Managing the most common tumors affecting young adults
Peculiarities, controversies, and clinical research

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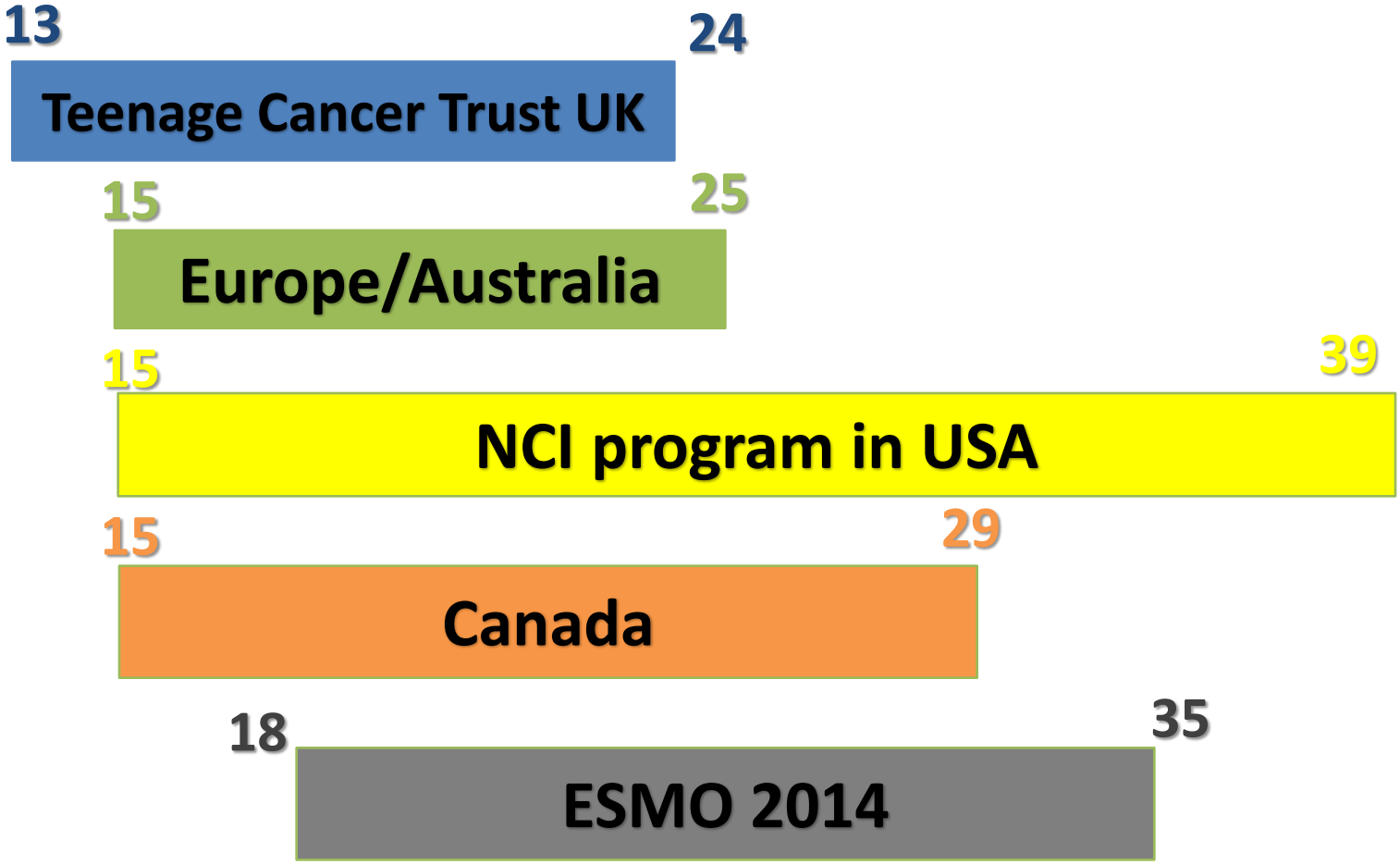
Young adults in oncology



Young adults in oncology

- WHO definition of adolescence 10-19 years, post adolescence 20-25 years
- What definition of YA in oncology?
  - Physical? Psychological?
  - Legal ? Social?
  - Type of tumours?
- ***Flexible time of adolescence*** **(Ian Lewis), so flexible time of adulthood?**

Adolescents and Young Adults share

- Psychosocial peculiarities
- Specific needs
- Survival challenges

Psychosocial peculiarities

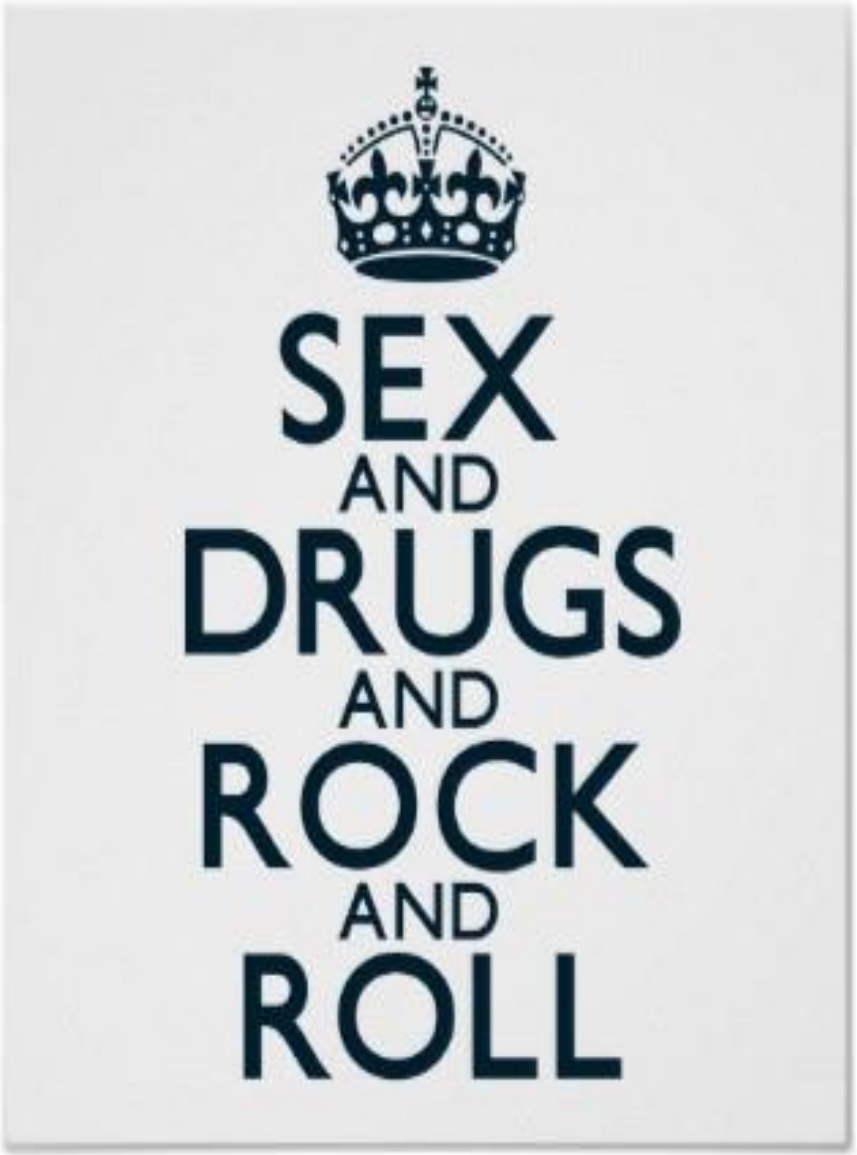
- (A)YA issues = key developmental tasks
  - Autonomy from parents
  - Personal set of values and identity
  - Strong peer relationships
  - Intimate and sexual relationships
  - Education
  - Joining workforce

Psychosocial peculiarities of young adults

- Reinforced by the concept of *emerging adulthood*
  - Protracted time of identity development and egocentrism
  - Roughly between 18-30 years

Psychosocial peculiarities

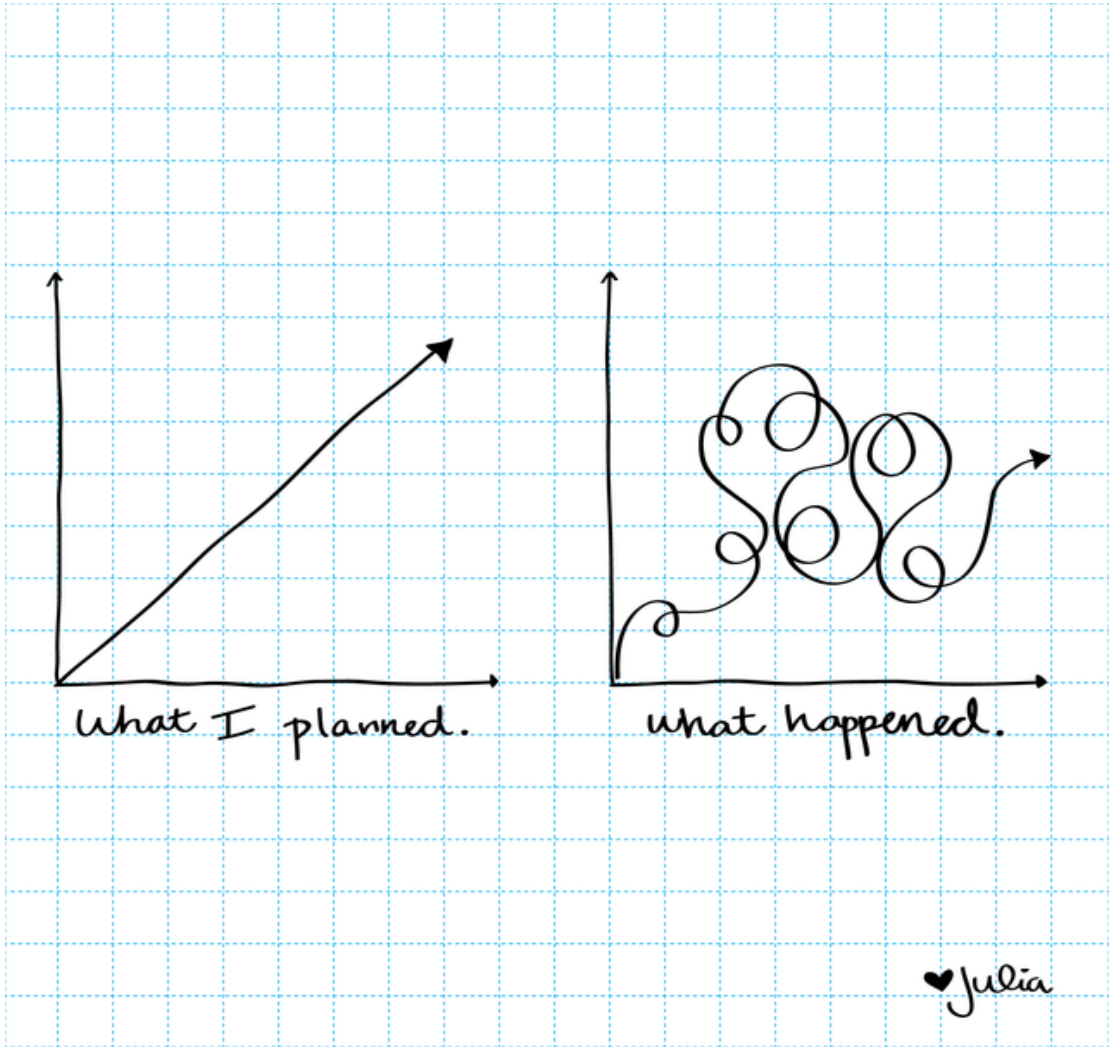
- A young adult can be
  - A child
  - A parent
  - A worker
  - Unemployed
  - A student
  - A friend
  - A spouse, a partner
  - A junkie, a rocker, a geek, a soldier….



Not a definition but a cornerstone for reflexion….

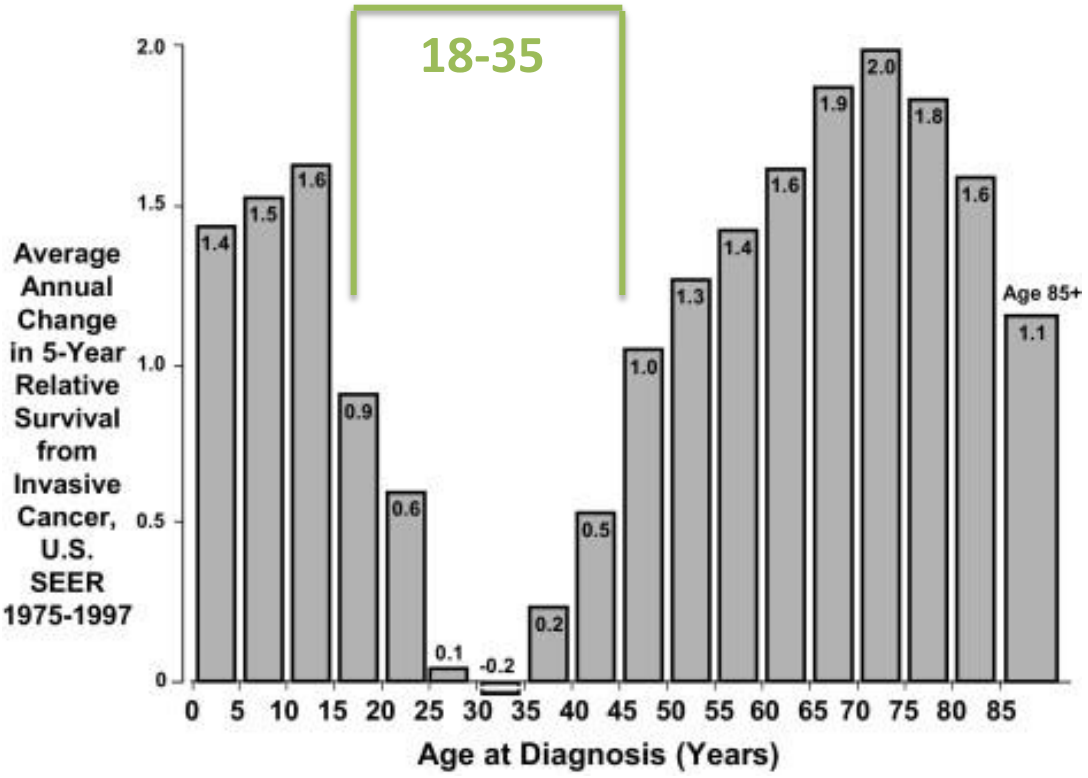
Specific impact of cancer for YA

- Challenge sense of self-esteem and loss of control
- Increased dependence on parents and decreased peer contact
- Challenge on education and work
- Body-image changes
- Challenge on compliance
- Potential impact on fertility
- Place of care and quality of health insurance



The (A)YA cancer journey…..

Lack of cancer survival improvement

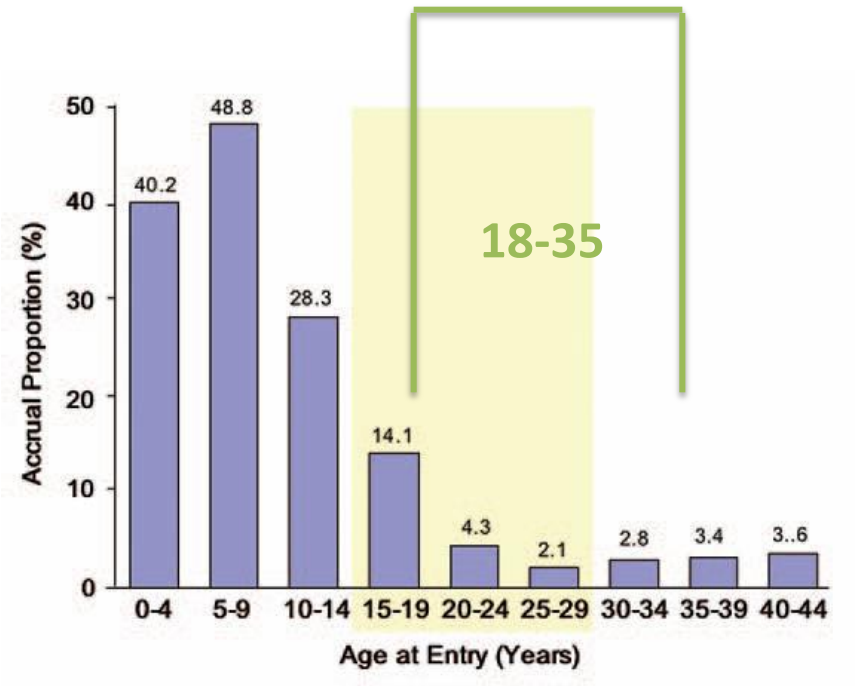


Albritton and al, Seminars in Oncol, 2009

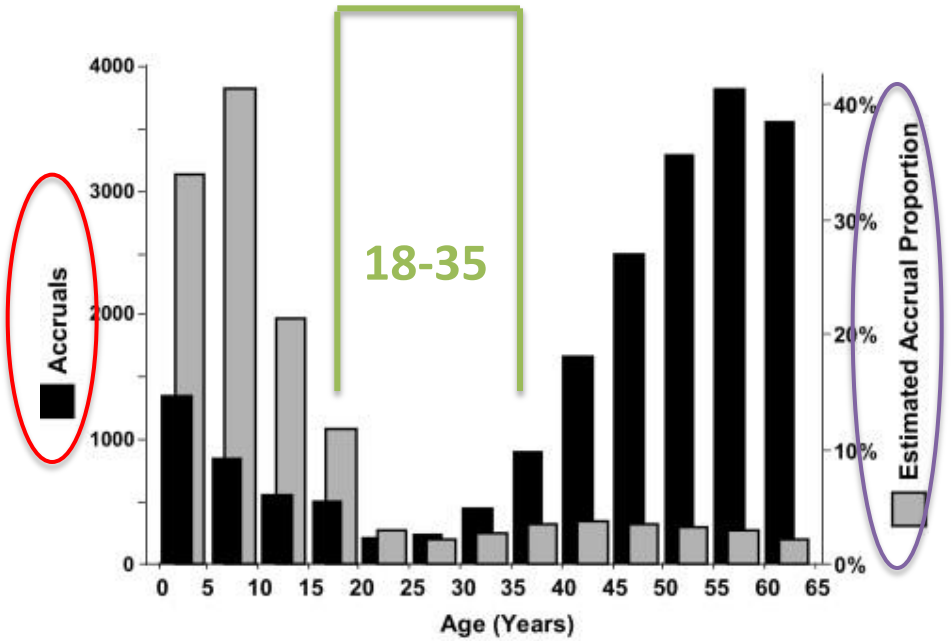
Why this lack of survival improvement ?

- Lack of inclusions in clinical trials?
- Type of treatment?
- Tumour biology?
- Patient biology?
- Compliance?
- Complex pathways of diagnosis and place of care?

Lack of accrual in clinical trial-US data



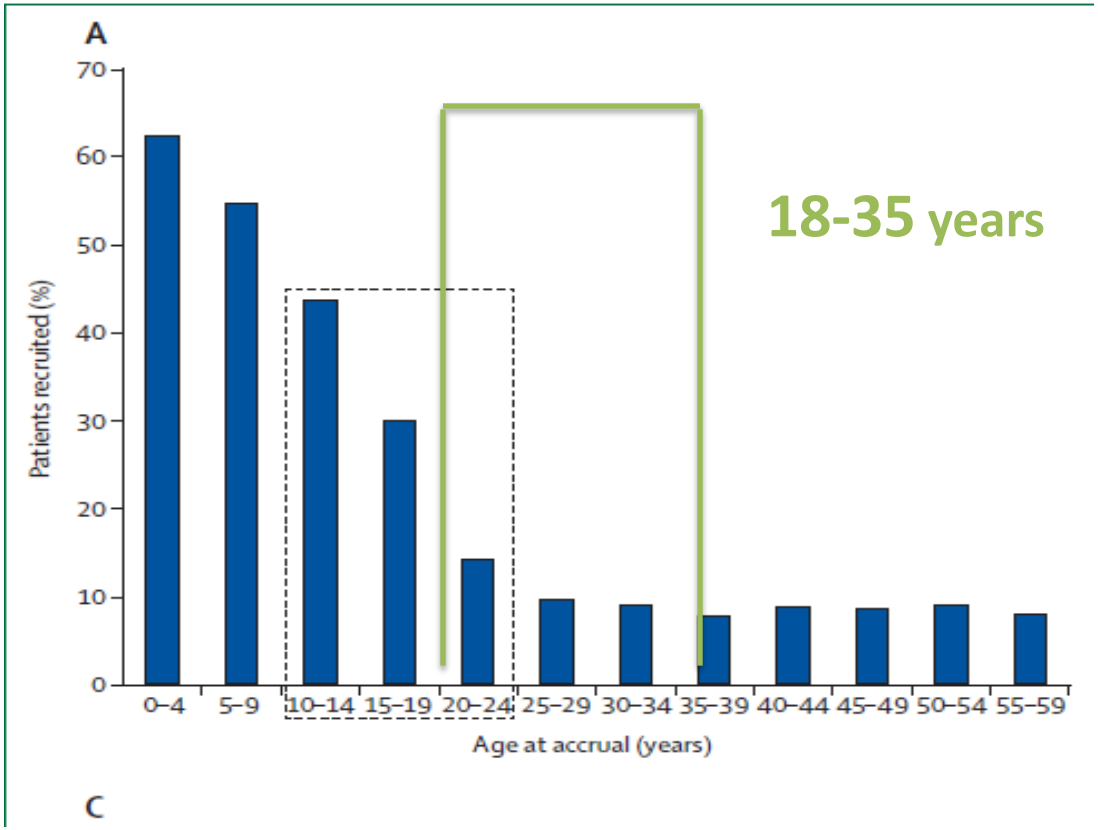
Estimated Proportion **of Newly Diagnosed Cancer Patients accrued to National Treatment Trials**, 1997 to 2003-SEER



Accrual to NCI Therapy Evaluation Program treatment trials by age at entry, 2001–2006-SEER

Bleyer , CA Cancer J Clin 2007, Albritton, et al, Seminars Oncol, 2009

Lack of accrual in clinical trial-UK data



Newly diagnosed cancer patients entered in NCRN and CCLG **lymphoma, leukemia, CNS, bone sarcoma, and male germ cell tumor phase III trials, 2005– 2008.**

Fern et al, Lancet Oncol, 2014

(A)YA clinical trial gap : why?

- Age criteria?
  - Rhabdomyosarcoma
    - RMS-05 : inclusion < 21 years
  - Medulloblastoma
    - High risk PNET5-HR : < 20 ans
    - Standard risk : next PNET-4 < 21 years
- Issues of overlapping age criteria for rare disease
  - Standard risk medulloblastoma in France

(A)YA clinical trial gap : why?

- Healthcare providers barriers?
  - Perception of poor compliance to complex protocols
  - Avoidance of adding the burden of a trial to a YA struggling with cancer
  - Lack of information on trial availibilities
  - Reluctance to spend time with a young people AND his/her family, partner, etc….
- Promoters barriers?
- Regulatory issues?

Pentheroudakis et al, Annal Oncol 2005, Fern et al , Lancet Oncol 2014

Improving participation of AYAs in clinical trials
the 5 As

- Trials should be
  - Available
  - Accessible
  - Appropriate
  - Acceptable
  - with Awareness of professionnals and patients

Fern et al , Lancet Oncol 2014

Type of treatment?
Localized STS in adults
ESMO Clinical Practice Guidelines

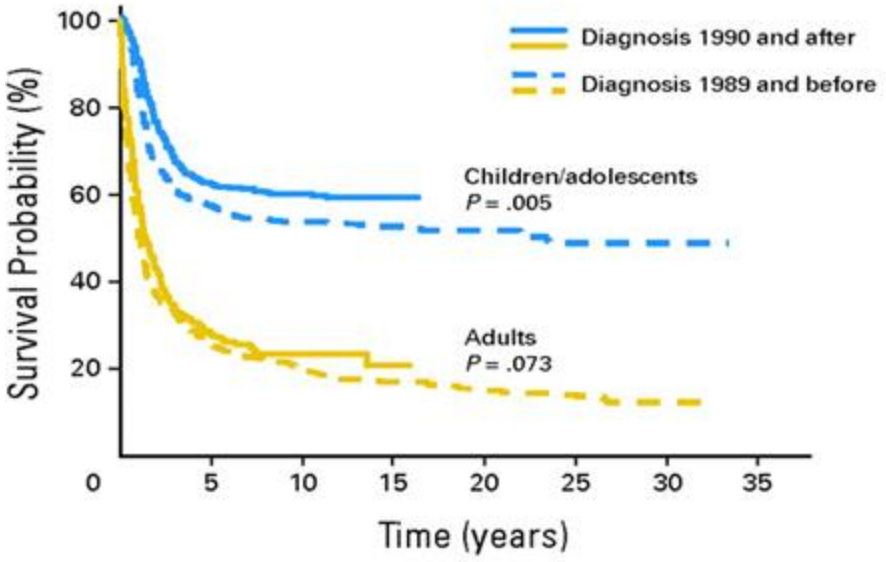
- **Surgery is the standard treatment: wide excision with negative margins (R0)**
- Re-operation in reference centers be considered in case of R1 initial resection if adequate margins can be achieved w/o major morbidity
- Re-operation in reference centers mandatory in case of R2 initial resection
- RTE is not given in the case of compartimental complete resection of a tumor contained within the compartiment
- **RTE is given as standard treatment after the wide excision of any high grade (G2-G3), deep**
- For all other cases, multidisciplinary discussion for adjuvant decision
- Anatomic site, histotype, and expected sequelae to be balanced

▸Adjuvant RT improves local control, but not overall survival

▸Adjuvant CT do not revise a non optimal initial surgery; option in high-risk patients (high-grade, >5 cm, deep tumor) with chemosensitive tumors; based on anthracyclines regimen

Type of treatment? Rhabdomyosarcomas

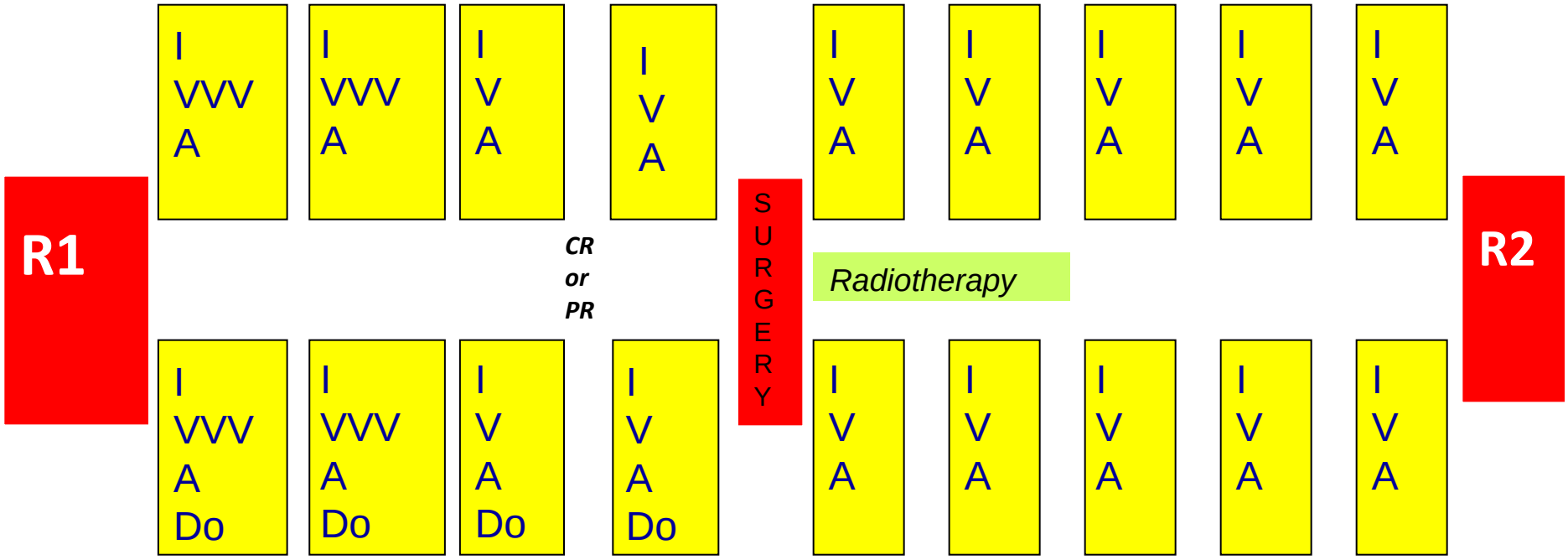
- Outcomes worse in young adults
  - More alveolar subtypes in YA
  - More advanced disease in GU tract, extremities and trunk



Comparing Adult and Pediatric Rhabdomyosarcoma in the SEER Program, 1973 to 2005: Analysis of 2600 Patients *5-years EFS 27 % in adults > 19 years vs 61 % in children/adolescents*, p 0.0001

Soliman et al, Seminars Oncol, 2009, Sultan et al, JCO 2009

Type of treatment?
RMS 05 trial < 21 years



1st phase IVADo versus IVA randomisation closed in 2014
No benefit of doxorubicin in addition to IVA

SIOP 2014, by permission of Dr D. ORBACH

Type of treatment? Rhabdomyosarcomas

- Currently 70 % of children cured with multidisciplinary approach including chemotherapy

- Retrospective study of 171 adults > 18 years pts in a single institution
  - 5 years overall survival 40 % in adults
  - Pts whose treatment adhered to current guidelines for children had similar outcome than children

Ferrari A et al, Cancer 2003

Type of treatment? Rhabdomyosarcomas

- Treatment
  - adopted from pediatric programs?
  - tailored for adults ?
  - Prospective trial including children adolescents AND adults

RMS in young adults
Type or treatment ..or biology?

- New somatic mutation in *MYOD1* defines a clinically aggressive subset of embryonal RMS
  - Spindle cells histology
  - In AYA ; median age 25 years(4-41 yrs)
  - Female
  - Head or neck primary site
  - Advanced stage
  - Poor prognosis identical to alveolar subtype

Kohsaka et al, Nature Genetics, 2014

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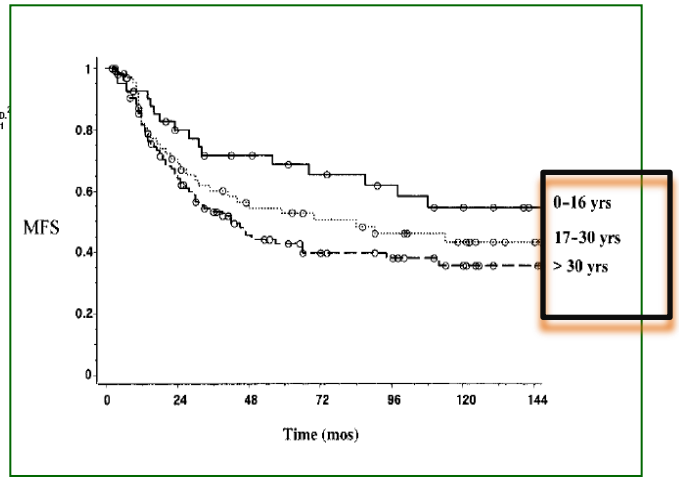
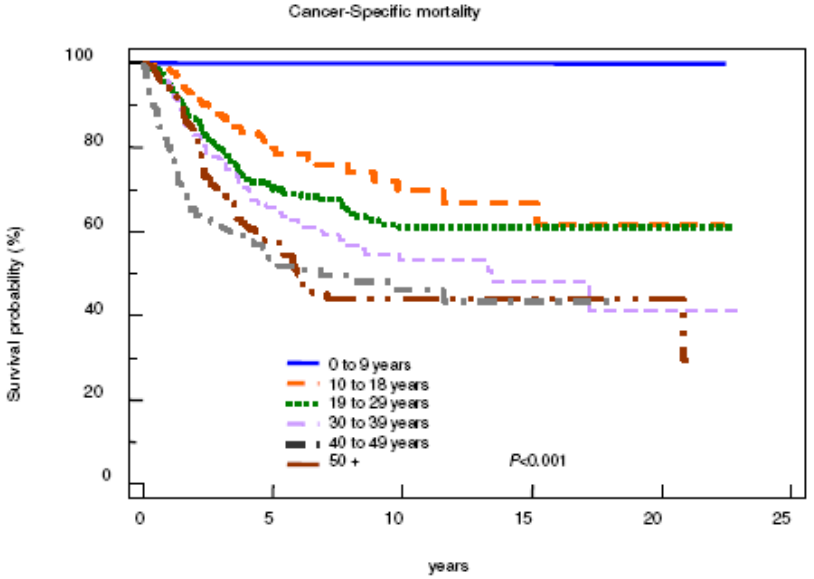
Type or treatment ..or biology?
Synovial Sarcomas

Synovial Sarcoma: A Retrospective Analysis of 271 Patients of All Ages Treated at a Single Institution

Andrea Ferrari, M.D.[1]
Alessandro Gronchi, M.D.[1]
Michela Casanova, M.D.[1]
Cristina Meazza, M.D.[1]
Lorenza Gandola, M.D.[3]
Paola Collini, M.D.[4]
Laura Lozza, M.D.[3]
Rossella Bertulli, M.D.[3]
Patrizia Olmi, M.D.[3]
Paolo G. Casali, M.D.[5]



Cancer 2004



Comparing Children and Adults With Synovial Sarcoma in the Surveillance, Epidemiology, and End Results Program, 1983 to 2005

An Analysis of 1268 Patients

Iyad Sultan, MD[1]; Carlos Rodriguez-Galindo, MD[2]; Raya Saab, MD[3]; Sameer Yasir, MD[4]; Michela Casanova, MD[5]; and Andrea Ferrari, MD[5]

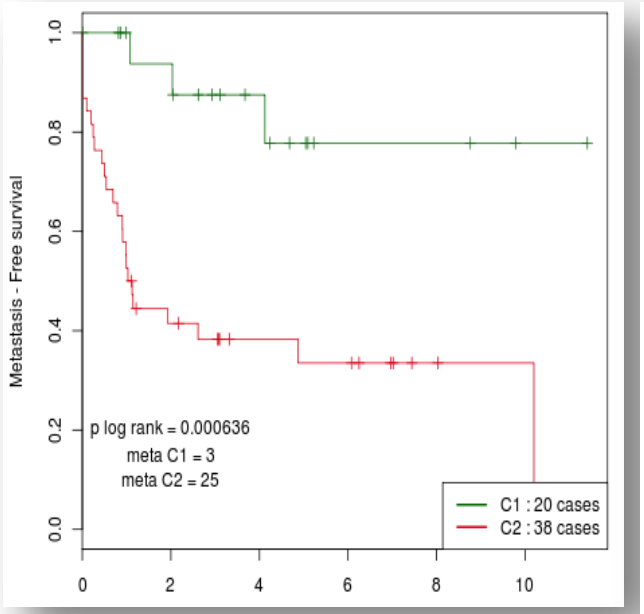
Synovial Sarcomas

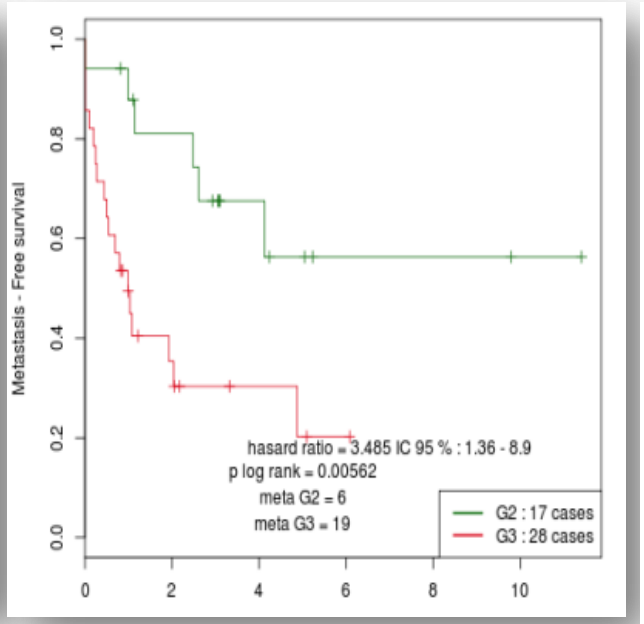
- Pediatric/adult patients share presentation, histology and translocations, chemosensitivity and prognostic factors
- For adults, decision based on FNCLCC grading
  - Surgery+/- RTE for local treatment
  - **CT in selected high risk patients based on IFO-DOXO regimen**
- For pediatricians, synovial sarcoma as a **chemosensitive tumor « RMS like »,** treatment designed with systemic therapy especially in Europe
- Biological features to explain survival differences?

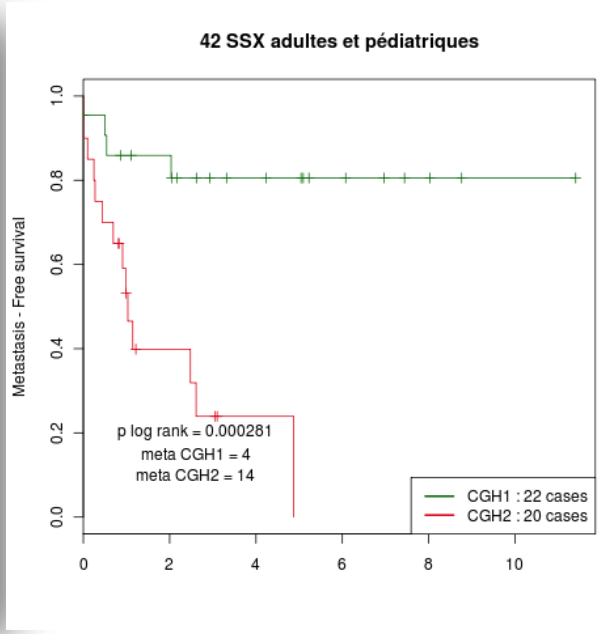
▸ CINSARC (Complexity Index in Sarcoma)

▸ Genomic Index (nb and type of chromosomal alterations)

Chromosome Instability Accounts for Reverse Metastatic Outcomes of Pediatric and Adult Synovial Sarcomas







CINSARC(C1,C2) **FNCLCC grade (G2,G3)** **Genomic index (CGH1,CGH2)**

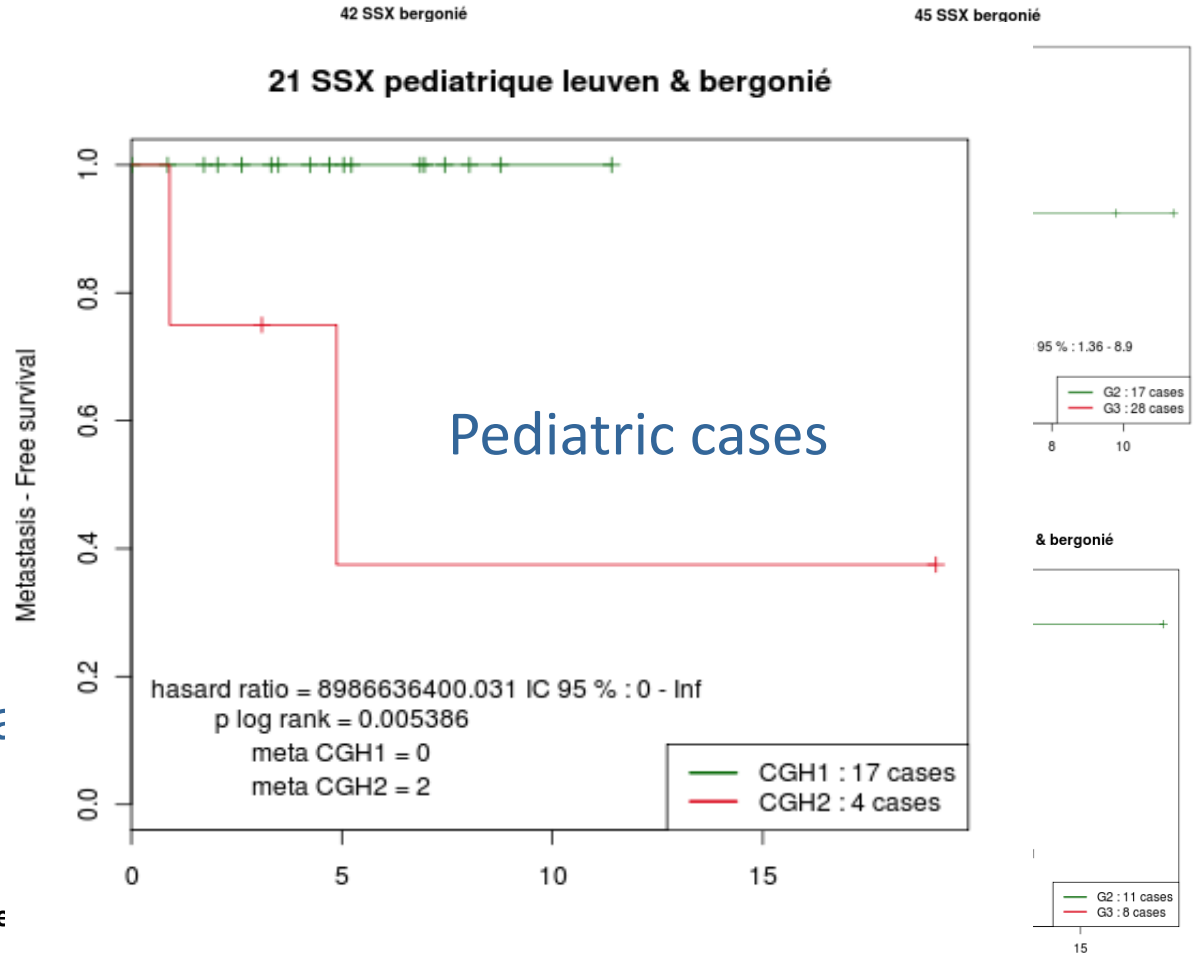
CINSARC and Genomic Index : significant prognostic factors independent from FNCLCC grade

Lagarde et al, JCO, 2013

Pediatric SS don’t metastazise unless there genomic profile is rearranged

All cases

Pediatric ca



Pediatric cases

FNLCC grading

No controversies on treatment Ewing sarcomas

- Peak incidence in 15-25 years patients
- Controversial evidences age as an independant prognostic factor
- COG studies includes patients < 40-50 years
- EuroEwing studies include patients from 1 year to 50 years
  - Some toxicities decrease with age → less treatment? different biology?

Wilhelm et al, Annals Oncol, 2014

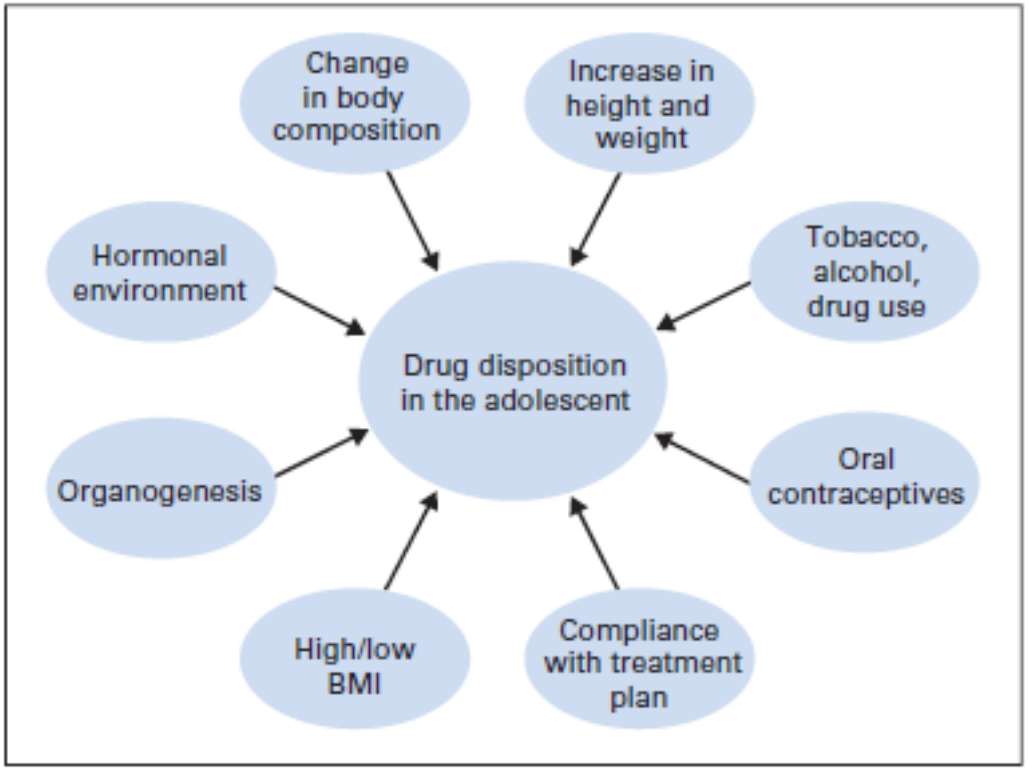
Type of treatment or biology? Osteosarcomas

- EURAMOS study until 40 years
- French study common in children, adolescents and adults from 5 to 50 years with Zoledronic acid randomisation
  - High dose Methotrexate based <18 years
  - Anthracycline, ifosfamide, and cisplatinum based > 25 years
  - Stratification by center for 18-25 years patients between high dose MTX and anthracycline based regimen
  - Common biological prospective studies+++++

Patient biology?
Specific pharmacology?

Age and drug clearance relation

- for dexamethasone, etoposide, methotrexate
- no for temozolomide, topotecan
- uncertain for vincristine and etoposide



Veal et al, JCO 2010

YA specificity and type of treatment? Breast cancer in young adults

- Fertility concerns survey
  - 68 % discussed fertility issues
  - 51 % were concerned about infertility
  - 10 % use fertility preservation strategies
  - Affected treatment decision in 26 % of pts
    - 1 % decline adjuvant CT
    - 2 % chose one regimen over another
    - 1 % considered not receiving endocrine therapy
    - 3 % decline adjuvant endocrine therapy
    - 11 % considered endocrine therapy < 5 years
    - 5 % underwent mastectomies

Ruddy et al, JCO, 2014

Pathways of diagnosis? Breast cancer

N=585

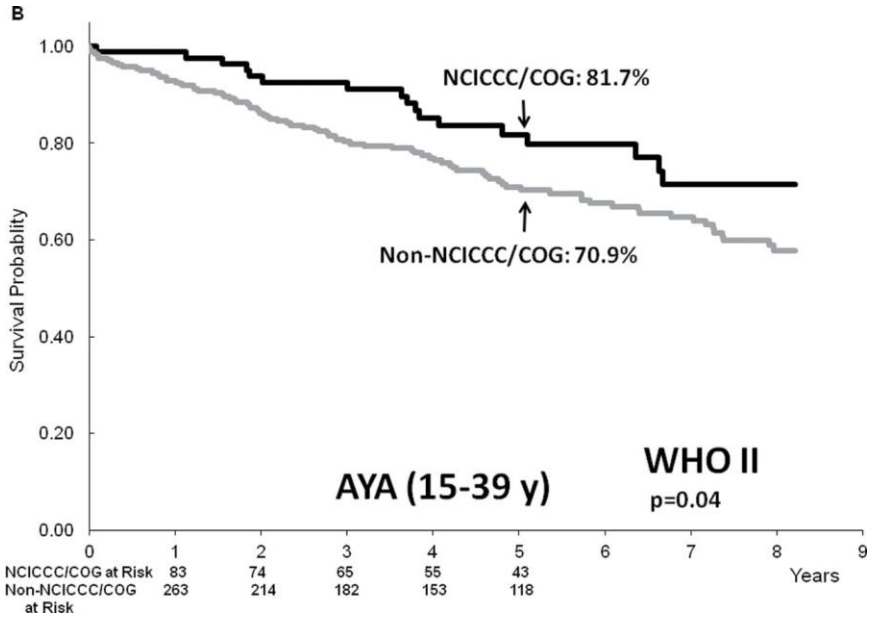
Primary Method of Cancer Detection	No. of Patients (%)
Self-detected	470 (80)
Exam-detected	33 (6)
Imaging-detected, eg, by mammogram or MRI	68 (12)
Detected based on systemic symptoms	7 (1)
Missing	7 (1)

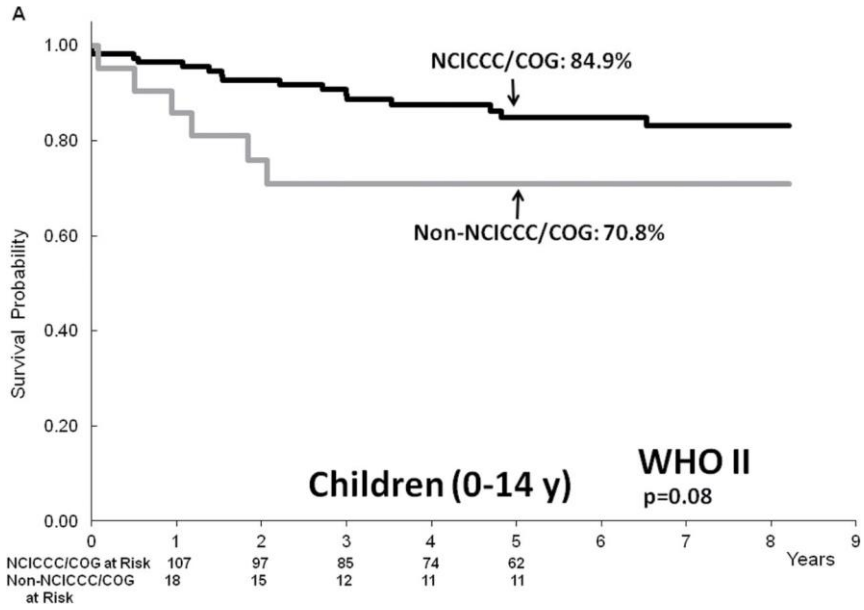
- Diagnosis delay ≥ 90days
  - 17 % self delay
  - 12 % care delay

- Financial issues
- Inadequate awareness of health-care professionnals : education++++

Ruddy et al, Cancer 2014

Place of care?
Central Nervous System Tumours





Worse outcome if not treated in NCI-Comprehensive cancer Centers or Children's Oncology Group centers

Wolfson et al, JNCI, 2014

Place of care?
Central Nervous System Tumors

- Worse outcome of AYAs 15-39 yrs abrogated if treated in NCI CCC/COG institutions

- Pts less likely to be treated in NCI-COG institutions
  - 15-21 AYAs
  - 22-39 YAs
    - With low socio-economic status
    - Public or no health insurance
    - Distance to care > 5 miles

Meeting the needs of YA in oncology

- Combined-modality treatment, multidisciplinary team
- Need of **specialised and expert care** for potentially curable disease
- **Strong interaction between paediatric oncologists and medical oncologists to improve survival and accrual in clinical trials**

they deserve the best (and not the worst...) of both worlds

- Biological prospective common studies
- Skilled nursing care and optimal interactions with peers, family and health-care providers
- Communication skills
- Continuous psychosocial support and educational support
- Physical environment

In conclusion

- No disease ends or begins at 18 years (Sallan, Haematology, 2006)
- (A)YA oncology is in its adolescence

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Thanks to Drs S. PIPERNO-NEUMANN ,

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Thank you for your attention

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