CCSS Neurology Committee Report: 6/08

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Chairman, Neurology
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"The first commandment is: Thou shalt not shoot the messenger."

Neurology Committee: CCSS

Was until 2007 component of Neuropsychology/Psychology/ Neurology Committee

Joint direction *(co-chairs: L. Zeltzer/R. Packer)*

- clear overlap
- unclear focus

Opportunities:

- missed "neurologic" complications/sequelae
- missed neurosensory issues
- primarily new cohort

Neurology Committee: CCSS

As of 2007:

R. Packer (chair)	*CNMC*	*Neurology*
G. Armstrong (co-chair)	*St. Jude*	*Oncology*
D. Bowers	*UT Southwestern(Dallas)*	*Oncology*
B. Cohen	*Cleveland Clinic*	*Neurology*
R. Hayashi	*Washington University*	*Oncology*
R. Goldsby	*Univ. of Calif. at San Fran.*	*Oncology*
A. King	*Washington University*	*Oncology*
B. Morris	*St. Jude*	*Neurology*
A. Reddy	*Univ. of Alabama (Birmingham)*	*Neurology*
C. Turner	*DFCC*	*Oncology*
P. Fisher	*Stanford*	*Neurology*
N. Ullrich	*Boston Children's*	*Neurology*

First Meeting: at COG 10/19/07

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Neurology Committee: Issues

Primary Focus on Brain Tumors

- Probably too limited
- Limited to data in survey (stroke; ? epilepsy; gross motor function; neurosensory (hearing/vision/? Peripheral sensation)
- Q of L, neuropsychological measures richer/easier to "mine"
- Other diseases - 1° leukemia understudied
- Limited neuroscience-oriented investigators
- Not focus of CCSS – more interventional/secondary tumors/ major health problems
- Is patient population representative of problems now

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Past Activities*

Gurney et al.	Endocrine/Cardiovasc. in BT	*Cancer, 2003*
Gurney et al.	Height and body Mass Index in BT	Cancer, 2003
Packer et al.	Neurologic and Neurosensory in BT	*JCO, 2003*
Zebrack et al.	Psychological Outcomes in BT	*JCO, 2003*
Bowers et al.	Stroke in Hodgkins	*JCO, 2005*
Bowers et al.	Stroke in Leukemia / BT	*JCO, 2006*
Neglia et al.	Second CNS Tumors	*JNCI, 2006*

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Current Activities ☺

- Reorganization
- Multiple conference calls
- First formal committee meeting 10/07
- Analyses
  - "Survey" study of B.T. near completion (*Armstrong*)
  - First "survey" study of leukemia in analysis (*Goldsby*)
  - Review of "Neurosensory Manuscripts" (*Whelan, Mertens, et al.)*
  - Studies on "BRIEF" being reported
  - Evaluation of sequelae of head and neck RT for Sarcomas(Ater)

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Long-term Neurologic Sequelae in Adult Survivors of Childhood Acute Lymphoblastic Leukemia: Results from the Childhood Cancer Survivor Study

Robert Goldsby, Paul Nathan, Daniel Bowers, Amanda Yeaton-Massey, Aimee Sznewajs, Les Robison, John Whitton, Lonnie Zeltzer, Greg Armstrong, Roger Packer

>5 years after diagnosis

Conditions	Neurosensory Deficits						Focal Neurologic dysfunction		Any Seizure Disorder
	Any Hearing impairment	Tinnitus	Persistent Dizziness	Legal Blindness in one or both eyes	Cataracts	Double Vision	Any Coordination problem	Any motor problem	
Yes	20	105	115	25	106	34	166	124	130
Rate‡	0.50	2.66	2.89	0.63	2.72	0.85	4.36	3.23	3.38
95% CI	0.31 - 0.78	2.18 - 3.22	2.39 - 3.47	0.40 - 0.92	2.23 - 3.29	0.59 - 1.19	3.72 - 5.07	2.69 - 3.85	2.82 - 4.01
RR § ,_	1.88; P=0.0396	1.73; P=<.0001	2.73; P=<.0001	1.85; P=0.0310	18.18; P=<.0001	2.44; P=0.0003	4.17; P=<.0001	5.12; P=<.0001	4.90; P=<.0001

Late-onset neurologic outcomes by exposure

	Neurosensory Deficits		Focal Neurologic Dysfunction		Any Seizure Disorder	
	RR (95% CI)	**P-value**	**RR (95% CI)**	**P-value**	**RR (95% CI)**	**P-value**
Cranial only	2.03 (0.18-22.37)	0.5636	1.48 (0.15-14.24)	0.7339	1.89 (0.35-10.33)	0.4616
Craniospinal	1.37 (0.28-6.59)	0.6947	1.15 (0.31-4.25)	0.8322	0.99 (0.31-3.17)	0.9923
Any cranial+IT	3.51 (0.87-14.12)	0.0774	***3.38 (1.08-10.55)***	***0.0358***	***2.94 (1.10-7.88)***	***0.0318***
IT alone	1.61 (0.39-6.66)	0.5126	1.72 (0.54-5.47)	0.3607	1.73 (0.63-4.71)	0.2850
None	1.00		1.00		1.00	
High dose MTX						
Yes	1.22 (0.94-1.60)	0.1365	***1.37 (1.11-1.70)***	***0.0040***	***1.50 (1.23-1.81)***	***<.0001***
No	1.00		1.00		1.00	
Recurrence						
Yes	***2.76 (2.18-3.50)***	***<.0001***	***2.26 (1.84-2.77)***	***<.0001***	***2.17 (1.80-2.61)***	***<.0001***
No	1.00		1.00		1.00	

Long-term Outcomes Among Survivors of CNS Tumors

- High risk for poor long-term outcomes due to aggressive surgery, RT & chemo
- CCSS cohort includes 1,876 CNS tumor survivors
  - 1,233 Astrocytomas
  - 395 Medulloblastoma/PNET
  - 148 Ependymoma
- 8 Major outcomes: mortality, SMN, health status, chronic conditions, education, employment, insurance, marital status

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Long-term Outcomes Among Survivors of CNS Tumors

- Analysis: assess outcomes by specific tumor diagnoses, treatment type, and region specific cumulative RT dose

- Findings:
  - Survival probability =74.2% @ 30 years
  - RT associated w/ 3x risk of SMN

- Platform presentation at ASCO

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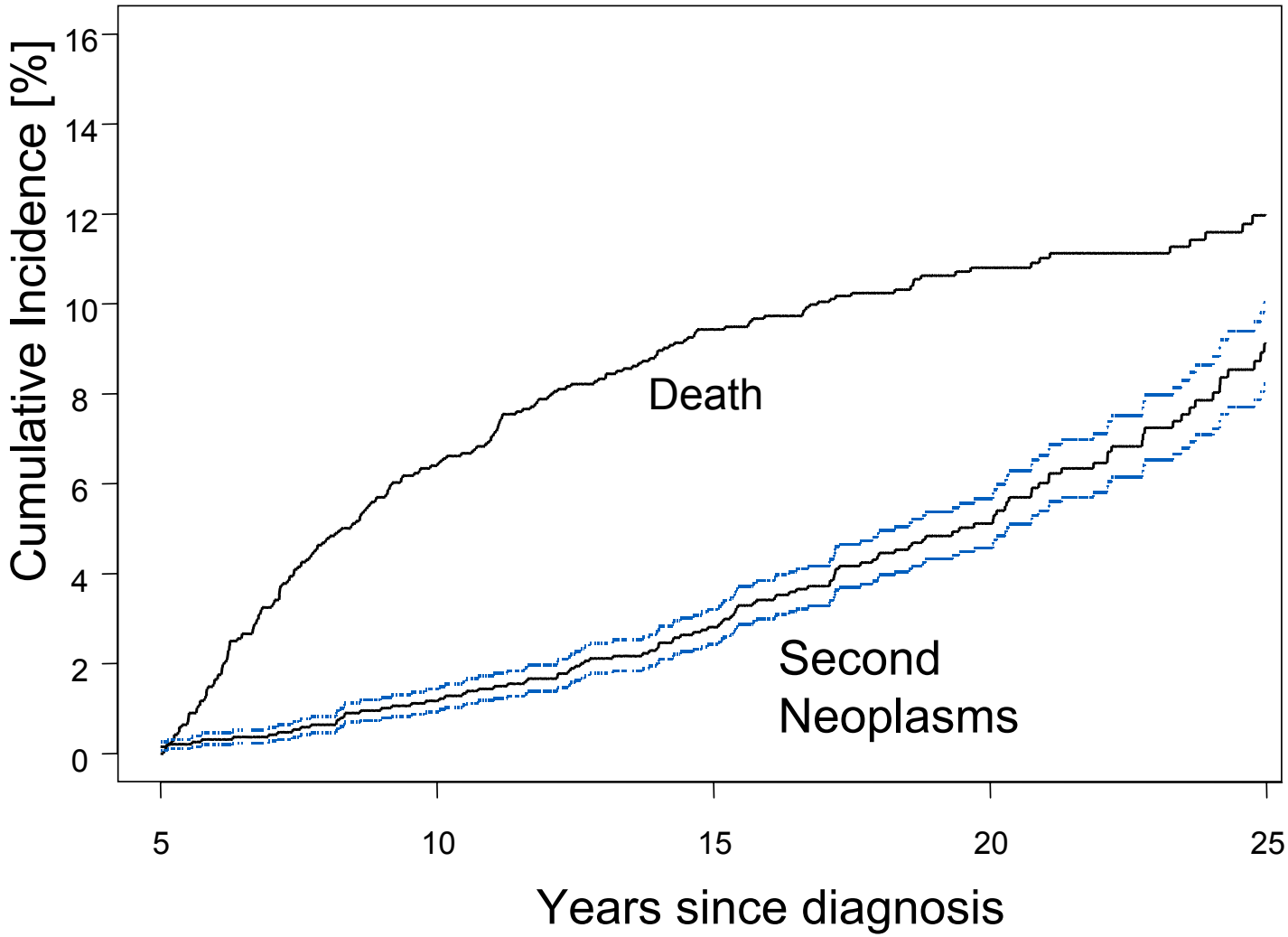
Second Neoplasms



9.1%

Opportunities: FU2007

Use 2007 to provide "10 Year Updates" including:

1) STROKE in Lymphoma/B.T. populations (aging population)

2) NEUROSENSORY DEFICITS (update Packer paper)

3) Work with psychology committee to better define risk factors involved in poor neuropsychological/psychosocial outcomes in B.T. survivors

4) Evaluate across different tumor types frequency of "Softer" neuro deficits like headaches/vertigo and their impact

Opportunities: FU2007

Using 2007 survey, secondary brain tumors are a major issue

- Increasing incidence of MENINGIOMAS their morbidity

  -Seizures

  -Hemiparesis

  -Headaches

  -(?Mortality)

- Are we picking up more SECOND MALIGNANT CNS TUMORS?

  -Where is the cross point between recurrence and secondary tumors?

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Opportunities: Expansion

Expansion of other cohort opportunities in addition to 1º CNS population

-Change in CNS Tumor management
-decreased RT, increased chemo

-Change in leukemia management
-Decreased CRT
-Increased intrathecals/systemic MTX

- Wider use of T.B.I./Transplant
  -Strokes
  -Neurocognitive Damage
  -Leukoencephalopathy
  -Spasticity
  -Headaches
  -Fatigue
  -Sleep Disturbance

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Opportunities: RFA

RFA

- Determination of MOLECULAR PREDISPOSITIONS to sequelae in brain tumor/ALL/lymphoma/transplant survivors:
  - -Neurocognitive outcome
  - -Stroke (vascular complications)
  - -Neurosensory loss (platinum and/or RT associated hearing loss, etc.)
  - -Seizures
- NEUROLOGY QUESTIONAIRRE: high-risk populations
  - -Incidence and severity of headaches
  - -Seizure incidence and control
  - -Sleep disruption
  - -Peripheral neuropathy(?)
  - -Telephone based assessment of neurocognitive status (memory, attention, etc.)

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Aims

- **Determine the incidence of adverse neurologic conditions, stratified by the time period in which the outcome was reported to first occur.**
- **Compare late-onset (>5 years post-diagnosis) adverse neurologic conditions among survivors to that of a group of participating siblings.**
- **Evaluate the effect of treatment on the risk of developing a late adverse neurologic condition.**

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Neurology Committee:
Long-term Priorities

1) **Utilize DNA availability to determine "at risk" population**

2) **Work closely with Psychology Committee on BRIEF and other Q.O.L data**

3) **Major focus on new 1986+ cohort**
   - **Major changes in B.T. / ? ALL management**
   - **Reduction of RT (CSRT)**
   - **Use of CPDD in B.T.**
   - **Use of Alkylator / VP 16 in B.T. (? SMN)**
   - **Cohort of "stem cell" survivors**

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Incidence Rates and Relative Risks by Time Period of Onset of Adverse Neurologic Outcomes

Conditions	Neurosensory Deficits						Focal Neurologic dysfunction		Any Seizure Disorder
	Any Hearing impairment	Tinnitus	Persistent Dizziness	Legal Blindness in one or both eyes	Cataracts	Double Vision	Any Coordinatio Problem	Any motor Problem	
Reported outcome									
Yes	**56**	**145**	**143**	**46**	**181**	**65**	**314**	**267**	**253**
	1.36%	**3.50%**	**3.45%**	**1.11%**	**4.38%**	**1.57%**	**7.64%**	**6.52%**	**6.15%**

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Survival by Primary Diagnosis

25 years:

Astro/Glial = 80.1%

Medullo/PNET = 75.2%

Ependymoma = 74.1%

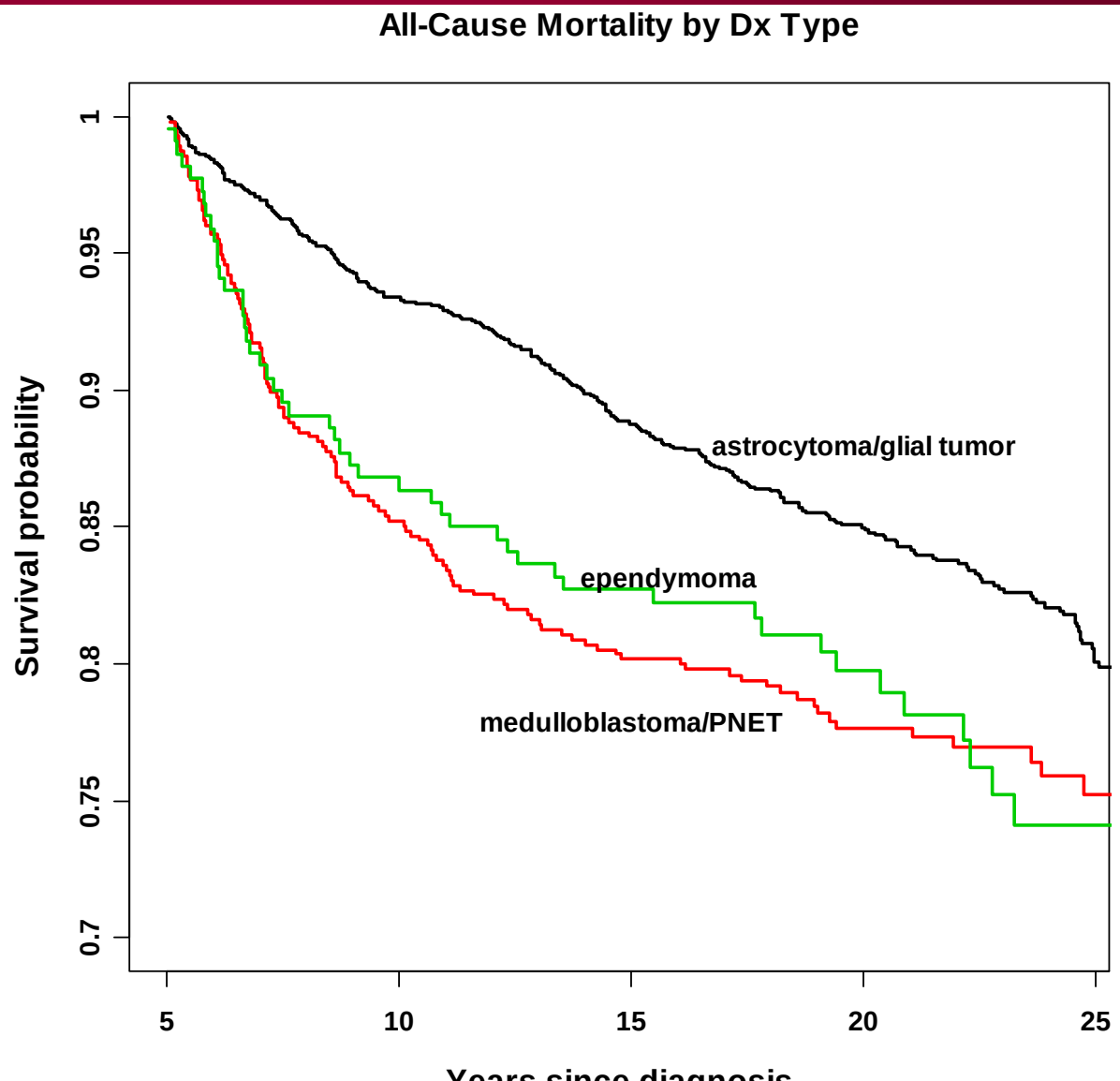
p= .0003

SMR

Medullo/PNET = 18.0

Ependymoma = 15.9

Astro/glial = 11.2



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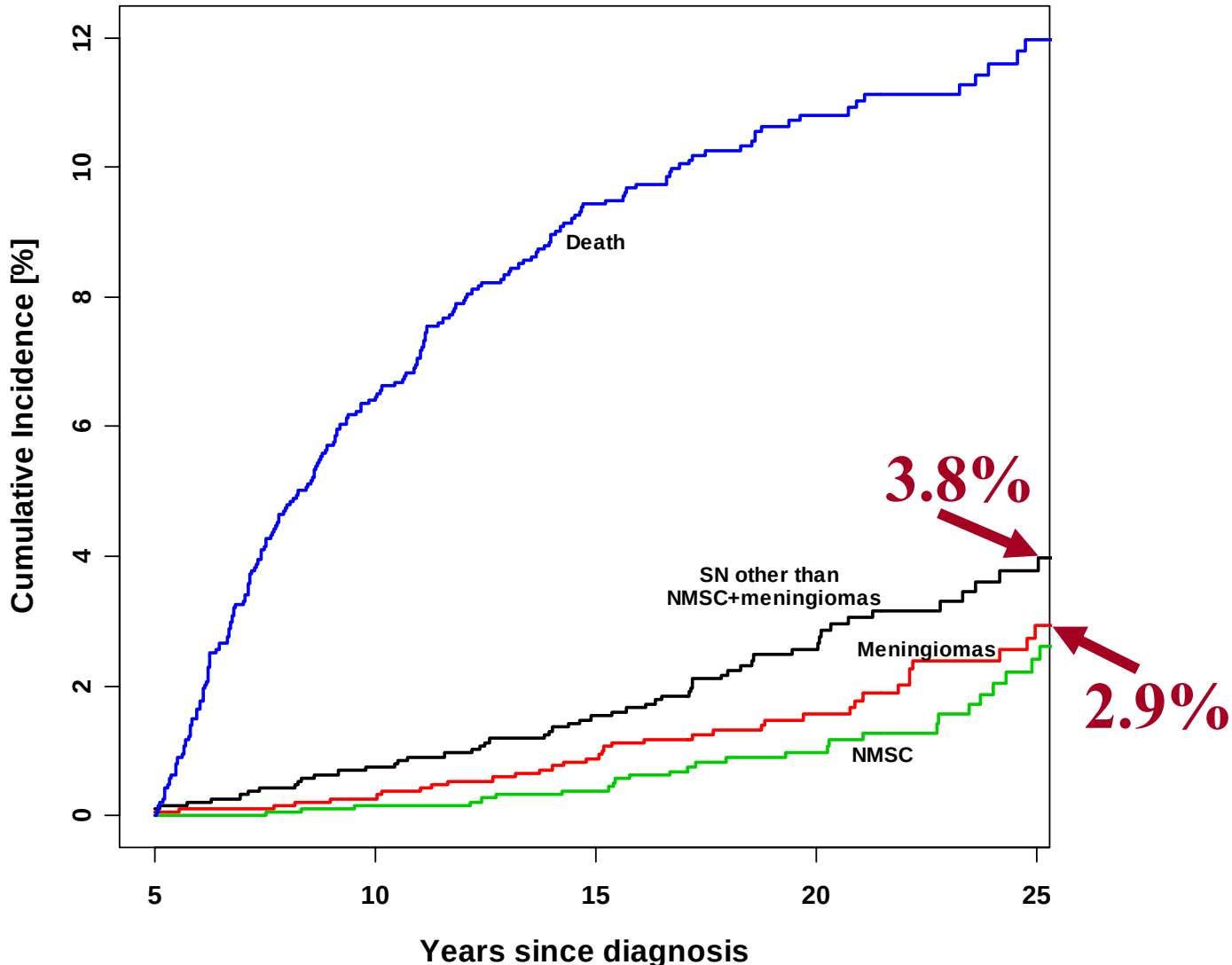
Second Neoplasms



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Conclusions

- ↑ Late Mortality
  - Largely due to recurrence
  - ↑ recurrence among males
- >9% develop a second neoplasm by 25y
- New medical conditions after 5y
- Poor health status

Table 2. Incidence Rates and Relative Risks by Time Period of Onset of Adverse Neurologic Outcomes

Conditions	Neurosensory Deficits						Focal Neurologic dysfunction		Any Seizure Disorder	Any headache
	Any Hearing impairment	Tinnitus	Persistent Dizziness	Legal Blindness in one or both eyes	Cataracts	Double Vision	Any coordination problem	Any motor problem		
Reported outcome										
Yes										
	56	145	143	46	181	65	314	267	253	858
	1.36%	3.50%	3.45%	1.11%	4.38%	1.57%	7.64%	6.52%	6.15%	20.98%
No										
	4065	3995	4003	4093	3951	4076	3796	3830	3860	3232
	98.64%	96.50%	96.55%	98.89%	95.62%	98.43%	92.36%	93.48%	93.85%	79.02%
DX to 5 years										
Yes	36	40	28	21	74	31	148	143	123	277
Rate‡	1.75	1.94	1.36	1.02	3.61	1.50	7.36	7.15	6.09	14.12
95% CI	1.23 - 2.43	1.39 - 2.65	0.90 - 1.96	0.63 - 1.55	2.84 - 4.54	1.02 - 2.13	6.22 - 8.65	6.02 - 8.42	5.06 - 7.27	12.50 - 15.88
RR§,_	4.53; P=<.0001	2.11; P=<.0001	2.40; P=<.0001	2.84; P=0.0004	20.62; P=<.0001	4.97; P=<.0001	7.40; P=<.0001	13.73; P=<.0001	6.15; P=<.0001	6.05; P=<.0001
95% CI	2.79 - 7.36	1.47 - 3.04	1.61 - 3.57	1.60 - 5.03	12.02 - 35.38	3.02 - 8.16	5.81 - 9.43	10.38 - 18.16	4.68 - 8.08	4.61 - 7.94
5 years after Dx										
Yes	20	105	115	25	106	34	166	124	130	581
Rate‡	0.50	2.66	2.89	0.63	2.72	0.85	4.36	3.23	3.38	16.70
95% CI	0.31 - 0.78	2.18 - 3.22	2.39 - 3.47	0.40 - 0.92	2.23 - 3.29	0.59 - 1.19	3.72 - 5.07	2.69 - 3.85	2.82 - 4.01	15.37 - 18.12
RR§,_	1.88; P=0.0396	1.73; P=<.0001	2.73; P=<.0001	1.85; P=0.0310	18.18; P=<.0001	2.44; P=0.0003	4.17; P=<.0001	5.12; P=<.0001	4.90; P=<.0001	4.70; P=<.0001
95% CI	1.03 - 3.43	1.32 - 2.25	2.05 - 3.63	1.06 - 3.25	10.18 - 32.47	1.50 - 3.97	3.22 - 5.40	3.83 - 6.83	3.58 - 6.70	3.46 - 6.39

Abbreviation: RR, relative risk.
*Excludes conditions prior to diagnosis.
†Includes “not sure” and missing responses.
‡Rate per 1,000 person-years.
§Adjusted for sex and age; relative to siblings.
_*P* _ .0001.

Long-term Outcomes Among Survivors of Childhood CNS Tumors:

A Report from the Childhood Cancer Survivor Study

Greg Armstrong, Kirsten Ness, John Whitton, Wendy Leisenring, Qi Liu, Yutaka Yasui, Lonnie Zeltzer, Sarah Donaldson, Melissa Hudson, Leslie Robison, Roger Packer

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Department of Epidemiology and Cancer Control

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Disclosure

I have no relationships to disclose

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Background

- Modern therapy
  - Surgery, RT & Chemotherapy
  - ↑ long-term survival
  - ↑ potential for long-term morbidity & late mortality

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Study Objective

- Describe:
  - Long-term survival
  - Incidence of second neoplasms
  - Chronic medical conditions
  - Sociodemographic outcomes
  - Health status

Among adult survivors of childhood CNS tumors diagnosed 1970-1986

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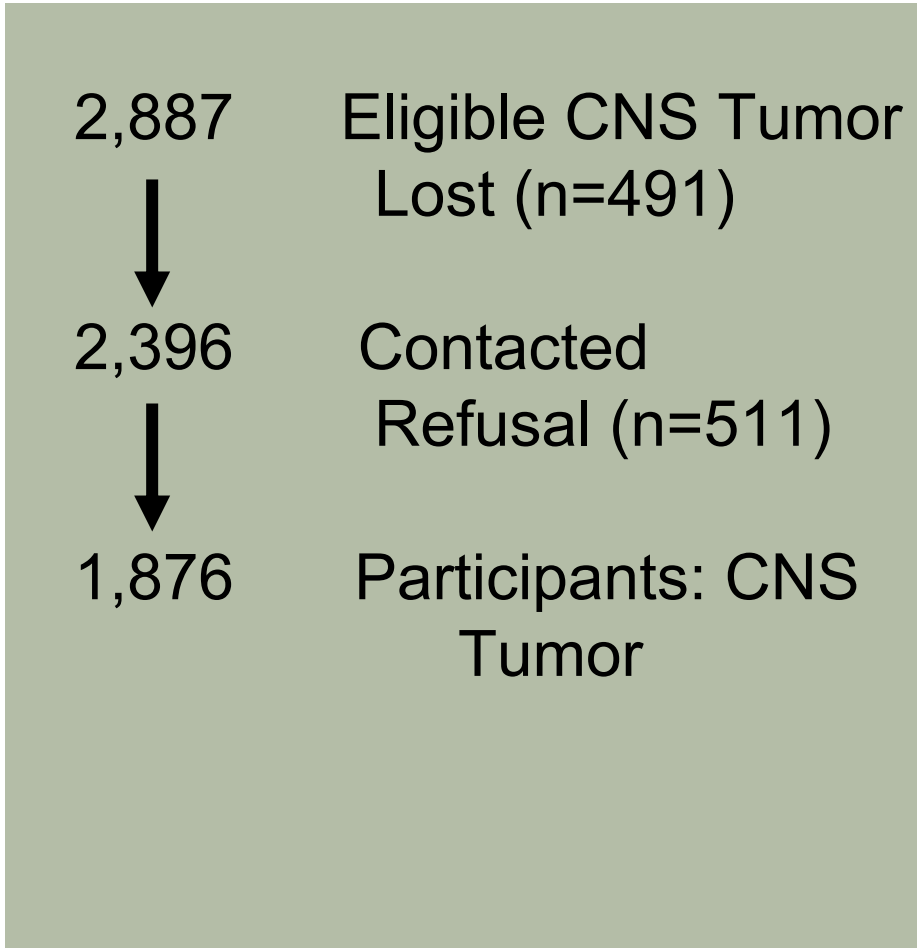
Study Overview

- Retrospective Cohort
- 5-Year Survival
- Diagnosis 1970-1986
- < 21 Yrs. At Diagnosis
- Detailed Treatment Data
- Wide Range of Outcomes
- 26 Contributing Centers



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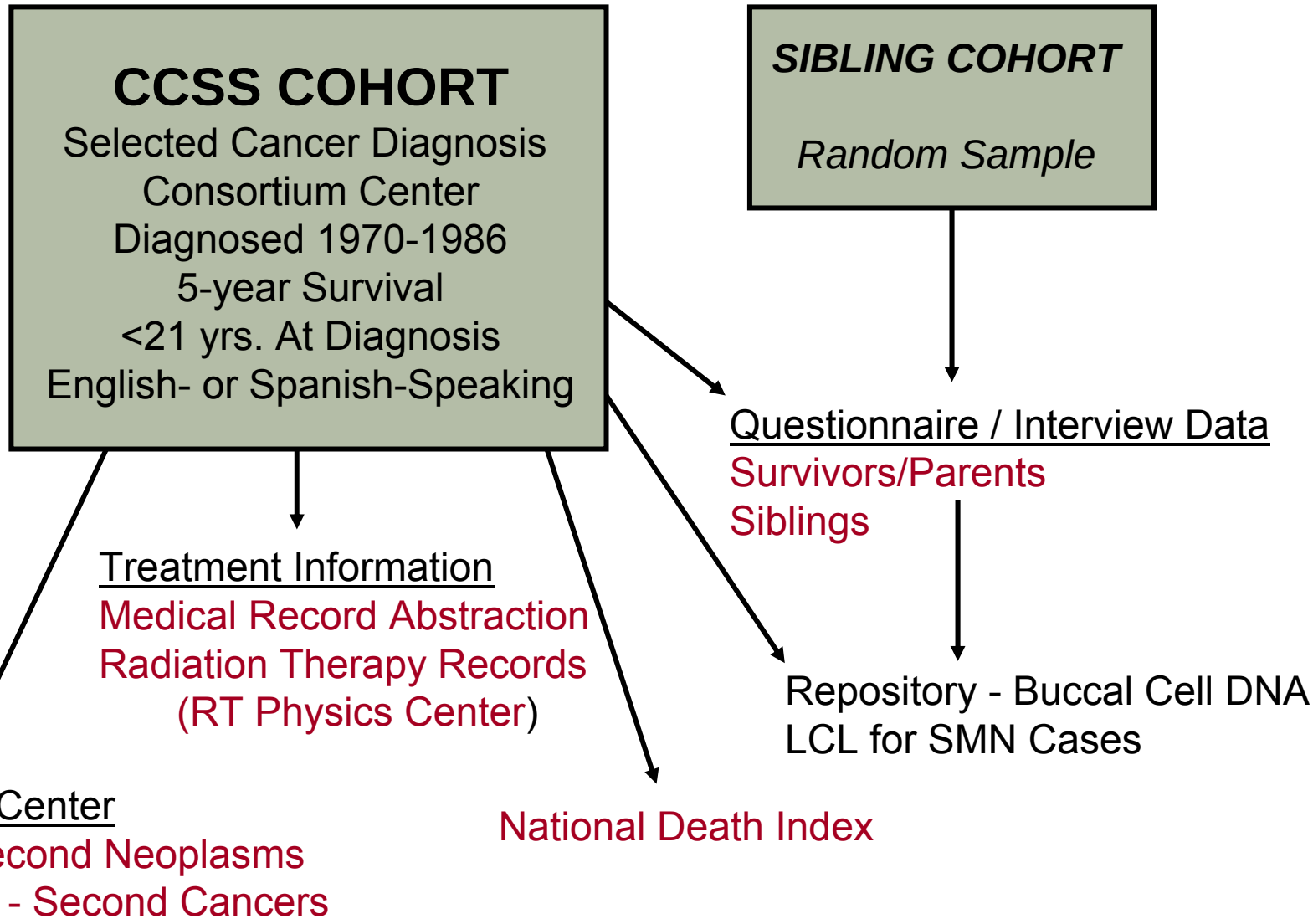
Study Overview



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Population

	Survivors	Siblings
Mortality	2,820	_
Second Neoplasms	1,876	_
Medical Conditions	1,876	3,899
Socio-demographic	1,032	2,358
Health Status	1,000	2,951

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Participant Characteristics

	N (%)
Female	843 (45)
Male	1033 (55)
Astro/glial	1233 (66)
Medullo/PNET	395 (21)
Ependymoma	148 (8)
Other	100 (5)

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Participant Characteristics

	N (%)
Treatment Type	
Surgery only	438 (26)
Surgery + RT	692 (42)
Surgery + RT + Chemo	451 (27)
Other	79 (5)
Cranial RT Dose	
None	483 (30)
1-49.9 Gy	278 (18)
≥50 Gy	826 (52)

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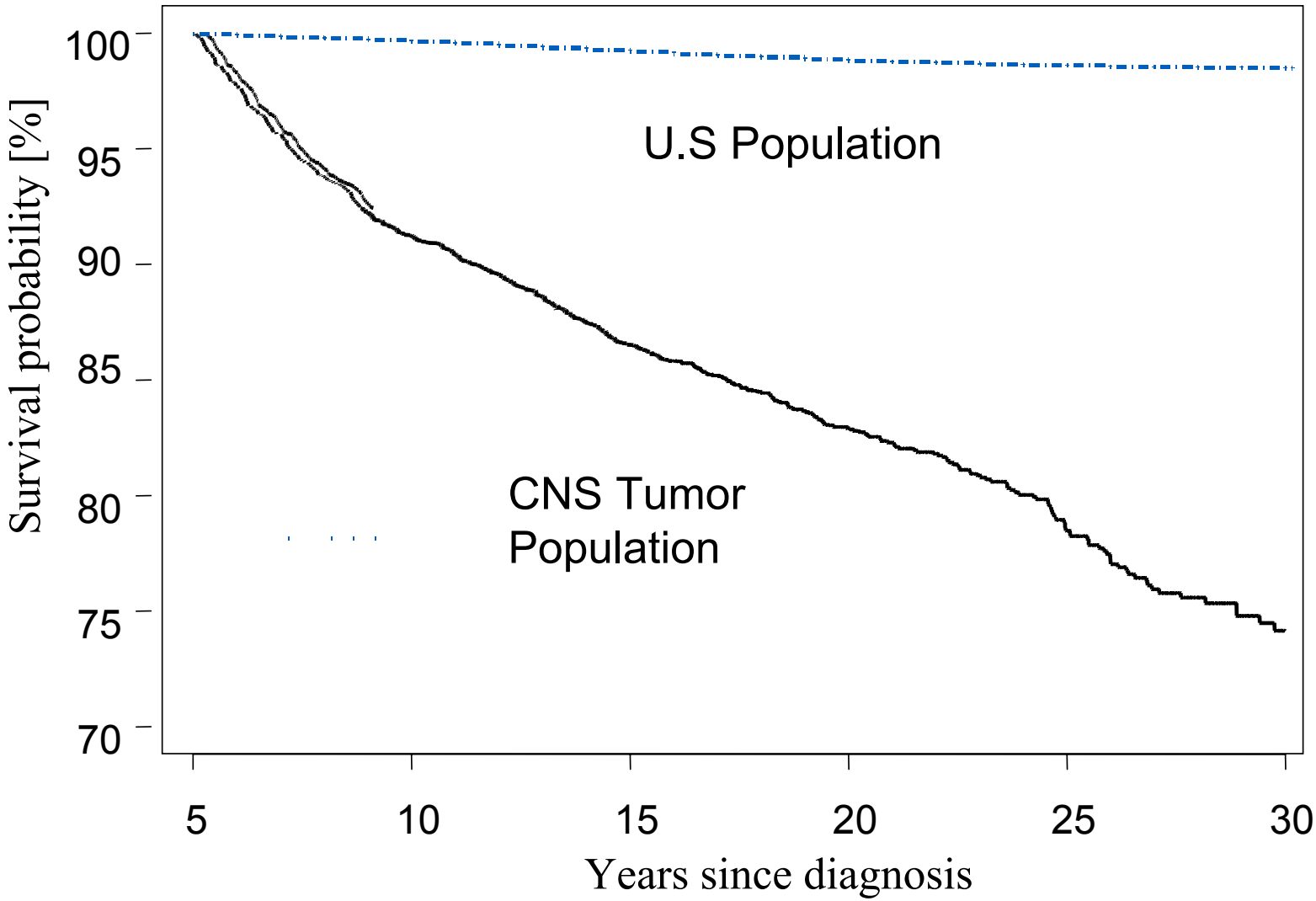
Overall Survival (n = 546 deaths)



98.5%

74.2%

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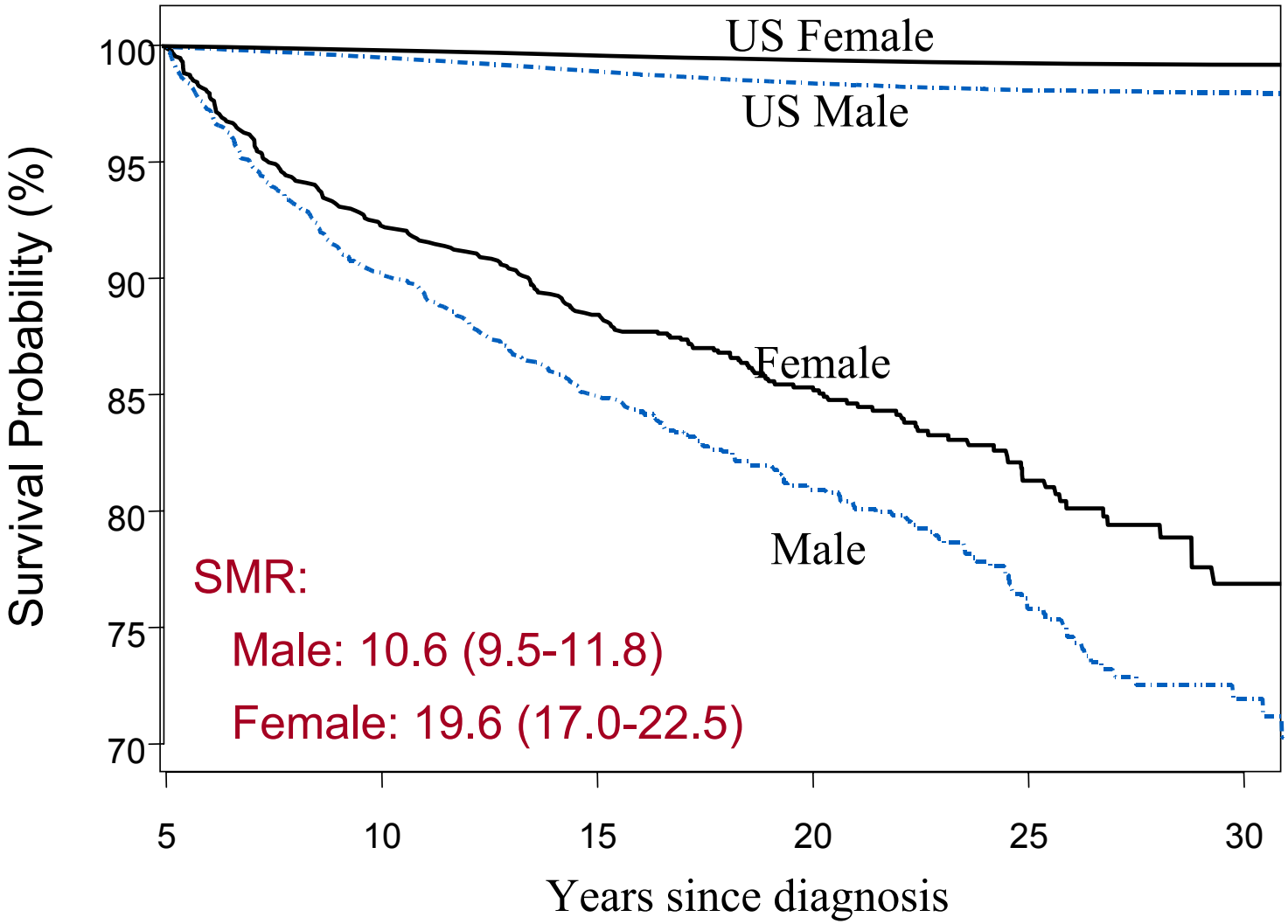
Overall Survival by Gender



99.6%

98.0%

76.9%

71.9%

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Cause of Death (n = 546 deaths)

	N	%
Recurrence/Prog	335	61%
Other Medical	112	21%
Second Neoplasm	51	9%
Cardiac	17	3%
Pulmonary	16	3%
External Causes	31	6%
Unknown	68	12%

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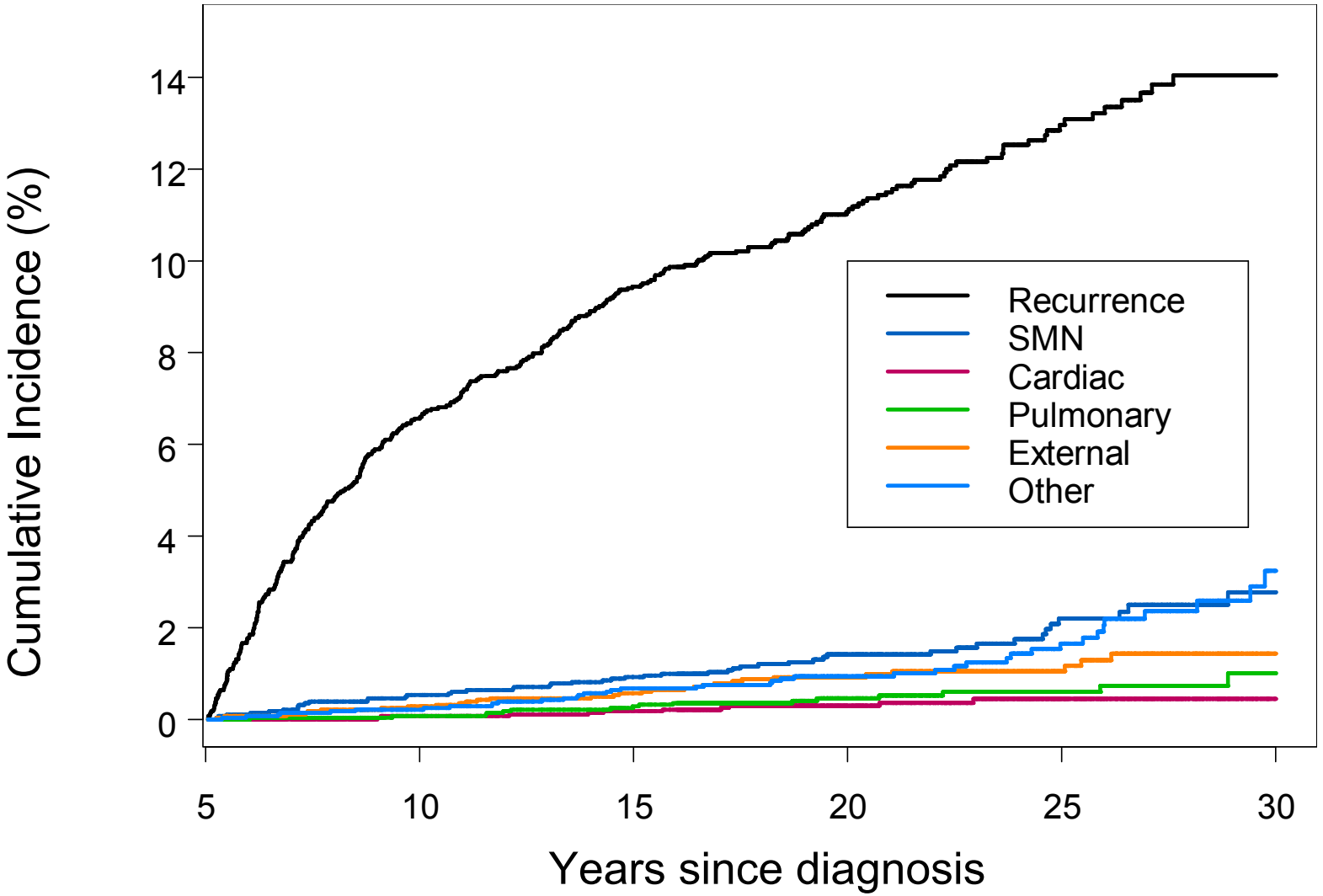
Cause Specific Mortality



14.0%

SMN= 2.8%

Table 3. Late-onset neurologic outcomes by age, CNS therapy and chemotherapy exposures (Univariate analysis).

	Neurosensory Deficits		Focal Neurologic Dysfunction		Any Seizure Disorder		Any headache	
	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
Age at Dx								
<1	1.38 (0.50-3.84)	0.5330	1.98 (1.06-3.72)	0.0331	1.91 (1.07-3.39)	0.0283	2.26 (1.29-3.97)	0.0045
1-9	1.08 (0.80-1.48)	0.6114	0.88 (0.69-1.12)	0.2954	0.86 (0.70-1.07)	0.1770	0.91 (0.73-1.15)	0.4277
10+	1.00		1.00		1.00		1.00	
Cranial radiation								
Unknown	3.03 (0.74-12.43)	0.1245	2.93 (0.92-9.29)	0.0678	2.46 (0.90-6.71)	0.0784	3.14 (0.99-9.95)	0.0522
Cranial only	2.03 (0.18-22.37)	0.5636	1.48 (0.15-14.24)	0.7339	1.89 (0.35-10.33)	0.4616	3.34 (0.56-19.98)	0.1866
Craniospinal	1.37 (0.28-6.59)	0.6947	1.15 (0.31-4.25)	0.8322	0.99 (0.31-3.17)	0.9923	1.58 (0.45-5.60)	0.4788
Any cranial+IT	3.51 (0.87-14.12)	0.0774	3.38 (1.08-10.55)	0.0358	2.94 (1.10-7.88)	0.0318	3.96 (1.27-12.34)	0.0176
IT alone	1.61 (0.39-6.66)	0.5126	1.72 (0.54-5.47)	0.3607	1.73 (0.63-4.71)	0.2850	2.28 (0.72-7.24)	0.1619
None	1.00		1.00		1.00		1.00	
Cranial XRT dose								
Unknown	1.87 (1.23-2.84)	0.0032	1.74 (1.24-2.44)	0.0013	1.41 (1.03-1.91)	0.0295	1.44 (1.04-2.01)	0.0290
>18 Gy	1.96 (1.38-2.78)	0.0002	1.88 (1.42-2.49)	<.0001	1.64 (1.29-2.09)	<.0001	1.70 (1.31-2.21)	<.0001
0.1-18 Gy	2.33 (1.61-3.39)	<.0001	1.94 (1.43-2.63)	<.0001	1.71 (1.31-2.24)	<.0001	1.82 (1.37-2.42)	<.0001
None	1.00		1.00		1.00		1.00	
High dose IV MTX								
Unknown	1.00 (0.70-1.42)	0.9985	1.08 (0.81-1.44)	0.5814	1.10 (0.84-1.43)	0.5001	1.06 (0.81-1.41)	0.6599
Yes	1.22 (0.94-1.60)	0.1365	1.37 (1.11-1.70)	0.0040	1.50 (1.23-1.81)	<.0001	1.49 (1.22-1.82)	<.0001
No	1.00		1.00		1.00		1.00	
MTX cumulative non-IT dose								
Unknown	1.06 (0.74-1.52)	0.7499	1.22 (0.91-1.64)	0.1876	1.20 (0.92-1.58)	0.1817	1.18 (0.89-1.57)	0.2576
5000.1+ mg/m2	1.20 (0.80-1.78)	0.3737	1.50 (1.09-2.05)	0.0119	1.60 (1.21-2.11)	0.0009	1.54 (1.14-2.06)	0.0044
1501-5000 mg/m2	1.44 (1.02-	0.0374	1.63 (1.22-	0.0009	1.70 (1.32-	<.0001	1.78 (1.37-	<.0001

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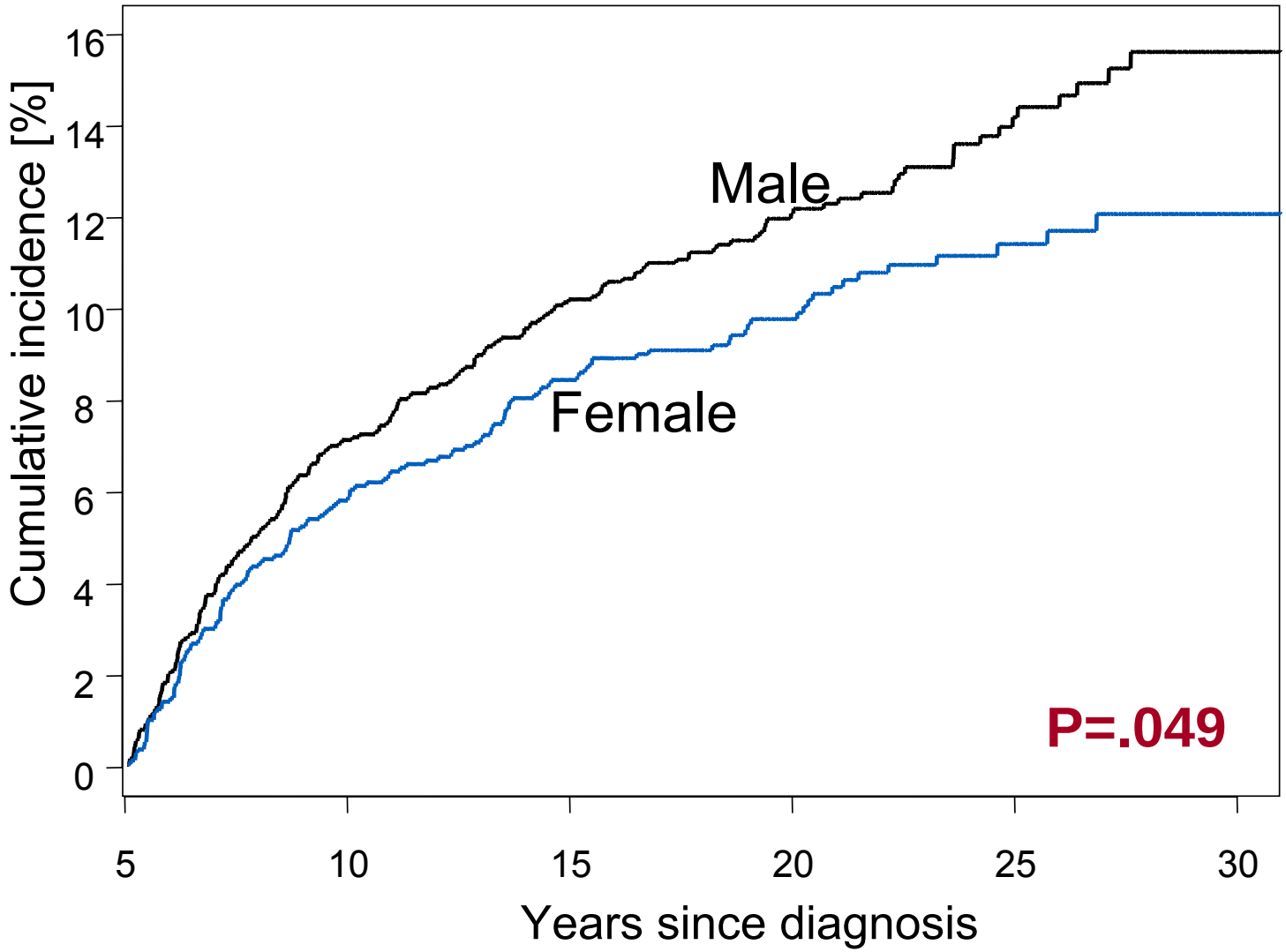
Death Due to Recurrence



15.6%

12.1%

P=.049

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Death from Recurrence

Primary Diagnosis	Annual Rate (%)	p value
Astro/glial	.64	<.001
Medullo/PNET	1.15	
Ependymoma	1.26	

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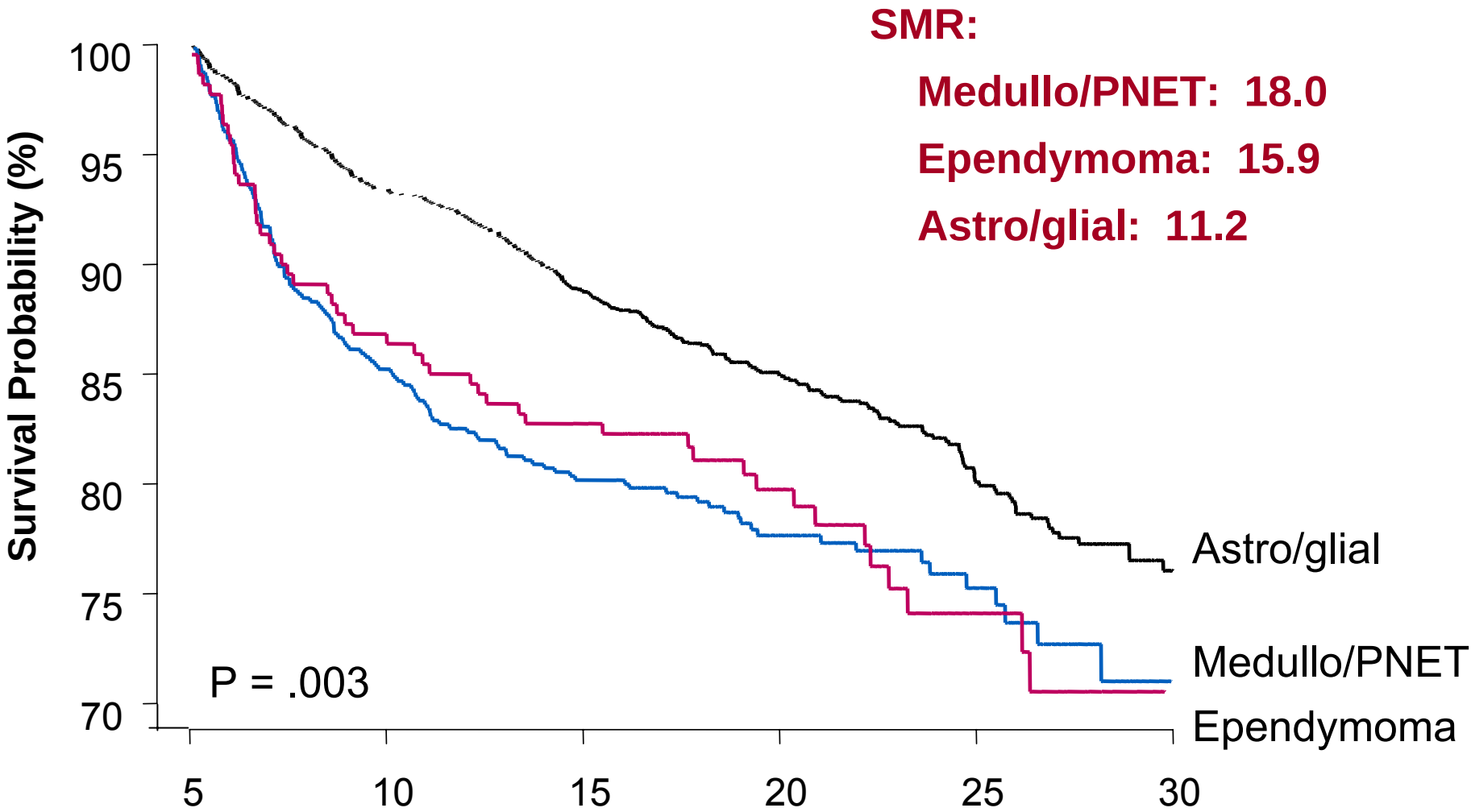
Survival by Primary Diagnosis



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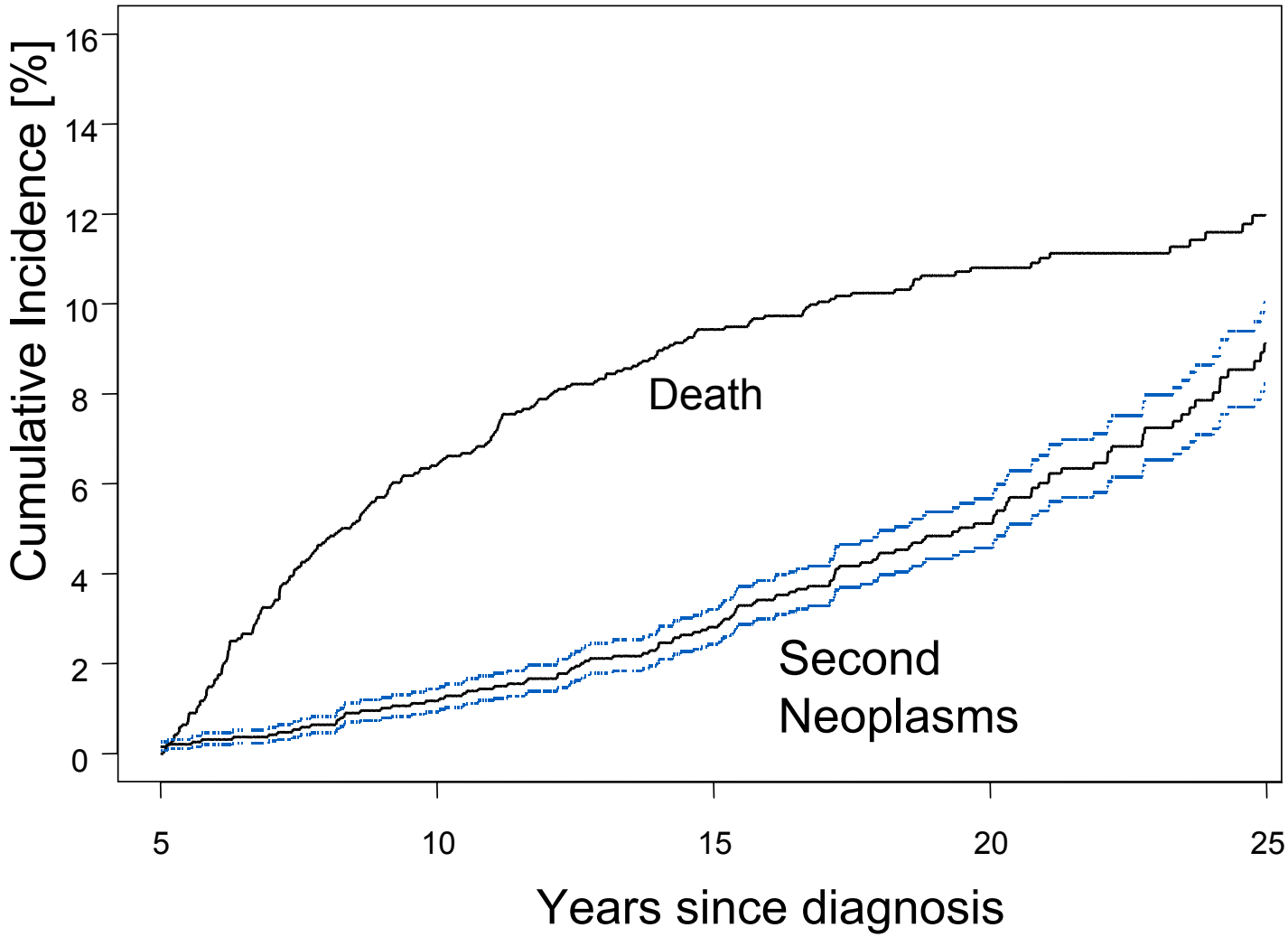
Second Neoplasms



9.1%

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Second Neoplasms

	N
Total	223
Non-Malignant	
Meningiomas	53
Malignant	
Non-melanoma skin	100
Other SMNs	70

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Second Malignant Neoplasms

	Obs.	Exp.	SIR (95%CI)
All SMNs	70	18.5	3.8 (0.2-0.3)
CNS malignancies	14	0.8	17.8 (12.3-37.9)
Soft-tissue Sarcoma	12	1.0	12.5 (6.7-22.6)
Thyroid	12	1.1	11.2 (5.4-18.2)
Leukemia	3	0.7	4.1 (1.1-16.3)
Other	29	-	-

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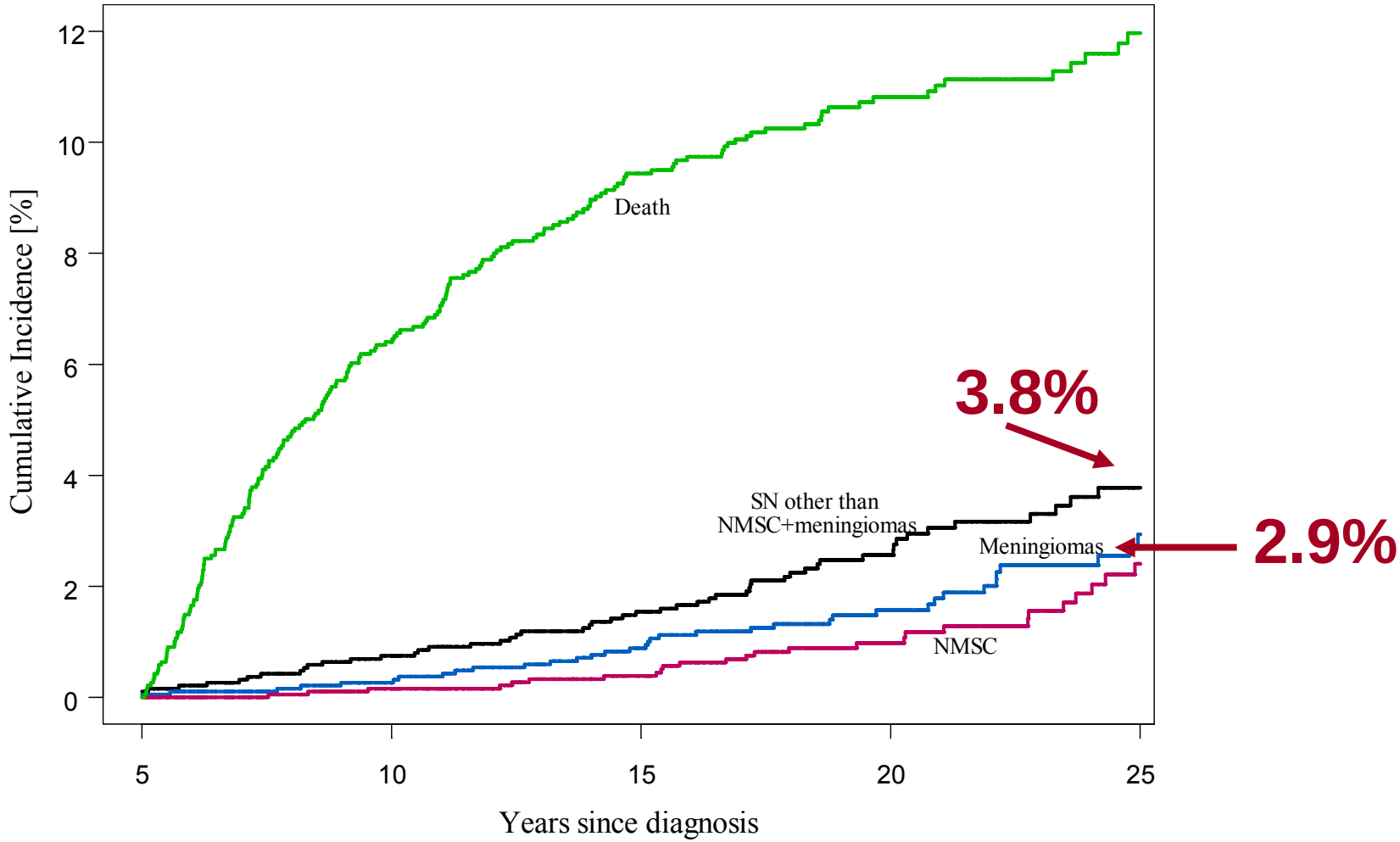
Second Neoplasms



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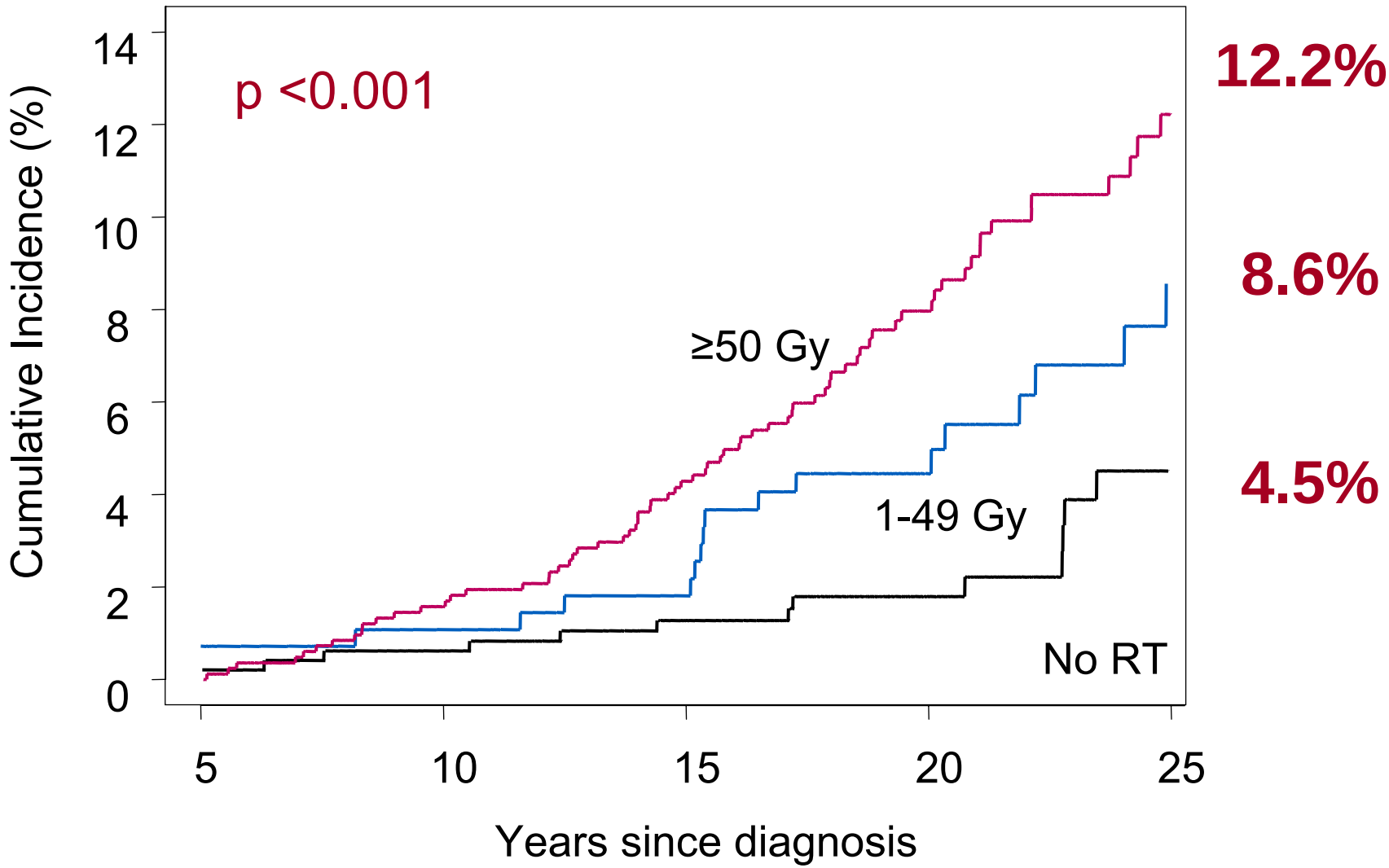
Second Neoplasms by RT dose



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Chronic Health Conditions: Incidence after 5 years

	Cumulative Incidence (%)	Rate Ratio (95% CI)
Endocrine (any)	32.2	19.8 (14.5-27.1)
-GH deficiency	23.1	140.4 (51.3-384.1)
-Hypothyroidism	19.0	13.0 (9.2-18.3)
Musculoskeletal	7.3	13.8 (7.4-25.7)
Neurological (any)	72.4	5.6 (4.8-6.7)
-Seizure	32.9	15.1 (10.7-21.2)
-Balance	51.6	18.0 (13.4-24.1)
- Blindness	15.5	7.5 (4.1-13.5)

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Socio-economic Outcomes

	Survivors %	Sibs %	Odds Ratio (95%CI)*
High School Graduate	91	99	3.7 (2.5-5.5)
Married	33	69	4.3 (3.7-5.1)
Employed	67	94	12.0 (9.1-15.8)
Insured	88	91	1.1 (.8-1.4)
Income >20,000	76	93	3.7 (2.9-4.8)

* Adjusted for age, sex and intra-family correlation

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Health Status

	Survivors %	Sibs %	Odds Ratio (95%CI)*
Poor General Health	53	17	22.5 (14.3-35.3)
Poor Mental Health	21	14	1.4 (1.2-1.7)
Poor Functional Status	38	3	25.9 (18.9-35.4)
Poor Activity Level	19	0.6	39.5 (22.7-68.7)
Pain	10	1	7.6 (4.9-11.8)
Anxiety	8	1	10.0 (6.2-16.2)

***Adjusted for age at interview, sex, ethnicity, education, income and health insurance**

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Conclusions

- High Risk for Late Mortality
  - >25% at 30 years
  - Largely due to recurrence
- >9% develop a second neoplasm by 25y
- New medical conditions after 5y
- Poor health status