



Associazione Italiana
Radioterapia Oncologica
Gruppo Interregionale
Lazio/Abruzzo/Molise

Le terapie di supporto in Radioterapia:

Verso una Guida Pratica

Lunedì 4 Dicembre 2017
Centro Studi Cardello
Via del Cardello 24 – Roma

Tossicità nei trattamenti del distretto toracico
Moderatori: L. Trodella, R. Santoni

ESOFAGO – ESOFAGITI
Cenni di patogenesi e strumenti di valutazione
S. Arcangeli

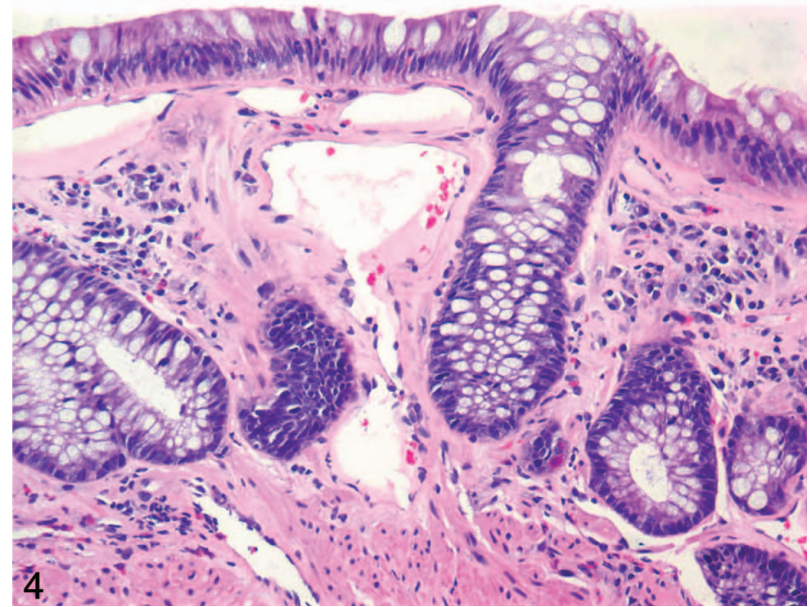
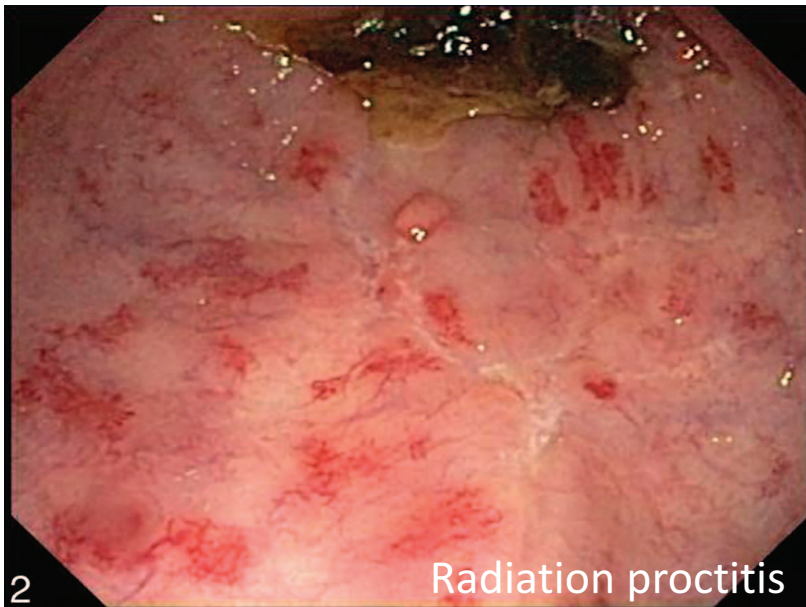
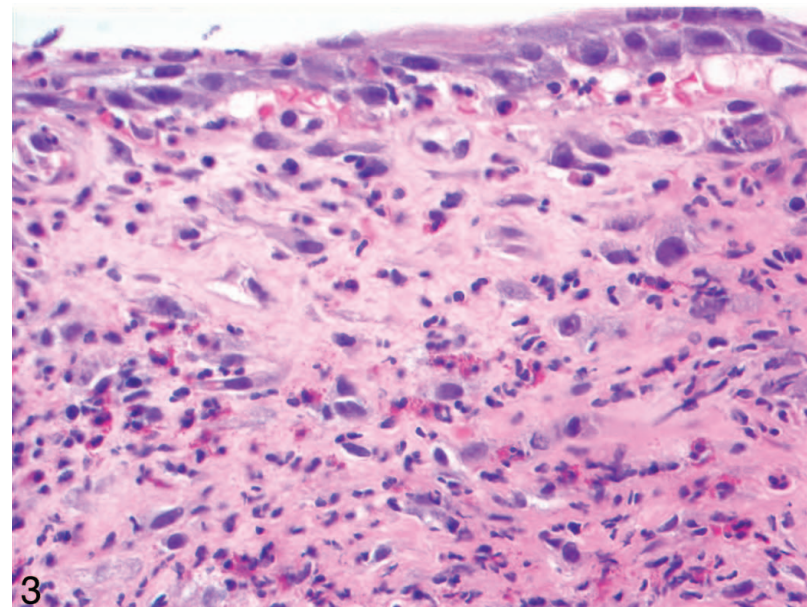
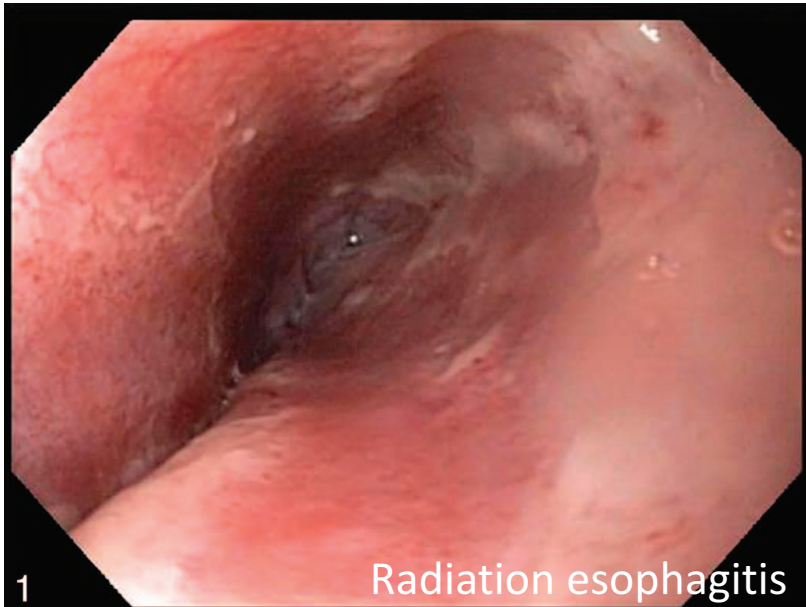


S. Arcangeli
S. Camillo-Forlanini



Acute esophageal toxicity

- The current standard of care for locally-advanced NSCLC is daily RT given with concurrent platinum-based chemotherapy.
- A meta-analysis of 19 randomized trials of radical CRT versus RT alone, including concurrent and sequential systemic therapy, reported that the addition of chemotherapy increases acute esophagitis by approximately **five** times.
- In a randomized trial testing the CHART regimen against conventional RT for NSCLC, hyperfractionated treatment increased severe dysphagia **from 3% to 19%**.



Esofagite – Cenni di patogenesi e strumenti di valutazione

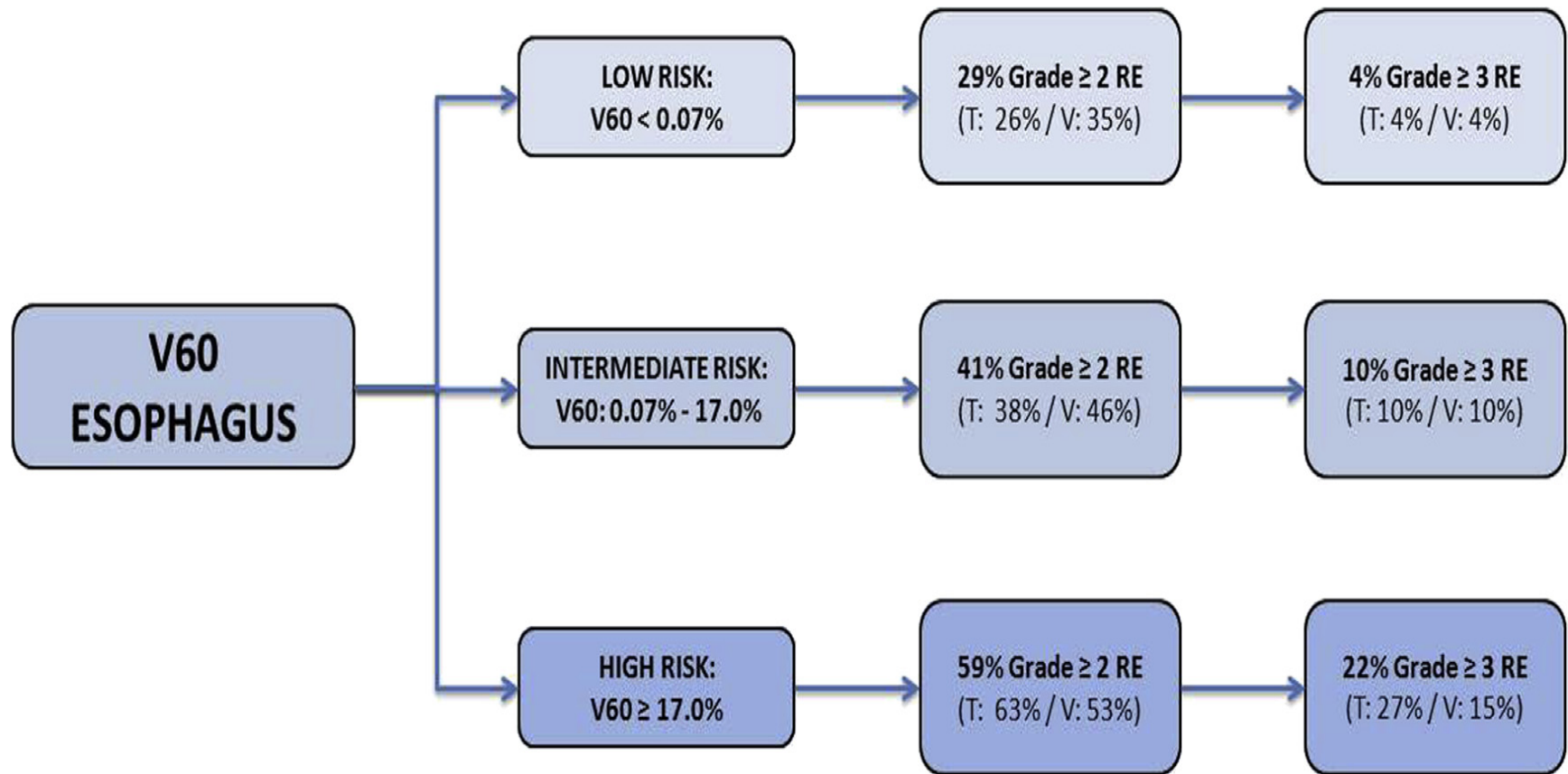
Table 3 Incidence rates of acute esophagitis with different treatment RT techniques for non-small cell lung cancer

Treatment	Regimen ^a	Technique / N	Acute esophagitis
Curative-intent conventional RT with concurrent cytotoxic chemotherapy	<ul style="list-style-type: none"> 60 Gy or 74 Gy Carboplatin and paclitaxel 	IMRT or 3DCRT N=544	<ul style="list-style-type: none"> ≥ Grade 3^d: 21% vs 7% ≥ Grade 4: 0
	<ul style="list-style-type: none"> Median dose 65Gy Platinum-based chemotherapy 	IMRT or 3DCRT N=1,082 ^b	<ul style="list-style-type: none"> Grade 2: 32.2% Grade 3: 17.1% Grade 4: 0.9% Grade 5: 0
	<ul style="list-style-type: none"> 69.6 Gy/58 delivered as 1.2 Gy BID Cisplatin and etoposide 	2D/N=528 ^b	<ul style="list-style-type: none"> ≥ Grade 2: 75% of patients (no difference between arms) ≥ Grade 3: 70% in hyperfractionated arm vs 22% in standard RT arms ($P<0.0001$) ≥ Grade 4: 2%
	<ul style="list-style-type: none"> 63 Gy Cisplatin and vinblastine 		
	<ul style="list-style-type: none"> 69.6 Gy Cisplatin and vinblastine 		
	<ul style="list-style-type: none"> 60 Gy Sequential cisplatin and vinblastine or etoposide 	2D/N=461 ^b	<ul style="list-style-type: none"> Grade ≥3: 1.3% Grade ≥3: 6% Grade ≥3^d: 34%
	<ul style="list-style-type: none"> 60 Gy Sequential and concurrent cisplatin and vinblastine or etoposide 		
	<ul style="list-style-type: none"> 69.6 Gy/58 delivered as 1.2 Gy BID Concurrent cisplatin and vinblastine or etoposide 		
<ul style="list-style-type: none"> Concurrent CRT Sequential CRT 			
CHART versus curative-intent conventional RT	<ul style="list-style-type: none"> 54 Gy/36 delivered as 1.5 Gy TID over 12 consecutive days (CHART) 60 Gy (conventional) 	2D/N=563	<ul style="list-style-type: none"> Acute severe dysphagia: 19% (CHART) vs 3% (no P-value)
SBRT	<ul style="list-style-type: none"> 45 Gy/5 	SBRT/N=108	<ul style="list-style-type: none"> When median esophageal maximum dose >30 Gy, grade >2 esophagitis seen in 50% when target volume overlapped the esophagus
	<ul style="list-style-type: none"> 54 Gy/3^c 	SBRT/N=44	GI adverse events: <ul style="list-style-type: none"> Grade 1: 7.3% Grade 2: 1.8% Grade 3: 1.8% Grade 4–5: 0%
Palliative-intent conventional RT	<ul style="list-style-type: none"> 25 Gy/10 followed by 2 week break, followed by 25–32.5Gy/10–13 (split course) 	2D or 3DCRT N=140	Acute esophagitis: <ul style="list-style-type: none"> Mild 34% Moderate to severe 10%
	<ul style="list-style-type: none"> Various regimens^a 	2D or 3DCRT N=3473 ^b	Physician-assessed dysphagia: <ul style="list-style-type: none"> Low-dose regimens: 15% High-dose regimens: 21%

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)*

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated) [†]	Endpoint	Dose (Gy), or dose/volume parameters [†]	Rate (%)	Notes on dose/volume parameters
Esophagus	Whole organ	3D-CRT	Grade ≥ 3 acute esophagitis	Mean dose < 34	5–20	Based on RTOG and several studies
	Whole organ	3D-CRT	Grade ≥ 2 acute esophagitis	V35 $< 50\%$	< 30	A variety of alternate threshold doses have been implicated. Appears to be a dose/volume response
	Whole organ	3D-CRT	Grade ≥ 2 acute esophagitis	V50 $< 40\%$	< 30	
	Whole organ	3D-CRT	Grade ≥ 2 acute esophagitis	V70 $< 20\%$	< 30	

Data from 1,082 patients undergoing curative-intent CRT for locally advanced NSCLC





Practical Radiation Oncology

Available online 19 July 2017

In Press, Corrected Proof



Basic Original Report

Dosimetric predictors for acute esophagitis during radiation therapy for lung cancer: Results of a large statewide observational study

Results

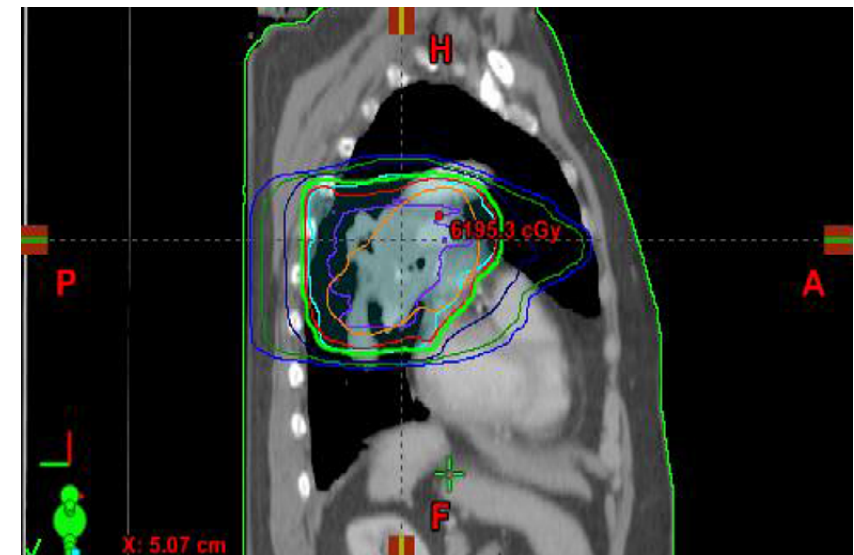
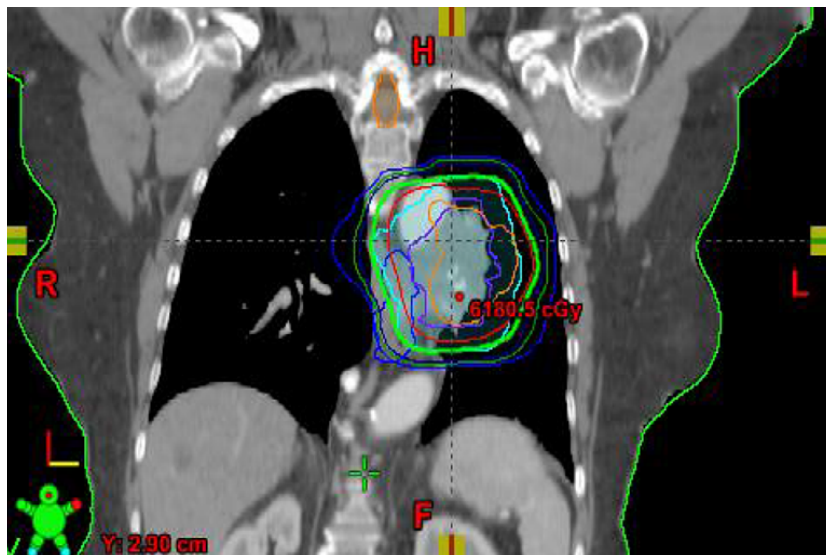
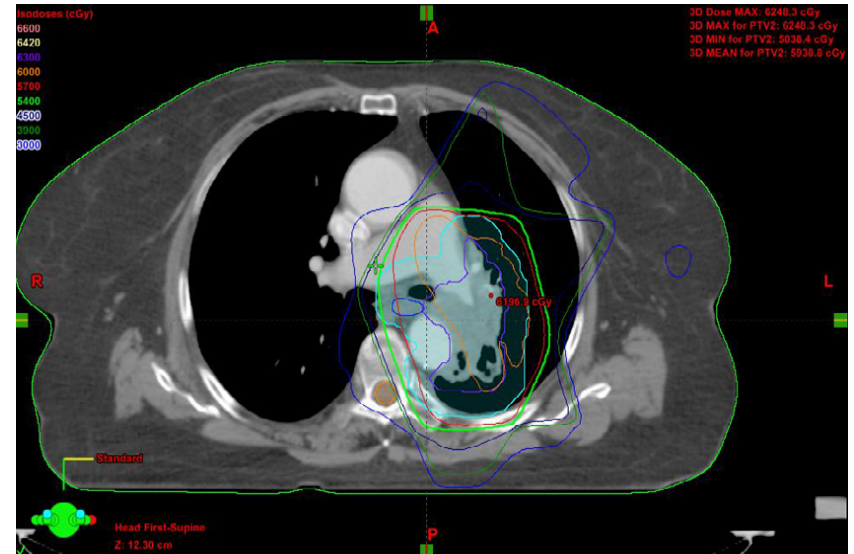
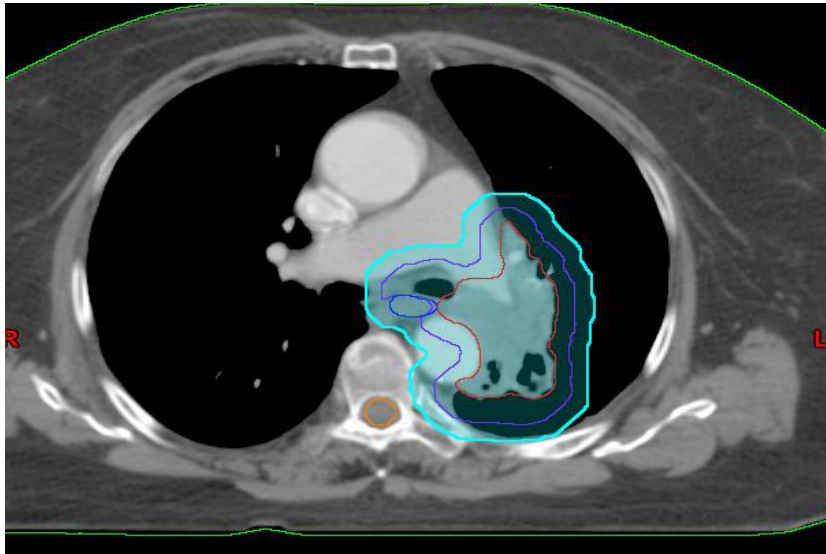
There were 533 patients who met study criteria and were included; 437 (81.9%) developed any grade of esophagitis. Significant variables on univariate analysis for grade ≥ 2 esophagitis were concurrent [chemotherapy](#), V20, V30, V40, V50, V60, MD, D2cc, and gEUD. For grade ≥ 3 esophagitis, the predictive variables were: V30, V40, V50, V60, MD, D2cc, and gEUD. In multivariable modeling, gEUD was the most significant predictor of both grade ≥ 2 and grade ≥ 3 esophagitis. When gEUD was excluded from the model, D2cc was selected as the most predictive variable for grade ≥ 3 esophagitis. For an estimated risk of grade ≥ 3 esophagitis of 5%, the threshold values for gEUD and D2cc were 59.3 Gy and 68 Gy, respectively.

Risk factors for severe acute esophageal toxicity

Patients factors

1. Age ≥ 70 years
2. Female sex
3. Poor baseline KPS
4. Low BMI
5. Gastro-esophageal reflux disease
6. Higher tumor and nodal stage (presence of N2 disease)

Esofagite – Cenni di patogenesi e strumenti di valutazione



Risk factors for severe acute esophageal toxicity

Treatment factors

1. Volume of tissue irradiated
2. Total dose
3. Dose per fraction (fraction size)
4. Overall treatment time
5. Concurrent systemic therapy
6. RT technique

Validated common scoring to track acute toxicity

Table 1 Common Terminology Criteria for Adverse Events
Version 4.03 grading for acute esophagitis

Grade	Description
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; altered eating/swallowing; oral supplements indicated
3	Severely altered eating/swallowing; tube feeding, total parenteral nutrition, or hospitalization indicated
4	Life-threatening consequences; urgent operative intervention indicated
5	Death

Late esophageal toxicity

- Compared to acute esophagitis, late esophageal toxicity is relative rare.
- In the control arm (60 Gy) of the RTOG 0617 trial, the incidence of grade ≥ 3 late esophagitis was $< 1\%$, irrespective of the addition of Cetuximab.
- The severity of acute esophagitis is a powerful predictor of late esophageal toxicity[¶]

[¶]Ahn S, et al. *Int J Radiat Oncol Biol Phys* 2005

Validated common scoring to track late toxicity

Table 2 RTOG/EORTC late esophagitis morbidity grading criteria

Grade	Description
0	None
1	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing
2	Unable to take solid food normally; swallowing semisolid food; dilatation may be indicated
3	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilatation required
4	Necrosis/perforation, fistula

Validated common scoring to track late toxicity

LENT SOMA SCALES FOR ALL ANATOMIC SITES

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Subjective				
Dysphagia	Difficulty eating solid foods	Difficulty eating soft foods	Can take liquids only	Totally unable to swallow
Pain	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating
Objective				
Weight loss from time of treatment	≥ 5% - 10%	> 10% - 20%	> 20% - 30%	> 30%
Stricture	> 2/3 normal diameter with dilatation	> 1/3 - 2/3 normal diameter with dilatation	≤ 1/3 normal diameter	Complete obstruction
Ulceration	Superficial ≤ 1 cm ²	Superficial > 1 cm ²	Deep ulcer	Perforation, fistulae
Bleeding (melena or hematemesis)	Occult	Occasional, normal hemoglobin	Intermittent, 10% - 20% decrease in hemoglobin	Persistent, > 20% decrease in hemoglobin
Anemia		Fatigue	Exhaustion	
Management				
Dysphagia / Stricture	Diet modification or antacids	Diet modification and occasional dilatation	Temporary NG tube or regular dilatation	Parenteral feeding, prosthesis, gastrostomy or permanent NG tube
Weight loss	Diet modification	Nutritional supplements	Tube feeding	Surgical bypass, PEG
Pain / Ulceration	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Bleeding	Iron therapy	Occasional transfusion	Frequent transfusions	Surgical intervention
Analytic				
Barium esophagram	Assessment of esophageal lumen, stricture, dilatation			
Endoscopy	Assessment of esophageal lumen, mucosal integrity, ulceration			
CT	Assessment of esophageal wall thickness, lumen, stricture, dilatation			
MRI	Assessment of esophageal wall thickness, lumen, stricture, dilatation			
Ultrasonography	Assessment of esophageal wall thickness, lumen, stricture, dilatation			
Mobility esophagram	Assessment of motility of bolus and peristalsis			
Electromyogram	Assessment of motility of bolus and peristalsis			

Table 4 Recommended workup for a patient previously irradiated for lung cancer and presenting with late-onset dysphagia

Investigation	Findings
History and physical examination	<ul style="list-style-type: none"> • Symptoms of recurrent disease (weight loss, worsening respiratory status, hoarseness) • Evaluate oral cavity for thrush • Cervical or supraclavicular lymphadenopathy may be suggestive of disease recurrence • Respiratory examination can rule out aspiration pneumonia
Barium swallow	<ul style="list-style-type: none"> • Esophageal stricture • Impaired peristalsis is demonstrated by peristaltic waves above and below the irradiated segment of esophagus
CT chest/abdomen	<ul style="list-style-type: none"> • Mediastinal lymphadenopathy causing extrinsic esophageal compression • Characterization of stricture(s) (location, number, severity) • Fistula^a
Upper endoscopy	<ul style="list-style-type: none"> • Stricture • Ulceration • Fistula^a • Biopsy

Note: ^aBronchoscopy may be required if there is a concern regarding bronchoesophageal fistula.

Assessment of acute esophageal toxicity

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
A	I pazienti con esofagite attinica acuta devono essere valutati <i>clanicamente</i> mediante l' utilizzo di strumenti validati come le scale RTOG/EORTC o CTCAE v.4	Positiva forte

Assessment of late esophageal toxicity

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
D	I pazienti con tossicità esofagea tardiva dovrebbero integrare la valutazione clinica con una <i>strumentale</i> per d.d. (stenosi postattinica vs neoplastica)	Positiva forte