



# Seminoma From More to Less

Dr Padraig Warde



Princess Margaret Hospital  
University Health Network

# 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

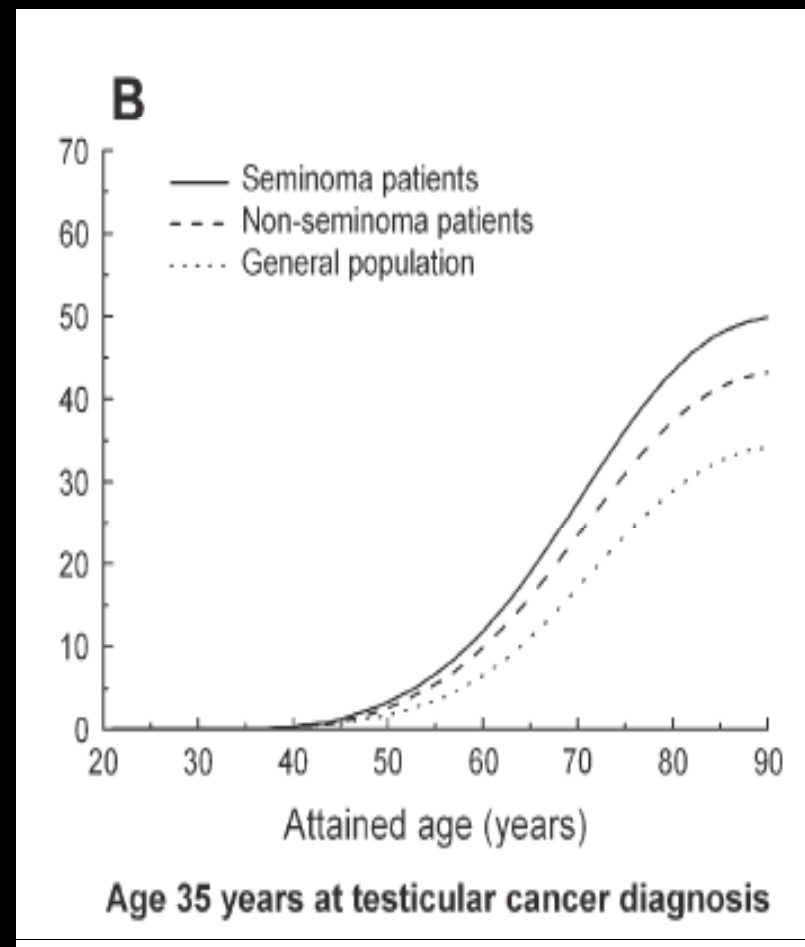
- Management Options
  - Surveillance
  - Adjuvant Radiation Therapy
  - Adjuvant Chemotherapy
- ~100% cure with all strategies
  - Key issue for oncologists is
    - Reduce overall “Burden of Treatment” while maintaining excellent results

# 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 2<sup>nd</sup> Solid Tumour at age 75 36% vs 23% in general population

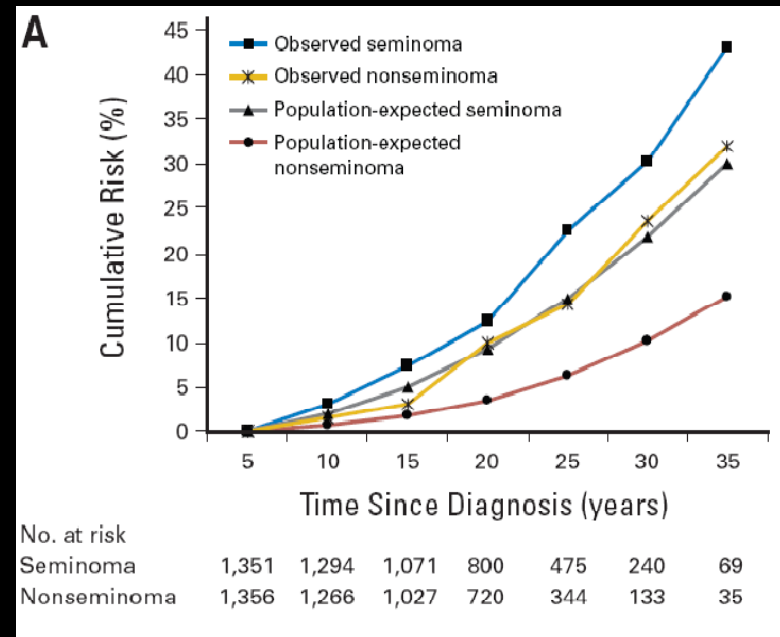


# Second Malignancy after RT for Seminoma

- Dutch population based study
  - 2707 Testicular Cancer survivors
  - Median Follow-up 17.6 years
  - 2<sup>nd</sup> 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 2<sup>nd</sup> malignancy diagnosis was 1.4 years
  - 5 year survival was 41%
- 2<sup>nd</sup> 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

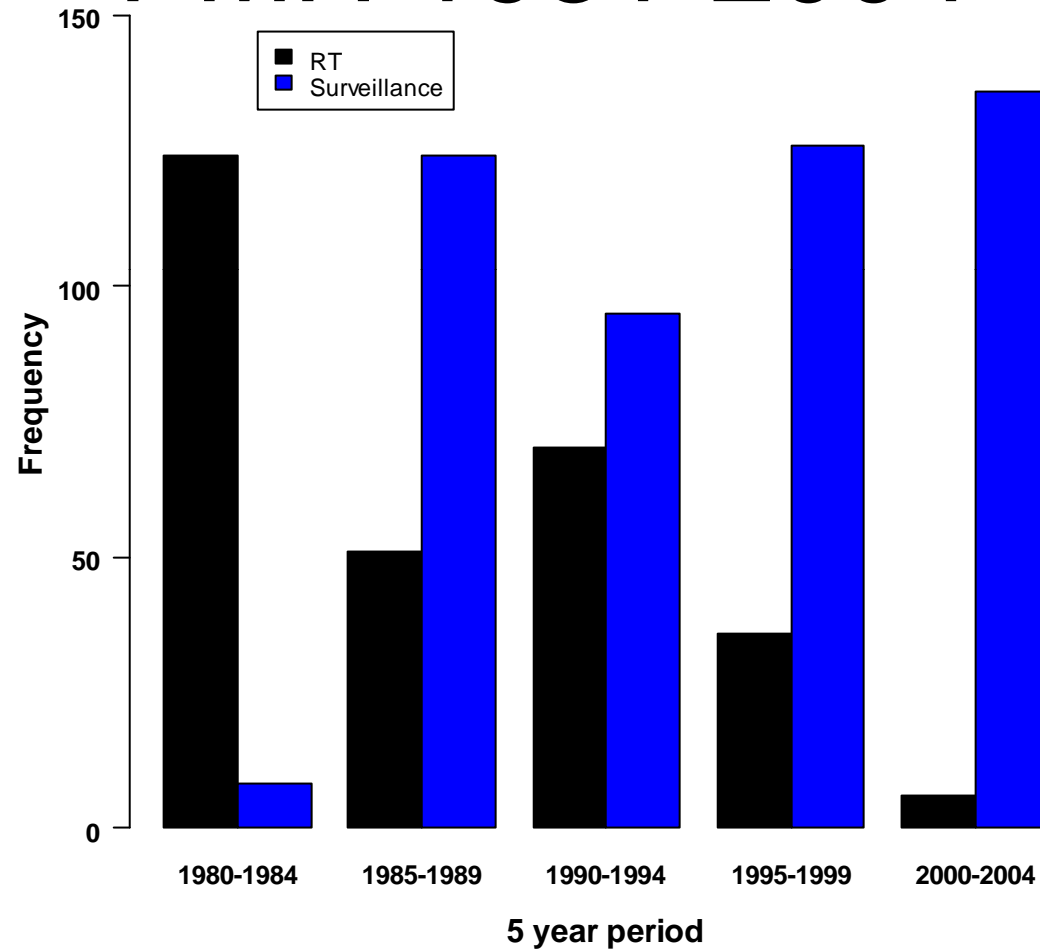
Daugaard et al APMIS 111:76-85, 2003

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



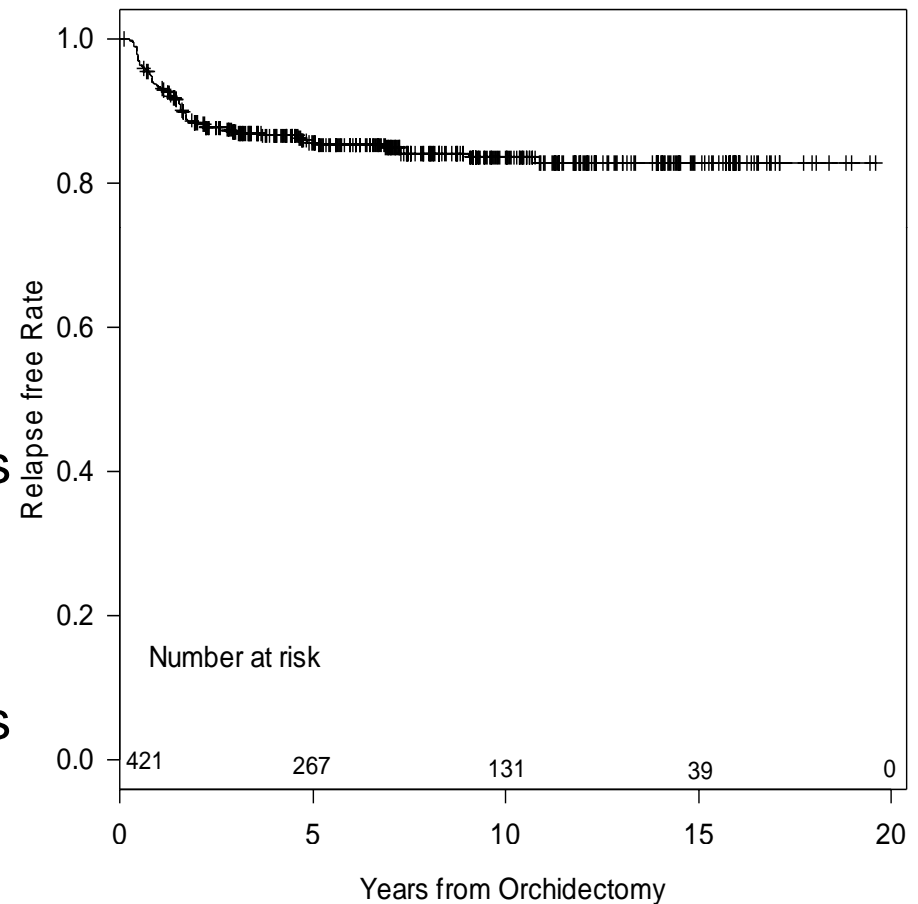
# Stage I Seminoma PMH 1981-2004

|                         | Surveillance | Adjuvant RT |
|-------------------------|--------------|-------------|
| Median Age              | 35           | 34          |
| Median Tumour<br>Size   | 3.5 cm       | 4.5 cm      |
| Rete Testis<br>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

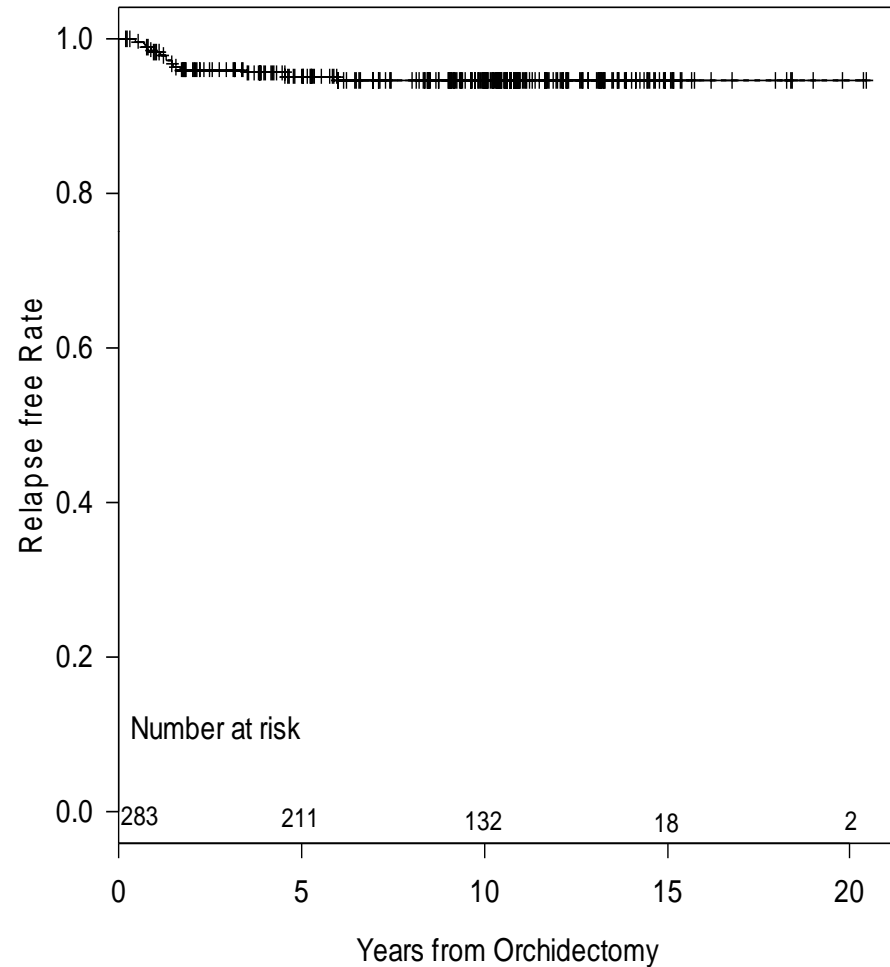
## PMH 1981-2004

- 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<br>Risk of<br>Requiring<br>Chemotherapy | 4.6%         | 3.9%      |
| Number of pts<br>avoiding any<br>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<br>2 courses       | 107      | 74              | 0             | -             |
| Steiner<br>2 courses      | 108      | 60              | 1.85          | PA            |
| Aparico<br>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

1447 pts  
Stage I  
Seminoma

30 Gy Paraaortic  
nodes only

Carboplatin  
1 course

RT (Para-aortics alone) – 4.1% relapse

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

# Adjuvant Chemotherapy

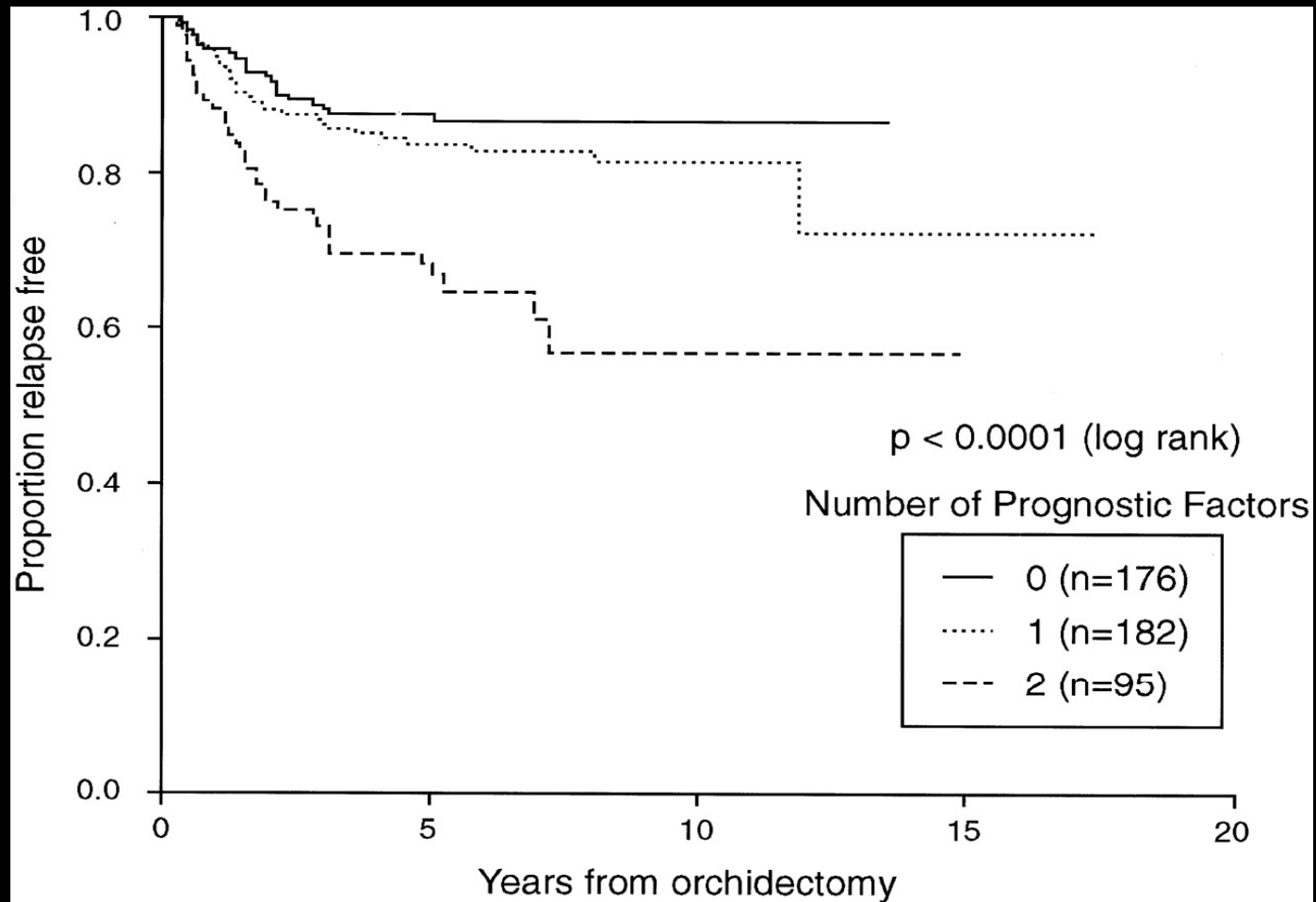
- However 1 Course Carboplatin
  - At best reduces relapse rate from 15% to 5%
  - Unnecessary treatment in 85% cases
  - Late Relapse in seminoma is well recognised
    - Short Median Follow-up in MRC trial

**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

# Acknowledgements

- Radiation Medicine
  - Gillian Thomas
  - Mary Gospodarowicz
  - Nigel Hawkins
  - Alisdair Munro
  - Charles Catton
  - Andrew Bayley
  - Mike Milosevic
  - Peter Chung
  - Betty Tew-George
- Medical Oncology
  - Jeremy Sturgeon
  - Malcolm Moore
  - David Hogg
- Urology
  - Michael Jewett
  - Neil Fleshner
- Biostatistics
  - Tony Panzarella
  - Anthea Lau
  - Mary Madunic/Carol Noble
- Pathology
  - Diponkar Banarjee
  - Hugh Richmond
  - Linda Sugar
  - Joan Sweet
  - Andrew Evans
  - William Chapman

-