National Cancer Centre Singapore
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SingHealth DUKE NUS ACADEMIC MEDICAL CENTRE
ONCOLOGY

# What is the treatment of a sarcoma arising in a teratoma?

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# Disclosure slide

- Research and education funding
  - Novartis, Bayer, JNJ, Pfizer
- Consulting or advisory role
  - Novartis, Merck
- Travel Grants
  - Novartis, Roche

# Definitions

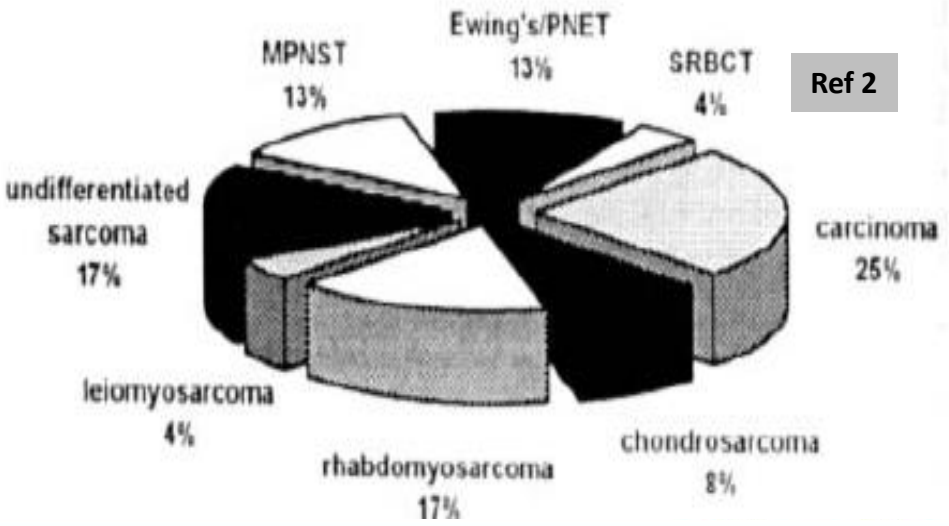
- Mature teratoma displays fully differentiated somatic elements such as hair, teeth, cartilage
- 3-9% of germ cell tumors undergo malignant transformation [1,2]
- This observation first reported by Waldeyer in 1868 where he noted sarcomatous elements in a pt with testicular teratoma[3]
- Included into the WHO classification in 1977

1 J Urol. 2014;192:1403-1409
2 J Urol. 1998;159:859-863
3 Surg,, Gynec. & Obst. 1911;12:230

# Epidemiology

- Malignant transformation comprise of diverse histologies
- Approx 50% of cases belong to sarcoma family
- The most common sarcoma histologies are
  - Rhabdomyosarcoma
  - Ewing's/ primitive neuroectodermal tumor (PNET) family

| Histology [1] | N=121 (%) |
|---|---|
| Sarcoma | 59 (48.8) |
| Carcinoma | 31 (25.6) |
| Sarcomatoid yolk sac tumor | 17 (14) |
| Nephroblastoma | 4 (3.3) |
| Mixed | 3 (2.5) |
| Others | 7 (5.8) |



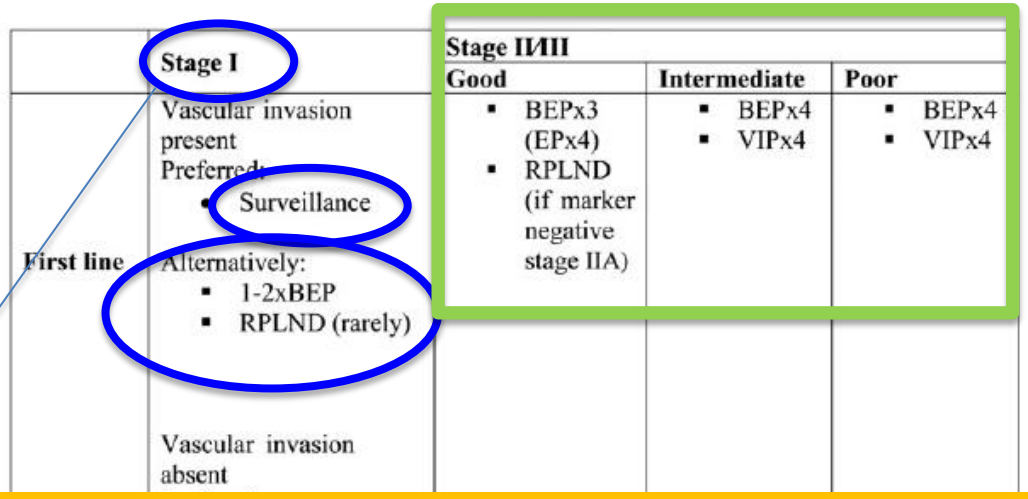

Ref 2



1 Rice et al. J Urol. 2014;192:1403-1409

2 J Urol. 1998;159:859-863

# ESMO guidelines for management of Non seminomatous Germ Cell Tumor (NSGCT)



| | Stage I | Stage IИII | | |
|---|---|---|---|---|
| | | Good | Intermediate | Poor |
| First line | Vascular invasion present<br>Preferred:<br>▪ Surveillance<br>Alternatively:<br>▪ 1-2xBEP<br>▪ RPLND (rarely) | ▪ BEPx3 (EPx4)<br>▪ RPLND (if marker negative stage IIA) | ▪ BEPx4<br>▪ VIPx4 | ▪ BEPx4<br>▪ VIPx4 |
| | Vascular invasion absent | | | |

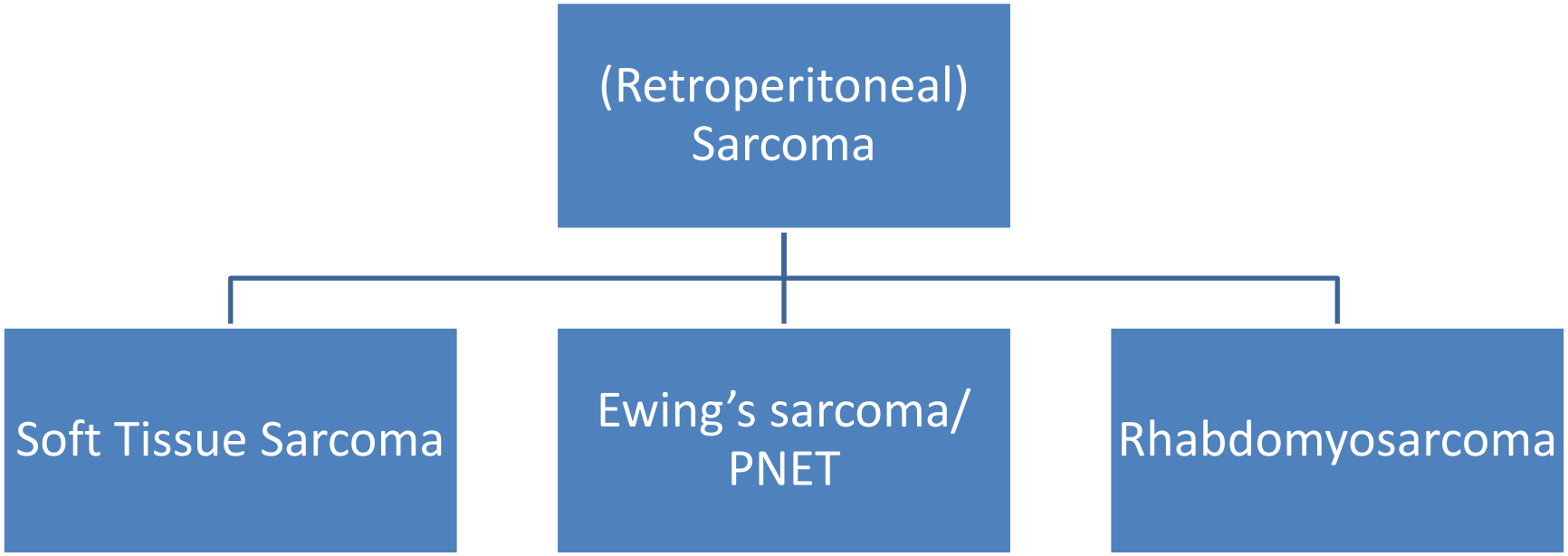
In patients with teratoma and somatic transformation some experts consider nerve-sparing RPLND the preferred treatment

## High Cure rates

- Stage 1 => 98%
- In men with disseminated disease
  - Complete remission rates 70% with cisplatin based chemo
  - Cure rates of 70-80%


Ann of Oncol. 2013;24 (Supplement 6):vi125–vi132

# Treatment Paradigm for Management of Retroperitoneal Sarcoma



# Treatment Paradigm for Management of Sarcoma

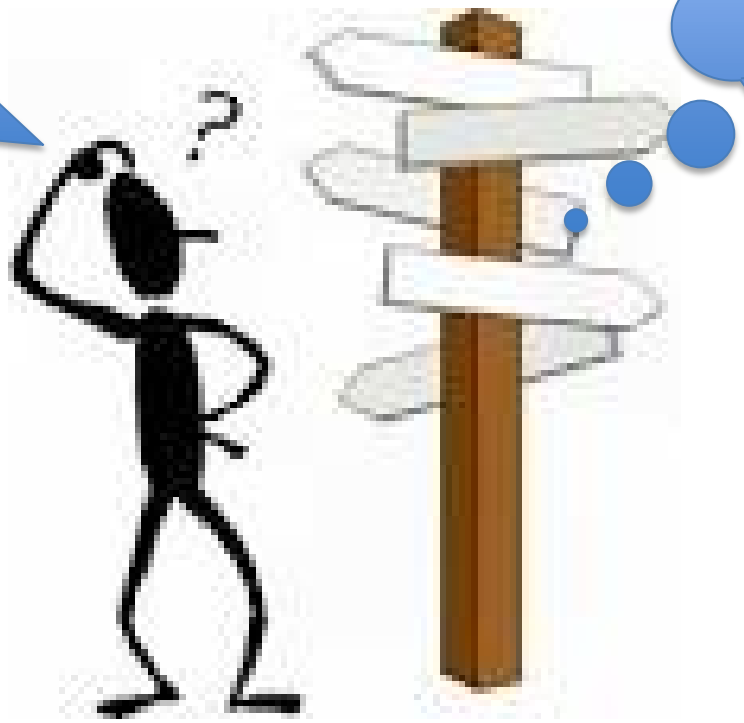
- Retroperitoneal soft tissue sarcoma [1]
  - Oncological surgery with negative margins
  - Adjuvant radiation of limited benefit
  - Adjuvant chemotherapy controversial

- Ewing's sarcoma/ Primitive neuroectodermal tumor (PNET) [2,3,4]
  - Multimodality approach
  - Extended duration of systemic chemotherapy (9-12 months)
  - Combination chemo typically comprising of
    - Cyclophosphamide
    - Doxorubicin (or dactinomycin)
    - Vincristine
    - Ifosfamide
    - Etoposide
  - 14 cycles
  - Interval compression for localized disease

1 Ann Oncology. 2014;25 (Supplement 3):iii102–iii112
2 N Engl J Med 2003;348:694-701
3 J Clin Oncol. 2012;30:4148-4154
4 J Clin Oncol 2009;27:5182-8 (COG D9803)

# Treatment of a Sarcoma arising from a Teratoma

Manage as for Sarcoma



Treat like a Teratoma?

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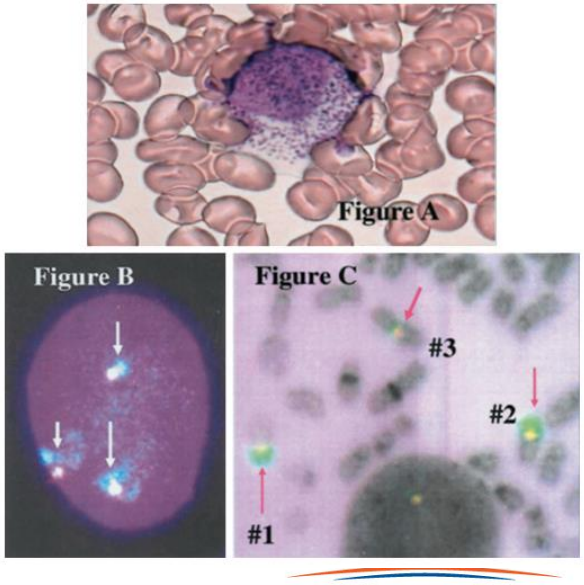
# Genetics of Transformed Histology

- What is the molecular identity of the transformed tumor?
- Is this still a germ cell tumor (GCT)?
- Isochromosome 12p (i12p) is a specific biomaker in GCT
- Clonality with GCT demonstrated with presence i(12p) or extra copies of chromosome 12p
  - 11/ 12 pts (92%) [1]
  - 5/5 samples studied (100%) [2]





1 J Urol. 1998;159(1):133-138
2 J Clin Oncol. 2003;21:4285-4291

# Genetics of Transformed Histology

- N=12 tumors[1]
- In addition to finding of i(12p) in 11 pts, **4 pts** had chromosomal abnormalities associated with somatic malignancies
  - 2 RMS: rearrangement 2q
  - 1 PNET: rearrangement 11q24
  - 1 Leukemia: del5q
- Transformed histologies thus have molecular features of **BOTH** GCT (i12p) and somatic malignancy

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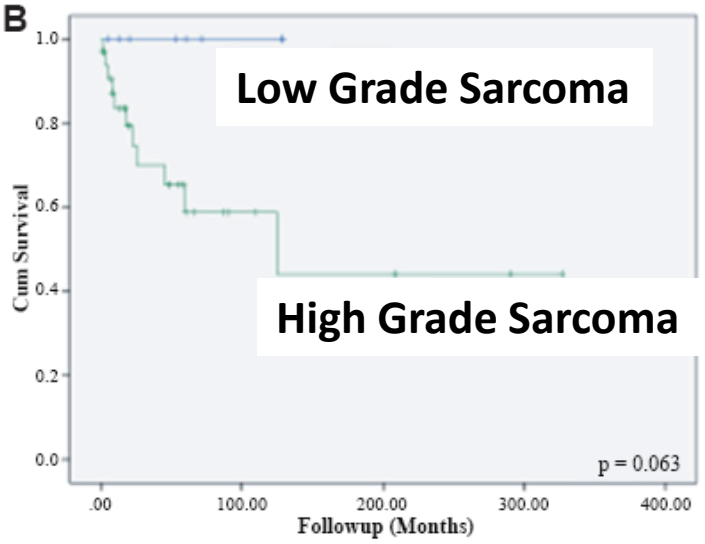
1 J Urol. 1998;159(1):133-138

# Prognostic factors of somatic malignancies arising from teratoma

- Adverse prognostic factors unclear

- Necchi et al (n=48) [1]
  - Stage 3 disease at malignant transformation
  - Incomplete surgical removal
  - PNET and adenocarcinoma histologies

- Rice at al (n=121) [2]
  - Tumor grade (univariate analysis)
  - Tumor grade in sarcoma (p=0.063)




BJU Int. 2011;107(7):1088-1094
J Urol. 2014;192:1403-1409

# Clinical Outcomes with GCT-type chemotherapy

- BEP (bleomycin/ etoposide/ cisplatin) is standard treatment in Germ cell tumor (GCT)
- Clinical CR rates to initial cisplatin based chemo in pts with transformed histology 12 – 30% vs 70% which is expected in GCT [1,2]
- Another 38% rendered CR after post-chemo surgery [2]
- 5 year median survival 64% [1]

1 J Urol. 2014;192:1403-1409
2 J Urol. 1998;159(1):133-138

# Malignant transformed (MT) histology directed chemotherapy

- Small study of 10 pts with measurable disease
- 5 with sarcoma

| | | Chemotherapy | Response | RT | Surgery | Duration of response | Status |
|---|---|---|---|---|---|---|---|
| 1 | **PNET** | P6 | **PR** | Yes | No | 8+ mth | Alive |
| 2 | **RMS** | Modified P6 | **PR** | No | Yes | 1+mths | Alive |
| 3 | **RMS** | VIP<br>Paclitaxel | **PR** | No | Yes | 1+ yr | Alive |
| 4 | **RMS** | EP => Ifos<br>MAID | **PR** | No | Yes | 7yrs | Dead |
| 5 | **RMS** | CAV | NR | Yes | Yes | 1yr 5mth | Dead |



J Clin Oncol. 2003;21:4285-4291

# Outcome of Transformed Teratoma to Primitive Neuroectodermal Tumor (PNET)

- Some studies suggest that PNET should be managed differently
- Cohort of 76 teratoma pts with PNET at initial diagnosis
- 26pts had primary retroperitoneal lymph node dissection (RPLND)
- 50pts had initial chemo for disseminated disease
- Median follow-up 38mth (4 - 235mth)

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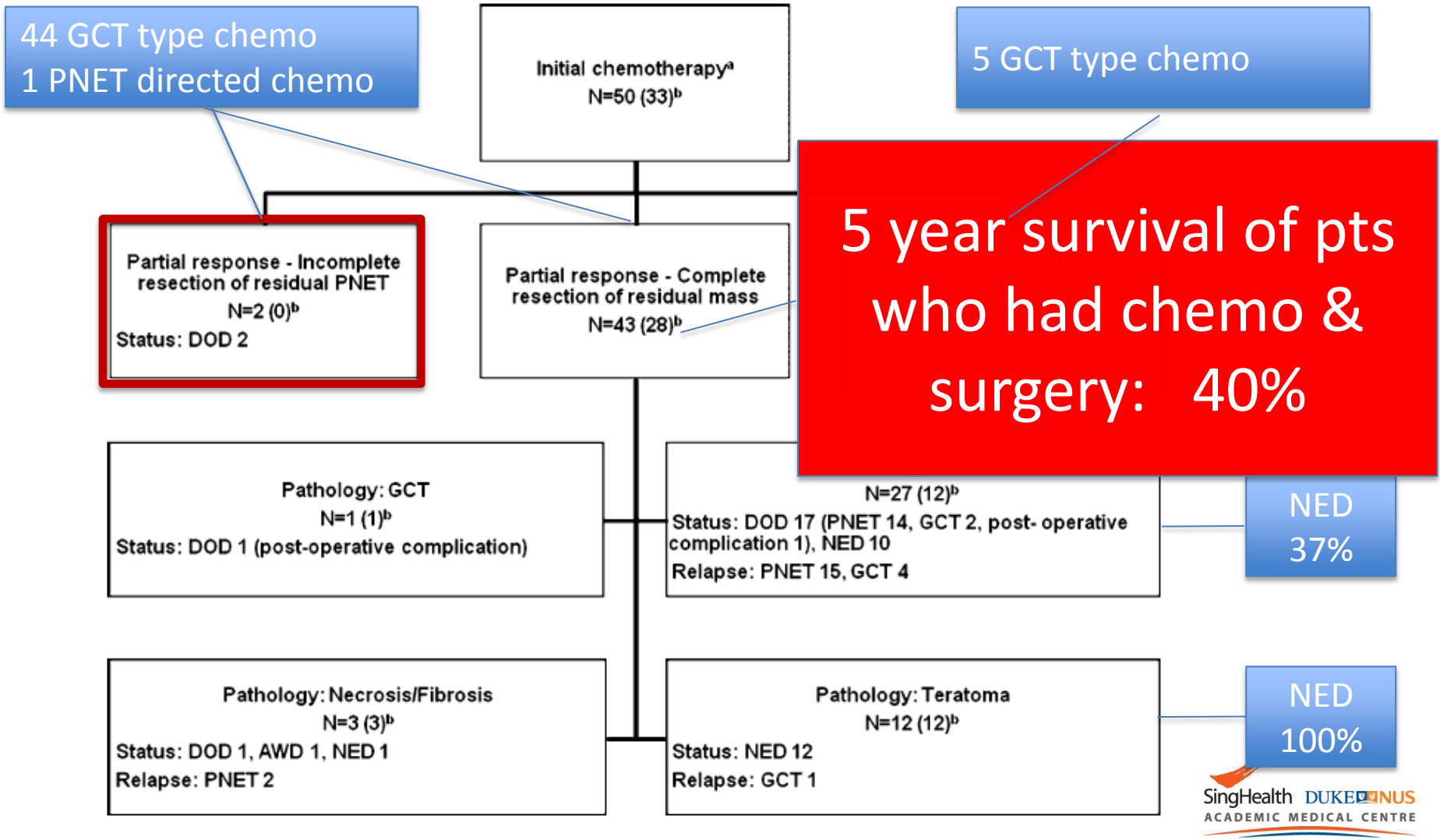
Ann Oncol. 2010;21(9): 1846–1850

# PNET pts treated with initial chemotherapy



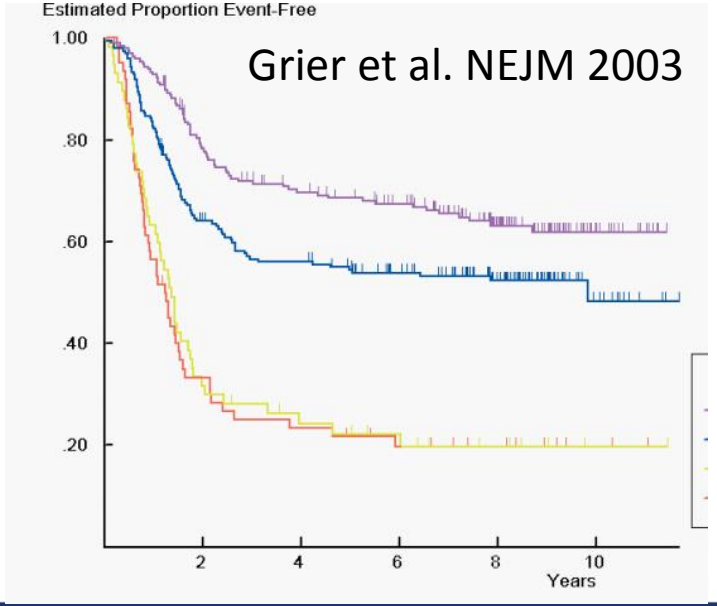


Ann Oncol. 2010;21(9): 1846–1850

# PNET pts treated with initial chemotherapy

- CAV/IE chemo given to 10pts with advanced disease
- 8 had prior platinum chemotherapy
- 8 achieved a response to CAV/IE
  - NED = 1
  - Alive with disease = 4 (21 – 73mths)
  - All alive underwent surgery following chemo
  - Some had multiple surgeries

- Grier et al
  - Non metastatic pts 5yr EFS 69%
  - Metastatic pts 5yr EFS 54%





Ann Oncol. 2010;21(9): 1846–1850
N Engl J Med 2003;348:694-701

# Summary (I)

- So, how do we treat sarcoma arising from a teratoma?
- No standard guidelines exist
- Prognosis is poorer as compared to pts with GCT alone
- Treatment is controversial
  - Multimodality treatment is likely to be important
  - Surgery still an important aspect of treatment
  - Optimal chemotherapy is uncertain

# Summary (II)

- While some experts advocat use of histology driven therapies, the benefit is unclear

- In view of poor outcomes with cisplatin based chemo, one may argue that it is not unreasonable to adopt a histology based approach. Having said that, prospective data in support of this argument is lacking

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# Thank you

# Etiology of Germ Cell Tumor with Malignant Transformation

- Etiogenesis
  1. Malignant transformation of the pleuripotential teratoma
  2. Development of the pleuripotential teratoma into somatic type malignancy

- Unlikely to be chemotherapy induced secondary cancers[1]
  1. High proportion of cases are associated with teratoma
  2. Occur de novo


J Urol. 1998;159:859-863