Neuroblastoma

Management options
&
What's new in Radiation Therapy!

Dr Nehal R Khanna
Tata Memorial Hospital, Mumbai

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Neuroblastoma

Cancer	Children	Adults
Acute Leukemia	28%	2.3%
CNS tumors	21%	1.6%
Lymphomas	11%	4.3%
Neuroblastoma	7.5%	0%
Wilms' tumor	6%	0% (2.2%)
Soft tissue sarcoma	6%	< 0.5%
OS and Ewing's sarcoma	5%	< 0.5%
Retinoblastoma	3%	0%
Others	12.5%	> 90%

Cancer	< 1 month	< 1 year	≤15 years
Leukemia	12	14	27
Brain	3	15	20
Neuroblastoma	54	25	7
Retinoblastoma	0	11	3
Kidney	13	10	6
Liver	0	4	1
Soft tissue	10	3	7
Bone	0	0	5
Others	8	25	24

Bader et al. (TNCS), Am J Dis Child 1979; Gurney et al. (SEER), Cancer 1995

2000 cases per year

Neuroblastoma

- Heterogenous group of tumors
- Varying degrees of differentiation
- GN → GNB → NB
- Varying malignant potential

- Biology!!
- Treatment algorithms!!
- Outcomes!!

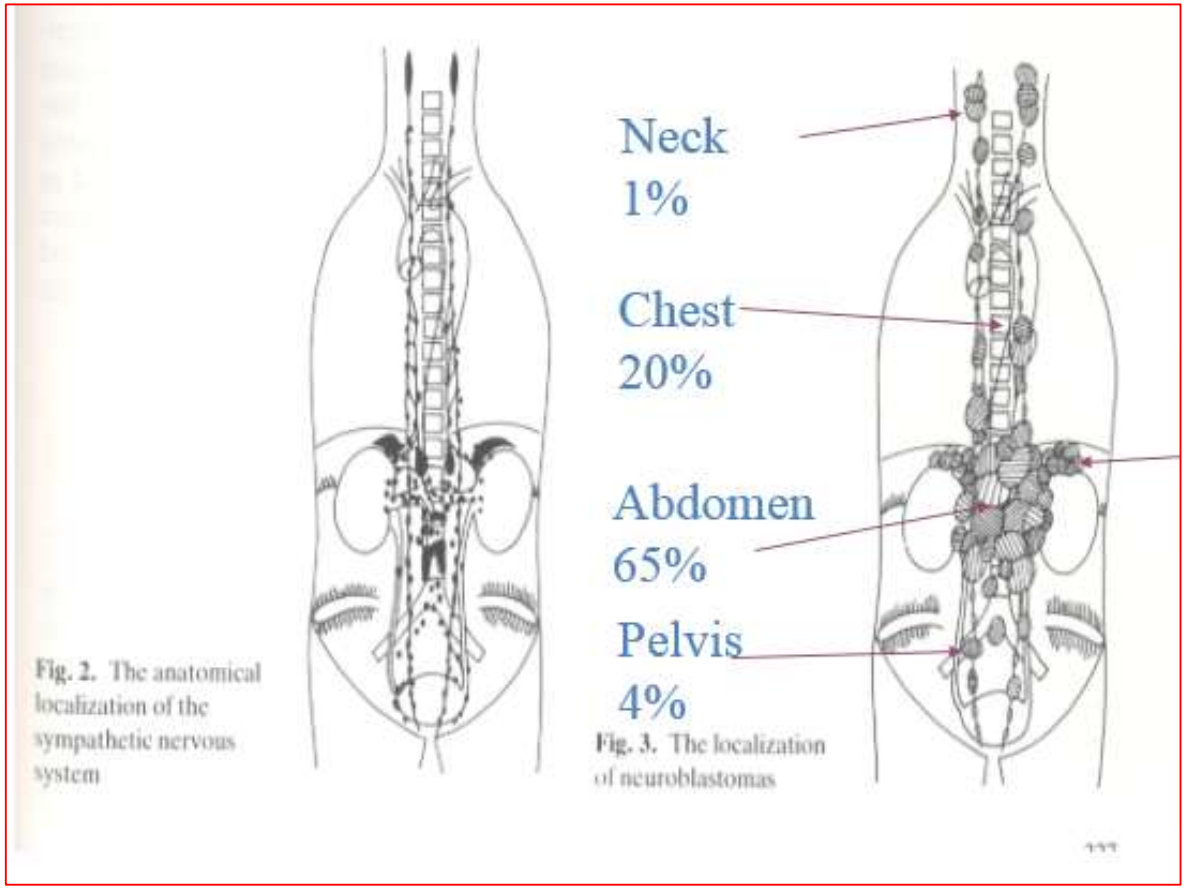


Fig. 2. The anatomical localization of the sympathetic nervous system

Fig. 3. The localization of neuroblastomas

Neuroblastoma & radiotherapy

- Radiosensitive tumor
- Multimodal treatment
- Role of radiation evolving
  - Low risk
  - Intermediate risk
  - High risk
  - Other indications

- Clinical presentation
- Staging investigations
  - Local imaging MRI/ CT
  - Staging workup
    - MIBG, PET CT
    - Urine catecholamines
    - Biopsy (diagnosis as well as *MYCN* copy number, DNA index, and the presence of segmental chromosomal aberrations)
    - BM studies

Classification systems, staging and risk grouping

- INPC
  - Favourable and unfavourable
- INSS
  - Stage 1, 2 (A, B), 3, 4 and 4S
    - 40% of <1yr are stage I
    - 70% of >1yr are stage 4
    - 50% across all ages are stage 4
- Staging in relation to IDRF
  - L1, L2, M and MS
- COG
  - Low, intermediate and high risk
- INRG
  - Very low, low, intermediate and high risk

Curie score
SIOPEN score
INRC

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			H Intermediate
				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

Risk	Age	INRG	MYCN status	SCA	Histology
Low	Any	L1	Non-Amp	Any	Any
	<547 days	L2/MS	Non-Amp	No	Any
	>547 days	L2	Non-Amp	No	FH
Intermediate	<547 days	L2	Non-Amp	Yes	Any
	<547 days	M	Non-Amp	Any	Any
	>547 days	L2	Non-Amp	Yes	FH
	>547 days	L2	Non-Amp	Any	UH
High	Any	Any	Amp	Any	Any
	Any	MS	Non-Amp	Yes	Any
	>547 days	M	Any	Any	Any

Low risk Nb Management options

- Observation without biopsy
  - Patients younger than 6 months with solid adrenal tumors smaller than 3.1 cm (or cystic tumors smaller than 5 cm) and INSS stage 1 disease (Ref: COG ANBL00P24)

- Surgery followed by observation
  - Surgery alone, even without complete resection, can cure nearly all patients with stage 1 neuroblastoma and the vast majority of patients with asymptomatic, favorable-biology, INSS stage 2A and stage 2B disease (Ref: COG- P9641)

Low risk Nb Management options

- Chemotherapy with or without surgery
  - Symptomatic disease. (e.g., spinal cord compression) (Ref: COG- P9641)
    - Carboplatin, cyclophosphamide, doxorubicin, and etoposide.
    - Cumulative chemotherapy dose of each agent is kept low to minimize long-term effects
    - Symptomatic patients with stage 2A/2B or 4S disease are categorized as intermediate risk and receive chemotherapy.
  - Unresectable progressive disease after surgery

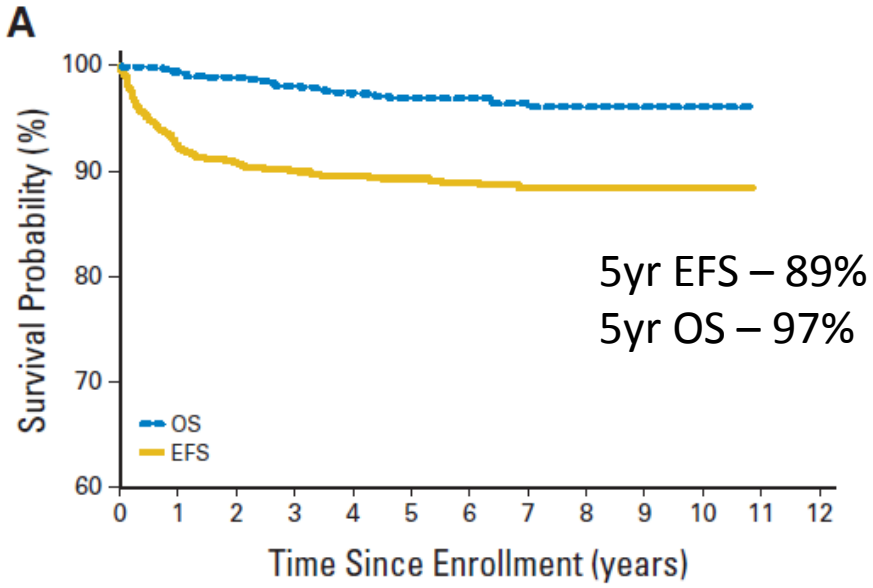
Role of RT in low risk disease

- COG – P9641 prospective non randomized phase III study

Table 1. Children's Oncology Group Low-Risk Neuroblastoma

INSS Stage	Age	*MYCN* Status	Histopathology	DNA Ploidy
1	0-21 years	Any	Any	Any
2a/2b	< 365 days	Any	Any	Any
	≥ 365 days to 21 years	Nonamplified	Any	—
	≥ 365 days to 21 years	Amplified	Favorable	—
4s	< 365 days	Nonamplified	Favorable	≥ 1

Abbreviation: INSS, International Neuroblastoma Staging System.



5yr EFS – 89%
5yr OS – 97%

Use of surgery alone is curative for most patients with LR-NBL
Complete resection NOT mandatory
Use of CT may be restricted to specific situations.

Strother et al. JCO 2012

Role of RT in low risk disease

- LNESG1 study by the SIOPEN
- Localized resectable stage I and II
- Approx 50% had residual disease after surgery

		RFS	OS
Stage I MYCN normal	n = 288	94.3%	98.9%
Stage II MYCN normal	n = 123	92.8%	93.2%

- In stage 2, OS and RFS were worse for patients with MYCN A, elevated LDH and UH.
- In conclusion, surgery alone yielded excellent OS for both stage 1 and 2 neuroblastoma without MYCNA

Intermediate risk Nb Management options

- Chemotherapy with or without surgery
  - Surgery → 4-8#s (Ref: COG A3961, ANBL0531)
- Surgery and observation (in infants)
  - The need for chemotherapy in all asymptomatic infants with stage 3 or stage 4 disease is controversial, as some European studies have shown favorable outcomes with surgery and observation. (Ref: De Bernardi JCO 2009, Minard V SFOP BJC 2000, Hero B NB95-S NB97 JCO2008)
- Radiation therapy
  - Reserved for patients with progressive disease during treatment with chemotherapy or progressive unresectable disease after treatment with chemotherapy.

Role of RT in intermediate risk disease

- Randomised trial published in 1991 (Castleberry et al. JCO 1991)
- Low-dose, sequential cyclophosphamide/doxorubicin with or without RT

	With RT	Without RT	p
CR	76%	46%	0.013
EFS	59%	32%	0.009
OS	73%	41%	0.008

- However, in the context of more dose-intensive chemotherapy, and accounting for the status of MYCN copy number, this may no longer be true.

Role of RT in intermediate risk disease

- COG – P9641 prospective non randomized phase III study
- Provides data for further reduction in treatment with refined risk stratification
- Almost 500 patients treated with moderate doses of CTh and additional surgery in some instances
- Radiotherapy restricted to only 2.5% of (n=12) patients

- Very high rate of survival
- The 3-year OS for the entire group was 96%

Baker DL et al. NEJM 2010

Role of RT in low and intermediate risk

- Currently most cooperative groups are withholding RT for intermediate risk group except in conditions like – progression despite surgery and chemotherapy, unresectable primary after chemotherapy having unfavourable biology

- Emergency therapy reserved for patients with
  - Symptomatic life-threatening or organ-threatening tumor that does not respond rapidly enough to chemotherapy and/or surgery
  - Progressive disease.

High risk Nb Management protocol

Induction chemotherapy -
Cisplatin, Vincristine, Carboplatin, Etoposide, Cyclophosphamide

Surgical excision of primary

Myeloablative therapy & **peripheral blood stem cell rescue**

Radiotherapy to site of primary tumour

Minimal residual disease :13-*cis* retinoic acid +/- anti-GD2 ab

? Role of ASCT

Role of RT in high risk disease

- Although distant relapse is the main obstacle to cure in these patients, local failure remains a significant problem

- Late local recurrences even in aggressively treated cases, some more than 5 years after completion of therapy

Role of RT in high risk disease

- GPOH NB 97 study for INSS stage IV (Simon et al. JCO 2013)
- Study compared ASCT and oral maintenance CTh
- 178 pts >18 months
- No difference in outcome based on the extent of resection
- 40Gy was advised for cases with gross disease (n = 28;median dose 36Gy)
- Benefit of RT NOT documented in the paper

Higher RT dose may explain the equivalent survival.

Stenman et al. Letter to the editor JCO 2017

RT improves LC in patients with microscopic residual disease

- Joint Center for Radiation Therapy/Dana-Farber Cancer Institute/Children's Hospital experience.
- 118 patients with complete or near complete remission after chemotherapy and surgery
- 40% local failure in patients who received RT
- 86% local failure in patients who did NOT receive RT

Rosen et al. JCO 1984

RT improves LC in patients with gross residual disease

- St Jude's data
- 63 patients with HR Nb
- Seventeen patients received RT, and 46 did not.
- RT group
  - Greater percentage of patients had residual disease before consolidation than did those in the no-RT group (88.2% vs 69.6%, P = .008).
  - Gross total resection was achieved less often in the RT group (65% vs 89%, P = .055)
  - 5-year cumulative incidences of local failure were similar (35.3% vs 32.6%).
- Although there was no difference in 5-year event-free survival, overall survival was better in the no-RT group (47.8% vs 23.5%, P = .026).

Robbins JR. J Ped Surg 2009

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 5, pp. 1549–1554, 2009

0360-3016/09/$–see front matter

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CLINICAL INVESTIGATION **Pediatrics**

EXCELLENT LOCAL CONTROL FROM RADIATION THERAPY FOR HIGH-RISK NEUROBLASTOMA

HEATHER G. GATCOMBE, M.D.,* R. B. MARCUS, JR., M.D.,§ HOWARD M. KATZENSTEIN, M.D.,†
MOURAD TIGHIOUART, PH.D.,‡ AND NATIA ESIASHVILI, M.D.*

*Department of Radiation Oncology, †Children's Healthcare of Atlanta, ‡Biostatistics and Informatics at Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA; and §Department of Radiation Oncology, University of Florida, Gainesville, FL

- 34 high risk Nb treated between 2001-2007
- All had gross residual disease post chemotherapy and surgery
- 21 – 24Gy RT to the tumor bed

3yr LC	94%
3yr EFS	66%
3yr OS	86%

Gatcombe et al. IJROBP 2009

There is evidence from the literature that all patients with high-risk neuroblastoma may benefit from local RT, and those with only microscopic residual disease may benefit the most.

Thus, all current high-risk neuroblastoma protocol incorporate RT for all patients.

What is the optimum dose of RT?

	Local control	RT dose
Marcus KJ et al. J Pediatr Hematol Oncol 2003	97%	12Gy TBI+ 10.5-18Gy
Gatcombe GG et al. IJROBP 2009	94%	21-24Gy
Bradfield et al. Cancer 2004	93%	21Gy
Kushner BH et al. J Clin Oncol 2001	90%	21Gy
Browne M et al. Chicago pilot II protocol J Pediatr Surg 2006	97%	24Gy

21–24 Gy are adequate for local control……

RT dose response relationship?

- CCG – 3891 study
- 539 patients
- Median follow up of 66 months

RT dose	5 year local control (p0.022)
10Gy RT to the primary + 10Gy TBI	52%
10Gy RT to the primary + continued chemotherapy	22%

- Minimum of 21Gy should be adequate for patients with complete resection
- Higher doses proposed for gross residual disease

Haas Kogan DA et al. CCGS IJROBP 2003

Can dose be reduced in children with GTR?

- MSKCC (Casey D et al. IJROBP 2016)
- 245 children (dose-intensive chemotherapy + gross total resection)
- No residual disease at the time of RT
- 21Gy in twice-daily fractions of 1.5Gy each.
- Median follow up of 6.4yrs, LC = 90.2% (most relapses were distal)
- 86% of local failures within the RT field

Given the young patient age, concern for late effects, and local control >90%, dose-reduction may be appropriate for patients without MYCN amplification who achieve GTR.

Is dose escalation needed in gross disease??

- 19/331 (5.7%) underwent subtotal resection
- Median follow-up among surviving patients was 6.0 years
- Median RT dose was 25 Gy (range, 21 Gy - 36 Gy)
- The 5yr Local failure - 17.2%, EFS – 44.9% and OS 68.7%
- LF at 5 years was 30% in those who received <30 Gy versus 0% in those who received 30–36 Gy (p=0.12).

- Doses of 30–36 Gy are likely needed for optimal control of gross residual disease at the time of consolidative RT

Dana Casey, MSKCC, PBS 2018

ASTRO 2019

Role of radiotherapy dose-escalation for high-risk neuroblastoma with post-surgical primary site gross residual disease: A report from the COG ANBL0532 study

Boost radiation does NOT seem to help. No difference in OS, EFS and Local progression

Tandem transplant better than single transplant

>90% should be resected

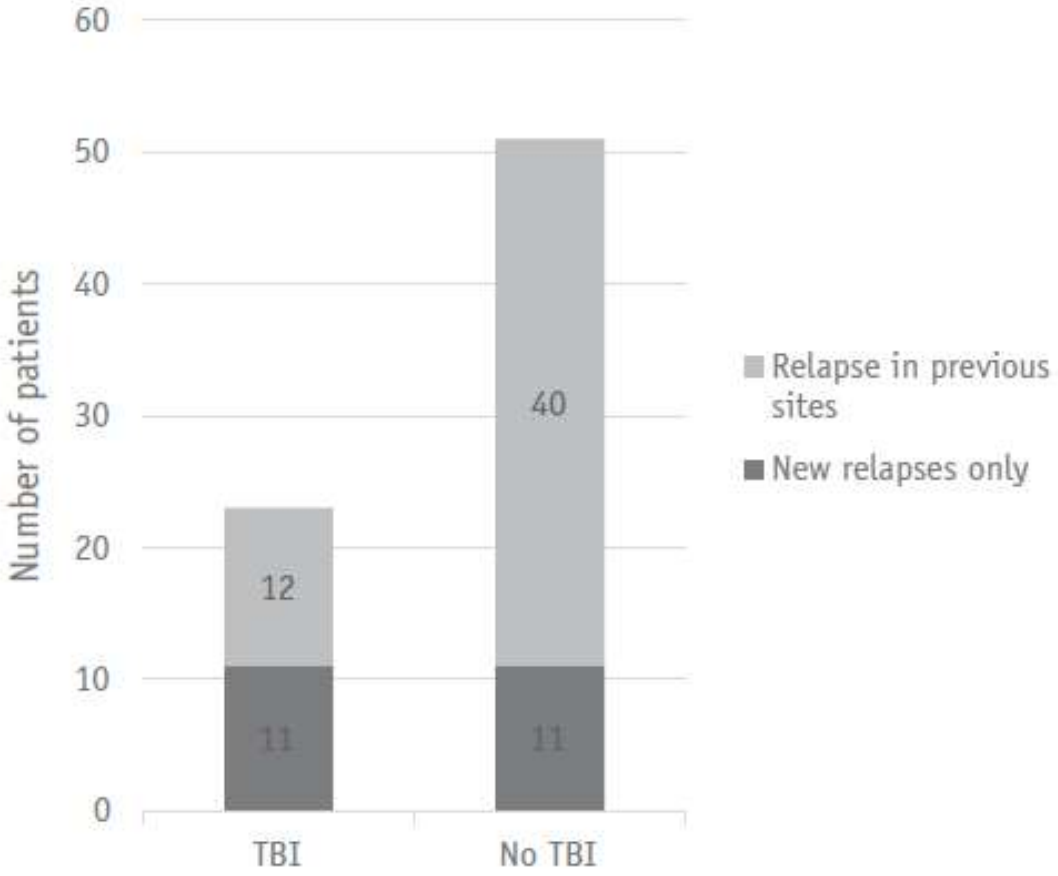
Research on new chemotherapy regimens!!!

Role of RT to metastatic sites ??

Pattern of relapse w.r.t. to the metastatic site

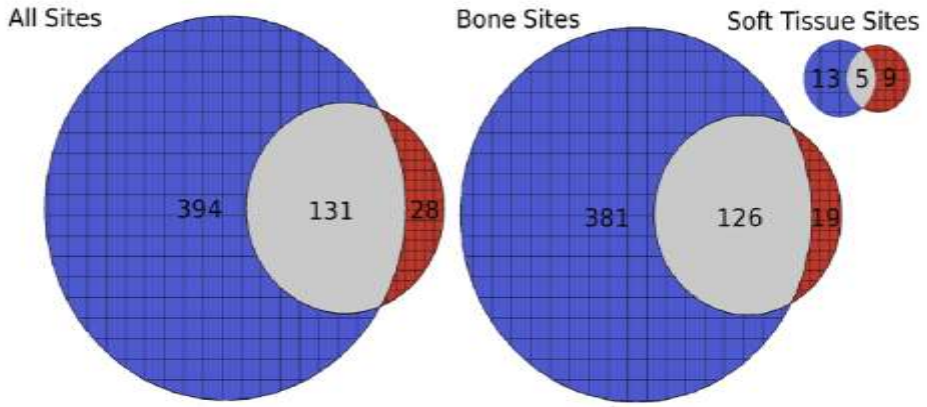
- 70% of patients had relapse in previously involved site.
    - Richard Li, et al. IJROBP 2016
- 46 patients treated without TBI, 82.4% of 159 metastatic sites at relapse were present at initial diagnosis.
    - Polishchuk AL, et al. IJROBP 2014
- 30 patients treated with focal EBRT that the most common sites of relapse (19 of 23, 82.6%) were initially MIBG positive and converted to negative after induction of chemotherapy.
    - Zage PE, et al. PBC 2008

These findings suggest that the HR Rx protocol may be suboptimal in terms of disease control at metastatic sites that are detectable at diagnosis.



52% of patients who received TBI had relapse in prior sites versus 78% of patients who did not receive TBI (p = 0.03).

Richard Li, et al. IJROBP 2016



Lower relapse rate at irradiated metastatic sites, 16.7Vs 25.2% (p=0.48)

Polischuk et al. IJROBP 2017

RT to avid sites after induction therapy

- 30 children with HR Nb
- All patients had atleast PR as per INRC
- 24 – 30Gy RT to primary
- MIBG avid sites were treated with 24Gy
- 5 yr PFS and OS were 48% and 59%

5 yr local control at primary site	84%
5 yr local control at metastatic sites	74%

- Number of MIBG avid sites present after induction therapy was predictive of PFS and OS

Mazloom A, et al. IJROBP 2014

RT to avid sites after induction therapy

- 13/ 37 pts received RT
- Median dose of RT 21.6Gy
- Local control at primary 94% (excellent)
- In-field recurrence was observed in 23% at metastatic sites
- Calvareal metastases have poor outcome
    - Kandula S, et al. Pediatr Hematol Oncol. 2015

? RT dose suboptimal

RT→ no effect on OS

- > 20 Gy RT dose has better response in terms of palliation of bone metastases.
    - Caussa et al. IJROBP 2011

Radiation Therapy to Sites of Metastatic Disease as Part of Consolidation in High-Risk Neuroblastoma: Can Long-term Control Be Achieved?

- 159 patients, 244 metastases were irradiated.
- Med F/u7.4 years.
- Over 85% of the irradiated metastases were treated with 21 Gy (range, 10.5-36 Gy).
- The 5-year LC rate of treated metastatic sites was 81%.
- Metastatic sites that cleared with induction chemotherapy had improved LC compared (92% vs 67%; P <.0001).
- Though response to chemotherapy is an important prognostic factor for LC, consolidative RT appears to be an effective modality of LC.

Dana Casey, MSKCC, IJROBP 2018

ANBL0532, the recently completed COG phase 3 frontline trial, received EBRT to up to 5 sites of MIBG-avid metastatic disease (Results awaited)

TBI as conditioning regimen

- Older treatment protocols included TBI accompanying autologous BMT as conditioning regimens
    - Kun LE, et al. IJROBP 1981
    - Philip T, et al. JCO 1991
- Most current protocols use either carboplatin/etoposide/melphalan or busulfan/melphalan as conditioning for SCT
    - Elborai Y, et al. Pediatr Transplant 2016.

Considerable late toxicities with TBI

Increased experience with chemotherapy based regimens

Flandin et al IJROBP 2006

Role of emergency RT

- Symptomatic spinal cord compression
- Respiratory distress due to hepatomegaly in 4S

Treatment of spinal cord compression

- Complete neurologic recovery inversely correlated with the severity of the presenting neurologic deficits.
- Neurologic outcome appears to be similar with chemotherapy, radiation therapy, or surgery
    - Bernardi D, et al. JCO 2001
- Fewer orthopedic sequelae observed with chemotherapy
    - POG experience
    - Katzenestein HM, et al. JCO 2001

Treatment of spinal cord compression

- Patients treated with chemotherapy usually did not require additional therapy, whereas patients treated either with radiotherapy or laminectomy commonly did.
    - Bernardi D, et al. JCO 2001
- No patient presenting with (or developing) severe motor deficit recovered or improved.
    - Bernardi D, et al. JCO 2001
- No change once paraplegia is established
    - Bernardi et al, PBC 2014 AEIOP experience
- Most of the patients exhibit residual neurological deficit needing special care.

Treatment of spinal cord compression

- The completed COG low-risk and intermediate-risk neuroblastoma clinical trials recommend immediate chemotherapy for cord compression in low-risk or intermediate-risk patients.
- The role of radiation is questionable as a first line!!
- RT can be considered in children NOT responding to CTh or Sx ……..as the last resort.

The key lies in greater awareness and timely intervention!!

Role of RT in 4S

- Most do not require therapy.
- RT can be life saving is rare cases
- 3 – 6Gy is delivered in fractionated doses.
- Entire liver need not be irradiated
    - Nickerson HJ, et al. J Clin Oncol 2000.
    - Hsu LL, et al. Med Pediatr Oncol 1996.
    - M dore, et al. Cancer Radiother 2015

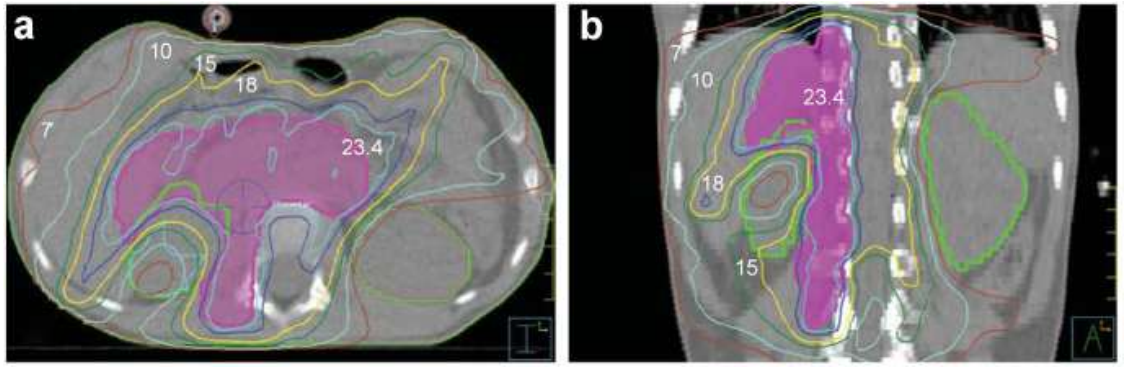
RT in CNS relapse and for palliation

- CNS has emerged as a sanctuary site leading to relapse.
- CNS relapses are almost always fatal, with a median time to death of 6 months.
- Treatment options include
  - Surgery and radiation therapy.
  - Novel therapeutic approaches.
- RT remains the mainstay for palliation of end stage disease.

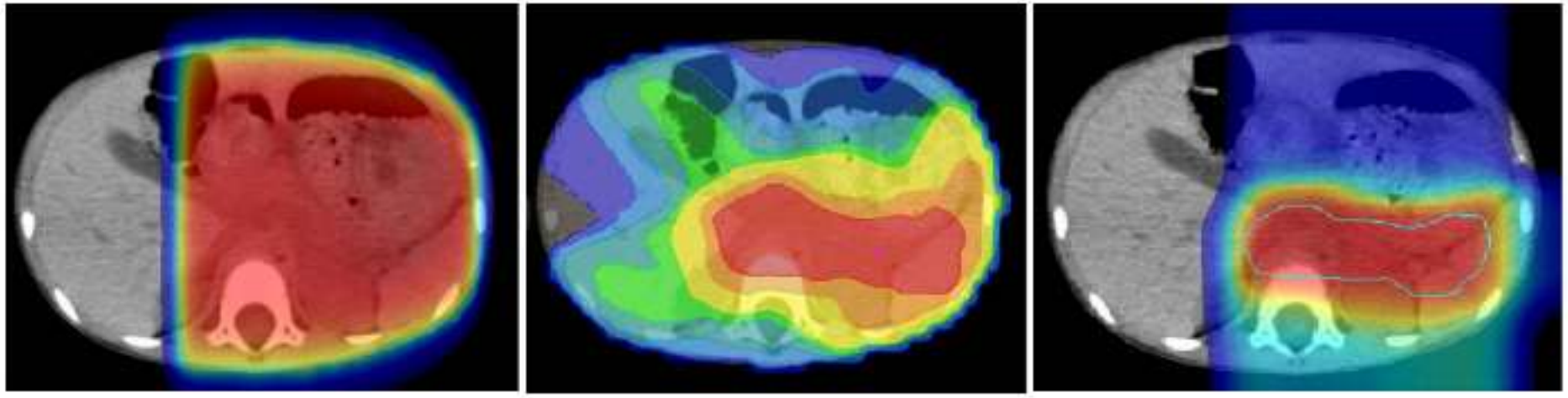
Kramer K, et al. Cancer2001
Matthey KK, et al. Cancer 2003

Technique of RT

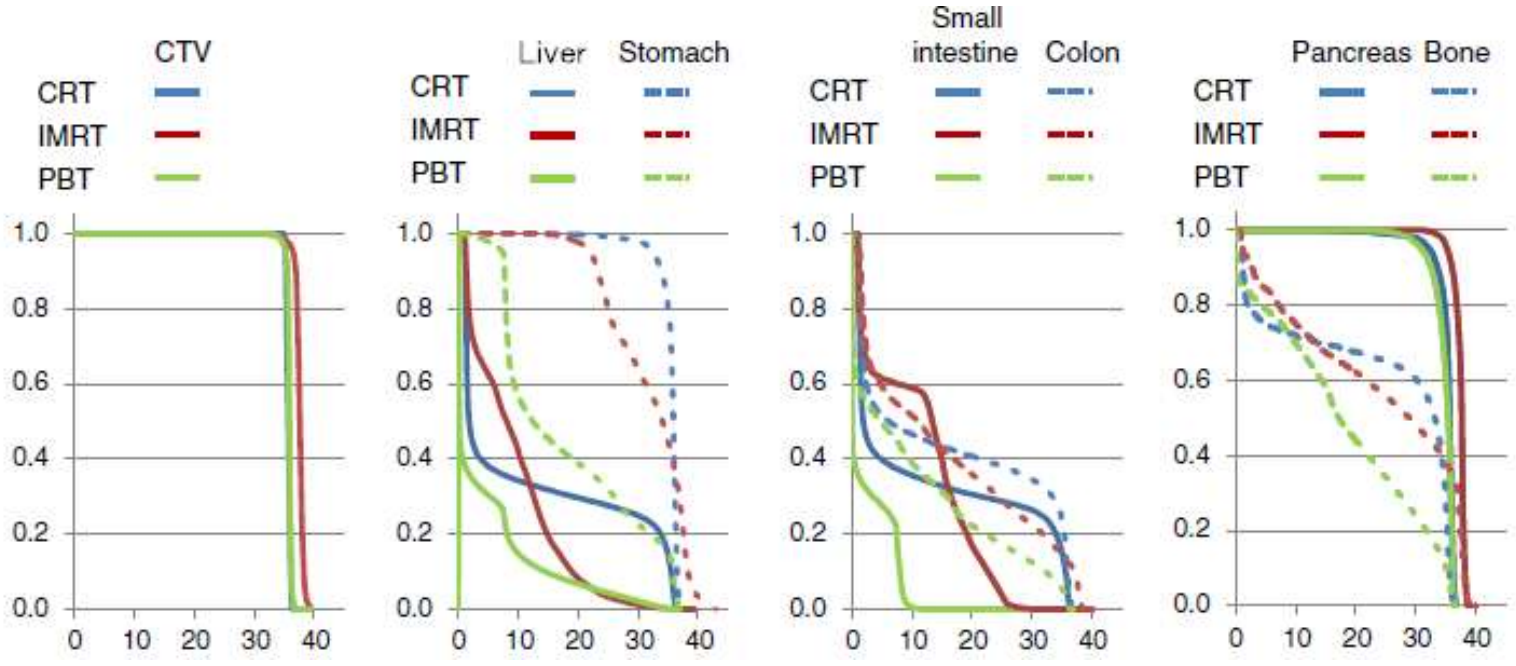
- Irregular volume & proximity to the many critical normal structures
- Young age
- Though the doses are moderate, late sequelae are a major concern
- Conformal radiotherapy

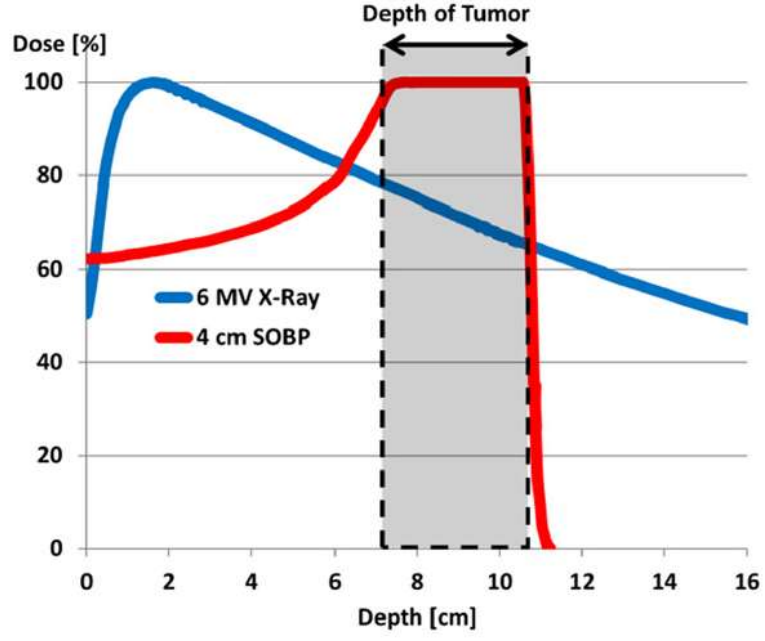


- IMRT provides excellent local control
- Dose escalation beyond 30.6Gy may be unnecessary with improved target volume coverage.
    - Panandikar et al. St Judes data. PBC 2013



CRT IMRT PBT





Fuji H et al. Radiat Oncol 2013

Proton therapy in Nb

- The dosimetric evaluations and the first clinical results of PT in high-risk neuroblastoma are promising.
- The potentiality of PT to reduce the dose to organs outside the target volume could improve
  - Tolerance of a very aggressive multimodal treatment
  - Decrease the incidence of secondary cancer.
- Customized approach with careful evaluation of renal dosimetry; IMRT may be preferred for select patients

Hatttangadi JA, et al. IJROBP 2012
Hill-Kayser C, et al. PBC 2013
Fuji H et al. Radiat Oncol 2013
Hill-Kayser C, et al. PBC 2013

Efficacy of **proton therapy** in children with high-risk and locally recurrent neuroblastoma

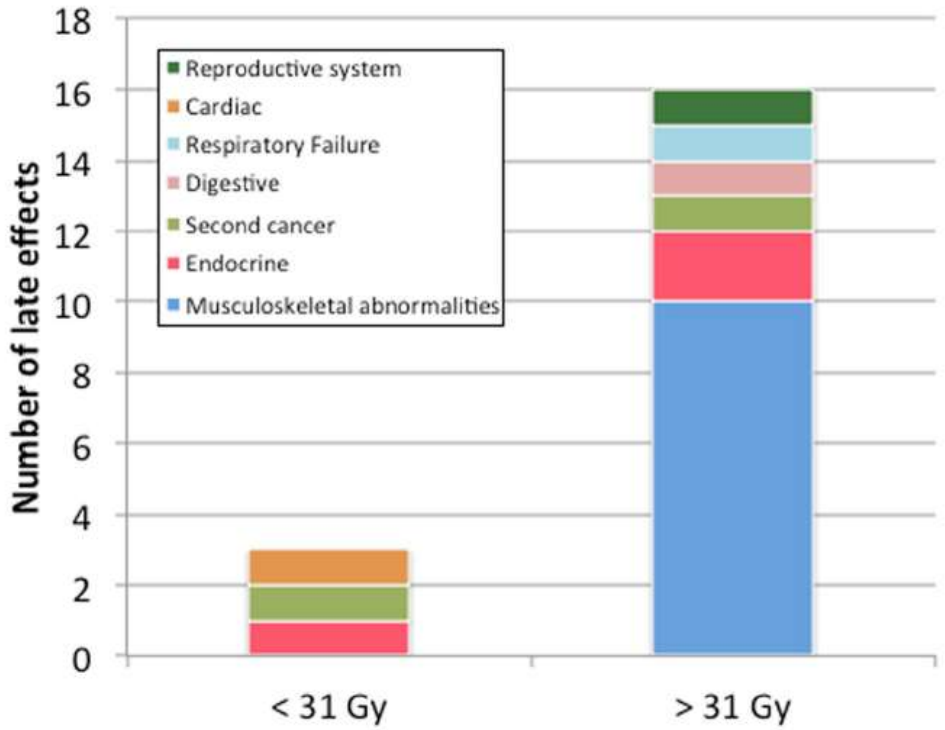
Excellent local control was achieved using proton therapy to the primary and post induction MIBG-positive distant sites

Distant failures!!

Acceptable toxicity

Long-term side effects of RT for localized Nb

- Results from clinical trials NB90 and NB94
- 22 alive patients
- Median follow up 14yrs
- Late effects → 73 %
- Within the RT field → 50 %
- musculoskeletal abnormalities (most common) → only with doses > 31 Gy



Mean kidney doses of 15 Gy to the more exposed kidney and 11 Gy to the less exposed kidney are safe.

Beckham et al. MSKCC. IJROBP 2017

Ducassou A, et al. Strahlenther Onkol 2015

Take home message

- No longer used for patients with low- and intermediate-risk disease, as outcome is excellent
- Plays important role in multidisciplinary treatment of patients with high-risk disease (local + post induction therapy avid metastatic sites)
- Conformal approach
- Can be used for emergency situations

SIOP 2019
Lyon France

Thank you!!

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