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● *Editorial*

TOXICITY CRITERIA OF THE RADIATION THERAPY ONCOLOGY GROUP (RTOG) AND THE EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC)

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The therapeutic use of ionizing radiations is predicated on sparing normal tissue effects while attempting to achieve lethal effects on tumor cells. From quite early in the history of radiation therapy, it was apparent that there were striking differences in effects in the panoply of normal tissues. Although there was early appreciation of some late effects in normal tissues, often not predicted by acute reactions, only in recent years has there been full documentation of the slow and progressive increase in severity of late damage. Pathophysiological mechanisms of acute and late radiation effects are better understood today (2), but interactions of other modalities with radiation therapy require constant monitoring to recognize and mitigate untoward sequelae.

The work of Stone (3) is a classic example of unanticipated late effects, which resulted from irradiation with fast neutrons. Acute reactions were moderate and tolerable, but the late sequelae were so marked that there was little interest in pursuing therapy with fast neutrons for nearly three decades.

The Late Morbidity Scoring Criteria were developed as a joint effort between physicians with renewed interests in fast neutron therapy and Radiation Therapy Oncology Group (RTOG) staff. In the late 1970s, the Neutron/Particle Committee was one of several modality committees of the RTOG. Recognizing the results of Stone, this committee, led by Lawrence Davis worked with RTOG staff to establish criteria and scoring for possible late effects from fast neutron radiation therapy. Investigators from the European Organization for Research and Treatment of Cancer (EORTC), led by William Duncan of the Western General Hospital of Edinburgh, wished to have common toxicity criteria in anticipation of joint studies.

RTOG Protocol 7929, an international registry of patients treated with heavy particles, was started in 1980. At the annual meetings of the international participants in particle studies, there were attempts to monitor interobserver variations in scoring effects in normal tissues and to seek consistency in reporting toxicity, but no publications document these efforts. The first prospective trial to use the Late Morbidity Scoring Criteria was RTOG Protocol 8001, a study of fast neutron therapy for malignant tumors arising in salivary glands.

Although the RTOG began to use these criteria in reporting toxicity in patients enrolled in all studies from 1981 (beginning with RTOG Protocol 8115), the criteria only became a published part of protocols in 1983. At that time, statistical methods began to be used, which presented time-adjusted estimates of late effects, the rationale for which was described by Cox (1). It is now considered standard to represent cumulative probabilities of late effects with methods similar to those for estimating local control and survival.

The Acute Radiation Morbidity Scoring Criteria were developed in 1985 as complimentary to the Late Effects Scoring Criteria. The National Cancer Institute promulgated standard toxicity criteria in 1990, but late effects were not considered. An abbreviated version of the RTOG/EORTC toxicity criteria was published by Winchester and Cox in 1992 as part of the Standard for Breast Conservation Treatment.

The current RTOG Acute Radiation Morbidity Scoring Criteria are presented in Table 1. The RTOG/EORTC Late Radiation Morbidity Scoring Scheme is detailed in Table 2. In both tables, 0 means an absence of radiation effects and 5 means the effects led to death. The severity

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Table 1. RTOG acute radiation morbidity scoring criteria

Organ Tissue	[0]	[1]	[2]	[3]	[4]
Skin	No change over baseline	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating	Tender or bright erythema, patchy moist desquamation/moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Mucous membrane	No change over baseline	Injection/may experience mild pain not requiring analgesic	Patchy mucositis that may produce an inflammatory serosanguinous discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
Eye	No change	Mild conjunctivitis with or without scleral injection/increased tearing	Moderate conjunctivitis with or without keratitis requiring steroids &/or antibiotics/dry eye requiring artificial tears/ iritis with photophobia	Severe keratitis with corneal ulceration/objective decrease in visual acuity or in visual fields/acute glaucoma/ panopthalmitis	Loss of vision (unilateral or bilateral)
Ear	No change over baseline	Mild external otitis with erythema, pruritis, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline	Moderate external otitis requiring topical medication/serous otitis medius/hypoacusis on testing only	Severe external otitis with discharge or moist desquamation/symptomatic hypoacusis/tinnitus, not drug related	Deafness
Salivary gland	No change over baseline	Mild mouth dryness/slightly thickened saliva/may have slightly altered taste such as metallic taste/these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness/thick, sticky saliva/markedly altered taste	—	Acute salivary gland necrosis
Pharynx & esophagus	No change over baseline	Mild dysphagia or odynophagia/ may require topical anesthetic or non-narcotic analgesics/may require soft diet	Moderate dysphagia or odynophagia/may require narcotic analgesics/may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss > 15% from pretreatment baseline) requiring N-G feeding tube, i.v. fluids or hyperalimentation	Complete obstruction, ulceration, perforation, fistula
Larynx	No change over baseline	Mild or intermittent hoarseness/ cough not requiring antitussive/ erythema of mucosa	Persistent hoarseness but able to vocalize/referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic/ cough requiring antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic/confluent fibrinous exudate, marked arytenoid edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary
Upper G.I.	No change	Anorexia with < =5% weight loss from pretreatment baseline/ nausea not requiring antiemetics/abdominal discomfort not requiring parasympatholytic drugs or analgesics	Anorexia with < =15% weight loss from pretreatment baseline/ nausea &/or vomiting requiring antiemetics/ abdominal pain requiring analgesics	Anorexia with > 15% wt loss from pretreatment baseline or requiring N-G tube or parenteral support. Nausea &/ or vomiting requiring tube or parenteral support/abdominal pain, severe despite medication/hematemesis or	Ileus, subacute or acute obstruction, perforation, GI bleeding requiring transfusion/abdominal pain requiring tube decompression or bowel diversion

				melena/abdominal distention (flat plate radiograph demonstrates distended bowel loops)	
Lower G.I. including pelvis	No change	Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (e.g., Lomotil)/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
Lung	No change	Mild symptoms of dry cough or dyspnea on exertion	Persistent cough requiring narcotic, antitussive agents/dyspnea with minimal effort but not at rest	Severe cough unresponsive to narcotic antitussive agent or dyspnea at rest/clinical or radiological evidence of acute pneumonitis/intermittent oxygen or steroids may be required	Severe respiratory insufficiency/continuous oxygen or assisted ventilation
Genitourinary	No change	Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication	Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium)	Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/without clot passage	Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration, or necrosis
Heart	No change over baseline	Asymptomatic but objective evidence of EKG changes or pericardial abnormalities without evidence of other heart disease	Symptomatic with EKG changes and radiological findings of congestive heart failure or pericardial disease/no specific treatment required	Congestive heart failure, angina pectoris, pericardial disease responding to therapy	Congestive heart failure, angina pectoris, pericardial disease, arrhythmias not responsive to nonsurgical measures
CNS	No change	Fully functional status (i.e., able to work) with minor neurological findings, no medication needed	Neurological findings present sufficient to require home care/nursing assistance may be required/medications including steroids/antiseizure agents may be required	Neurological findings requiring hospitalization for initial management	Serious neurological impairment that includes paralysis, coma, or seizures > 3 per week despite medication/hospitalization required
Hematologic WBC (×1000)	=> 4.0	3.0–< 4.0	2.0–< 3.0	1.0–< 2.0	< 1.0
Platelets (×1000)	> 100	75–< 100	50–< 75	25–< 50	< 25 or spontaneous bleeding
Neutrophils (×1000)	=> 1.9	1.5–< 1.9	1.0–< 1.5	0.5–< 1.0	< 0.5 or sepsis
Hemoglobin (GM %)	> 11	11–9.5	< 9.5–7.5	< 7.5–5.0	—
Hematocrit (%)	=> 32	28–< 32	< 28	Packed cell transfusion required	—

Guidelines: The acute morbidity criteria are used to score/grade tocity from radiation therapy. The criteria are relevant from day 1, the commencement of therapy, through day 90. Thereafter, the EORTC/RTOG Criteria of Late Effects are to be utilized.

The evaluator must attempt to discriminate between disease and treatment related signs and symptoms.

An accurate baseline evaluation prior to commencement of therapy is necessary.

All toxicities Grade 3, 4 or 5* must be verified by the Principal Investigator.

* Any toxicity which caused death is Graded 5.

Table 2. RTOG/EORTC late radiation morbidity scoring scheme

Organ Tissue	0	Grade 1	Grade 2	Grade 3	Grade 4	5
Skin	None	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Market atrophy; gross telangiectasia	Ulceration	
Subcutaneous tissue	None	Slight induration (fibrosis) and loss or subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; < 10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture > 10% linear measurement	Necrosis	
Mucous membrane	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucous	Marked atrophy with complete dryness Severe telangiectasia	Ulceration	
Salivary glands	None	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis	
Spinal cord	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadraplegia	
Brain	None	Mild headache; slight lethargy	Moderate headache Great lethargy	Severe headaches; severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis Coma	
Eye	None	Asymptomatic cataract Minor corneal ulceration or keratitis	Symptomatic cataract Moderate corneal ulceration; minor retinopathy or glaucoma	Severe keratitis; severe retinopathy or detachment Severe glaucoma	Panopthalmitis/Blindness	
Larynx	None	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis	
Lung	None	Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever; patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis Dense radiographic changes	Severe respiratory insufficiency/Continuous O_2/ Assisted ventilation	
Heart	None	Asymptomatic or mild symptoms; transient T wave inversion & ST changes; sinus tachychardia > 110 (at rest)	Moderate angina on effort Mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low ORS	Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; EKG abnormalities	Tamponade/Severe heart failure/Severe constrictive pericarditis	

DEATH DIRECTLY RELATED TO

Esophagus	None	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semisolid food; dilatation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilatation required	Necrosis/Perforation Fistula	
Small/Large intestine	None	Mild diarrhea; mild cramping; bowel movement 5 times daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement > 5 times daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/Perforation Fistula	
Liver	None	Mild lassitude; nausea, dyspepsia; slightly abnormal liver function	Moderate symptoms; some abnormal liver function tests; serum albumin normal	Disabling hepatitic insufficiency; liver function tests grossly abnormal; low albumin; edema or ascites	Necrosis/Hepatic coma or encephalopathy	
Kidney	None	Transient albuminuria; no hypertension; mild impairment of renal function; urea 25–35 mg %; creatinine 1.5–2.0 mg %; creatinine clearance > 75%	Persistent moderate albuminuria (2+); mild hypertension; no related anemia; moderate impairment of renal function Urea > 36–60 mg %; creatinine clearance (50–74%)	Severe albuminuria; severe hypertension; persistent anemia (< 10 g %); severe renal failure; urea > 60 mg %; creatine > 4.0 mg %; creatinine clearance < 50%	Malignant hypertension Uremic coma Urea > 100%	
Bladder	None	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)	Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria	Severe [illegible]ncy & dysuria; severe [illegible]elangiectasia (often [illegible]iae); frequent hematuria; reduction in bladder capacity (< 150 cc)	Necrosis/Contracted bladder (capacity < 100 cc) Severe hemorrhagic cystitis	
Bone	None	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or [illegible]ness; growth retardation; irregular bone sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis/Spontaneous fracture	
Joint	None	Mild joint stiffness; slight limitation of movement	Moderate stiffness; intermittent or moderate joint pain; moderate limitation of movement	Severe joint stiffness; pain with severe limitation of movement	Necrosis/Complete fixation	

RADIATION LATE EFFECTS

of reactions is graded from 1 through 4. In most RTOG publications, "major" toxicities have been reported as Grades 3, 4, and 5 taken together. Grade 4 and 5 toxicities have been presented in detail. Cumulative probabilities of "major" or Grade 4 and 5 toxicities are presented as risk estimates at discrete intervals, such 1 year, 2 year, etc. More often the probabilities are presented graphically to show the propensity for continued increases with time.

Late radiation morbidity criteria differ substantially from those of other modalities. Long periods of observation are required to assess effects of radiation therapy alone or combined with surgical resection, cytotoxic drugs, and hormones.

Late effects of radiations on normal tissues may increase with time and it is conceivable that interventions could lessen the risk or severity of these effects. Early predictors and more quantitative measures of severity are desirable.

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