-NEUROBLASTOMA-

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DIAGNOSIS

CELL OF ORIGIN:

- Neural Crest cells in sympathetic NS (Adrenal medulla or paraspinal)

PRESENTATION:

- Abdominal mass
- Retrobulbar
- Liver
- Bone

PARANEOPLASTIC SX:

- VIP syndrome
- Opsoclonus/ Myoclonus/ Ataxia syndrome

WORK UP

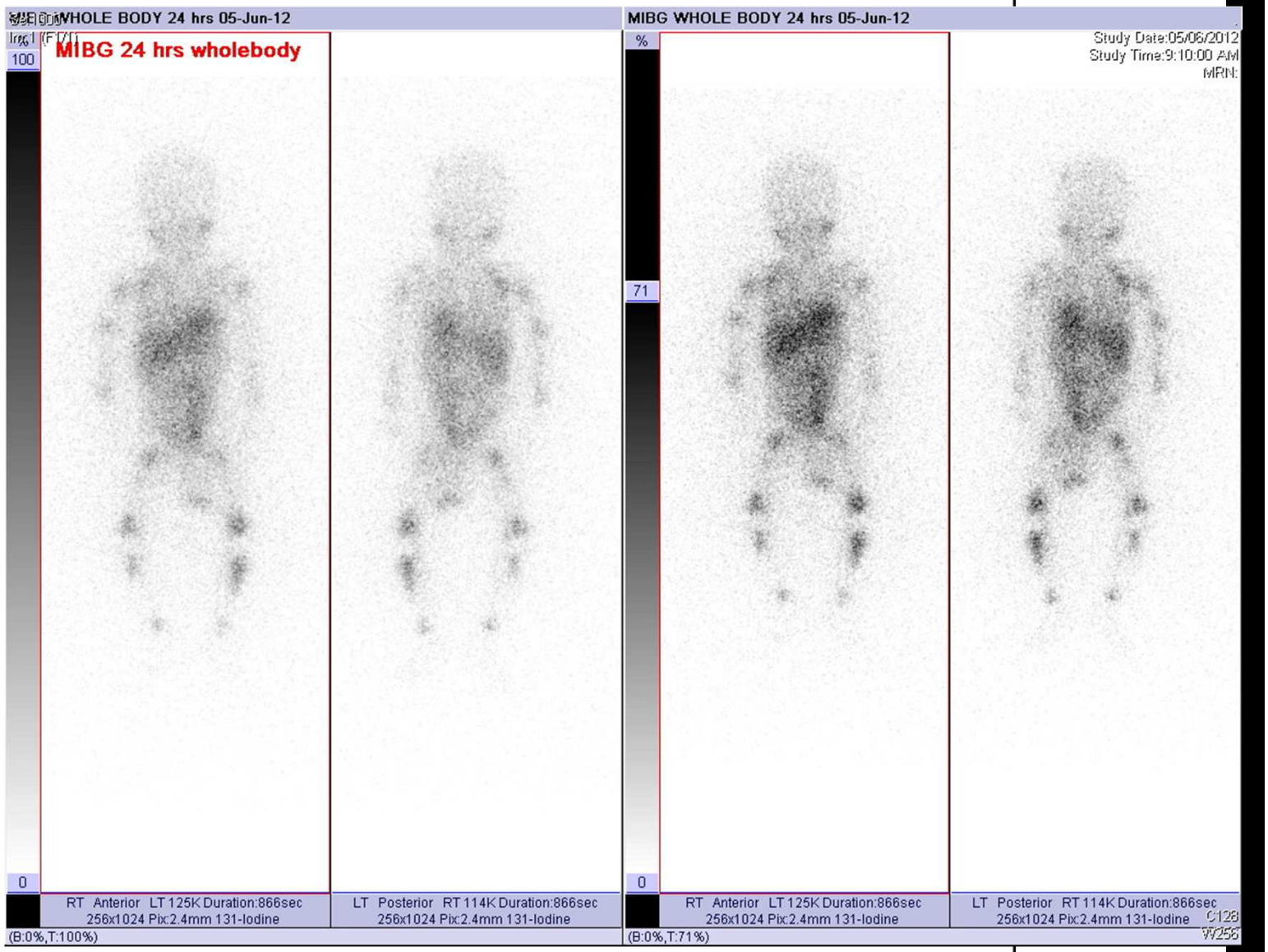
STAGING WORK UP:

- **CT** contrast OR **MRI** contrast (of primary site)
  OR **FDG-PET** (for primary and for residual after rx and for MIBG negative tumors)
- **I-123 MIBG** scan (superior to FDG-PET for bone and soft tissue mets)
- **Bone Marrow Biopsy**
- Urine **VMA** /mg creat AND **HVA** /mg creat
- Serum Dopamine and Serum Norepinephrine (as necessary only)

BIOPSY:

- Adequate tissue by **trucut or open**
- Accurate histology classification
- **MYCN** amplification and **11q** Deletion by FISH

Brisse, Consensus Project, INRG, Radiology 2011;261(1): 243-
Papathanasiou, J Nucl Med 2011;53(4): 519-


MIBG WHOLE BODY 24 hrs 05-Jun-12
MIBG 24 hrs wholebody
100
0
RT Anterior LT 125K Duration:866sec
256x1024 Pix:2.4mm 131-Iodine
LT Posterior RT 114K Duration:866sec
256x1024 Pix:2.4mm 131-Iodine
(B:0%,T:100%)
MIBG WHOLE BODY 24 hrs 05-Jun-12
%
71
0
Study Date:05/06/2012
Study Time:9:10:00 AM
MRN:
RT Anterior LT 125K Duration:866sec
256x1024 Pix:2.4mm 131-Iodine
LT Posterior RT 114K Duration:866sec
256x1024 Pix:2.4mm 131-Iodine
(B:0%,T:71%)

INTERNATIONAL NEUROBLASTOMA STAGING SYSTEM (INSS)

Sta	
1	
2A	
2B	
3	
4	
4S	

Brodeur, JCO 1993;11(8): 1466-

COG RISK GROUPS

NSS Stage	Age	MYCN	Histopathology	DNA ploidy	Risk group
			SHIMADA		
1	0–21 years	Any	Any	Any	Low
2A/2B	<365 days	Any	Any	Any	Low
	≥365 days – 21 years	Non-amp	Any	–	Low
	≥365 days – 21 years	Amp	FH	–	Low
	≥365 days – 21 years	Amp	UH	–	High
3	<365 days	Non-amp	Any	Any	Intermediate
	<365 days	Amp	Any	Any	High
	≥365 days – 21 years	Non-amp	FH	–	Intermediate
	≥365 days – 21 years	Non-amp	UH	–	High
	≥365 days – 21 years	Amp	Any	–	High
4	<365 days	Non-amp	Any	Any	Intermediate
	<365 days	Amp	Any	Any	High
	≥365 days – 21 years	Any	Any	–	High
4S	<365 days	Non-amp	FH	DI > 1	Low
	<365 days	Non-amp	Any	DI = 1	Intermediate
	<365 days	Non-amp	UH	Any	Intermediate
	<365 days	Amp	Any	Any	High

Brodeur, JCO 1993;11(8): 1466-

INTERNATIONAL NEUROBLASTOMA RISK GROUP (INRG) STAGING SYSTEM

Stage	Description
L1	Localised tumour not involving vital structures, as defined by list of IDRFs*, and confined to one body compartment Includes spinal invasion that dos not fulfil the criteria for an IDRF
L2	Local-regional tumour with one or more IDRFs Includes ipsilateral tumour extending across 2 contiguous body compartments eg lower chest to upper abdomen
M	Distant metastatic disease (except stage MS) Includes distant lymph nodes and contralateral involvement of 2 body compartments eg right chest and left abdomen Ascites and pleural effusion, with or without identifiable malignant cells, not included
MS	Metastatic disease in children younger than 18 months (547 days), with metastases confined to skin, liver, and/or bone marrow Bone marrow involvement consists of < 10% of nucleated cells in culture smears or biopsy MIBG –ve in bone/ bone marrow Primary tumour may be with or without IDRFs ie L1 or L2

Monclair, INRG Task Force, JCO 2009;27(2):298-

INRG STAGING SYSTEM – IMAGE DEFINED RISK FACTORS

Ipsilateral tumor extension within two body compartments:	Neck-chest, chest-abdomen, abdomen-pelvis
Neck:	Tumor encasing carotid and/or vertebral artery and/or internal jugular vein Tumor extending to base of skull Tumor compressing the trachea
Cervico-thoracic junction:	Tumor encasing brachial plexus roots Tumor encasing subclavian vessels and/or vertebral and/or carotid artery Tumor compressing the trachea
Thorax:	Tumor encasing the aorta and/or major branches Tumor compressing the trachea and/or principal bronchi Lower mediastinal tumor, infiltrating the costo-vertebral junction between T9 and T12
Thoraco-abdominal:	Tumor encasing the aorta and/or vena cava
Abdomen/pelvis:	Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament Tumor encasing branches of the superior mesenteric artery at the mesenteric root Tumor encasing the origin of the coeliac axis, and/or of the superior mesenteric artery Tumor invading one or both renal pedicles Tumor encasing the aorta and/or vena cava Tumor encasing the iliac vessels Pelvic tumor crossing the sciatic notch
Infiltration of adjacent organs/structures:	Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block and mesentery

INRG is an image based pre surgery staging system !

Monclair, INRG Task Force, JCO 2009;27(2):298-

INRG PRETREATMENT RISK GROUPS

Pretreatment risk group	INRG stage	Age (months)	Histology WHO	MYCN	11q aberration	Ploidy
Very low	L1/2		GN; GNBi			
	L1		GNBn; NB	NA		
	MS	<18		NA	No	
Low	L2	<18	GNBn; NB	NA	No	
	L2	≥18	GNBn; NB, diff	NA	No	
	M	<18	GNBn; NB, diff	NA	No	Hyperdiploid
Intermediate	L2		GNBn; NB	NA	Yes	
	M	<18		NA		Diploid
High	L1		GNBn; NB	A		
	L2	≥18	GNBn; NB	A		
	M	<18		A		
	M	≥18				
	MS	<18		NA	Yes	
	MS	<18		A		

Monclair, INRG Task Force, JCO 2009;27(2):298-

RX – LOW RISK GROUP

Resectable stg 1 or 2:

- **SURGERY ALONE** ***5YR OS 95 – 99%***

Symptomatic OR <50% Resection OR Progression after surgery:

- **CHEMOTHERAPY X 2 – 4 CYCLES AND SURGERY**
  5YR OS 99%

Asymptomatic AND <1 yr AND MYCN nonamplified:

- **OBSERVATION ALONE**

CHEMO AGENTS

Cyclophosphamide
Carboplatin
Etoposide
Doxorubicin

Strother, POG P9641, JCO 2012;30(15): 1842-

RX – INTERMEDIATE RISK GROUP

Favourable Histology:

- CHEMOTHERAPY X 4 CYCLES AND SURGERY
  5YR OS 98%

Unfavourable Histology:

- CHEMOTHERAPY X 8 CYCLES AND SURGERY
  5YR OS 93%

Life/organ threatening with slow response to chemo:

- RADIATION

CHEMO AGENTS

Cyclophosphamide
Carboplatin
Etoposide
Doxorubicin

Baker, COG A3961, NEJM 2010;363(14): 1313-

RX – HIGH RISK GROUP

INDUCTION

- Dose – intense VAC/ Etoposide+Cisplatinum x 6 – 7 cycles

OR

- Dose- intense Topotecan + Cyclophosphamide x 2 then VAC/EC x 4 cycles

LOCAL THERAPY

- Surgery
- Radiation (if indicated)

CONSOLIDATION

- Chemo x 1-2 cycles
- High Dose Melphalan + Busulfan and Autologous Stem Cell Transplant

MAINTENANCE

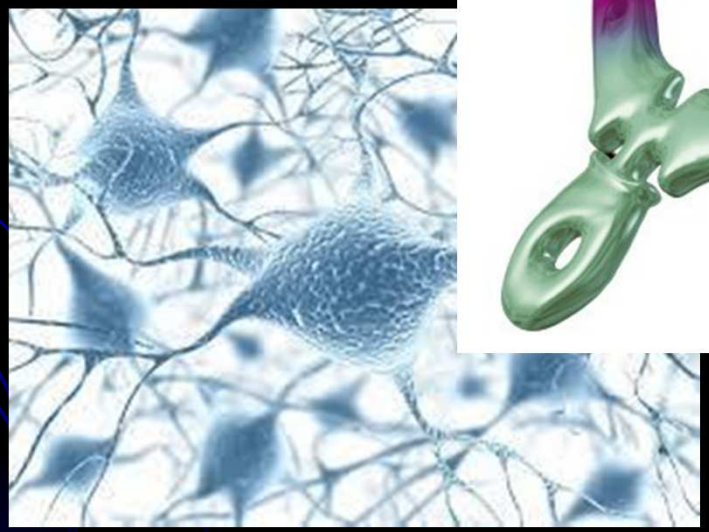
- Dinutuximab + GM-CSF + Interleukin2 x 5 cycles
- Isotretinoin x 6 cycles

5yr EFS 66%

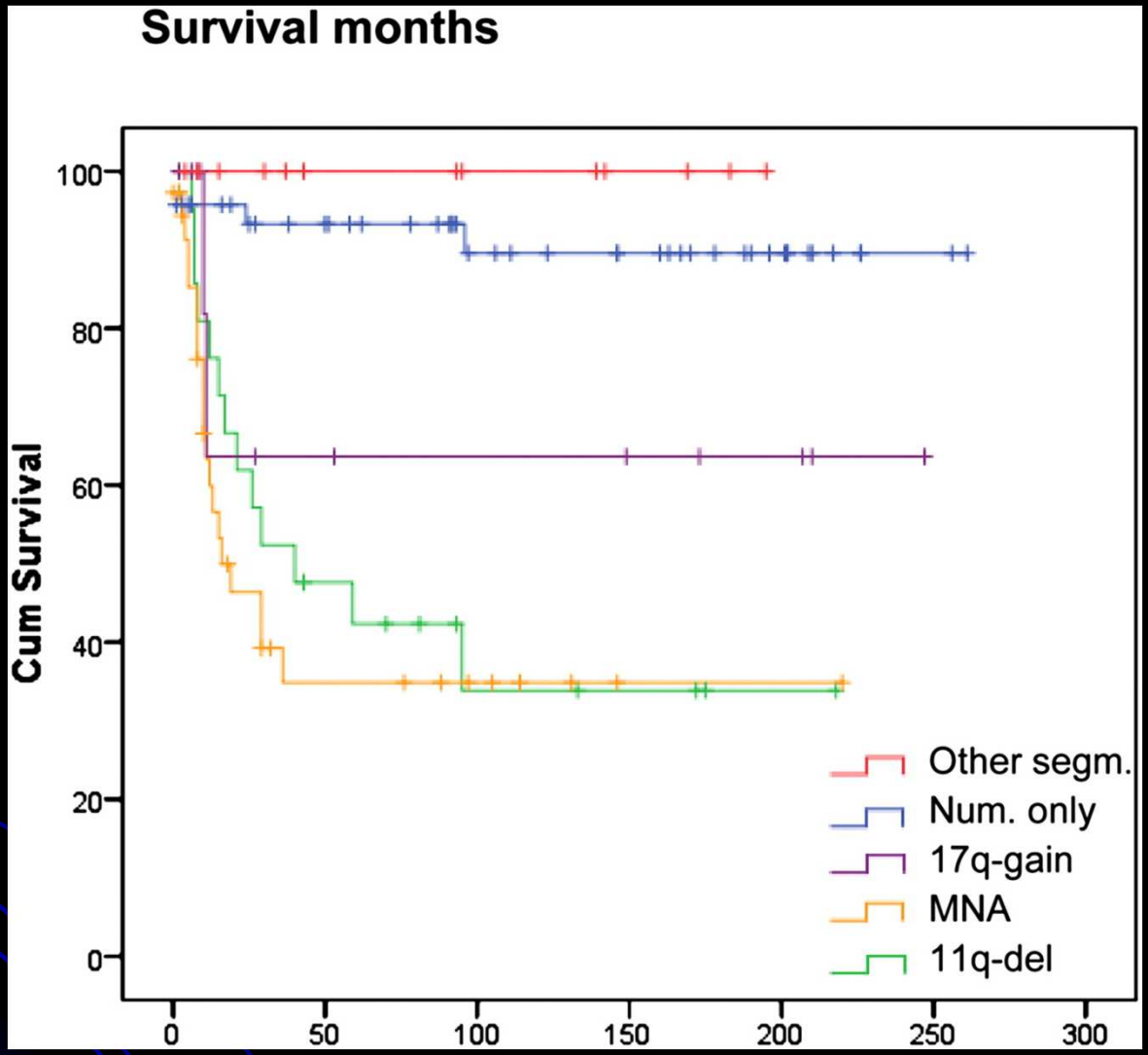
Kushner, JCO 1994;12(12): 2607-
Park, JCO 2011;29(33): 4351-
Granger, Ped Blood Ca 2012;59(5): 902-
Yu, NEJM 2010, 363(14): 1324-

AGENTS USED FOR HIGH RISK GROUP

CHEMO	TARGETED	DIFFERENTIATING	STEM CELL
CTX	Dinutuximab	Isotretinoin	High Dose **Bu+Cy**
Carboplat	(anti GD2 ab)	(13 cis RA)	AND autologous
Doxorubicin			**Stem Cell Transpl**
Ifosfamide			
Cisplatinum			
Vincristine			
Etoposide			
Topotecan			



OUTCOMES



Num = Whole chromosomal changes without segmental alterations

Segm = Segmental alterations (1p/3p/11q deletions OR 1q/2p/17q gains)

MNA = MYCN amplified ***MS 16 mths***

11q- ***MS 40 mths***

Caren, PNAS 2010;107(9): 4323-

Explore….

What Cost, this Care…..?