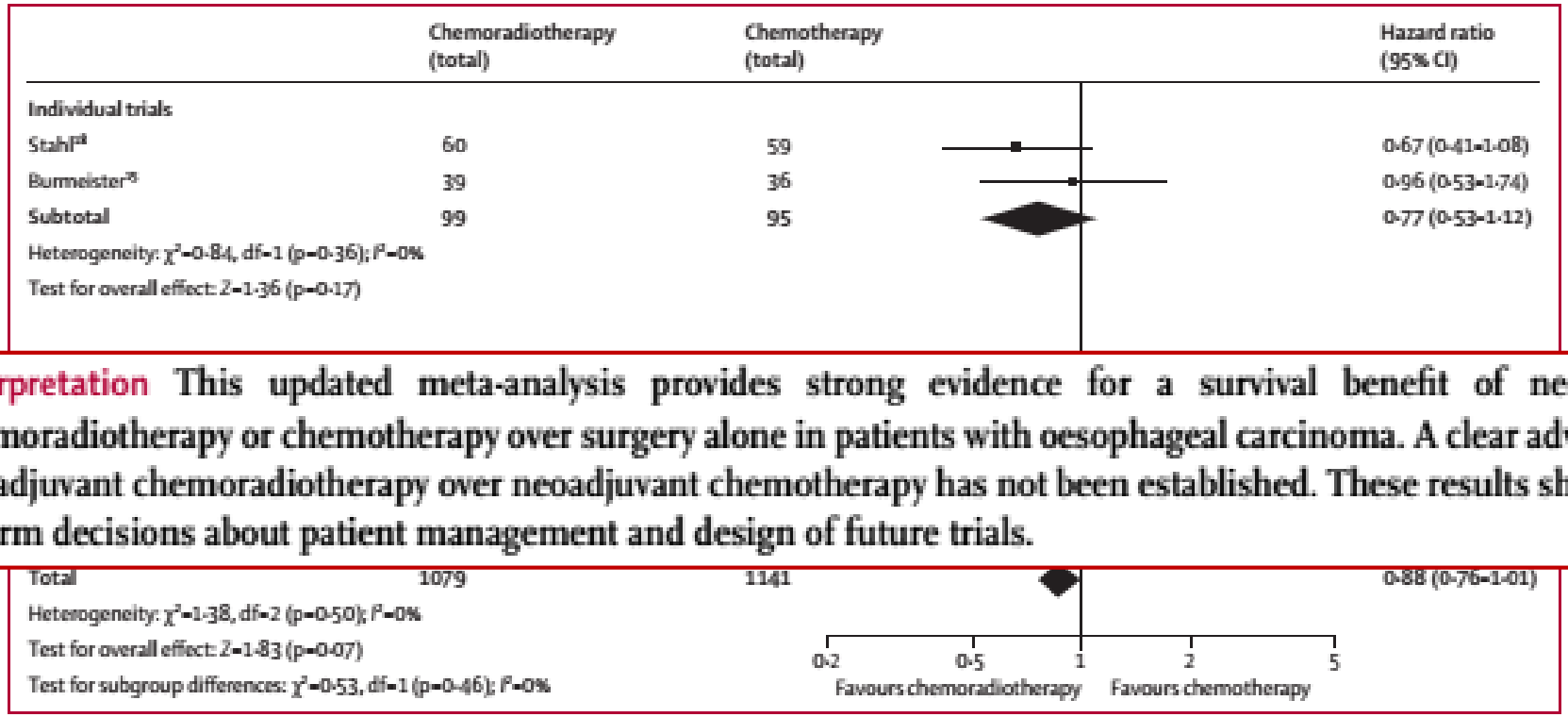
Cunningham et al – MRC MAGIC Trial – NEJM July 2006

Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis

Squamous-cell carcinoma			
Nygaard[9]	53	25	0·76 (0·45–1·28)
Apinop[39]	35	34	0·80 (0·48–1·34)
Le Prise[38]	45	41	0·85 (0·50–1·46)
Urba[40]	13	12	0·83 (0·36–1·89)
Bosset[12]	148	145	0·96 (0·73–1·27)
Walsh[15]	29	32	0·74 (0·46–1·18)
Burmeister[22]	44	48	0·68 (0·40–1·15)
Lv[41]	80	80	0·55 (0·36–0·84)
Lee[17]	51	50	0·88 (0·48–1·62)
Subtotal	498	467	0·80 (0·68–0·93)
Heterogeneity: χ^2=5·31, df=8 (p=0·72); I^2=0%			
Test for overall effect: Z=2·90 (p=0·004)			
Adenocarcinoma			
Urba[40]	37	38	0·69 (0·42–1·14)
Walsh[14]	58	55	0·58 (0·38–0·88)
Burmeister[22]	80	77	0·94 (0·66–1·34)
Subtotal	175	170	0·75 (0·59–0·95)
Heterogeneity: χ^2=3·11, df=2 (p=0·21); I^2=36%			
Test for overall effect: Z=2·40 (p=0·02)			
Combined results (pooled SCC and adenocarcinoma)			
Tepper[43]	30	26	0·35 (0·18–0·68)
Mariette[21]	97	98	1·09 (0·74–1·59)
van der Gaast[42]	176	188	0·67 (0·49–0·91)
Subtotal	303	312	0·74 (0·59–0·93)
Heterogeneity: χ^2=9·09, df=2 (p=0·01); I^2=78%			
Test for overall effect: Z=2·62 (p=0·009)			
Total	976	949	0·77 (0·69–0·86)
Heterogeneity: χ^2=17·87, df=14 (p=0·21); I^2=22%			
Test for overall effect: Z=4·55 (p<0·0001)			
Test for subgroup differences: χ^2=0·35, df=2 (p=0·84), I^2=0%			

Sjoquist et al. Lancet Oncology 2011

Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis



Interpretation This updated meta-analysis provides strong evidence for a survival benefit of neoadjuvant chemoradiotherapy or chemotherapy over surgery alone in patients with oesophageal carcinoma. A clear advantage of neoadjuvant chemoradiotherapy over neoadjuvant chemotherapy has not been established. These results should help inform decisions about patient management and design of future trials.

Sjoquist et al. Lancet Oncology 2011

Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial

-368 patients with resectable tumor underwent randomization,

178 in **RT-CT** → **Surgery** group and 188 in the **Surgery alone** group

-Adenocarcinoma 75% - Squamous carcinoma 25%

-CT regimen: Carboplatin and Paclitaxel – **RT schedule: 4150** cGy in 23 fractions, 5 days per week

J. Shapiro et al.Lancet Oncology 2015; 16: 1090–98

Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial

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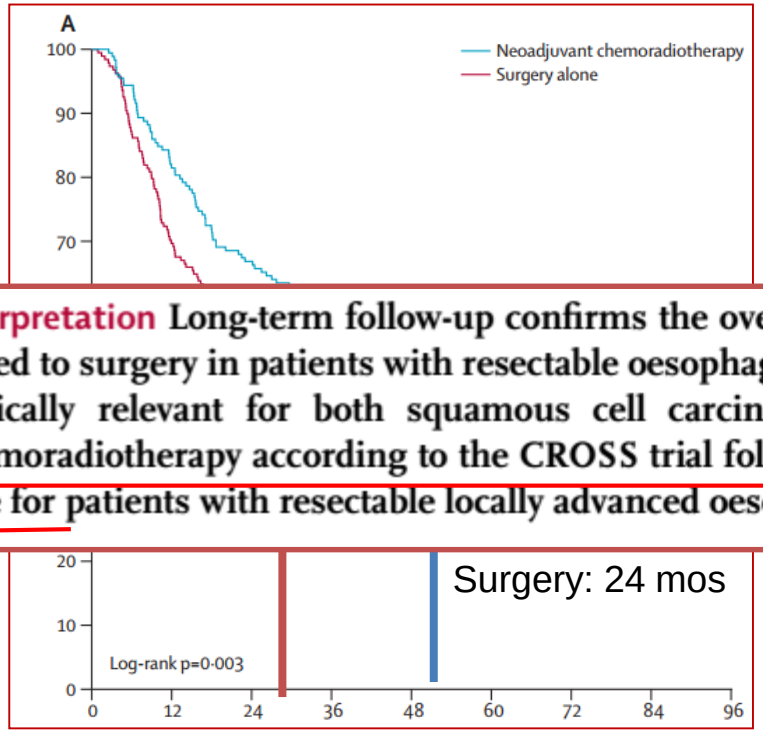
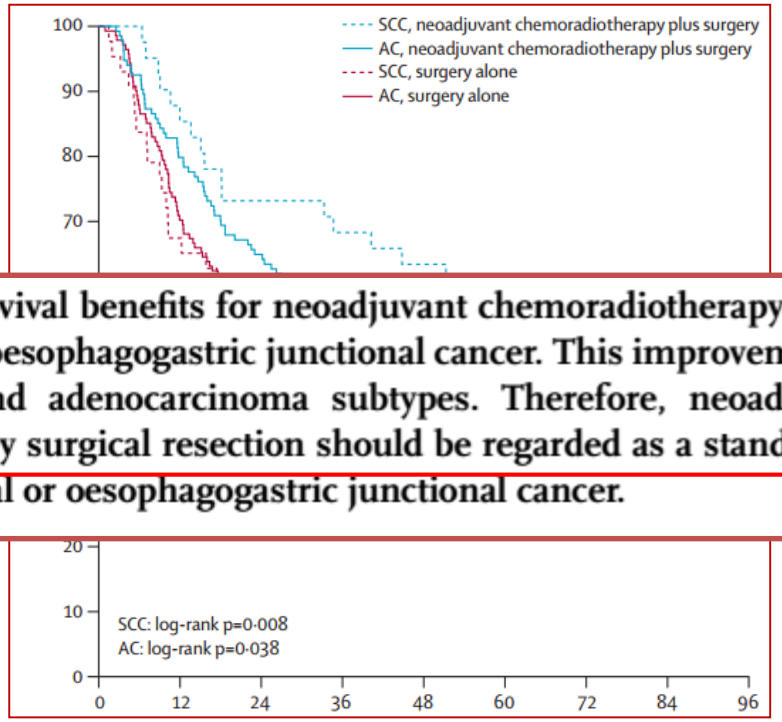
median FUP: **84 months**





Interpretation Long-term follow-up confirms the overall survival benefits for neoadjuvant chemoradiotherapy when added to surgery in patients with resectable oesophageal or oesophagogastric junctional cancer. This improvement is clinically relevant for both squamous cell carcinoma and adenocarcinoma subtypes. Therefore, neoadjuvant chemoradiotherapy according to the CROSS trial followed by surgical resection should be regarded as a standard of care for patients with resectable locally advanced oesophageal or oesophagogastric junctional cancer.

Median OS:

SCC pts: 81·6 months in **RT-CT plus surgery** vs and 21·1 in **surgery alone**

ADC pts: 43·2 months in **RT-CT plus surgery** vs 27·1 months in **surgery alone**

J. Shapiro et al.Lancet Oncology 2015; 16: 1090–98

Treatment of Locally Advanced Inoperable Esophageal Cancer

RTOG 8501: Randomized121 unresectable cases with squamous carcinoma or adenocarcinoma of esophagus to **CT+RT** or **RT alone**

-RT dose: **6400 cGy** in 32/fx in **RT alone** arm vs **5000 cGy** in 2[illegible] **arm**

-CT regimen: 2 cycles of Cisplatin/5FU during R[illegible] 2 additional cycles of Cisplatin/5FU

-Improved median survival wi[illegible] versus 8.9 months (p = 0.001)

-2-year OS (38 vers[illegible] recurrence (16 versus 24%) – DM rate (22 versus 38%) all favor CT+R[illegible]

-Updated [illegible] OS: 25% in CT+RT versus 0% in RT alone

Definitive CT+RT is superior to RT alone

Cooper et al. JAMA 1999

RT DOSES AND FRACTIONATION

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✓ **PRE-OPERATIVE** RT: **45-50 Gy** (1.8-2 Gy/die)

✓ **DEFINITIVE** RT: **50-50.4 Gy** (1.8-2 Gy/die)

- higher doses (**60-66 Gy**) may be appropriate for tumors of the cervical esophagus, especially when surgery is not planned.

RADIATION THERAPY TECHNIQUE

1. Patient immobilization in a supine position with both arms up during planning and treatment

2. Simulation: CT scan of chest and abdomen (5 mm thick slices) with IV and oral contrasts

3. **PET/CT scan** for accurate delineate the Gross tumor volume (GTV)

4. IMRT vs 3DCRT: superior conformity, homogeinety and **reduction RT dose to lungs and heart**

RADIATION THERAPY TECHNIQUE

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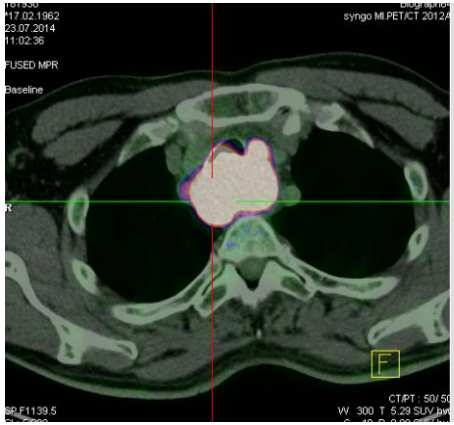
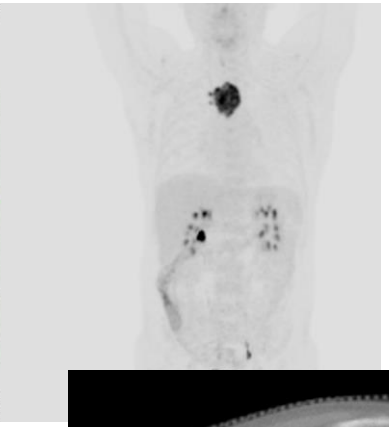
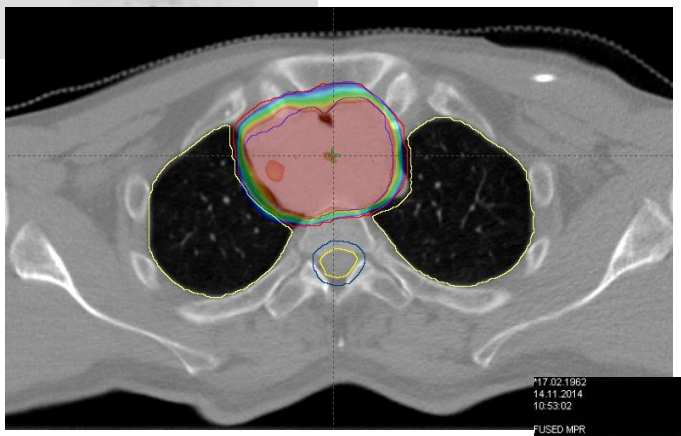
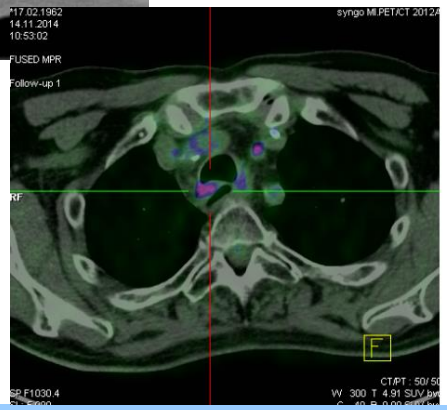




PET-TC pre-RT



RT planning



PET-TC post-RT

TIMING OF SURGERY AFTER RT-CT

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✓ The typical interval, **4 to 7 weeks**, with the intent of allowing resolution of acute inflammation and allowing for tumor regression while minimizing the chronic fibrotic changes in the surgical field

✓ Most tumors regress slowly after RT…

✓ Increasing the interval between RT-CT and surgery may allow the tumor to continue to regress, thereby improving resectability, and increase the chance of observing pathologic complete response (pCR)

✓ Delaying surgery beyond six to seven weeks would likely impact the clinical outcome negatively of those who have residual cancer after RT-CT

Tessier et. al Ann ThoracSurg 2014

Conclusions

✓ Multi-modality treatment is indicated for cancer of esophagus and GEJ

✓Neoadjuvant (preoperative) RT - CT is now preferred for locally advanced resectable cancer of esophagus/GEJ

✓Definitive RT - CT is used for locally advanced inoperable cancer of esophagus or cervical tumors

✓ Multidisciplinary discussion is crucial to define **therapeutic strategy**

THANKS FOR ATTENTION!