MANAGEMENT OF PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA WITH ^{131}I

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INTRODUCTION

SEER (Surveillance, Epidemiology, and End Results) Cancer Statistics Review

- In 2011, there were an estimated 566,708 people living with thyroid cancer in the United States.
- Approximately 1.1 % of men and women will be diagnosed with thyroid cancer at some point during their lifetime, based on 2008-2010 data.
- The number of new cases of thyroid cancer was 12.9 per 100,000 men and women per year. These rates are age-adjusted and based on 2007-2011 cases.

INTRODUCTION

- Thyroid cancer is a malignant neoplasm originating from follicular or parafollicular thyroid cells.
- Thyroid cancers can be classified according to their histopathological characteristics. The papillary (75-85%) and follicular (10-20%) types together can be classified as "differentiated thyroid cancer (DTC)".
- DTC has a more favorable prognosis than the medullary (5-8%) and undifferentiated types.

INTRODUCTION

- Thyroid cancer is one of the most curable cancers. The overall 10-year survival for PTC and FTC is 93% and 85%, respectively.
- 20–30% of patients develop recurrences over several decades, and 2/3 of recurrences appear within the first decade after initial treatment.
- Distant metastases occur late more often in patients with follicular carcinoma while M1-initial is detected more often in patients with papillary carcinoma. Survival is not significantly different among patients with M1-intial and M1-late. The risk of death from M1 increased ≥45 years (Mihailovic et al. Nucl Med Comm 2009)

INTRODUCTION

- DTC patients with distant metastases may have relatively long-term survival. Better outcome of disease is influenced by several prognostic factors. Patients' age, histopathology of the tumor, and initial therapy significantly influence the survival (Mihailovic et al, Cancer Biother & Radiopharm 2007)
- The iodine avidity of distant metastases is a strong predictor of survival (Mihailovic et al, Thyroid 2009)

MANAGEMENT OF DTC

Papillary and Follicular Carcinoma

1. Initial treatment

1. Surgery
(thyroid surgery and LN surgery)

2. Radioiodine ablation

3. LT4 therapy

2. Follow-up

Guidelines

- To provide guidance and recommendations for particular practice areas concerning thyroid disease and thyroid cancer.
- The Guidelines are not inclusive of all proper approaches or methods, or exclusive of others.
- The Guidelines do not establish a standard of care and specific outcomes are not guaranteed.
- Treatment decisions must be made based on the independent judgment of health care providers and each patient's individual circumstances.
- A guideline is not intended to take the place of physician judgment in diagnosing and treatment of particular patients.
- Multiple Guidelines [ATA; NCCN; SNM; EANM], Serbian

I-131 THERAPY (RAIT)

- **Definition**

"Systemic administration of 131-sodium or potassium iodide (^{131}I) for selective irradiation of thyroid remnants, microscopic DTC or other nonresectable or incompletely resectable DTC, or both purposes"

Luster, et al. Guidelines for radioiodine therapy of differentiated thyroid cancer. Eur J Nucl Med Mol Imaging, 2008

RAIT - 1

- The first form, radioiodine ablation, (post-surgery)
- The second form, radioiodine treatment of perstent or recurrent disease.

Luster, et al. Guidelines for radioiodine therapy of differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 2008

RAIT- 2

GOALS

- To eliminate thyroid remnants in order to increase sensitivity and specificity of follow-up testing of tumor persistence or recurrence (Tg; dx WBS)
- To detect previously occult metastases
- To treat microscopic tumor deposits (if any)

Thyroid Carcinoma Prognosis: Recurrence & Cancer Death

- Characterize as High Risk or Low Risk
- Risk factors
  - Age at diagnosis
  - Tumor stage [size, invasiveness]
  - Male gender
  - Delay in therapy
  - Surgical and medical management

Mazzaferri: Am J Med. 1994;97:418–428.

Assessment of risk of recurrence- three-level stratification

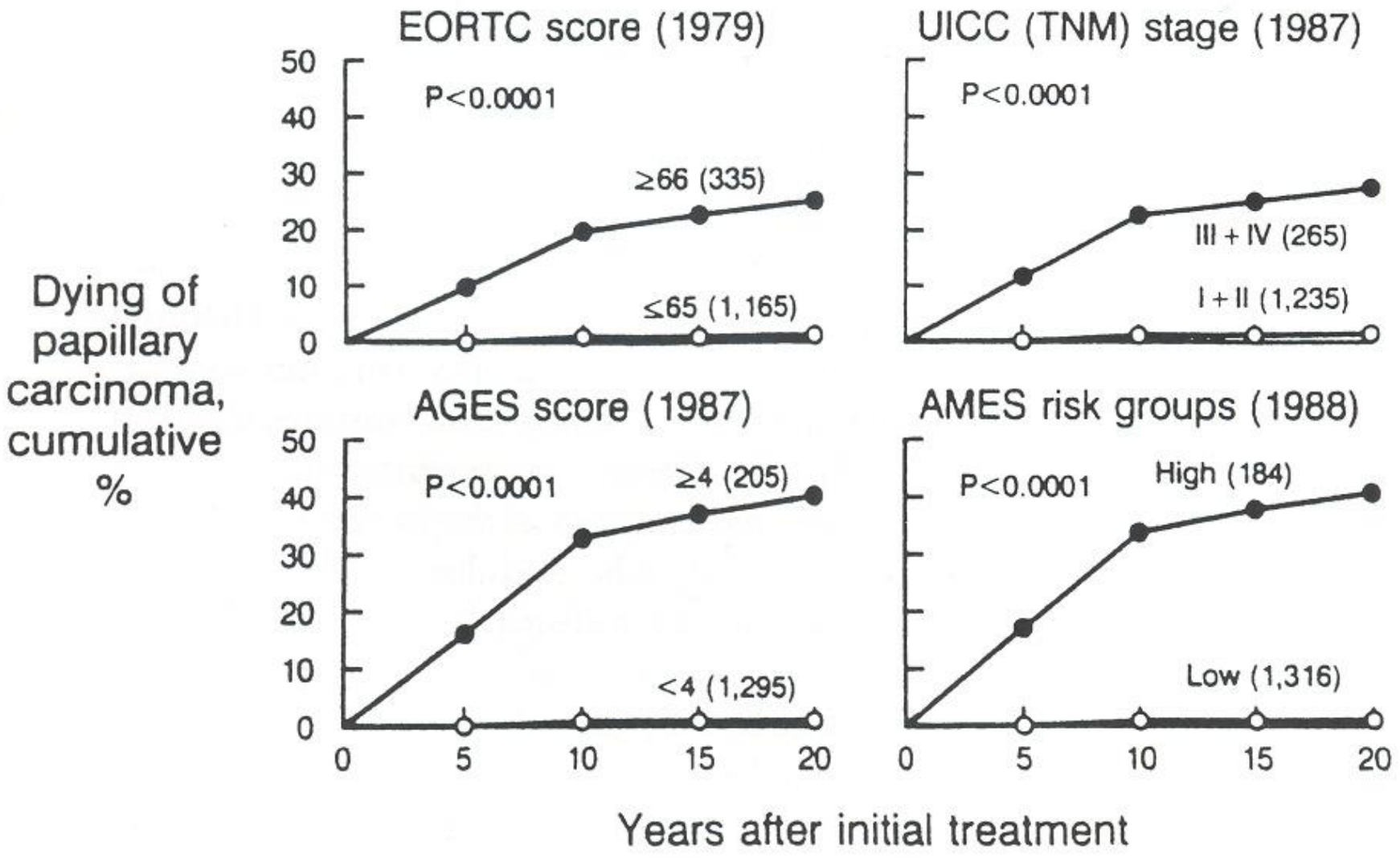
- Low-risk: N0M0; no locoregional invasion; no aggressive PH or vascular invasion; no ^{131}I uptake outside the thyroid bed on 1st Rx WBS
- Intermediate-risk: microscopic tumor invasion into the perithyroidal soft tissues; N1 or ^{131}I uptake outside the thyroid bed on 1st Rx WBS; aggressive PH or vascular invasion
- High-risk: macroscopic tumor invasion; incomplete tumor resection; M1; Tg out of proportion to what is seen on Rx WBS

ATA guidelines

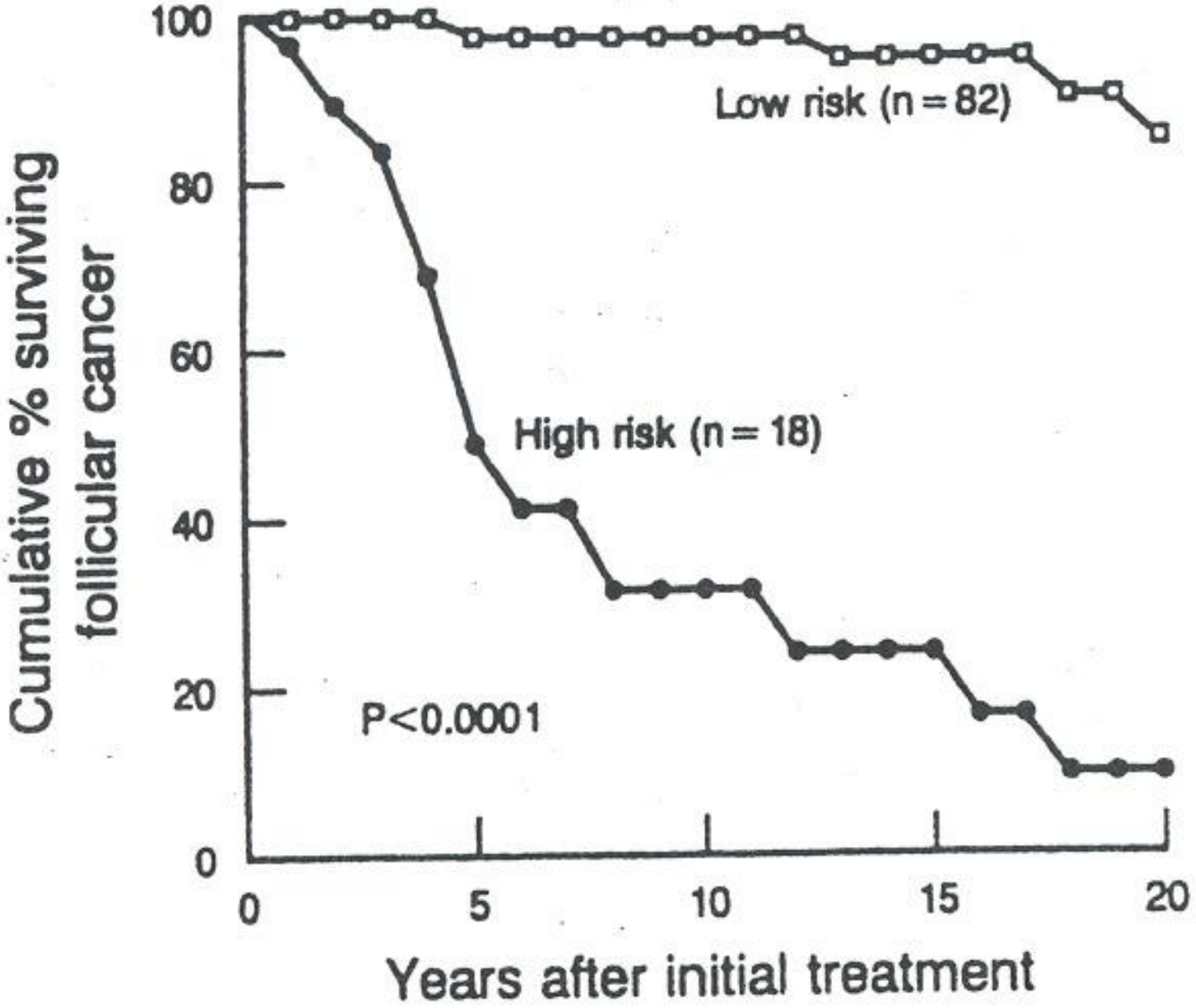
Staging systems

- AJCC/IUCC staging was developed to predict risk for death, not recurrence
- CAEORTC, AGES, AMES, U of C, MACIS, OSU, MSKCC, and NTCTCS systems

Risk Assignment at Dx and Mortality in Papillary Thyroid Ca



Risk Assignment and Mortality in Follicular Thyroid Ca



To ablate or not to ablate?

EANM	SNM	ATA
No ablation: ➢ Unifocal ≤1cm ➢ N0M0 ➢ No capsular invasion ➢ No radiation history ➢ Favourable PH	**Controversial:** ➢ Very low risk ➢ Low risk No statistically significant improvement in DSS; recurrence rates may decrease	**No ablation:** ➢ As EANM ➢ Multifocal tu if all foci ≤1cm with favourable PH

Management of Thyroid Microcarcinoma

- Microcarcinoma of the thyroid gland = “occult”, “small thyroid carcinoma” measuring ≤1 cm.
- Multifocality is common; associated with an increased rate of recurrence
- Controversial management
- TT/NTT + RAIT should be the optimal treatment. However, a simple follow-up may be appropriate for those who undergo unilateral lobectomy based on preoperative assessment as low risk (Mihailovic et al. Clinical Nucl Med 2013).

Republic of Serbia
Ministry of Health

Guidelines for DTC

PATIENT SELECTION FOR RAIT

1. No indication

Low risk of mortality and relapse:

- Unifocal tumor, <10mm, N0M0, favourable histology
- Minimally invasive follicular TC without vacular invasion, <20mm
- No tumor spread beoynd thyoid capsule

PATIENT SELECTION FOR RAIT

*2. **Indication***

- Distal metastases
- Incomplete tumor/tumor tissue resection
- Complete tumor excision but high risk of mortality and relaps:
- Spread beoynd thyoid capsule
- Metastases into locoregional or distal lymph nodes

PATIENT SELECTION FOR RAIT

3. Probable indication

- Less than total thyroidectomy
- Lymph node status was not defined during the operation
- Tumors > 10mm < 40mm
- Tumors < 10mm + unfavourable histology:
  - PAP: tall-cell, columnar-cell, diffuse sclerosing;
  - FOL: wide invasive, poorly differentiated
- Multifocal tumors < 10mm

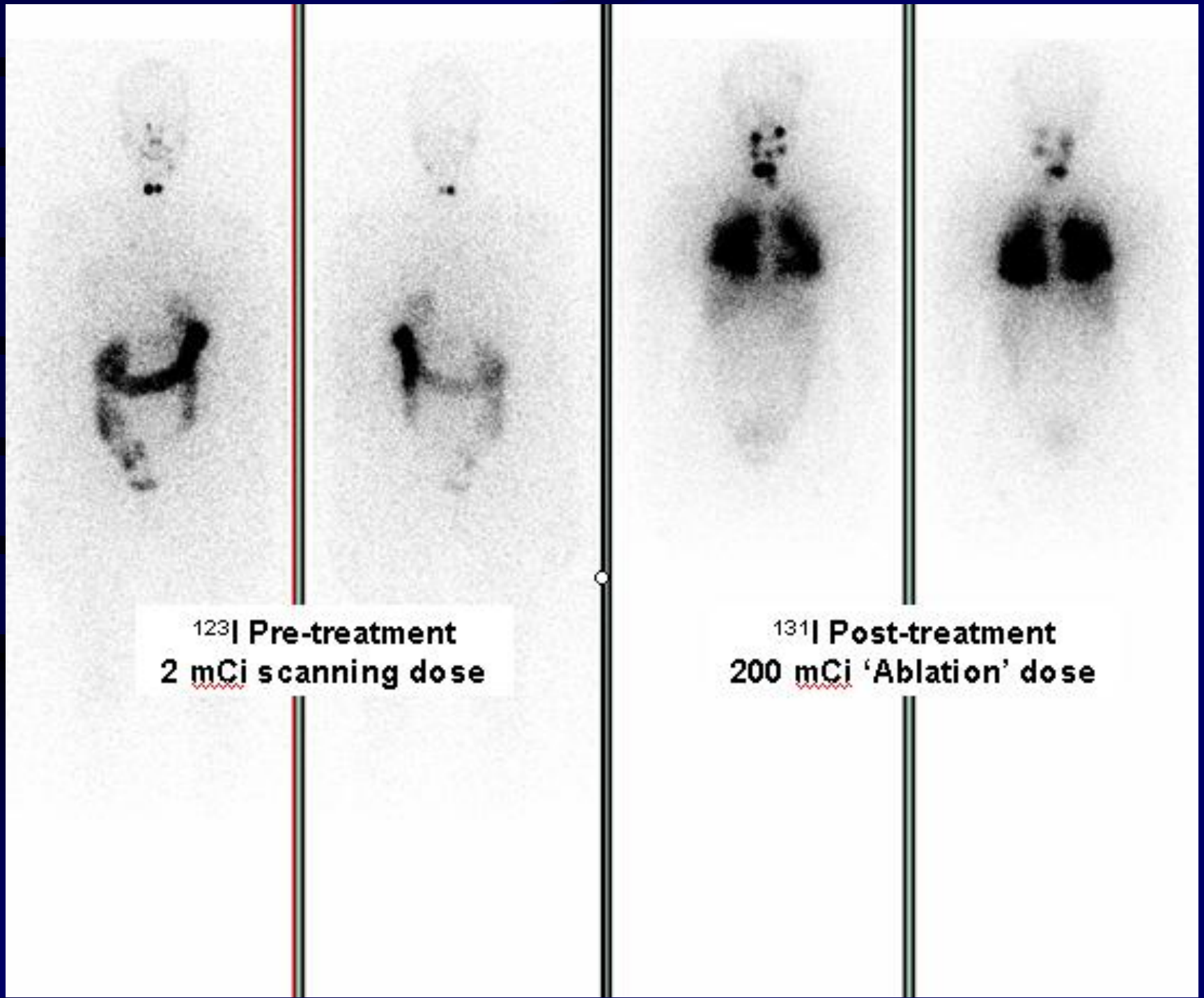
I-131 THERAPY (RAIT)

- **Preparation**
  - **Low iodine diet [salt, sea food, supplements, red dye]**
  - **Withdraw T4 for 4 weeks**
  - **Substitute with T3; withdraw for 2 weeks**
  - **Assess clinically; confirm TSH > 30 mIU/L**

Pre - treatment WBS?
Stunning Effect
Relationship to Diagnostic Dose

I-131 Diagnostic Dose	Stunning Effect
10 mCi, 370 MBq	89%
5 mCi, 185 MBq	67%
3 mCi, 111 MBq	40%
0.025 mCi, 0.185 MBq	0%
Any I-123 dose	0%

HM Park, Thyroid, 1994


^{123}I Pre-treatment
2 mCi scanning dose
^{131}I Post-treatment
200 mCi 'Ablation' dose

RAIT

- Theories differ on the amount of ^{131}I needed for proper therapy
- Bierwaltes' [University of Michigan – pre1990] treatment protocol varies based on site of uptake
  - 3.7 GBq (100 mCi) thyroid bed
  - 5.55 GBq (150 mCi) cervical lymph nodes
  - 6.5 GBq (175 mCi) distal metastases

RAIT

- Fixed administered dose
  - Depends on extent of disease
  - 200 mCi maximum
- Patient specific dosimetry for mets beyond regional lymph nodes
  - Determine maximum safe dose based on blood radiation absorbed dose; Blood is a surrogate for bone marrow
  - Marrow dose is determined by irradiation of marrow by blood radioactivity [primarily β] and whole body radioactivity [primarily γ]
  - Clinical observations at MSKCC years ago [Benua & Leeper]: No adverse bone marrow effects if dose to blood does not exceed 200 cGy [per year]

Radiation Dosimetry in Thyroid Cancer Therapy

- Patient specific dosimetry is most relevant in treating metastatic disease [^{131}I doses > 200 mCi]; determines the energy absorbed from radiation (Radiation Absorbed Dose – “rad”. The “rad” has been re-designated “centiGray [cGy]” and is numerically equivalent to the “rad”)
- Patient differences due to renal function; age; body iodine pool
- Allows administration of largest safe dose; determination of the Maximal Tolerated Activity; 200 cGy to marrow is used as the maximal radiation absorbed dose [Maximum Tolerated Activity (MTA)] (some latitude exists)

Radiation Dosimetry in Thyroid Cancer Therapy

- ❖Estimate Bone Marrow radiation absorbed dose by calculating rads to Blood [Quimby-Marinelli]
- ❖Since ^{131}I is NOT deposited in bone marrow:
- Bone marrow receives β radiation from blood within marrow
- Additional γ radiation is received from activity throughout the body

Radiation Dosimetry in Thyroid Cancer Therapy

Quimby-Marinelli Formulation:

- Dose β_{blood} = 51.2 (constant) X Eβ x C(t)
- Dose $\gamma_{whole\ body}$ = 0.024 (constant) x $\gamma T_{1/2}$ x p (density =1) x Γ(geometric constant)
- Total Blood Dose [per mCi] =

  Dose β_{blood} $\rightarrow$ blood + Dose $\gamma_{whole\ body}$ $\rightarrow$ blood

MIRD

- MIRD formulation can also be used

$$D = \frac{A \times 1.44 T_{1/2eff} \times S}{m}$$

Thyroid Cancer – Remnant Ablation Activity

Group [n= 149]	25 - 35 mCi	35 - 64 mCi	65 -119 mCi	120 - 200 mCi
Activity (mCi)	30.0 ± 1.5 **[1.1 GBq]**	50.6 ± 5.4 **[1.85 GBq]**	88.6 ± 14.0	155.0 ± 28.7
Radiation Absorbed Dose (cGy)	19,800 ± 992	31,372 ±3,355	49,616 ±7,858	130,200 ± 24,162
# Success (%)	17/27 (63.0)	42/54 (77.8)	28/38 (73.7)	23/30 (76.7)

Bal et al; Cancer, 1996

Activity for ablation in children

EANM	German	ATA
• body weight (BW) (1.85 -7.4 MBq/Kg) • surface area /age (SA/A) ✓5 yr: 1/3 adult dose ✓10 yr: ½ adult dose ✓15 yr: 5/6 adult dose	• 24-h RAIU ✓<5%=50 MBq/kg ✓5-10%=25 MBq/kg ✓10-20%=15 MBq/kg	• BW • SA

METHOD

- Hospitalization in isolated room is OBLIGATED (dose in patients body <0.40 GBq)
- Application of ^{131}I per os (liquid, capsula)
- WBS is performed 72 hrs day after the therapy
- Repeated therapies are obligated in rest tumor and recurrent disease; Period between 2 RIT shouldn't be less than 4 - 6 months; there is no limit to the cumulative dose of ^{131}I (risk of cancer and leukemia rises with higher cumulative doses). If there is no uptake on post-therapy ^{131}I-WBS – any further RAI is useless
- It is contraindicated in pregnancy and lactation
- Pregnancy shouldn't be allowed before 1 year after the last performed therapy

COMPLICATIONS:

Short-term complications

- Transient sialoadenitis (11.5% pts)
  Appear in the 3 first days after the therapy: pain, swelling (bilateral), (dry mouth, metallic taste during several weeks)- ample fluids and hard sour candy for promoting salivary secretion during the first 24 hr
- Radiation gastritis (uncommon) dose large than 7.4 GBq ^{131}I;
  - vomiting (5% pts)

- Acute radiation sickness

Occurs within 12hr after the high doses of RIT:
fatigue, headache, nausea, vomiting (rarely)

- Thyroid storm

Rare in pts who have hyperthyroidism secondary to large masses of functioning metastases
-antithyroid drugs, beta-blocking drugs prior to the RIT

- Vocal cord paralysis

Rare complication that may require tracheostomy

- Bone marrow depression

Transitory occurs within 1 month of RIT therapy

- transient anemia (36% pts)
- leukopenia (10% pts)
- thrombocytopenia (3% pts)

- Local effects

(caused by radiation inflammation)

Pain, hemorrhage, edema may develop at the site of metastases.

- pain (functioning bone metastases)
- cerebral hemorrhage and edema (cerebral metastases)

Long term complications

- Myelogenous leukemia (2% pts)

Average cumulative dose is 34 GBq; occurs between 3-7 yrs

- Anaplastic transformation (rare)
- Azoospermia
- Pulmonary fibrosis

Must be considered if lung metastases are treated with RIT

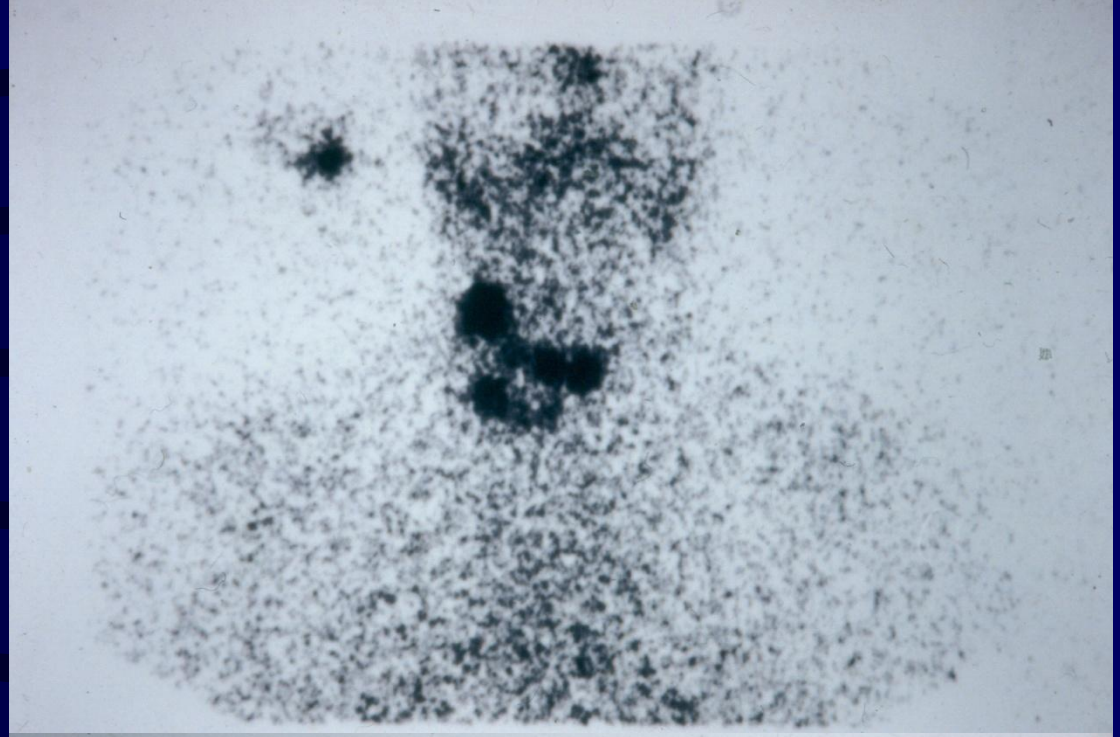
- Hyperparathyroidism

Success of Ablation

Successful remnant ablation is usually defined at 6-12 months after the therapy:

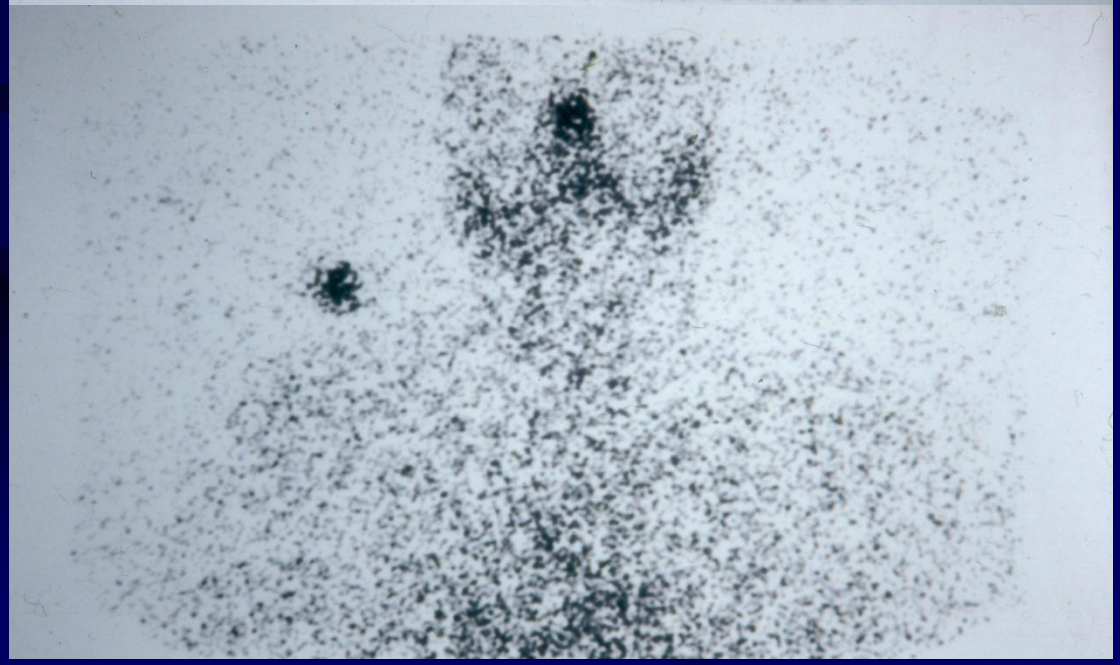
- Negative Dx WBS or thyroid bed uptake < 0.1%
- Absence of detectable TSH-stimulated Tg
  if TgAbs have been excluded
- Absence of suspicious US report

Pre ^{131}I Rx



1 year

Post ^{131}I Rx



CONCLUSIONS

- Radioiodine therapy is important part of the management of DTC (initial treatment and treatment of recurrence).
- It is a safe therapeutic procedure.
- Long-term monitoring in requested.