Opsoclonus Myoclonus Ataxia (OMA) Syndrome and Oncology

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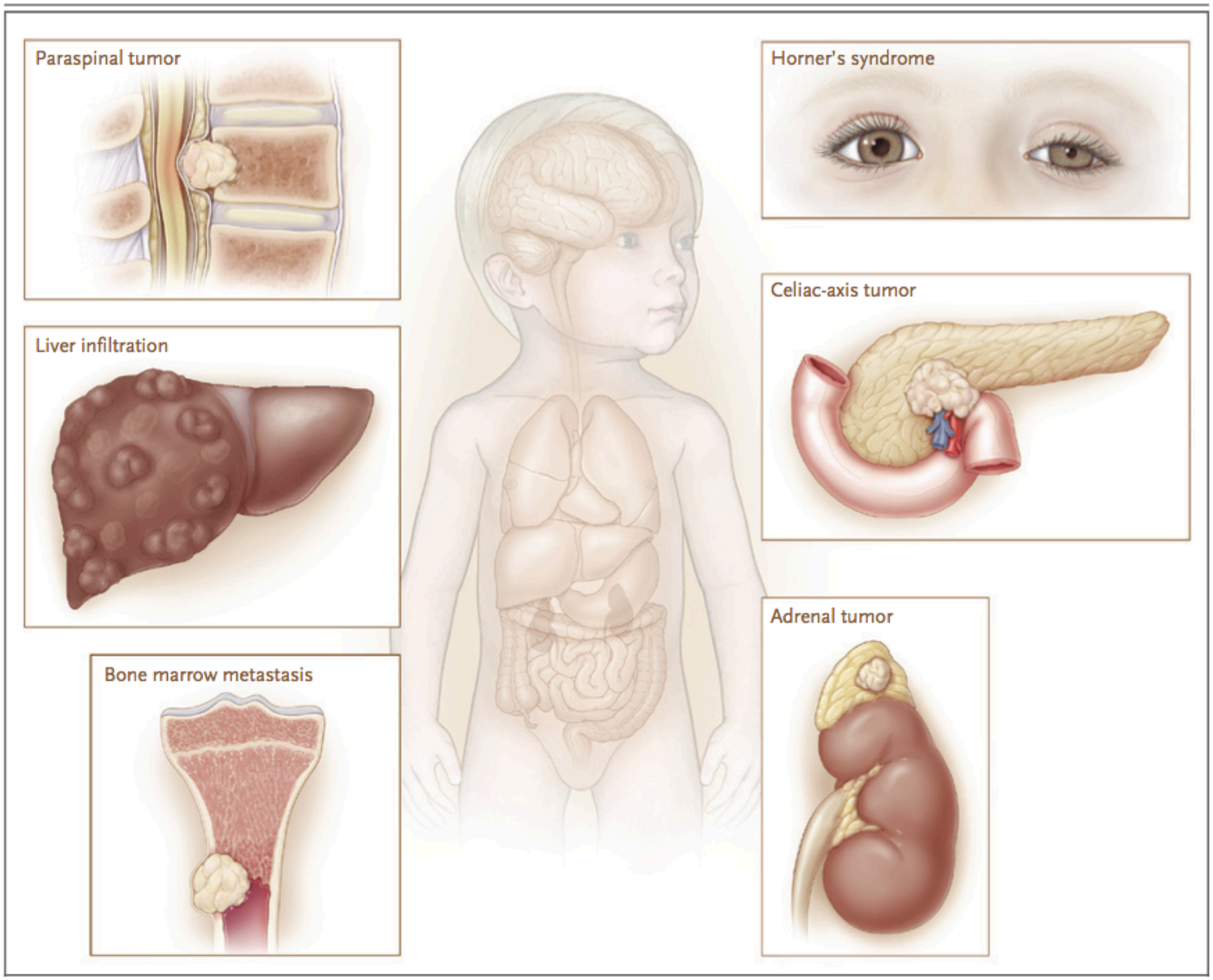
Neuroblastoma

- 2nd most common solid tumor in pediatrics (behind brain tumors)
- Most common solid tumor in < 1 year olds
- Contribute 15% of cancer-related deaths
- ~650 cases/year in US
- Median age 22 months
  - 36% < 1 year
  - 79% < 4 years
- 2/3 of patients present with metastases
- Less than 5% are > 10 years



Maris, N Engl J Med 2010;362:2202-11.

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Neuroblastic Tumors with OMA

- Gambini et al, Virchows Arch 442:555, 2003:
  - 10/15 (66%) Ganglioneuroblastoma, intermixed
  - 4/15 (27%) Neuroblastoma s of NB with OMA had abundant interstitial or perivascular lymphoid infiltrates
  - 1/15 (7%) Ganglioneuroma

Other Clinical Features

Tate et al, Neurology A447, 2003:

88 cases (41% with NB)

- Irritability and mood disturbances
- Facial palsy described rarely; drooling common
- Head tilt and strabismus in 33%
- Seizures in 10%
- Early symptoms: falling, body jerks, drooling
- Later symptoms: opsoclonus, hypotonia, speech problems
- Misdiagnosis as acute cerebellitis (brain inflammation) common

OMA with Neuroblastoma

- > 50% of OMS = paraneoplastic syndrome
- 2-3% of neuroblastoma present with OMS
- Prognosis of tumor is excellent
  - 90% 2 year survival
- Prognosis for OMS
  - 70-80% with neurologic sequelae
  - Motor and speech delay, behavioral difficulties, cognitive deficits
- Favorable disease stage correlates with worse neurologic outcome

POG Experience with OMA

(Russo et al, MPO 28:284, 1997)

- 29 children with NB and OMA, 1983-1993
- Stage A 18, stage B 3, stage C 7, stage D 1
- *MYCN* amplification (High Risk) in 0/17
- Treatment NB
  - surgery alone 19/29
  - surgery + chemotherapy 10/29
- Treatment OMA
  - Steroids 26 (prednis. 12/ ACTH 14)
  - IVIG 6

POG Experience with OMA (cont)

Outcome of OMA

- Resolution OMA 18/29 (62%)
  - 37% with surgery alone in one study
- Persistent neurologic deficit in 20/29 (69%)
  - speech delay
  - cognitive
  - motor
  - behavioral
- Complete recovery in 9 patients, of whom 6 received chemotherapy as part of treatment

CCG Experience with OMA

(Rudnick et al, MPO 36:612. 2001)

- Questionnaire study 1980-1994 all NB with serum banked
- Demographics, presentation, treatment, survival and neurologic outcome
- Sera tested for variety of anti-neuronal antibodies (case-control)
- OMA in 21/675 patients (3%)

Presentation of OMA

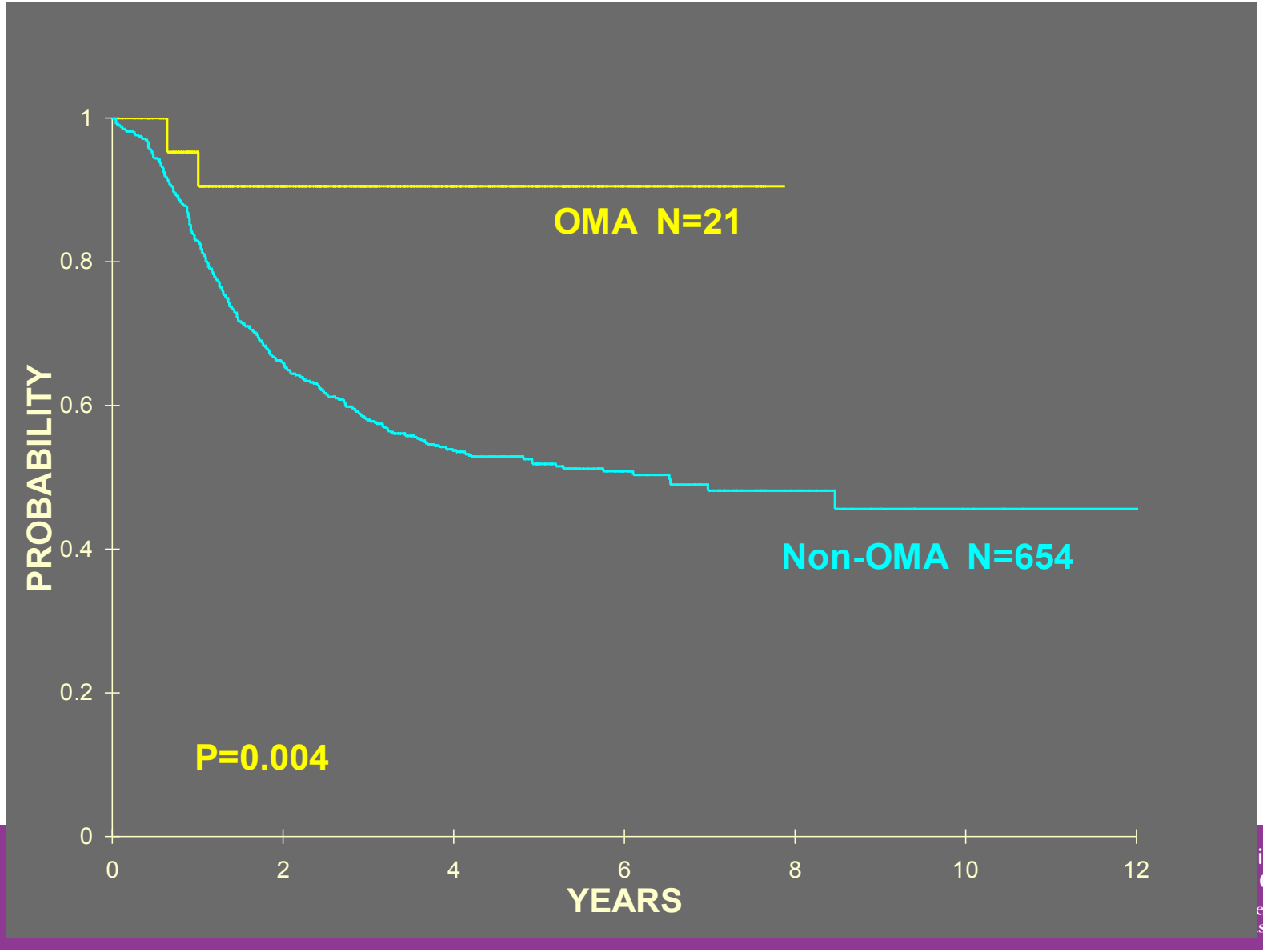
- Opsoclonus, Myoclonus and Ataxia 13 (60%)
- Two of the above 6 (30%)
- Either opsoclonus or ataxia alone 2 (10%)

- Time to diagnosis of NB <6 months 18 (85%)
- Time to diagnosis of NB ≥6 months 3 (15%)

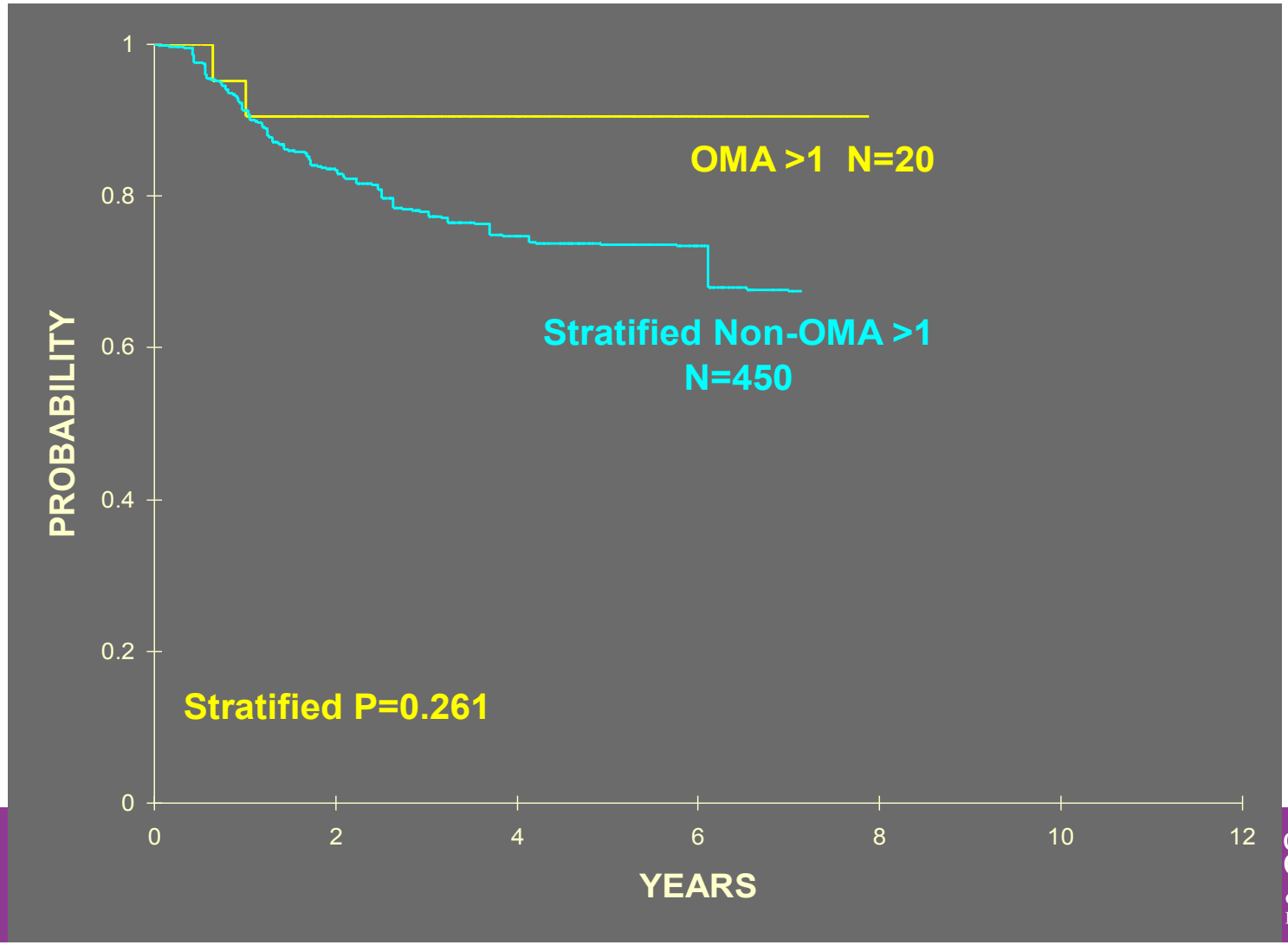
Treatment: 15 resolved OMA

- Treatment of OMA
  - Steroids 10
  - Steroids + ACTH 1
  - ACTH alone 2
  - IVIG + steroids/ACTH 5
  - None 3
- Treatment of Tumor
  - Surgery + chemotherapy 12 (57%)
  - Surgery alone 9 (43%)

Survival of Patients with OMA



Survival with OMA
Age >1 and Stage-stratified



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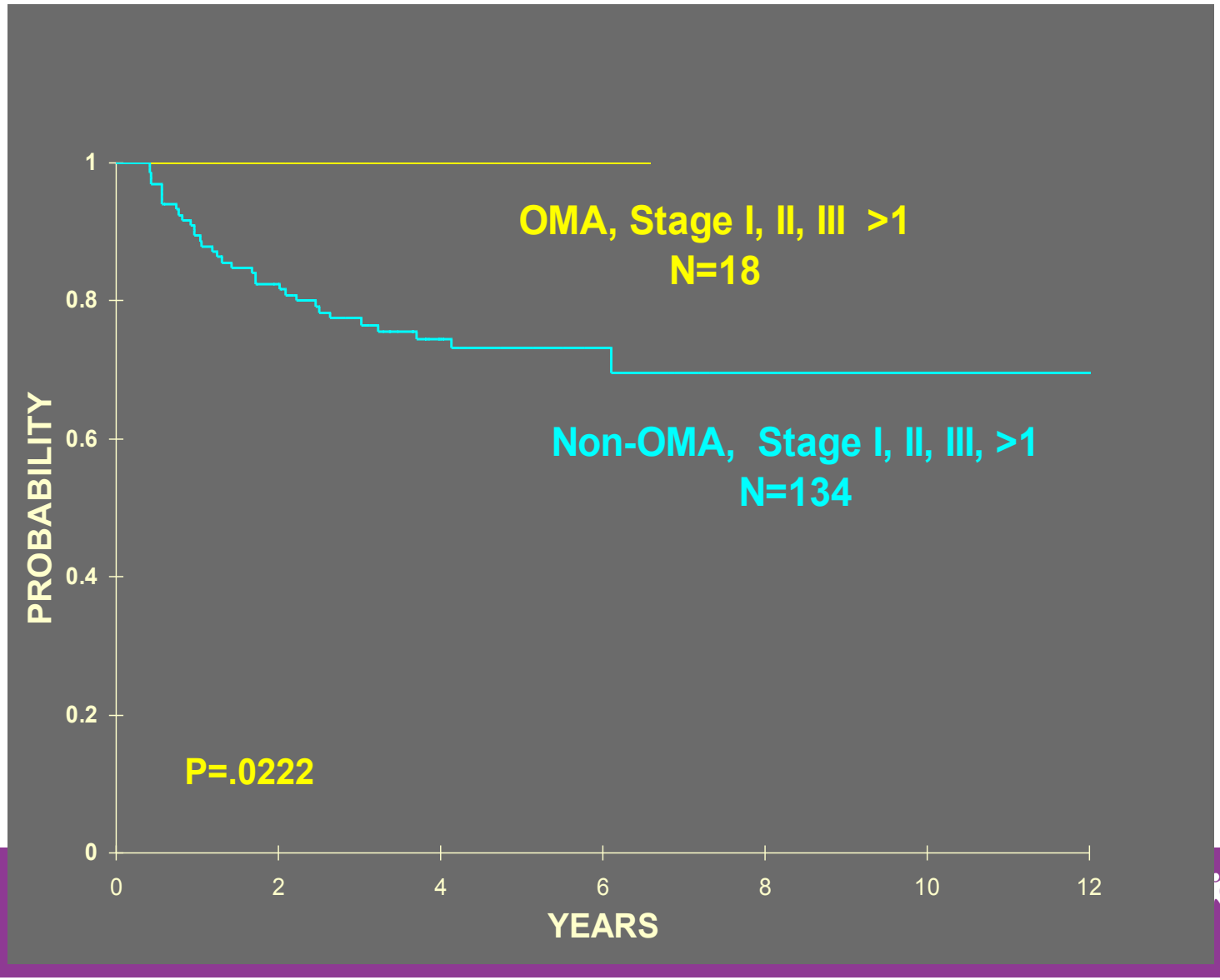
Survival with Loco-regional Neuroblastoma and OMA



Patient characteristics in OMA different than non-OMA

- Age: Only 1/21 OMA patients <1 yr at Dx
- Advanced stage (3+4) in 43% OMA vs. 75% non-OMA
- Male:female: 0.5 in OMA vs. 1.22 in non-OMA*
- Abdominal primary in 69% vs. 79%*
- *MYCN* amplification in 6% vs. 23%*
- Histology unfavorable in 18% vs. 52%*

*None of these differences significant after stratification for stage and age

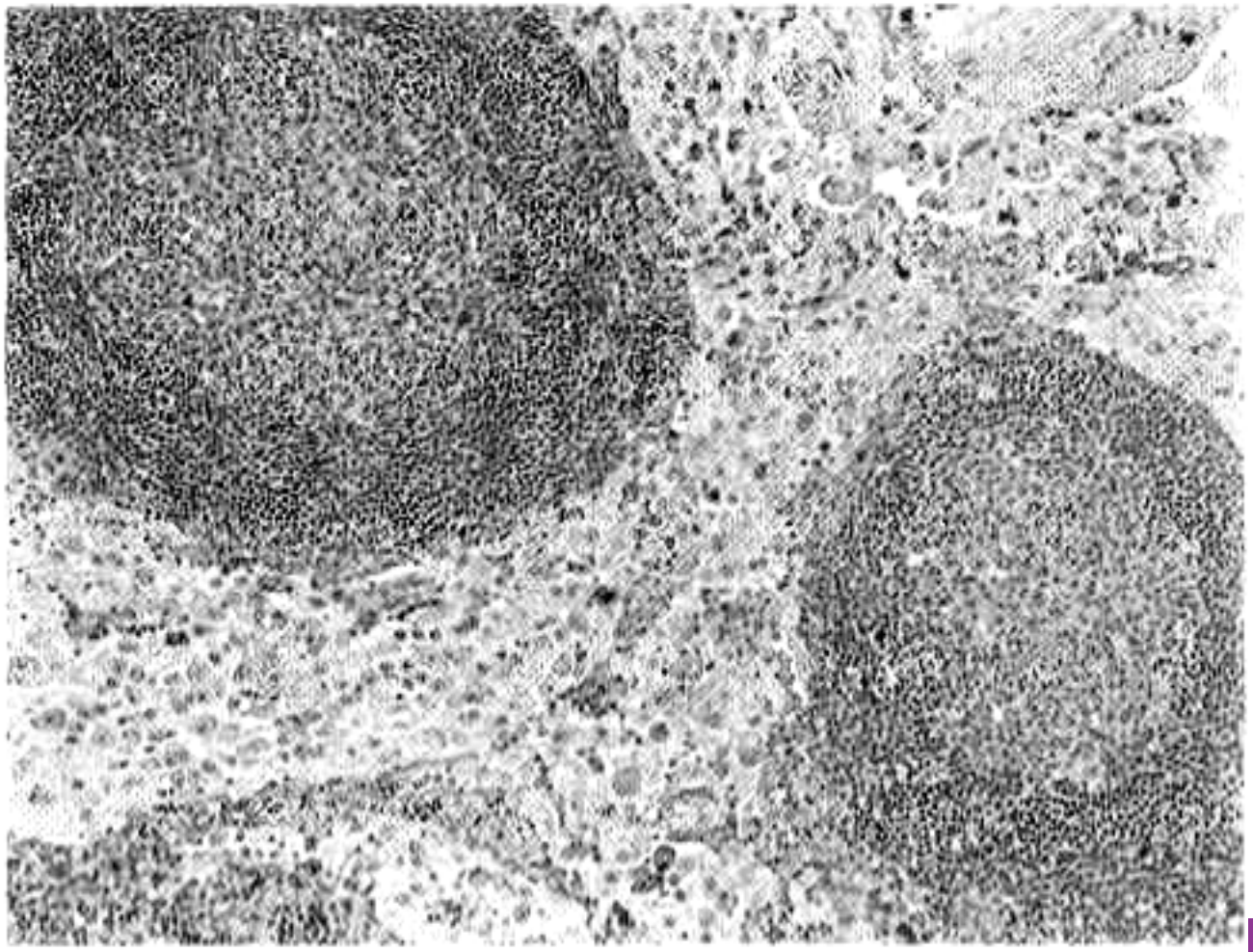
Relative Risk of Neurologic Sequelae

	N	N-Sequelae	RR	P-value
Age <2	12	10	1.14	
≥2	7	4	0.78	0.3
Stage 1+2	12	11	1.25	
3+4	7	3	0.59	**0.04**
OMA to Dx <6 mo.	17	13	1.04	
≥6 mo.	2	1	0.71	0.47
Primary abdominal	11	9	1.06	
non-abd	7	5	0.93	0.62

Relative Risk of Neurologic Sequelae cont

	N	N-Sequelae	RR	P-value
Rx OMA steroids	13	9	0.91	
IVIG + steroids	4	4	1.33	
none	2	1		0.52
Rx tumor: surgery	12	10	1.14	
Surgery + chemo	7	4	0.78	0.30
Antineuronal Ab +	11	7	0.90	
Ab -	3	3	1.43	0.51

Lymphocytic infiltrates and follicles in neuroblastoma with OMA



(Cooper et al, MPO 36:623, 2001)

Lymphocyte Infiltrates

- Gambini et al, Virchows Arch 442:555, 2003:
  - 12/15 (80%) cases of NB with OMA had abundant interstitial or perivascular lymphoid infiltrates
  - 91 age- and stage-matched NB without OMA had much less lymphoid infiltration

Antineuronal Antibodies

- Dalmau et al, Cancer 75:99, 1995:
  - 4/71 NB had anti-Hu Ab, but antigens present on more than half the tumors without Ab
  - Seropositive patients had longer survival
- Connolly et al J Pediatr 130:878, 1997:
  - 9 children with OMA (3 NB) and 41 controls
  - All OMA had anti-neuronal Ab; none of controls

Antineuronal Antibodies

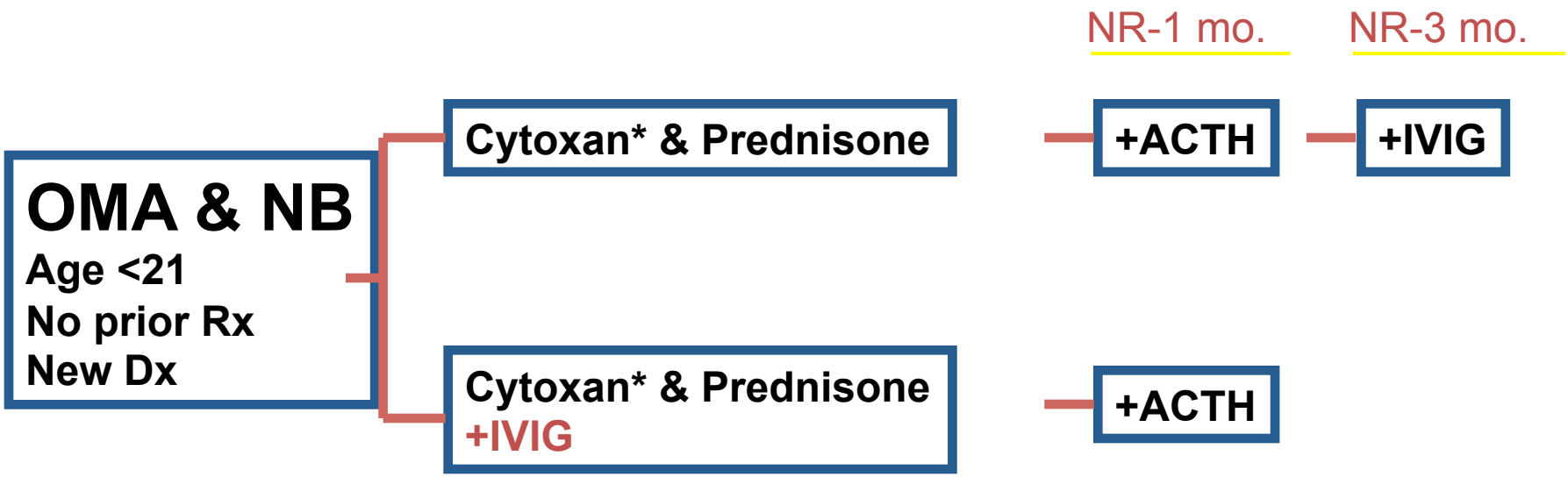
(Antunes et al. JPHO 2000; 22:315)

- Sera from 16 children with OMA associated with NB, and 48 age-stage matched controls
- Human cerebellum and rat brain IHC
- Western Blot using neurons, Purkinje cells, HuD, NBL cells
- 81% of OMA Vs. 21% of controls had IgG anti-neuronal Ab

COG OMA Study: ANBLOOP3 Specific Aims

- Outcome using chemotherapy + prednisone
- Determine in a randomized study whether IVIG improves response of OMA
- Determine whether chemotherapy, prednisone and IVIG improves functional outcome compared to historical control
- Investigate the biology of OMA
  - Antineuronal antibodies, CSF, MRI, Tumor biology
- Better define the long-term prognosis

ANBL00P3 Schema



*Stage 3/4: A3973 or A3961 + Prednisone ± IVIG

NR - 6 mo.: Off protocol therapy

OMA summary

- Neurologic and developmental sequelae in about 70%
- Survival >90%
- Low stage in 80%
- Anti-neuronal antibodies in >80%
- Unknown if more immunosuppressive treatment can prevent late sequelae

OMA and Oncology

Questions?