



Seminoma From More to Less

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Testis Cancer

- 44% increase in incidence of GCT in United States 1973-1998 (mostly Seminoma)
 - In 2008
 - 8090 new cases testicular GCT in US
 - 890 new cases testicular GCT in Canada
 - 60% Seminoma (85% Stage I)
 - > 4100 new cases Stage I Seminoma in US
 - > 450 new cases Stage I Seminoma in US
- » McGlynn KA et al Cancer 97:63-70, 2003.
- » Jemal A et al CA Cancer J Clin; 57:43-66, 2008

Stage I Seminoma

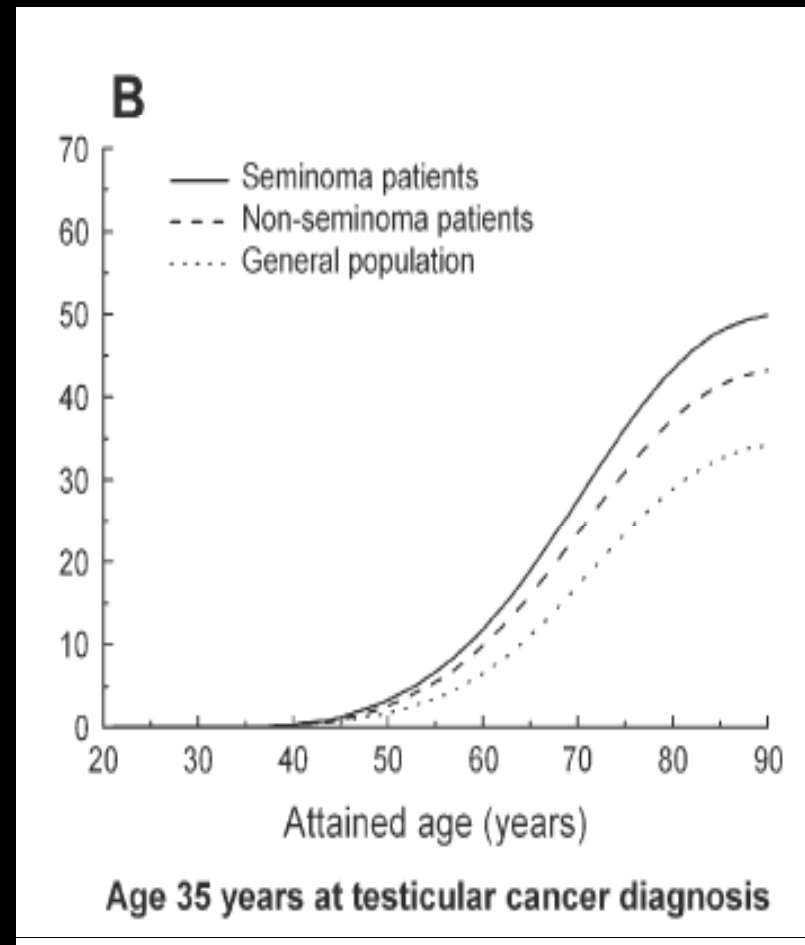
- Management Options
 - Surveillance
 - Adjuvant Radiation Therapy
 - Adjuvant Chemotherapy
- ~100% cure with all strategies
 - Key issue for oncologists is
 - Reduce overall “Burden of Treatment” while maintaining excellent results

Outline

- Compare
 - Surveillance versus Adjuvant Radiation Therapy
 - Surveillance versus Adjuvant Chemotherapy
 - Single agent Carboplatin
- Unresolved issues

Second Malignancy after RT for Seminoma

- NIH Study
 - 14 population based registries
 - 22,424 patients with Seminoma
 - For 35 yr patient with seminoma cumulative risk of 2nd Solid Tumour at age 75 36% vs 23% in general population

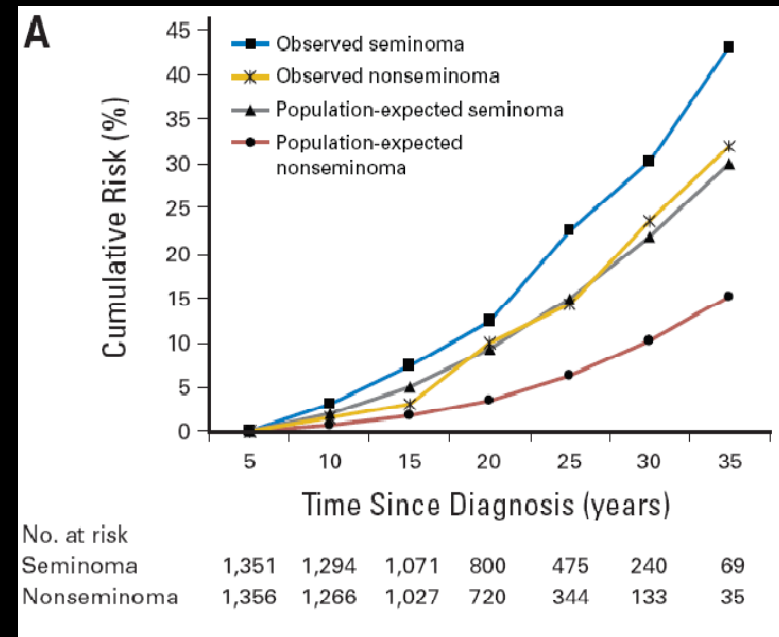


Second Malignancy after RT for Seminoma

- Dutch population based study
 - 2707 Testicular Cancer survivors
 - Median Follow-up 17.6 years
 - 2nd malignancy risk with subdiaphragmatic RT was 2.6 fold increased as compared to surgery alone
 - Mainly in-field or adjacent to RT field

Second Malignancy after RT for Seminoma

- Risk increase similar to that of smoking
- Median survival after 2nd malignancy diagnosis was 1.4 years
 - 5 year survival was 41%
- 2nd Malignancy Risk



Long term RT morbidity

Cardiovascular

- Royal Marsden Hospital
 - 1603 germ cell tumour pts treated 1982-1992
 - 341 ineligible (200 overseas, 141 dead)
 - Cardiac morbidity data on 992 patients
 - 242 surveillance patients with cardiac morbidity data – reference group
 - 230 RT alone with cardiac morbidity data
 - 183 Stage 1 seminoma
 - 92% Dog-leg RT (8% mediastinal RT)

Long term RT morbidity

Cardiovascular

- Royal Marsden Hospital Study
 - Relative risk of cardiac event 2.40 (95% CI 1.04-5.45)
 - Death from Myocardial Infarction
 - Documented Myocardial Infarction or history of Angina
 - Surgery for CAD
 - Increased Risk starts 5-8yrs after treatment
 - Actuarial risk of cardiac event at 10 years
 - Surveillance 1.4%
 - Radiotherapy 7.2%
 - Chemotherapy 3.43%

Cardiovascular morbidity

– MD Anderson

- 477 pts treated RT 1951-1999
 - 453 never relapsed,
 - » 373 Stage I (93% subdiaphragmatic RT alone)
- Median follow-up 13.3 years
- Standardised Mortality Ratio
 - Cardiac death - 1.61
 - Retroperitoneal RT only (> 15 years F/U) 1.80

Surveillance

Author	# Patients	5-year Relapse	CSS
Horwich	103	17.3%	100%
Daugaard	394	17%	100%
Warde	638	17.7%	99.3%

Horwich et al Br J Cancer 65: 775-778, 1992

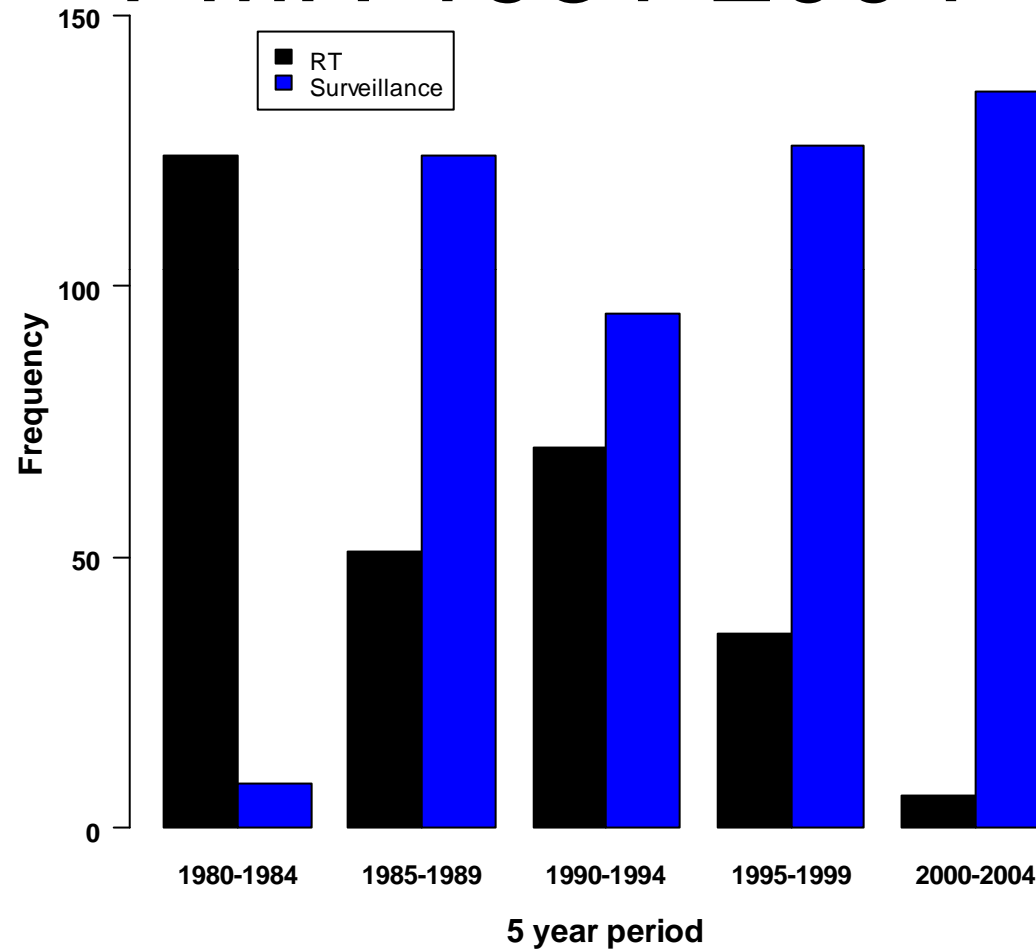
Daugaard et al APMIS 111:76-85, 2003

Warde et al. J Clin Oncol; 20:4448-4452 2002

Stage I Seminoma PMH 1981-2004

- 776 Cases
 - Prospective data collection,
 - Phase II study of surveillance 1985 - 1994, patient choice since 1994
 - Follow-up - median 9.1 years (range 0.1-20.4)
 - 489 Surveillance - median f/u 8 years (0.1-19.8)
 - 287 Adjuvant RT - median f/u 10.1 years (0.2-20.4)
 - 4 monthly X 3 years, 6 monthly to yr 7, then annual to year 10
 - CT Abdomen/Pelvis if surveillance

Stage I Seminoma PMH 1981-2004



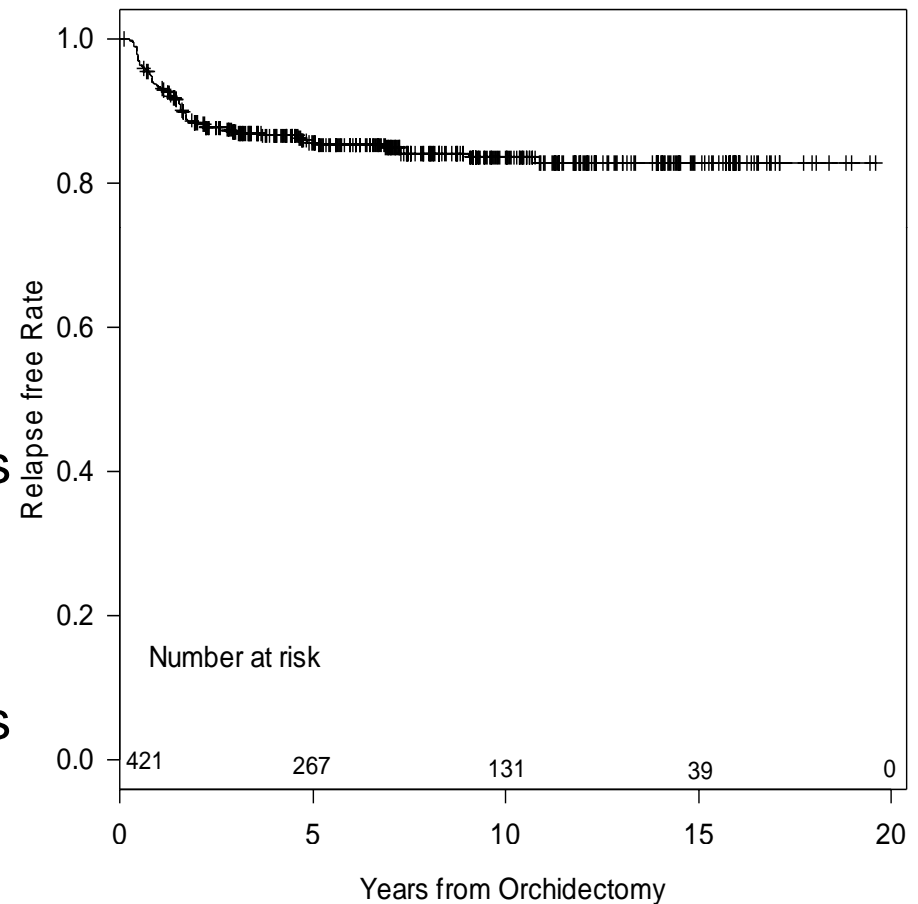
Stage I Seminoma PMH 1981-2004

	Surveillance	Adjuvant RT
Median Age	35	34
Median Tumour Size	3.5 cm	4.5 cm
Rete Testis invasion	23%	29%
Cryptorchidism	8%	9%

Stage I Seminoma

PMH 1981-2004

- Surveillance
 - 72 Relapses - 85% Relapse-Free Rate at 5 Years
 - Sites of Relapse
 - 57 (89%) Para-aortics alone
 - 3 (4.7%) Para-aortics + Pelvic nodes
 - 3 (4.7%) Pelvic nodes alone
 - 1 (1.6%) Other



Stage I Seminoma

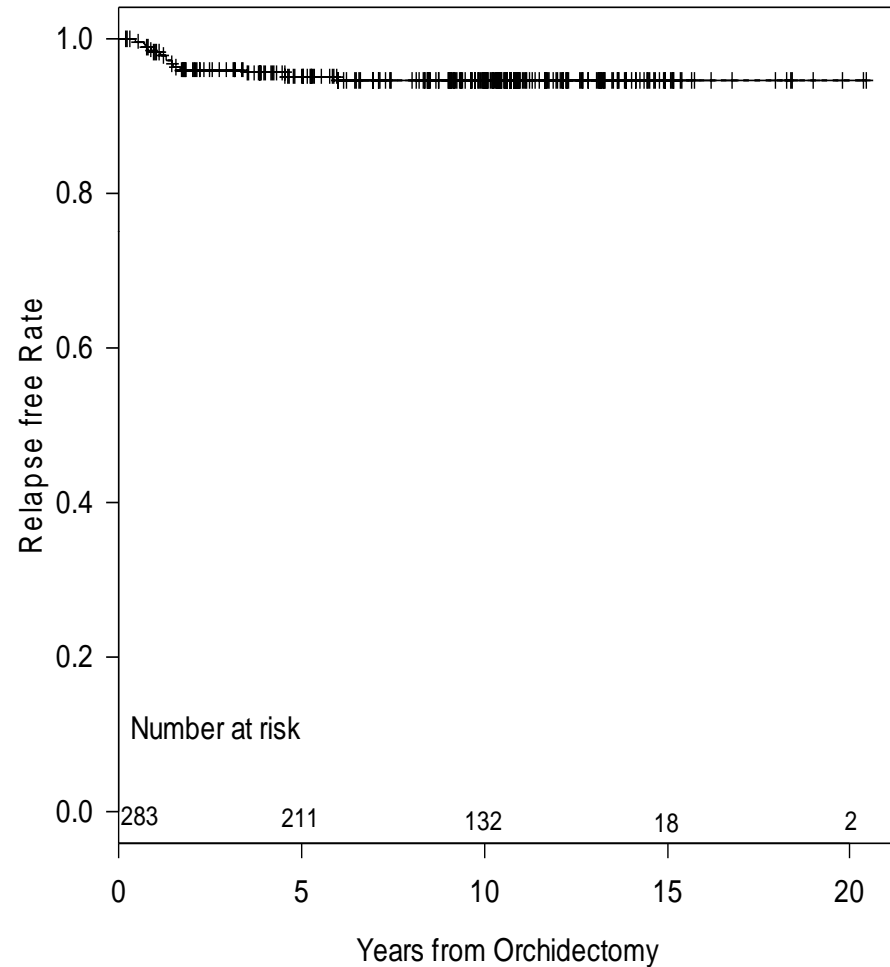
PMH 1981-2004

- Surveillance – treatment of relapse
 - 64 Relapses
 - 48 treated with RT
 - 5 second relapse all salvaged with chemotherapy
 - 14 Chemotherapy
 - 2 Surgery
 - 1 patient died from Seminoma

Stage I Seminoma

PMH 1981-2004

- Adjuvant RT
 - 14 Relapses - 95% Relapse-Free Rate at 5 Years
 - Sites of Relapse
 - 4 (29%) Inguinal nodes
 - Radiation/Surgery
 - 10 (71%) Supra-diaphragmatic
 - Chemotherapy



Stage I Seminoma PMH 1981-2004

	Surveillance	Radiation
RFR at 5 Years	85%	95%
CSS at 5 Years	99.8%	100%
10 yr Actuarial Risk of Requiring Chemotherapy	4.6%	3.9%
Number of pts avoiding any treatment	357 (85%)	0

Adjuvant Chemotherapy

- Single Agent Carboplatin
 - 78 Pts
 - 55 had 2 courses 1 relapse
 - 23 had 1 course 0 relapse
- Hope that treatment with 1 course of Carboplatin was all that was necessary

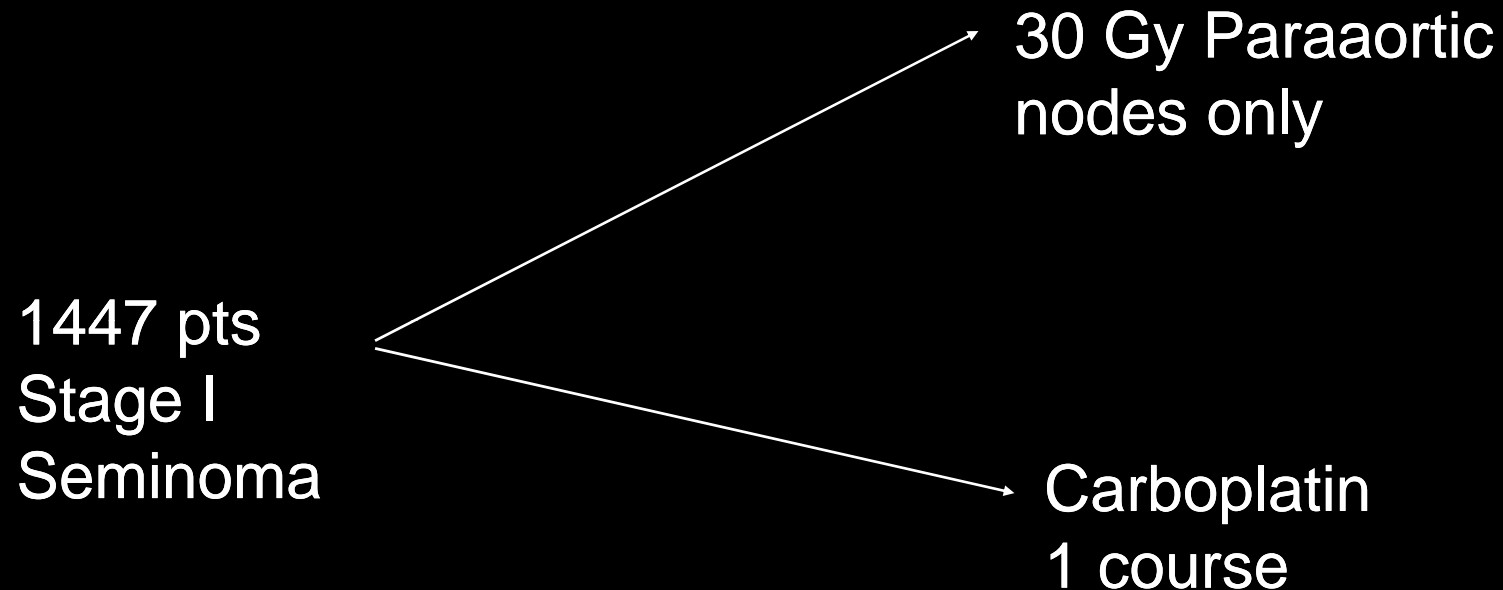
Adjuvant Chemotherapy

Author	No. pts.	Median f.u. (m)	Relapse rates	Relapse sites
Dieckmann (1 & 2 courses)	93	48	8.6	PA
	32		0	-
Reiter 2 courses	107	74	0	-
Steiner 2 courses	108	60	1.85	PA
Aparico 2 courses	60	52	3.3	PA

1. Dieckmann et al Urol 55:102-106;2000
2. Reiter et al J Clin Oncol; 19: 101-04, 2001
3. Steiner et al Urol 60:324-328;2002
4. Aparico et al Ann Oncol 14:867-872; 2003

Adjuvant Chemotherapy

Phase III data MRC TE19 study



RT (Para-aortics alone) – 4.1% relapse

Carboplatin – 1 course – 5.2% relapse
74% in retroperitoneum

Adjuvant Chemotherapy

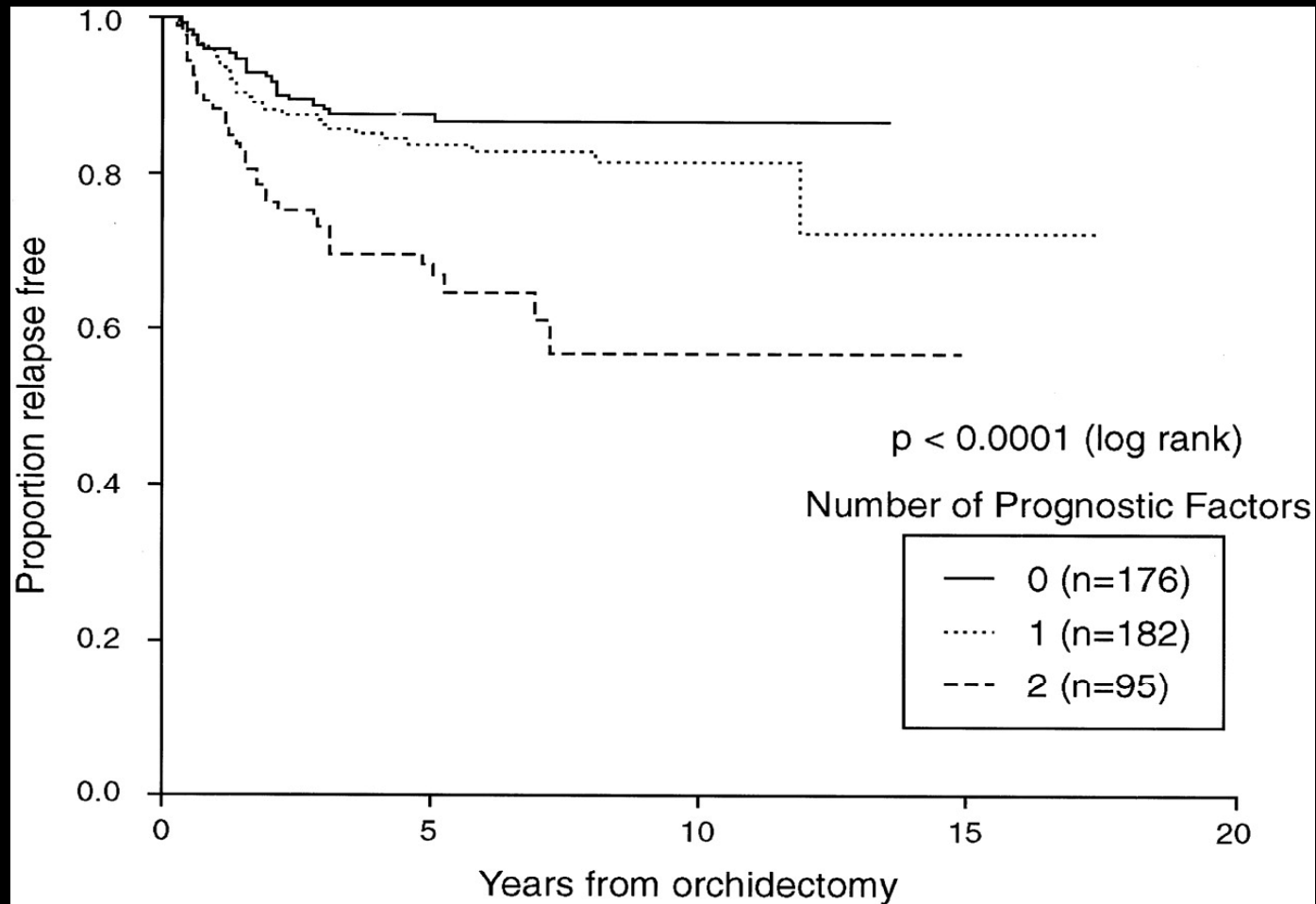
- However 1 Course Carboplatin
 - At best reduces relapse rate from 15% to 5%
 - Unnecessary treatment in 85% cases
 - Late Relapse in seminoma is well recognised
 - Short Median Follow-up in MRC trial

Must continue to do Cross Sectional Imaging because of risk of Retroperitoneal Relapse if adjuvant chemotherapy chosen as management strategy

Prognostic Factors for Relapse

- Pooled analysis
 - 638 pts from 4 institutions
 - PMH, RMH, DATECA, RLH
 - Median follow-up 7 years
 - 121 pts relapsed
 - 5 year relapse free rate of 82.7%
 - On multivariate analysis
 - Tumour size
 - Rete Testis invasion

Prognostic Factors for Relapse



Risk-Adapted Approach

- Spanish Cooperative Group Study
 - 314 patients Stage I seminoma
 - 100 no adverse risk factors
 - Surveillance
 - » 6% relapse
 - 214 one/two risk factors
 - 2 courses adjuvant Carboplatin
 - » 3.3% relapse (6% in patients with 2 factors)

Risk-Adapted Approach

- Prognostic Model
 - Not validated in independent dataset
 - Low discrimination
 - “High-risk” group still has 65% relapse-free rate
- Risk-adapted approach
 - Study Protocols only

Hypothetical Cohorts Of 1000 patients each

	Surveillance	Radiation	Adj Carbo
5 Yr Relapse	15%	5%	5%
CSS	100%	100%	100%
# requiring Salvage Chemo	40	40	? 40
# avoiding any trt	850	0	0
Second Malignancy at age 75	230	360	?

Optimal Strategy in Stage I Seminoma

- Surveillance
 - allows > 80% of patients to avoid *any* post-orchidectomy treatment
 - No increase in % patients requiring chemotherapy
 - Long-term safety established
 - with no increase in cause specific mortality
 - should be *offered* to all patients

Surveillance – Issues

- Follow-up Policy
 - CT
 - q 4 months X 3 years
 - q 6 months X 4 years
 - q 12 months X 3 years
 - 20 CTs/10 yrs
 - ? Reduce frequency esp in low risk cases
 - Compliance
- Future Directions
 - Low dose CT or MRI in follow-up
 - PMH Low dose CT study – 56% less dose in first 120 pts
 - MRC TRISST study
 - MRI vs CT
 - Frequency of Imaging
 - Molecular Markers predictive of relapse

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