XXIII Congresso AIRO 2013

Taormina –Giardini Naxos

29 ottobre 2013

Sarcomi delle parti molli dell'età pediatrica

Moderni approcci di trattamento

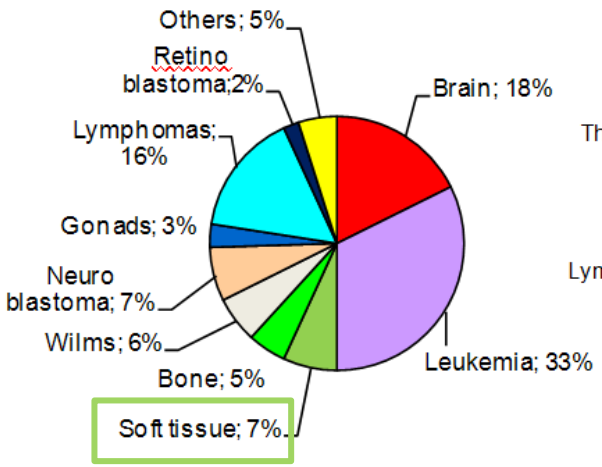
Maurizio Mascarin,

Centro di Riferimento Oncologico - Aviano (PN)

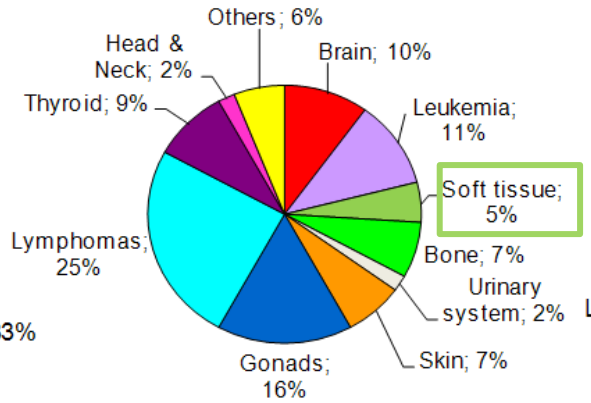
S.O.S. di Radioterapia Pediatrica,

Dip. Terapia Radiante e Metabolica

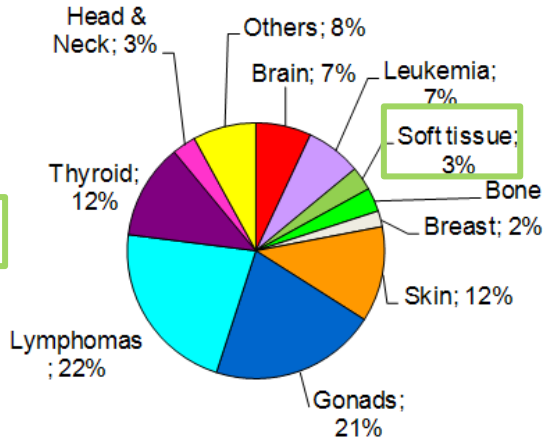
Distribution of malignant disease by age



Age 0-14 years



Age 15-19 years



Age 20-24 years

Incidence pediatric and AYA tumors

Age 0-14 years: 164 cases/million/years (≈ 1380 new cases)

Age 15-19 years: 269 cases/million/years (≈ 804 new cases)

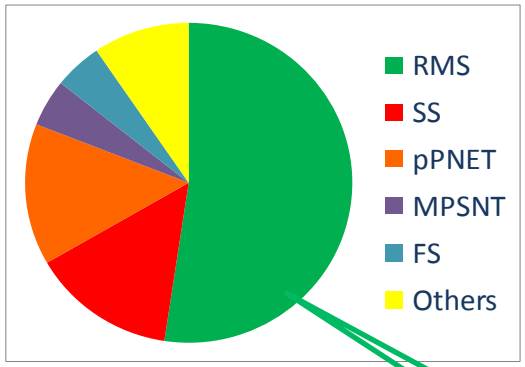
Age 20-24 years: 352 cases/million/years (≈ 1096 new cases)

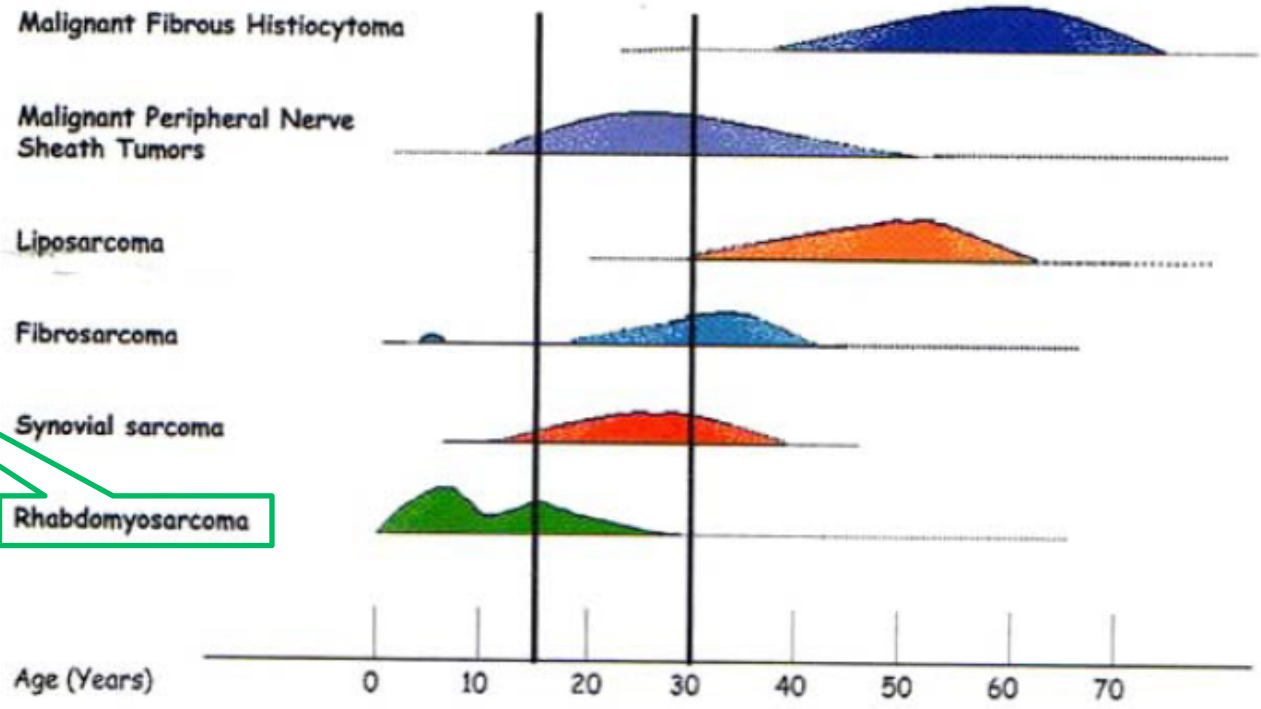
Age 25-29 years: 547 cases/million/years (≈ 1944 new cases)

AIRTUM, E&P 2008
I tumori in FVG 1995-2005, Agenzia Regionale Sanità
SEER 1975-2000 - Cancer in 15-29 Years-Old
ISTAT 2012
Epidemiol Prev 2013; 37 (1) suppl 1

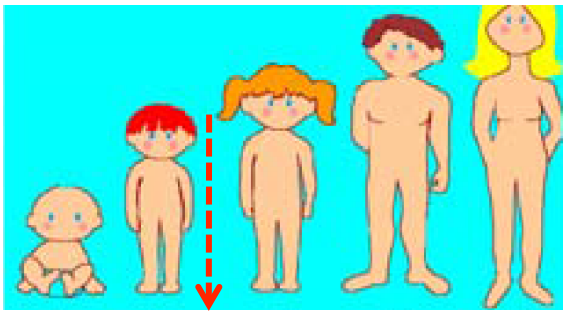
Incidence and epidemiology

- **6%-7% of all tumors in childhood**
- ≈70-80 pts/year in Italy
- **Ratio between O/E 0,76:** → **0,95 0-14 years**
  → **0.42 15-19 years**





Age and median age at diagnosis (years)

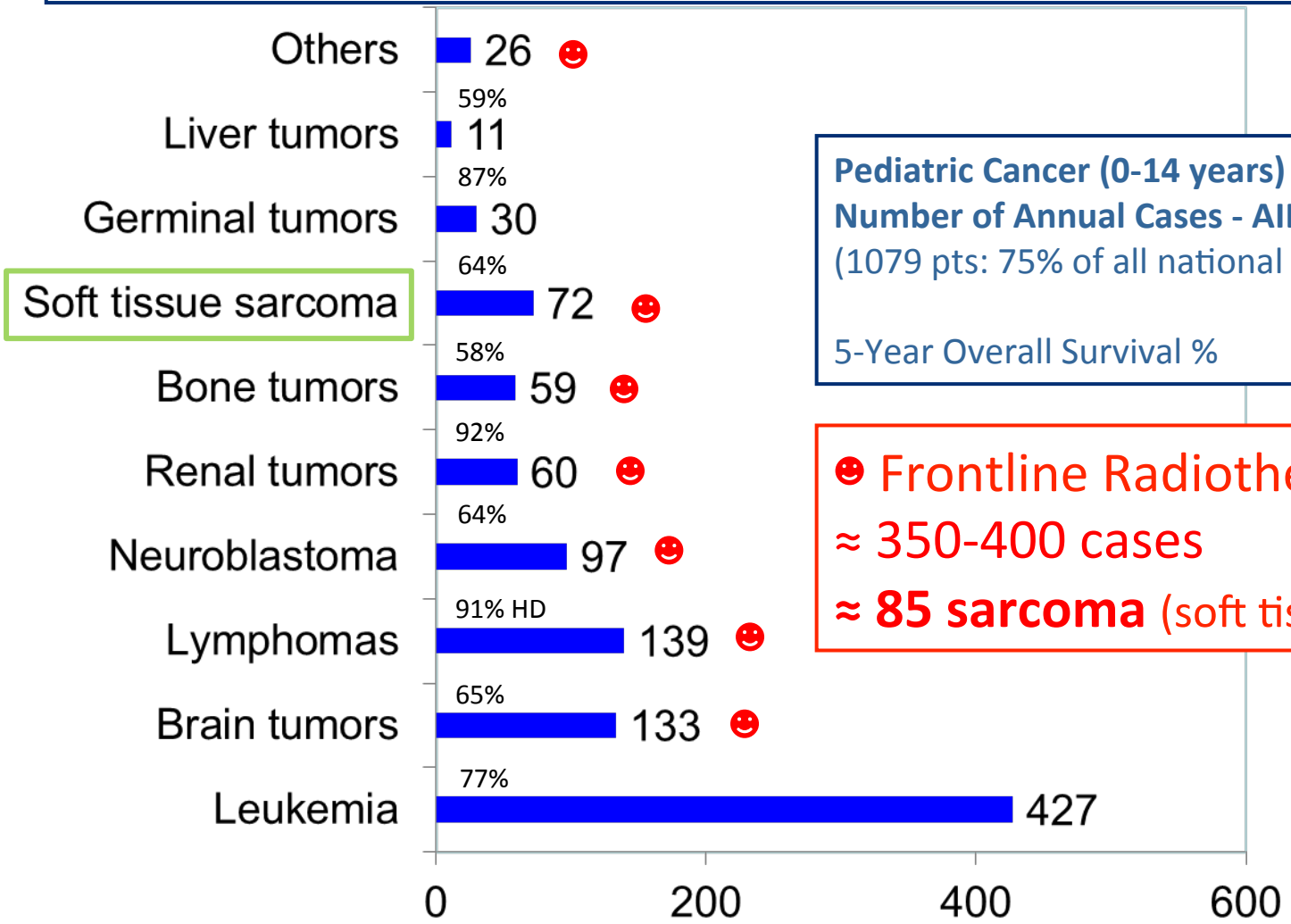


<1y	1-4y	5-9y	10-14y	15-21y
4%	34%	25%	22%	15%

Mascarin M. – CRO Aviano

Epidemiol Prev 2013; 37 (1) suppl 1: 1-296
K Pritchard Jones, C4K 3025, 2012

Pediatric Cancer 1989-1998
Number of Annual Cases - AIEOP Registry



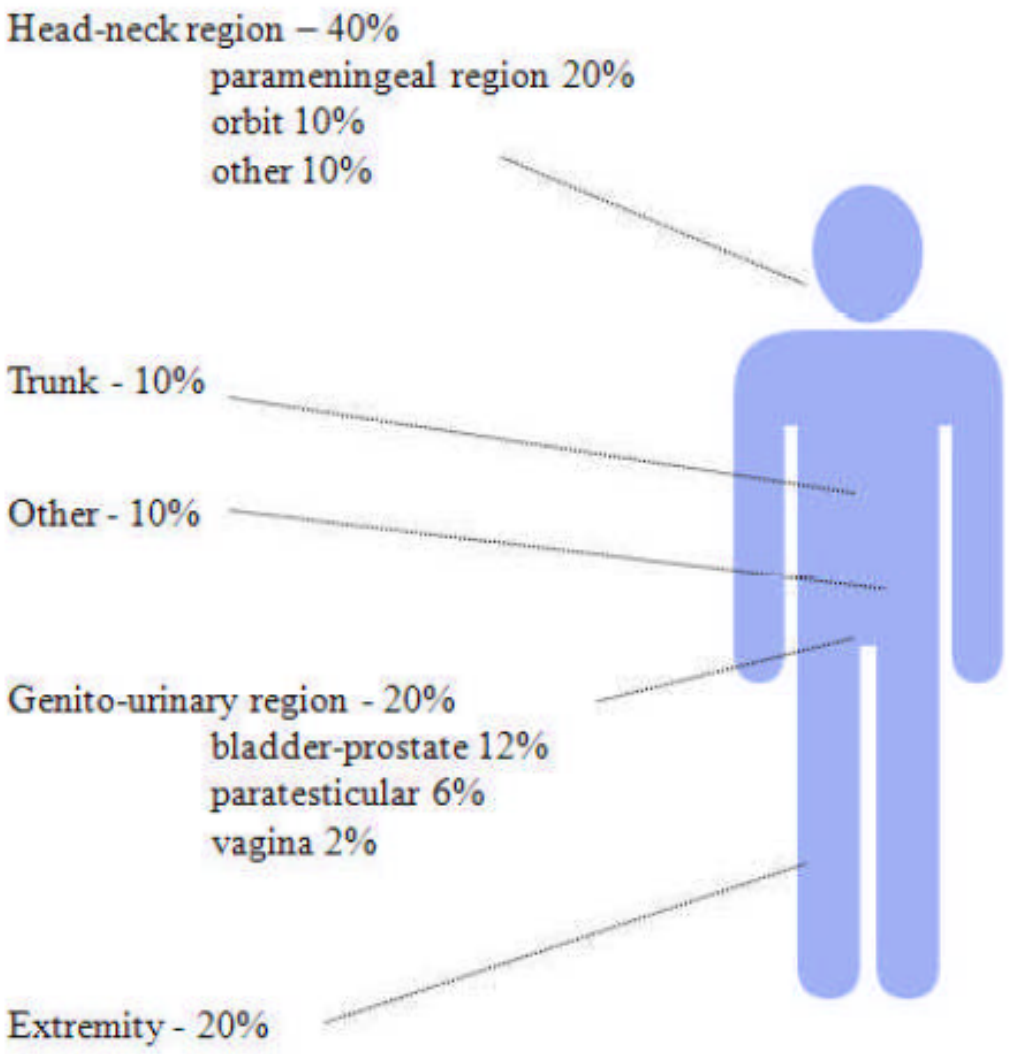
Pediatric Cancer (0-14 years)
Number of Annual Cases - AIEOP Registry
(1079 pts: 75% of all national childhood cancer)

5-Year Overall Survival %

☻ Frontline Radiotherapy
≈ 350-400 cases
≈ **85 sarcoma** (soft tissue + bone)

Modified from:
Pession A. et al. AIEOP study, E J Cancer 4 4 (2 0 0 8) 1 2 8 2 –1 2 8 9

RMS, Primary sites distribution

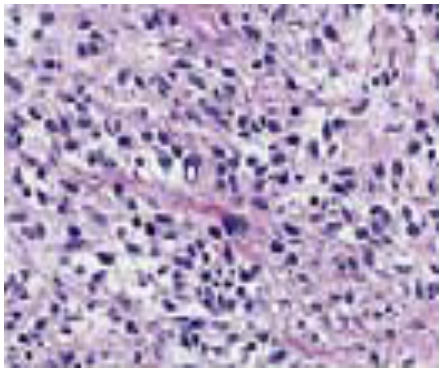


Survival by primary site

	5 years OS
Paratesticular – vagina	90-95%
Orbit	85-90%
Bladder Prostate	75-80%
Head & Neck non PM	75-85%
Para Meningeal	40-70%
Others	60-65%
Extremity	55%

Ferrari A, Oncopedia 2010

RMS, Pathology and Subtypes



▪Embrional RMS (resembling embrional muscle)

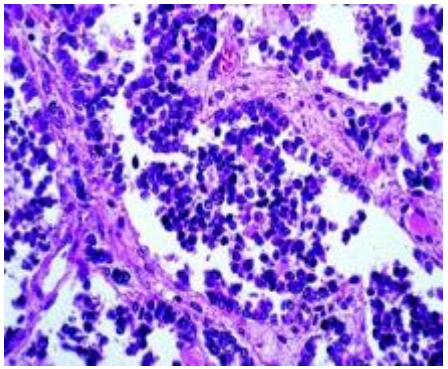
A. Botryoid

B. Spindle cell

C. Typical

D. Anaplastic

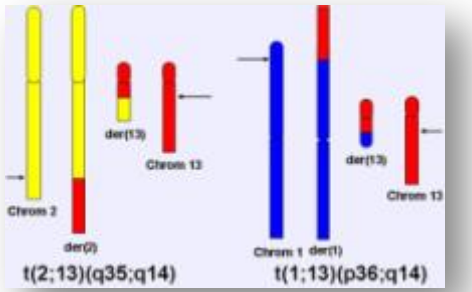
- ✓More common
- ✓Younger children
- ✓Better prognosis



▪Alveolar RMS (resembling pulmonary alveoli)

A. Typical

B. Solid

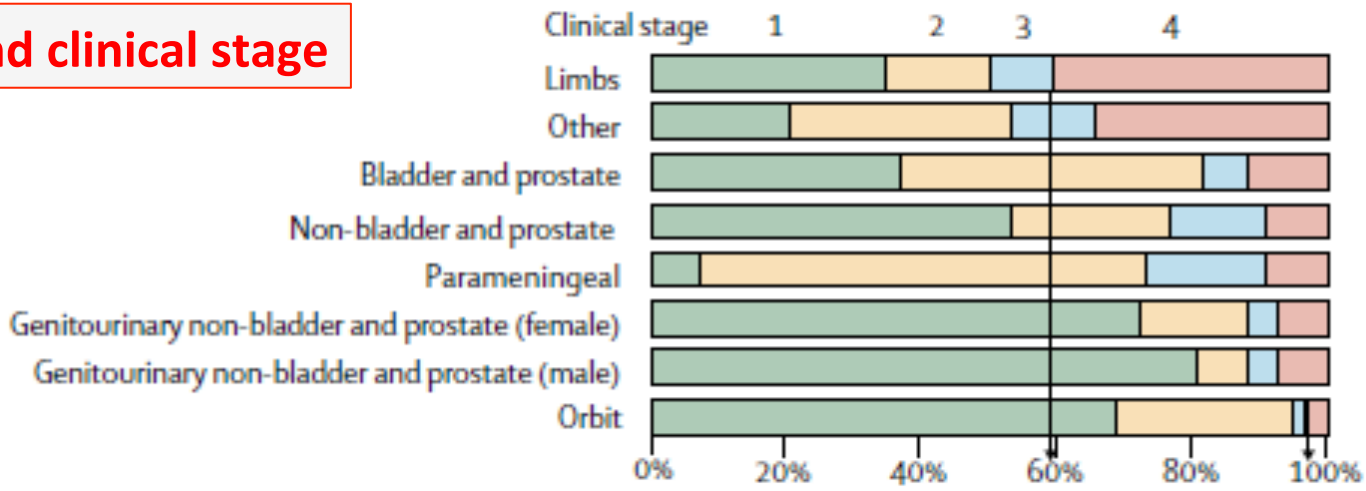


- ✓Less common
- ✓Older children
- ✓Worse prognosis
- ✓Very rare in GU tumours
- ✓Fusion gene pathognomonic (PAX/FOX01 fusion gene)

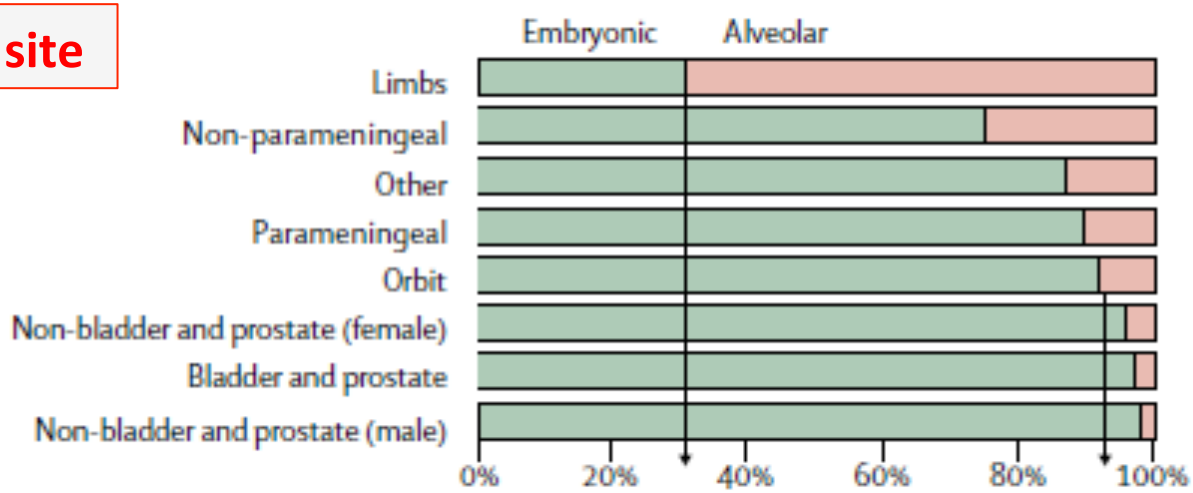
▪Pleiomorphic RMS (adults)

Pathology, Site and Clinical Stage

SITE and clinical stage

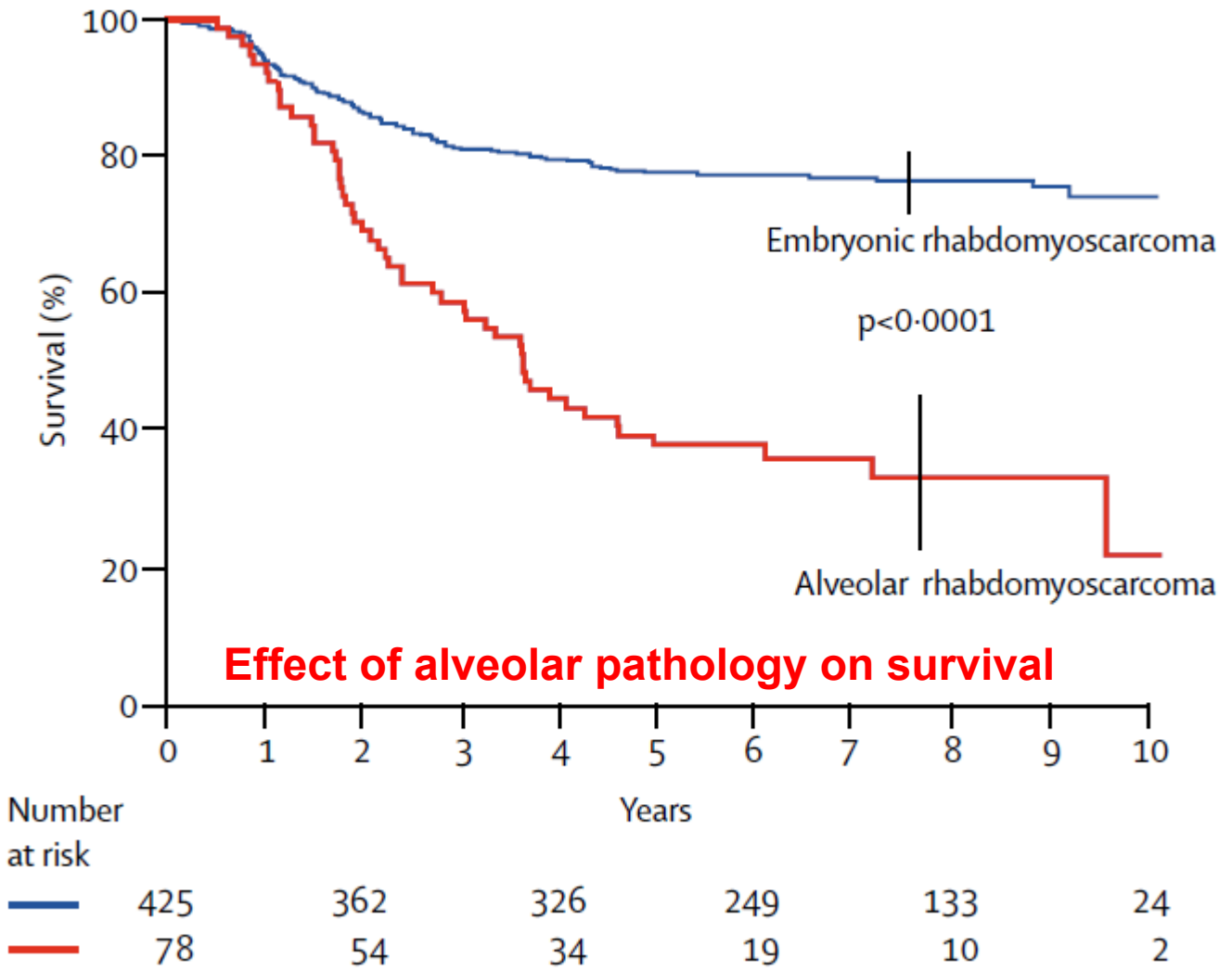


Histology and site



Stevens MCG, Lancet Oncology 2005

RMS, Pathology and Survival



Stevens MCG, Lancet Oncology 2005

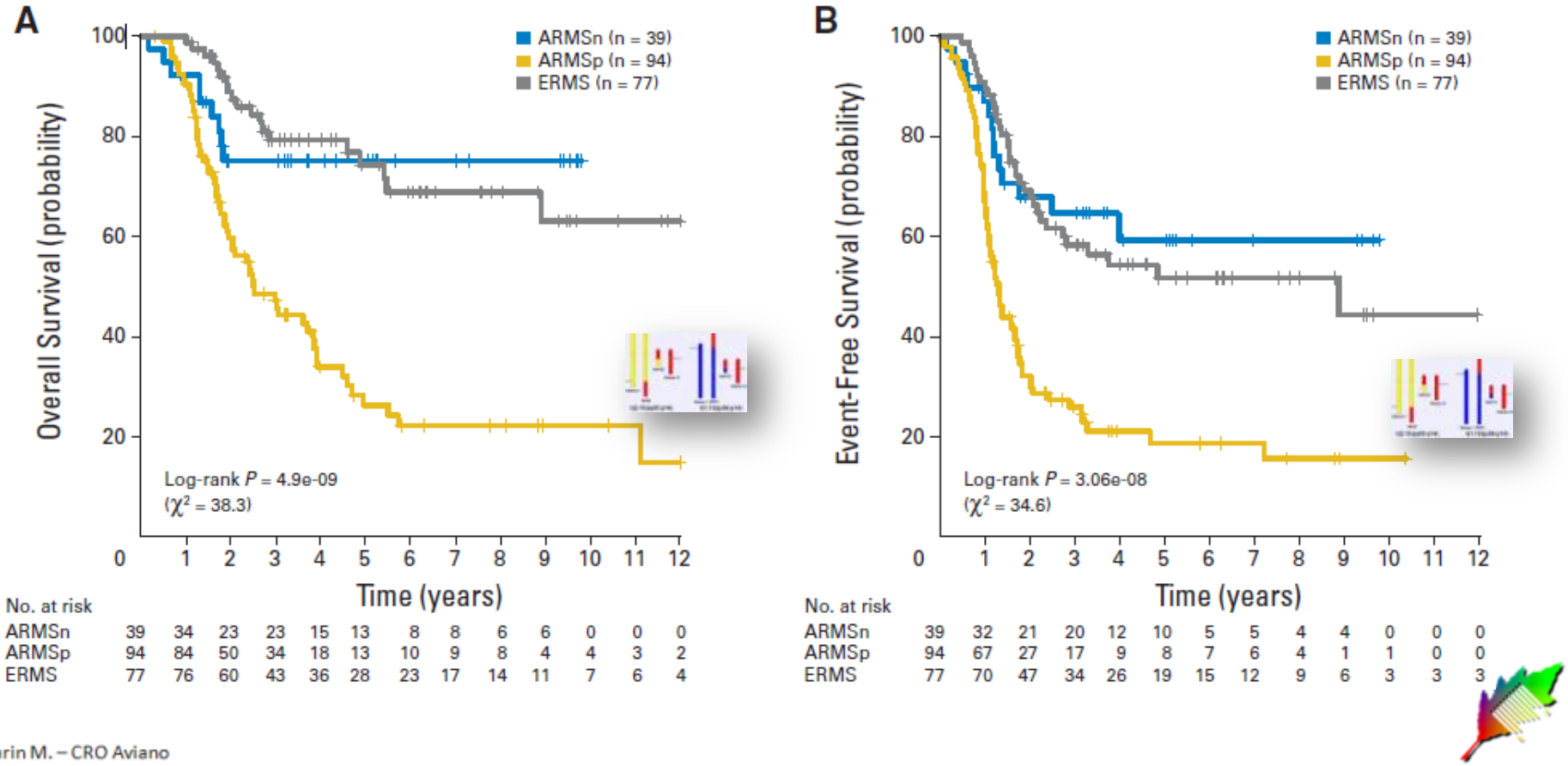
RMS, Alveolar Subtypes and Fusion Gene ±

VOLUME 28 · NUMBER 13 · MAY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

Fusion Gene–Negative Alveolar Rhabdomyosarcoma Is Clinically and Molecularly Indistinguishable From Embryonal Rhabdomyosarcoma

Daniel Williamson, Edoardo Missiaglia, Aurélien de Reyniès, Gaëlle Pierron, Benedicte Thuille, Gilles Palenzuela, Khin Thway, Daniel Orbach, Marick Laé, Paul Fréneaux, Kathy Pritchard-Jones, Odile Oberlin, Janet Shipley, and Olivier Delattre



RMS, Therapy

- **"primary surgery" –** only if easily removable
  - ✓ **e.g.** paratesticular (NB: inguinal approach),
  - ✓ **not in orbital** disease, majority children have biopsies only

AVOID MUTILATING SURGERY at diagnosis

- **chemotherapy**

- **"delayed resection"** according to response
  - ✓ **Responding tumours can remain *in situ for longer***
  - ✓ **Non-responding tumours need earlier local therapy – Surgery or RT**

- **radiotherapy**

- **high dose therapy** ? no role ?

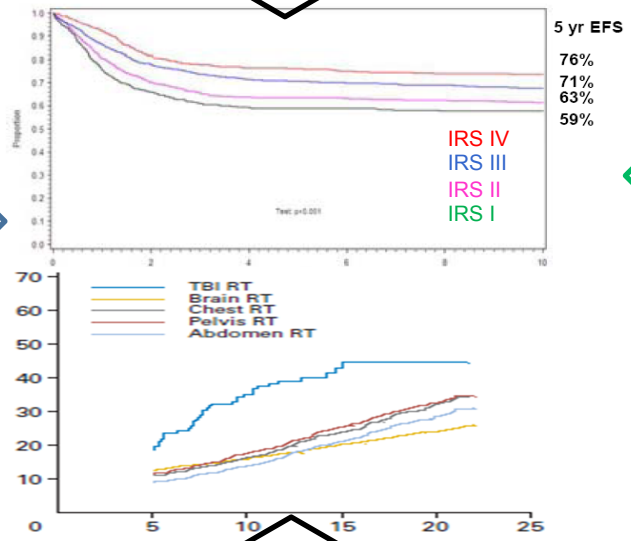
RMS, Prognostic factors & Risk adapted RT

PATIENT

- **age** (<1; >10 y)

TUMOR

- **histology** (RMSa)
- **size** (>5cm)
- **site** (limb, PM)
- **stage** (IRS II, III, N1)
- **Biology** (PAX/FOX1)



TREATMENT

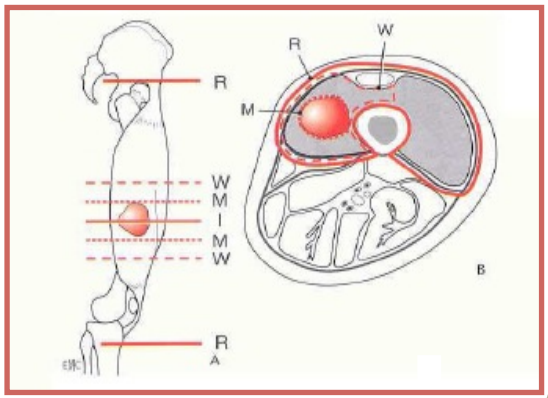
- **Surgery timing**
- **modality**
- **response**

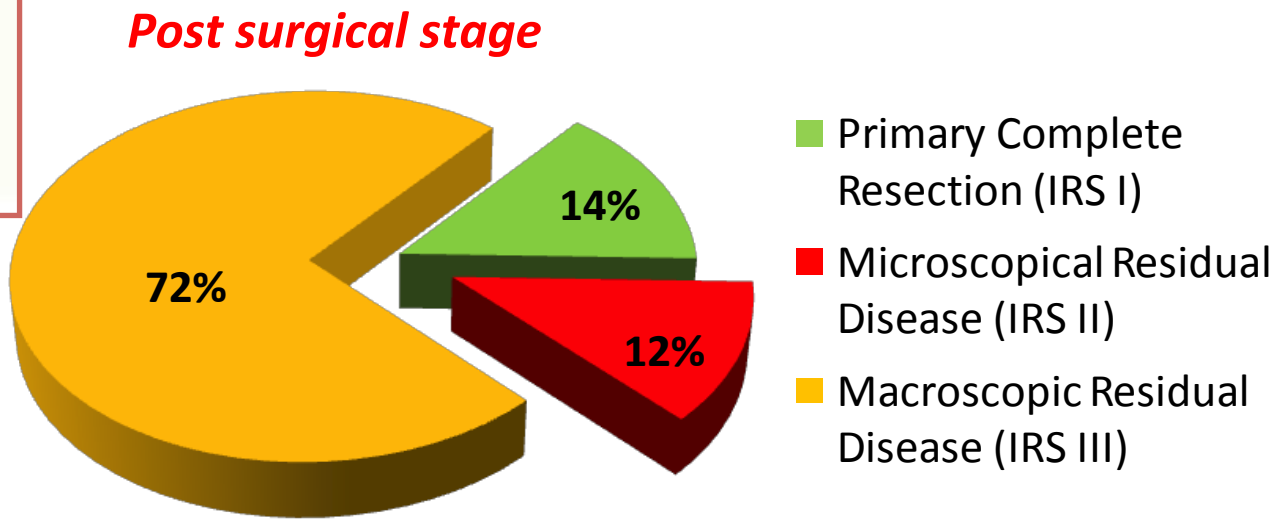
RISK ADAPTED RADIOTHERAPY

Age | **Organ dysfunction** | **Endocrine late effects** | **Infertility** | **Esthetic / growing damages** | **Secondary cancer**

RMS, Surgery

- **Complete tumour removal** is the goal of surgical resection.
- **Organ preservation** is also a primary aim in this paediatric population.





Stevens MCG, Lancet Oncology 2005

RMS, Surgery

- The **persistence of radiographic masses at the end of RMS therapy** is well known, but **their biologic potential is uncertain**.
- **Only 50%** of pathologic specimens from end of therapy masses among participants **with a best response of PR/NR** demonstrated **viable tumor**.

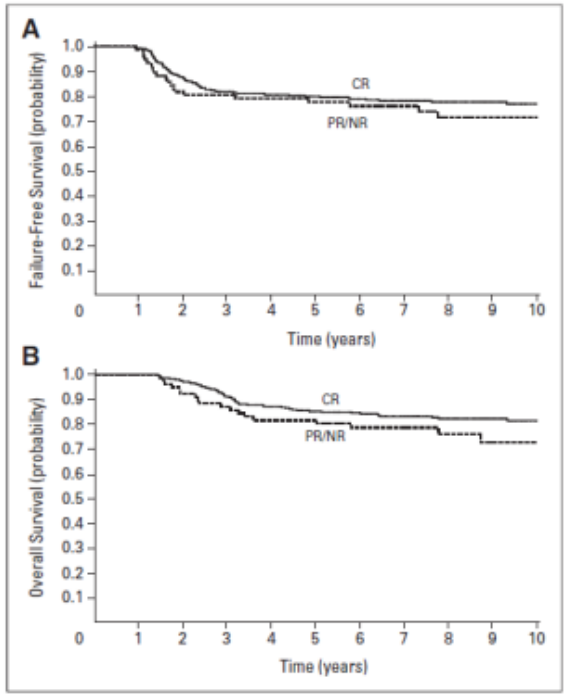
VOLUME 27 · NUMBER 22 · AUGUST 1 2009

JOURNAL OF CLINICAL ONCOLOGY

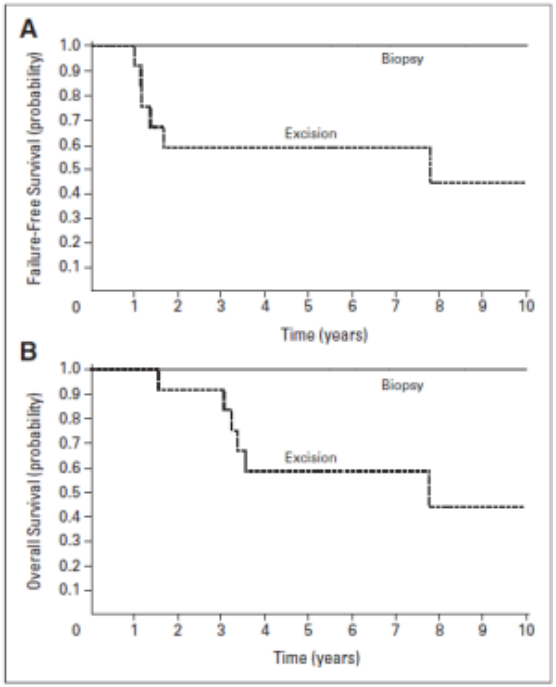
Prognostic Significance of Tumor Response at the End of Therapy in Group III Rhabdomyosarcoma: A Report From the Children's Oncology Group

David A. Rodeberg, Julie A. Stoner, Andrea Hayes-Jordan, Simon C. Kao, Suzanne L. Wolden, Steve J. Qualman, William H. Meyer, and Douglas S. Hawkins

IRS IV: 419 pts Group III



Complete Response at the end of therapy compared with PR/NR

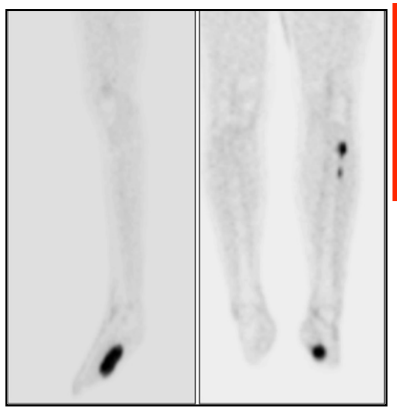


Resection compared with biopsy

RMS, Surgery, Extremity, Nodal involvement

REGIONAL NODAL INVOLVEMENT AND PATTERNS OF SPREAD ALONG IN-TRANSIT PATHWAYS IN CHILDREN WITH RHABDOMYOSARCOMA OF THE EXTREMITY: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

Trang H. La, M.D.,* Suzanne L. Wolden, M.D.,† David A. Rodeberg, M.D.,‡ Douglas S. Hawkins, M.D.,§ Kenneth L. Brown, M.D.,¶ James R. Anderson, Ph.D.,‖ and Sarah S. Donaldson, M.D.*

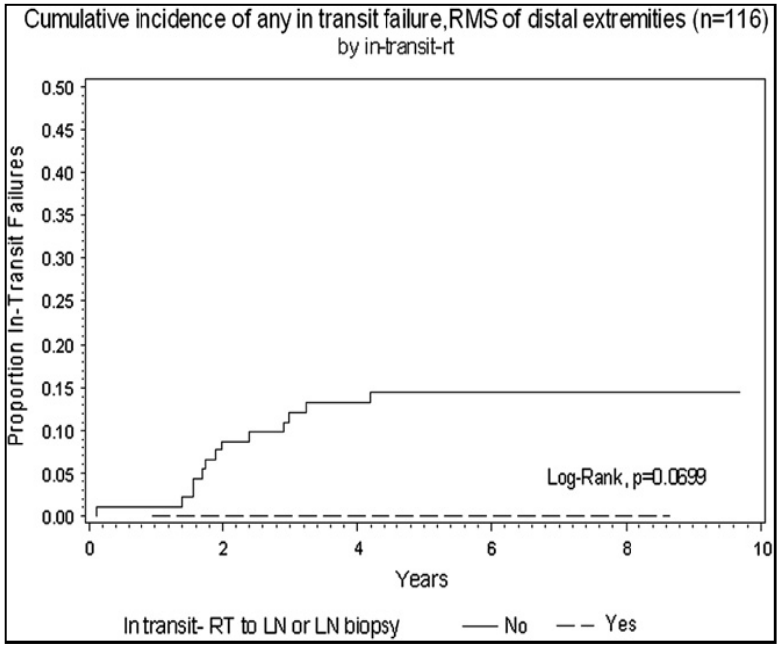


International Journal of Radiation Oncology biology • physics

IJROBP 80, 2011

- **Patients who underwent lymph node sampling and/or RT to the intransit nodal sites had a slightly lower risk of in-transit failure** (0% vs 15%).

- Patients should received **complete and accurate nodal staging to guide treatment**, which should include RT to any involved regional nodal site.



RMS, Chemotherapy

- Combinations of **VCR, Act-D, EDX** the mainstay of CT in US (**VAC**)
- **IFO** was introduced in Europe (**VAI**)
- IRS IV **no differences between EDX and IFO regimens**
- IFO **potentially nephrotoxic** (risk is small below 60g/m^2)
- IFO **fewer gonadal toxic effects** (?)

- **Anthracycline**:

✓IRS no benefit

✓Europe: EpSSG: main question in HR patients (IVA vs IVADo)

- The **optimum duration of adjuvant CT** is still unknown

(Europe "shorter" than USA)

RMS, Chemotherapy

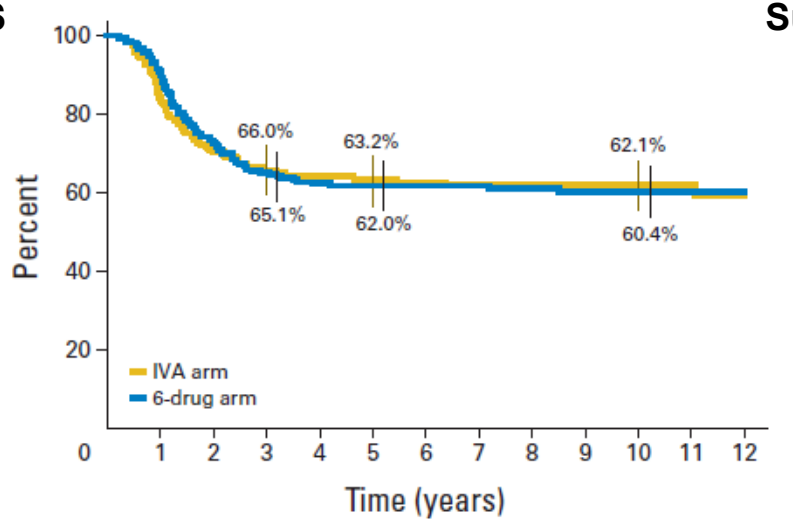
VOLUME 30 · NUMBER 20 · JULY 10 2012

JOURNAL OF CLINICAL ONCOLOGY

Randomized Comparison of Intensified Six-Drug Versus Standard Three-Drug Chemotherapy for High-Risk Nonmetastatic Rhabdomyosarcoma and Other Chemotherapy-Sensitive Childhood Soft Tissue Sarcomas: Long-Term Results From the International Society of Pediatric Oncology MMT95 Study

Odile Oberlin, Annie Rey, José Sanchez de Toledo, Hélène Martelli, Meriel E.M. Jenney, Marcelo Scopinaro, Christophe Bergeron, Johannes H.M. Merks, Nathalie Bouvet, Caroline Ellershaw, Anna Kelsey, David Spooner, and Michael C.G. Stevens

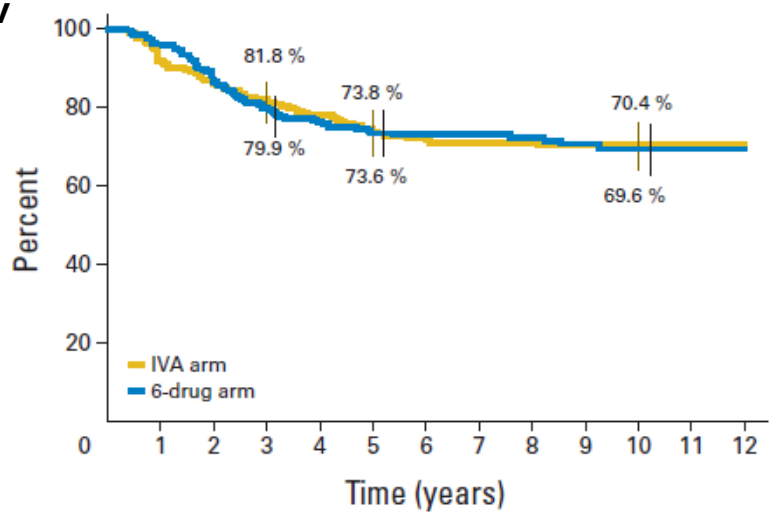
EFS



No. at risk

IVA arm	224	185	155	144	138	128	113	95	77	60	45	28	7
6-drug arm	233	206	168	148	141	129	108	91	76	59	43	21	8

Surv



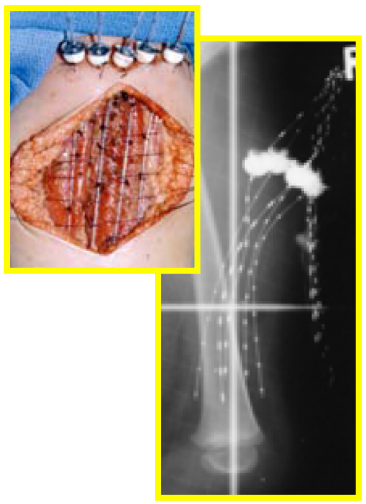
No. at risk

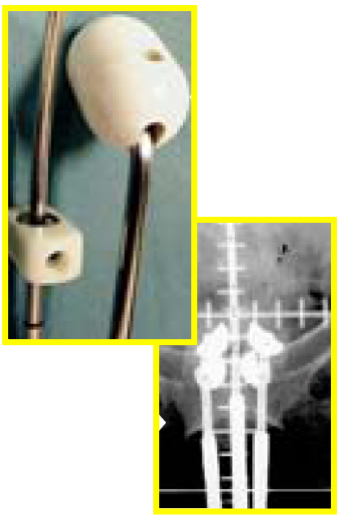
IVA arm	224	203	189	179	168	150	132	112	91	70	52	34	9
6-drug arm	233	220	199	181	172	152	127	109	92	73	51	27	11

RMS, radiotherapy

Approaches to local control

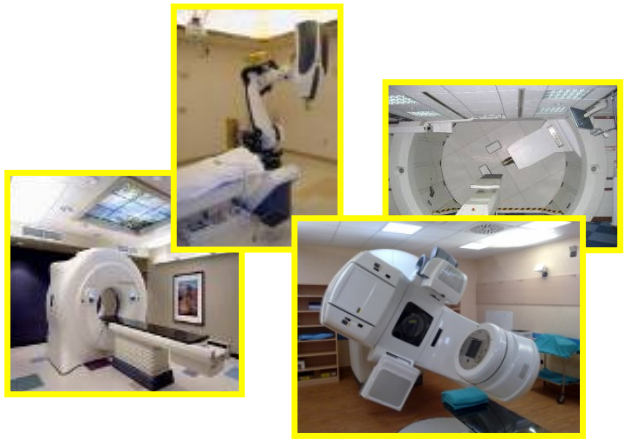
- Brachytherapy





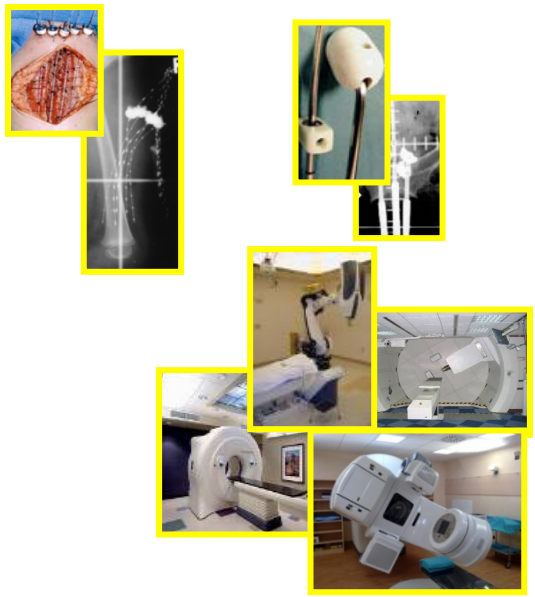
M Krasin SJCH

- External Beam Radiation



RMS, radiotherapy

Tumors that remain unresectable after CT, or that have been incompletely resected by second Surgery after initial CT, are mostly treated with radiation.



IRS1: **embrional → no RT**
alveolar → RT

IRS2: most groups **recommend RT**

IRS3: **IRS3 with CR after CT→ RT?**

The response by CT is sufficient to ensure local control?

Depending by primary tumor site(GU no BP; H&N no PM; orbit)

Others IRS3→RT

RMS, radiotherapy, reduce dose

Local Control With Reduced-Dose Radiotherapy for Low-Risk Rhabdomyosarcoma: A Report From the Children's Oncology Group D9602 Study

John Breneman, M.D.,* Jane Meza, Ph.D.,† Sarah S. Donaldson, M.D.,‡ R. Beverly Raney, M.D.,§,¶ Suzanne Wolden, M.D.,‖ Jeff Michalski, M.D.,** Fran Laurie, B.S.,†† David A. Rodeberg, M.D.,‡‡ William Meyer, M.D.,§§ David Walterhouse, M.D.,¶¶ and Douglas S. Hawkins, M.D.‖‖

International Journal of Radiation Oncology biology • physics

IJROBP 83, 2012

Reduced-dose radiotherapy (36Gy) does not compromise local control for patients with **microscopic tumor after surgical resection** or with **orbital primary** tumors when…….

Cyclophosphamide (0% LR vs 15%) is added to the treatment program.

RMS, radiotherapy, Hyperfractionation

RESULTS FROM THE IRS-IV RANDOMIZED TRIAL OF HYPERFRACTIONATED RADIOTHERAPY IN CHILDREN WITH RHABDOMYOSARCOMA—A REPORT FROM THE IRSG

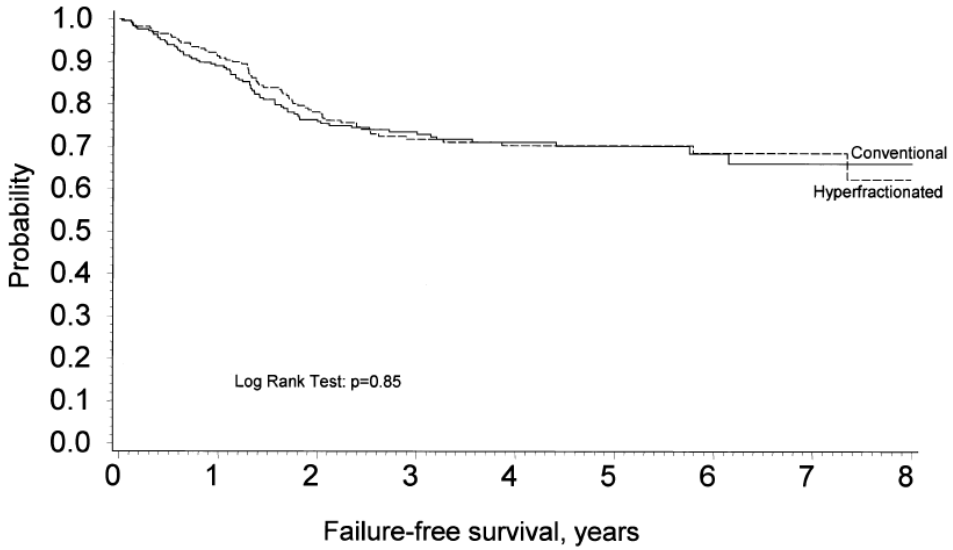
SARAH S. DONALDSON, M.D.,* JANE MEZA, PH.D.,† JOHN C. BRENEMAN, M.D.,‡ WILLIAM M. CRIST, M.D.,§ FRAN LAURIE, M.S.,‖ STEPHEN J. QUALMAN, M.D.,¶ AND MOODY WHARAM, M.D.,# FOR THE CHILDREN'S ONCOLOGY GROUP SOFT TISSUE SARCOMA COMMITTEE (FORMERLY INTERGROUP RHABDOMYOSARCOMA GROUP) REPRESENTING THE CHILDREN'S ONCOLOGY GROUP AND THE QUALITY ASSURANCE REVIEW CENTER

Int. J. Radiation Oncology Biol. Phys., Vol. 51, No. 3, pp. 718–728, 2001

International Journal of Radiation Oncology biology • physics

Group III (randomization):

- 239 pts **HFRT** (59.4 Gy in 54, 1.1-Gy twice daily fractions)*
- 251 pts **CFRT** (50.4 Gy in 28, 1.8-Gy daily fractions)



*Parameningeal RMS had lower survival with HFRT

RMS, radiotherapy, Accelerated Hyperfractionated

SARCOMI DELLE PARTI MOLLI IN ETÀ PEDIATRICA: RISULTATI A LUNGO TERMINE DEI PROTOCOLLI COOPERATIVI ITALO-TEDESCHI RMS '79, RMS '88 E RMS '96

G. Scarzello[1], M.S. Buzzaccarini[1], L. Gandola[2], M. Mascarin[3], S. Barra[4], A. Mussano[5], S. Scoccianti[6], L. Vinante[1], E. Pane[1], G. Bisogno[7], G. Cecchetto[7], I. Zanetti[7], G. Sotti[1]

[1]IOV-IRCCS, Padova; 2INT, Milano; [3]CRO, Aviano; [4]IST, Genova; [5]O. Sant'Anna, Torino; [6]AOUC, Firenze; [7]AOU, Padova, Italia

Anni 1979-2005.
1015 pazienti con RMS (centri AIEOP)

La **RT iperfrazionata accelerata** (32 o 48Gy/ 1.6Gy x fraz), come erogata nei protocolli RMS88 e RMS96,
non ha migliorato il controllo locale o la sopravvivenza.

RMS, radiotherapy adherence

INFLUENCE OF NONCOMPLIANCE WITH RADIATION THERAPY PROTOCOL GUIDELINES AND OPERATIVE BED RECURRENCES FOR CHILDREN WITH RHABDOMYOSARCOMA AND MICROSCOPIC RESIDUAL DISEASE: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

LYNN MILLION, M.D.,* JAMES ANDERSON, PH.D.,† JOHN BRENEMAN, M.D.,‡ DOUGLAS S. HAWKINS, M.D.,§ FRAN LAURIE, B.S.,¶ JEFF MICHALSKI, M.D.,‖ DAVID RODEBERG, M.D.,** MOODY WHARAM, M.D.,†† SUZANNE WOLDEN, M.D.,‡‡ AND SARAH S. DONALDSON, M.D. §§ SOFT TISSUE SARCOMA COMMITTEE OF THE CHILDREN'S ONCOLOGY GROUP

International Journal of Radiation Oncology biology • physics

IJROBP 80, 2011

- ✓The **operative bed recurrence** rate for Group II patients treated on IRS I–IV was **12%** (83/695 pts).
- ✓**70% compliance with RT protocol guidelines**
- ✓**More than half (57%) of the Group II patients with an operative bed recurrence have a RT deviation**.
- ✓Of the 83 patients with operative bed recurrence, 63 **(76%) died.**

RMS, radiotherapy, IMRT in H&N tumors

Intensity modulated radiotherapy for head and neck rhabdomyosarcoma

Suzanne L. Wolden et al, Memorial Sloan-Kettering, New York

International Journal of Radiation Oncology biology • physics

IJROBP 61, 2005

… showed **excellent local control** can be maintained with the use of decrease margin using **IMRT** for Head and Neck tumors

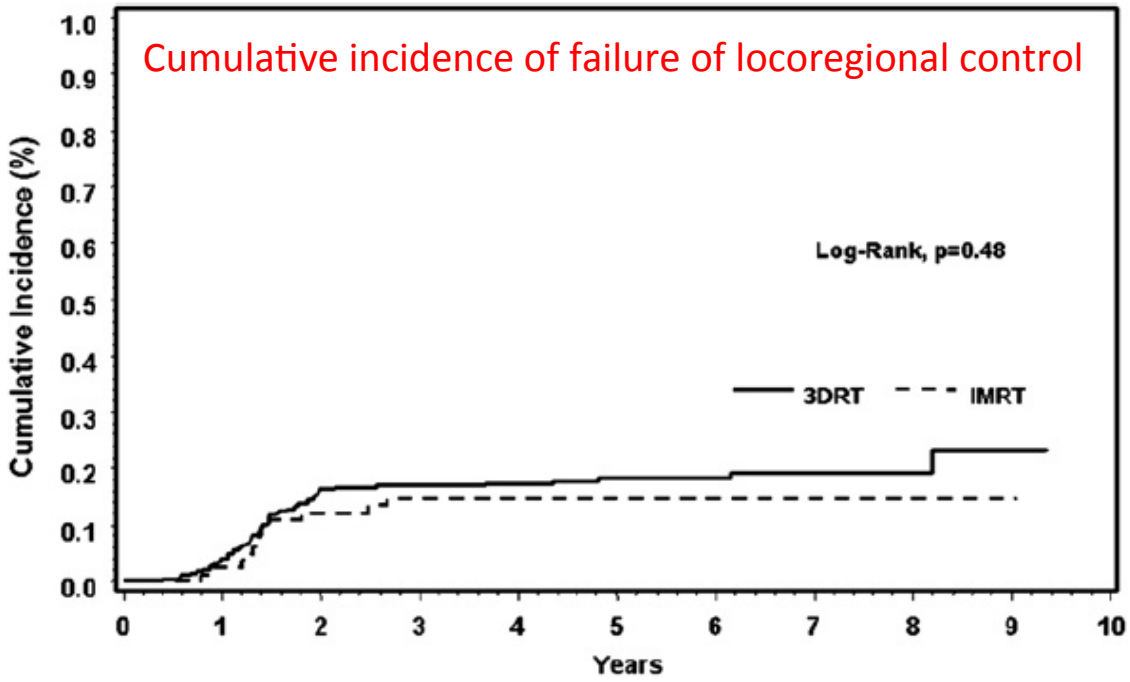
3 years FFP 95% locally
80% nodal

RMS, radiotherapy, 3DRT vs IMRT

EFFECT OF RADIOTHERAPY TECHNIQUES (IMRT VS. 3D-CRT) ON OUTCOME IN PATIENTS WITH INTERMEDIATE-RISK RHABDOMYOSARCOMA ENROLLED IN COG D9803—A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

International Journal of Radiation Oncology biology • physics

Chi Lin et al, IJROBP 2012



IMRT improved the target dose coverage compared with 3D-CRT, although an improvement in locoregional control or FFS could not be demonstrated in this population.

RMS, radiotherapy for very young children

THE CHALLENGING ROLE OF RADIATION THERAPY FOR VERY YOUNG CHILDREN WITH RHABDOMYOSARCOMA

Dev R. Puri, M.D.,* Leonard H. Wexler, M.D.,† Paul A. Meyers, M.D.,†
Michael P. La Quaglia, M.D.,‡ John H. Healey, M.D.,‡ and Suzanne L. Wolden, M.D.*

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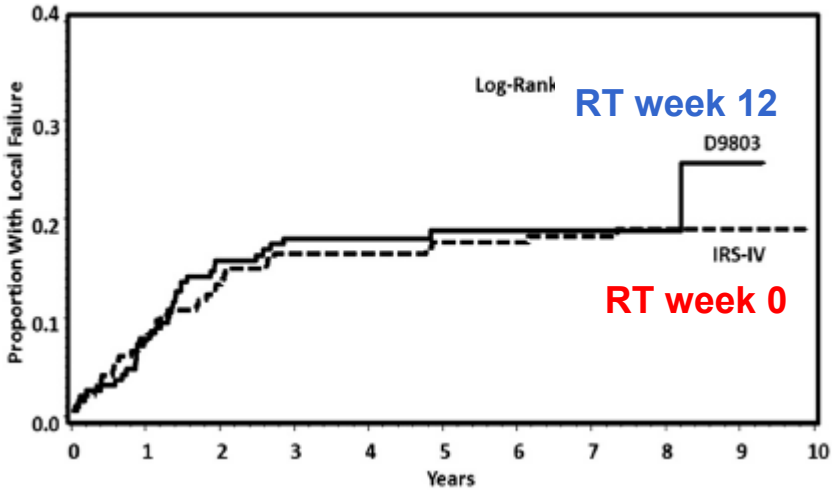
- A reduced dose of 36-Gy EBRT after delayed gross total resection may maximize local control,
- Unresectable tumors (e.g., parameningeal) require higher doses.
- Normal-tissue-sparing techniques such as IMRT and IOHDR are encouraged.

RMS, radiotherapy timing

- **Timing of radiotherapy still being evaluted**
- For **parameningeal cases** (including intracranial extension) early RT (week 3-4)
- For **others**: week 12-13



No risk features
Cranial nerve palsy
Base of skull erosior
} ns

The Effect of Radiation Timing on Patients With High-Risk Features of Parameningeal Rhabdomyosarcoma: An Analysis of IRS-IV and D9803

Aaron C. Spalding, MD, PhD,* Douglas S. Hawkins, MD,† Sarah S. Donaldson, MD,‡ James R. Anderson, PhD,§ Elizabeth Lyden, MS,§ Fran Laurie, BSc,‖ Suzanne L. Wolden, MD,¶ Carola A.S. Arndt, MD,# and Jeff M. Michalski, MD**

International Journal of Radiation Oncology biology • physics

IJROBP 87, 2013

Proton Therapy

POINT/COUNTERPOINT

Pediatric medulloblastoma: Is proton beam the only ethically appropriate radiation reatment?

Anthony Zietman, MD, FASTRO, *Editor in Chief IJROBP*

International Journal of Radiation Oncology biology • physics

IJROBP 87, 2013

… **"spiritual core" of all we do as radiation oncologist:** its pits the **ideal against the pragmatic**, the **dosimetry against the clinical data**, and **one form of high technology against another.**

Pediatric CSI: Are Protons the Only Ethical Approach?

Peter A.S. Johnstone et al., Indiana University Proton Therapy Center

Yes

… ***proton beam is the only ethical approach.***
… to treat children we need expertise.
"Expertise" in this case is really *center expertise,* not simply the physician.

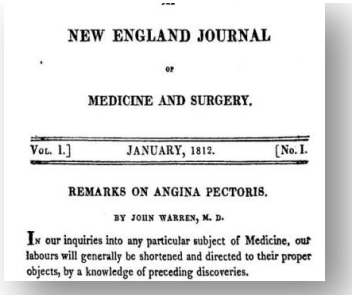
Protons for Craniospinal Radiation: Are Clinical Data Important?

Suzanne L. Wolden, Memorial Sloan-Kettering, New York

No

… **there is not sufficient clinical data** to argue that proton therapy is the only acceptable treatment.

The NEW ENGLAND JOURNAL of MEDICINE



NEW ENGLAND JOURNAL

OF

MEDICINE AND SURGERY.

Vol. 1.] JANUARY, 1812. [No. I.

REMARKS ON ANGINA PECTORIS.

BY JOHN WARREN, M. D.

In our inquiries into any particular subject of Medicine, our labours will generally be shortened and directed to their proper objects, by a knowledge of preceding discoveries.

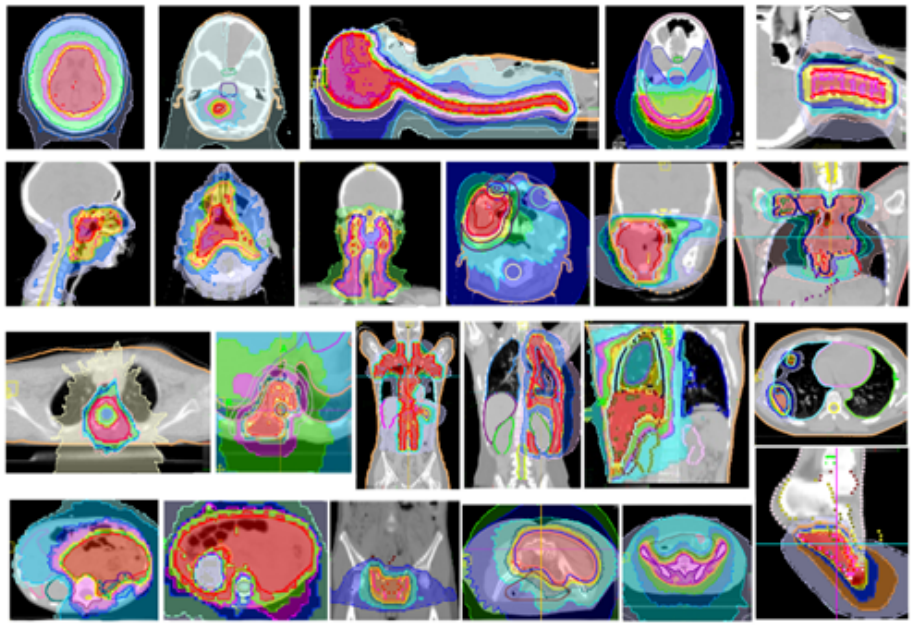
Account of an operation for the Extirpation of a Tumour, in which a ligature was applied to the Carotid Artery. By Mason F. Cogswell, M.D.

[Communicated in a Letter to the Editors of the New-England Journal of Medicine and Surgery.]

In the year 1800 Mrs L. of Lebanon, about 35 years of age, came to consult me respecting a tumour situated on the left side of her neck, occupying nearly the whole of the hollow between

Its character was that of a firm sarcoma, resembling a goose egg, in shape and smoothness, and weighing exactly a pound.

convenient size, but never from pain. I advised an immediate extirpation; she consented, and I removed it without difficulty. Its character was that of a firm sarcoma, resembling a goose egg, in shape and smoothness, and weighing exactly a pound. No vessel was divided during the operation which required a ligature, the wound healed by the first intention, and she rode home on horse-back in about ten days from the operation. About



RMS, Conclusion

- **Survival depends on risk group**.
- **Histology and staging work-up** are essential prior to starting therapy.
- The treatment is **multidisciplinary** to maximize local control and minimize morbidity.
- **CT is an essential component of therapy** for RMS along with surgery and/or RT for local control.
- **Almost all our decision are nuanced and difficult**, some of them extremely so.
- We have to know not only the history of disease, **but we have to imagine that one day this child will become an adult.**

Grazie