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



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







- 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

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



Cervical Esophagus Tumors

✓ Which RT doses?

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

+ concomitant chemotherapy (CDDP and 5-FU).





Zhang et al. Radiother Oncol 2015; 116:257



(T2 - T3 - T4 or Node positive - M0)

- Adjuvant (Postoperative) Radiotherapy + Chemotherapy 1. Surgery
- 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)



(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)







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

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Subtotal 303 312 Heterogeneity: χ²=9-09, df=2 (p=0-01); P=78% Test for overall effect: Z=2-62 (p=0-009) Total 976 949 Heterogeneity: χ²=17-87, df=14 (p=0-21); P=22% Test for overall effect: Z=4-55 (p=0-0001) 0-2 0-5 1 2 5	Mariette ²¹	97	98		1.09 (0.74=1.59)
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Total 976 949 Heterogeneity: χ²-17-87, df-14 (p=0-21); P-22% Test for overall effect: Z=4-55 (p<0-0001) 0-2 0-5 1 2 5	Heterogeneity: χ²=9-09, df=2 (p=	0-01); P=78%		-	
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Test for overall effect: Z=4-55 (p=0-0001) 0-2 0-5 1 2 5	Total	976	949	•	0-77 (0-69=0-86)
02 03 1 2 5	Heterogeneity: χ²=17-87, df=14 (g	p=0-21); P=22%		•	
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use on wedness how we have the out the out the out the out the out of the out the out of	Test for subgroup differences: χ ² -	•0-35, df=2 (p=0-84), P=0%			

Sjoquist et al. Lancet Oncology 2011



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

	Chemoradiotherapy (total)	Chemotherapy (total)		Hazard ratio (95% CI)
Individual trials				
Stahl ^{ak}	60	59		0-67 (0-41=1-08)
Burmeister ³⁵	39	36		0.96 (0.53=1.74)
Subtotal	99	95		0-77 (0-53-1-12)
Heterogeneity: χ²=0-84, df=1 (p=0	-36); ^µ =0%		-	
Test for overall effect: Z=1-36 (p=0-	17)			

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.

Total	1079	1141	•		0-88 (0-76-1-01)	
Heterogeneity: χ²=1-38, df=2 (p=0-50)	;P-0%					
Test for overall effect: Z=1-83 (p=0-07)		0-2	0.5	1 2	5	
Test for subgroup differences: χ²=0-53, df=1 (p=0-46); l²=0%		Favou	Favours chemoradiotherapy			

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



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

Sacro Cuore Don Calabria

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 ip?

is superior to RT alone -CT regimen: 2 cycles of Cisplatin/5FU during

Cisplatin/5FU

-Improved median surviva versus 8.9 months (p = 0.001)

efinitive CT -2-year OS (38 ver ecurrence (16 versus 24%) – DM rate (22 versus 38%) all favor CT+P -Update S: 25% in CT+RT versus 0% in RT alone



RT DOSES AND FRACTIONATION

✓ 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

- 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





TIMING OF SURGERY AFTER RT-CT



✓ 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



- ✓ 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!