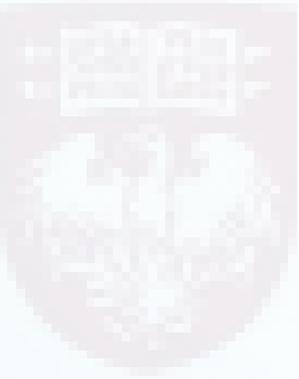




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“35 Year-old Woman with a History of Retinoblastoma Presenting with Thyroid Nodules”

Dr. Dickens does not have any relevant financial relationships
with any commercial interests.



ENDORAMA: Case 2

Laura Dickens

December 8, 2016

Objectives

1. Discuss the role of RB1 as a tumor-suppressor gene and its contribution to the pathogenesis of retinoblastoma and other malignancies
2. Review ultrasound characteristics of thyroid nodules which increase probability of malignancy
3. Discuss the effects of radiation exposure on the thyroid including risk for thyroid cancer and non-malignant thyroid disease
4. Review the recommendations for monitoring for second malignancies in patients with a history of radiation exposure

Chief complaint

**35 year old woman referred for evaluation of
thyroid nodules**

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HPI

- In 2012 gynecologist palpated a thyroid nodule. Ultrasound revealed multiple nodules.
- Thyroid function was normal. Never on treatment for hyper or hypothyroidism.
- She underwent ultrasound-guided FNA of a large left sided nodule. First FNA was inadequate, second FNA reported as benign colloid.
- Follow up ultrasounds showed no significant change.
- US performed at UCMC recently without the previous images for comparison. Referred to Endocrinology for evaluation.

Past Medical History

Bilateral retinoblastoma

- Treated with **cranial radiation** and cryotherapy at age 3 months
- Genetic testing showed RB1 p.R579x also known as c. 1735C>T

Multiple nevi, severe atypia on biopsy (2015)

No additional specific evaluation has been done related to her radiation exposure

Retinoblastoma

- Aggressive intraocular cancer of childhood
- High mortality in countries with low and middle income
- Initial sign is leukocoria, which occurs when tumor confined to the eye



RB1 gene

- RB1 gene was the first described tumor-suppressor gene
- With heritable retinoblastoma, the first RB1 mutation is constitutional. Subsequent somatic mutations initiate tumor growth
- Constitutional RB1 mutation increases risk of other malignancies: lung, bladder, bone, soft tissue, skin, brain

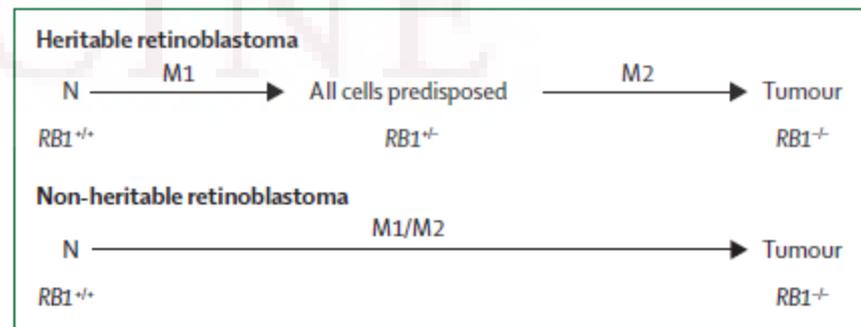


Figure 2: Genetics of heritable and non-heritable retinoblastoma
N=normal. RB1^{+/+}=two normal RB1 alleles. M1=constitutional RB1 mutation.
RB1^{+/-}=one mutated, one normal RB1 allele. M2=somatic RB1 mutation.
RB1^{-/-}=two mutated RB1 alleles.

Retinoblastoma treatment

- Molecular genetic testing of children with affected parents is 95% sensitive
- External beam radiation was first used in the early 1950s. This continued until the 1980s when it was recognized that radiation greatly increases risk of second cancer in children with constitutional RB1 mutation
- Primary treatment is chemotherapy (systemic and local) and focal laser treatment
- Enucleation is a definitive cure for early stage, non-metastatic disease



Additional History

ROS: No local neck symptoms. Vision limited in both eyes, R sees only light and shapes.

PSH: Surgical correction for strabismus, knee surgery

Meds: Inhaled albuterol PRN, vitamin D3, vitamin B, fish oil, multivitamin

Social: Married, no children. Works as a teacher. No tobacco, 2-3 alcoholic drinks/week, no drugs.

Family:

Mother- mitral valve prolapse, HTN, HLD, arthritis

Father- hyperthyroidism, mitral valve prolapse

Maternal GF- prostate cancer

Paternal uncle- lung cancer

No history of thyroid, ovarian, breast, cervical, or colon cancer

Physical exam

VITALS: BP 113/58, HR 61, BMI 20.4

Constitutional: She appears well-developed and well-nourished.

HENT: Conjunctivae are normal. **Right esotropia. Left moves normally**

Neck: Trachea normal. Normal carotid pulses present. Carotid bruit is not present. Thyroid mass and thyromegaly present. **Thyroid firm irregular 1 cm nodule on right 2 cm on left non-tender move with swallowing**

Cardiovascular: Normal rate, regular rhythm, normal heart sounds and intact distal pulses.

Pulmonary/Chest: Effort normal and breath sounds normal.

Abdominal: Soft. Normal appearance and bowel sounds are normal. There is no hepatomegaly. There is no tenderness.

Musculoskeletal: **No deformities; spine non-tender**

Lymphadenopathy: She has no cervical adenopathy. No supraclavicular adenopathy present.

Neurological: She is alert. She has normal strength. She displays no tremor.

Reflex Scores: Bicep reflexes are 2+ on the right side and 2+ on the left side. Patellar reflexes are 3+ on the right side and 3+ on the left side.

Skin: Skin is warm and dry. She is not diaphoretic. **Dressing on left upper back**

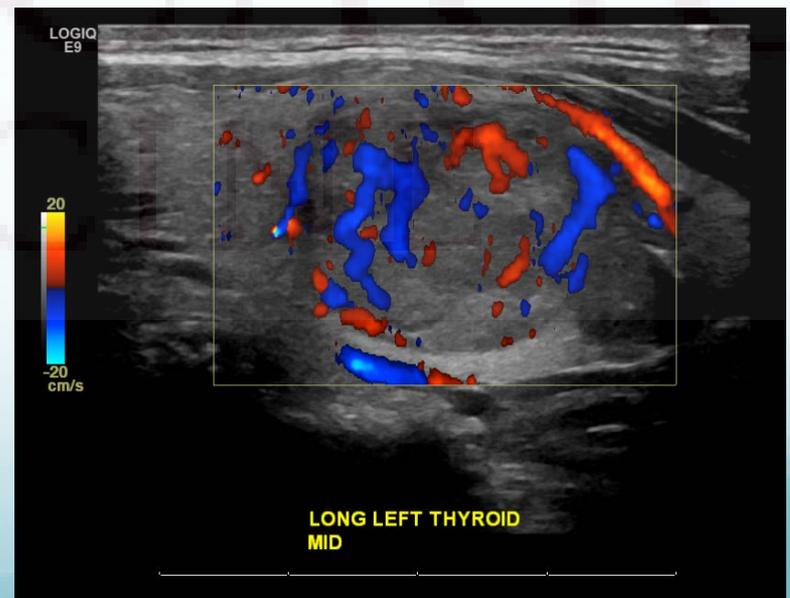
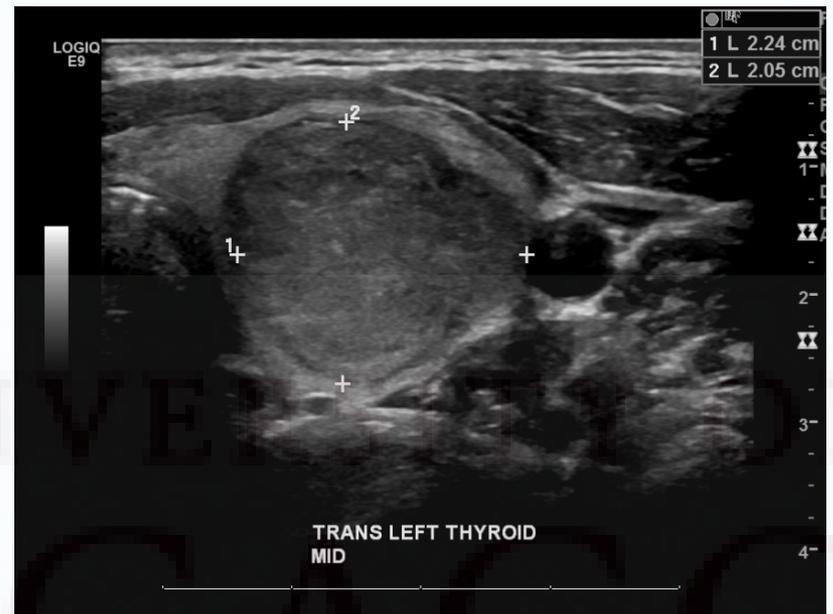
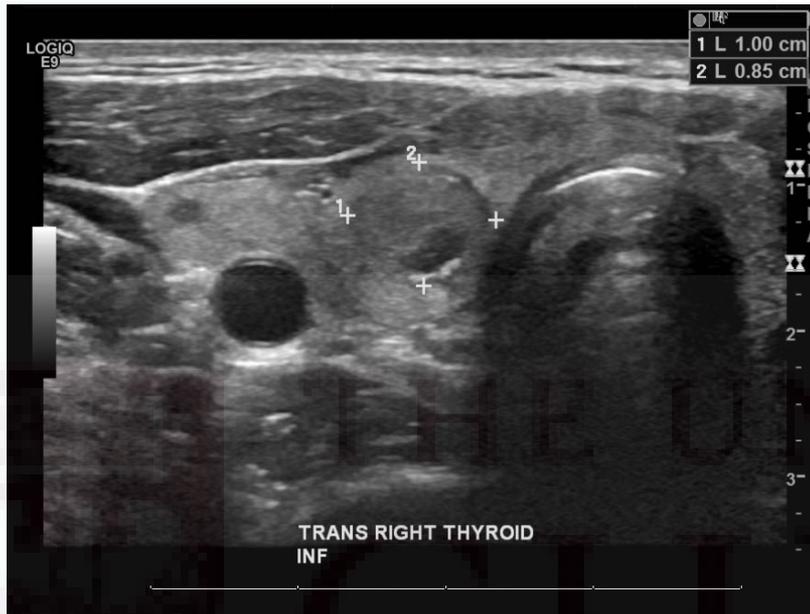
Labs

- TSH 1.08
- T3 = 107
- Free T4 = 1.24

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Thyroid Ultrasound

- Right lobe: 6.0 x 2.5 x 1.7 cm
- Left lobe: 5.7 x 2.7 x 2.3 cm
- Right lobe has multiple nodules. The more superior within the inferior pole of the right lobe has peripheral calcification, heterogeneous appearance, and central vascularity and measures 0.9 x 1.0 x 0.9 cm. A more inferiorly located relatively homogeneous hypoechoic nodule displays vascularity and measures 0.8 x 0.7 x 0.6 cm
- Left lobe contains a large heterogeneous predominantly solid mass with somewhat irregular contours, a discontinuous hypoechoic rim, coarse calcification, and central vascularity measuring 2.4 x 2.2 x 2.1 cm. A smaller more medial nodules also appears to have peripheral calcification and measures 0.8 x 0.8 x 0.8 cm



FNA

- Left nodule (2.3 x 1.7 x 2.2 cm) → previously benign
- Right mid inferior nodule (0.8 x 0.8 x 0.9 cm) → colloid
- Right inferior anterior nodule (0.8 x 0.6 x 0.7 cm) → non-diagnostic, limited cells

REPEAT

- Right inferior anterior nodule (0.7 x 0.6 x 0.7 cm) → atypical cells suspicious for follicular neoplasm

ATA 2015 Guidelines

Although there are several known clinical risk factors for thyroid cancer in patients with thyroid nodules including immobility with swallowing, pain, cough, voice change, growth, lymphadenopathy, and a history of childhood radiation therapy (either therapeutic, such as cranial radiation in childhood leukemia, or for benign conditions, such as enlarged thymus or tonsils) or familial thyroid cancer (96), these have not been incrementally included in multivariate analyses of gray-scale sonographic features and thyroid cancer risk. However, given the higher pretest likelihood of thyroid cancer associated with these clinical risk factors, FNA can be considered at lower size cutoffs for all of the sonographic appearances described above.

Radiation exposure and the thyroid



- Major determinants of risk for thyroid cancer
 - Dose
 - Age
- Internal versus external exposures
- Spectrum of thyroid disease after radiation:
 - Hypothyroidism – associated with high dose exposures
 - Benign nodules
 - Thyroid cancer
- Other tumors
 - Parathyroid tumors, salivary gland neoplasm, neural tumors (meningioma, acoustic neuroma)

Evaluation of patients with radiation history

- Identify high risk patients
- Physical exam
- TSH yearly
- Calcium yearly
- Ultrasound
- FNA of nodules >1 cm*

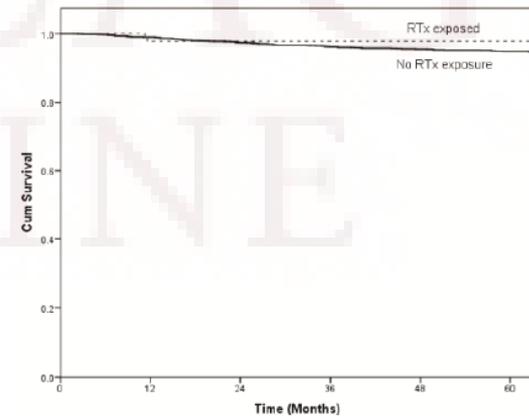
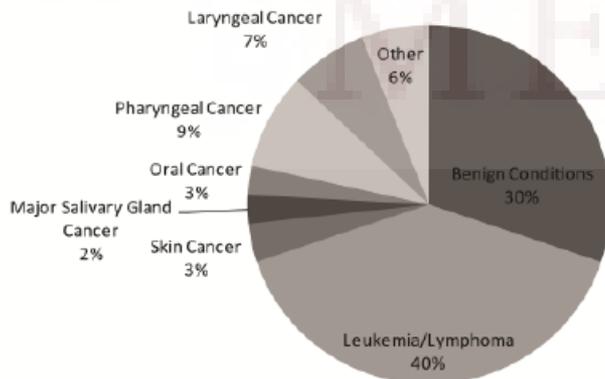
Radiation-related thyroid cancer

- Characteristics of radiation related thyroid cancer
 - Papillary most common
 - Somatic mutations with gene rearrangements – RET/PTC in >50% of cases
 - Multicentric
 - Behavior is similar to other papillary thyroid cancers (except Chernobyl*)
- Surgery: Total thyroidectomy favored by some

Prognosis of Thyroid Cancer with History of Radiation Exposure

- Study in 2016 identified 116 patients with a previous history of radiotherapy to the head/neck with differentiated thyroid cancer between 1986 and 2010.
- No significant difference in 5 year disease specific survival or 5 year recurrence free survival between patients with history of RT and no RT

Indication for Prior Head and Neck Radiotherapy



Patients at risk	Baseline	12 months	24 months	36 months	48 months	60 months
No RTx exposure	3509	2775	2399	1978	1599	1264
RTx exposed	116	89	83	68	62	53

Recommendation for our patient

- Given multiple risk factors for secondary malignancy and multiple nodules, recommended total thyroidectomy instead of lobectomy
- Thyroidectomy pathology:
 - Thyroid gland 29 grams
 - Microfollicular adenomatous nodules (largest 3.4cm, left lobe)
 - Chronic thyroiditis
 - Parathyroid tissue right side
 - One benign lymph node

Risk of Secondary Cancers in Retinoblastoma Survivors

- Cohort of 1,601 survivors of retinoblastoma
- 60% hereditary
- Hereditary patients were typically treated with radiation for Rb (88%), compared to 18% of nonhereditary patients

Table 1. Radiation Scatter Doses After a Typical Treatment* for Retinoblastoma for a 1-Year-Old Patient

Organ Site†	Type of External-Beam Treatment	
	Orthovoltage‡ Dose (Gy)	Betatron§ Dose (Gy)
Brain (average)	3.60	1.60
Pineal gland	4.00	1.40
Eye plus orbit		
Untreated side	18.2	34.5
Treated side	60.0	45.0
Nasal region	34.0	3.20
Head and neck (soft tissue)		
Untreated side	9.00	5.50
Treated side	22.0	11.0
Facial bones	27.5	8.00
Salivary glands¶	4.25	1.60
Thyroid (average left and right)	2.00	0.90
Breast (average left and right)	0.40	0.40
Upper trunk	0.60	0.45
Lung (average left and right)	0.45	0.40
Kidney (average left and right)	0.13	0.28
Stomach	0.18	0.36
Pancreas	0.16	0.33
Liver	0.16	0.24
Colon	0.10	0.25
Bladder	0.07	0.19
Uterus	0.08	0.20
Rectum	0.07	0.19
Total active bone marrow	1.20	1.00

*Dose administered 50 Gy each to lateral and nasal field (4 cm × 4 cm) for orthovoltage and 50 Gy to one lateral field for betatron.

†Organs listed in descending order of distance from the treated eye.

‡Half-value layer = 1.9 mm Cu.

§23 MV photons.

¶Includes parotid, submaxillary, submandibular, and sublingual glands.

Risk of Second Cancer: Hereditary vs Non-Hereditary

Table 3. Risk of New Cancers in 1-Year Survivors of Retinoblastoma by Hereditary Status

Cancer Site (ICD-O classification)	Hereditary (n = 963; person-years at risk, 25,309)				Nonhereditary (n = 638; person-years at risk, 18,972)			
	O	E	SIR*	95% CI	O	E	SIR	95% CI
All sites†	260	13.9	19	16 to 21	17	13.9	1.2	0.7 to 2.0
Bone (170)	75	0.21	360	283 to 451	0	0.16	0.0	0.0 to 22.6
Connective and soft tissue (171, 192.4, 192.5)	34	0.28	122	84 to 170	0	0.22	0.0	0.0 to 16.8
Nasal cavities (160)	32	0.03	1,111	760 to 1,569	0	0.03	0.0	0.0 to 135
Cutaneous melanoma (173 and M872-878)	29	1.05	28	18 to 40	0	1.00	0.0	0.0 to 3.7
Eye and orbit (190)	17	0.06	266	155 to 426	0	0.05	0.0	0.0 to 81
Brain, CNS (191, 192.0-192.3, 192.9)	10	0.74	13.6	6.5 to 25	2	0.58	3.43	0.4 to 12
Female breast (174)	10	2.52	3.96	1.9 to 7.3	7	2.46	2.84	1.1 to 5.9
Corpus uteri (182)	7	0.35	20	8.0 to 41	0	0.35	0.0	0.0 to 10
Buccal cavity (140-149)‡	7	0.34	20	8.2 to 42	0	0.37	0.0	0.0 to 9.9
Lung (162)	5	0.84	5.94	1.9 to 14	0	1.11	0.0	0.0 to 3.3
Pineoblastoma (194.4)	5	0.06	90.8	29 to 212	0	0.04	0.0	0.0 to 93
Colon (153)	3	0.48	6.28	1.3 to 18	0	0.58	0.0	0.0 to 6.3
Hodgkin's lymphoma (M9650-67)	3	0.88	3.4	0.7 to 10	1	0.70	1.4	0.04 to 8.0
Bladder (188, 189.9)	2	0.32	6.15	0.7 to 22	0	0.41	0.0	0.0 to 8.8
Thyroid (193)	2	0.60	3.34	0.4 to 12	2	0.53	3.78	0.4 to 14
Leukemia (204-207)	2	0.89	2.25	0.3 to 8.1	1	0.66	1.47	0.04 to 8.2
Excess absolute risk per 10,000 person-years§	97.2				1.63			

Abbreviations: SIR, standardized incidence ratio; O, observed; E, expected; ICD-O, International Classification of Diseases for Oncology.

*SIR is the ratio of O No. of subsequent (ie, second and third) cancers to E No. of cancers. E cancers as derived from Connecticut Tumor Registry.

†Cancer sites not listed for hereditary patients include two each of kidney (ICD-O 189.0) and other lymphoid tissue (ICD-O 202.2, 202.8); one each of small intestine (ICD-O 152.0) retroperitoneal tissue (ICD-O 158.0), male breast cancer (ICD-O 175.9), and abdomen, ill-defined (ICD-O 195.0); and nine of cancer, not otherwise specified (ICD-O 199.1). Cancer sites not listed for nonhereditary patients include one each of rectum (ICD-O 154.0); prostate (ICD-O 185.0); and two of cancer, not otherwise specified (ICD-O 199.1).

‡Buccal cavity for hereditary patients includes two each of cancer of the tongue (ICD-O 141; SIR, 25; 95% CI, 2.8 to 91) nasopharynx (ICD-O 147); (SIR, 47; 95% CI, 5.3 to 170), and three cancers of the salivary glands (ICD-O 142); (SIR, 49; 95% CI, 9.9 to 144).

§Excess risk, O minus E/person-years × 10,000.

Risk of Second Cancer: Radiation vs No Radiation

Table 4. Risk of New Cancers in 1-Year Survivors of Hereditary Rb by Radiation for Rb

Cancer Site (ICD-O classification)	Radiation (n = 849; person-years at risk, 21,706)*				No Radiation (n = 114; person-years at risk, 3,602)			
	O	E	SIR*	95% CI	O	E	SIR	95% CI
All sites†	241	11.2	22	19 to 24	19	2.77	6.9	4.1 to 11
Heavily irradiated sites (≥ 1 Gy)								
Bone (170)	73	0.18	406	318 to 511	2	0.03	69	8.4 to 250
Soft tissue (171, 192.4, 192.5)	33	0.23	140	96 to 196	1	0.04	23	0.6 to 131
Nasal cavities (160)	32	0.02	1,364	933 to 1925	0	0.01	0.0	0.0 to 688
Eye and orbit (190)	17	0.05	312	181 to 499	0	0.01	0.0	0.0 to 392
Brain, CNS (191, 192.0-192.3, 192.9)	10	0.62	16	7.7 to 29	0	0.11	0.0	0.0 to 33
Pineoblastoma (194.4)	5	0.05	104	34 to 244	0	0.01	0.0	0.0 to 509
Buccal cavity (140-149)‡	7	0.27	26	10 to 53	0	0.07	0.0	0.0 to 54
Thyroid (193)	2	0.50	4.0	0.5 to 15	0	0.11	0.0	0.0 to 35
Moderately irradiated sites (0.4-1.0 Gy)								
Female breast (174)	8	1.91	4.2	1.8 to 8.2	2	0.61	3.3	0.4 to 12
Cutaneous melanoma (173 and M872-878)	26	0.85	30	20 to 45	3	0.20	15	3.1 to 44
Lung (162)	2	0.63	3.2	0.4 to 11	3	0.21	14	3.0 to 42
Leukemia (204-207)	1	0.76	1.3	0.03 to 7.3	1	0.13	7.8	0.2 to 43
Hodgkin's lymphoma (M9650-67)	1	0.75	1.3	0.03 to 7.4	2	0.13	16	1.9 to 56
Lightly irradiated sites (< 0.4 Gy)								
Corpus uteri (182)	5	0.25	20	6.4 to 46	2	0.10	20	2.5 to 74
Colon (153)	3	0.37	8.1	1.7 to 24	0	0.11	0.0	0.0 to 34
Bladder (188, 189.9)	2	0.25	7.9	0.9 to 28	0	0.07	0.0	0.0 to 52
Excess absolute risk per 10,000 person-years				105.9				45.1

Abbreviations: Rb, retinoblastoma; SIR, standardized incidence ratio; O, observed; E, expected; ICD-O, International Classification of Diseases for Oncology.

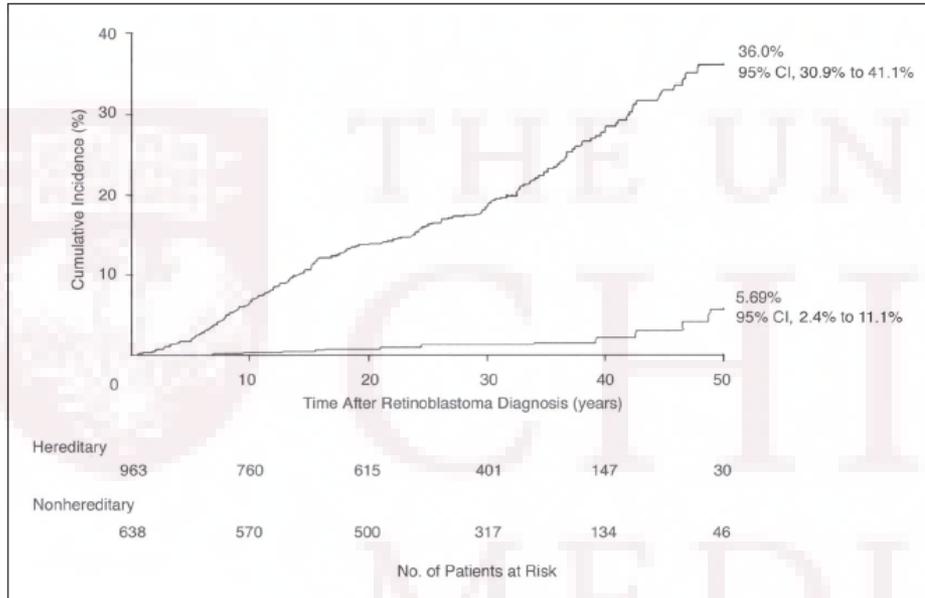
*SIR is the ratio of O No. of subsequent (ie, second and third) cancers to E No. of cancers. Expected cancers derived from Connecticut Tumor Registry.

†Cancer sites not listed for irradiated patients include one each of other lymphoid tissue (ICD-O 202.2), retroperitoneal tissue (ICD-O 158.0), male breast cancer (ICD-O 175.9), and abdomen, ill-defined (ICD-O 195.0); two of kidney (ICD-O 189.0); and eight of cancer, not otherwise specified (ICD-O 199.1). Cancer sites not listed for nonirradiated patients include one each of small intestine (ICD-O 152.0) other lymphoma (ICD-O 202.8), and cancer not otherwise specified (ICD-O 99.1).

‡Buccal cavity for radiation patients includes two each of cancer of the tongue (ICD-O 141; SIR, 32; 95% CI, 3.5 to 114) and nasopharynx (ICD-O 147; SIR, 57; 95% CI, 6.3 to 204), and three cancers of the salivary glands (ICD-O 142; SIR, 60; 95% CI, 12 to 174).

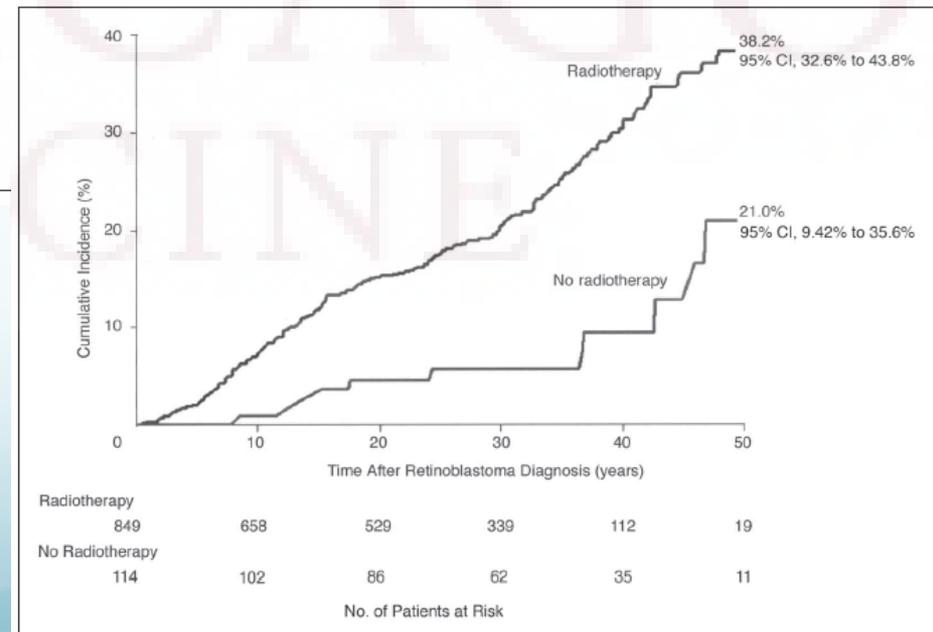
§Excess risk, O minus E/person-years × 10,000.

Cumulative Incidence of Second Cancers



By Hereditary Status

By Radiotherapy



Cancer Risk Assessment

- Symptom based approach
- Sarcoma screening- rapid whole body MRI
- Brain tumor screening- brain MRI
- Melanoma screening- yearly TBSE
- Uterine leiomyosarcoma screening- pelvic ultrasounds
- General cancer screening- mammograms at 40, colonoscopy at 50, pap per guidelines

Pre-conception counseling

- Hereditary retinoblastoma is inherited in an autosomal dominant fashion
- Options discussed
 - Pre-implantation genetic diagnosis
 - Egg donor
 - Prenatal diagnosis (CVS, amniocentesis)
- Decided to conceive naturally and likely pursue prenatal diagnosis
- Conceived with clomid and IUI. Currently 11 weeks pregnant

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