Infant Neuroblastoma

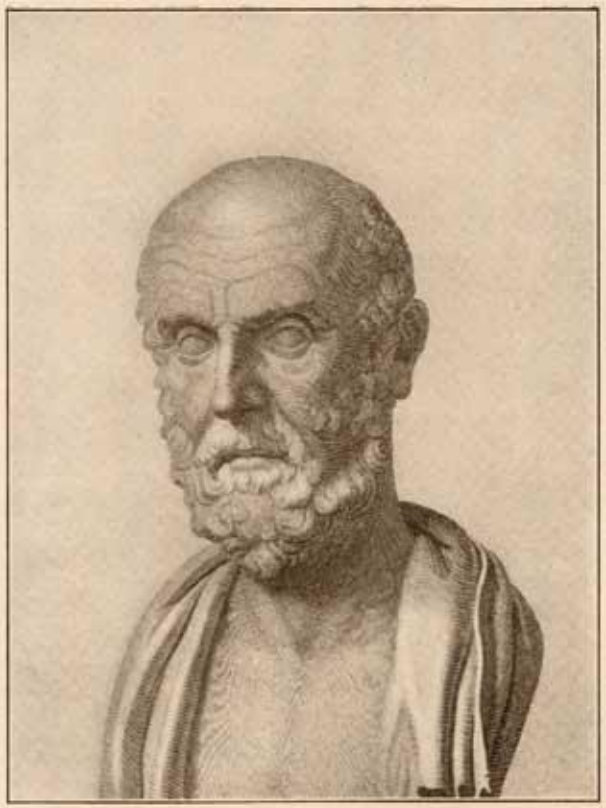
Where do we stand?

IPSO Education Day: ICH
London

Summary

- Infant neuroblastoma generally has an excellent prognosis
- Many tumours need minimal treatment
- Occasional tumours are more aggressive

How to pick the ones that need more treatment?



HIPPOCRATES.

INRG – distribution and predicted outcome of patients

Table 4. Proportion of Patients When Arbitrary EFS Cut Points Are Applied to Cluster Rows of the International Neuroblastoma Risk Group Consensus Stratification (for illustrative purposes)

Pretreatment Risk Group	%	
	5-Year EFS	Proportion of Patients
Very low	> 85	28.2
Low	> 75 to ≤ 85	26.8
Intermediate	≥ 50 to ≤ 75	9.0
High	< 50	36.1

Abbreviation: EFS, event-free survival.

Independent risk factors

- Stage (L1, L2, M, Ms)
- Age - 18 months
- Histological category - INPS (Shimada)
- Tumour differentiation
- MYCN amplification status
- 11q aberration
- DNA ploidy

INSS

Stage 1:	Localized tumor confined to the area of origin
Stage 2A:	Unilateral tumor with incomplete gross resection; identifiable ipsilateral and contralateral lymph nodes negative for tumor
Stage 2B:	Unilateral tumor with complete or incomplete gross resection; with ipsilateral lymph nodes positive for tumor; with contralateral lymph nodes negative for tumor
Stage 3:	Tumor infiltrating across midline with or without regional lymph node involvement; or unilateral tumor with contralateral lymph node involvement; or midline tumor with bilateral lymph node involvement
Stage 4:	Dissemination of tumor to distant lymph nodes, bone marrow, bone, liver, or other organs except as defined by stage 4S
Stage 4S:	Age <1 year old with localized primary tumor as defined in stage 1 or 2, with dissemination limited to liver, skin or bone marrow (less than 10 percent of nucleated bone marrow cells are tumors)

↕

INRGSS

•L1:	Locoregional tumour not involving structures as defined on list of Image Defined Risk Factors (IDRF)
•L2:	Locoregional tumour with presence of one or more IDRF's
•M:	Distant metastatic disease (except Ms)
•Ms:	Metastatic disease confined to skin, liver and bone marrow in <18 months.

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JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

From the Department of Pediatrics, The University of Chicago, Chicago, IL; Section of Paediatrics, Institute of Cancer Research and Royal Marsden Hospital, Surrey; Children's Cancer and Leukaemia Group Data Centre, University of Leicester, Leicester, United Kingdom; Children's Oncology Group Statistics and Data Center, University of Florida, Gainesville, FL; Section for Paediatric Surgery, Division of Surgery, Rikshospitalet University Hospital, Oslo, Norway; Children's Cancer Research Institute, St Anna Kinderkrebsforschung

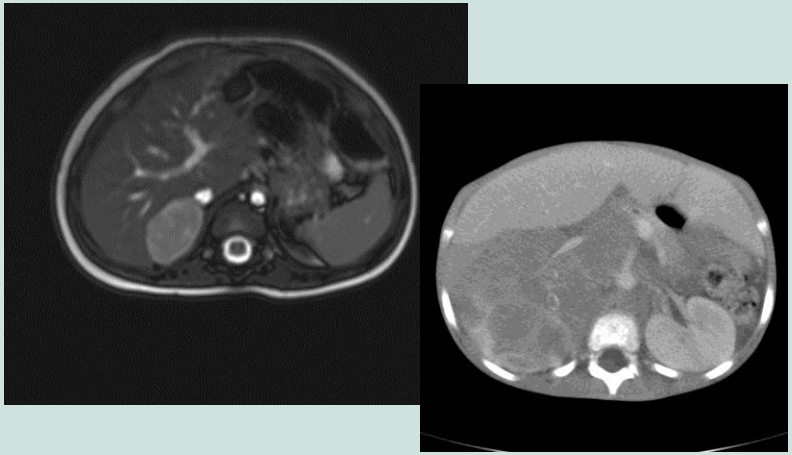
The International Neuroblastoma Risk Group (INRG) Classification System: An INRG Task Force Report

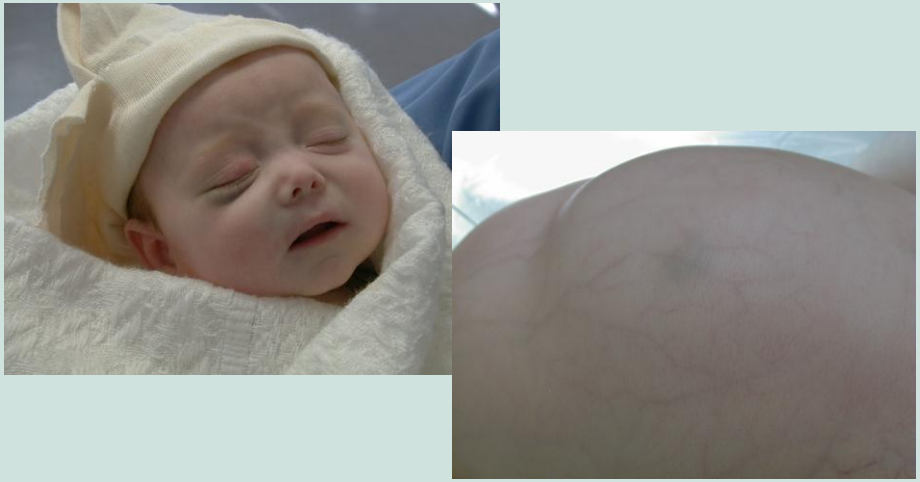
Susan L. Cohn, Andrew D.J. Pearson, Wendy B. London, Tom Monclair, Peter F. Ambros, Garrett M. Brodeur, Andreas Faldum, Barbara Hero, Tomoko Iehara, David Machin, Veronique Mosseri, Thorsten Simon, Alberto Garaventa, Victoria Castel, and Katherine K. Matthay

INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	*MYCN*	11q Aberration	Ploidy	Pretreatment Risk Group	
L1/L2		GN maturing; GNB intermixed					A Very low	*
L1		Any, except GN maturing or GNB intermixed		NA			B Very low	*
				Amp			K High	
L2	< 18	Any, except GN maturing or GNB intermixed		NA	No		D Low	*
					Yes		G Intermediate	*
	≥ 18	GNB nodular; neuroblastoma	Differentiating	NA	No		E Low	
					Yes		H Intermediate	
			Poorly differentiated or undifferentiated	NA				
				Amp			N High	
M	< 18			NA		Hyperdiploid	F Low	*
	< 12			NA		Diploid	I Intermediate	*
	12 to < 18			NA		Diploid	J Intermediate	
	< 18			Amp			O High	*
	≥ 18						P High	
MS	< 18			NA	No		C Very low	*
					Yes		Q High	*
				Amp			R High	*

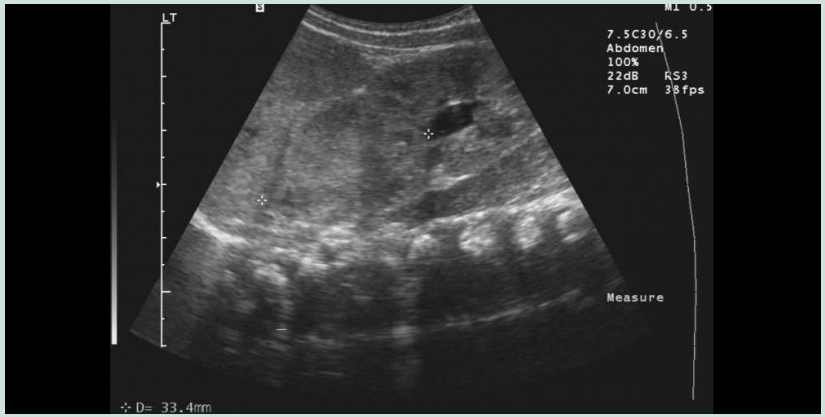
Stratifying treatment -risk grouping

- Incidental neonatal adrenal tumours
- Localised neuroblastoma under 18 months
- Metastatic neuroblastoma under 12 months
- MS tumours





Incidental neonatal masses



Many neonatal supra-renal masses spontaneously regress

Progression is rare

Risks of intervention outweigh benefits

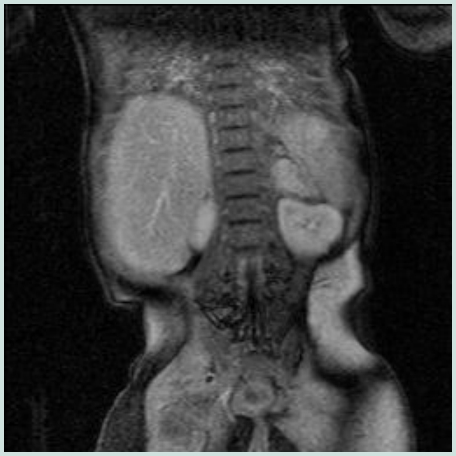
<u>Sources of data</u>

- Screening studies
- Anecdotal reports
- COG study

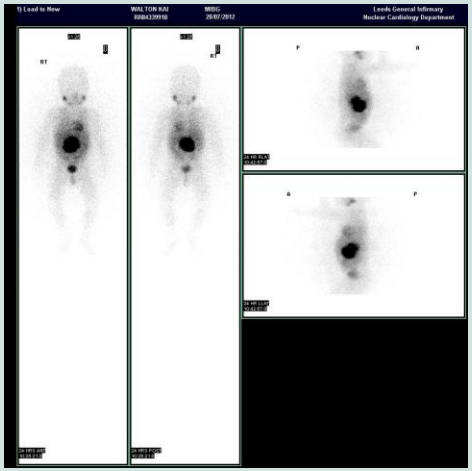
SIOPEN R NET

European Low and Intermediate Risk Neuroblastoma

18. NEONATAL ADRENAL MASSES: AN OBSERVATIONAL STUDY



- Age < 90 days when adrenal mass discovered
  - Not crossing midline
  - Diameter ≤ 5 cm
  - No evidence of metastases/regional spread
- US validated by MR and MIBG
- Regular follow up: US and catecholamines
- Resection if:
  - 50% increase in tumour volume
  - 50% increase in catecholamine levels
  - Clinical concern about progressive disease
  - Persistent mass after 12 months



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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Localized Infant Neuroblastomas Often Show Spontaneous Regression: Results of the Prospective Trials NB95-S and NB97

Barbara Hero, Thorsten Simon, Ruediger Spitz, Karen Ernestus, Astrid K. Gnekow, Hans-Guenther Scheel-Walter, Dirk Schwabe, Freimut H. Schilling, Gabriele Benz-Bohm, and Frank Berthold

From the Children's Hospital, University of Cologne; Children's Hospital, Augsburg; Children's Hospital, University of Tuebingen; Children's Hospital, University of Frankfurt, Frankfurt; and the Olgahospital, Stuttgart, Germany.

Submitted May 25, 2007; accepted December 14, 2007.

Supported by grants from the Deutsche Krebshilfe.

Presented in part at the Advances of Neuroblastoma Research Meeting, May 17-20, 2006, Los Angeles, CA.

Clinical trials Nos. NCT00002803 and NCT00017225.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/08/2609-1504/$20.00

DOI: 10.1200/JCO.2007.12.3349

ABSTRACT

Purpose
The excellent prognosis of localized neuroblastoma in infants, the overdiagnosis observed in neuroblastoma screening studies, and several case reports of regression of localized neuroblastoma prompted us to initiate a prospective cooperative trial on observation of localized neuroblastoma without cytotoxic treatment.

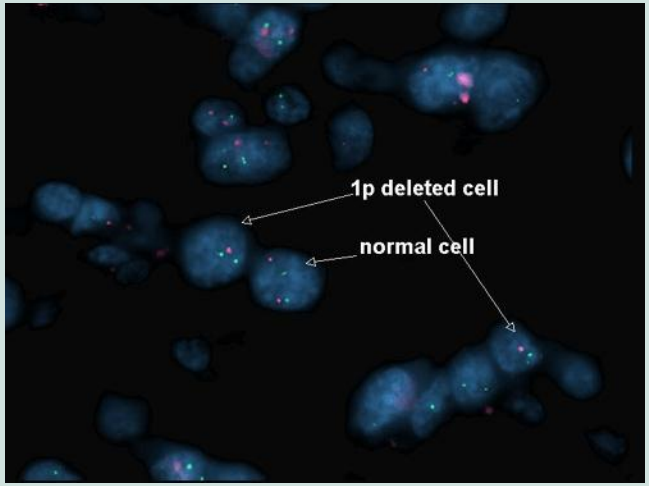
Patients and Methods
For infants with localized neuroblastoma without *MYCN* amplification, chemotherapy was scheduled only in cases with threatening symptoms; otherwise, the tumor was either resected or observed by ultrasound and magnetic resonance imaging (MRI).

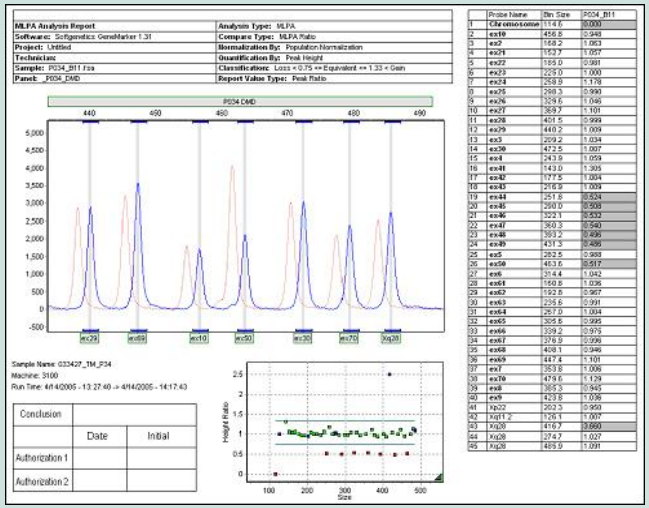
Results
Of 340 eligible participants, 190 underwent resection, 57 were treated with chemotherapy, and 93 were observed with gross residual tumor. Of those 93 patients with unresected tumors, spontaneous regression was seen in 44, local progression in 28, progression to stage 4S in seven, and progression to stage 4 in four. Time to regression was quite variable, with first signs of regression noted 1 to 18 months after diagnosis and in 15 of 44 patients even after the first year of life. So far, complete regression was observed in 17 of 44 patients 4 to 20 months after diagnosis. Known clinical risk factors were not able to differentiate between patients with regression and regional or metastatic progression. Overall survival (OS; 3-year OS, 0.99 ± 0.01) and metastases-free survival (rate at 3 years, 0.94 ± 0.03) for patients with unresected tumors was excellent and was not different from patients treated with surgery or chemotherapy.

Conclusion
Spontaneous regression is regularly seen in infants with localized neuroblastoma and is not limited to the first year of life. A wait-and-see strategy is justified in those patients.

J Clin Oncol 26:1504-1510. © 2008 by American Society of Clinical Oncology

Infant localised tumours





- Good prognosis up to 18 months of age
- Well defined predictors of worse prognosis
  - MYCN
  - 11q aberrations
  - Other genetic markers?

<u>Histology required</u>

Surgical Risk Factors in Primary Surgery for Localized Neuroblastoma: The LNESG1 Study of the European International Society of Pediatric Oncology Neuroblastoma Group

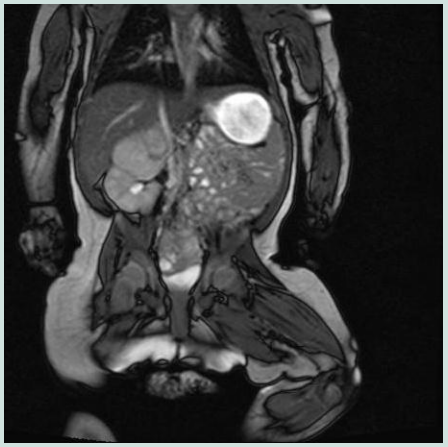
Giovanni Cecchetto, Veronique Mosseri, Bruno De Bernardi, Pierre Helardot, Tom Monclair, Elisa Costa, Ernst Horcher, Sylvia Neuenschwander, Paolo Tomà, Antonino Rizzo, Jean Michon, and Keith Holmes

Image Defined Risk Factors

Negative

L1

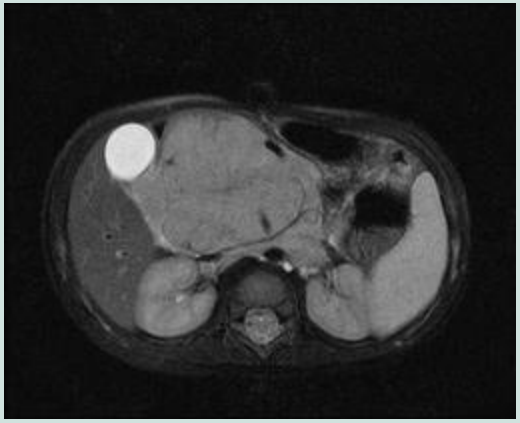
Resect

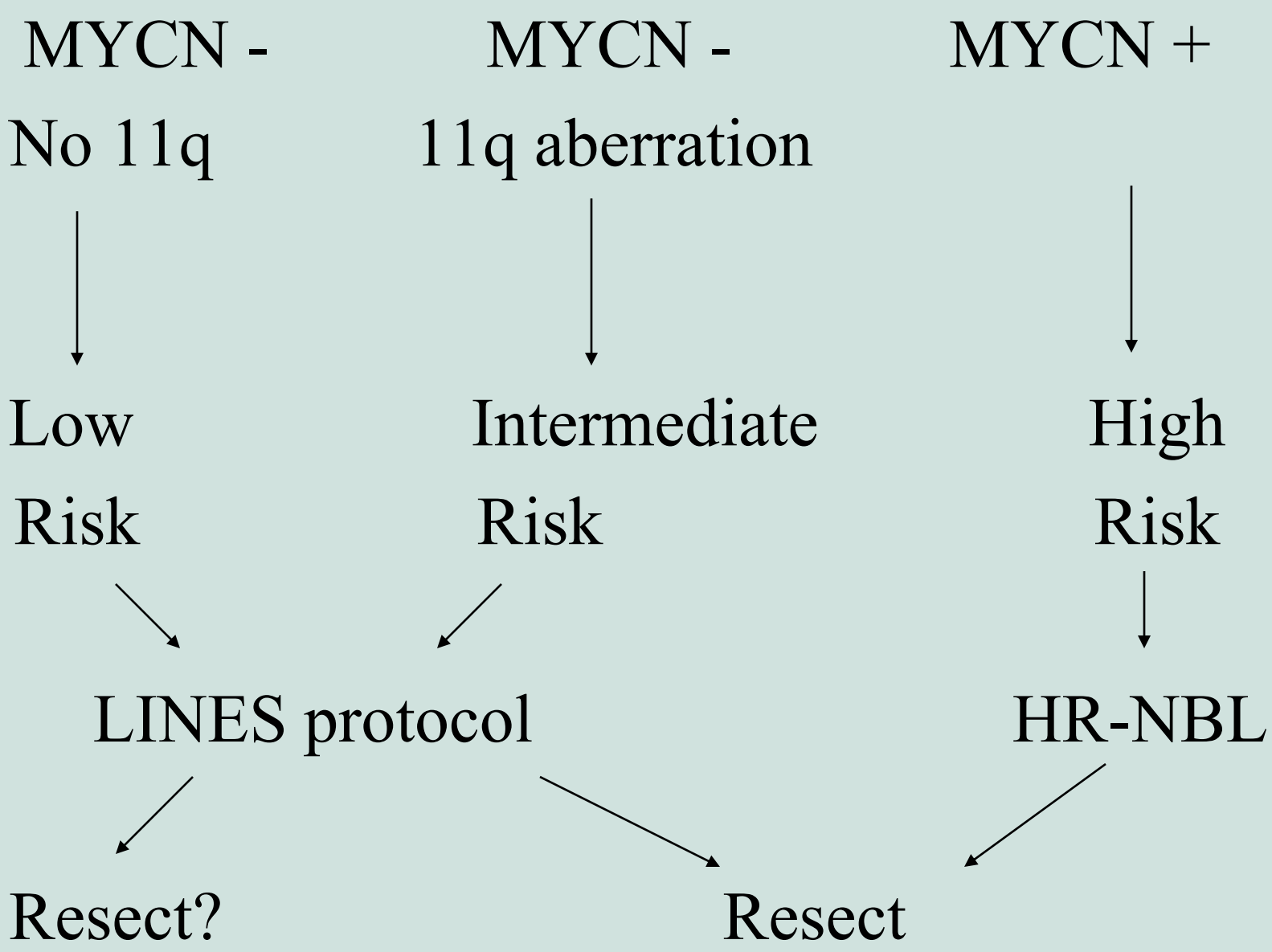


Positive

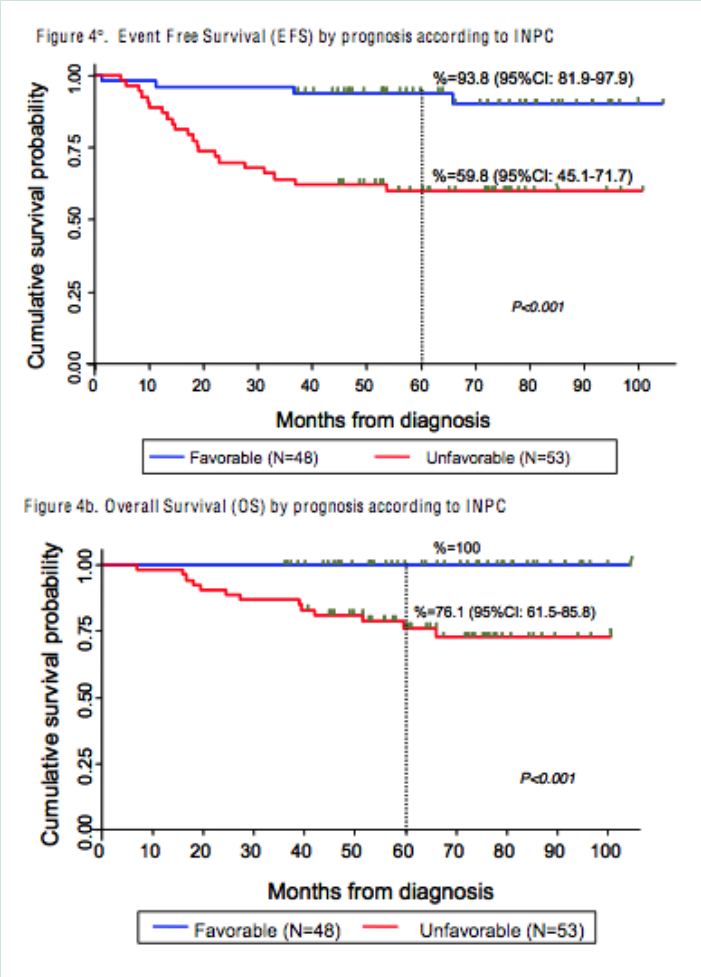
L2

Biopsy

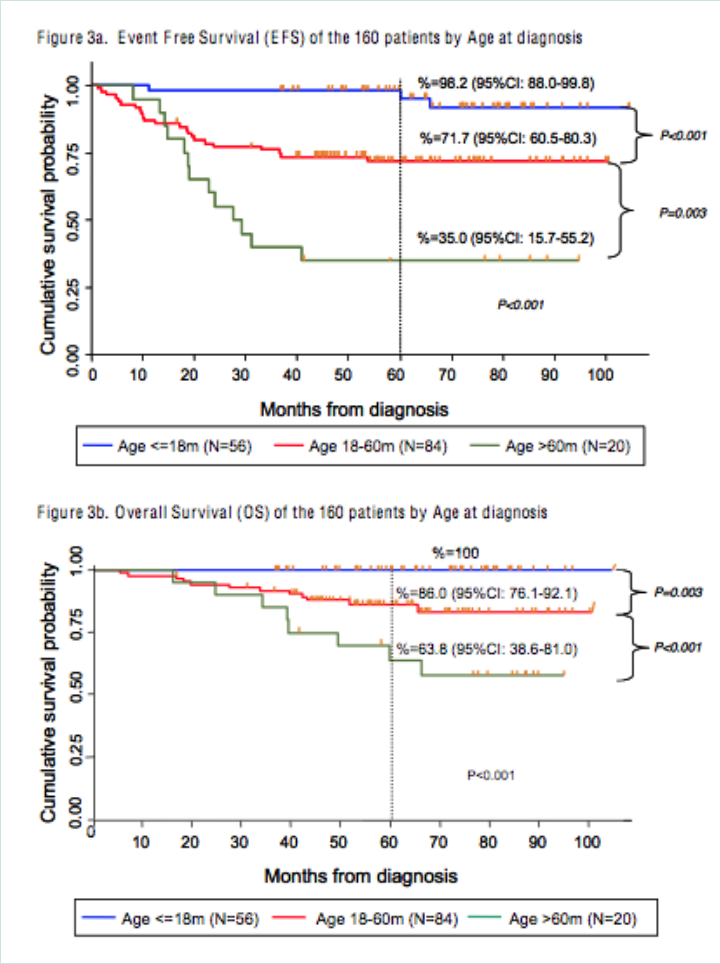



MYCN -
No 11q
MYCN -
11q aberration
MYCN +
Low
Risk
Intermediate
Risk
High
Risk
LINES protocol
HR-NBL
Resect?
Resect

SIOPEN unresectable study: Impact of age & pathology



Pathology



Age

COG data

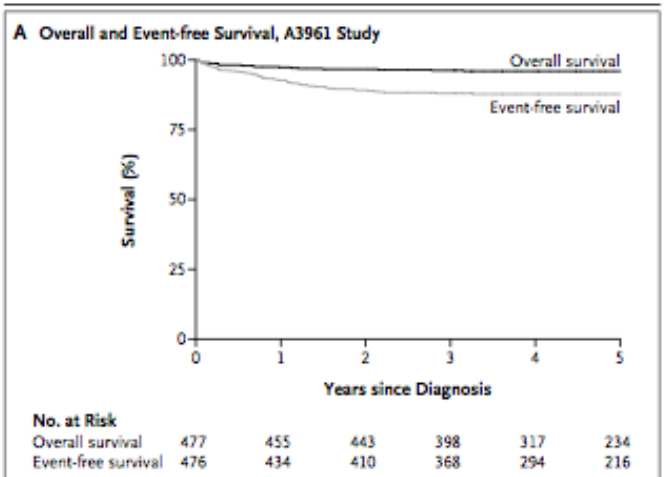
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Outcome after Reduced Chemotherapy for Intermediate-Risk Neuroblastoma

David L. Baker, M.D., Mary L. Schmidt, M.D., Susan L. Cohn, M.D., John M. Maris, M.D., Wendy B. London, Ph.D., Allen Buxton, M.S., Daniel Stram, Ph.D., Robert P. Castleberry, M.D., Hiroyuki Shimada, M.D., Anthony Sandler, M.D., Robert C. Shamberger, M.D., A. Thomas Look, M.D., C. Patrick Reynolds, M.D., Ph.D., Robert C. Seeger, M.D., and Katherine K. Matthay, M.D., for the Children's Oncology Group*

- Phase 3 non randomized trial
  - Reduce chemotherapy
  - Maintain >90% survival
  - Stratified into 2 treatment arms
- Chemotherapy (carboplatin, etoposide, cyclophos, doxorubicin)
  - FH: 4 cycles
  - UH: 8 cycles
- Not a surgical study
  - Surgery to completely remove the tumor where feasible
  - Variable timing
  - Early resection recommended if possible, as may 'down-stage' the tumor
- Radiotherapy not specified



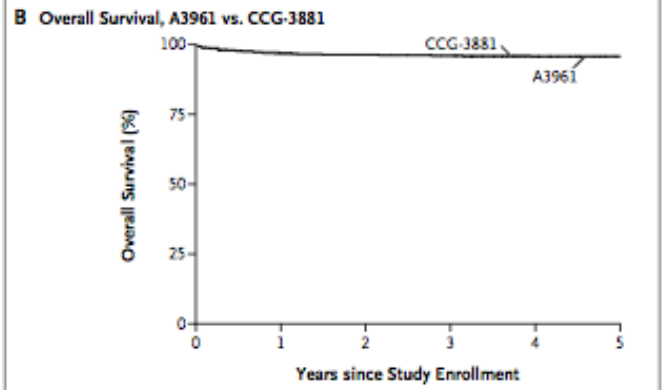


Figure 1. Event-free and Overall Survival among Patients with Intermediate-Risk Neuroblastoma.

Panel A shows overall and event-free survival in the Treatment for Infants and Children with Intermediate-Risk Neuroblastoma study (A3961), and Panel B shows overall survival among the 476 patients in the A3961 study as compared with overall survival among the 276 patients in the Children's Cancer Group study (CCG-3881).

Ref: Baker NEJM 2010,363;1313-23

European Infant Study (99.0 & 99.1)
-effect of chemotherapy

- Children under 1 year of age at diagnosis
  - MYCN negative
  - No metastases
- 454 eligible infants
- Surgical Risk Factors assessed in 407

- 204 risk factor positive
  - 11q status not recorded
  - Assume most 'low risk'

- 92 reassessed after chemotherapy
  - 38 (41%) now risk factor negative

Unpublished data

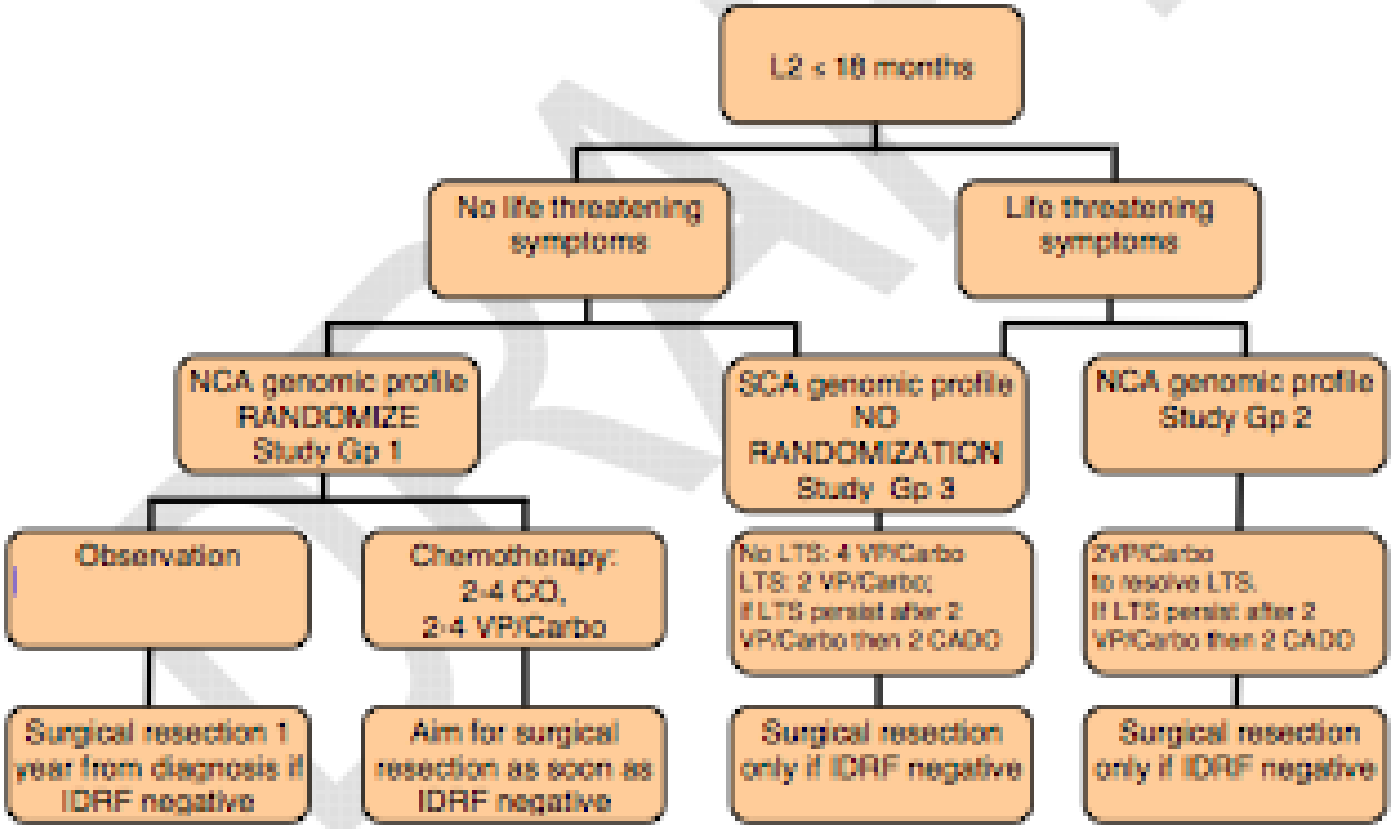
Risks of resection

Author	Patient group	No of Patients	Major complications %	Nephrectomies %	Deaths %
Baker (2010)	COG intermediate	479	28	1	0
Cecchetto (2005)	Localized: Risk factor positive	155	17	18	0.7
INES (unpublished)	Infant localized: Risk factor positive	55	17	6	0
Cecchetto (2005)	Localized: risk factor negative	363	5	0.3	0.3
INES (unpublished)	Infant localised: risk factor negative	195	3	1	0.5

Residual tumour post-chemotherapy

- IDRFs not validated
- Data required
- IDRF negative: resect
- IDRF positive: observation

LINES: randomisation


L2 < 18 months
No life threatening symptoms
Life threatening symptoms
NCA genomic profile RANDOMIZE Study Gp 1
SCA genomic profile NO RANDOMIZATION Study Gp 3
NCA genomic profile Study Gp 2
Observation
Chemotherapy: 2-4 CO, 2-4 VP/Carbo
No LTS: 4 VP/Carbo LTS: 2 VP/Carbo; If LTS persist after 2 VP/Carbo then 2 CADO
2xP/Carbo to resolve LTS. If LTS persist after 2 VP/Carbo then 2 CADO
Surgical resection 1 year from diagnosis if IDRF negative
Aim for surgical resection as soon as IDRF negative
Surgical resection only if IDRF negative
Surgical resection only if IDRF negative

MYCN amplification status and prognosis in infant neuroblastoma.

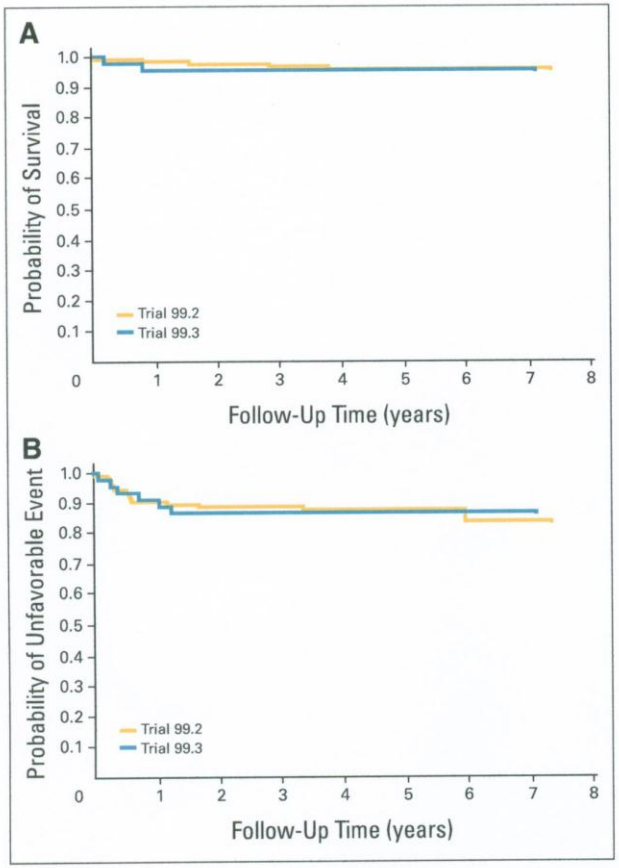
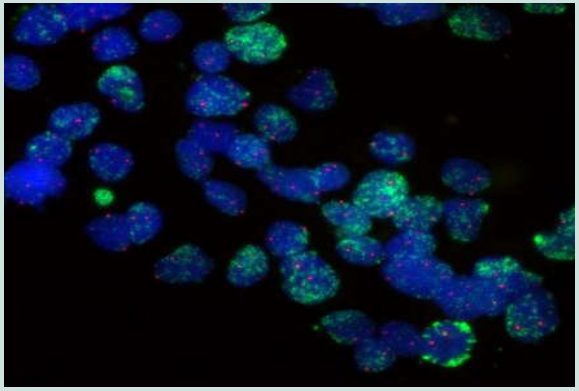
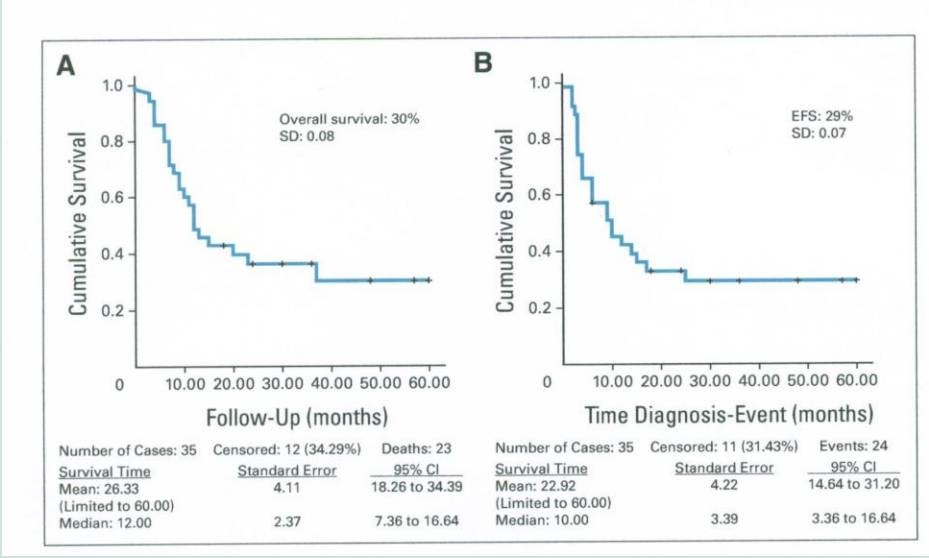


Fig 2. (A) Overall survival and (B) event-free survival of 99.2 and 99.3 trial patients.

Metastatic MYCN **non amplified** < 1yr patients





Number of Cases: 35	Censored: 12 (34.29%)	Deaths: 23
Survival Time	Standard Error	95% CI
Mean: 26.33 (Limited to 60.00)	4.11	18.26 to 34.39
Median: 12.00	2.37	7.36 to 16.64

Number of Cases: 35	Censored: 11 (31.43%)	Events: 24
Survival Time	Standard Error	95% CI
Mean: 22.92 (Limited to 60.00)	4.22	14.64 to 31.20
Median: 10.00	3.39	3.36 to 16.64

Metastatic MYCN **amplified** < 1yr patients

Metastatic infant tumours

Is there any grounds to treat primary tumour differently from localised infant tumours?

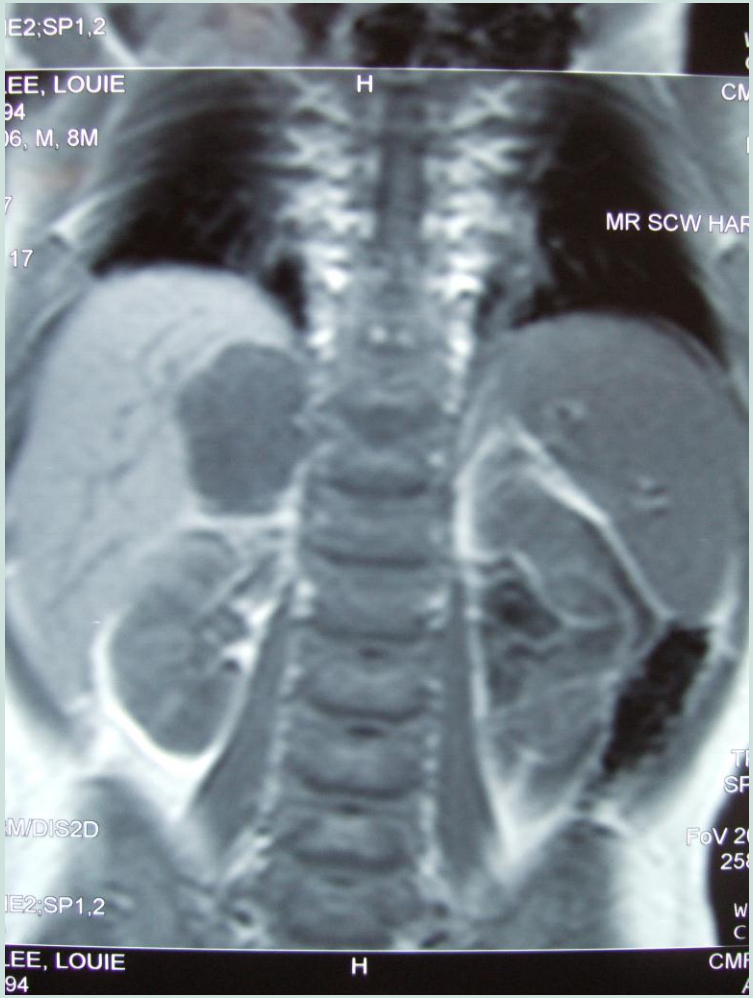
age thresholds:

- L1 &L2) <18 m
- M <12 m

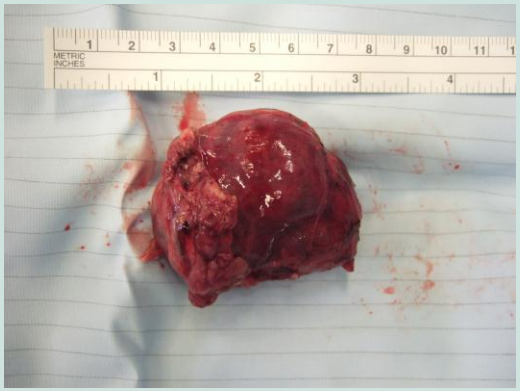
MS tumours

- No significant change since Evans staging in 1967
- ‘special’
  - Small primary
  - Light bone marrow infiltration
  - Metastases only in favourable sites
    - Skin/soft tissues
    - liver

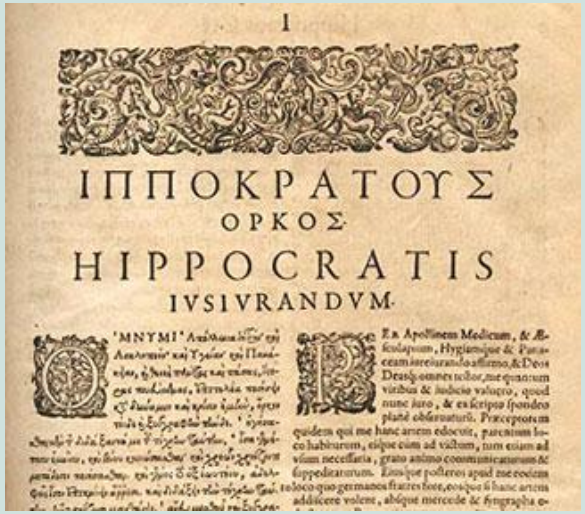
Healthy infant



- Antenatal hydronephrosis
- Postnatal US
  - Improving
- Further US
  - Suprarenal mass
- Catecholamines slightly raised



Bone marrow infiltration: histology required



Conclusions

- Small incidental neonatal tumours can be observed without histology
- All other tumours are stratified by histology/cytogenetics
- Only resect at presentation if IDRF negative
- IDRF positive: biopsy to guide chemo regime
- If favourable biology carefully balance risks of resection vs. risk of tumour

Default: Do no harm