

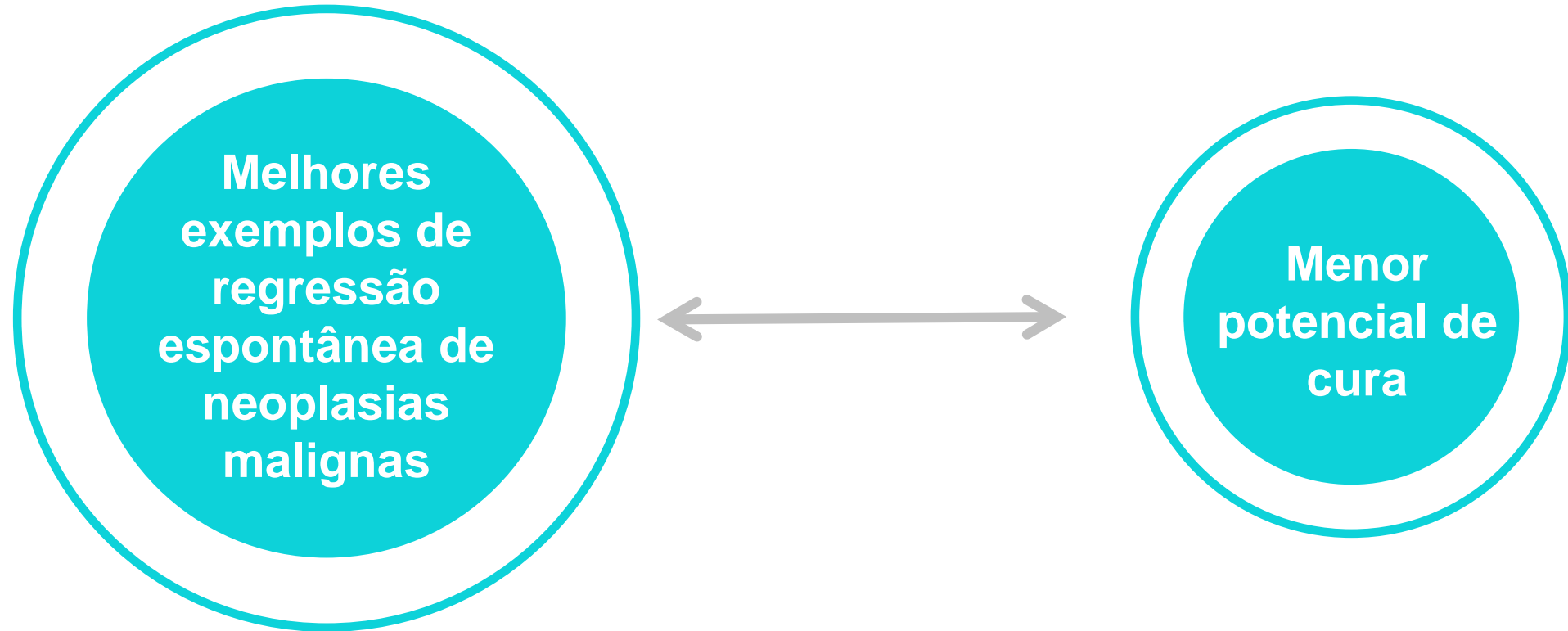
# **A interface entre a nutrição e o tratamento dos neuroblastomas**

Nutr. Luiza Albuquerque

# Neuroblastoma (NB)

- Grupo mais frequente de neoplasias sólidas extracranianas em crianças
- $\cong$  10% de todos os diagnósticos de câncer em crianças com menos de 15 anos
- 15% de todos os óbitos decorrentes de neoplasias infantis
- No Brasil são diagnosticados cerca de 500 novos casos por ano
- A maioria tem menos de 5 anos de idade
- A idade média é de 22 meses
- Etinia? Fatores climáticos e geográficos? Agentes físicos ou químicos?
- Países industrializados e desenvolvidos

# Neuroblastoma (NB)

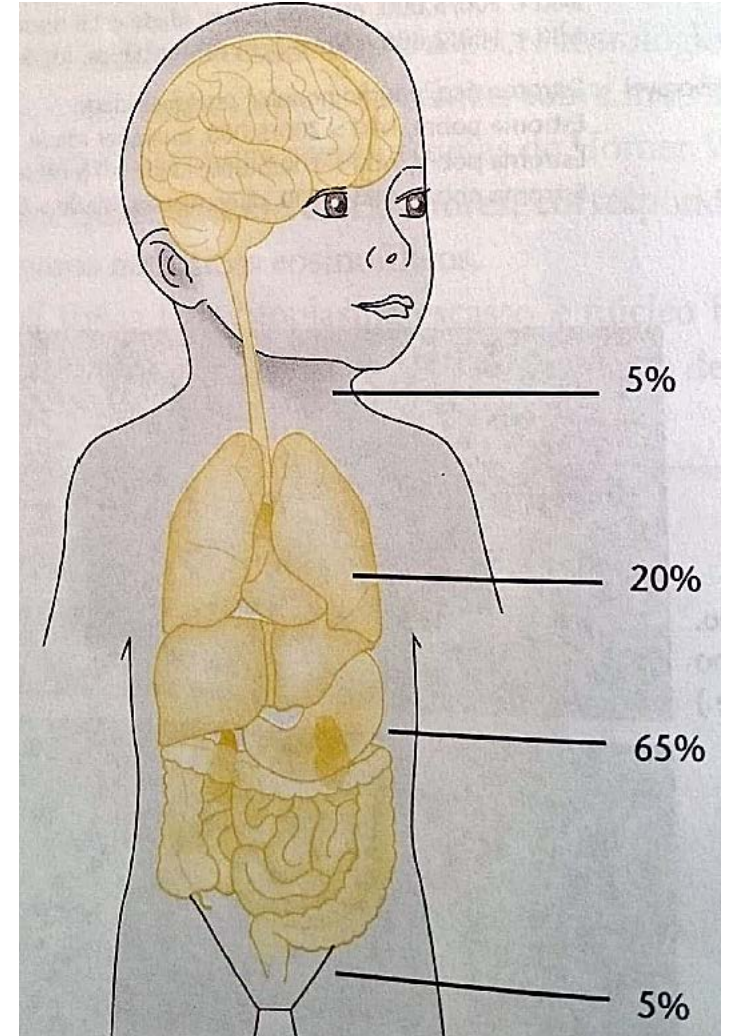


# Patologia

Os neuroblastomas são tumores neuroendócrinos e pertencem ao mesmo grupo dos ganglioneuromas e ganglioneuroblastomas

Durante o desenvolvimento embrionário, as células-tronco pluripotentes migram e se diferenciam, formando o sistema nervoso simpático

Tumores em áreas anatômicas diversas



# Quadro Clínico

## Sinais e sintomas

Manifestações gerais

Dor abdominal

Dor óssea

Vômitos

Perda de peso

Anergia

Manifestações da doença avançada

Dor generalizada (infiltração óssea)

Febre e anemia (infiltração da medula óssea)

Equimoses periorbitais

Fraturas patológicas

Macrocefalia

# Quadro Clínico

## Sinais e sintomas

Tumores abdominais

Assintomático (às vezes)  
Distúrbio respiratório obstrutivo  
Hipertensão renovascular

Tumores paraespinais

Perda de força muscular  
Paralisia  
Extensão podálica  
Disfunção vesical  
Disfunção retal

Tumores cervicotorácicos

Massa mediastinal posterior (achado ocasional)  
Síndrome de Horner

Lactentes (alguns)

Hepatomegalia  
Nódulos cutâneos (blueberry muffin baby)

Doenças paraneoplásicas

Diarréia aquosa prolongada (secreção de VIP)  
Opsoclonia, mioclonia, ataxia (Sind. De Kinsbourne – 2% dos casos)



Blueberry muffin baby



Síndrome de Horner



Sinal de Guaxinim

# Diagnóstico



## **Investigação Laboratorial**

Hemograma, perfil eletrolítico, ácido úrico, enzimas hepáticas, uréia e creatinina, ferritina, albumina, TP e TTPa, T4, Imunoglobulinas, DHL, Catecolaminas urinárias.



## **Investigação por Imagens**

Radiografia simples de tórax e abdome, Tomografia computadorizada, Ressonância magnética



## **Outros exames**

Ecocardiograma, audiometria, depuração de creatinina



# Diagnóstico



## **Procedimentos**

Aspirações e  
biópsias de medula



## **Diagnóstico diferencial**

Tumor de Wilms,  
rabdomiossarcoma



## **Estadiamento**

Estádio, idade,  
fatores biológicos,  
histologia

# Tratamento

- **Pacientes de baixo risco**



Boas chances de cura  
Cirurgia  
Observação de regressão espontânea

- **Pacientes de risco intermediário**



Quimioterapia  
Índice de sobrevida a longo prazo: acima de 80%

# Tratamento

- **Pacientes de alto risco**



Apesar de o tratamento inicial poder apresentar boas respostas, muitos casos recidivam



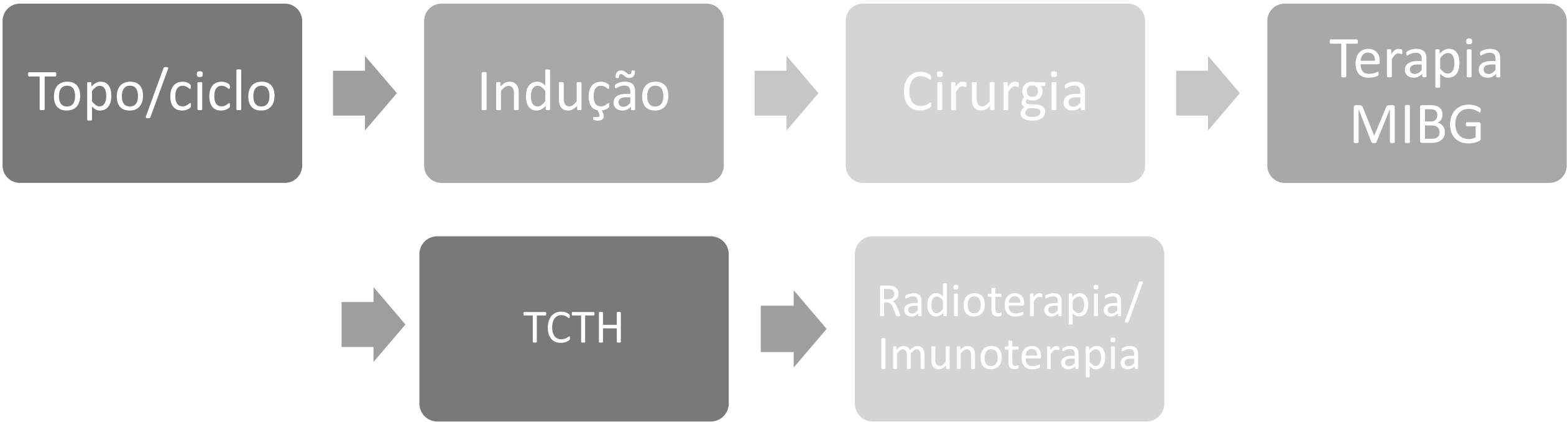
Transplante autólogo de medula óssea



Imunoterapia, MIBG, Inibidores de angiogênese....

# Tratamento

## Esquema Geral



# Desnutrição

- Fator de risco modificável
- 80% ao diagnóstico
- 20 a 50% durante o tratamento
- Compromete o sistema imune, ↑ susceptibilidade à infecções, afeta órgãos sensíveis ao tratamento
- ↓ tolerância ao tratamento, ↑ atrasos

Lemos et al., Rev Bras Hematol Hemoter, 36(6):420-423, 2014

Sala et al., Cancer,100(4):677-87, 2004

Rickard et al., Cancer,58(8 Suppl):1904-10, 1986

# Desnutrição

Pediatr Res. 2008 Mar;63(3):332-6. doi: 10.1203/PDR.0b013e318163a2d4.

## **Resting energy expenditure in children newly diagnosed with stage IV neuroblastoma.**

Green GJ<sup>1</sup>, Weitzman SS, Pencharz PB.

### **⊕ Author information**

#### **Abstract**

Children with stage IV neuroblastoma (NBIV) are often malnourished at time of diagnosis, observed as high as 50%. The emphasis of this study was to determine whether an increased resting energy expenditure (REE) is a causative factor. Our hypothesis was that children diagnosed with NBIV have an increased REE, which normalizes with cancer treatment. Changes in nutritional status from time of diagnosis in response to nutritional support were examined. REE and nutritional evaluation were obtained three times: at diagnosis before starting treatment, where tumor burden is expected to be highest; after two courses of chemotherapy, where some response to treatment is expected; and after surgical excision of the primary tumor, where there was presumably minimal residual disease. Ten subjects completed the study. Results showed that REE was not increased, and there was no significant difference between phases ( $p = 0.29$ ). Fifty percent of our subjects were malnourished at diagnosis. Because REE is not increased in NBIV, it is concluded that malnutrition seen in NBIV is not due to increased energy needs, but is likely due to decreased intake because of the intra-abdominal mass and malignant malaise.

PMID: 18287973 DOI: [10.1203/PDR.0b013e318163a2d4](https://doi.org/10.1203/PDR.0b013e318163a2d4)

# Desnutrição

*Pediatr Res.* 2008 Mar;63(3):332-6. doi: 10.1203/PDR.0b013e318163a2d4.

## Resting energy expenditure in children newly diagnosed with stage IV neuroblastoma.

Green GJ<sup>1</sup>, Weitzman SS, Pencharz PB.

n= 10

Table 3. REE and response to treatment

	Phase 1	2	3	<i>p</i>
Actual REE (kcal/d)				
Mean	673.9	761.1	756.9	0.29
SD	±169.2	±216.3	±155.8	
Predicted REE (kcal/d)				
Mean	811.7	807.8	820.3	0.45
SD	±139.3	±136.9	±139.0	
%Predicted REE				
Mean	83.3	93.2	87.5	0.28
SD	±15.6	±15.9	±11.0	

Phase 1, patients newly diagnosed at start of treatment protocol; 2, patients received 2 cycles of chemotherapy; 3, patients received 5 cycles of chemotherapy, recovered postoperatively from primary tumor excision, admitted next cycle of chemotherapy.

There were no significant differences in REE with response to treatment using repeated analysis of variance.

# Desnutrição

- Inflamação
- ↑ perdas e ↓ absorção
- Uso de corticoesteróides



# Micronutrientes

Selênio

Folato

Zinco

Vitamina  
D

Vitamin  
a B12

Vitaminas  
Pré-natais

Kim , Nutr Res Pract. 4(6):455-61, 2010

Mazul et al, Cancer Causes Control, 27(10):1209-18, 2016

Morscher et al., Oncotarget, 7(13):17060-73, 2016

Revuelta Iniesta et al., Clin Nutr, 35(1):95-108, 2016

*Pediatr Blood Cancer*. 2011 Feb;56(2):202-5. doi: 10.1002/pbc.22880. Epub 2010 Nov 5.

## **Bone mineral density in newly diagnosed children with neuroblastoma.**

Al-Tonbary YA<sup>1</sup>, El-Ziny MA, Elsharkawy AA, El-Hawary AK, El-Ashry R, Fouda AE.

### **⊕ Author information**

#### **Abstract**

**BACKGROUND:** Neuroblastoma is the second most common extracranial malignant tumor of childhood and the most common solid tumor of infancy which is characterized by bone metastasis. Previous reports on bone mineral density (BMD) in patients with leukemia and solid malignancies concentrate on long-term survivors and on the effect of chemotherapeutic agents and irradiation. Also, evaluation of BMD in neuroblastoma was reported in few studies which were conducted upon adult survivors of childhood cancer. Previous studies on both acute leukemia and lymphoma patients suggested that the disease process itself played a role in decrease BMD.

**METHODS:** We evaluated 27 patients with newly diagnosed neuroblastoma for both lumbar (L2-L4) BMD and total BMD using dual energy X-ray absorptiometry (DXA) scan to highlight the effect of neuroblastoma as a disease process on BMD as this disease characterized by bone metastasis.

**RESULTS:** Three out of the 27 patients showed low bone mass in both lumbar and total BMD studies.

**CONCLUSION:** Low bone mass may occur in early disease process of neuroblastoma and it is important to consider BMD assessment during the early course of the disease as well as the long-term survivors as a part of the patient screening in suspected cases.

Copyright © 2010 Wiley-Liss, Inc.

# Tratamento nutricional

A avaliação nutricional no diagnóstico e o acompanhamento durante todo o tratamento devem ser uma parte integral do protocolo

## Nutrição Parenteral

- ↑ peso, melhora de massa magra, menos atrasos de tratamento, e melhora da reconstituição plaquetária
- Suporte a curto prazo
- Complicações

## Nutrição Oral, Enteral e suplementos

- Manutenção do estado nutricional



1980!

Rickard et al, Cancer, 1985;56(12):2881-2897, 1985

Rickard Cancer, 64(1):116-125, 1989

Rickard et al., Cancer, 64(1):116-125, 1989

Rickard et al., Am J Clin Nutr, 38(3):445-56, 1983

# Sobreviventes

## Crescimento

↓ do crescimento, mesmo quando recebem tratamento hormonal

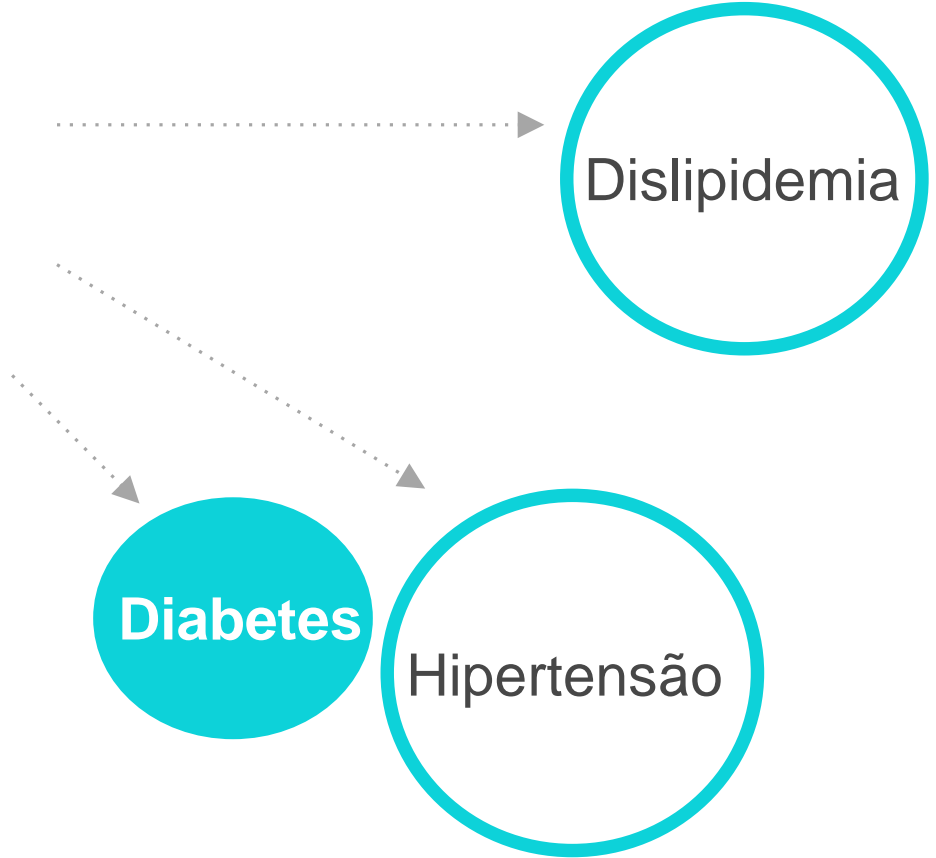
Insuficiência de hormônio do crescimento, hipotireoidismo, quimioterapia e radioterapia, nutrição inadequada

TBI: ↑ necessidade de tratamento hormonal

# Sobreviventes

## Peso

Sobrepeso e obesidade



Small et al., Medicine (Baltimore). 94(14):e713, 2015  
van Waas et al., PLoS One, 7(12):e52237, 2012

*Pediatr Blood Cancer*. 2016 Sep;63(9):1615-21. doi: 10.1002/pbc.26063. Epub 2016 May 20.

## Health-Related Quality of Life in Survivors of High-Risk Neuroblastoma After Stem Cell Transplant: A National Population-Based Perspective.

Portwine C<sup>1,2</sup>, Rae C<sup>2</sup>, Davis J<sup>3</sup>, Teira P<sup>4</sup>, Schechter T<sup>5</sup>, Lewis V<sup>6</sup>, Mitchell D<sup>7</sup>, Wall DA<sup>8</sup>, Pullenayegum E<sup>5</sup>, Barr RD<sup>1,2</sup>.

### ⊕ Author information

#### Abstract

**PURPOSE:** This study aimed to estimate the burden of morbidity, in terms of health-related quality of life (HRQL), in survivors of high-risk neuroblastoma (NBL) after myeloablative chemotherapy followed by autologous hematopoietic stem cell transplant (HSCT).

**PATIENTS AND METHODS:** A national population-based survey was undertaken of survivors of high-risk NBL (N = 99), diagnosed between 1991 and 2010 and treated with HSCT. Parents completed a proxy questionnaire incorporating two HRQL measures, Health Utilities Index (HUI) 2 and 3. Children >12 years of age provided self-assessments. Clinical and demographic data were collected. Independent t-test and one-way analysis of variance were used to assess differences. Comparative data were obtained from previously published work and Statistics Canada's 1998 National Population Health Survey.

**RESULTS:** On a scale of 0 (being dead) to 1.0 (perfect health), mean HRQL utility scores were 0.89 (SD = 0.11) in HUI2 and 0.84 (SD = 0.18) in HUI3. Parents reported morbidity in sensation (52.5%), pain (30.3%), cognition (28.0%), and emotion (24.2%) in HUI2 and in hearing (38.4%), pain (30.3%), cognition (27.3%), and speech (23.2%) in HUI3. HRQL was not significantly different compared to NBL survivors treated without HSCT, but was less than in nontransplanted survivors of acute lymphoblastic leukemia and Wilms tumor, and children in the general population, yet higher than in survivors of brain tumors.

**CONCLUSIONS:** HRQL is compromised in high-risk NBL survivors treated with and without HSCT. A differential effect on hearing reflects additional exposure to platinum-based chemotherapy. These results should inform long-term care and the development of new therapeutic interventions.

# Sobreviventes

**TABLE I. Clinical and Demographic Variables**

Cases (n)		99	Most commonly reported late effects (%) <sup>b</sup>	
Age at diagnosis (years)	Min/Max	0.2/13.15	Ototoxicity	66.0
	Mean (SD)	3.56 (2.37)	Poor growth	7.2
Sex	Male	52.6%	Urologic sequelae	7.2
	Female	47.4%	Renal impairment/disease	5.1
Years posttreatment	Mean (SD)	4.36 (3.44)	Nocturnal enuresis	2.1
Participated in clinical trial (%)		49.5	Adverse cardiac outcomes	7.2
Protocol <sup>a</sup>	CCG 3891	3.0	Visual loss	5.2
	POG 9340/41/42	3.0	Cognitive impairment	4.1
	POG 9640	8.1		
	A3973	42.4		
	ANBL0532	28.3		
	MADDOC	4.0		
	SIOP-COJEC	4.0		
	Other	5.1		
Clinical reports of late effects (%)		75.8		
Relapse (%)		24.2		
Current status	Disease free (%)	84.8		
	Residual/ persistent disease (%)	10.1		
	Secondary malignancy/ missing data (%)	5.0		

All patients received high dose platinum, myeloablative chemotherapy with autologous stem cell rescue, and local irradiation. CCG 3891 included total body irradiation; POG 9640 was a pilot study of tandem (double) rescue; ANBL 0532 included randomization to single or tandem rescue; and SIOP-COJEC included immunotherapy. <sup>a</sup>Percentages do not equal 100, remaining responses are missing. <sup>b</sup>Late effects reported by clinical staff via open-ended question.

# Para o futuro...

- *in vitro* e em modelos animais, dietas enriquecidas com ômega 3 ↓ crescimento tumoral
- Vitamina A: diferenciação de células, apoptose
- Glicose



Barnes et al., *Pediatr Res*, 71(2):168-78, 2012  
Niles, *Nutrition*, 16(11-12):1084-9 2000  
Morscher et al., *Oncotarget*, 7(13):17060-73, 2016  
Aminzadeh et al., *Transl Pediatr*, 4(1):20-32 2015  
Morscher et al., *PLoS One*, 10(6):e0129802, 2015  
Kim, *Nutr Res Pract*, 4(6):455-61, 2010



**Obrigada!**