XXI CONGRESSO NAZIONALE AIRO

Genova, 19-22 Novembre 2011

Associazione Italiana Radioterapia Oncologica

WORKSHOP
Quali tossicità con le nuove strategie terapeutiche in oncologia cervico-cefalica?

TOSSICITÀ DEI TRATTAMENTI INTEGRATI

F. Paiar

MULTIMODALITY TREATMENT

INDUCTION CHEMOTHERAPY

CONCOMITAN CHEMOTHERAPY

SEQUENTIAL THERAPY

TARGETED THERAPY

MACH-NC 2000

CONCOMITANT RADIOCHEMOTHERAPY CDDP BASED

Pignon 2000

«…the cost of cure»

Trial	Patients	Primary treatment	Adjuvant therapy	Grade 3 and 4 toxic effects	cal	Difference in overall survival in favor of chemoradiotherapy
EORTC[a] 22931 (2004)[13]	167 with high-risk features on pathology	Surgery	CRT (P); RT alone[c]	Acute: CRT 41%; RT 21% Chronic: difference NS	Yes: CRT 82%; RT 69% (at 5 years)	Yes: CRT 53%; RT 40% (at 5 years)
RTOG[a] 9501 (2004)[14]	459 with high-risk features on pathology	Surgery	CRT (P); RT alone[c]	Acute: CRT 77%; RT 34% Chronic: difference N	RT 72% (at 2 years)	No: CRT ~65.0%; RT ~57.5% (at 2 years – but significant difference in DFS)
Bachaud *et al.* (1996)[17]	83 with high-risk features on pathology	Surgery	CRT (P); RT alone	Acute: CRT 41%; RT 18% Chronic: difference NS	Y RT s)	Yes: CRT 72%; RT 46% (at 2 years)
Intergroup 91-11 Larynx (2003)[15]	510 with laryngeal cancer	CRT (P); RT plus induction chemotherapy; RT alone	NA	Acute: CRT 77%; RT+I 51%; RT 47%[a] Chronic: CRT 30%; RT+I 24%; RT 36% (difference NS)	Ye +I 64 RT s)	No: CRT 76%; RT+I 74%; RT 75% (at 2 years) but increased larynx preservation (CRT 88%; RT+I 75%; RT 70%)
Al-Sarraf *et al.* (1998)[25]	193 with NPC	CRT (P) plus consolidation with PF; RT alone	NA	Acute: CRT 75.6%; RT 50% Chronic: not reported	Y 74	CRT 76%; RT 46% ar OS)
Adelstein *et al.* (2003)[24]	295 with unresectable tumors	RT alone; CRT (P); CRT (PF) split course[b]	NA	Acute: RT 52%; CRT 85%[a]; CRT[b] 72% Chronic: not reported	N ed C therapy: RT 27%; CRT 41%; CRT[b] 37%	Yes: RT 23%; CRT 37%[e]; CRT[b] 27% (3-year OS)
Jeremic *et al.* (2000)[37]	130 with stage III or IV disease	HFX (RT); HFX (CRT and daily P)[f]	NA	Acute: difference NS[d] Chronic: difference NS	Yes: RT 27%; CRT 53%	Yes: RT 25%; CRT 46% (5-year OS)

41%

77%

41%

77%

75,6%

85%

«the cost of cure»
CRT: ACUTE TOXICITY

ARTICLES

Randomized Trial of Radiation Therapy Versus Concomitant Chemotherapy and Radiation Therapy for Advanced-Stage Oropharynx Carcinoma

Gilles Calais, Marc Alfonsi, Etienne Bardet, Christian Sire, Thierry Germain, Philippe Bergerot, Béatrix Rhein, Jacques Tortochaux, Patrick Oudinot, Philippe Bertrand

Table 2. Grad

Toxic Effect

apy Alone
171)

Toxic effect	RT (n = 113)	RT + CT (n = 109)	P†
Mucositis			
Patchy mucositis	32	57	.005
Confluent fibrinous mucositis	7	14	
Skin			
Erythema/pruritis/dry desquamation	47	44	.02
Moist desquamation	12	23	
Nutritional status			
Weight loss >10% of body mass	6	14	.04
Need for feeding tube	15	36	.02
Hematology			
Neutrophil count <0.9 cells/mm^3	0	4	.04
Platelet count <50 cells/mm^3	1	6	.04
Hemoglobin level <8 g/100 mL	0	3	.05
Toxic death	0	1	

total

Hem 5 (3)
Infect 2 (1)
Muco 41 (24)
Phary 32 (19)
Laryn 28 (16)
Derm 15 (9)
(i
Naus 0
Renal 0
Neur 0

RADIOCHEMOTHERAPY TREATMENT RELATED DEATH RANDOMIZED STUDY

AUTHOR	CT	RT	MORTALITY
CALAIS	CbF	Conv	1%
BRITZEL	PF	HF	2%
WENDT	PFL	HF – split	2%
ADELSTEIN	PF	Conv – split	2%
ADELSTEIN	P	Conv	4%
FORASTIERE	P	Conv	5%
BONNER	C	Conv	5%
POSNER	TPF→Cb	Conv	1%

RADIOCHEMOTHERAPY TREATMENT RELATED DEATH INSTITUTIONAL SERIES

AUTHOR	CENTER	PTS N	MORTALITY
ARGIRIS 2004	CHICAGO	324	9.3%
NGUYEN 2004	DALLAS	55	9.1%
ALDESTEIN 2006	CLEVELAND	222	14%
MERLANO 2008	CUNEO	155	6.4%
MATCHTAY 2008	3 STUDI RTOG	230	10%

Clinical Cancer Research

Competing Causes of Death and Second Primary Tumors in Patients with Locoregionally Advanced Head and Neck Cancer Treated with Chemoradiotherapy

Athanassios Argiris, Bruce E. Brockstein, Daniel J. Haraf, et al.

Table 3 Treatment-Related Death Rates After Chemoradiation as the Primary Treatment

Cause of Death	Relative Frequency	Median Time of Occurrence (years)
Disease progression	45%	1.5 (0.3-8.6)
Co-morbidities	21%	1.9 (0.07-8.8)
Treatment-related	15%	0.3 (0.03-3.4)
Second primary tumors	9%	3.5 (1.5-10.1)
Unknown	10%	5.1 (1.1-9.5)

Data from Argiris et al.[44]

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EDITORIAL

The Need for Adverse Effects Reporting Standards in Oncology Clinical Trials

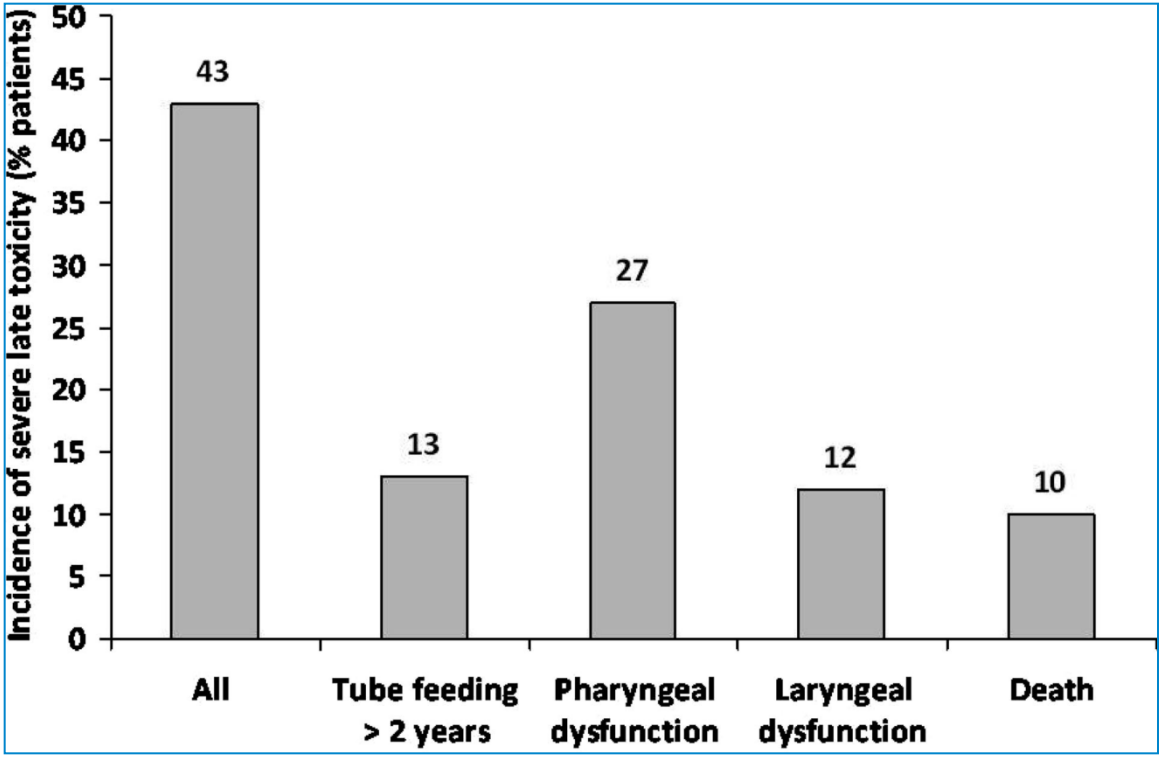
Andy Trotti, *H. Lee Moffitt Cancer Center, University of South Florida, Tampa, FL*
Søren M. Bentzen, *Gray Cancer Institute, Northwood, Middlesex, UK*

Table 1. Toxicity Reporting in Nine Head and Neck Chemoradiotherapy Trials

Author	Year of Publication	Acute Adverse Effects Grading System	Late Adverse Effects Grading System	No. of Acute Toxicity Items Reported	No. of Late Toxicity Items Reported	Grade 3–4 Rate (%) Late Effects Reported	
						Conventional Arm	Experimental Arm
Browman	1993 (31)	HNRQ	Late effects not reported	5	0	Not reported	
Browman	1994 (2)	WHO		–	–		
Adelstein	1997 (3)	CTC	Descriptive	10	3	Not reported	
Adelstein	2000 (30)	CTC	Descriptive	7	2		
Brizel	1998 (5)	Descriptive	Descriptive	7	2	15%	20%*
Dobrowsky	1998 (6)	Descriptive	Late effects not reported	3	0	Not reported	
Wendt	1998 (7)	WHO	RTOG/EORTC	6	6	6.4%	10%
Calais (GORTEC)	1999 (14)	CTC	RTOG/EORTC	10	4	9%	14%
Denis (GORTEC)	2003 (12)	RTOG/EORTC + CTC	RTOG/EORTC + CTC + SOMA	–	8	30%	56% (2 tools)
				8	–	47%	82% (3 tools)
Jeremic	2000 (9)	EORTC WHO	EORTC	6	4	34%	58%*
Staar	2001 (8)†	RTOG/EORTC	RTOG/EORTC	5	6	See footnote	
Adelstein	2003 (4)	CTC	Late effects not reported	10	0	Not reported	

CRT: LATE TOXICITY

230 pts underwent CRT
3 studies
RTOG 91-11, 97-03, 99-14



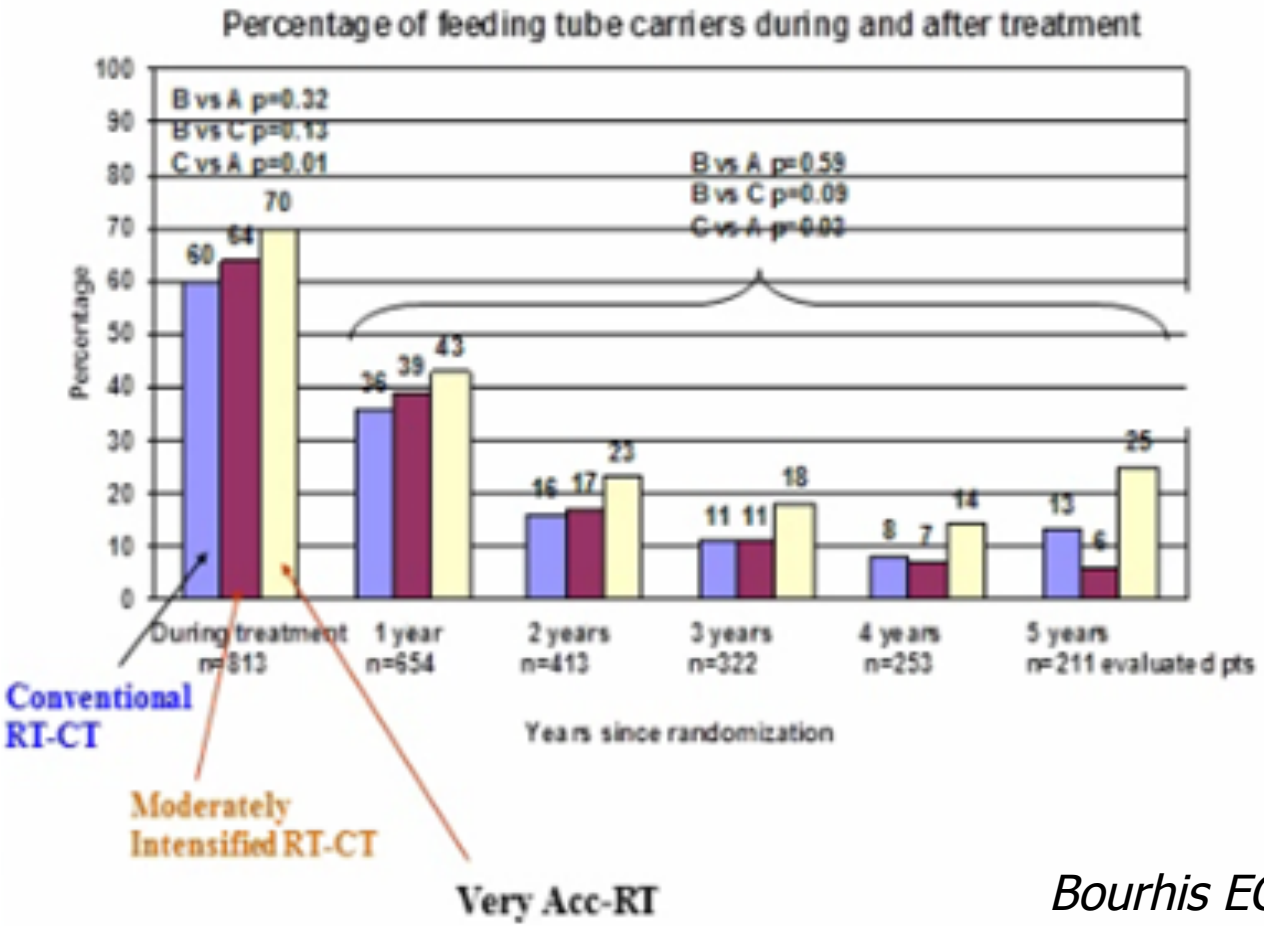
LATE TOXICITY RELATED FACTORS:

- OLD AGE
- T3,T4
- T site (larynx/ipopharynx)
- Neck nodes dissections after CRT

Machtay M et al, J Clin Oncol 2008

VERY ACCELERATED RADIOTHERAPY (RT) versus CONCOMITANT CHEMO-RADIOTHERAPY (CT-RT) IN LOCALLY ADVANCED HEAD AND NECK CANCER: LONG TERM RESULTS FROM 2 PHASES III GORTEC RANDOMIZED TRIALS

J Bourhis, C Sire, P Graff, V Grégoire, P Maingon, M Lapeyre, J. Tortochaux, G Calais, B Gery, L Martin, M Alfonsi, P Deprez, T Pignon, E Bardet, M Rives, A Pinna, M Ducoutieux, A Aupérin



Bourhis ECCO 2011

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COMMENTS AND CONTROVERSIES

Seduction by Induction?

Jonathan J. Beitler, *Departments of Radiation Oncology, Otolaryngology, and Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA*
Jay S. Cooper, *Maimonides Cancer Center, Brooklyn, NY*

New drugs combinations which could give potentially better results.

Pignon, Anti-Cancer Drugs 2004

Induction CT may improve local/regional control, while also reducing the rate of distant metastasis that may not be adeguately treated by local therapy or by lower-dose CT as part of CRT.

Cohen, JCO 2004

TPF versus PF

	TAX 323 [9]		TAX 324 [10]	
	PF (n = 181)	TPF (n = 177)	PF (n = 246)	TPF (n = 255)
Overall survival				
Median, mos	14.5	18.8	30	71
Hazard ratio (95% CI)	0.73 (0.56–0.94)		0.70 (0.54–0.90)	
p-value	.02[a]		.006[b]	
Progression-free survival				
Median, mos	8.2	11.0	13	36
Hazard ratio (95% CI)	0.72 (0.57–0.91)		0.71 (0.56–0.90)	
Log-rank p-value	.007[a]		.004[b]	
Overall response rate, %	59[c]	72[c]	64[d]	72[d]
p-value	.006[c]		.07[e]	

Vermoken JB, N Engl J Med2007

Posner MR N Engl J Med2007

TAX 323

TOXICITY	TPF	PF
G3-4 NEUTROPENIA	77%	53%
G3-4 NAUSEA	1%	7%
EMESIS	1%	5%
STOMATITIS	5%	11%
DEATH FOR TOXICITY	2%	6%

TAX 324

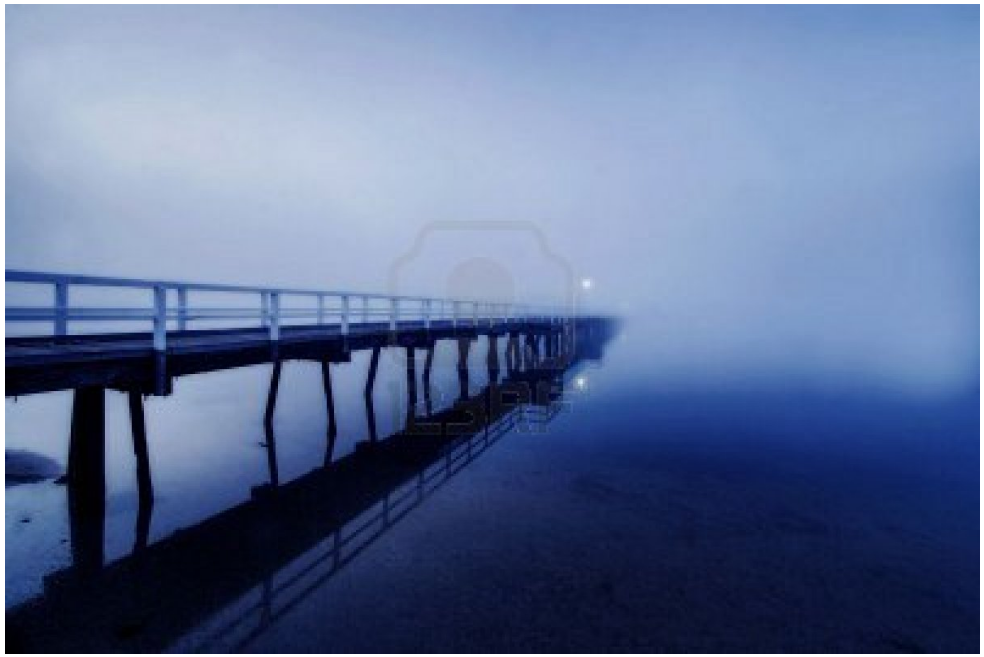
TOXICITY	TPF	PF
G3-4 NEUTROPENIA	83%	56%
FEBRILE NEUTROPENIA	12%	7%
G3-4 NAUSEA	14%	14%
EMESIS	8%	10%
STOMATITIS	21%	27%

Vermoken JB, N Engl J Med2007

Posner MR N Engl J Med2007

THE UNKNOWN OF NEW FRONTIERS

- New technologies (dose escalation, SIB)
- New integration stategies
- Targeted therapy



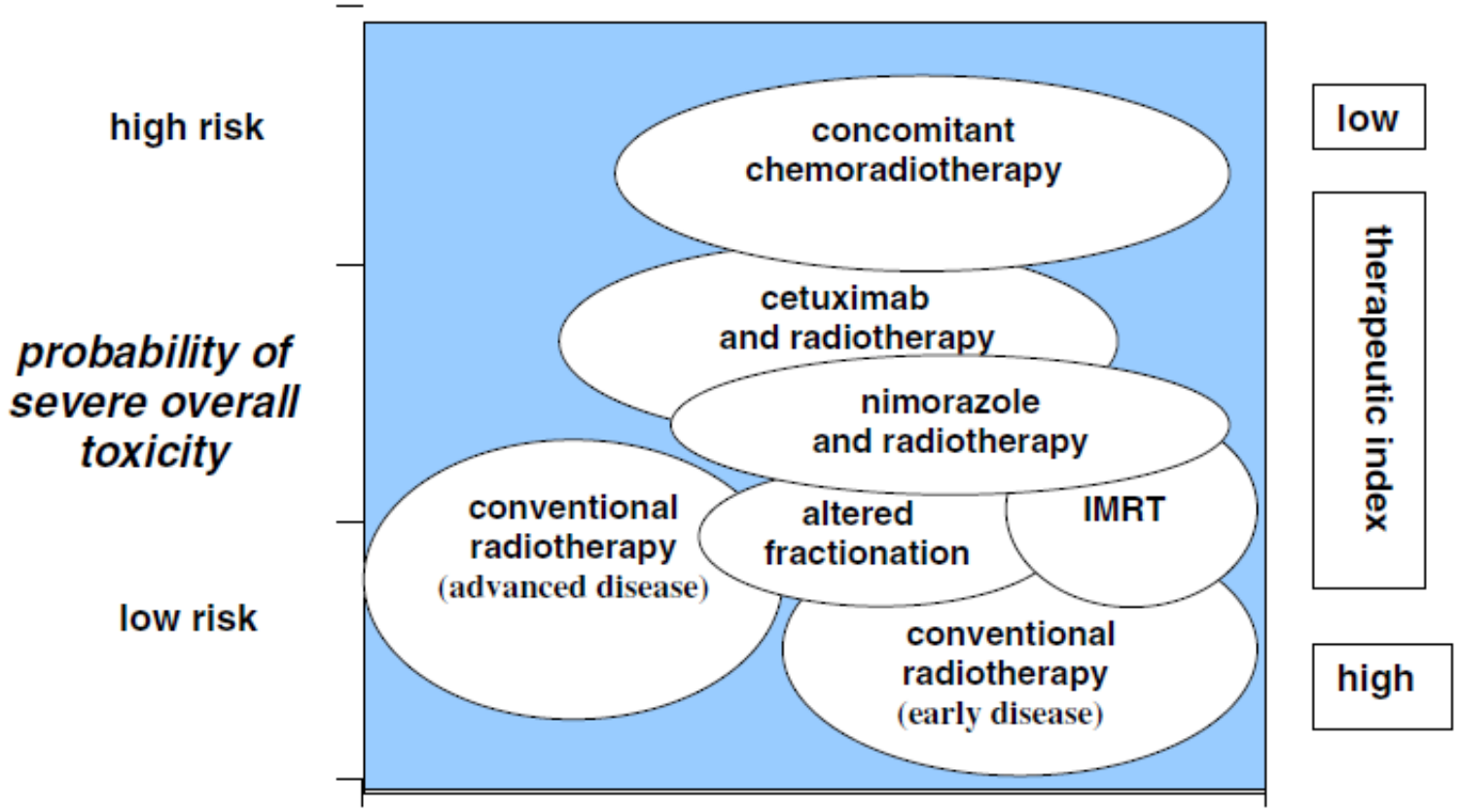
INCREASING TOXICITY IN NONOPERATIVE HEAD AND NECK CANCER TREATMENT: INVESTIGATIONS AND INTERVENTIONS

SØREN M. BENTZEN, PH.D., D.SC.,* DAVID I. ROSENTHAL, M.D.,†
ERNEST A. WEYMULLER, M.D.,‡ AND ANDY TROTTI, M.D.§

toxicity data has become a major challenge. With a growing number of treatment options, all with a characteristic spectrum of toxicities, understanding the scope and magnitude of the risks posed by different treatments has become a key component of clinical decision making. In addition, the po-

have become so prevalent that interpreting the deluge of toxicity data has become a major challenge. With a growing number of treatment options, all with a characteristic spectrum of toxicities, understanding the scope and magnitude of the risks posed by different treatments has become a key component of clinical decision making. In addition, the po-

Therapeutic index (cure / overall toxicity ratio) for evolving strategies



Corvò R Radiother Oncol 2007


The Future
NEXT EXIT

Improvements in the therapeutic index obtained by a rational selection of drugs based on their intrinsic cytotoxic mechanisms and their interaction with pathways leading to radiation-induced cell death

Better understanding of drug-radiation interactions in both tumor and normal tissues

A careful selection of patients, an accurate assessment of risk levels, and new algorithms properly tailoring therapy to the individual patient must be a priority