

Progress in Mesothelioma



Princess Margaret Hospital

University Health Network

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Adjunct Professor of Surgery, University of Toronto

Affiliate Scientist, Ontario Cancer Institute

Mesothelioma Research Program

- Early Detection Study
 - LDCT scan, questionnaire, biomarkers, spirometry
- Treatment Protocols
 - Trimodality therapy
 - Neo-adjuvant IMRT
 - Advanced disease chemo studies
- Basic Research Studies
 - Genetic profiling of tumours
 - Immunomodulation in mesothelioma
 - Screening new therapies
- Epidemiology Studies
 - Asbestos related lung disease



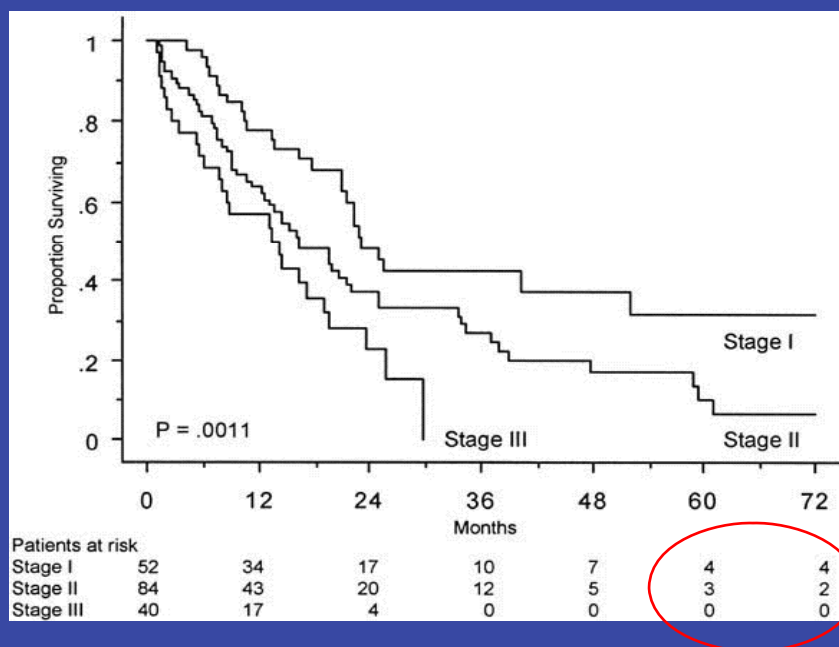
Mesothelioma Research Program

Michael R. Johnston, MD	Thoracic Surgeon
Heidi Roberts, MD	Radiologist
Marc de Perrot, MD	Thoracic Surgeon
Ming Tsao, MD	Pathologist
Ron Feld, MD	Medical Oncologist
Brenda O'Sullivan	Coordinator
Li Zhang, PhD	Immunologist
Masaki Anraku, MD	Thoracic Oncology Fellow
John Cho, MD	Radiation Oncologist
Geofrey Liu, MD, PhD	Molecular Epidemiologist
Martin Tammamagi, PhD	Epidemiologist
Demetris Patsios, MD	Radiologist
Gregory Pond	Statistician
Albert Ebidia	Database support



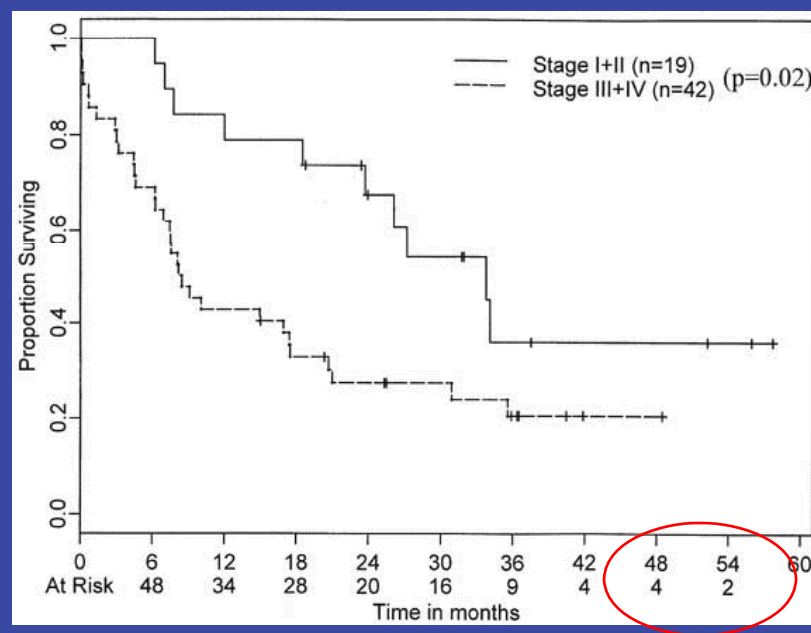
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Survival by Stage in Adjuvant Trials



Brigham (Sugarbaker)

EPP+chemo+rads+chemo



Memorial (Rusch)

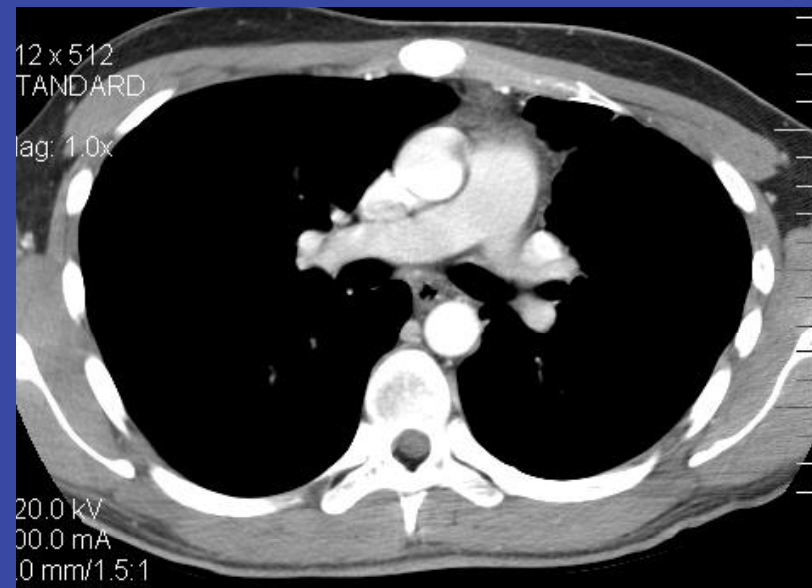
EPP+rads



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“Early” Mesothelioma

21 year old student



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First Sites of Relapse after EPP and 54 Gy Rad Tx

Locoregional only	2
Distant only	30
Locoregional and distant	5
Locoregional	7
Pleural	3
Nodal	4
Distant	30
Peritoneal	17
Intralateral visceral	5
Contralateral pleural	13
Contralateral lung	8
Bone	7
Central nervous system	0
Other	5

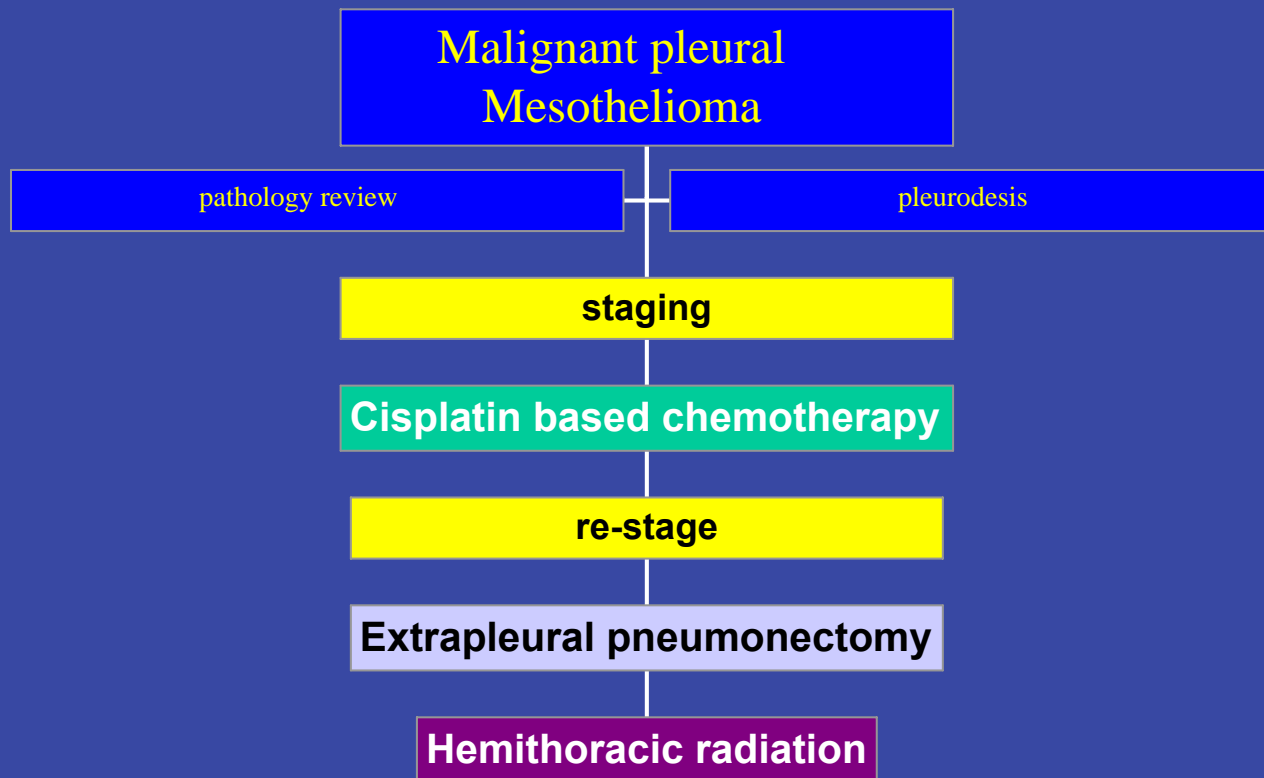
Some patients had more than one site of recurrent disease at relapse.



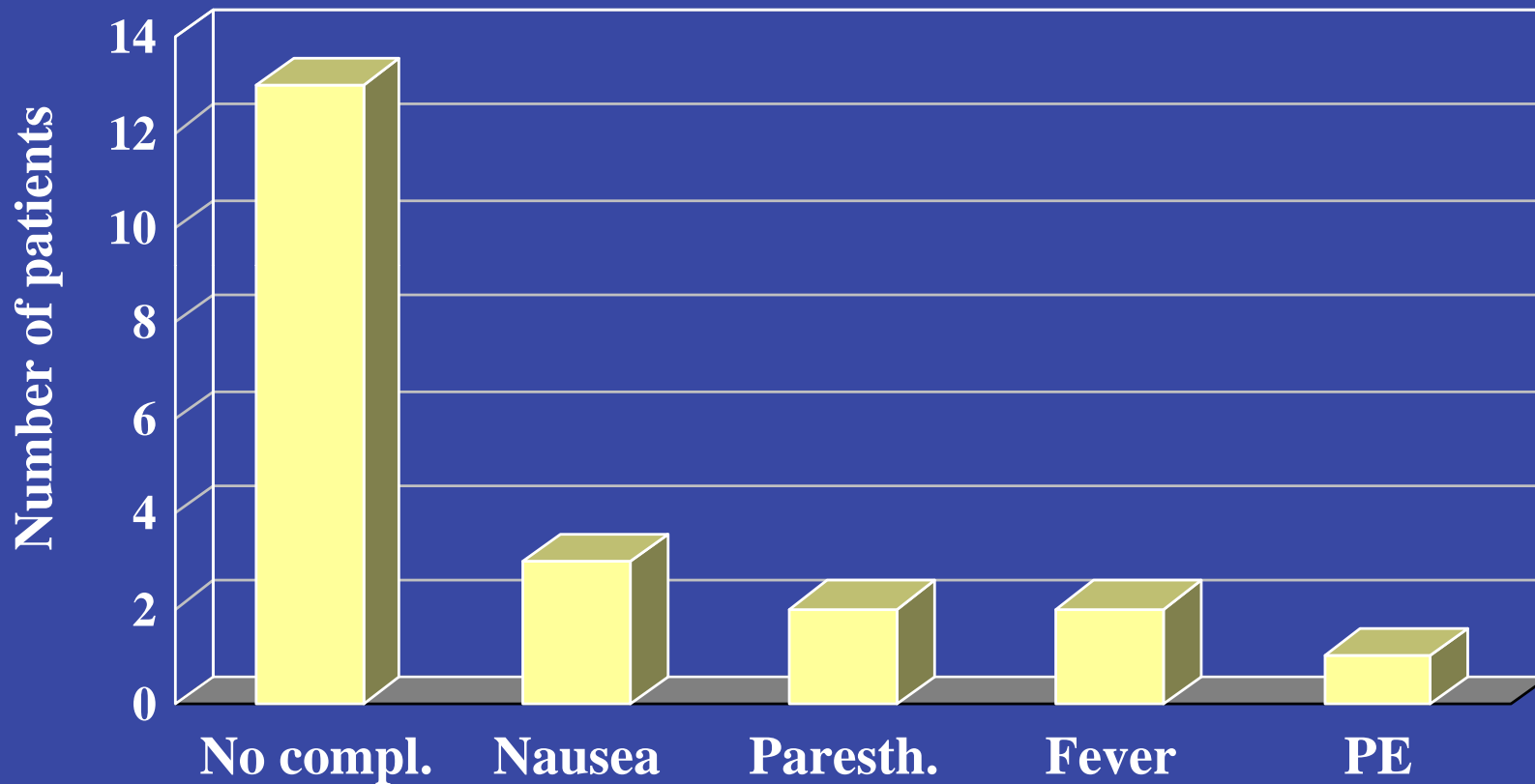
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Rusch. J Thorac Cardiovasc Surg 2001

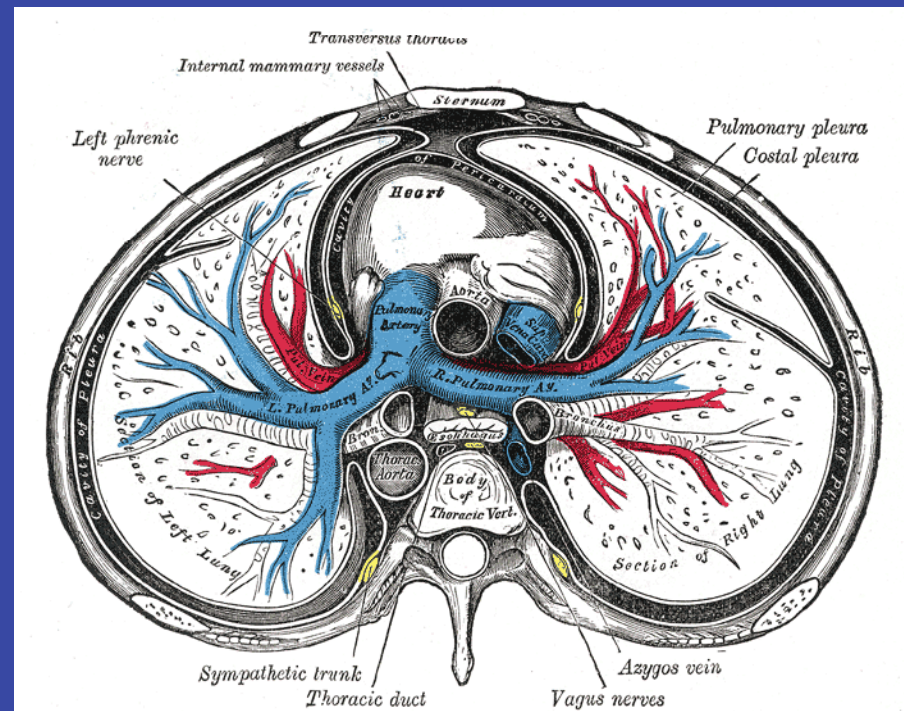
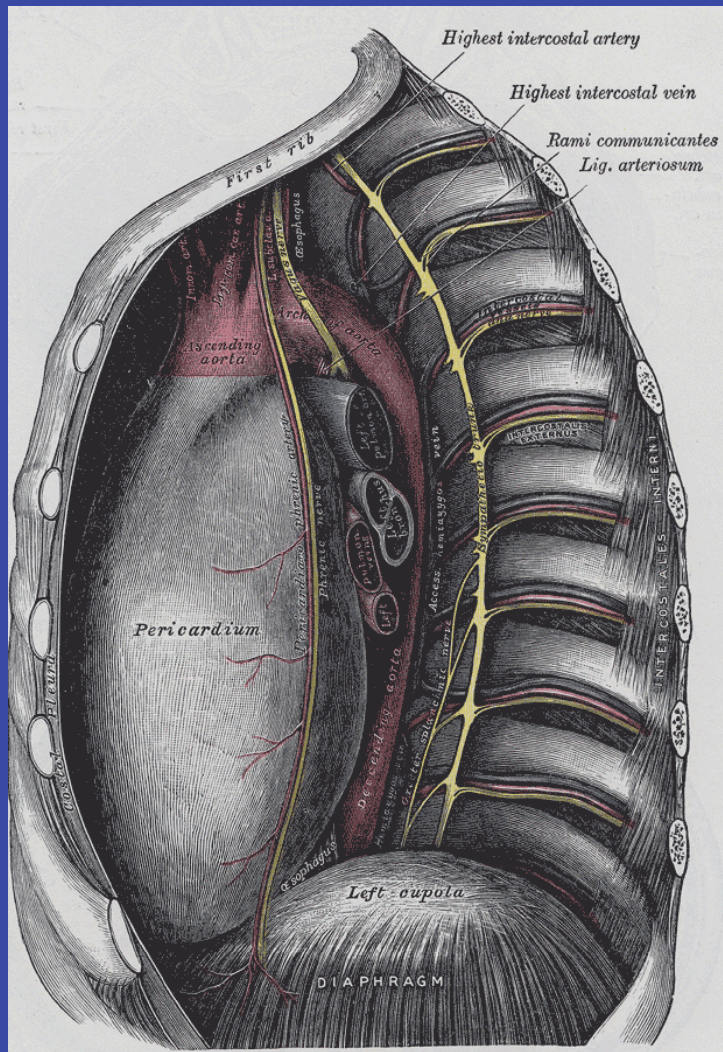
Treatment Protocol



Chemotherapy Toxicities (N=19)

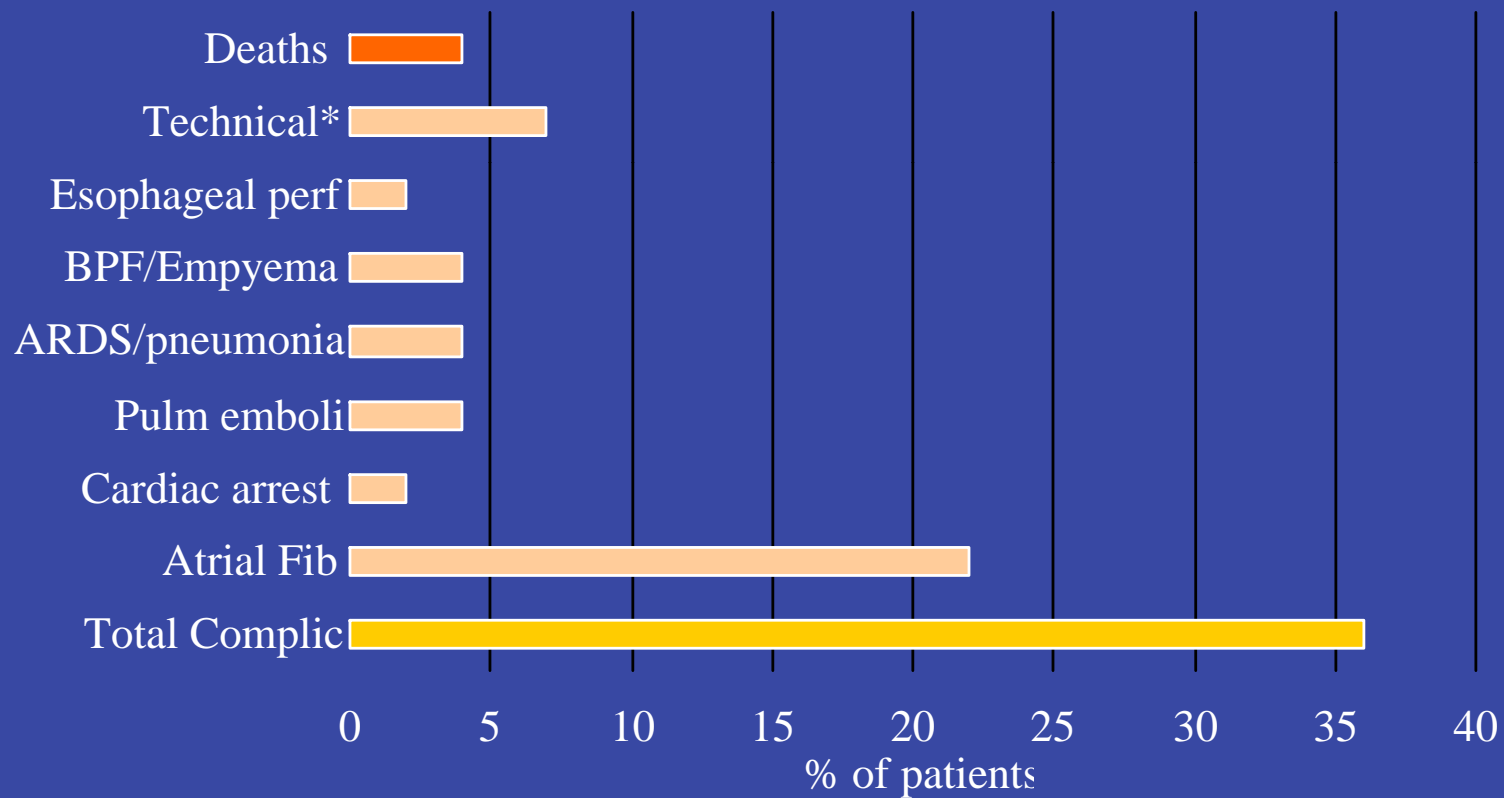


Extrapleural Pneumonectomy



Major Post-operative Complications

57 consecutive patients undergoing EPP

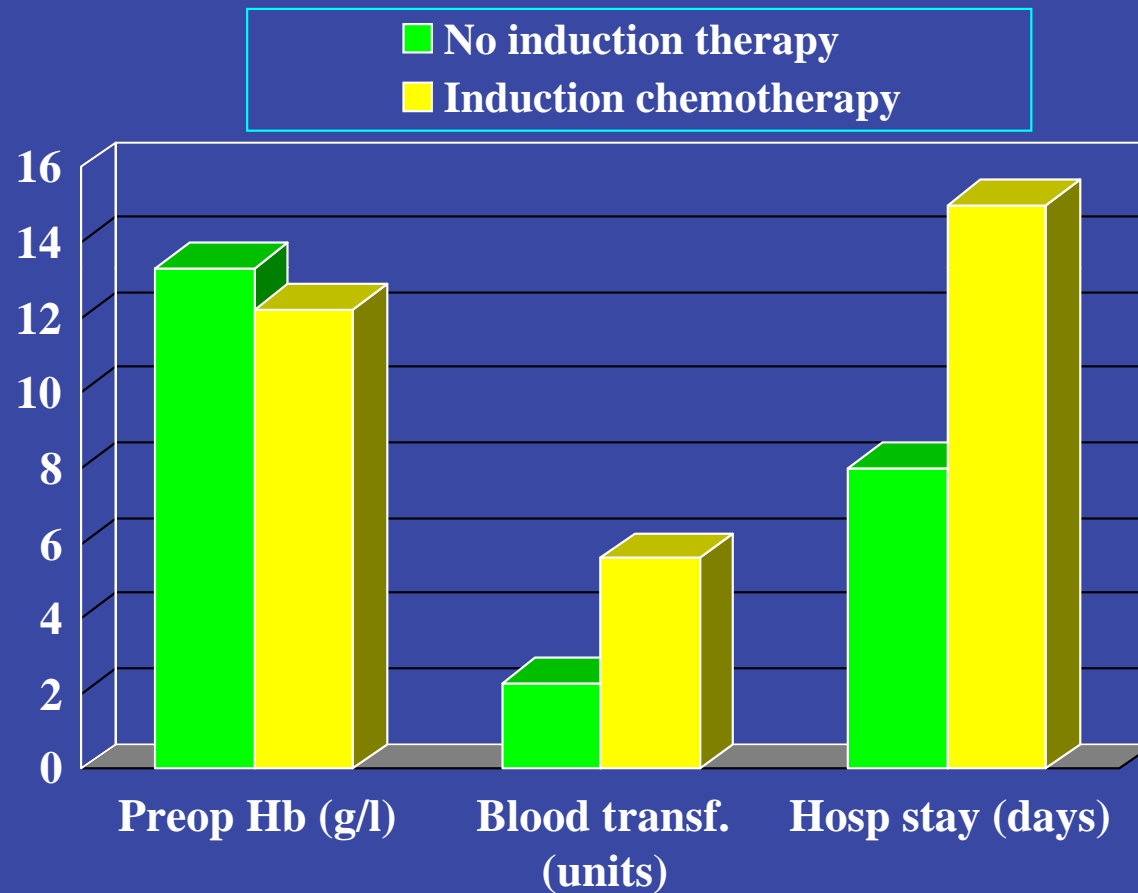


Risk Factors for Major Complications

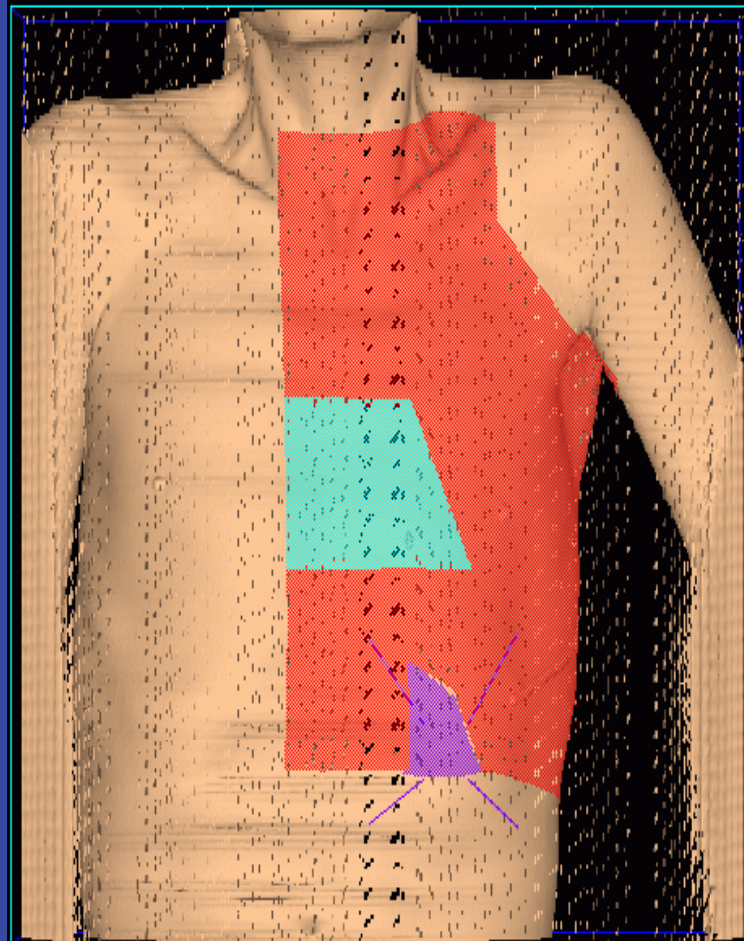
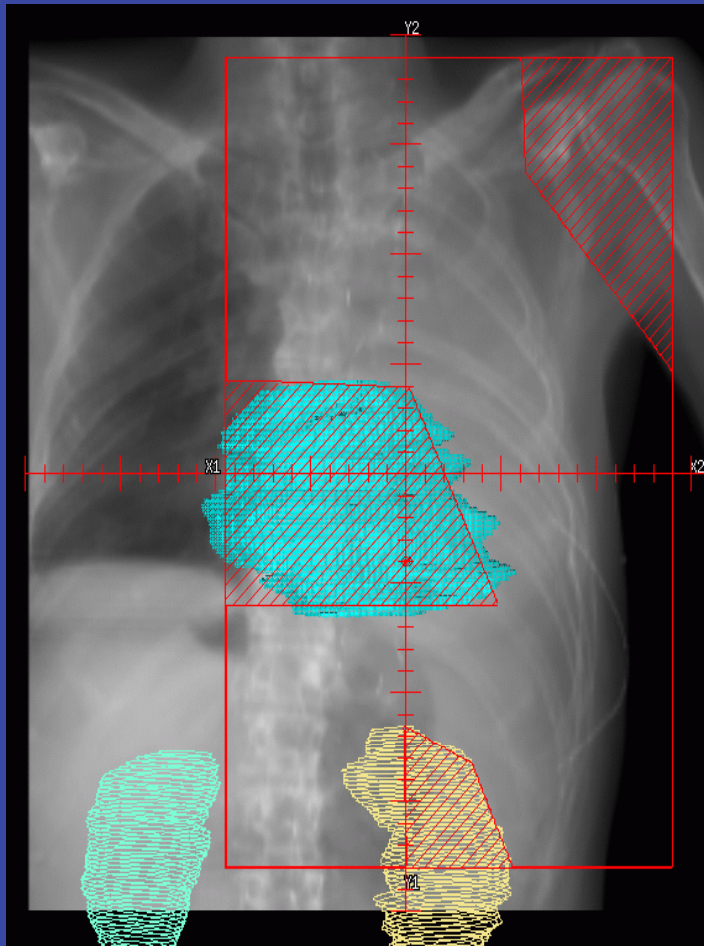
	<u>p-value*</u>	
	<u>Univariate</u>	<u>Multivariate</u>
• Right sided EPP	0.01	0.02
• RBC transf >4 units	0.03	0.03
• Age (\geq 60 yo)	0.06	0.1
• Induction chemo	0.5	0.5



Impact of Induction Chemotherapy



Hemi-thoracic Radiation



Planning

File Options Utilities View **Setup** Contours Points Beams Dose Eval IMRT Inv Plan Patient: [REDACTED] Plan: 0-MESO Rev: R01.P01.D01 0.Trial_1 Help

Regions Of Interest

PTV
PTVev
PTVev_50Gy
CTV_Boost60Gy
CTV_Avoid40Gy

Add ROI
Delete ROI...
Load Organ...

ROI Name: **CTV_Boost60Gy**
Data Set: [REDACTED]
Contours: 11
Volume: ? cm³ **Recompute**

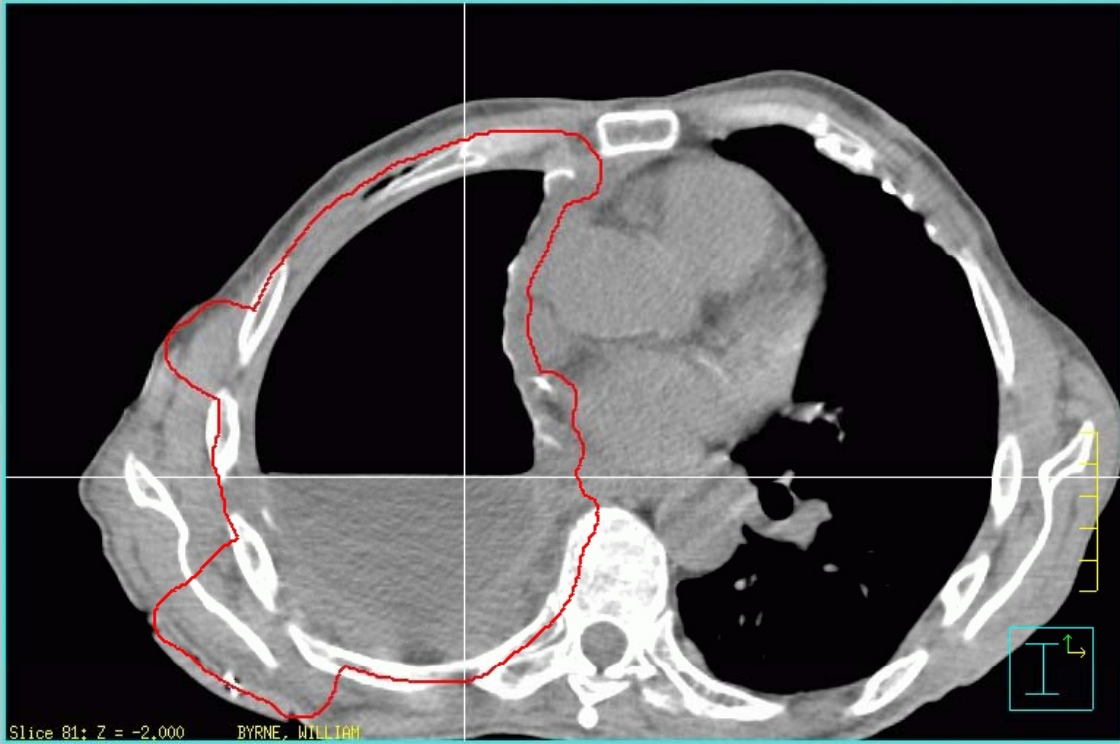
ROI Display Options

Color	2D Display	3D Display	Box Size	Line Width
purple	<input type="radio"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>


Display outline in BEV DRR Yes No

Edit Options


Autocontour thresholds: 800 (Lower) 4096 (Upper)
Autocontour Options...
Auto-close painted contours Yes No
Copy contours from last edited slice to:



Slide 81: Z = -2,000 BYRNE, WILLIAM



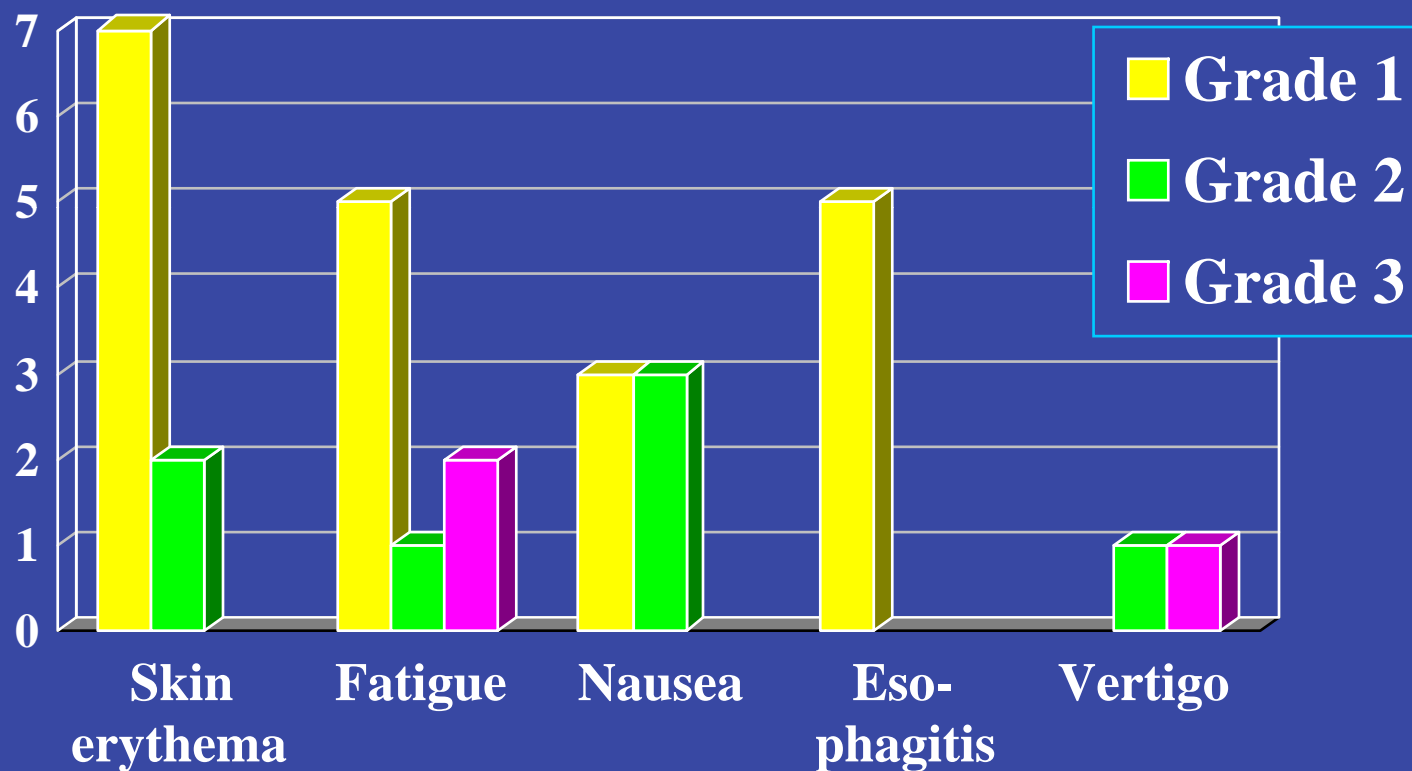
Slide 196: X = -5,317 BYRNE, WILLIAM



Slide 242: Y = -46,274 BYRNE, WILLIAM

Press Button 3 for image manipulation tools.

Hemithoracic Radiation (N=12)



Toronto Trimodality Therapy Update

- 2001 - December, 2007: 60 patients
 - Induction chemotherapy: 50
 - Cisplatin + vinorelbine 26; pemetrexed 24; other 10
 - No resection: 15
 - Progressive disease: 4
 - Unresectable: 6
 - Positive mediastinoscopy: 5
 - EPP: 45
 - Operative mortality: 3 (7%)
 - Adjuvant hemi-thoracic radiation: 30
 - 3-D conformal (54 Gy in 30 fractions)
 - IMRT (50 Gy in 25 fractions)



Complications of Trimodality Therapy

Table 2. Severe adverse events recorded during the tri-modality therapy*

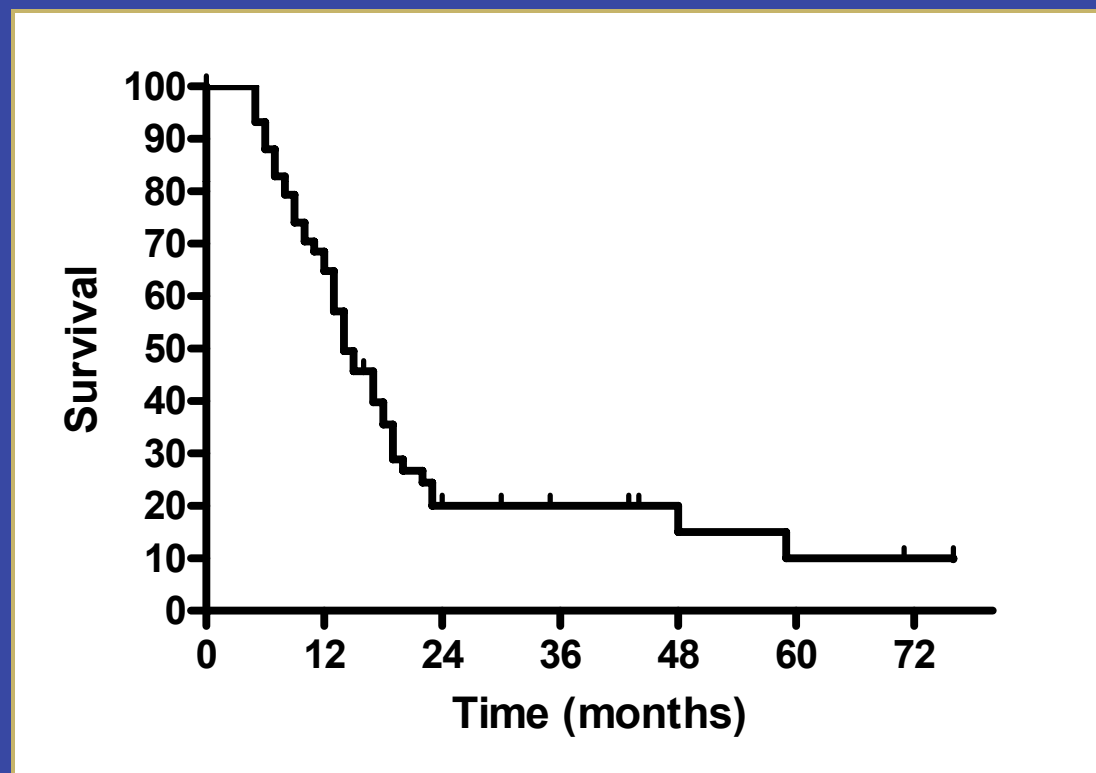
Complications	<u>Chemotherapy</u>			<u>Surgery</u>			<u>Radiation</u>		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Pulmonary emboli		3			1				
Leukopenia	1								
Cardiac herniation						1			
Cardiac arrhythmia				10		1			
Bronchopleural fistula				1		1			
Esophageal perforation					1				
Gastric herniation					1				
Chylothorax					1				
Fatigue							5		
Nausea							1		

* Severe adverse events defined by grade 3 to 5 toxicity according to the NCI CTCAE version 3.0 guidelines

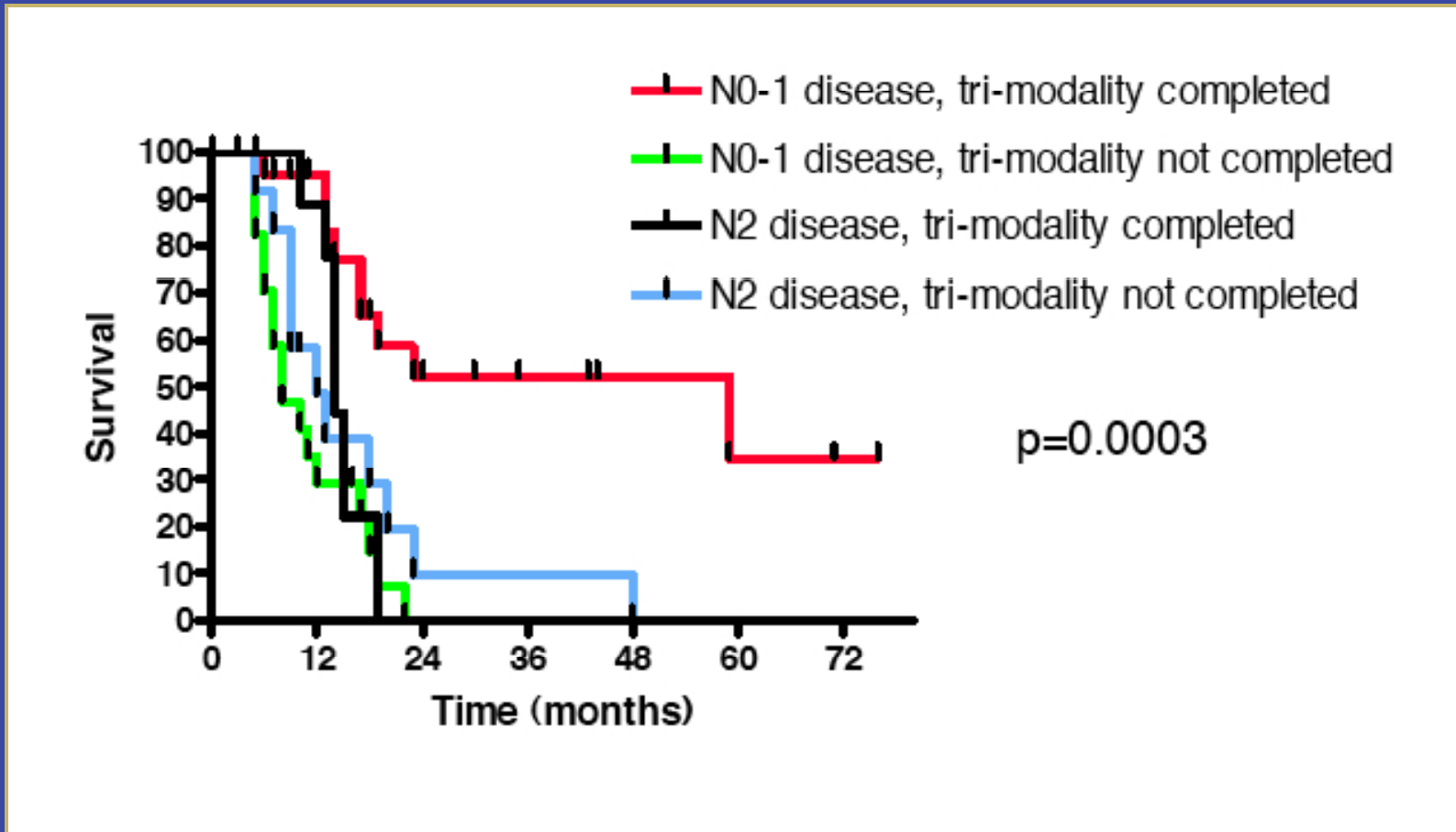


Overall Survival

60 patients; median survival 14 months

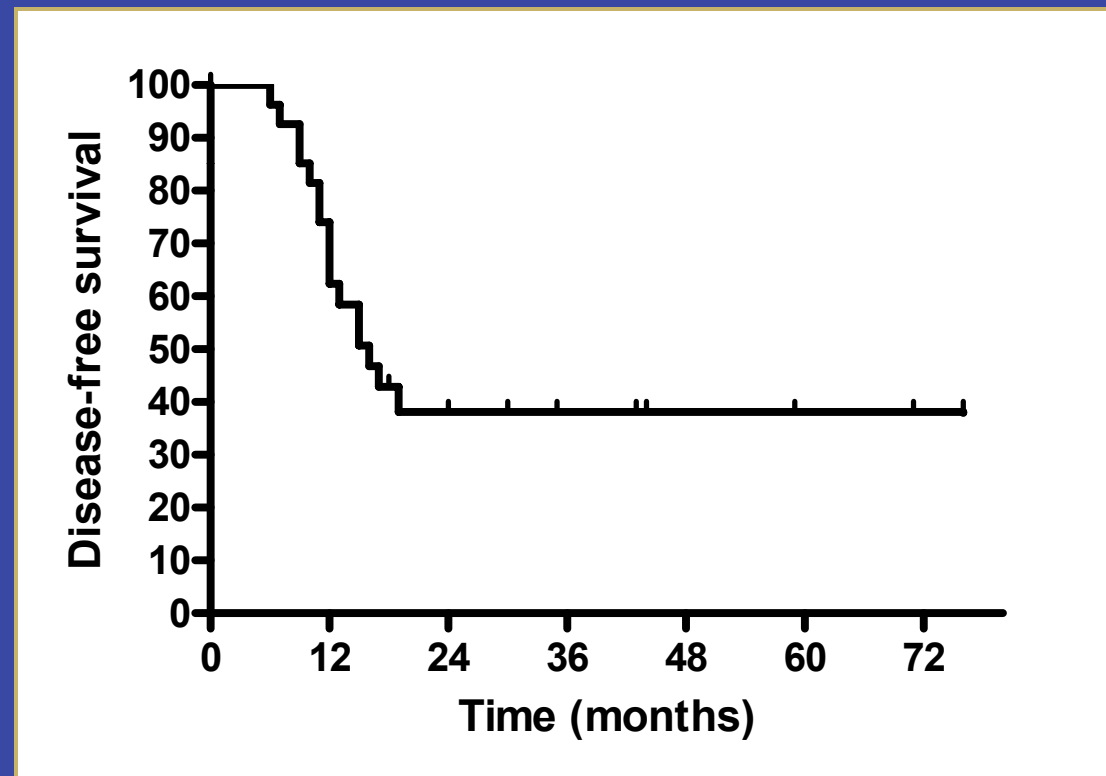


Survival According to Nodal Status and Therapy



Disease-free Survival in Patients Who Completed Trimodality Therapy

$N = 30$



Toronto Trimodality Therapy

- Median survival
 - Epithelial vs biphasic: 18 vs. 12 mo ($p=0.002$)
 - N 0 disease
 - Completed trimodality therapy vs incomplete
 - 59 vs. 8 mo ($p=0.0001$)
 - Chemo regimen: ns
- 5 year disease-free survival
 - 53% in all N0 patients
 - 75% in T1-2
 - 45% in T3-4



Recurrence Following Trimodality Therapy

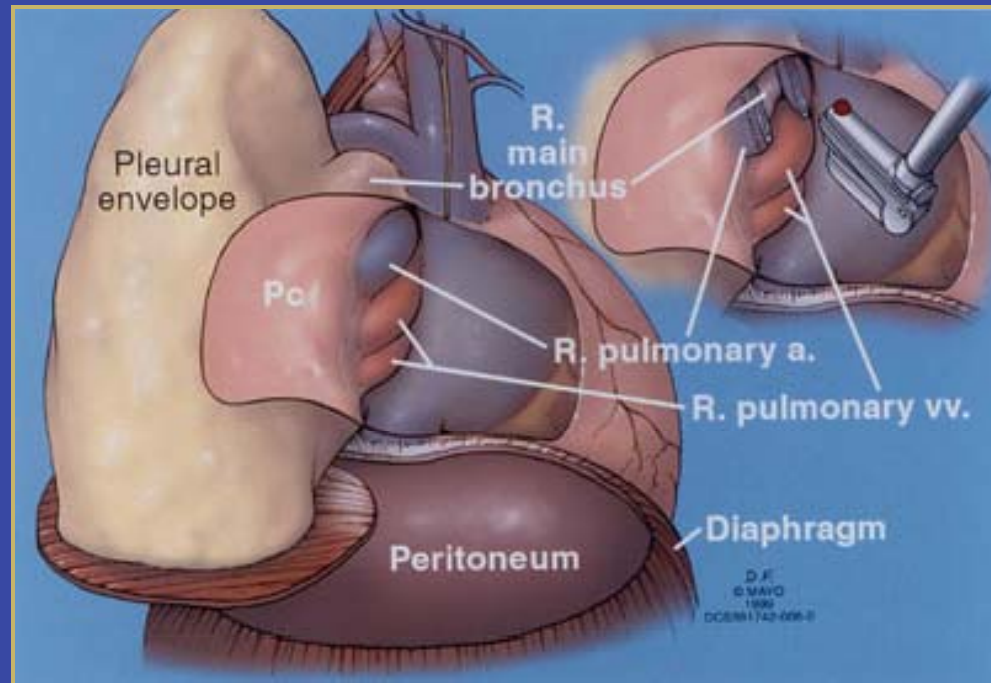
- Recurrences

- 16/30 patients

- Ipsilateral chest: 4 *local*
 - Pericardium: 1
 - Peritoneum: 5
 - Contralateral chest: 4
 - Chest and peritoneum: 2
- surgical seeding*
- vs distant mets?*



Tumour Seeding



Neo-adjuvant IMRT for Mesothelioma

Cho, dePerrot, Feld

- Phase 2 study in 25 patients with cT1-2 N0
 - Resectable patients only
- 25 Gy in 5 fractions over 1 week
 - 5 Gy boost to gross disease
- EPP 1 week following XRT
- Pathologic node negative > no treatment
- Pathologic node positive > adjuvant chemo



IMIG 2005

Low-dose Computed Tomography For The Early Diagnosis Of Mesothelioma And Lung Cancer In Prior Asbestos Workers: Preliminary Results

Michael R. Johnston, MD, FRCSC

Heidi Roberts, MD

University of Toronto University Health Network

Toronto, Ontario, Canada

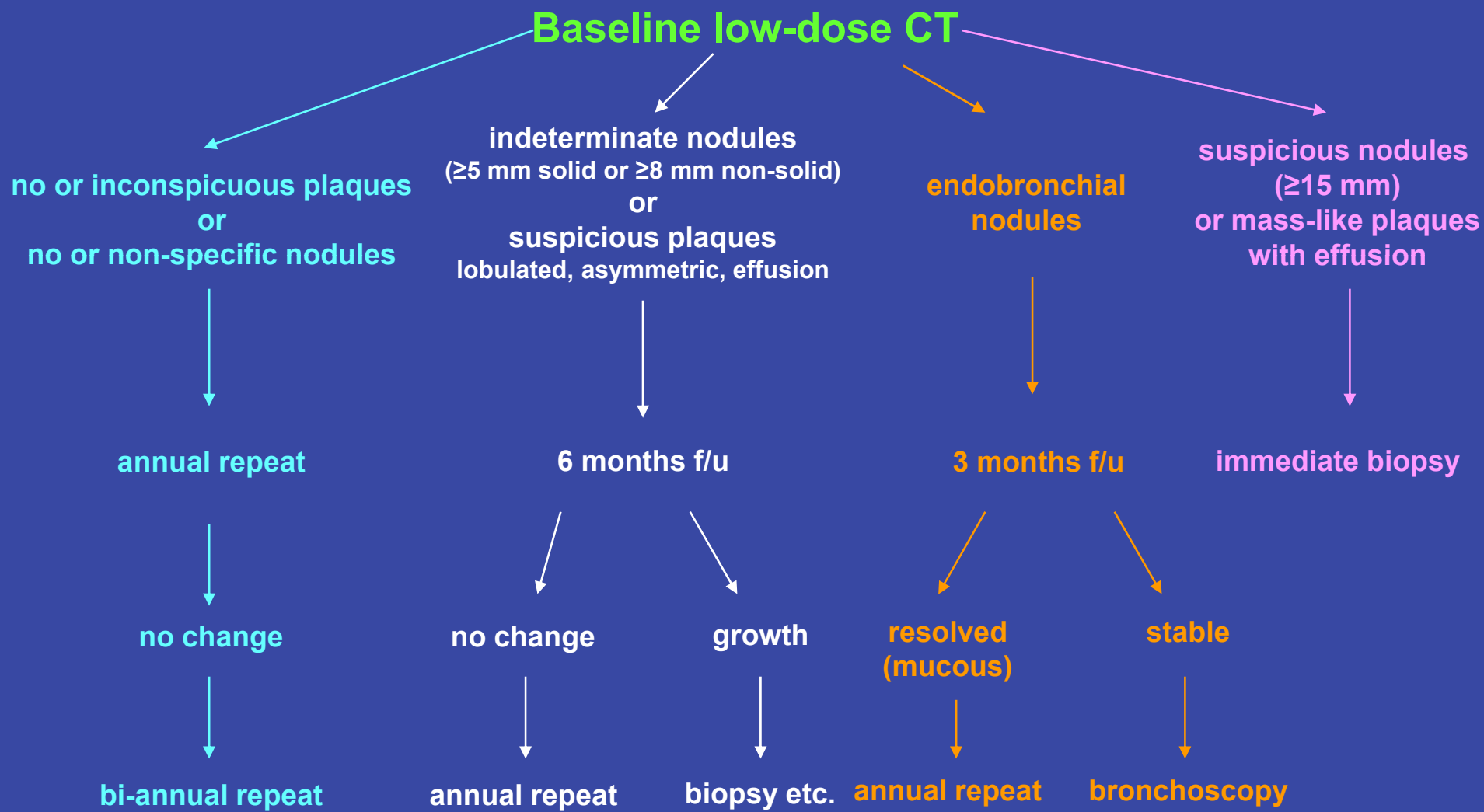


Methods

- Early detection study in a population at risk for pleural mesothelioma
 - Prevalence and incidence
- Inclusion criteria
 - History of asbestos exposure at least 20 years ago
 - Asbestos exposure with pleural plaques on chest x-ray



Methods: follow up flow chart



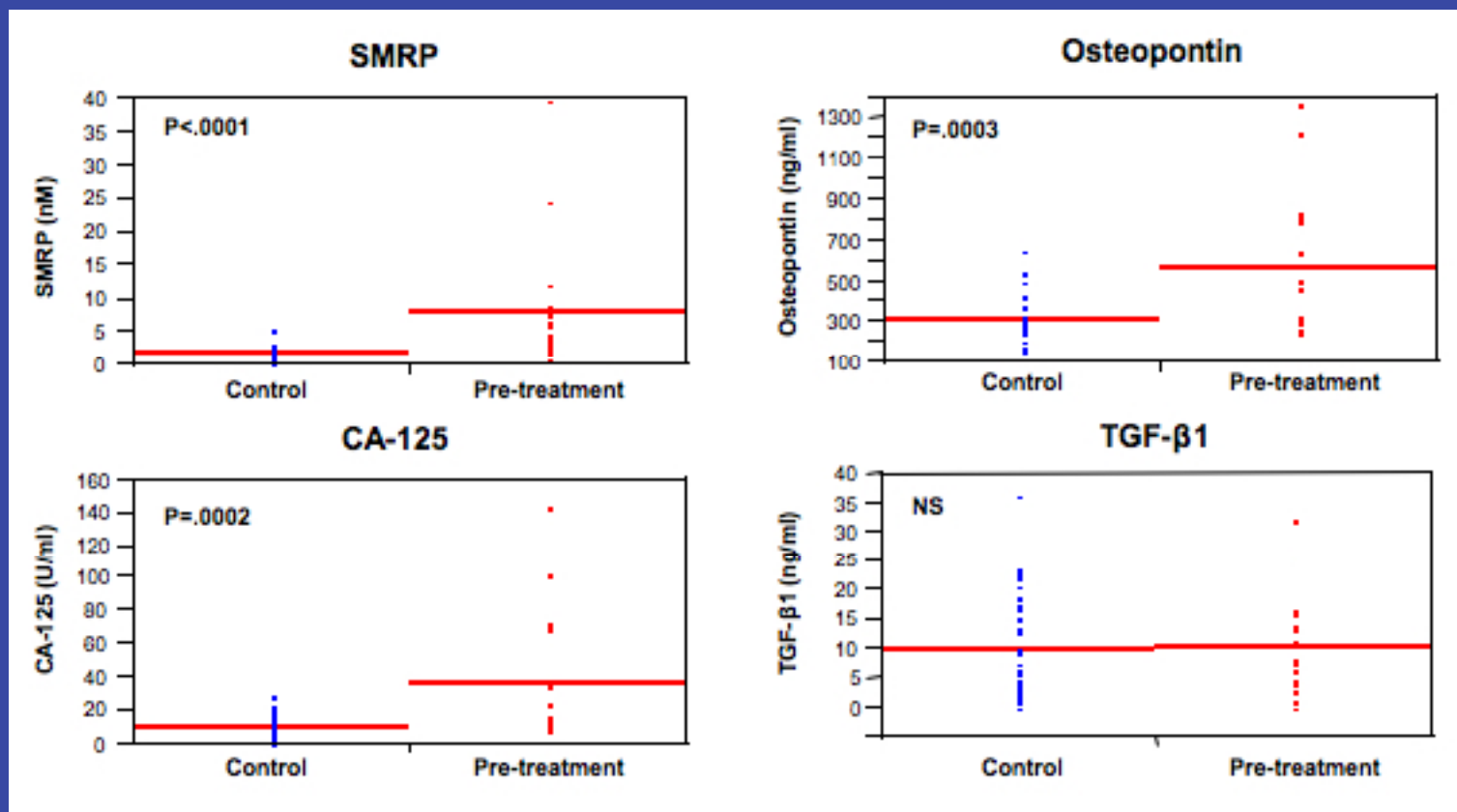
Update on Early Detection Study (9/08)

- 751 participants (98% male; average age 61)
 - 84% with lung nodule (20% > 4mm; 1% GGO)
 - 62% with pleural plaques
 - 2% with pleural effusion
- 14 cancers found
 - 6 meso (3 pleural, 3 peritoneal)
 - 8 lung cancers
- Mesothelin and osteopontin assays are in progress
- Expanding endpoints to include asbestos related lung disease



Plasma markers in patients with MPM

Prospective evaluation in patients with MPM (38) and asbestos exposed matched controls (64)



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Anraku, IMIG; 2008



Ketch Harbour, Nova Scotia