Role of Radiation Therapy in the Management of Esophageal Cancer

Possible Complications and Management
Presenter Disclosure

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Relationships with commercial interests: None
Learning Objectives:

Role of Radiation Therapy in the Management of Cancer of Esophagus and GE junction

Possible complications of Radiation Therapy

1. Indications for definitive, neoadjuvant, adjuvant, palliative RT

2. How RT is planned and delivered?

3. What are the short-term and long-term side-effects of RT?

4. How to manage those side-effects?
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 Edition - 2010)

Primary tumor (T)

- **TX**: Primary tumor cannot be assessed
- **T0**: No evidence of primary tumor
- **Tis**: Carcinoma in situ/High-grade dysplasia
- **T1**: Tumor invades lamina propria, or sub-mucosa
- **T1a**: Tumor invades mucosa or lamina propria or muscularis mucosae
- **T1b**: Tumor invades sub-mucosa
- **T2**: Tumor invades muscularis propria
- **T3**: Tumor invades adventitia
- **T4**: Tumor invades adjacent structures
- **T4a**: Tumor invades pleura, pericardium, diaphragm or adjacent peritoneum
- **T4b**: Tumor invades other adjacent structures such as aorta, vertebral body or trachea

Regional lymph nodes (N)

- **NX**: Regional lymph nodes cannot be assessed
- **N0**: No regional lymph node metastasis
- **N1**: Metastasis in 1–2 regional lymph nodes
- **N2**: Metastasis in 3–6 regional lymph nodes
- **N3**: Metastasis in 7 or more regional lymph nodes

Distant metastasis

- **MX**: Distant metastasis cannot be assessed
- **M0**: No distant metastasis
- **M1**: Distant metastasis
TNM staging for esophageal cancer – AJCC/UICC 7th Edition - 2010
Treatment of Loco-regionally Advanced Resectable Disease

(T2 – T3 – T4 or Node positive – M0)

1. Surgery → Adjuvant (Postoperative) Radiotherapy + Chemotherapy

2. Neoadjuvant (Preoperative) Chemotherapy → Surgery → Chemotherapy
   (Adenocarcinoma of distal esophagus and gastro-esophageal junction)

3. Neoadjuvant (Preoperative) Chemotherapy + Radiotherapy → Surgery
   (Adenocarcinoma and Squamous Carcinoma of Esophagus and GEJ)
Treatment of Loco-regionally Advanced Operable Disease (T2 – T3 – T4 or Node positive – M0)

- McDonald et al – Intergroup Trial 0116 – NEJM – 2001

- 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)
Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer

_Cunningham et al – MRC MAGIC Trial – NEJM July 2006_

- 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% \( p < 0.009 \), 5-year DFS, \( p < 0.001 \)

- 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
Kaplan–Meier Estimates of Progression-free Survival (Panel A) and Overall Survival (Panel B)
Study Enrollment

**Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer**

*CROSS Trial - van Hagen et al – NEJM – May 2012*

- 368 patients with resectable tumor underwent randomization, 178 in CT+RT → 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

- Complete resection (R0): 90% in CT+RT → Surgery group – 70% in surgery alone group

- Complete pathologic response with preoperative CT+RT: 30%

- Median survival: 50 months in CT+RT → Surgery group – 24 months in surgery alone group

- **Overall survival significantly better in CT+RT → Surgery group** *(p = 0.003)*

- Postoperative complications similar in the two treatment groups
Kaplan-Meier Plots of Estimated Overall 5-Year Survival

K-M plot of the estimated overall 5-year survival among patients with esophageal or GEJ cancer who underwent neoadjuvant (CT+RT) followed by surgery (178 patients) or surgery alone (188)

Overall survival at 5 years: 47% in CT+RT → Surgery group and 34% in Surgery alone group

*Van Hagen et al – NEJM – May 2012*
**Treatment of Locally Advanced Inoperable Esophageal Cancer**

Definitive CT+RT is superior to RT alone


- RTOG 8501: Randomized 121 unresectable cases with squamous carcinoma or adenocarcinoma of esophagus to CT+RT or RT alone

- RT dose: 6400 cGy in 32 daily fractions in RT alone arm – 5000 cGy in 25 daily fractions in RT+CT arm

- CT regimen: 2 cycles of Cisplatin/5FU during RT, followed by 2 additional cycles of Cisplatin/5FU

- Improved median survival with CT+RT: 12.5 versus 8.9 months (*p = 0.001*)

- 2-year OS (38 versus 10%) – local recurrence (16 versus 24%) – DM rate (22 versus 38%) all favor CT+RT

- Updated 5-year OS: 25% in CT+RT versus 0% in RT alone
INT 0123 (RTOG 9405)

Minsky et al – JCO – 2002

-Randomized 236 cases of T1-4,N0-1,M0 squamous carcinoma and adenocarcinoma of esophagus to high-dose (6500 cGy) versus conventional dose (5000 cGy) RT+CT

-CT regimen: 2 cycles of Cisplatin + 5FU during RT

-No difference between high-versus conventional-dose RT arms in median survival (13 versus 18 months), and 2-year OS (30 versus 40%)

-11 versus 2 treatment-related deaths in high-versus conventional-dose RT arms
Palliative Radiation Therapy

- Palliative RT is indicated for symptomatic patients (especially dysphagia) from the primary disease

- Patients with poor performance status, recurrent or metastatic disease

- RT dose: -2000 cGy/5 daily fractions
  - 3000 cGy/10
  - 3600 cGy/12

- A feeding tube or stent placement is often indicated for immediate relief of obstruction
Radiation Therapy Techniques

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. Clinical tumor volume (CTV): GTV with 3-4 cm proximal and distal margins, and 1 cm radial margins to encompass microscopic disease extension

   For tumors of distal esophagus and GEJ, CTV should include lymph nodes along lesser curvature of stomach and celiac axis nodes

5. Planning target volume (PTV): CTV plus 1-2 cm expansion for set-up errors and organ movement

6. Treatment planning: Standard beam arrangement in 3D Conformal RT uses 3-4 field arrangement

7. Dose and Fractionation: Conventional daily dosing at 180 cGy fractions to a total dose of 4500 cGy to 5040 cGy (5 – 5 ½ weeks) using 3D-CRT is standard practice

   Higher RT dose (6000-6600 Gy in 30-33 daily fractions) for cancers in the cervical esophagus and upper thoracic esophagus
Simulation and RT Planning

- Patient is placed in supine position with both arms up and immobilized

- CT scan with IV contrast or PET/CT scan for RT planning (5 mm thick slices)
RT Planning System: Delineate target volumes and adjacent critical organs at risk
Target delineation for cancer of distal esophagus and GEJ for 3D CRT

PET/CT scan showing the FDG avid primary tumor at distal esophagus and GE junction

Gross tumor volume (GTV) – Clinical target volume (CTV) – Planning target volume (PTV)
Target delineation of distal esophagus cancer for 3D Conformal RT

PET/CT scan images showing GTV – CTV – PTV in coronal view and sagittal view
Delineation of adjacent critical organs at risk (OAR) for 3D CRT

Normal tissue dose constraints:

Organs at risk (OAR):

Spinal cord – Lungs – Heart – Liver – Kidneys – Small bowel
Treatment Planning for 3D Conformal RT: Three- to four-field arrangement

Beam Shaping by Multileaf Collimator
Dose distribution of 3D Conformal RT using 4 fields for cancer of distal esophagus and GEJ

- 95% isodose line (4275 cGy) covering the PTV
- Prescription dose = 4500 cGy
Color-wash dose distribution for 3D Conformal RT for cancer of distal esophagus and GEJ

-95% isodose cloud (4275 cGy) covering the PTV

-Prescription dose – 4500 cGy
Linear Accelerator – Varian Trilogy

Beam time – 5 minutes

On treatment table – 10-15 minutes

In RT department – 30-40 minutes
RT Treatment Delivery by Linear Accelerator
Squamous cancer of cervical and upper thoracic esophagus

No Surgical resection - Radical RT (6000 cGy in 30 fractions using 3D Conformal RT) + concurrent CT

High-dose RT cloud encompassing the PTV but very close to critical structure (spinal cord)
Intensity-modulated RT (IMRT) or Volumetric-modulated arc therapy (VMAT)

- Improves the conformality of high-dose RT cloud around the target volume
- Maximum sparing the critical adjacent structures (organs at risk)
- Reduce RT related acute and late toxicities
- Escalate RT dose ~ Tumor control ~ Survival
**Organ At Risk (OAR) Tolerance**

- RT-induced acute and late toxicities can be reduced by observing dose-volume constraints

  - Spinal cord:  < 4500 cGy
  
  - Both lungs:  V2000 cGy < 30%

  - Heart:  V4000 cGy < 30% - V3000 cGy < 45%

  - Both kidneys:  V2000 cGy < 30% - V3000 cGy < 20%

  - Liver:  V3000 cGy < 50%

  - Pacemaker:  < 200 cGy
**Dose-Volume Histogram (DVH)**

Critical Organs at risk (OAR) contoured: Spinal cord – Lungs – Heart – Liver – Kidneys

DVH analysis quantifies dose received by tumor and critical organs at risk
Supportive Care during RT or RT+CT

-Treatment interruptions or RT dose reductions for manageable acute toxicities should be avoided during RT

-Careful patient monitoring and intensive supportive care preferable to treatment breaks

-During RT, patients should be seen once a week with notation of vital signs, weight, and blood counts

-Antiemetics should be given on a prophylactic basis when appropriate

-Antacid medications when needed – Pink lady before meals

-If estimated caloric intake < 1500 kcal/day, oral and/or enteral nutrition should be considered

-Feeding GJ tube or NG tube feeding tube may be placed to ensure adequate caloric intake

-Adequate enteral and/or IV hydration is necessary during and after RT+CT
Radiation-Induced Acute Side Effects

Acute side effects:

-Fatigue

-Skin reactions

-Nausea/Vomiting

-Esophagitis: Dysphagia – Odynophagia

   Pink lady before meals – Tylenol 3 – Liquid morphine

-Reflux symptoms

-Diarrhea

-Severe dysphagia: Stent placement before or during RT
Late Toxicities of RT

- Pneumonitis: Steroids – Antibiotics

- Pericarditis or Pericardial effusion

- Nephropathy

- Myelopathy

- Esophageal stricture: Endoscopy and dilatation

- Perforation/Fistula: Antibiotics – Stent placement

- Second malignancy
High-Dose-Rate Brachytherapy

- 1000-1400 cGy in 1-2 weekly fractions
- BT alone or in combination with EBRT is not recommended for definitive Rx
- Palliative modality for recurrent disease after radical RT+CT
- Rapid palliation of dysphagia
- Risk of perforation and fistula
“Take Home Message”

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

-Surgery → Adjuvant (post-operative) RT + CT can be used for distal esophagus/GEJ cancer

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

-Definitive RT + CT is used for locally advanced inoperable cancer of esophagus/GEJ

-Palliative RT is used for stage IV patients with obstructive symptoms (dysphagia)

-EBRT is offered using 3D Conformal RT – IMRT/VMAT preferable for cancer of cervical esophagus

-Brachytherapy can be used for palliation, its use in definitive setting is limited
**RT Indications and Dose-Fractionation**

1. **Definitive (Radical) RT** (with concurrent CT)
   
   Locally advanced inoperable tumor:
   
   - Thoracic esophagus and GEJ cancer: 4500 – 5000 cGy
   - Cervical and upper thoracic esophagus: 6000 – 6600 cGy

2. **Neoadjuvant (Preoperative) RT** (with concurrent CT)
   
   Locally advanced resectable tumor – 4500 – 5000 cGy

3. **Adjuvant Post-operative RT** (with concurrent CT)
   
   4500 cGy - Difficult to tolerate

4. **Palliative RT**
   
   Palliation of dysphagia or GI bleed – 3000 cGy