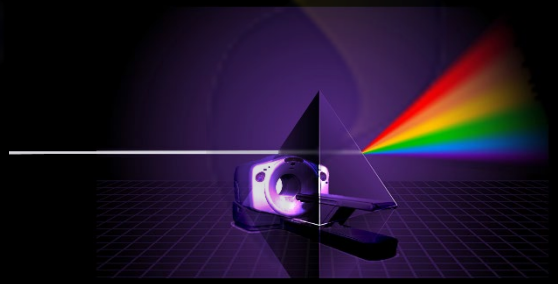
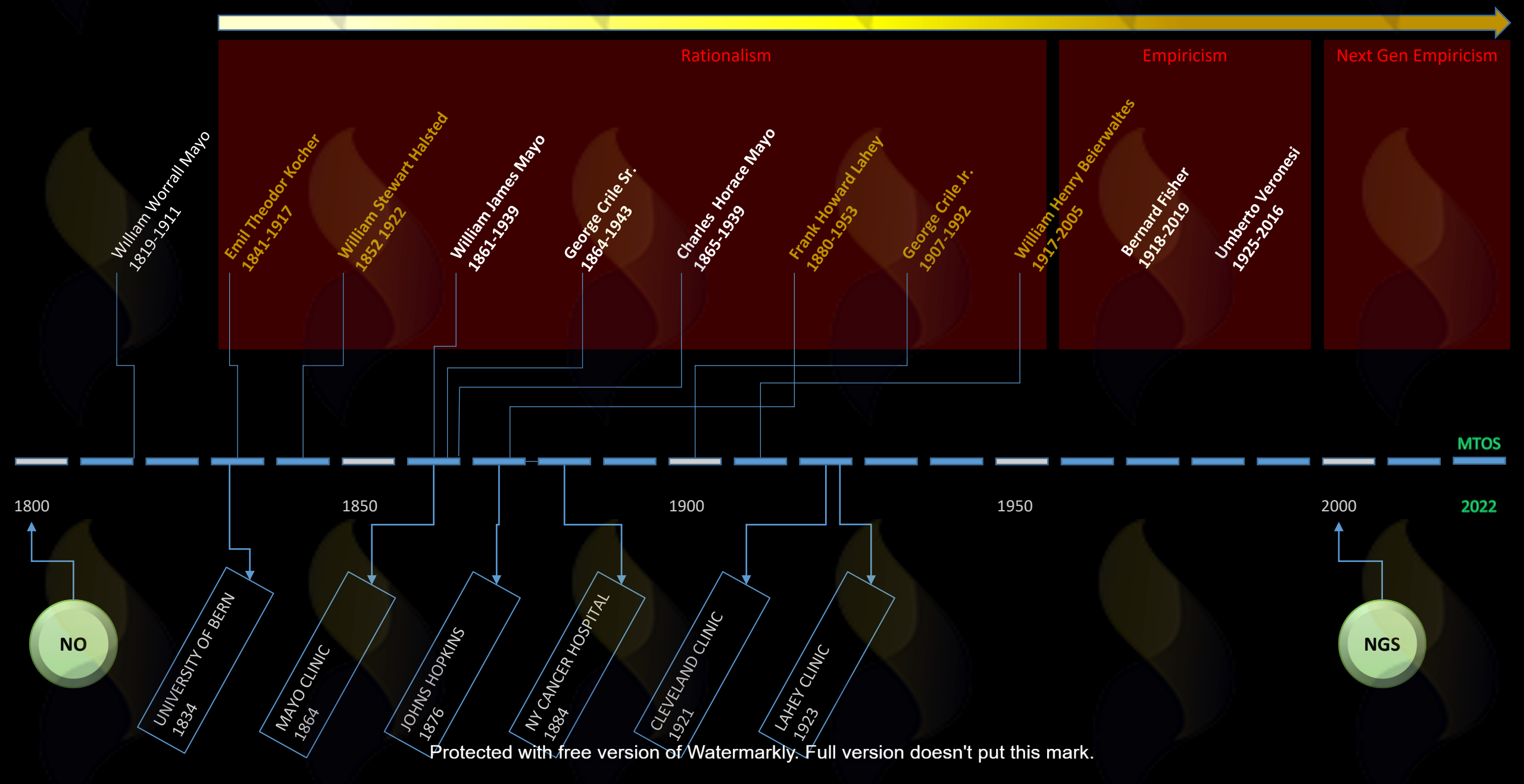


# Science of Thyroidectomy in the Molecular Theranostics Paradigm

*Seza Gulec*

*March 19, 2022*

# A brief history of knowledge of thyroidectomy



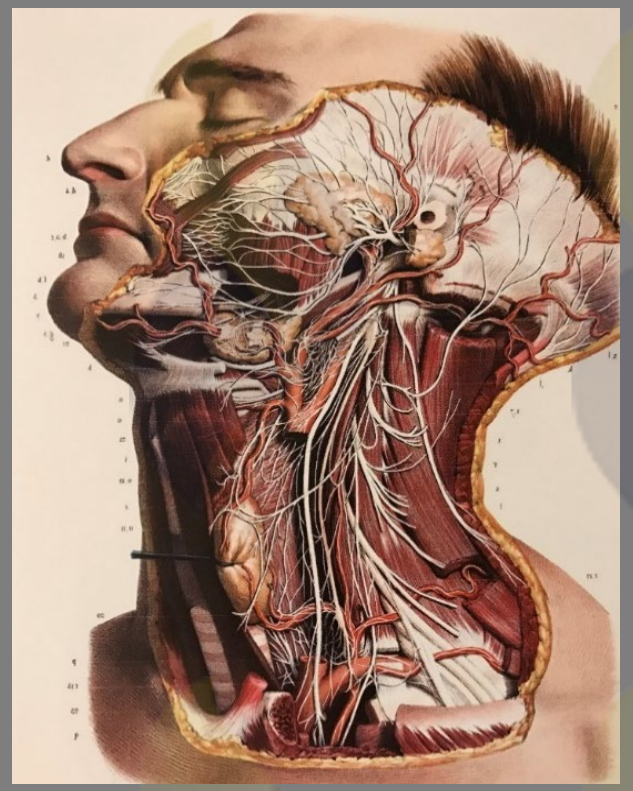
# *The Birth of Modern Thyroid Surgery, Theodor Kocher*

*Kocher, neat and precise, operating in a relatively bloodless manner, scrupulously removed the entire thyroid gland doing little damage outside its capsule… William Stewart Halsted, 1914*

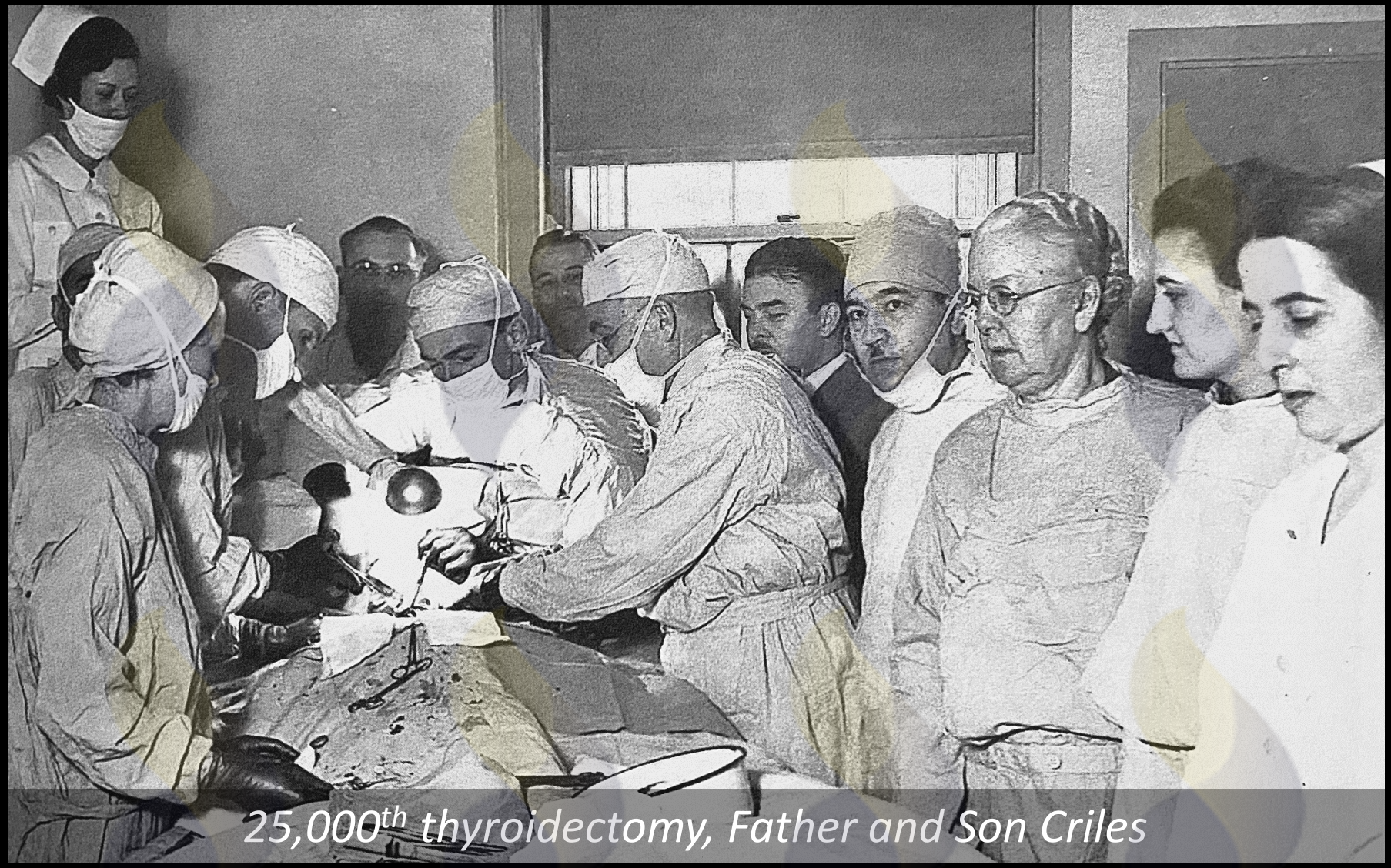
# *The Birth of Modern Surgical Oncology, William Halsted*

*Surgery of cancer is not the surgery of organs but their lymphatics… Berkeley G A Moynihan*

# *Radical Attack on Thyroid Cancer*

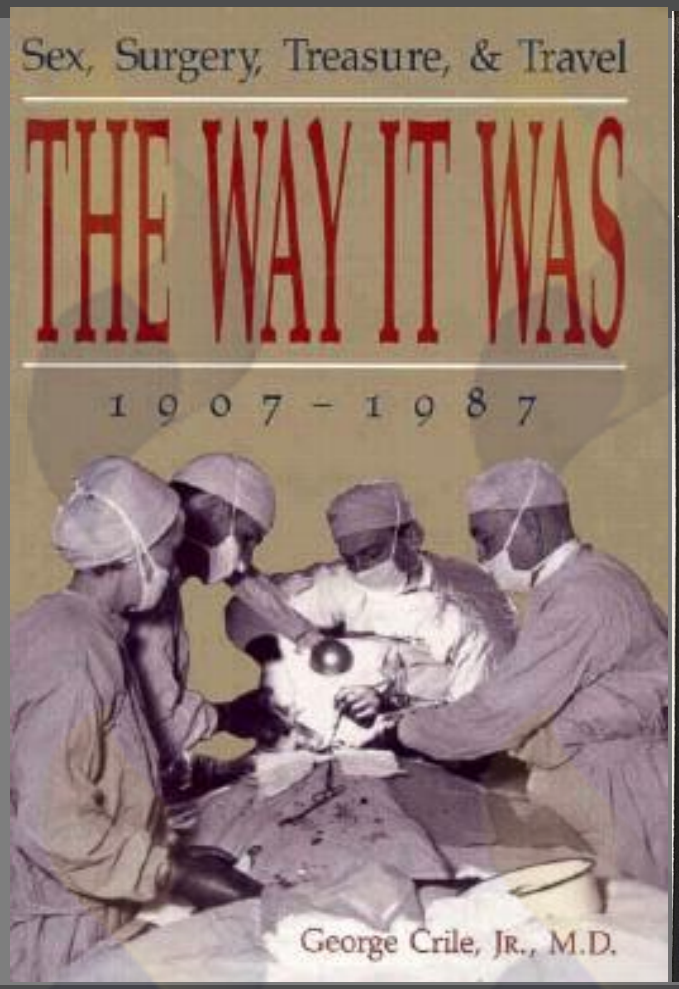


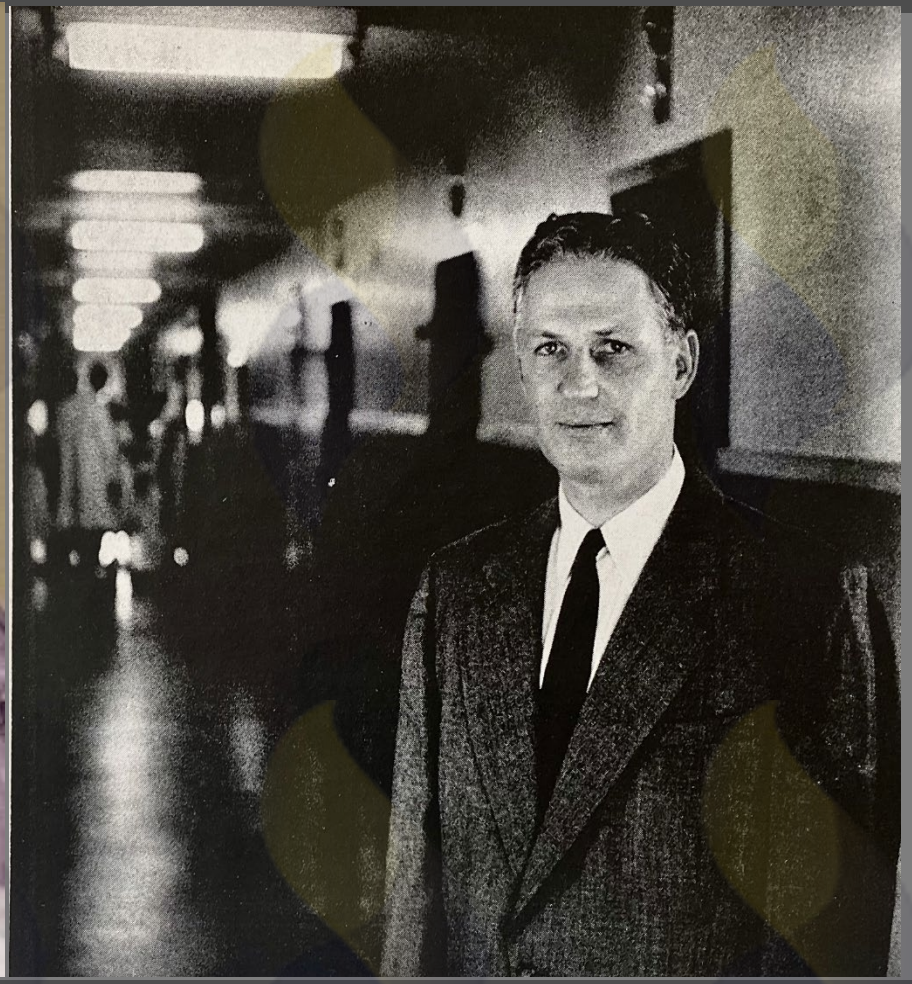
*Radical and extensive neck dissection should be done … Disfigurement is one of the prices patients must pay to obtain the benefits of the radicalness of the operative procedure …*
*When the carcinomatous adenoma has involved one lobe, it is unnecessary to perform a total thyroidectomy and remove the unaffected lobe…*



*25,000th thyroidectomy, Father and Son Criles*

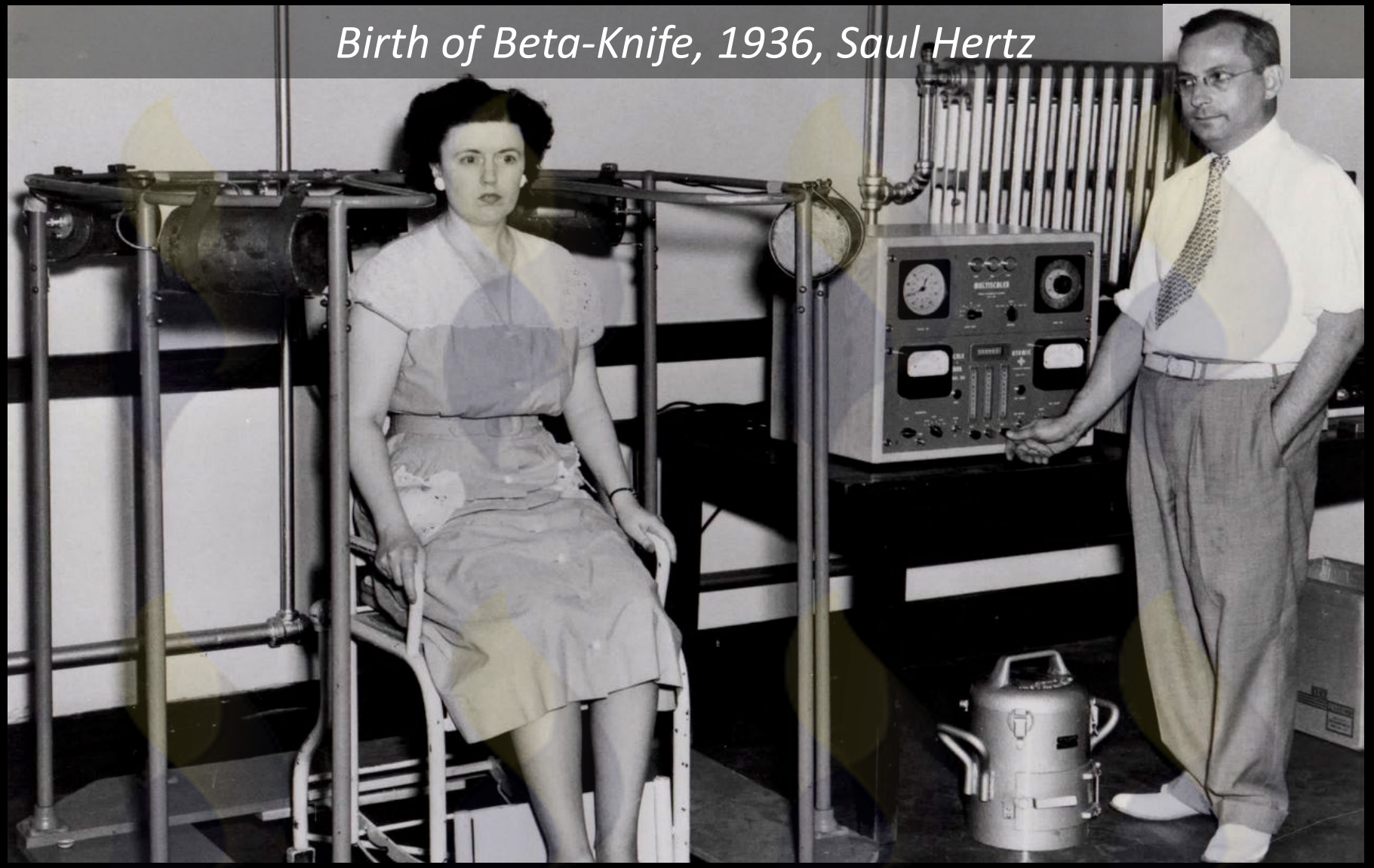
# “Radical attack” on radical surgery



*Radicality of the operation should be against the disease not to the patient…*

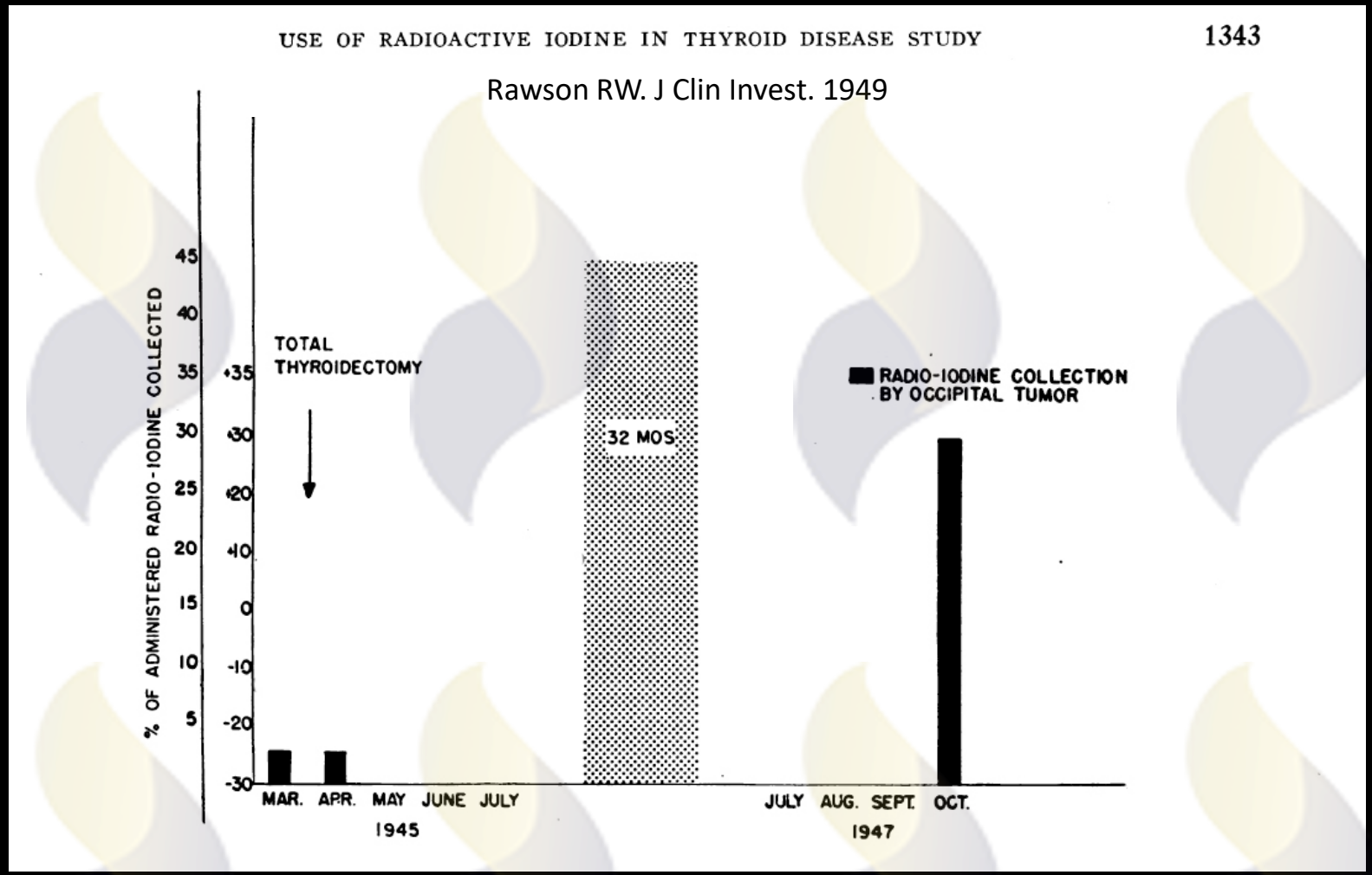
*Birth of Beta-Knife, 1936, Saul Hertz*



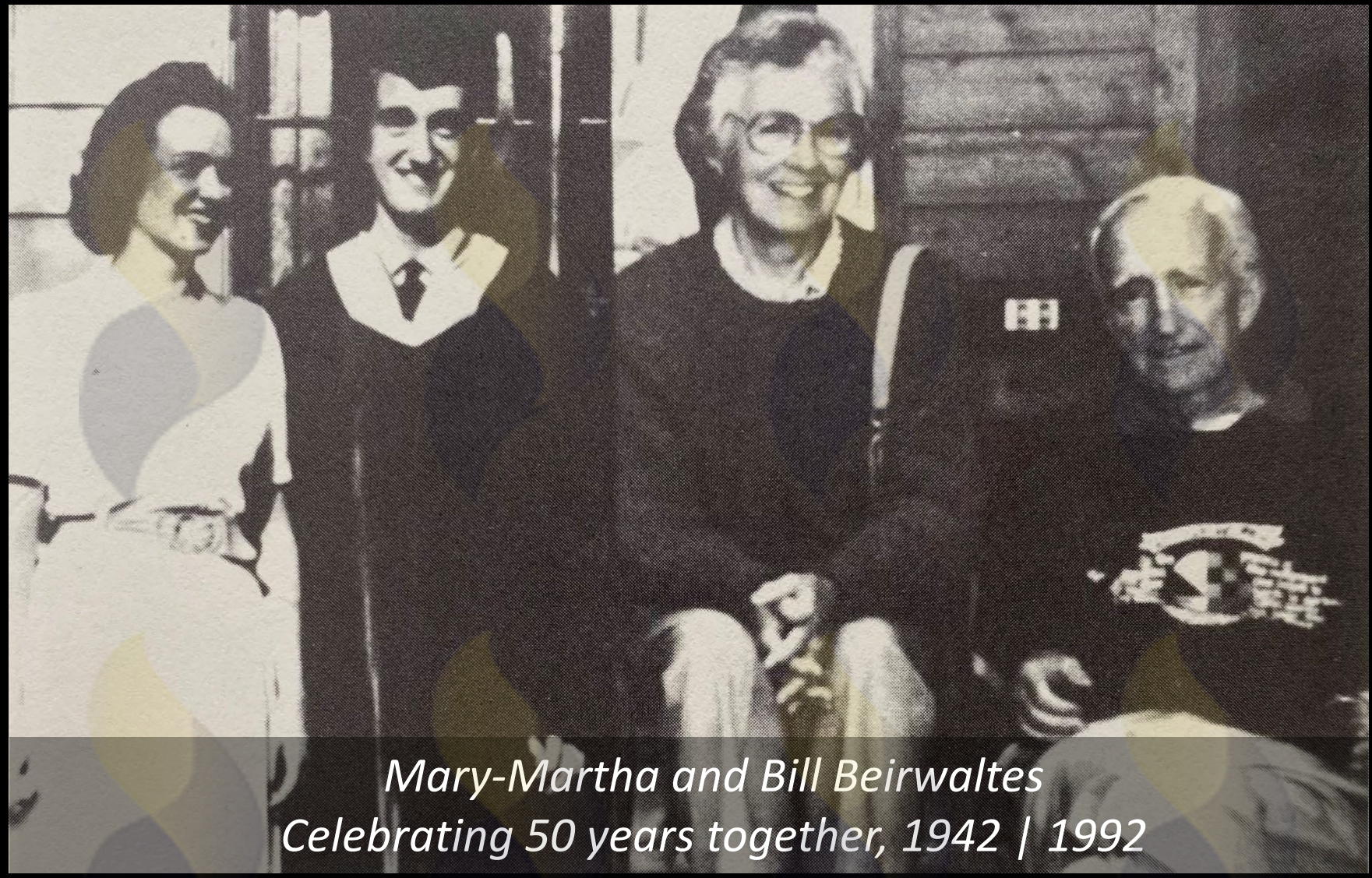
# *Beta Knife for Thyroid Cancer 1946, Seidlin*

*Certain tumor types do have limited capacity for retaining RAI. These iodide retaining types are the exception… Saul Hertz*

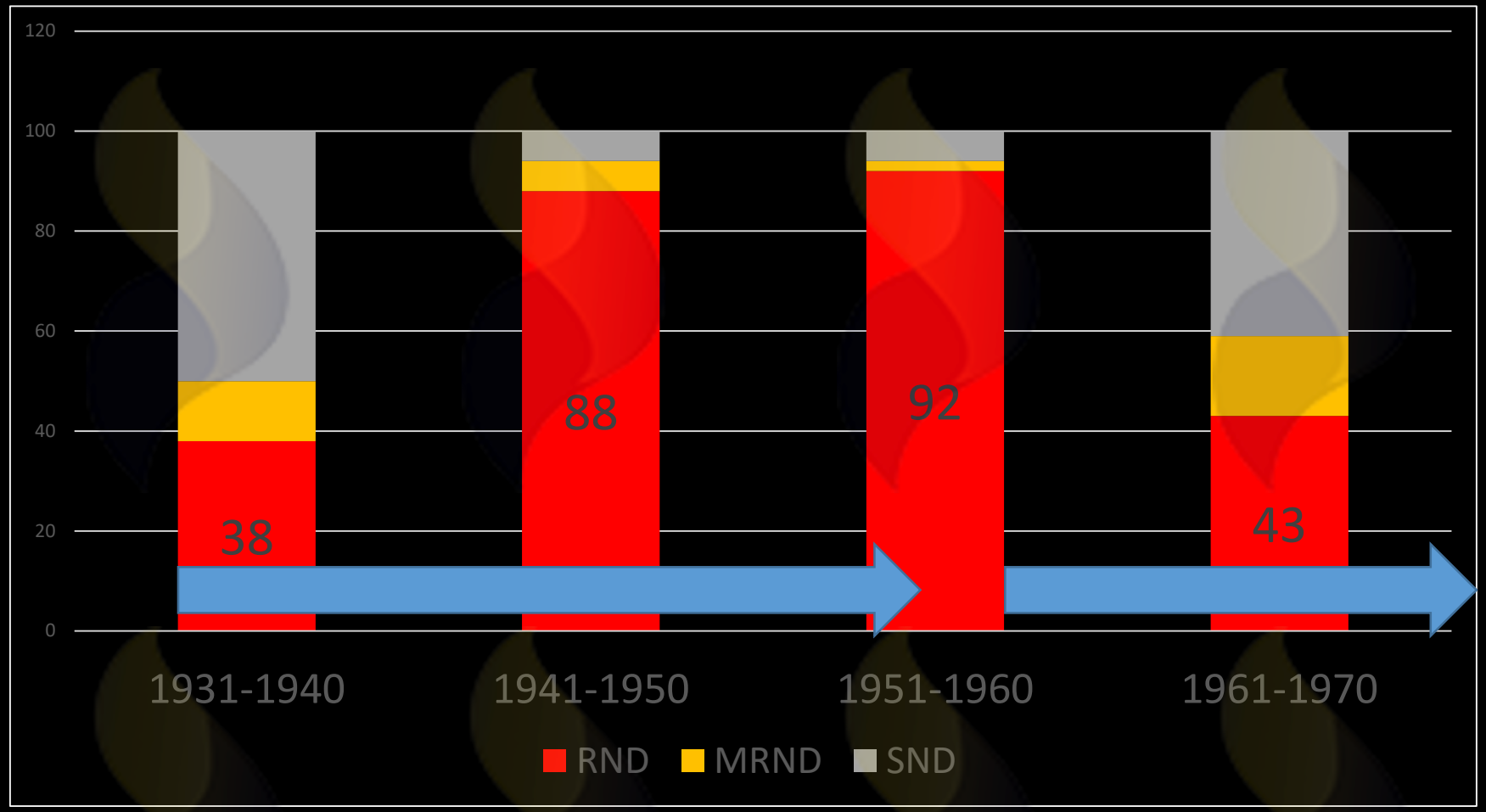
# *Beta-knife in Thyroid Cancer*




*Total thyroidectomy is the only measure proved to increase RAI uptake by metastases…*
*William H Beierwaltes*

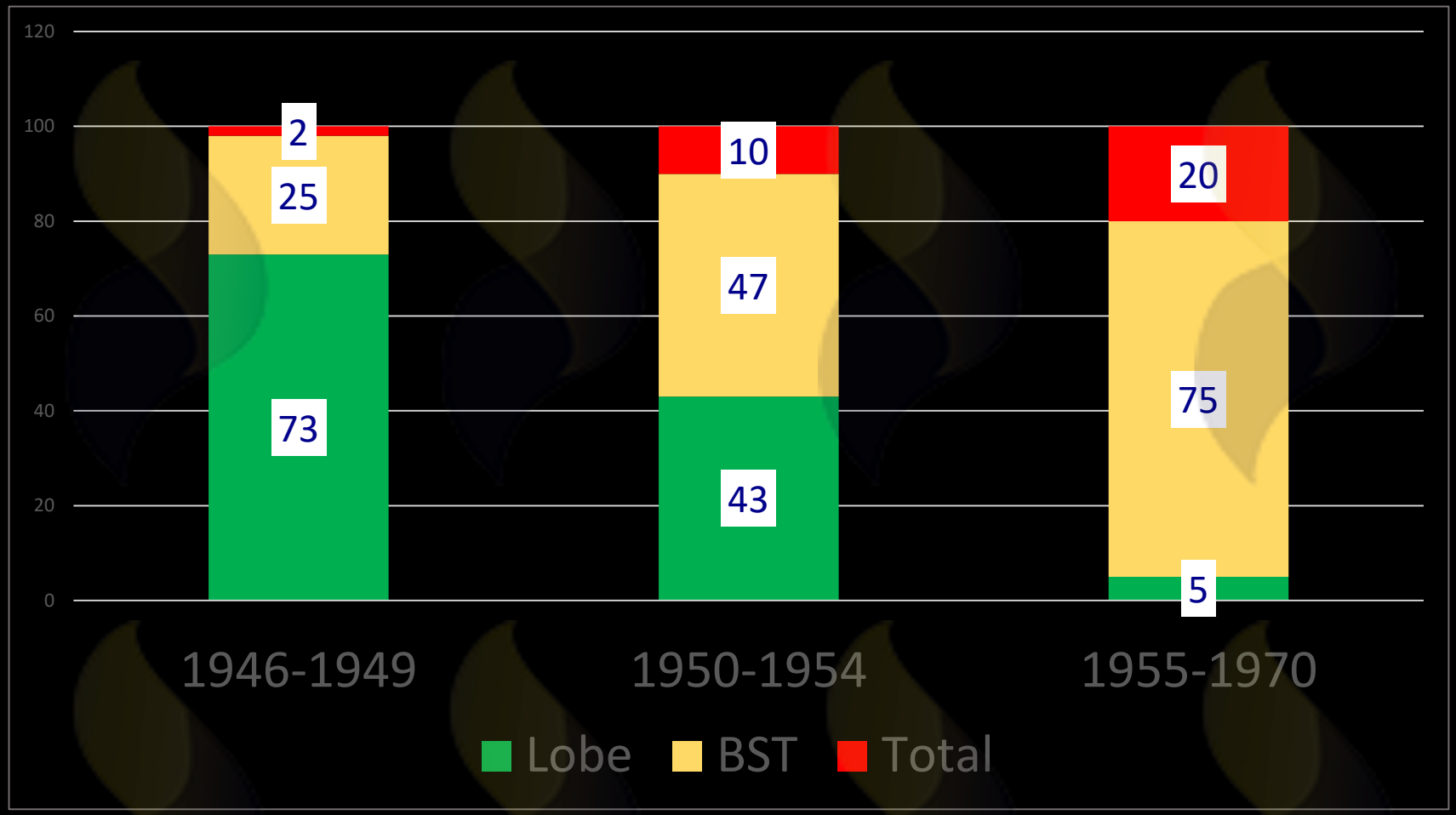


# Lahey v Crile Effect on Nodal Dissection




Lahey Clinic Data: 1930-1970_792 Patients

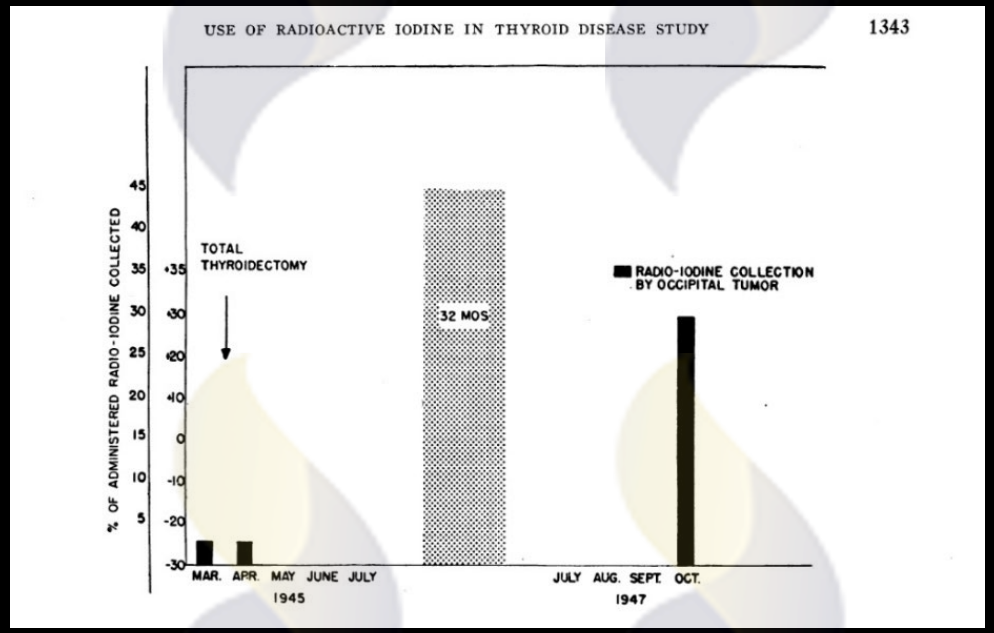
# Beierwaltes Effect on Thyroidectomy




Mayo Clinic Data: 1946-1970_859 Patients

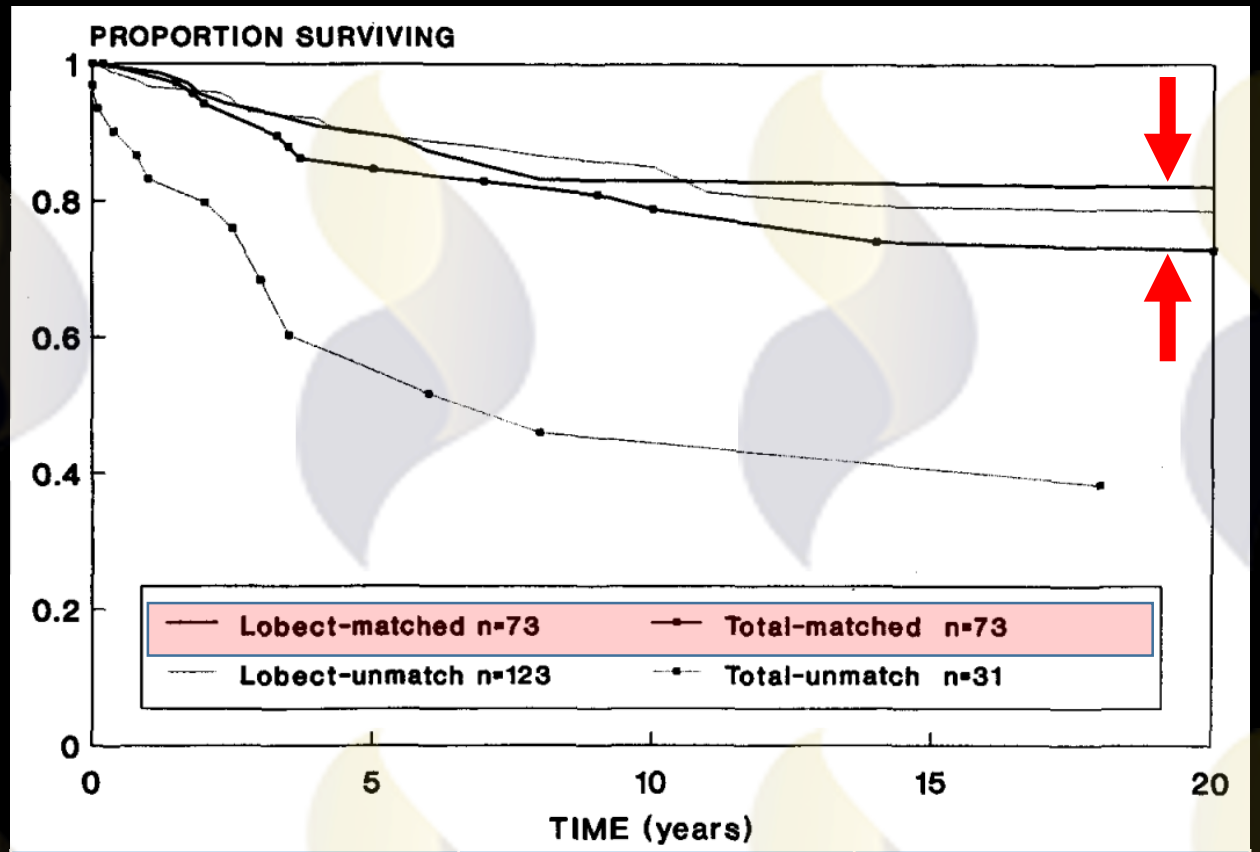
# Total Thyroidectomy | Complete Thyroidectomy

- Therapeutic significance of total thyroidectomy is indexed to RAI
- TT is performed to improve theranostic/therapeutic power of RAI
- TT alone does not have an intrinsic therapeutic advantage



# MSKCC, 1993, Shah, Matched-Pair Analysis

1930-1980, 931 patients 146 Patients Matched Pair (73|73)
PTC, Total thyroidectomy vs Lobectomy



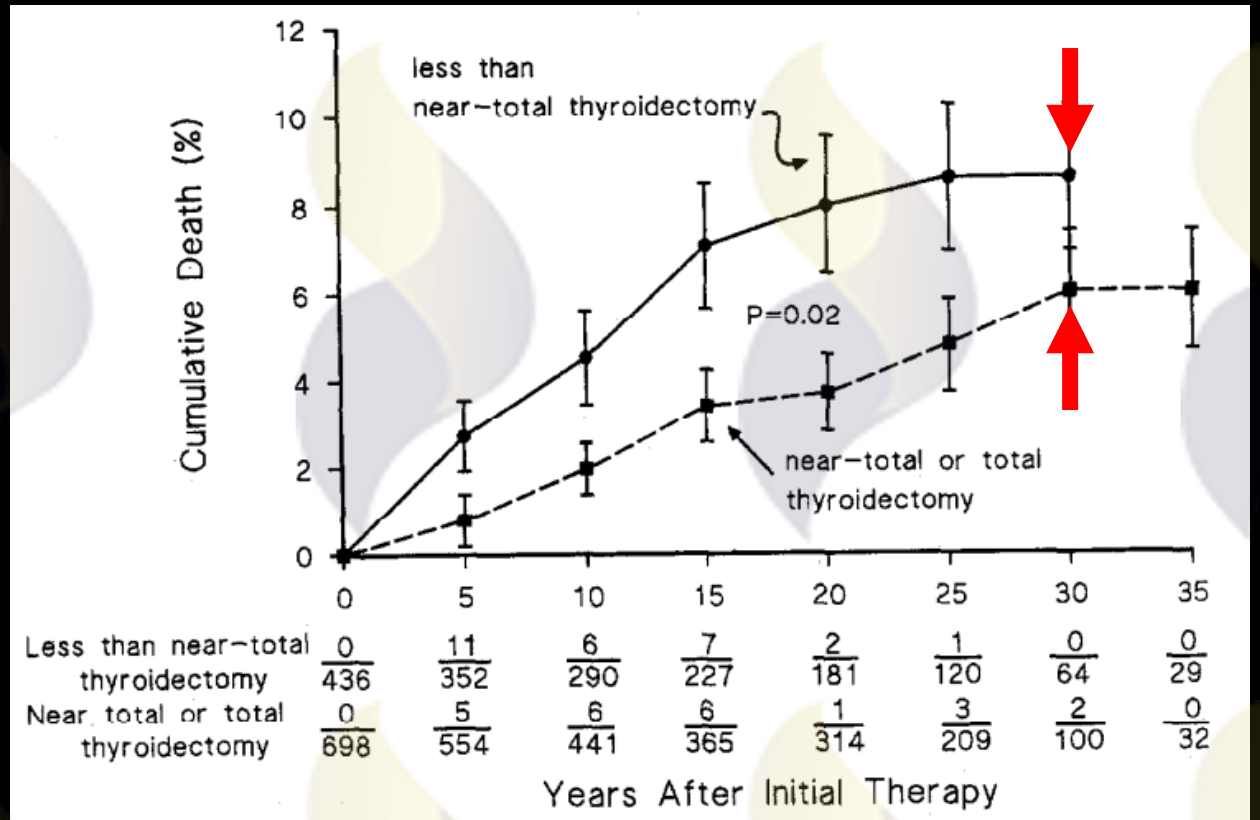

| Operation | Lobectomy | | Total Thyroidectomy |
|---|---|---|---|
| 20y survival | 82% | NS | 73% |
| Thyroidal recurrence | 7% | | 7% |
| Nodal recurrence | | | |



Shah J et al. Am J Surg. 1993; 166: 331

# USAF/OSU, 1994, Mazzaferri

1962-1992, 1335 patients Un-matched for risk category or RAI status
DTC, Total/Near-Total thyroidectomy vs Less than Total/Near-Total Thyroidectomy



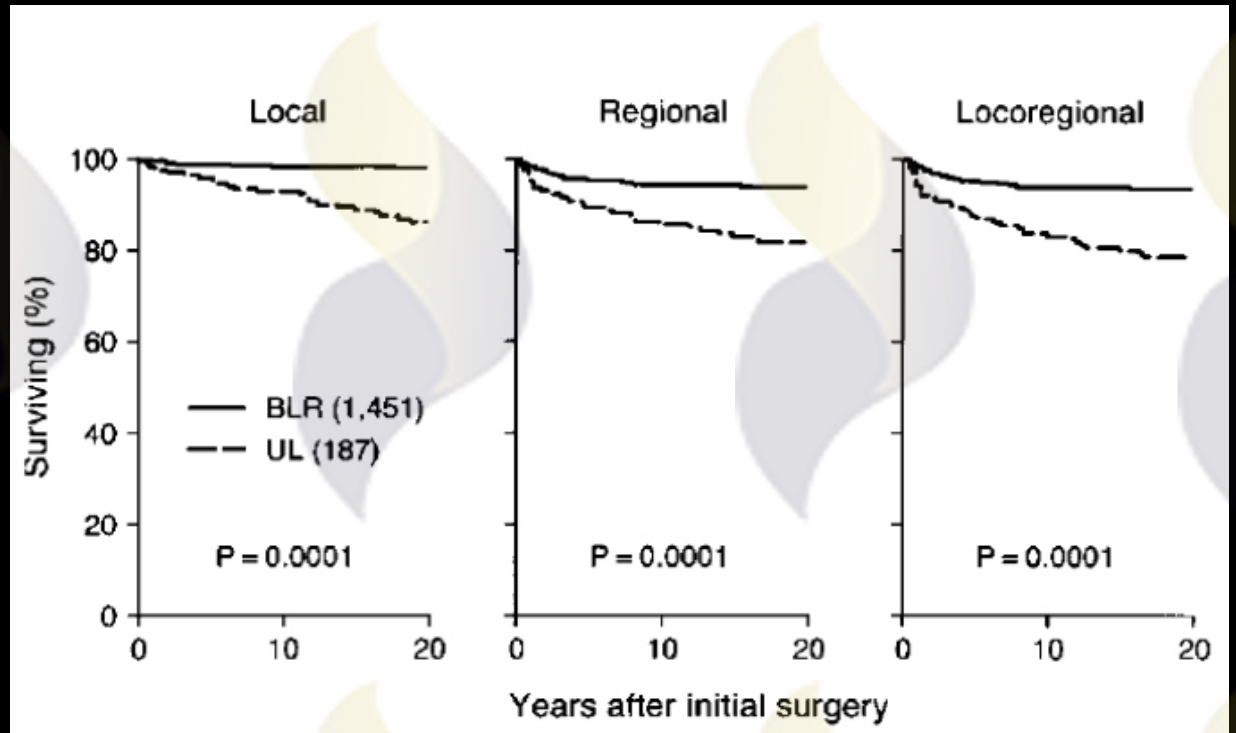

| Operation | < Total/Near-Total | | Total/Near-Total |
|---|---|---|---|
| 30y survival | 91% | P=0.02 | 94% |
| Thyroidal recurrence | 40% | | 26% |
| Nodal recurrence | | | |



Mazzaferri E et al. Am J Med. 1994; 97: 418

# Mayo, 1998, Hay

1940-1991, 1267 patients Matched for risk category (AMES Low-Risk) and RAI status (Non-RAI)
PTC, Lobectomy vs Total/Near-Total/Sub-TotalThyroidectomy




| Operation | Lobectomy | | Total Thyroidectomy |
|---|---|---|---|
| 20y survival | 98.7% | p=0.31 | 99.7% |
| Thyroidal recurrence | 14% | | 2% |
| Nodal recurrence | 19% | | 6% |



Hay ID et al. Surgery 1998; 124: 958

# NCDB, 2007, Bilimoria, North Western

1985-1998, 52,173 patients, Non-adjusted data
PTC, Lobectomy vs Thyroidectomy

- Data heterogeneity/inconsistency: 20 years, 1400 hospitals
  - Disease-specific
    - Unclear data on nodal dissection and node status
    - No histologic subtype information
    - No risk stratification data
  - Treatment-specific
    - Unclear data on RAI: 50% RAI Tx in TT, 20% RAI Tx TL groups
    - No data on TSH suppression
- No clear definition of recurrent disease

| Operation | Lobectomy | | Total Thyroidectomy |
|---|---|---|---|
| 10y survival | 97% | P<0.05 | 98% |
| Thyroidal recurrence | 10% | P<0.05 | 8% |
| Nodal recurrence | | | |



Bilimoria et al. Ann Surg. 2007; 246: 375

# NCDB, 2014, Adam, Duke

1998-2006, 61,775 patients, Data adjusted for demographics, clinical and pathologic factors
PTC, Lobectomy vs Thyroidectomy

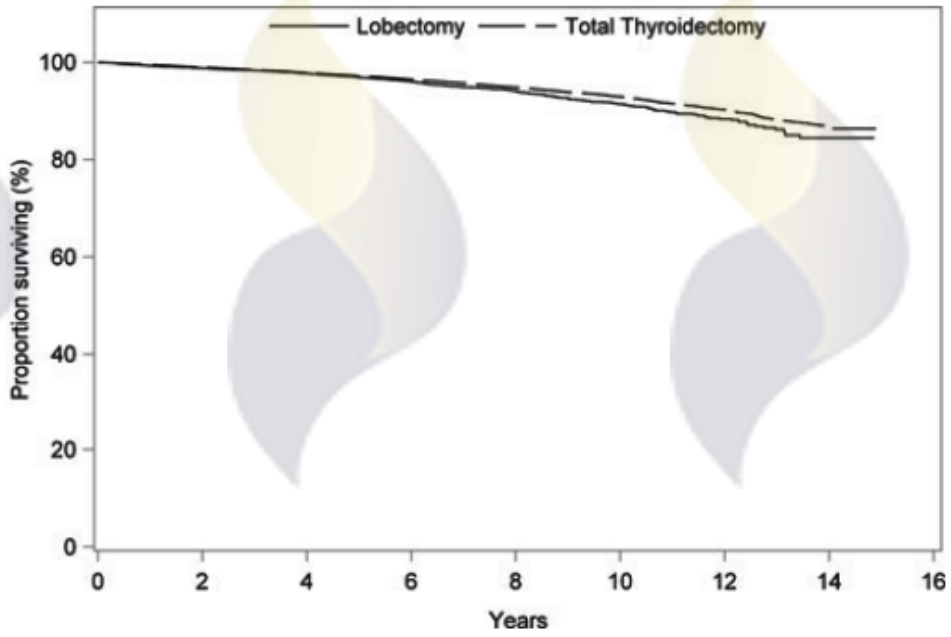



**FIGURE 1.** Unadjusted overall survival for patients undergoing total thyroidectomy versus lobectomy for PTC tumors 1.0–4.0 cm.

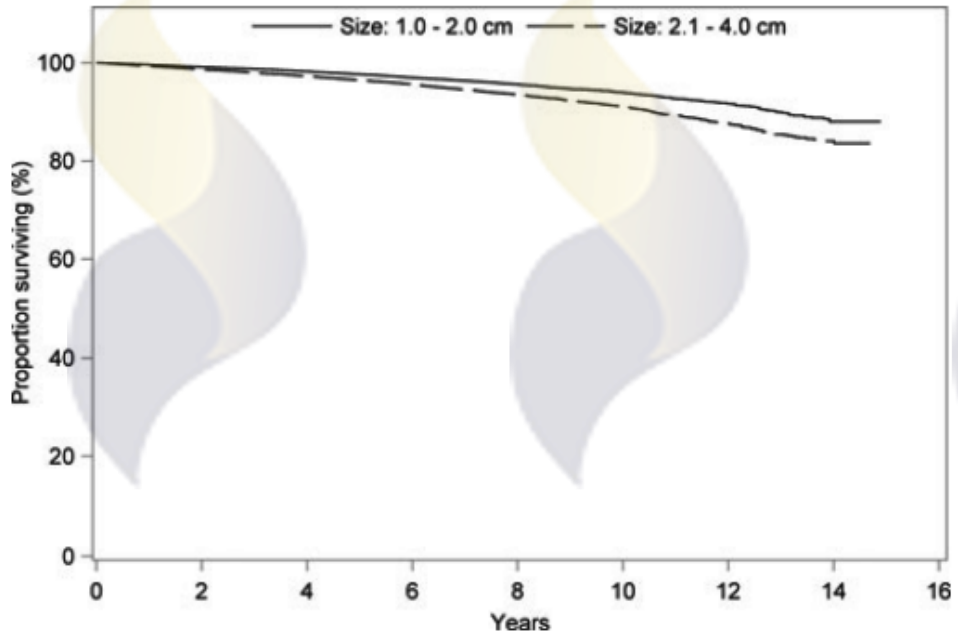



**FIGURE 2.** Unadjusted overall survival for patients with PTC tumors 1.0–2.0 cm versus 2.1–4.0 cm.

| Operation | Lobectomy | Total Thyroidectomy |
|---|---|---|
| 10y survival | 94%[1-2cm] 91%[2-4cm] | 94%[1-2cm] 91%[2-4cm] |
| Thyroidal recurrence | N/R | N/R |
| Nodal recurrence | | |

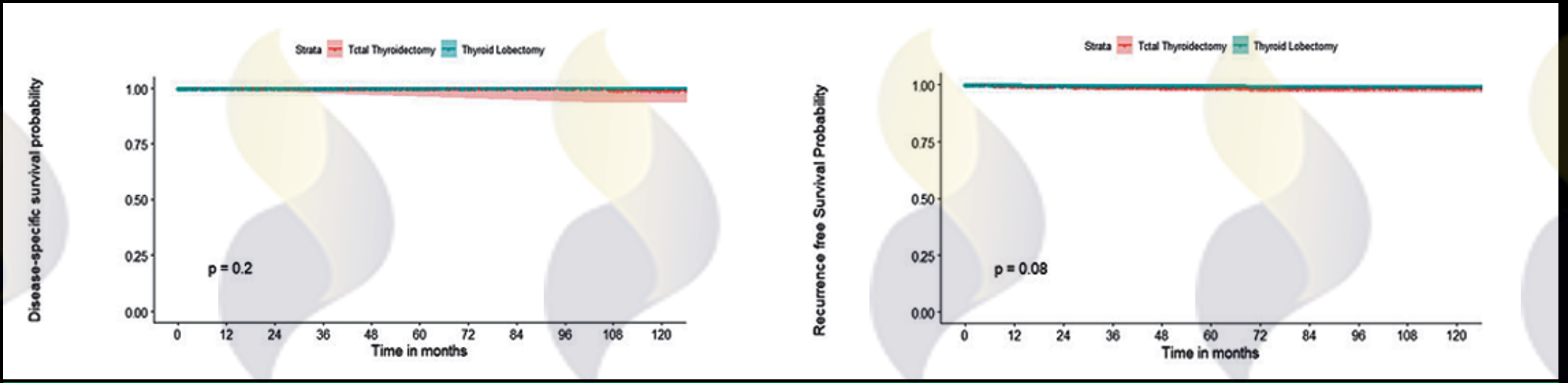


Adam et al. Ann Surg. 2014; 260: 601

# MSKCC, 2022, Matsuura, Propensity Matching Analysis

1930-1980, 1836 patients Matched Pair (918|918)

PTC, [T1/T2-N0/NX], Total thyroidectomy vs Lobectomy




- Standard surgical treatment
- Clear definition of recurrent disease: Structural abnormality by imaging, confirmed by Biopsy
  - Local recurrence: Thyroid bed/soft tissues OR Newly identified Dz in the contralateral lobe
  - Regional recurrence: Nodal disease, central compartment or lateral neck
- Propensity score matching:
  - Age | Sex | Histology | RAI | ATA risk group | pT stage | pN stage

| Operation | Lobectomy | | Total Thyroidectomy |
|---|---|---|---|
| 10y Overall Survival | 92% | NS | 91% |
| 10y Disease-specific Survival | 100% | | 99% |
| Recurrence | 0.05% | | 1.1% |



Matsuura et al. Thyroid 2022; 32: 28

Hay ID, MAYO [AMES]
Surgery. 1987 Dec;102(6):1088

Shah JP, MSKCC
Am J Surg. 1992 Dec;164(6):658

ATA 2015

**High Risk**
*Gross extrathyroidal extension, incomplete tumor resection, distant metastases, or lymph node >3 cm*

**Intermediate Risk**
*Aggressive histology , minor extrathyroidal extension, vascular invasion, or > 5 involved lymph nodes (0.2-3 cm)*

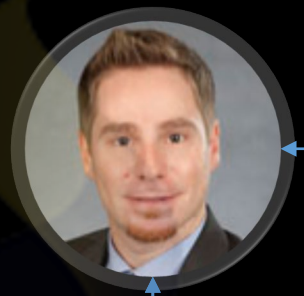
**Low Risk**
*Intrathyroidal DTC ≤ 5 LN micrometastases (< 0.2 cm)*

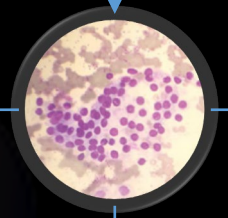
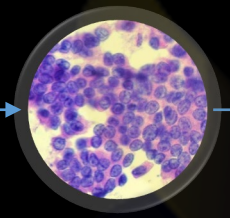
- FTC, extensive vascular invasion (≈ 30-55%)
- pT4a gross ETE (≈ 30-40%)
- pN1 with extranodal extension, >3 LN involved (≈ 40%)
- PTC, > 1 cm, TERT mutated ± BRAF mutated* (>40%)
- pN1, any LN > 3 cm (≈ 30%)
- PTC, extrathyroidal, BRAF mutated*(≈ 10-40%)
- PTC, vascular invasion (≈ 15-30%)
- Clinical N1 (≈20%)
- pN1, > 5 LN involved (≈20%)
- Intrathyroidal PTC, < 4 cm, BRAF mutated* (≈10%)
- pT3 minor ETE (≈ 3-8%)
- pN1, all LN < 0.2 cm (≈5%)
- pN1, ≤ 5 LN involved (≈5%)
- Intrathyroidal PTC, 2-4 cm (≈ 5%)
- Multifocal PTMC (≈ 4-6%)
- pN1 without extranodal extension, ≤ 3 LN involved (2%)
- Minimally invasive FTC (≈ 2-3%)
- Intrathyroidal, < 4 cm, BRAF wild type* (≈ 1-2%)
- Intrathyroidal unifocal PTMC, BRAF mutated*, (≈ 1-2%)
- Intrathyroidal, encapsulated, FV-PTC (≈ 1-2%)
- Unifocal PTMC (≈ 1-2%)

Tuttle, MSKCC
J Clin Endocrinol Metab. 2019 Mar 15;104(9):4087

# Almighty Nodule

FNA
Cytology



Molecular Testing

- **BRAF mutation**
  - 100% PTC
- **RAS mutations**
  - 100% Neoplasia
    - 50% FC or PTC –fv
    - 50% NIFTP or Adenoma
- Other mutations
- CNA
- **Gene Expression Profile** TDS

Afirma
THYROID FNA ANALYSIS

ThyroSeq®
Thyroid Genomic Classifier

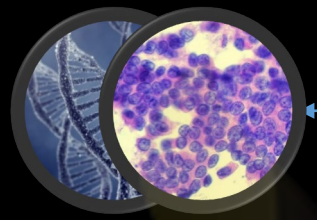
ThyGeNEXT®
THYROID ONCOGENE PANEL

ThyraMIR®
THYROID miRNA CLASSIFIER

DTC

Pre-operative Risk Assessment

Clinical Profile



Low-Risk

Molecular Profile

$BRAF_{V600}$ mutation

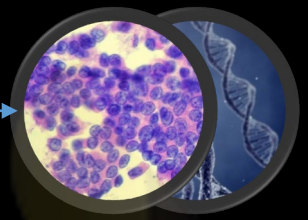
RAS mutations

Other mutations

CNA

**Gene Expression Profile**

TDS



High-Risk

Lobectomy

Total Thyroidectomy

Post-operative Risk Assessment

RAI

Post-RAI Risk Assessment

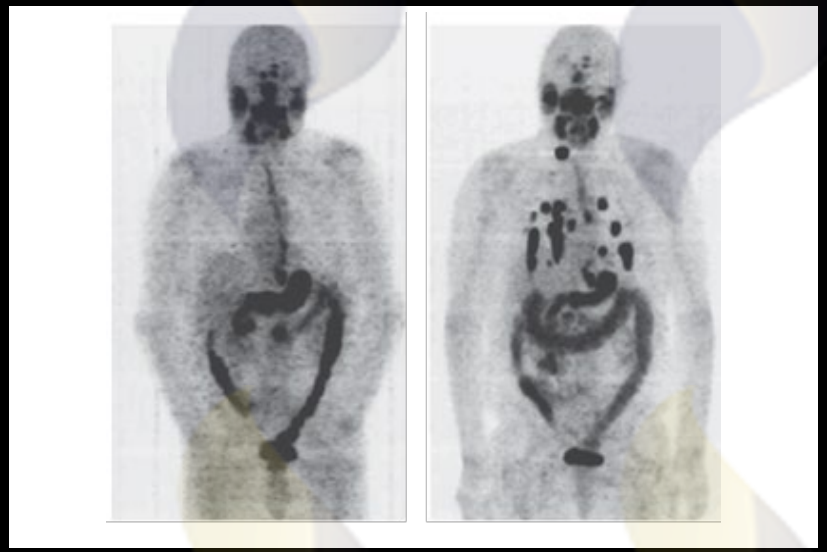
Follow-up

Dynamic Track

# Risk Stratification | Theranostic Risk Stratification

# Total Thyroidectomy | Complete Thyroidectomy

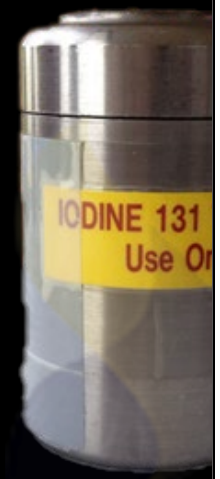
- Therapeutic significance of total thyroidectomy is indexed to RAI
- TT is performed to improve theranostic/therapeutic power of RAI
- RAI is the only effective systemic treatment for metastatic or high-risk thyroid cancer
  - Theranostic value of RAI established in 1940
  - Theranostic power of RAI attenuated in Thy Ca
    - Needs to be evaluated preoperatively
    - Restoration involves modulation of ERK output
    - Applies therapy for metastases and adjuvant therapy
    - Molecular testing is theranostic for surgery and RAI
- RAI ablation completes total thyroidectomy
- RAI ablation facilitates f/u evaluations

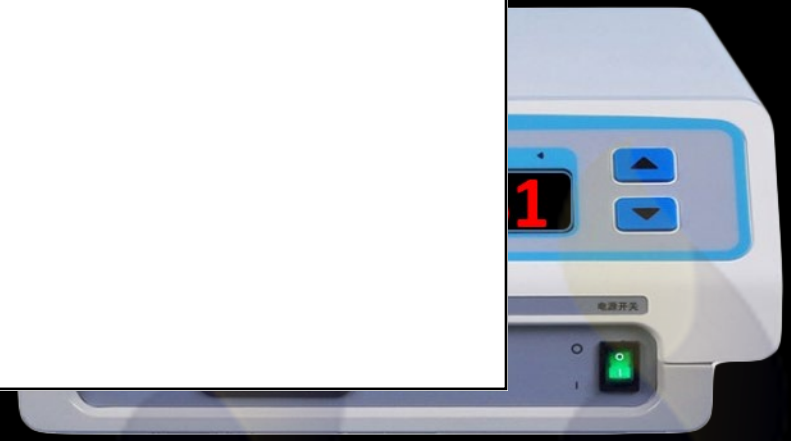


# Risk Stratification | Theranostic Risk Stratification

- Need to identify high-risk disease
  - Current wisdom dictates TT followed by RAI in high-risk disease
- Theranostic power of RAI is depressed in high-risk disease
  - Need to determine the theranostic power of RAI
  - Therapeutic value of TT is poor without optimized RAI theranostic power
- RAI refractoriness is RAI indifference of “mis-differentiated” thyroid cancer
  - Reinstate differentiation
- RAI is the only effective systemic treatment for metastatic or high-risk thyroid cancer

# Coupling of RAI with Total Thyroidectomy



*The rationale for total thyroidectomy is to increase RAI uptake  by metastases…*