National Cancer Institute

Division Of Cancer Epidemiology And Genetics
Radiation Epidemiology Branch

Cancer Risks Following Internally Administered Medical Radiation
Focus on Radioactive Iodine (I-131)

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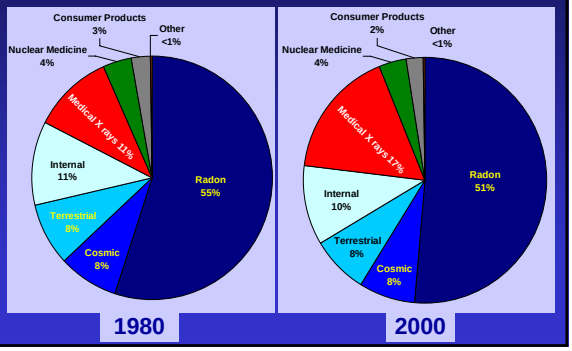
2007 Radiation Epidemiology Course

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Why Are We Interested In Medical Radiation?



Dramatic Increase in Medical Use of Radiation Over Last Two Decades

- Per capita radiation dose from medicine has increased almost 600 percent from 1980-2006
- Collective annual population dose from medicine has increased about 750 percent

Mettler, NCRP 2007

Collective Population Doses

- ~600,000 person-Sv worldwide over all time from entire Chernobyl release*
- ~930,000 person-Sv annually from radiology and nuclear medicine in U.S.
- ~900,000 person-Sv annually from natural background radiation (assuming old NCRP 100 calculations)

Mettler, NCRP 2007

* UNSCEAR

Internally Administered Medical Radiation: Background

- Internally administered medical radiation first used in 1920s
- Nuclear medicine developed as a field in late 1940s
- Initially used radioactive iodine (I-131) to diagnose and treat thyroid disease
- Radioisotopes are used in nuclear medicine primarily to provide diagnostic information about the functioning of an organ, but also to treat disease

Linear accelerator makes radioisotopes for medicine and research.

Nuclear Medicine Background

- Millions of nuclear medicine procedures performed each year and the number is increasing rapidly
- In developed countries frequency of diagnostic nuclear medicine is 1.9%/yr and frequency of radioisotope therapy about 0.2%.
- Use of radiopharmaceuticals in diagnosis is growing by >10%/yr

Some Isotopes Used in Medicine

- Over 200 radioisotopes used regularly
  - **Diagnosis:** Gallium-67, Iodine-123, Technetium-99, Thallium-201
  - **Cancer Treatment:** Iodine-125, Iodine-131, Iridium-192, Palladium-103, Yttrium-90
  - **Pain Management:** Rhenium-186, Samarium-153, Strontium-89

Metal seed containing radioactive iodine-125 used as an implant for treating prostate cancer.

Radioactive Iodine-131

Why Do We Want to Know About ^{131}I

- Safe use of radioiodines (current and new) in clinical practice
- Understanding of ^{131}I carcinogenesis
- Effective handling of future nuclear events
- Public concern about environmental ^{131}I

I-131 Background

- First used in endocrinology in 1946
- Emits beta and gamma radiation; has a half-life of about 8 days
- Concentrated in the thyroid through inhalation and ingestion
- Also absorbed by bone marrow, salivary glands, stomach, small intestine, and bladder, but in much smaller doses

I-131 Uses in Medicine

Concerns

- External radiation can cause thyroid cancer
- Children especially sensitive
- Childhood exposure from Chernobyl significantly increased risk of thyroid cancer
- Data scarce regarding childhood I-131 medical exposure
- Other late effects of I-131 not well known

Background

- Prior to Chernobyl, limited data on cancer risk from radioiodines
- Most information on ^{131}I came from studies of adults exposed to medical radiation and children exposed to fallout
  - *Little evidence of a dose response for thyroid cancer among adult patients*
  - *Data on childhood exposure inconsistent*

Medical Radiation Dilemma

- Necessary tool
- A potential carcinogen

^{131}I Medical Exposures

Procedure	No/1000 People (mean)	Mean Activity (MBq)
Uptake	0.8	3.1
Scan	5.3	17
Hyperthyroidism	0.15	415
Thyroid cancer	0.04	4,760

UNSCEAR 2000; 1991-96; health care level I

Cancers of Interest

Diagnostic	Thyroid, other organs but dose very, very low
Hyperthyroidism	Leukemia, salivary gland, bladder, stomach, kidney, breast
Thyroid cancer	All sites/organs

Problems in Evaluating Cancer Risk from I-131 Exposure

- Limited appropriate medical exposure
- Large uncertainties in dose estimates
- Inconsistent experimental data

I-131 Dose Uncertainties: Thyroid

- Administered activity little correlation with dose
- Thyroid size often not known
- Non-uniform distribution of I-131 in gland

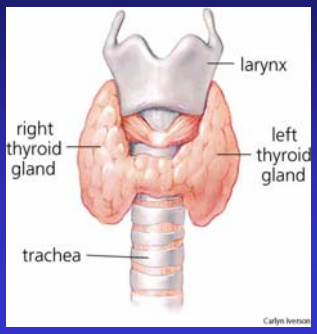
I-131 Dose Uncertainties: Other

- Small doses
- Based on extrapolation from general population models

I-131 Epidemiologic Studies

Use	Country	Patients	Activity
Diagnostic	Sweden	35,000	52μCi
Hyperthyroid	Sweden	10,000	13.7 mCi
	U.S.	35,000	10.4 mCi
	U.K.	7,500	8.5 mCi
	Finland	5,586	8.2 mCi
Thyroid cancer	Sweden	834	123 mCi
	England	258	>100 mCi
	Denmark	194	N.A.
	Italy	730	145 mCi
	Switzerland	298	>100 mCi

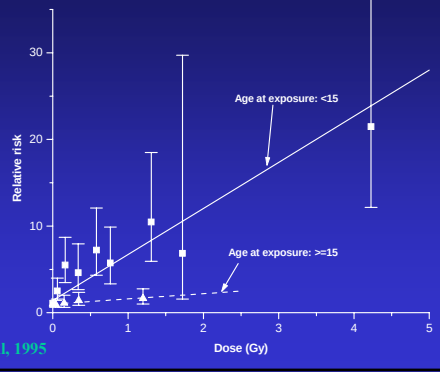
Thyroid



What Is Known About External Radiation

- Thyroid is uniquely sensitive to radiation
- Benign and malignant tumors occur at relatively low doses
- Dose-response consistent with linearity
- Excess relative risk increases with decreasing age at exposure
- Risk elevated >40 years after exposure

Relative Risk for Thyroid Cancer



Ron et al, 1995

What Is Not Known About I-131

- Is I-131 as tumorigenic as external radiation?
- Are patterns of risk the same?
- Is the clinical course of thyroid cancer similar?
- Are other thyroid diseases related to I-131?

Swedish Diagnostic I-131 Study

Study population	36,792
Prior external radiotherapy (%)	5
With suspected thyroid tumor (%)	32
Without suspicion of thyroid tumor	24, 010
Women (%)	77
Mean age at first exam (y)	43
Patients <20 y at exposure (%)	7
Mean follow-up (y)	27
Mean I-131 administered activity (MBq)	1.6
Mean thyroid dose (Gy)	0.9
Mean dose to other organs (Gy)	<0.01

Holm et al 1988, 1989, Hall et al, 1996; Dickman et al, 2003

Risk of Thyroid Cancer Incidence
Swedish Diagnostic ^{131}I

	Cancers	SIR	95% CI
Prior X-ray	24	9.8	6.3-14
Suspicion of Thyroid cancer	69	3.5	2.7-4.4
Other reasons	36	0.9	0.6-1.3

Dickman et al, 2003

Risk (SIR) Of Thyroid Cancer Incidence by Dose*
Swedish Diagnostic I-131

Time since exposure (y)	Thyroid Dose, Gy ≤0.25	0.25-0.5	0.5-1.0	>1
5-9	1.1	0	0.72	3.2 (1.2-6.9)
10-19	0.26	0.89	0.66	0.73 (0.15-2.1)
20+	0.23	1.13	1.19	1.05 (0.39-2.3)
ALL	0.45	1.07	0.86	1.27 (0.7-2.1)

**Persons without prior XRT or suspicion of thyroid tumor; n=24,010*

Risk Of Thyroid Cancer Incidence By Age at Exposure*
Swedish Diagnostic ^{131}I

Age (y)	Obs	SIR	95% CI
<20	2	0.96	0.12-3.5
21-50	23	0.89	0.57-1.3
51-75	11	0.94	0.47-1.7

** >5 years after exposure; Pts. without prior XRT or suspicion of thyroid tumor (n=24,010)*

Dickman et al, 2003

Thyroid Nodule Prevalence Following Diagnostic ^{131}I

Nodules	Dose (Gy) <0.25	0.25-	>1.0
Single			
No. women	26	19	23
RR	1.0	1.6	3.3
ERR/Gy		1.2 (0.4-3.2)	
Multiple			
No. Women	14	16	9
RR	1.0	2.4	2.1
ERR/Gy		0.1 (0.04-1.5)	

Hall et al, 1996

I-131 treatment of choice for hyperthyroidism

Hyperthyroidism Studies

	Sweden	U.S.	U.K.	Finland
Study population	10,552	35,593	7,417	5,586
I-131 treated (%)	100	65	100	50
Women (%)	82	79	83	83
Mean age at 1st treatment	57	46	57	62 median
Mean activity (mCi)	13.7	10.4	8.5	8.2

Holm et al, 1991; Hall et al, 1992; Ron et al, 1998; Franklyn et al, 1998, 1999; Metso et al, 2006, 2007

Risk of Thyroid Cancer Incidence
Swedish I-131 Hyperthyroidism Study

	OBS*	SIR
TOTAL	18	1.3 (0.8 - 2.0)
Type of hyperthyroidism^		
Graves' disease	6	0.8 (0.3 - 1.8)
Toxic nodular goiter	10	1.7 (0.8 - 3.2)
Years since treatment		
1-4	4	1.3 (0.4 - 3.4)
5-9	5	1.2 (0.4 - 2.8)
10+	9	1.3 (0.6 - 2.5)

** ≥ 1 year after therapy; ^ type unknown for 2 patients; Holm et al, 1991*

THYROID CANCER MORTALITY
U.S. Thyrotoxicosis Study

	Obs*	SMR
TOTAL	28	2.8 (1.8 - 4.0)
Treatment		
^{131}I	24	4.0 (2.5 - 5.9)
Graves' disease	*16*	2.8 (1.6 - 4.5)
Toxic nodular goiter	*7*	17.7 (7.1 - 36.5)
Surgery	4	1.1 (0.3 - 2.7)
Drugs	0	---
Years since ^{131}I treatment		
1-4	12	12.5 (6.4 - 21.8)
5-9	1	0.8 (0 - 4.7)
10+	11	2.8 (1.4 - 5.0)

** ≥1 year after therapy; Ron et al, 1998*

Risk Of Thyroid Cancer
U.K. I-131 Hyperthyroidism Study

	Thyroid Cancers	Thyroid Deaths
Observed	9	5
Expected	2.8	1.8
Obs./Exp.	3.2	2.8
95% CI	1.7-6.2	1.2-6.7

Franklyn et al, 1998, 1999

Risk Of Thyroid Cancer
Finnish I-131 Hyperthyroidism Study

	Thyroid Cancers	Thyroid Deaths
Cases	5	1
Comparisons	3	0
RR	1.8	
95% CI	0.4-7	

Metso et al, 2006, 2007

Medical ^{131}I Exposure Subsequent Thyroid Cancer

- Little evidence of an increased risk of thyroid cancer following diagnostic ^{131}I, but very few children exposed
- Following treatment for hyperthyroidism, thyroid cancer rate greater than expected in some studies, but the number of excess cases very small, no clear dose response, and potential confounding from underlying thyroid disease

But…

- Childhood ^{131}I exposure from Chernobyl increases the risk of thyroid cancer and the risks are consistent with external radiation
- RBE not yet defined, but likely between 0.6 and 1

Suggested RBE Values

Walinder, 1972	0.1 (Dose 2,200-11,000)
Lee et al, 1982	~1 (Dose 80 - 850 cGy)
NCRP, 1985	0.1-1.0 (0.3 recommended)
Laird, 1987	0.66 (95% CI 0.14 - 3.1)
IOM/NAS, 1998	0.66-1.0
Brenner, 1999	0.6
Chernobyl	~1

Reasons For Possible Differences Between ^{131}I And External Radiation

- Low dose rate of ^{131}I
- Non-uniform distribution of ^{131}I

  Cell killing at high doses
- Underlying thyroid disease
- Uncertainties in dose
- Limited statistical power

LEUKEMIA

Risk of Leukemia Mortality
U.S. Thyrotoxicosis Study

Treatment	Non-CLL Obs	Non-CLL SIR	CLL Obs	CLL SIR
^{131}I	55	1.2	19	1.3
Graves'	*52*	*1.2*	*19*	*1.3*
Toxic nodular goiter	*2*	*0.9*	*0*	*--*
Surgery	31	1.2	12	1.3
Drugs	1	0.5	0	--

Ron et al, JAMA 1998

Risk of Leukemia Mortality
U.S. Thyrotoxicosis Study

Yr since ^{131}I Exposure	Non-CLL Obs	Non-CLL SIR	CLL Obs	CLL SIR
<1	2	1.6	0	---
1-4	8	1.6	2	0.9
5-9	14	2.1*	5	2.0
10+	31	1.0	12	1.1

** Lower CI >1.0*

Ron et al, 1998

Risk of Leukemia Mortality U.S. Thyrotoxicosis Study

Bone Marrow Dose (mGy)	Non-CLL Obs	Non-CLL SIR	CLL Obs	CLL SIR
0	31	1.0	12	1.0
1 - 49	38	0.9	8	0.5
50+	13	1.1	3	0.6
P-trend		*>0.5*		*>0.5*

Ron et al, 1998

Risk of Leukemia Incidence Swedish ^{131}I Studies

	Diagnostic ^{131}I	Hyperthyroidism Therapy	Cancer Therapy
Patients	36,326	9,860	802
Mean bone marrow dose (mGy)	0.19	48	251
All leukemias			
Cases	152	37	6
SIR	1.2*	0.8	2.4*
Non-CLL			
Cases	103	25	2
SIR	1.2*	0.8	1.2

** Borderline statistical significance*

Risk of Leukemia Incidence Swedish ^{131}I Studies

Bone Marrow Dose (mGy)	Leukemia	RR
0 - 0.01	12	1.0
0.02 - 0.10	48	1.0
0.11 - 10	92	1.3
11 - 100	32	0.8
100+	11	1.8

Hall et al 1992

Risk of non-CLL Incidence Swedish ^{131}I Studies

Years since Exposure	Obs	SIR
2 - 9	38	1.0 (0.7-1.3)
10 - 19	63	1.3 (1.0-1.6)
20+	29	1.0 (0.6-1.4)

Hall et al, 1992

Risk of Leukemia Following ^{131}I Treatment for Thyroid Cancer

Study	Exposed Patients	Obs	SIR
de Vathaire et al, 1997	846	0	---
Dottorini et al, 1995	626	0	---
Hall et al, 1991	834	4	2.4 (0.7-6.2)
Edmonds & Smith, 1986	258	3	12 (2.4-35)
Brincker et al, 1973	194	2	20 (2.5-74)
Glanzmann, 1992	298	3	6.2 (1.3-2.5)

OTHER CANCERS

Cancer Risk After ^{131}I Therapy for Hyperthyroidism

Cohort	Subjects	Elevated Risks
Sweden	10,522	stomach, kidney, brain
U.S.	35,573	lung, breast, kidney, thyroid
England	7,417	Small bowel, thyroid

Cancer Risk Following ^{131}I Treatment for Thyroid Cancer

Cohort	Subjects	Elevated Risks
de Vathaire et al, 1997*	846	colorectal
Dottorini et al, 1995*	730	salivary, breast, bladder
Hall et al, 1991*	834	all sites, salivary, stomach, bladder
Glanzman, 1992	298	all sites, stomach, breast, bladder
Edmunds & Smith, 1986	258	all sites, breast, bladder
Rubino et al, 2003	4225	salivary

** Included in the pooled analysis, Rubino et al, 2003*

Conclusions: I-131 in Medicine

- I-131 plays an important role in medicine, particularly as treatment for hyperthyroidism and thyroid cancer.
- Potential cancer risks appear to be taken into account when recommending therapy.
- I-131 is rarely used to treat hyperthyroidism in children which seems appropriate since not enough is known about risks.
- I-131 appears to be less effective in inducing leukemia and solid tumors other than thyroid

Thorotrast (thorium-232)

- Radiographic contrast agent used 1928-1954
- Between 2.5 and 10 million people exposed worldwide
- A-particle emitter with biological half-life 400 yr
- Primarily deposited in liver (60%), spleen (20%), red bone marrow (12%)

Cancer Risks after Cerebral Angiography with Thorotrast

- Dose response for all cancers combined
  - Incidence RR 3.4 (2.9; 4.1)
  - Mortality RR 4.0 (2.5; 6.7)
- Risks elevated for 50 yr
- Dose response for cancers of the liver, bile ducts and gallbladder, and non-CLL leukemia; borderline for pancreas

Travis et al, 2003

Radium-226 (Ra-226)

- Radium was discovered in 1898 by Mme. Curie
- Radium-226 is a potent source of gamma rays primarily from the short-lived daughter products of radon-222
- In the 1920's and later radium was injected intravenously for a variety of diseases
- Used to treat cervical cancer and benign gynecological diseases

Cancer Mortality following Treatment with Intrauterine Ra-226

- 4153 patients treated for benign gynecologic disorders, 1925-65
- Mean follow-up 26.5 years
- 2763 total deaths; 2687 expected (SMR) = 1.03
- Increased risk of cancer mortality (SMR = 1.30) 10 or more years following irradiation organs
- ERR per Gy: 0.006 for uterus, 0.4 for other genital organs, 0.5 for colon, 0.2 for bladder, and 1.9 for leukemia

Inskip et al, 1990

Conclusions

- Millions of nuclear medicine procedures performed each year and demand for radioisotopes continues to grow
- Cancers that concentrate I-131 have been associated with the exposure, but risks are not yet well quantified
- Further research will be needed since new diagnostic procedures and treatments are using uncommon isotopes