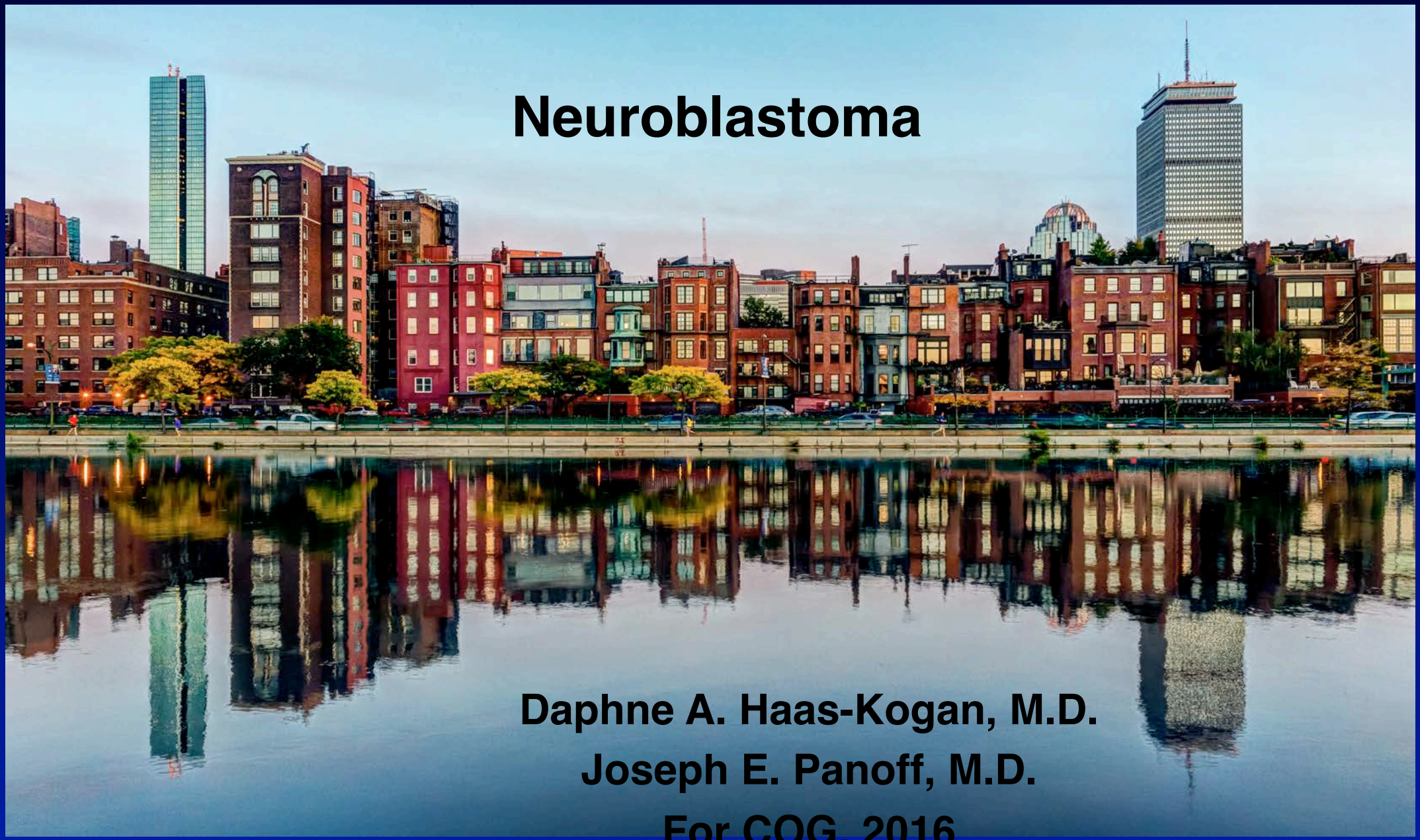
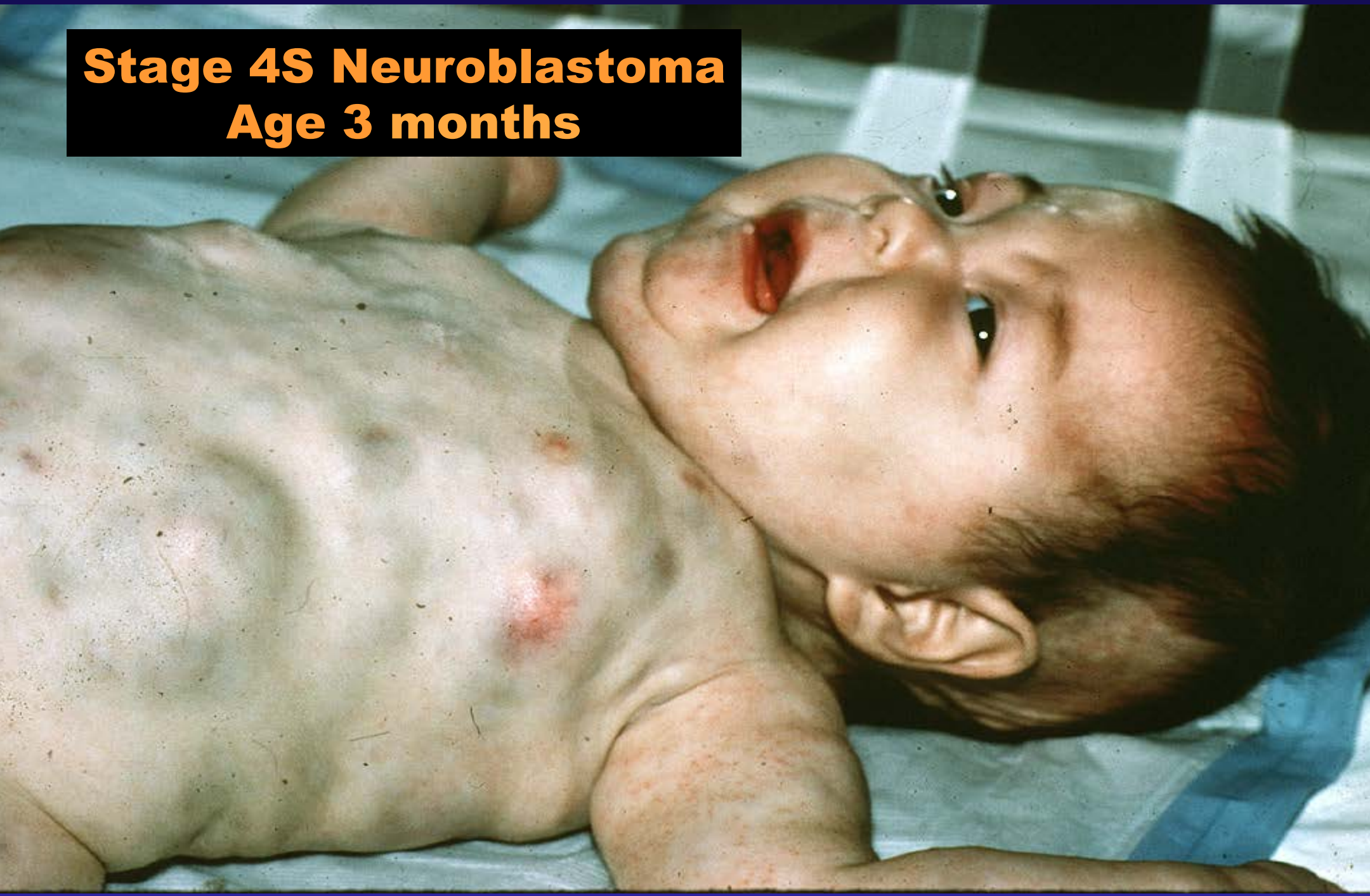
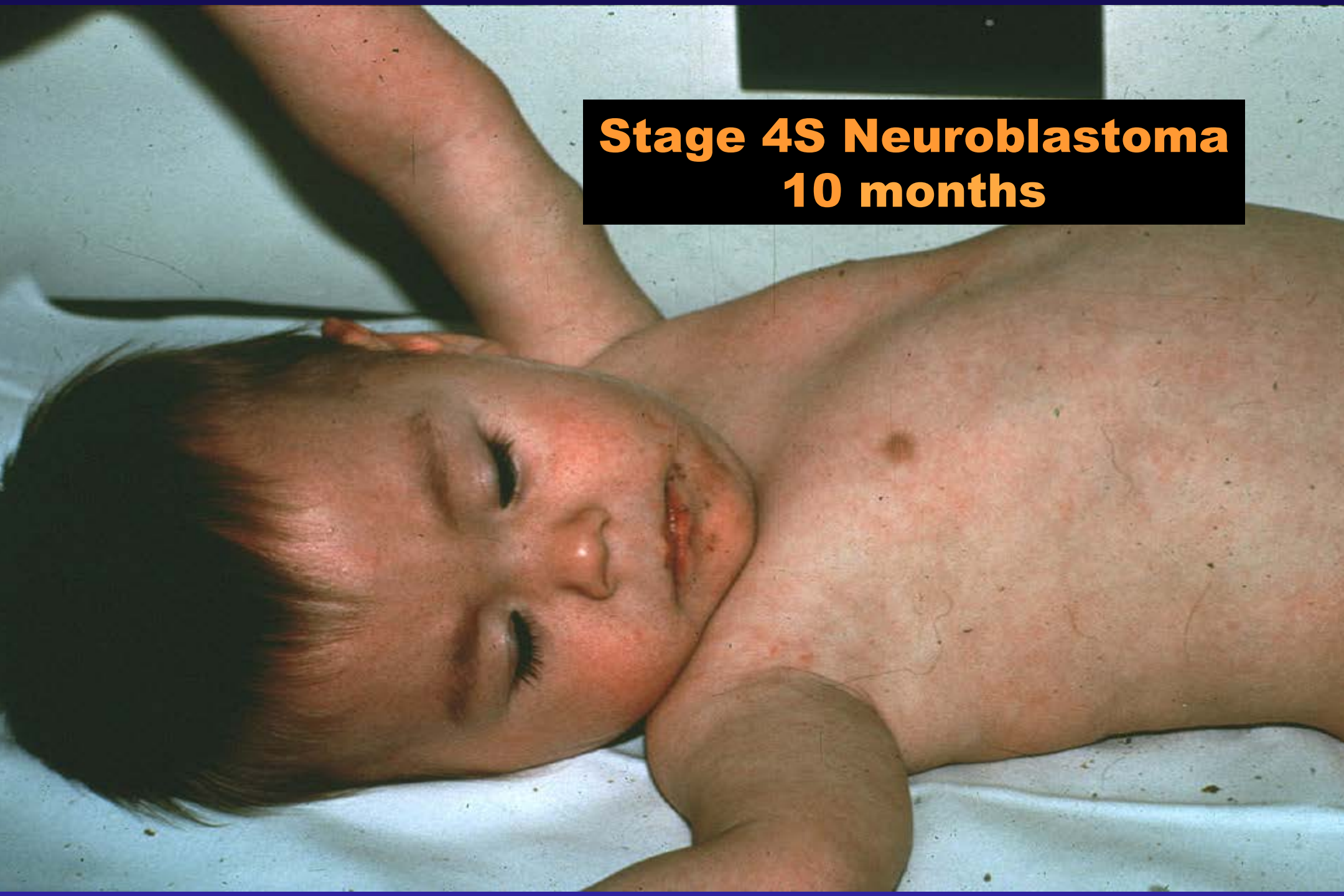


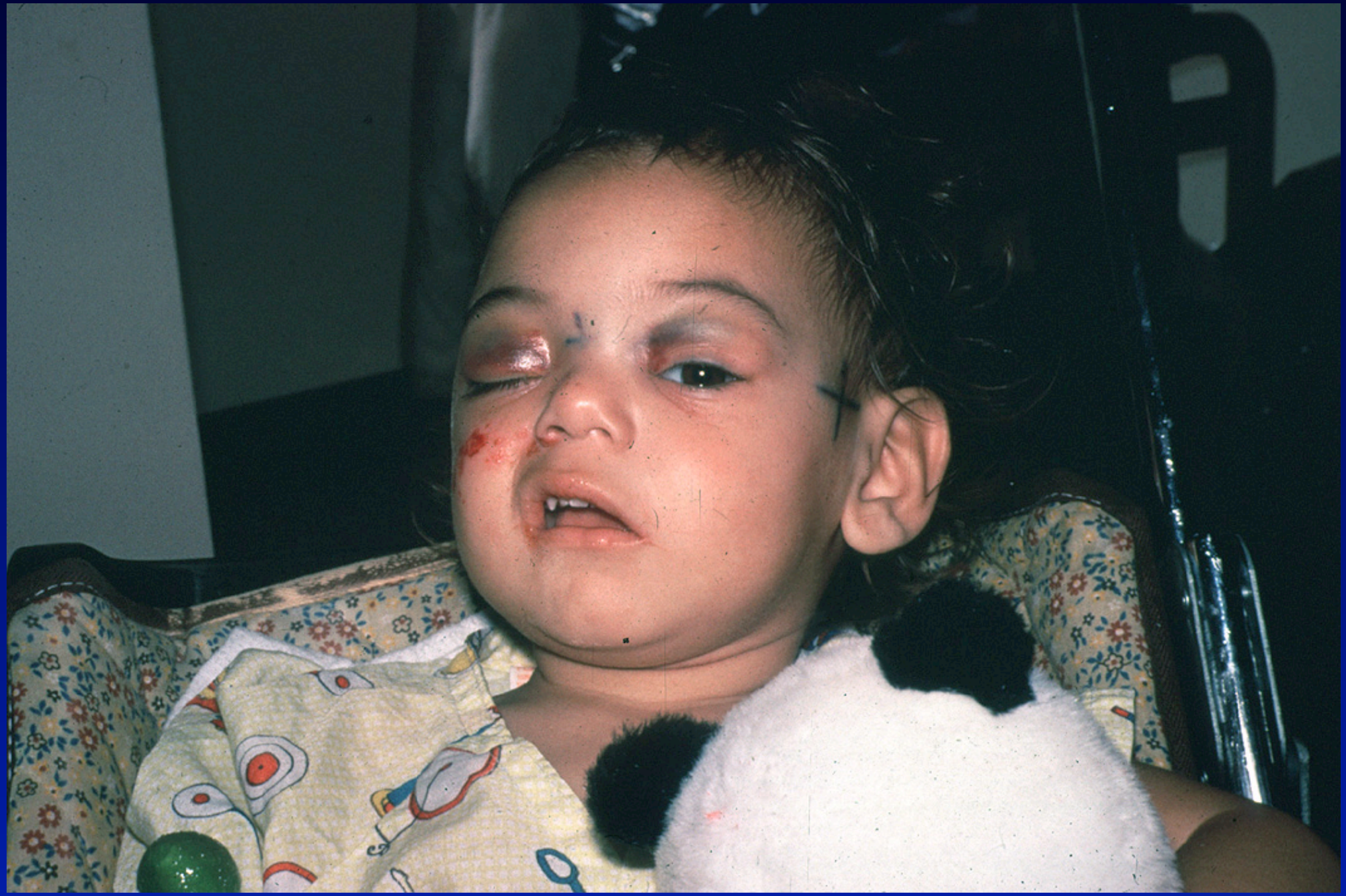
Neuroblastoma

Daphne A. Haas-Kogan, M.D.
Joseph E. Panoff, M.D.

For COG, 2016

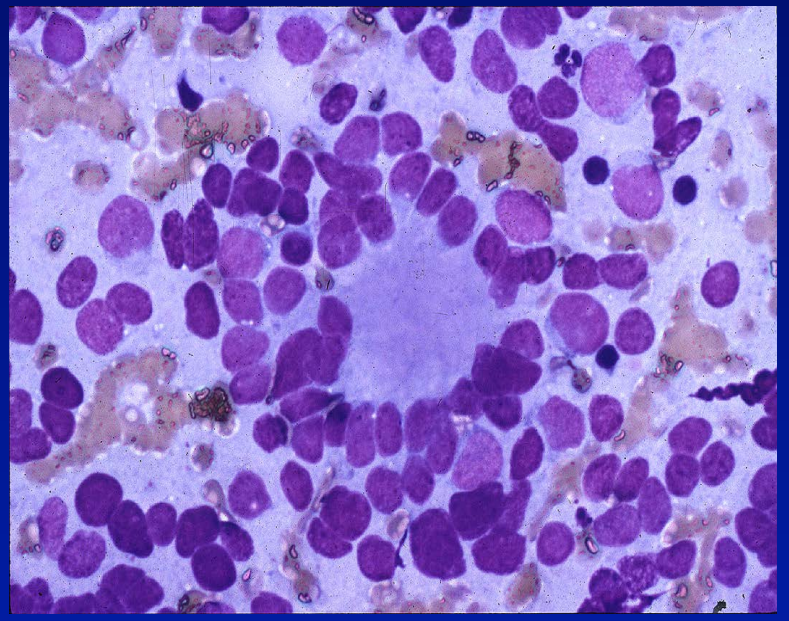

Stage 4S Neuroblastoma
Age 3 months


Stage 4S Neuroblastoma
10 months

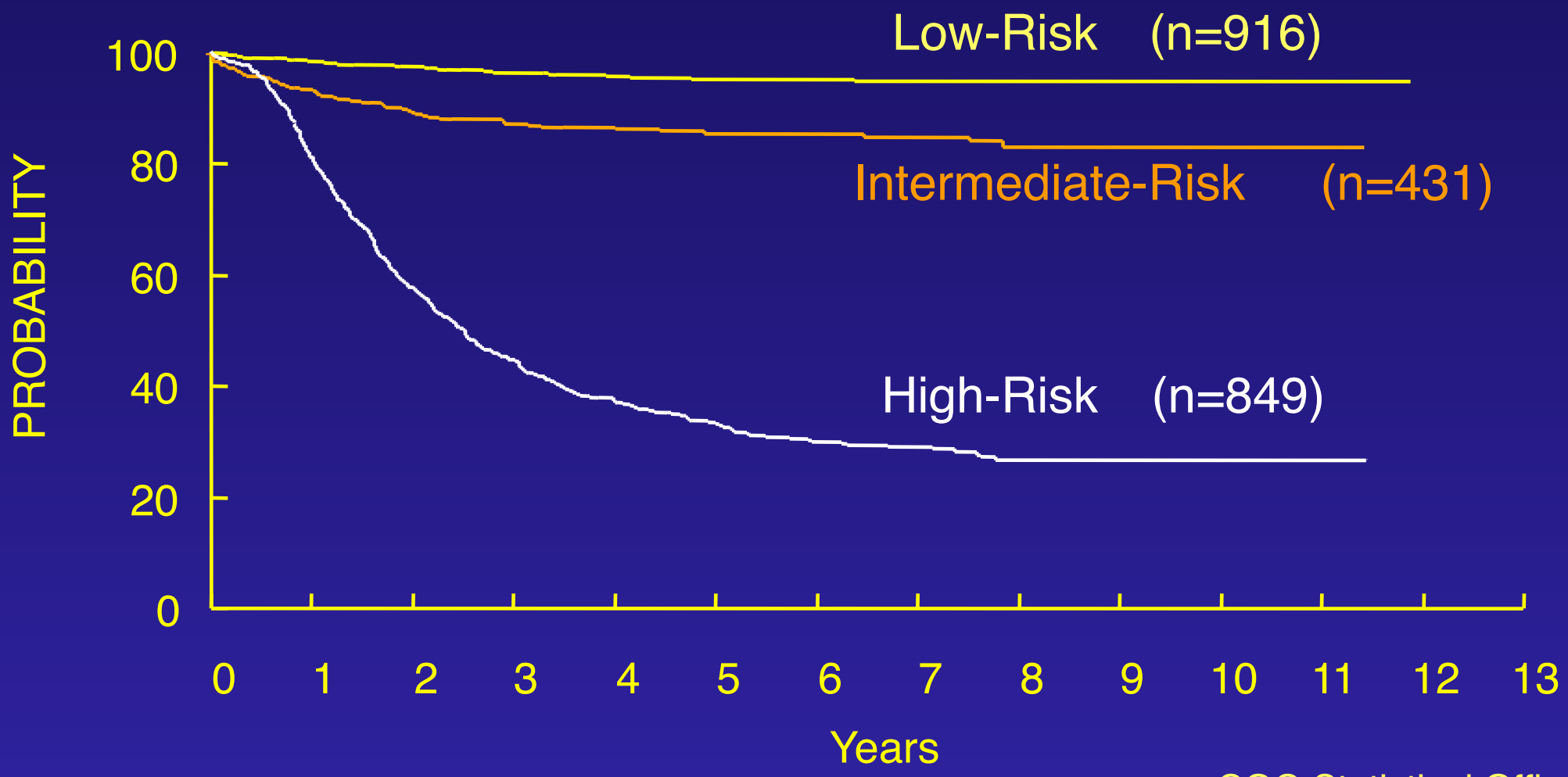


Neuroblastoma

- Derived from sympathetic nervous system
- Most common extra-cranial solid tumor of childhood
- Most common malignancy in newborn period
- Outcome depends on tumor biology

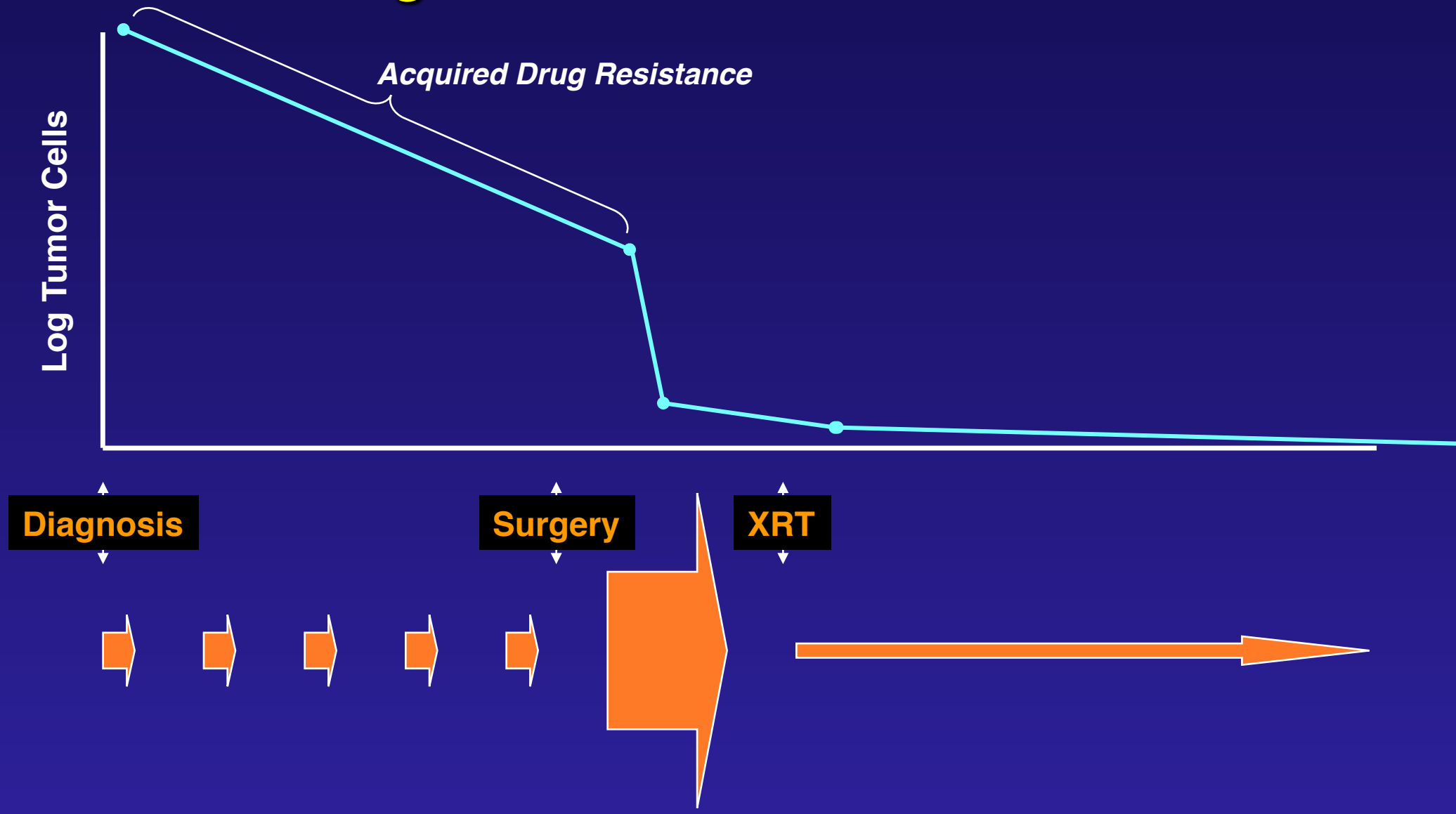


EFS According to Risk Group



COG Statistical Office

High-risk Neuroblastoma



Radiation Therapy for Neuroblastoma: Important Questions

- Is local recurrence a dominant form of disease relapse?
- Does radiation to the primary site contribute to local control?
- How should local RT be incorporated into multimodality treatment of neuroblastoma?
- Is there a dose-response to primary site irradiation and does a subtotal resection require a higher radiation dose?

High-Risk Neuroblastoma: Local Recurrence

- Relapse at the primary site presents a significant challenge:
  - Primary tumors are large, invasive and rarely eradicated by chemotherapy.
  - Local recurrences occur in 5-74% of patients with high-risk disease.
- No randomized trials have addressed the role of radiation in stage IV neuroblastoma.

High-Risk Neuroblastoma: Local Recurrence

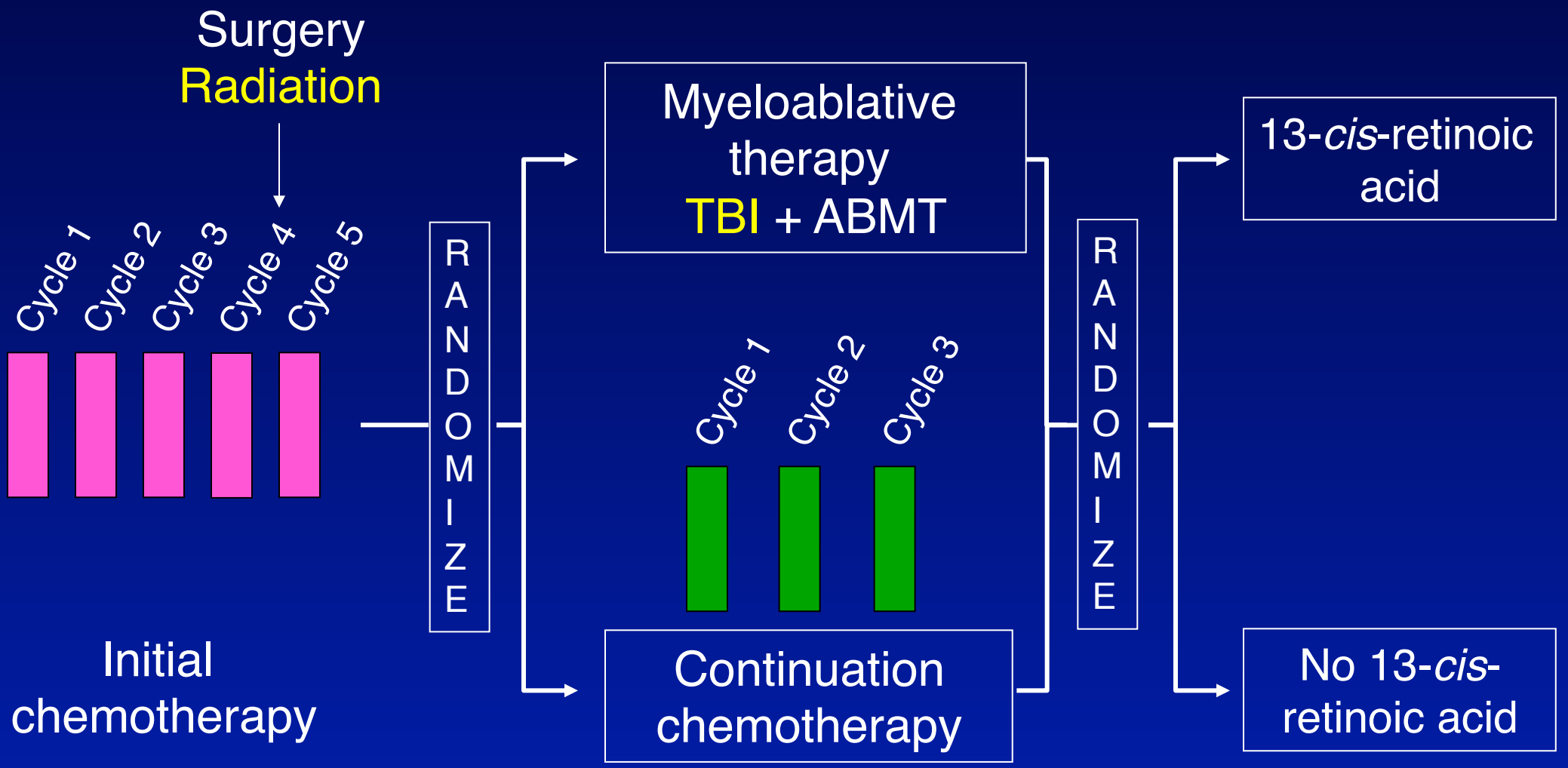
Author	Radiation dose	Local relapse
Rosen *et al.,* 1984	25-40 Gy	74%
Kremems *et al.,* 1994	21 Gy (1.5 bid)	15%
Ikeda *et al.,* 1992	7.5-22 Gy (+10 Gy TBI)	17%
Villablanca *et al.,* 1999*	21 Gy (1.5 bid)	5%
Sibley *et al.,* 1995	8-24 Gy (+12 Gy TBI)	16%
Haas-Kogan. *et al* 2002*	10 Gy IORT	9%
Kushner *et al.,* 2001	21 Gy (1.5 bid)	10%
Matthay *et al.,* 1993	Residual dz: 20 Gy	26%
	No residual: 10 Gy TBI	31%

* abstract

Rationale for Radiation Guidelines

- Is local recurrence a dominant form of disease relapse?
- Does radiation to the primary site contribute to local control?
- How should local RT be incorporated into multimodality treatment of neuroblastoma?
- Is there a dose-response to primary site irradiation and does a subtotal resection require a higher radiation dose?

CCG 3891 Schema

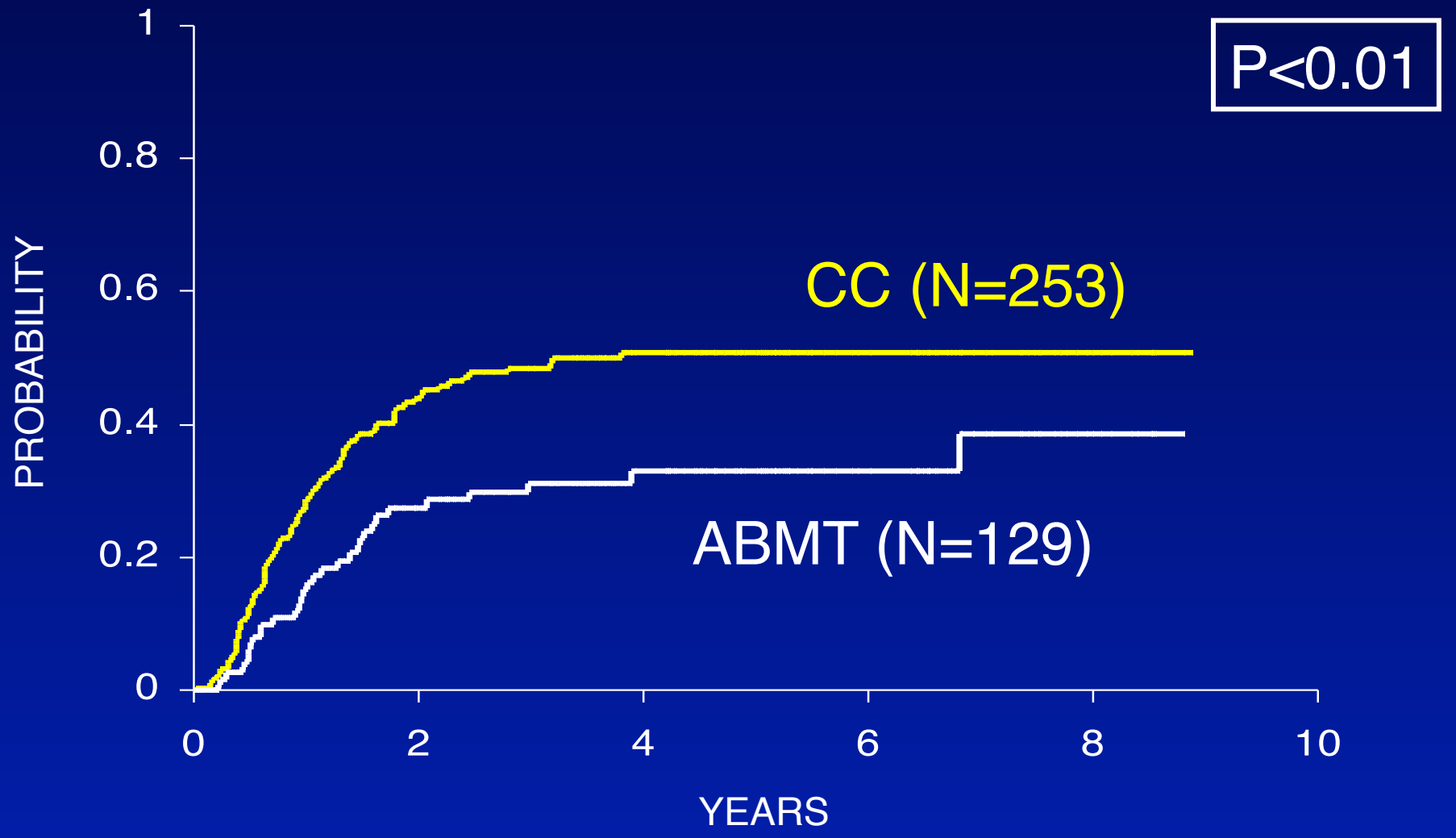


CCG 3891: Radiation Guidelines

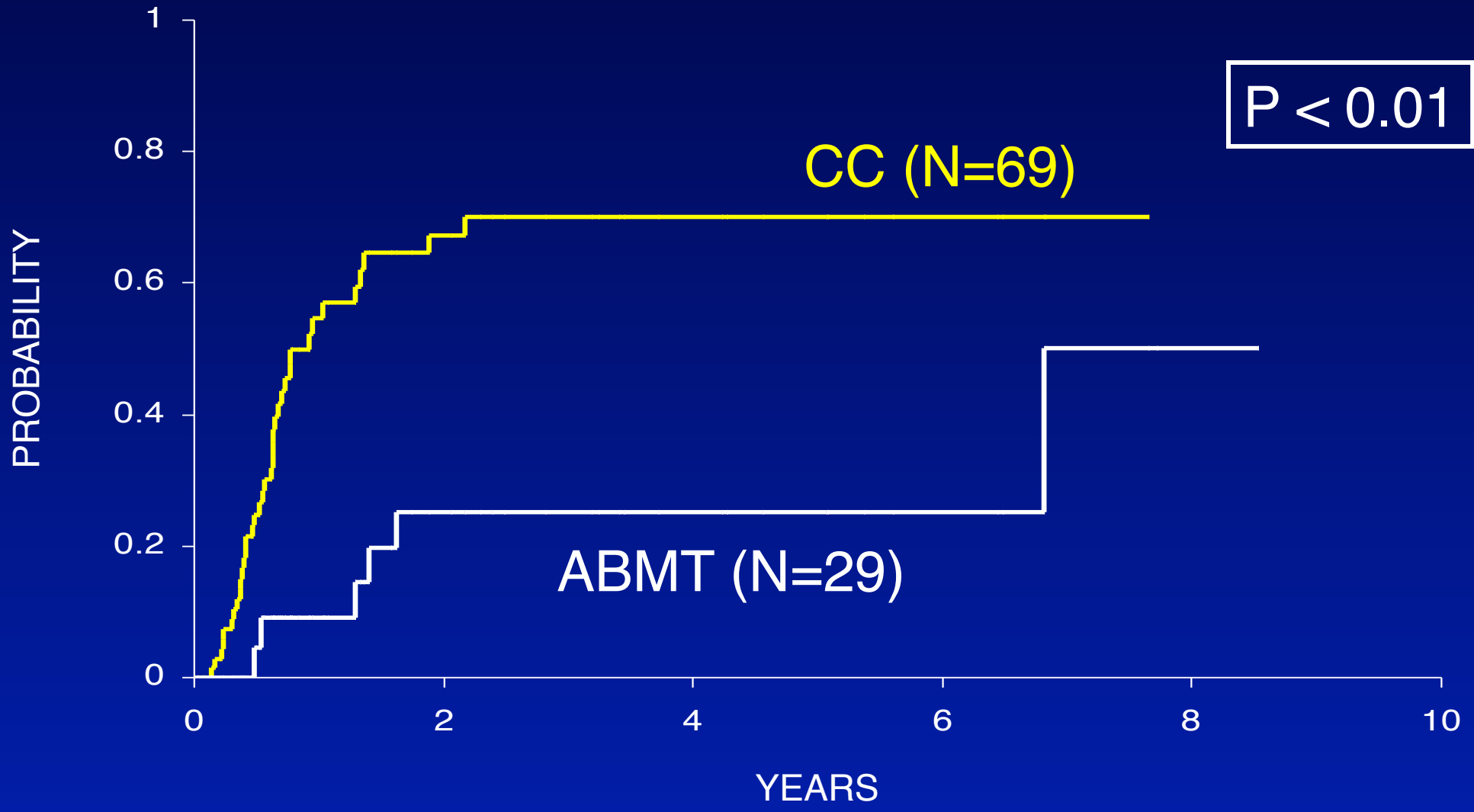
- Local radiation was NOT administered in a randomized fashion.
- External beam radiation therapy (EBRT) administered to gross residual disease prior to ABMT or continuation chemo (CC).
- Dose: 20 Gy (2 Gy qD) to extra-abd tumors.
  10 Gy to mediastinal or intra-abd tumors.

Matthay et al. *NEJM* 1999; 341:1165-1173

Primary Site Relapse by Treatment Received (CCG 3891)



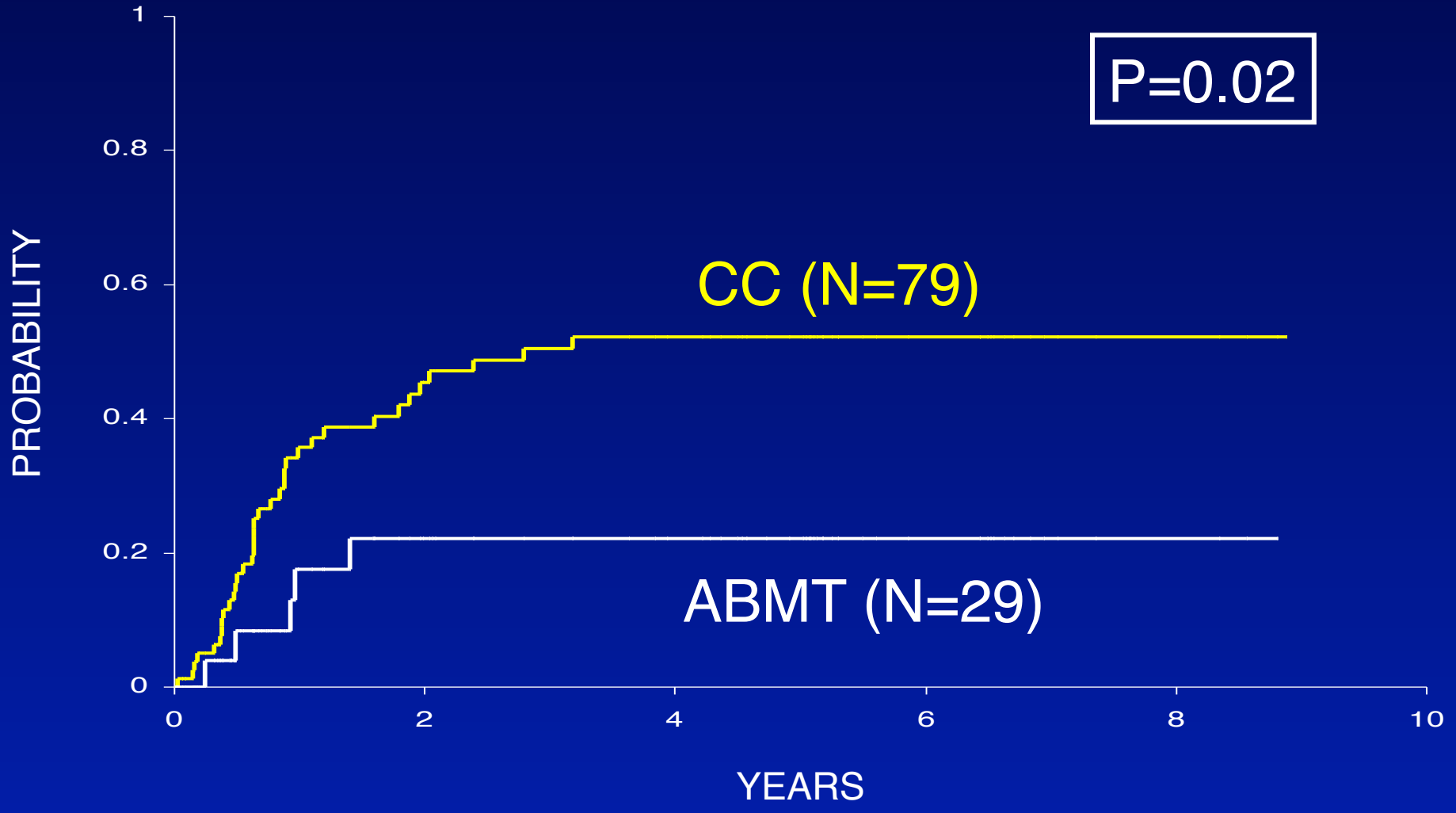
Patients with *MYCN* amplification: Primary Site Relapse (CCG 3891)



Does radiation to the primary site contribute to local control?

- Examined a group with more uniform patient characteristics by evaluating separately the group that received EBRT for gross residual disease.
- Ask whether the addition of 10 Gy of TBI as a component of ABMT improved local control.

Patients Receiving EBRT: Primary Site Relapse (CCG 3891)



Radiation and Local Control

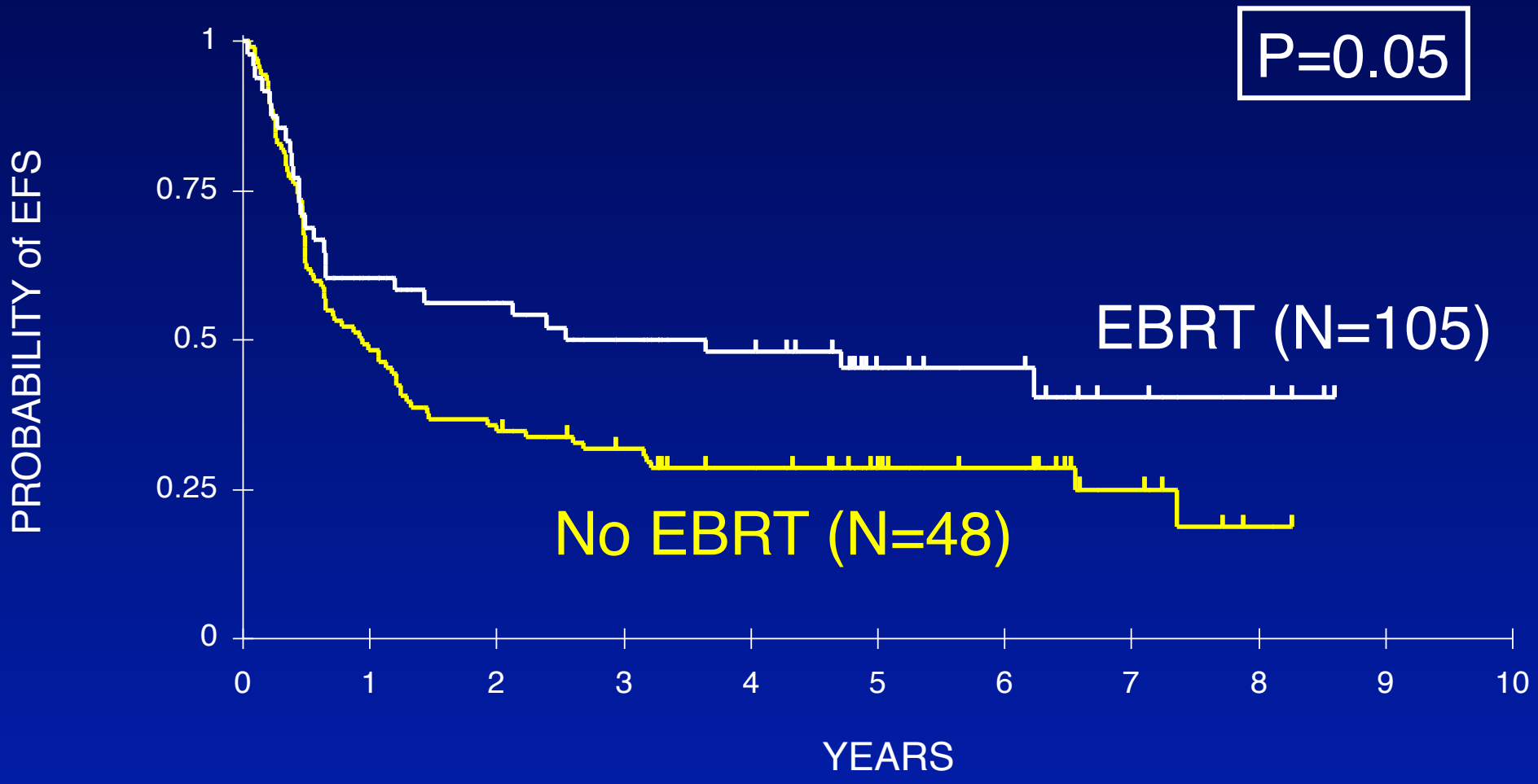
- Word of caution: all ABMT patients received myeloablative chemotherapy as well as additional radiation in the form of TBI.

- Nevertheless: the results suggest that 20 Gy in the form of 10 Gy TBI + 10 Gy EBRT (as part of ABMT) may improve local control compared to 10 Gy alone (without ABMT).

Rationale for Radiation Guidelines

- Is local recurrence a dominant form of disease relapse?
- Does radiation to the primary site contribute to local control?
- How should local RT be incorporated into multimodality treatment of neuroblastoma?
- Is there a dose-response to primary site irradiation and does a subtotal resection require a higher radiation dose?

Patients Receiving 13-*cis*-retinoic acid: 5-year Event Free Survival



CCG 3891: Implication

- The benefit of local control emerges as metastases are better controlled by treatment directed at systemic and minimal residual disease.
  - myeloablative therapy.
  - 13-*cis*-retinoic acid.

Rationale for Radiation Guidelines

- Is local recurrence a dominant form of disease relapse?
- Does radiation to the primary site contribute to local control?
- How should local RT be incorporated into multimodality treatment of neuroblastoma?
- Is there a dose-response to primary site irradiation and does a subtotal resection require a higher radiation dose?

Is there a dose-response to primary site irradiation and does a subtotal resection require a higher radiation dose?

Surrogate question:

- How did we arrive at our current “standard” dose of radiation?

Answer:

- Empirically!!
- Based on studies performed during a time period in which all but stage I patients received radiation.

"Pediatric Neuroblastoma: Postoperative Radiation Therapy Using Less Than 2000 Rad"

Jacobson HM, Marcus RB, Thar TL, Million RR, Graham-Pole JR, Talbert JL.

Results:

- Doses of 9-15 Gy for patients <1 yr and 12-19 Gy for patients 1-2 yrs prevented all local recurrences.
- Data did not support benefit of doses higher than 20 Gy.

Stage:	II, III	IV
Patient #:	21	0

Int J Radiation Oncology Biol Phys 9:501-505, 1983

Evidence for a dose-response?

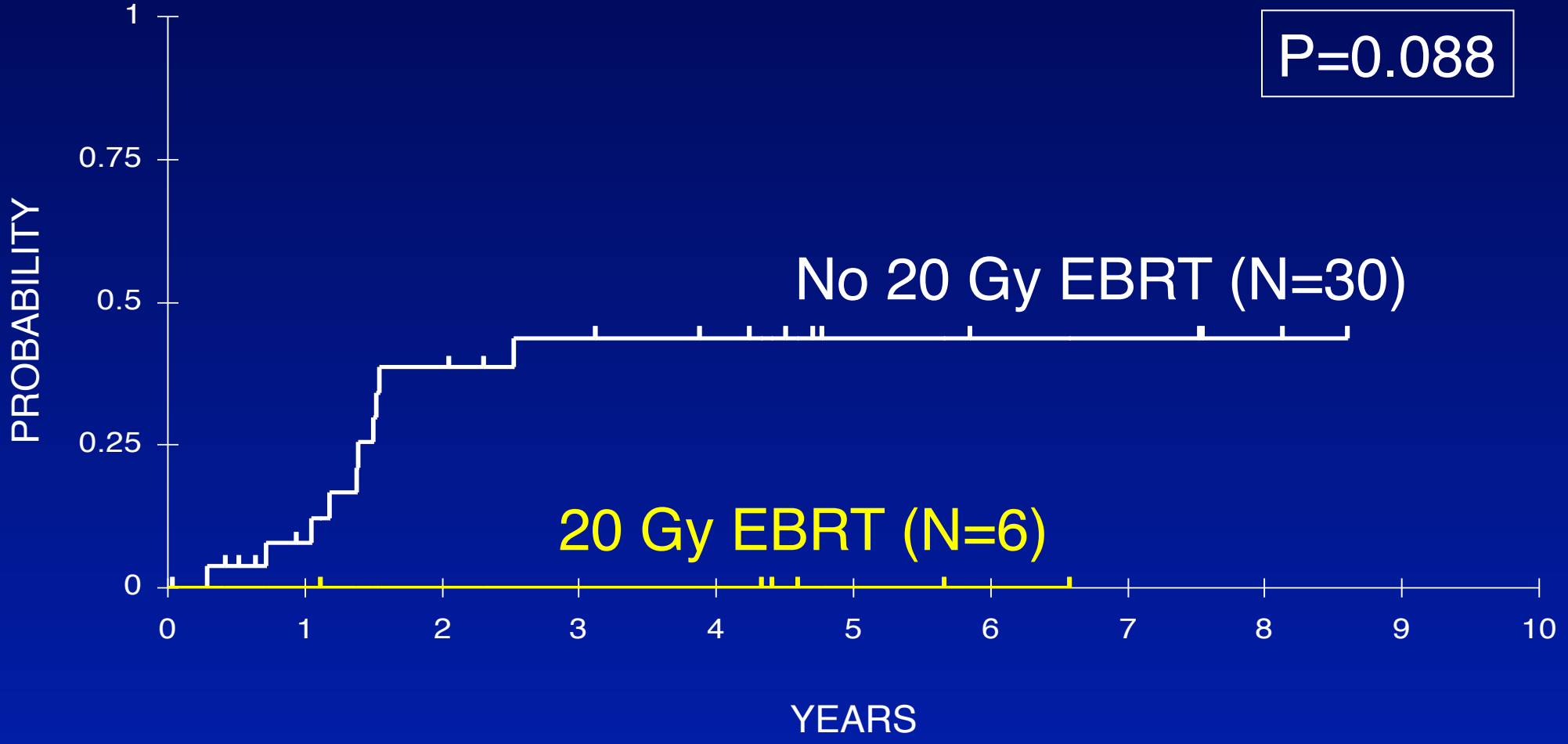
- Analysis of CCG 3891, in which local radiation was NOT administered in a randomized fashion. Rather, external beam radiation therapy (EBRT) administered to gross residual disease prior to ABMT or continuation chemo (CC).

  Dose: 20 Gy (2 Gy qD) to extra-abdominal tumors.

  10 Gy to mediastinal or intra-abdominal tumors.

- Examine the subgroup of patients who received 20 Gy for extra-abdominal primary tumors.
- Of 36 patients with extra-abdominal primaries, 6 patients received 20 Gy EBRT while 30 patients received no EBRT.

20 Gy to Extra-Abdominal Primary: Primary Site Relapse



Radiation Dose-Response?

- More pronounced benefits in local control and EFS are seen in the small group in which EBRT consisted of 20 Gy rather than 10 Gy.

- Perhaps a dose-response exists for radiation administered to the primary tumor.

Do patients with less than a complete resection need higher radiation doses?

- 99 high-risk neuroblastoma pts in 1st remission.
- RT to primary site delivered after dose-intensive chemotherapy and tumor resection.
- Dose: 1.5 Gy bid to 21 Gy total.
- Probability of primary-site failure was 10.1% at 36 months after RT.
- No primary-site failures among the 23 patients whose tumors were excised at diagnosis.
- Three primary-site relapses occurred among seven patients who received local RT with evidence of residual disease at the primary site.

Kushner et al., *JCO* (2001) 19:2821-2828

Evidence for a dose-response?

- Intensified external beam radiation therapy improves the outcome of stage 4 neuroblastoma in children >1 year with residual local disease.
- Retrospective study of 110 stage 4 neuroblastoma patients on NB97 trial: induction chemotherapy, surgery, ABMT.
- Intensified local EBRT (36 Gy) for residual viable tumor on MRI and MIBG.
  - 74 patients had CR to induction chemotherapy: no EBRT.
  - 23 had residual disease but did not receive EBRT.
  - 13 with residual disease underwent EBRT (36 Gy).

University Children's Hospital in Cologne

Simon T, *et al.,* Advances in Neuroblastoma Research: Abstract 314, 2006

Evidence for a dose-response?

Patient Characteristics	3-year EFS (%)	3-year OS (%)
Patients in CR after induction chemotherapy and did not receive EBRT (n=74)	61 ± 10	75 ± 6
Patients with residual disease who DID receive EBRT (n=13)	85 ± 10	92 ± 7
Patients with residual disease who DID NOT receive EBRT (n=13)	25 ± 10 P<0.001	51 ± 11 P=0.003

Authors Conclude: EBRT (36 Gy) "seems to compensate for the disadvantage of incomplete response to induction therapy."

University Children's Hospital in Cologne

Simon T, *et al.,* Advances in Neuroblastoma Research:Abstract 314, 2006

NB97 Trial: Isolated localized residual disease

Patient Characteristics	3-year EFS (%)	3-year OS (%)
Patients with isolated localized residual disease who DID receive EBRT (n=8)	100	100
Patients with isolated localized residual disease who DID NOT receive EBRT (n=6)	20 ± 18 P<0.001	20 ± 18 P<0.001

On multivariate analysis, EBRT was an independent prognostic factor for EFS (HR=0.27, 95% CI 0.09-0.76) and OS (HR=0.17, 95% CI 0.04-0.81).

University Children's Hospital in Cologne
Simon T, *et al.,* Advances in Neuroblastoma Research:Abstract 314, 2006

ANBL0532: Local Control Question

- Hypothesis:
  - Increasing the dose of local radiation for patients with <GTR will reduce local tumor failure rates.
- Dose for post-ABMT radiation to the primary tumor bed based on residual disease:
  - 21.6 Gy for GTR
    - pre-operative tumor volume
  - 36.0 Gy for < GTR
    - 21.6 Gy to pre-operative tumor volume
    - 14.4 Gy boost to gross residual disease
- Historical comparison with primary tumor relapse rates on A3973
- Question:
  - Can we detect an improvement in local control after an additional 14 Gy administered to children with < GTR?

Radiation Therapy for Neuroblastoma: Important Questions

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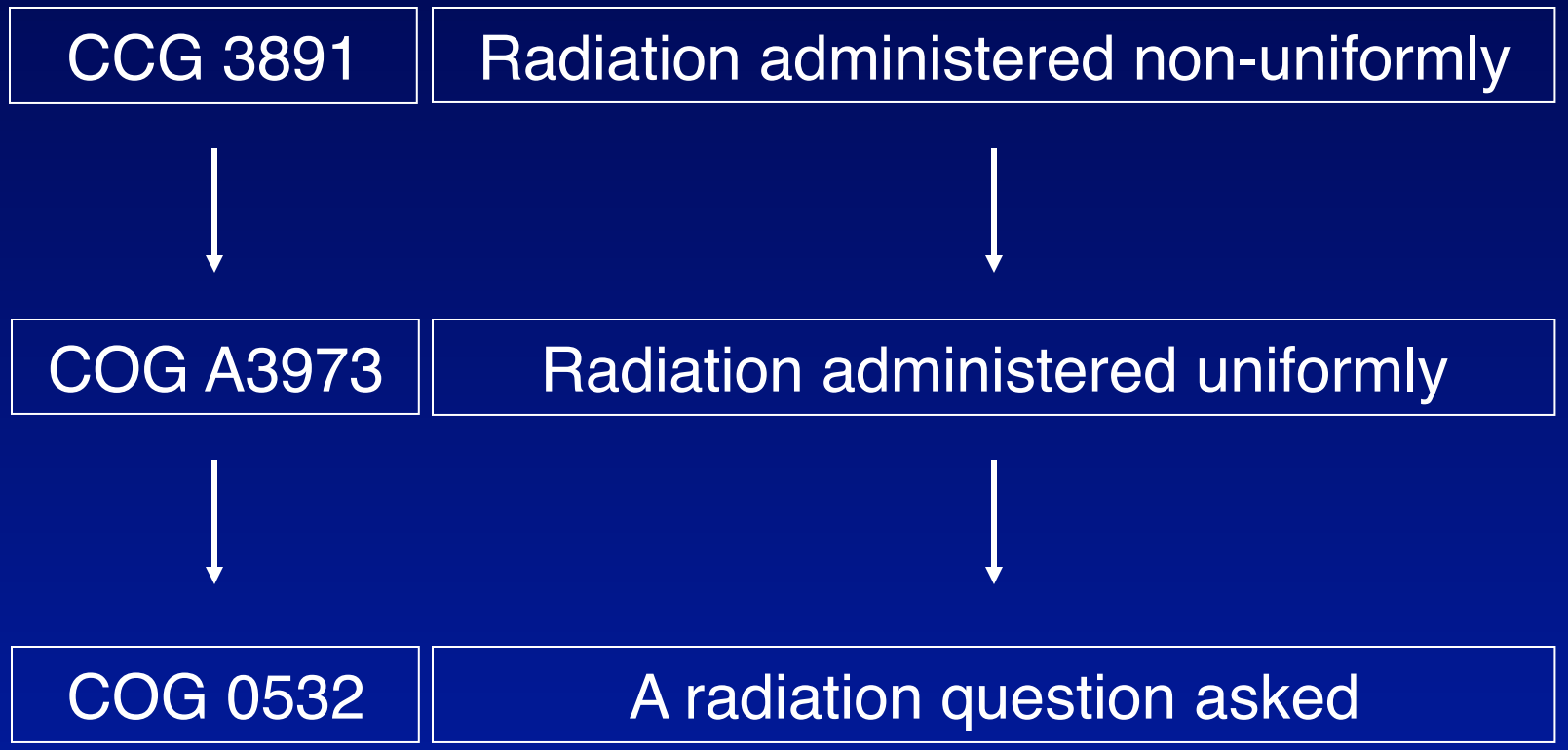
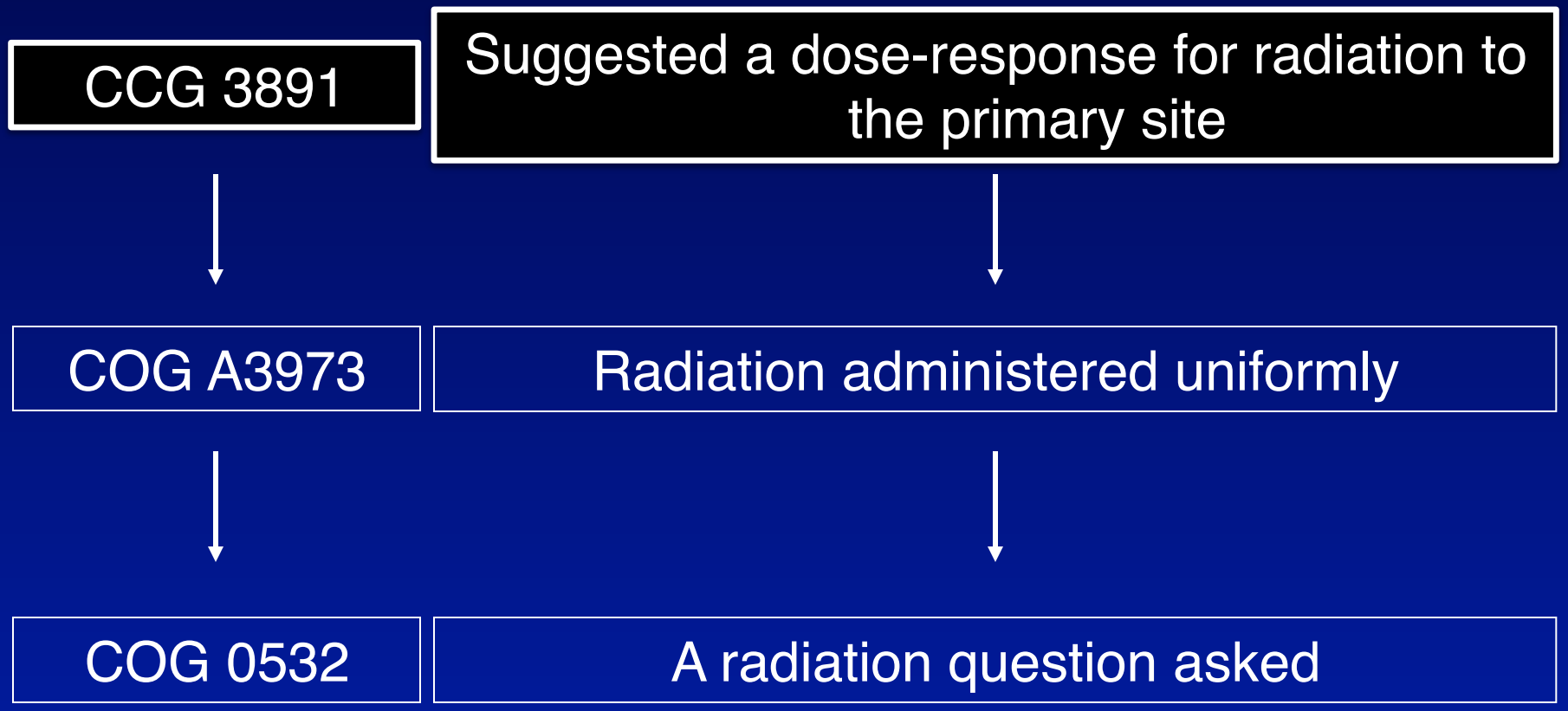
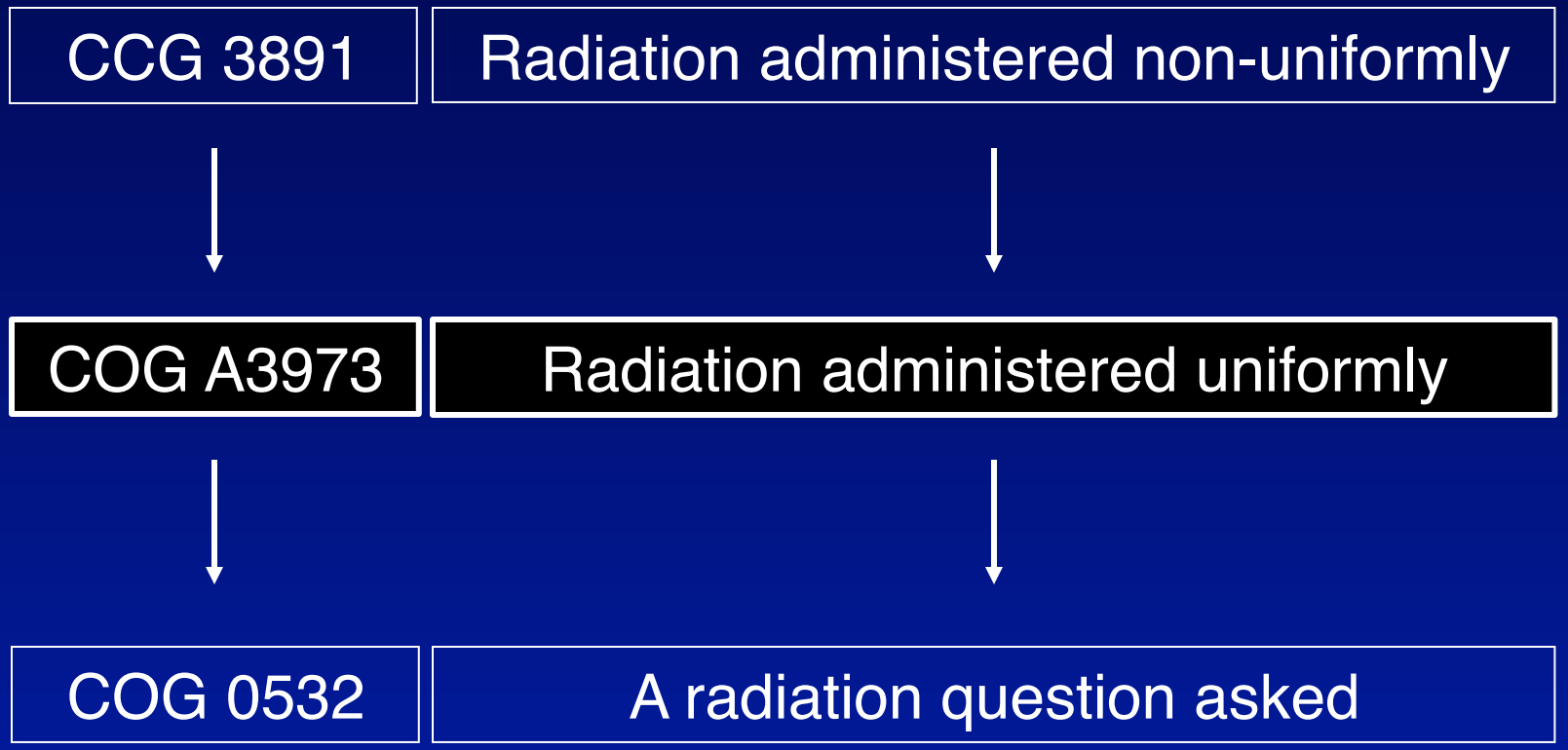
Progress in COG high-risk neuroblastoma studies



Progress in COG high-risk neuroblastoma studies



Progress in COG high-risk neuroblastoma studies



COG Protocol for High-Risk Neuroblastoma Patients

CHILDREN'S ONCOLOGY GROUP

A3973

A Randomized Study of Purged versus Unpurged Peripheral Blood Stem Cell Transplant Following Dose Intensive Induction Therapy for High Risk Neuroblastoma

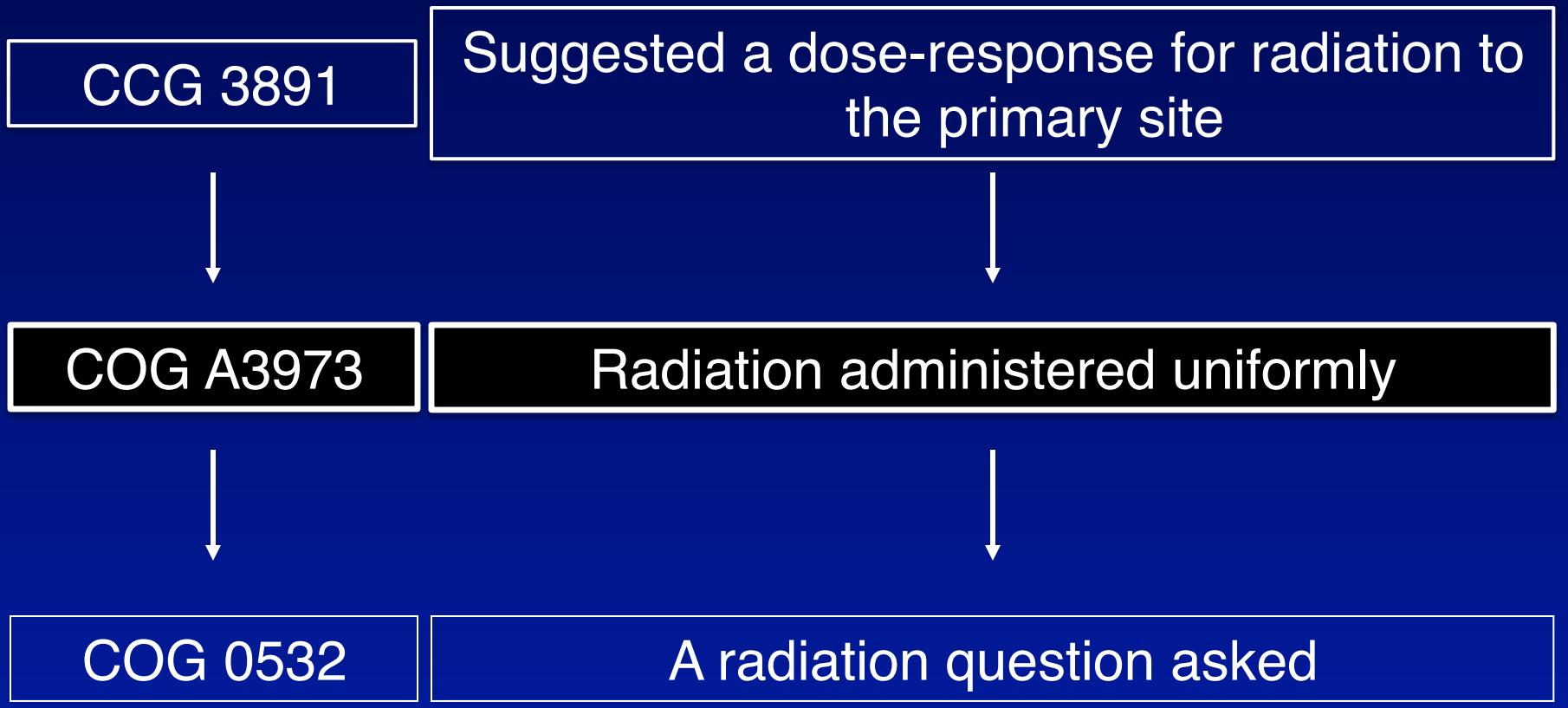
High-risk neuroblastoma, A3973: Radiation guidelines

- Radiation given following myeloablative stem cell transplant to all areas of residual disease.
- Primary site receives radiation regardless of extent of resection.
- Volume of primary site RT: pre-surgical tumor volume, regardless of extent and timing of the surgical resection or response to chemotherapy.
- Dose: 21.6 Gy in 1.8 Gy daily fractions.

High-risk neuroblastoma, A3973:

- Immunomagnetic tumor-selective PBSC purging in stem-cell transplantation for autologous stem-cell transplantation did not improve outcome, perhaps because of incomplete purging or residual tumor in patients. Non-purged PBSC are acceptable for support of myeloablative therapy of high-risk neuroblastoma.
- Radiation results pending.

Progress in COG high-risk neuroblastoma studies



COG A3973 Protocol for High-Risk Neuroblastoma Patients

A Randomized Study of Purged versus Unpurged Peripheral Blood Stem Cell Transplant Following Dose Intensive Induction Therapy for High Risk Neuroblastoma

- 486 eligible patients
- 156 had no radiation, were ineligible, or not data submitted
- Reviewed 339 radiation plans and associated diagnostic scans and clinical data

What is the best approach to radiation of un-involved lymph nodes stations?

- What do we base our lymph node coverage on?
- What does the literature support?

Not much…

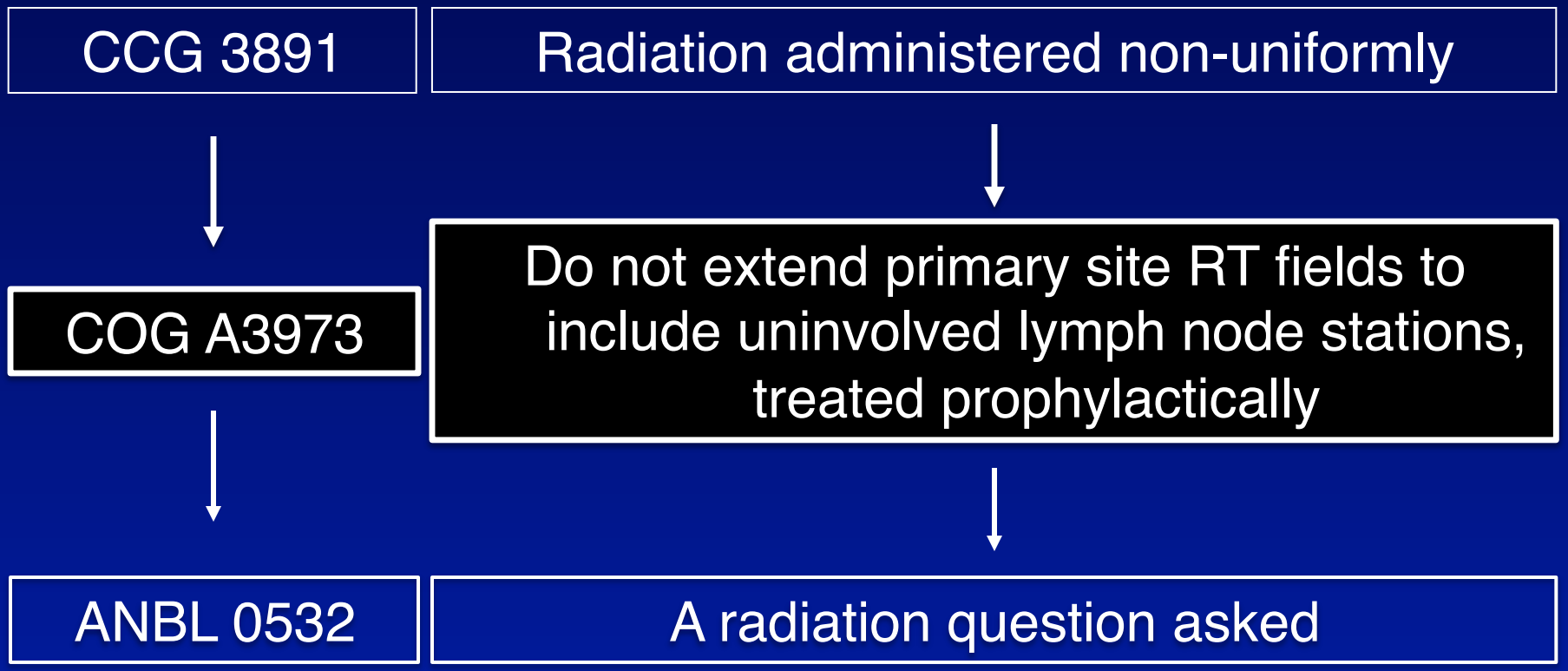
- A3973 helped us answer the question

Results: 5-year estimates

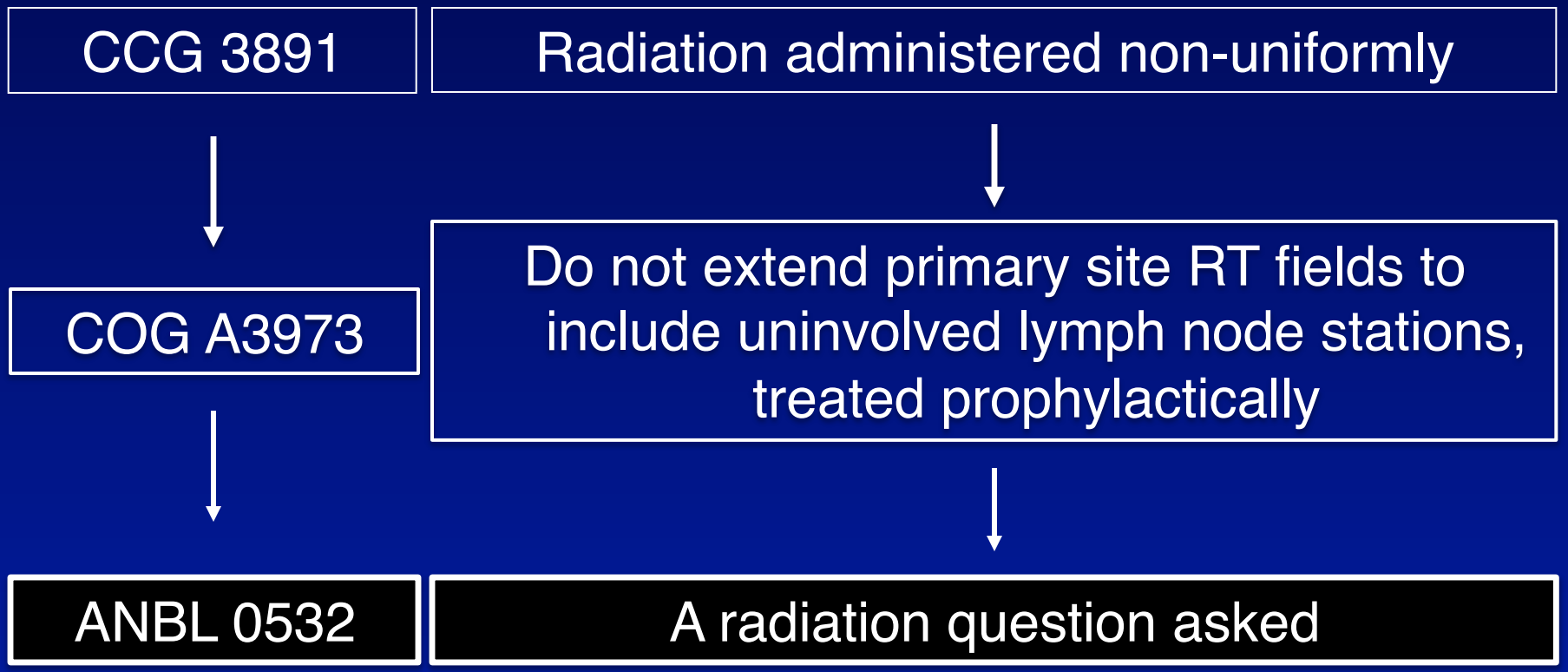
Lymph node coverage	N (%)	EFS ± std error (%)	EFS p-value	CILR ± std error (%)	CILR p-value	OS ± std error (%)	OS p-value
< 40% ≥ 40%	75 (23%) 255 (77%)	50.8 ± 6.0 46.2 ± 3.4	0.49	6.9 ± 3.0 9.0 ± 1.8	0.55	61.7 ± 6.2 59.0 ± 3.4	0.35
< 60% ≥ 60%	148 (45) 182 (55)	50.1 ± 4.5 45.0 ± 4.0	0.51	6.9 ± 2.1 9.9 ± 2.2	0.32	59.6 ± 4.4 59.7 ± 4.0	0.61
< 80% ≥ 80%	239 (74) 91 (26)	46.8 ± 3.5 48.2 ± 5.6	0.83	8.0±1.8 9.9±3.2	0.59	59.0±3.5 61.3±5.5	1.00

Effects of extent of lymph node irradiation were neither clinically nor statistically significant.

Progress in COG high-risk neuroblastoma studies



Progress in COG high-risk neuroblastoma studies

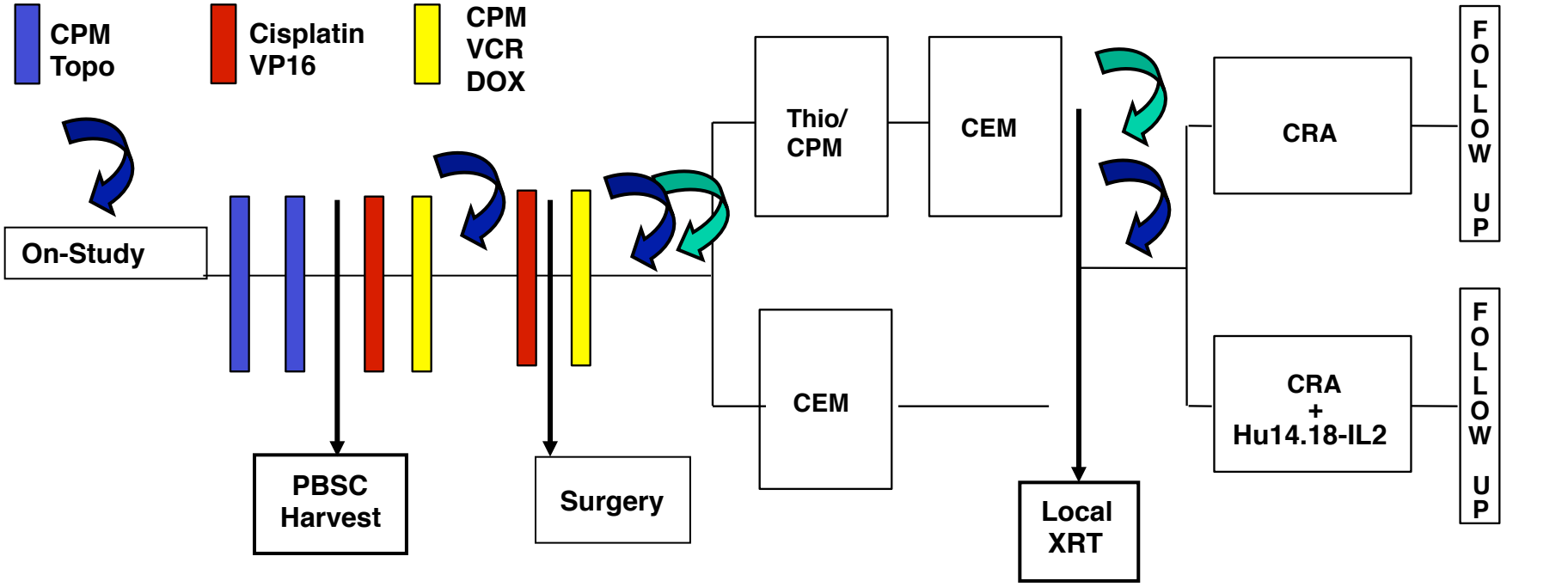


High-Risk Neuroblastoma Study

ANBL0532

Phase III Randomized Trial of Single versus Tandem Myeloablative Consolidation Therapy for High-Risk Neuroblastoma

High risk task force consensus schema



CEM=Carboplatin/Etoposide/Melphalan

<u>To Ultra-high risk study if:</u>

- **PD during induction therapy, *or***
- **"Bad" PR defined by Relative Curie score after 4 cycles**

Randomization time point

Disease assessment

COG ANBL 0532

- Primary Aim: Is 3-year EFS of high-risk patients improved using a tandem consolidation of Thiotepa/Cyclophosphamide followed by Carboplatin/Etoposide/Melphalan (CEM) superior when compared to single CEM consolidation
- 652 patients
- 3-year EFS and OS were 50.9% and 68.0%.
- The 3-year EFS following tandem myeloablative therapy (63.2%) was statistically significantly superior to single myeloablative therapy (48.6%; p=0.0064)
- The 3-year OS following tandem myeloablative therapy versus single myeloablative therapy was 73.5% and 68.8% (p=0.2207)

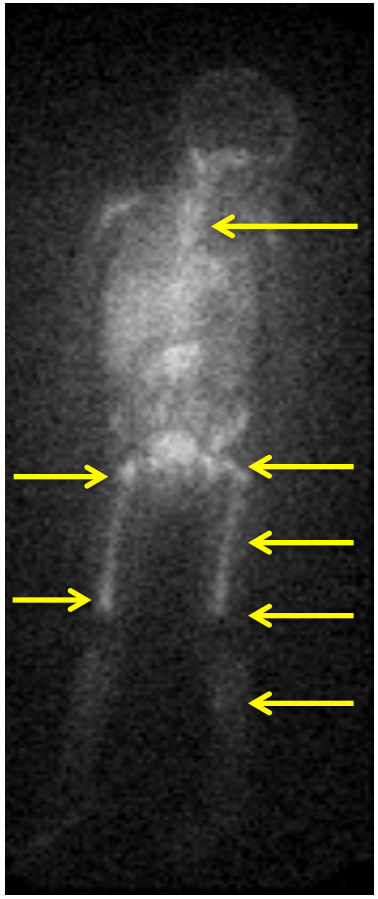
COG ANBL 0532

Hypothesis:

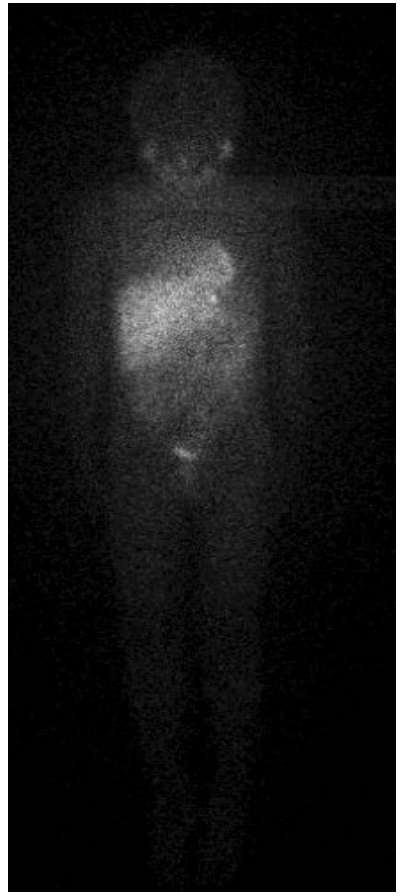
There is a dose-response to primary site irradiation and a subtotal resection requires a higher radiation dose

High-Risk Patients Often Relapse in Previously Involved Metastatic Sites

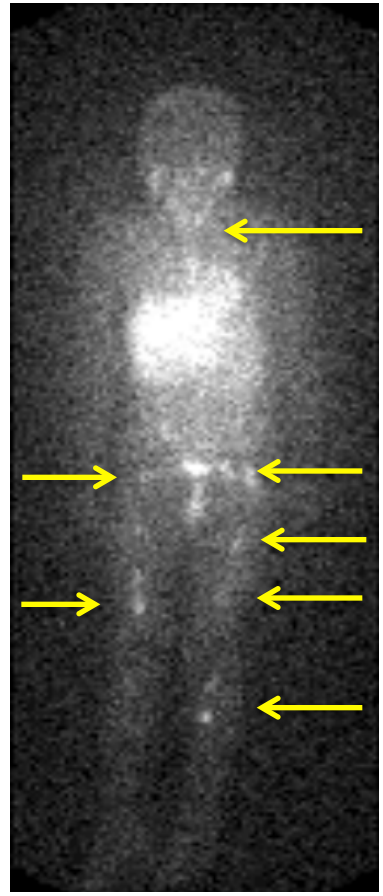
DIAGNOSIS



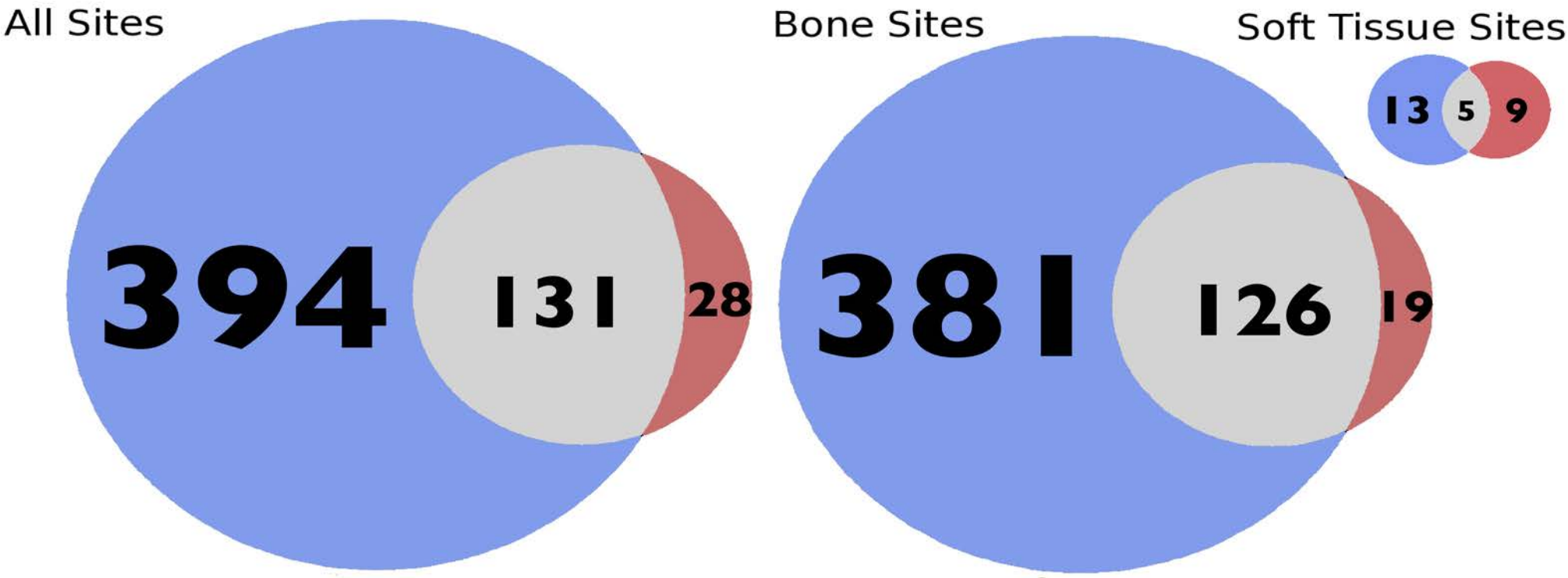
CR PRE-SCT (+6 mo)



RELAPSE (+2 yrs)



Relapses at New Sites is Unusual



18% of sites at relapse previously uninvolved

Polishchuk et al., IJROBP 2014

Radiation Therapy Effective at Preventing Relapse At Residual Metastatic Sites

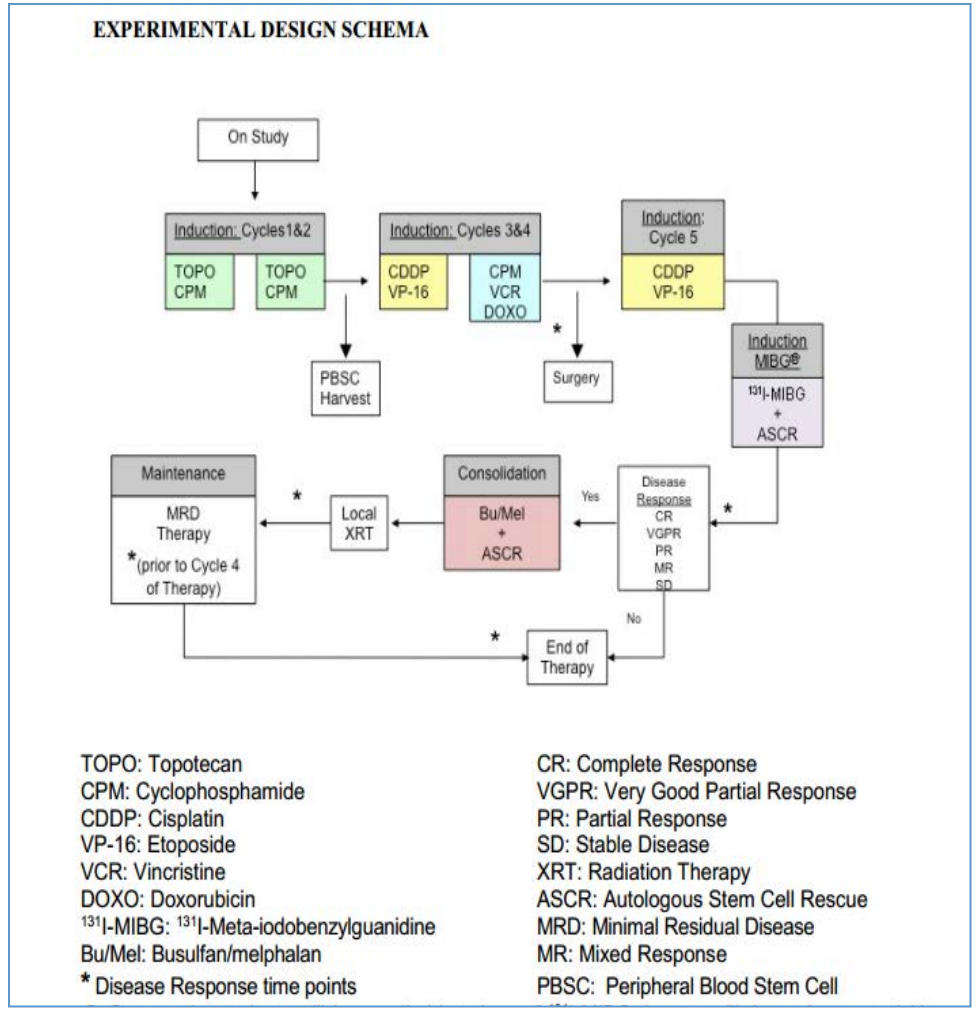
- 21 metastatic sites in 14 patients irradiated for persistence following induction therapy

- 4/21 (**19%**) irradiated residual sites relapsed as compared to 126/504 resolved un-irradiated sites (**25%**)

Polishchuk et al., IJROBP 2014

ANBL 09P1: Closed to Accrual 1/6/16

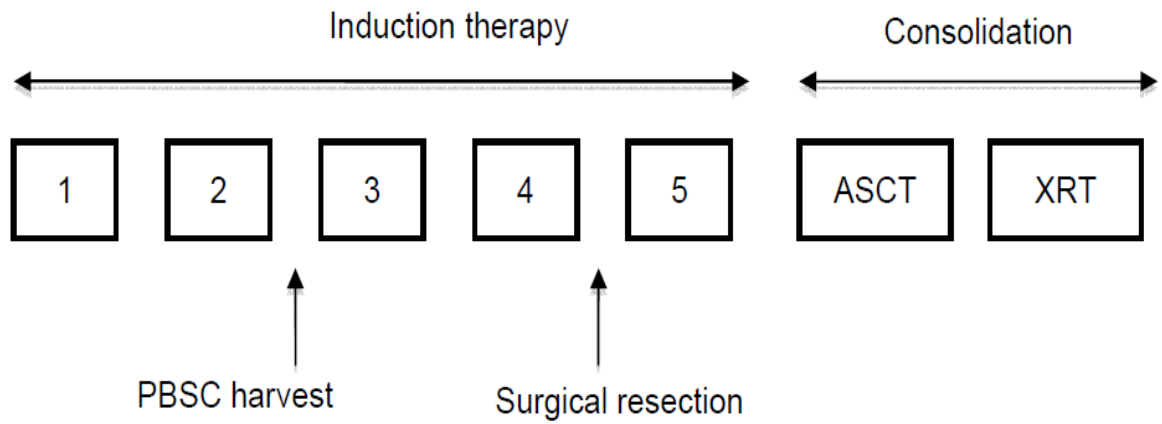
Question: Is it safe to combine Bu-Mel consolidation with therapeutic MIBG?



ANBL 12P1: Closed to accrual on 4/17/15

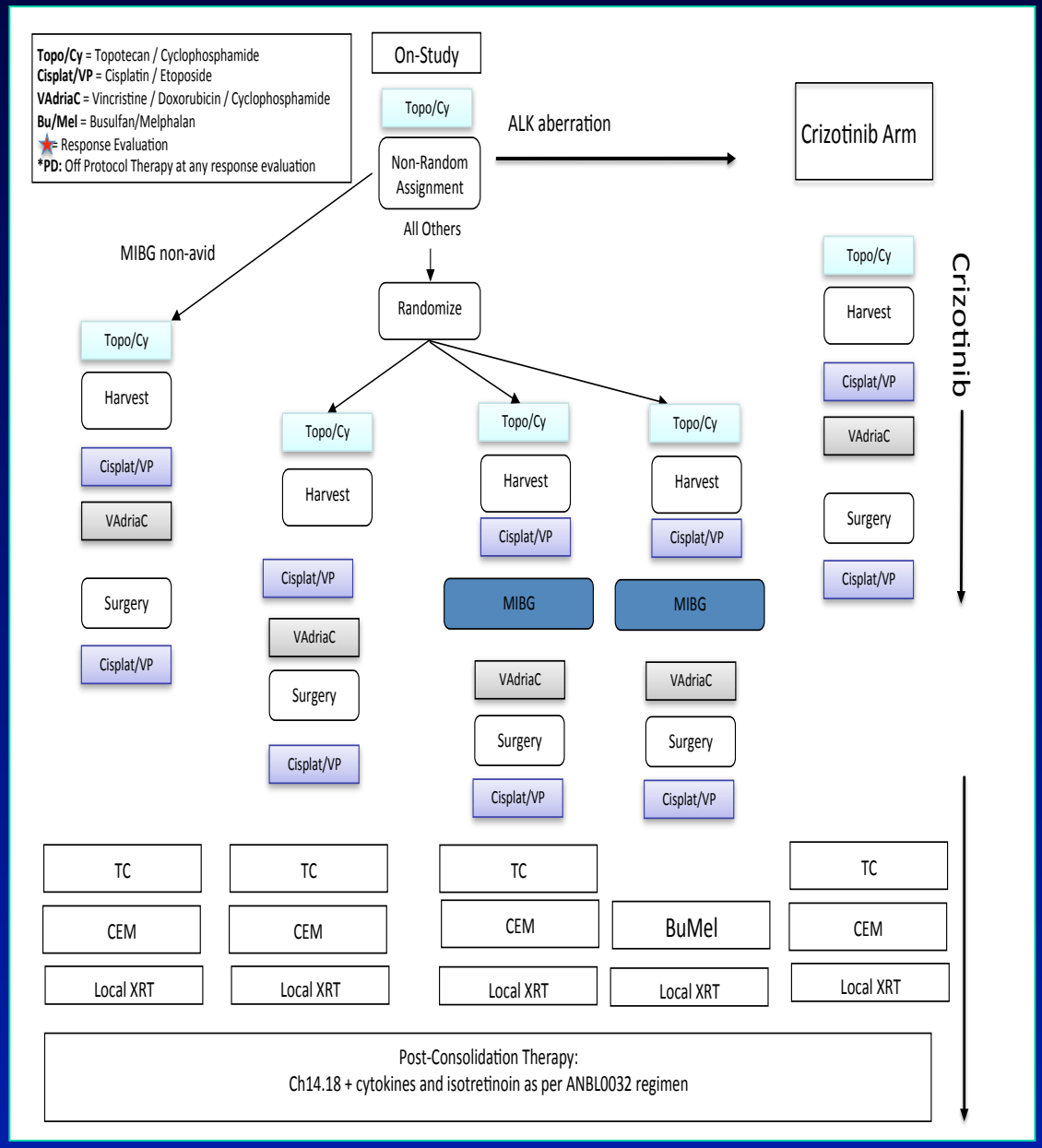
Is it safe to use Bu-Mel as a conditioning regimen in the framework of a COG induction platform (as opposed to a SIOPEN induction platform)?

EXPERIMENTAL DESIGN SCHEMA



Study therapy:
Induction Cycles 1 & 2: topotecan, cyclophosphamide
Induction Cycles 3 & 5: cisplatin, etoposide
Induction Cycle 4: cyclophosphamide, doxorubicin, vincristine.
PBSC harvest: Peripheral blood stem cell harvest.
ASCT: autologous stem cell transplant (busulfan, melphalan)
XRT (Radiotherapy) to primary and metastatic sites, beginning ≥ 28 days post-ASCT.

High-risk NB study in development: ANBL 1531



ANBL 1531 Radiation Questions

- Should we decrease our margins for CTV and PTV?
- Superior/inferior pre-chemotherapy volumes?
- Only expand into areas where the tumor was before chemotherapy
- Should we decrease upfront surgery treatment volumes?
- Change deviation criteria and normal tissue constraints
- Should we increase the metastatic dose to 36 Gy if persistently MIBG positive?
- Hypofractionation option/biological advantage? Can we treat more metastatic lesion with a hypofraction scheme? 3 Gy per fraction?
- Normal tissue constraint changes

ANBL 1531 Normal Constraint and Deviation Criteria Suggested Modifications

Structure	Volume	Dose (Gy)
Ipsilateral Kidney	<75% Mean dose ≤ 18 Gy <100%	18 14,4
Contralateral Kidney	<25%	18
Ipsilateral Lung	<30%	20
Contralateral Lung	<10%	20
B/L Lung	<30%	20
Liver	<15% Mean < 15 Gy	30
Vertebral Bodies	If vertebral body requires treatment, the entire vertebral body and posterior elements mean dose should be >18 Gy. **Remove vertebral body from CTV**	Mean dose >18 Gy
CTVs	>99% receives 95% of prescribed dose	
PTVs	>90% receives 95% of prescribed dose	

Acknowledgements

A3973 Study Committee:
Chair (Sue Kreissman)
Vice Chair (Judy Villablanca)
Mike LaQuaglia (surgery)
Statistician (Wendy London)
James G. Douglas (RT)
Bob Shamberger (surgery)

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