Definition of Risk in the Management of Differentiated Thyroid Carcinoma

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Arcispedale S. Maria Nuova Reggio Emilia
Prognostic indicators in differentiated thyroid carcinoma

The biology of thyroid cancer represents a spectrum of behavior ranging from well differentiated thyroid lesions with an excellent prognosis to anaplastic carcinoma. It is important that clinicians have methods at their disposal to assess the behavior of a patient’s thyroid malignancy.

DS Dean & ID Hay, Cancer Control 2000
Accurate prognostic assessment of DTC patients is fundamental, in order to:

- Define an appropriate treatment strategy
  conservative vs extensive surgery
  indication to $^{131}$I ablation treatment

- Define an appropriate follow-up strategy

  Avoid potentially harmful and morbid measures
  Avoid waste of resources
The practical problems associated with risk management

- Two basic questions: who is at risk and risk of what?
- Obtaining current data useful to calibrate models and doing actual risk comparisons
- Persuading people to balance risks, rather than passively assume traditional concepts, habits, procedures
From data analysis to operational models

• 1. Obtaining data to calibrate models.
  Large retrospective studies → univariate and multivariate analysis of different risk factors → elaboration of scoring systems

• 2. Doing actual risk comparisons
  Validation and comparison of different scoring systems in DTC patient populations
Risk assessment in the patient with DTC: the available scoring systems

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC</td>
<td>European Organization for Research and Treatment of Cancer, 1979</td>
</tr>
<tr>
<td>AGES</td>
<td>Mayo Clinic, Rochester, 1987</td>
</tr>
<tr>
<td>MACIS</td>
<td>Mayo Clinic, Rochester, 1993</td>
</tr>
<tr>
<td>AMES</td>
<td>Lahey Clinic Foundation, Boston, 1988</td>
</tr>
<tr>
<td>EOD</td>
<td>Extent of Disease; University of Chicago, 1990</td>
</tr>
<tr>
<td>OSU</td>
<td>Ohio State University, Columbus, 1994</td>
</tr>
<tr>
<td>MSKCC</td>
<td>Sloan Kettering Centre, New York, 1995</td>
</tr>
<tr>
<td>NCTCS</td>
<td>National Cancer Treatment Cooperation Study, 1998</td>
</tr>
</tbody>
</table>
### AMES
312 DTC patients

( Lahey Clinic Foundation, Boston 1960-1981)

<table>
<thead>
<tr>
<th>Low risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger patients (men ≤ 40, women ≤ 50) M0</td>
<td>All patients M+</td>
</tr>
<tr>
<td>Older patients if intrathyroid PTC,</td>
<td>Older patients if</td>
</tr>
<tr>
<td>minimally invasive FTC</td>
<td>- Extrathyroid PTC</td>
</tr>
<tr>
<td>Primary cancer &lt; 5 cm</td>
<td>- FTC major capsular invasion</td>
</tr>
<tr>
<td>No distant metastases</td>
<td>- Primary cancer ≥ 5 cm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk class</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 yr Survival</td>
<td>99.2%</td>
<td>46%</td>
</tr>
</tbody>
</table>

Cady & Rossi Surgery 104: 947, 1988
**MACIS SCORE**
1779 PTC patients
( Mayo Clinic 1940-1989)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>distant Metastasis:</td>
<td>yes = 3 no = 0</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>&lt;40 years = 3.1 ≥ 40 = 0.08 x age</td>
</tr>
<tr>
<td>inComplete resection:</td>
<td>yes = 1 no = 0</td>
</tr>
<tr>
<td>Invasion:</td>
<td>yes = 1 no = 0</td>
</tr>
<tr>
<td>Size of tumor</td>
<td>0.3 x size in cm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MACIS Score</th>
<th>&lt; 6.0</th>
<th>6.0 - 6.99</th>
<th>7.0 - 7.99</th>
<th>&gt; 8.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 yr Survival</td>
<td>99%</td>
<td>89%</td>
<td>56%</td>
<td>24%</td>
</tr>
</tbody>
</table>

*Hay et al., Surgery 1993; 114:1050-1058*
**MSKCC (Games)**

n = 1038 DTC patients
(Memorial Sloan Kettering 1930-1985)

<table>
<thead>
<tr>
<th></th>
<th>LOW</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>&lt;45</td>
<td>&lt;45</td>
<td>&gt;45</td>
</tr>
<tr>
<td><strong>M0/M1</strong></td>
<td>M0</td>
<td>M1</td>
<td>M0</td>
</tr>
<tr>
<td><strong>T (size/extracaps)</strong></td>
<td>T1/T2</td>
<td>T3/T4</td>
<td>T1-T2</td>
</tr>
<tr>
<td><strong>Histology and Grade</strong></td>
<td>PTC</td>
<td>FTC and/or high grade</td>
<td>PTC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk class</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
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<tbody>
<tr>
<td><strong>20 yr Survival</strong></td>
<td>99%</td>
<td>85%</td>
<td>57%</td>
</tr>
</tbody>
</table>

*Shaha et al., Surgery 1994; 116:1036-1041*
### UICC/AJCC (TNM) Staging System

**n = 700 DTC patients**

(University of California, 1970-1995)

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Age &lt; 45 years</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Age ≥45 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>any T</td>
<td>any N</td>
<td>M0</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>any T</td>
<td>any N</td>
<td>M1</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td>T4 or N1b or M1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival rate follow-up 11.3 year</td>
<td>98.3%</td>
<td>84.2%</td>
<td>70.0%</td>
<td>38.1%</td>
</tr>
</tbody>
</table>

*Loh et al., JCE&M 1997, 82:3553-62*
Comparing the Performance of different DTC Scoring Systems

<table>
<thead>
<tr>
<th>Criterium</th>
<th>Best performing scoring systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectivity in detecting high-risk population</td>
<td>MACIS, AMES, TNM, EORTC</td>
</tr>
<tr>
<td>Mortality rate in high vs. low-risk patients</td>
<td>MACIS, AMES, EORTC, Ohio, TNM, EOD</td>
</tr>
<tr>
<td>Survival rate among different risk classes</td>
<td>TNM, Ohio, EORTC, EOD</td>
</tr>
</tbody>
</table>

*Brierley et al., Cancer 1997*
# RISK OF DEATH IN DTC PATIENTS

## TABLE II.
Differentiated Carcinoma of Thyroid: Impact of Risk Groups on Survival.

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>No. (%)</th>
<th>Death Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memorial⁸</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>403 (39)</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>403 (39)</td>
<td>13</td>
</tr>
<tr>
<td>High risk</td>
<td>232 (22)</td>
<td>54</td>
</tr>
<tr>
<td>Mayo⁷</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>737 (86)</td>
<td>2</td>
</tr>
<tr>
<td>High risk</td>
<td>121 (14)</td>
<td>46</td>
</tr>
<tr>
<td>Lahey⁶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>277 (89)</td>
<td>1.8</td>
</tr>
<tr>
<td>High risk</td>
<td>33 (11)</td>
<td>46</td>
</tr>
</tbody>
</table>

Shaha et al., Laryngoscope 2004, 114:393-402
Risk group distribution for low-risk thyroid cancer

Low Risk Thyroid Cancer

- Local rec: 5%
- Reg rec: 10%
- Dist mets: 2%
- 5 yr surv: 100%
- 20 yr surv: 99%
- DOD: 1%

Shaha, Laryngoscope, 2004; 114:393-402
Lower locoregional control in patients with PTC

(difference not statistically significant – $p = 0.19$)

Clark et al. Laryngoscope 2005, 115:661-667
Some Limitations of the available scoring systems 1.

- Definition of low vs. high risk patients is not always consistent among different scoring systems.
- Scoring systems may not reflect the actual clinical presentation of patients with DTC.
- They do not consider the impact of early diagnosis and therapy on DTC outcome:

  Most DTC patients nowadays have a stage I/II disease and the proportion of high risk patients is supposed to be small.
Some Limitations of the available scoring systems 2.

- Insufficient “risk of what?” definition

Risk of loco regional metastasis
Risk of distant metastasis

Risk of disease recurrence
Risk of death
Towards a dynamic definition of Low-risk DTC: the pyramid paradygm
Definition of risk in DTC: operational settings

1. Pre-surgical setting
   Patient-related factors: Age/sex – clinical history
   Tumor-related factors: US and cytological findings

2. Post surgical setting
   Tumor-related factors: Histological findings
   Thyroglobulin levels
   Negative US imaging

3. Post $^{131}$I ablative setting
   Thyroglobulin levels
   WBS and other imaging studies
Defining of Low-risk DTC in the pre-surgical setting

$\leq 1 \text{ cm } \emptyset$ tumor (cytological pattern of PTC or follicular neoplasm) without US evidence of capsular involvement, multifocality and neck node metastasis
1. Pre-surgical setting

US findings

Size

Multifocality/Bilaterality ?

Extracapsular extension/invasiveness ?

Neck lymph node metastases ?
Histological indexes of aggressiveness in a series of $\leq 1$ cm $\varnothing$ DTC

- Bilateral: 32%
- Multifocal: 45%
- N1: 16%
- Extracapsular: 25%
Capsular invasion?
# Tumor-related factors in M1 vs. M0 patients

<table>
<thead>
<tr>
<th></th>
<th>M1</th>
<th>M0</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTC:FTC</td>
<td>76:24</td>
<td>85:15</td>
<td>NS</td>
</tr>
<tr>
<td>Histol. var.</td>
<td>23.5%</td>
<td>(5-10%)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Size</td>
<td>38±32 mm</td>
<td>22±13 mm</td>
<td>0.003</td>
</tr>
<tr>
<td>% Multifocal</td>
<td>50</td>
<td>38</td>
<td>NS</td>
</tr>
<tr>
<td>% ETE</td>
<td>57%</td>
<td>7.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>%N1</td>
<td>57%</td>
<td>26%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tg level</td>
<td>141±119</td>
<td>24.8±62.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Clark et al., Laryngoscope 2005, 115:661
DTC Survival by different prognostic factors

Shaha, Laryngoscope 2004, 114:393-402
Pre-surgical lymph node assessment in DTC: false negative US results

<table>
<thead>
<tr>
<th>Site of FN US</th>
<th>DTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>151</td>
</tr>
<tr>
<td>FN US</td>
<td>47</td>
</tr>
<tr>
<td>Central</td>
<td>43</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>5</td>
</tr>
<tr>
<td>Controlateral</td>
<td>3</td>
</tr>
</tbody>
</table>

US sensitivity in detecting central compartment lymph node metastases = 52%

*Kouvaraki et al., Surgery 2003 134:946-954*
Pitfalls in the pre-surgical prognostic assessment

• US cannot reliably detect extracapsular extension
• US/FNA cannot reliably detect mutifocality
• US cannot reliably detect metastatic lymph nodes in the central compartment
• Cytological examination cannot identify more aggressive DTC variants
Towards a dynamic definition of Low-risk DTC: the pyramid paradigm

- HIGH-RISK patients
  - Post ablative setting
  - Post-surgical setting
  - Pre-surgical setting

- LOW RISK
Defining Low-risk DTC in the post-surgical setting

T1N0 DTC without histological clues of possible aggressiveness (PTC variants, FTC angioinvasivity)

Low ($\leq 2$ vs. $\leq 10$ vs. $\leq 30$ ng/ml ?) post-surgical off T4 Tg levels

Negative US imaging
# Papillary thyroid carcinoma: histological variety and prognosis

<table>
<thead>
<tr>
<th>Histologic variant</th>
<th>Tumor disease mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated</td>
<td>3.8</td>
</tr>
<tr>
<td>Follicular</td>
<td>4.4</td>
</tr>
<tr>
<td>Diffuse sclerosis</td>
<td>-</td>
</tr>
<tr>
<td>Solid</td>
<td>66.7</td>
</tr>
<tr>
<td>Tall cell</td>
<td>55.6</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>83.3</td>
</tr>
</tbody>
</table>

Ortiz Sebastian et al., Arch Surgery, 2000
Clinical outcome according to serum Tg at the time of remnant ablation

Serum Tg levels measured at the time of $^{131}$I ablation: predictive value for DTC recurrence

<table>
<thead>
<tr>
<th>Tg level</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq 2$ ng/ml</td>
<td></td>
<td>98.4%</td>
</tr>
<tr>
<td>$\geq 2$ ng/ml</td>
<td>23.1%</td>
<td></td>
</tr>
<tr>
<td>$\leq 10$ ng/ml</td>
<td></td>
<td>96.1%</td>
</tr>
<tr>
<td>$\geq 10$ ng/ml</td>
<td>42.2%</td>
<td></td>
</tr>
</tbody>
</table>

Pitfalls in the post-surgical prognostic assessment

• In case of conservative surgery, risk of missing bilaterality (30%)

• In case of Total Thyroidectomy without central neck dissection, risk of missing N1a

• Post-surgical Tg levels: which cut-off? what if ↑↑aTG?

• US limitations in the evaluation of thyroid remnants
Towards a dynamic definition of Low-risk DTC: the pyramid paradigm

Pre-surgical setting
Post-surgical setting
Post ablative setting
Pre-surgical setting

HIGH-RISK patients
LOW RISK

Low-risk DTC: the pyramid paradigm
Defining Low-risk DTC in the post-ablative setting

Younger (< 45 yrs.) patients with T1-3 N0-1 DTC
Older patients (≥ 45 yrs.) patients with T1-2 N0 DTC

No histological clues of possible aggressiveness (PTC variants, FTC angioinvasivity)

Undetectable/Very low post-¹³¹I ablation TG levels
Negative US imaging
Negative WBS
Prognostic significance of successful $^{131}$I ablation in DTC patients

Distribution of Clinical Events according to Tg Level after $^{131}$I ablation (Tg2) and Lymph Node Status

<table>
<thead>
<tr>
<th>Tg2 level and lymph node status</th>
<th>No events</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>N– and Tg2 $\leq$ 10 ng/mL</td>
<td>72</td>
<td>2</td>
</tr>
<tr>
<td>N+ or Tg2 $&gt;$ 10 ng/mL</td>
<td>21</td>
<td>14</td>
</tr>
</tbody>
</table>

N– = node invasion absent; N+ = node invasion present.

*Toubeau et al., J Nucl Med, 2004, 45(988-94).*
Low-risk DTC: towards a dynamic definition

…”The definition “low risk” is no longer based on initial staging but rather now refers to patients treated by adequate surgery and, when indicated, adjuvant radioiodine treatment, who have no evidence of disease in evaluation performed in the 6-12 months following initial treatment.”…

Towards a dynamic definition of Low-risk DTC: the pyramid paradigm

- Pre-surgical setting
- Post-surgical setting
- Post ablative setting
- Pre-surgical setting

HIGH-RISK patients

LOW RISK
Low-Risk Differentiated Thyroid Carcinoma: Traditional Surgery

Geoffrey B. Thompson, MD
Professor of Surgery
Mayo Clinic College of Medicine
Papillary Thyroid Cancer (PTC)

- Most common endocrine malignancy
- 80% of new cases worldwide
- Extent and type of therapy → controversial
- No long-term prospective controlled trials
Extent of Thyroidectomy (PTC) Recommendations (Late 90’s)

- **American Thyroid Association**
  Near-total or Total

- **AACE**
  Near-total or Total

- **Society of Surgical Oncology**
  Low Risk: Unilateral Lobectomy
  High Risk: Total thyroidectomy
Papillary Thyroid Cancer (PTC)

- Societal recommendations
  - Bilobar resection (BLR) = Near total / Total thyroidectomy
  - Radioiodine remnant ablation (RRA)
Papillary Thyroid Cancer (PTC)

- Why? (Multicentric Cancer)
  - Improves cause-specific mortality (CSM)
  - Reduces tumor recurrence (TR)
  - Facilitates radiiodine scanning and use of therapeutic RAI
  - Improves effectiveness of thyroglobulin (Tg) screening
Differentiated Thyroid Carcinoma
MACIS (PTC)

Metastasis (distant)
Age (at diagnosis)
Completeness of primary tumor resection
Invasion of extrathyroidal structures
Size (of primary tumor)
MACIS Prognostic Scoring System

Score = 3.1 (if age = 39 yrs) or 0.08 X age (if age = 40 yrs)
+ 0.3 X tumor size (cm-max diameter)
+ 1 (if incompletely resected)
+ 1 (if locally invasive)
+ 3 (distant spread)
Influence of MACIS Score on Survival from PTC

- <6 (1,552:84%)
- 6-6.99 (155:8%)
- 7-7.99 (60:3%)
- ≥8 (84:5%)

N = 1,851
1940-90
p < 0.0001
MACIS score

Years After Initial Treatment
Survival by MACIS Score @ 20 yrs

• <6  99%

• 6.00-6.99  89%

• 7.00-7.99  56%

• >8  24%
In low-risk patients:

- **No survival benefit:** unilateral lobectomy vs bilobar resection
  - Hay et al 1987

- **TR higher** with unilateral procedure
  - Grant et al 1988, Hay et al 1988
Risk of Locoregional Recurrence
Unilateral Lobectomy

4x-7x higher compared to BLR @ 20 years
Low-Risk DTC Patients: Limited Surgery?

Local Recurrence

↑ Patient anxiety
↑ Physician anxiety
↑ Surgeon anxiety
↑ Need for reoperation
↑ Time away
↑ Cost
PTC

In high-risk patients

• CSM and TR rates higher: unilateral lobectomy vs BLR
  – Hay et al 1987
Low-Risk DTC Patients: Limited Surgery?

Total Thyroidectomy (Morbidity)

• The risk of permanent hypoparathyroidism is significantly greater than lesser resections in many series

• 3% vs 1.4% @ Mayo Clinic (Total vs NT)

• Rates as high as 15-20% have been reported

Hay et al. Surgery 1998; 124:958-966
PTC

Near-Total vs Total Thyroidectomy (BLR)

• **No difference in CSM or TR in either low- or high-risk groups**

  - Hay et al 1987
First-Time Operations for Low-Risk PTC

1999-2000 (24 months)
124 patients

- Lobectomies (n=13) 10%
- Near-Total Thyroidectomies (n=54) 44%
- Total Thyroidectomies (n=57) 46%
Permanent Vocal Cord Paralysis

None
Permanent Hypoparathyroidism

- 3 patients (Total) 5.3%
- 1 patient (NT) 1.9%

3.2%
Low-Risk DTC Patients: Limited Surgery?

These additional local recurrences can be nearly eliminated without a significant increase in permanent hypoparathyroidism.
Low-Risk DTC Patients: Limited Surgery?

How?

Near-Total Thyroidectomy

Not routine Total Thyroidectomy or Unilateral Lobectomy
PTC

- Mayo Clinic: 1940-2000
- 2,512 consecutive patients
- 43,095 person-years of follow-up
- Median follow-up: 14 years (60 years)

Hay et al, 2002
PTC

- Death from PTC: 106 patients (4%)

- Excluded (TR):
  - Distant mets within 30 days
  - Incomplete resection

Hay et al, 2002
Papillary Thyroid Carcinoma 1940-2000

Presenting Disease

p TNM Stages

- I (60%)
- II (21%)
- III (18%)
- IV (1%)

MACIS Scores

- <6 (84%)
- 6+ (16%)

N = 2,512

Hay et al, 2002

1940-2000
Papillary Thyroid Carcinoma 1940-2000
Trends in Extent of Surgery & RRA

- Bilateral lobar resection (2,179)
  - n = 2,512
  - p<0.001

- Unilateral lobectomy (293)

- Remnant ablation
  - n=662
  - 1940-2000
    - 1%
    - 3%
    - 32%
    - 46%

Hay et al, 2002
Papillary Thyroid Carcinoma 1970-2000
Changing Frequency of Remnant Ablation

Hay et al, 2002
Papillary Thyroid Carcinoma 1940-2000
Overall Outcome

Mortality from PTC
n = 2,512
Mayo Clinic 1940-2000

Recurrence, any site
n = 2,370

Hay et al, 2002
Papillary Thyroid Carcinoma 1940-2000

Overall Outcome

Occurrence of postoperative events (cumulative %)

- Postoperative nodes
- Local recurrences
- Distant metastases

Years After Initial Surgery

N = 2,370
1940-2000

Hay et al, 2002
Papillary Thyroid Carcinoma 1940-2000

Survival to Death

Surviving death from PTC (%)

MACIS Risk Groups
n=2,512
1940-2000
p < 0.001

Hay et al, 2002
Papillary Thyroid Carcinoma
Comparison of Outcome

Mortality

MACIS <6
N=296
P=0.31

MACIS 6+
N=391
P=0.007

Recurrence

1940-1954
UL (135)
N=256
P=0.007

1940-2000
UL (60)
N=280
P=0.015

Hay et al, 2002
Papillary Thyroid Carcinoma 1955-2000

Cause Specific Mortality

Hay et al, 2002
Papillary Thyroid Carcinoma 1955-2000

Tumor Recurrence

Hay et al, 2002
# Papillary Thyroid Carcinoma 1970-2000

<table>
<thead>
<tr>
<th>Low-Risk</th>
<th>20-yr Mortality</th>
<th>20-yr Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>(MACIS &lt;6) 1970-2000</td>
<td>NT/TT Alone</td>
<td>NT/TT and RRA</td>
</tr>
<tr>
<td>Node-negative (n=636)</td>
<td>0%</td>
<td>3.4%</td>
</tr>
<tr>
<td></td>
<td>P=NA</td>
<td>P=0.80</td>
</tr>
<tr>
<td>Node-positive (n=527)</td>
<td>1.2%</td>
<td>19.5%</td>
</tr>
<tr>
<td></td>
<td>P=0.99</td>
<td>P=0.19</td>
</tr>
</tbody>
</table>

Hay et al, 2002
Scar @ 3 months
Extent of Lymphadenectomy
Value of Preoperative Ultrasound in PTC


- US identified nonpalpable lateral nodes: 15% in first time operations

- Reops-NLLN’s: 64% ; NCLN’s: 28%

- US altered extent of operation in 41% of initial and 43% of reoperative pts. with palpable nodes

Why Perform Cervical Lymphadenectomies

- Thyroglobulin levels (withdrawal, Thyrogen® stimulated)
- High resolution ultrasound
- Radioiodine and PET scans
- Tg mRNA
PTC

Lymph Node Dissection (PTC)

- **Children**
  - 80-90% clinically positive

- **Adults**
  - 10-20% clinically positive

- **Extensive prophylactic dissections**
  - 80% positive

- **Therapeutic dissections**
  - 7-8% develop positive nodes

- **Immune surveillance very effective**
PTC

“Berry-Picking” vs Formal Nodal Dissection

- Nodal recurrences increased in all series
- Reoperations more difficult
  - Increased morbidity
- Metastatic carcinoma in lymph nodes > 3 mm always associated with disease in smaller lymphatics
Choice of Nodal Dissection

- **Central compartment** (ipsilateral paratracheal, pretracheal, upper mediastinal) in virtually all cases

- **Modified or Selective Neck Dissection** for clinically detectable nodes (ultrasound, palpation, biopsy)
Do Lymph Nodes Affect Survival?

- Probably not in most cases
- Nodes beget nodes (not death)
PTC

Exceptions:

• Bulky, matted nodes  
• Extracapsular spread  
• $\oplus$ nodes in stage III disease  yes
Practical Algorithm

⊕ FNA for PTC (or suspicious)

US Mapping ± FNA

⊕ Lateral Nodes

Extensive
- MRND
  + TTx
  + CCND

Limited
- SND
  + TTx
  + CCND

Total Thyroidectomy (TTx)

CN’s grossly ⊕ Multifocal
Larger tumor Extrathyroidal

Bilateral level VI ± VII Delphian Pretracheal

CN’s grossly ⊖ Tumor unifocal < 1 cm Intrathyroidal

Ipsilateral level VI Delphian Pretracheal

MRND = modified radical neck dissection
SND = selective (lateral) neck dissection
PTC

Radical Neck Dissections:

- Never
- Increased complications (esp. wound)
- No survival or TR benefit
Conclusion (1)

• **BLR and conservative nodal dissection (CND) reduces TR in low-risk patients**

• **BLR and CND reduces TR and CSM in high-risk patients**

• **RRA does not further reduce CSM or TR in MACIS low-risk patients**
Follicular Thyroid Cancer (FTC)

- 10-15% of thyroid malignancies
- Cytology insufficient
- Capsular / vascular invasion
- 90% unifocal
- Hematogenous spread
- Lung and bone metastases: 15%
- Nodal metastases: FCC 5%
Follicular Thyroid Cancer

• Lymph node metastases (< 5%)
  – Usually associated with locally advanced tumor
  – Worse prognosis
FTC

Minimally Invasive (80%)

Microscopic vascular and capsular invasion

Widely Invasive (20%)

Gross involvement of vessels and contiguous structures
FTC

- Prognostic indicators
  - Age > 50
  - Marked vascular invasion
  - Metastatic disease

Brennan et al, 1991
FTC

- **High risk** (2/3 risk factors)
  - Survival: 47% and 8% @ 5 and 20 years

- **Low risk** (0-1/3 risk factors)
  - Survival: 99% and 86% @ 5 and 20 years
FTC

Cumulative % surviving follicular cancer

Low risk (n=82)

High risk (n=18)

Years after initial treatment

Brennan et al, 1991

Brennan et al, 1991
FTC

- Tumors < 2 cm with
  - minimal capsular invasion alone
    - \(\sqrt{\text{No metastases or deaths}}\)
    - \(\sqrt{\text{Recent 10-year follow-up}}\)
    - Lobectomy Alone

van Heerden et al, 1992
Hurthle Cell Cancer

- <5% of all thyroid cancers
- More locally aggressive
- Less avidity for RAI
- Nodal metastases in 1/3
Follicular and Hurthle Cell Carcinoma

- Lymph node mets from FTC rare (<5%); if present consider FVPTC
- Routine CCND and LND for FTC not necessary unless positive nodes are present grossly or by US
- HCC has positive nodes in up to 30%; manage nodes like PTC
FTC/HCC

**Treatment:**

- Total / NT Thyroidectomy
- Sample central nodes*
- Formal node dissection when nodes ⊕
- CCND for HCC
- RRA, THST except in small tumors with minimal capsular invasion

*may be only indication of FVPTC
Papillary Thyroid Carcinoma-FNAB
Widely Invasive Follicular Carcinoma
Hurthle Cell Adenoma or Carcinoma?
Follicular Carcinoma-Capsular Invasion
Follicular Carcinoma-Vascular Invasion
Follicular Neoplasms: Frozen Section

Results: 1023 Patients

- 286 (28%)
- 737 (72%)

Mean age: 52.1 years
<table>
<thead>
<tr>
<th>Perm</th>
<th>Frozen Section</th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ca</td>
<td>Non-Ca</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Ca</td>
<td>65 TP</td>
<td>18 FN</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Non-Ca</td>
<td>7 FP</td>
<td>933 TN</td>
<td>940</td>
<td></td>
</tr>
</tbody>
</table>

65/83 (78%) Ca Dx by FS
Follicular Neoplasms: Frozen Section Dependent Upon:

- Good pathologists
- Significant exposure to frozen section, especially thyroid
- Superb support system
Low-Risk differentiated thyroid cancer

Mini-invasive video-assisted thyroidectomy (MIVAT)

Maurizio Bagarani
C. Morano, F. Cilurso, U. Basile, A. Cardillo

Departement of General Surgery
Endocrine Surgery Unit
Regina Apostolorum Hospital
Albano Laziale, Rome

Verona 2006
M. Gagner
Endoscopic subtotal parathyroidectomy in patients with primary hyperparathyroidism
Br. J. Surg. 1996; 83 : 875
Endoscopic thyroidectomy

Extracervical approach

Cervical approach


Gagner, Thyroid 2001;11:161
MIVAT
(minimally invasive videoassisted thyroidectomy)

• Video-assisted thyroid lobectomy has been introduced since 1998 by Miccoli at University of Pisa

• This technique uses a gasless video-assisted approach with a small central incision (1.5 cm)

Miccoli P. Surgery 2001;130:1039
Multiinstitutional experience

Miccoli P. Bellantone R. World J Surg 2002;26:972

- The mivat technique is safe and feasible.
- The complication rate is not different from that of standard thyroidectomy.
- The operating time appears longer than with conventional procedure and the number of patients eligible remains low.
- The advantages in terms of cosmetic results and postoperative distress are evident.
Established Indications

- Single nodule
- Nodule largest diameter < 3.5 cm
- Benign or low-grade follicular tumor (low-risk papillary carcinoma)
- Thyroid volume < 20 ml

Contraindications

**Absolute**
- Previous neck surgery
- Large goiter
- Local advanced cancer
- Lymph node metastases

**Relative**
- Previous neck irradiation
- Hyperthyroidism
- Thyroiditis
- Severe obesity
Preparation for intervention

- Position of patient: neck hyperextension not needed
- Surgical staff: 3-4 surgeons
- Monitor: better two at the top of the patient
instrumentations
Video-assisted technique
Personal experience

33 patients

2005  15 out of 315  4.7%
2006  18 out of 225  8.0%

Mean age  47.7
F/M  29/4
**Diameter of main nodule**

- Mean: 15.8 mm
- Range: 6-40

**Thyroid volume**

- Mean: 31 ml
- Range: 12-68

- 8 pat. > 30

**Pathology**

- Papillary carcinoma: 9
- Follicular carcinoma: 2
- Nodular hyperplasia: 10
- Follicular adenoma: 10
- Thyroiditis: 2

**Type of surgery**

- Total thyroidectomy: 26
- Emithyroidectomy: 7
Results

- Mean Hospital stay: 3.5 days
- Majors complications: 0 cases
- Conversion: 1 case
- Laringeal nerve palsy: 0 cases
- Mild transient dysphonia: 3 cases (permanent: 0)
- Transient hypocalcemia: 3 cases (permanent: 0)
Possible causes of dysphonia first training phase
two opposite techniques?

conventional

video-assisted

S. Giovanni “decollato”, Caravaggio
La Valletta, Malta

Madame Pompadour, Modigliani
Art Institute Chicago
Mivat and conventional thyroidectomy

Two integrated techniques

- **Classical Indications**
  - Volume < 20 ml
  - 10%

- **Wider Indications**
  - Volume < 30 ml
  - 15-20%

Bellantone WJS 2006
Is it possible to widen the indication between videoassisted and conventional incision?

<table>
<thead>
<tr>
<th></th>
<th>Miccoli 1998</th>
<th>Bellantone 2000</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5 cm (vol.&lt;20)</td>
<td>2.0 cm (vol.&lt;30)</td>
<td>5.0 cm</td>
</tr>
</tbody>
</table>
probably yes by a

2.5-3.0 cm neck incision

Smaller than conventional incision

Without being too invasive

2.5 cm (vol.<50)

5.0 cm
rationale for larger incision

- Increased number of treated patients
- Treatment of patients with underestimated volume
Mivat with enlarged incision 2.5-3.0 cm
Conventional minimal incision 4.0-6.0 cm
Prospective controlled study

Patients with thyroid volume between 20-50 ml

- Conventional minimal Cervical incision 4.0-6.0 cm
- Video-assisted technique Cervical incision 2.0-3.0 cm

Main evaluation criteria
- Postoperative complications
- Mean hospital stay
- Cosmetic evaluation
- Patient’s satisfaction
- Volume of residual gland
Conclusions

• Mivat is a safe technique which provides excellent cosmetic results and decreases patients’ discomfort.

• It is not an alternative to the conventional surgical technique but integrates with it.

• It requires particular attention in the preparation of upper pole especially during the learning curve.
Conclusions 2.

- Lymph node dissection requires skilled operators; hence, a careful preoperative US neck assessment is mandatory.
- Currently, MIVAT seems the procedure of choice when performing thyroidectomy for a solitary nodule with cytological diagnosis of follicular lesion.
- In the future, the indications might be extended to larger thyroid glands (up to 30 ml): the advantages must be verified in controlled studies.
Update in Clinical Endocrinology

Low-risk Differentiated Cancer
Ablative Treatment:
Always or “à la demande” or with rhTSH

Marco Ferdeghini - Chiara Colato - Claudio Traino
Dipartimento di Scienze Morfologico-Biomediche e di Patologia
Università degli Studi di Verona
Fisica Medica Azienda integrata Universitaria Ospedaliera - Pisa

Verona - 27 ottobre 2006
A multidisciplinary team with expertise and interest in the management of DTC

Endocrinologist/Oncologist, Surgeon, Pathologist, Nuclear Medicine Physician, Medical Physicist, Radiologist, Radiotherapist, Biochemist, Specialist Nurse

To decrease
- the recurrence rate and possibly the mortality rate

To improve
- sTg assessment as cornerstone tumor marker
- post-therapy and follow-up $^{131}$I-WBS sensitivity and specificity
- Tg-Abs assessment as tumor markers when present
Differentiated Thyroid Carcinoma

- Surgery
- (Near)-total Tx
- Pathology
- $^{131}$I post-surgical remnant ablation
- Follow-up
- $sTg$

Indications can be individualized according to the surgeon’s and pathologist’s reports.
Differentiated Thyroid Carcinoma

Follow-up

Surgery

131I ablation

Total Rx

Near total Rx

Remnant

Post-surgical remnant
### 131I Ablation and the Decrease of DTC Recurrence and Mortality Rates

<table>
<thead>
<tr>
<th>Series</th>
<th>N</th>
<th>Follow-up (yrs)</th>
<th>131I Effectiveness cancer mortality</th>
<th>131I Effectiveness cancer recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic</td>
<td>2444</td>
<td>&gt;25</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Illinois Registry</td>
<td>2282</td>
<td>6.5</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>MD Anderson</td>
<td>1599</td>
<td>11</td>
<td>P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Ohio State</td>
<td>1510</td>
<td>16.6</td>
<td>P&lt;0.0001</td>
<td>P&lt;0.016</td>
</tr>
<tr>
<td>Pisa</td>
<td>964</td>
<td>12</td>
<td>NS</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>587</td>
<td>9.2</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Toronto</td>
<td>382</td>
<td>10.8</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Gustave Roussy</td>
<td>273</td>
<td>7.3</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>229</td>
<td>5</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Gunderson/Lutheran</td>
<td>177</td>
<td>7.2</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>UCSF</td>
<td>187</td>
<td>10.6</td>
<td>NS</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

*Sawka JCEM 2004 Metanalysis of 131I effectiveness*
Comment by Bryan R Haugen JCE&M 2004

Taken together, these data would suggest that patients with low-risk DTC may benefit from radioiodine remnant ablation by decreased risk of locoregional recurrence (69%) and decreased risk of distant metastatic disease (50%).

Comment by Ernest Mazzaferri JCE&M 2004

The main conclusions are that it may be beneficial in decreasing recurrence of DTC, but the results are inconsistent and the benefit of remnant ablation remains unclear in low-risk patients treated with bilateral thyroidectomy and thyroid hormone suppression of TSH.
Figure 2. Relationship between intensive primary treatment and recurrence rate. Analysis of juvenile differentiated thyroid carcinoma (JDT) outcomes from selected published studies. The prevalence of patients with both total thyroidectomy and radioiodine ablation increases, JTC recurrence rate decreases.

It should be noted that the obtained model is not a formal meta-analysis approach and is not weighted according to the power of evidence.
Radioiodine Remnant Ablation

lack of evidence of improved outcome. The issue of RRA in low-risk patients remains unsettled; a case-by-case decision is recommended, guided by clinical judgment and experience.
**Indications (!)**

**UK GL 2002 III, B**

- The majority of adult Pts with tumour size $\emptyset \geq 1$ cm following total Tx

**EU Guidelines 2006 - High-risk group**

Consensus: recommended

- Reduces the recurrence rate, possibly prolongs survival, permits early detection of persistent disease

- Documented persistent disease: $M_1, R_{1-2}$

- Complete tumor resection stages III and IV disease or N1, at high risk of persistent or recurrent disease

**ATA GL 2005 R32 - Recommendation B fair evidence**

- All stages III and IV disease (AJCC 6th edition)

- All stage II disease <45 years
Indications (!?)

EU Guidelines 2006 - Low-risk group

No consensus: controversial benefits

Uncertainties: administered to all Pts or only to selected Pts

- less than total Tx or no lymph node dissection
- Age <18 yrs
- T1 >1 cm N0 M0 or multifocal T1 N0 M0
- T2 N0 M0
- Unfavorable histology
  - PTC: tall cell, columnar cell, diffuse sclerosing
  - FTC: widely infiltrating follicular

ATA GL 2005 R32 - Recommendation B fair evidence

- Most stage II disease ≥45 years
- Selected stage I disease, ... multifocal disease, nodal metastases, extrathyroidal or vascular invasion, and/or more aggressive histologies
Indications (?)

EU Guidelines 2006 - Very low-risk group

Consensus: no benefits, no indication

- Complete surgery
- Unifocal T1 ≤1 cm N0 M0
- Favorable histology
- No extrathyroidal extension
- No lymph node metastases
Multifocality, bilaterality
Lymph node occult metastases

E&H

TTF-1

Galectin-3

HBME
Multifocality & node metastasis
DTC Histology

● **Favorable histology**

- Papillary
- Follicular variant of Papillary
- Minimally Invasive Follicular

● **Unfavorable histology**

- "Tall cell"
- Columnar
- Widely Invasive Follicular
- Insular
Oporto
La ciudad más bonita del mundo
the term **papillary microtumor (PMiT)** was chosen… *(specifically for)* a **single focus** of papillary carcinoma measuring <1 cm in diameter contained **within the thyroid** gland of an **adult** patient found **incidentally** at thyroidectomy done for some other reason.

…where **2 or more** lesions are present, each **individually <1 cm**, but **>1 cm** when **taken together**;… it would be safer **not to use** the term **PTiM** under these circumstances

… excludes … those rare instances in which the tumor has features that may be indicative of a potential for an aggressive behavior… cases accompanied by invasion of the thyroid capsule, blood vessel permeation, or tall cell features

If a papillary carcinoma of <1 cm Ø incidentally found at **US, CT, or MRI** examination performed for some other reason, … should still be classified as **PMiT**. Conversely, the use of the term is not recommend if the tumor were to be found in the presence or suspected presence of metastases
Patient preparation
A low-iodine diet before remnant ablation?

**ATA Guidelines 2006**  
R38 - **Recommendation B**

- A low-iodine diet for 1–2 weeks is recommended particularly for Pts with high iodine intake

Ablation success rates after a stringent low-iodine diet
- significantly improved in Dutch DTC (Plujmen 2003)
- + instruction to avoid salt, seafood iodine-containing multivitamins compared to a regular diet not improved in an American study (Morris 2001)

**ATA Guidelines 2006**  
R38

- Measurement of iodine excretion may be a useful way to identify iodine intake that could interfere with $^{131}$I uptake
Pre-ablation diagnostic WBS before remnant ablation?

Procedure avoided without loss of information

- Low clinical utility
- Post-therapy WBS performed 3–8 days after $^{131}$I administration is much more sensitive
- Possibility of a stunning effect on the subsequent therapeutic activity of $^{131}$I

$^{131}$I Low activity (3.7 MBq, 100 µCi)
- to reduce stunning
- to perform dosimetric studies

$^{123}$I-WBS (2 to 5 mCi 74-185 MBq) or $^{99m}$Tc-WBS
- in uncertainty concerning the extent of Tx
- to reduce the risk of stunning
- at 24 h comparable but not superior images to both $^{131}$I diagnostic and post-ablation scans (Sarkar 2002 - Siddiqi 2001)
Pre-ablation diagnostic WBS before remnant ablation?

\[ \text{ABLATED} \quad \text{NOT ABLATED} \]

$131^I \text{ DxWBS } 1 \text{ mCi}$

Bianchi 2005
Remnant mass

Inversely correlated with the success of $^{131}$I ablation

Doi SA, Woodhouse NJ. Clin Endocrinol 2000; 52: 765–73
### Studies comparing different activities of $^{131}I$ for thyroid remnant ablation

| Study                          | $^{131}I$ activity mCi | Pts N. | ‘Successful ablation’ | | | |
|--------------------------------|-------------------------|--------|-----------------------|---|---|
| McCowen, 1976                  | ≤30 80-100              | 36 28  | Recurrence Free Survival & Actuarial Survival Rate | NS |
| DeGroot & Reilly, 1982         | 26-30                   | 18     | 83                    | 100 |
|                                | 50-60                   | 21     | 100                   | 100 |
|                                | >60                     | 9      | 100                   | 100 |
| Ramacciotti, 1982              | 30                      | 20     | 40                    | 71  |
|                                | 50                      | 10     | 30                    |     |
|                                | 75                      | 14     |                       |     |
| Creutzig, 1987                 | 30                      | 10     | 50                    | 60  |
|                                | 100                     | 10     |                       |     |
| Johansen, 1991                 | 29                      | 36     | 81                    | 84  |
|                                | 100                     | 27     |                       |     |
| Mazzaferri & Jhiang, 1994      | 29-50                   | 59     | Recurrence Rate       | NS  |
|                                | 51-100                  | 79     | 80                    | 80  |
| Hodgson, 1998                  | 29                      | 20     | 80                    | 80  |
|                                | 50                      | 5      |                       |     |
| Sirisalipoch, 2004             | 50                      | 63     | 65                    | 89  |
|                                | 100                     | 75     |                       |     |
Studies comparing different activities of $^{131}\text{I}$ for thyroid remnant ablation

<table>
<thead>
<tr>
<th>$^{131}\text{I}$ activity $\text{mCi}$</th>
<th>Patients N.</th>
<th>‘Successful ablation’ %</th>
</tr>
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<tbody>
<tr>
<td>Bal, 1996</td>
<td></td>
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<tr>
<td>25-34 (30±1.5)</td>
<td>27</td>
<td>63</td>
</tr>
<tr>
<td>35-64 (50.6±5.4)</td>
<td>54</td>
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<tr>
<td>65-119 (88.6±14)</td>
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<tr>
<td>120-200 (155±28.7)</td>
<td>30</td>
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<tr>
<td>Bal, 2004</td>
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<tr>
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<td>84,4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>81,8</td>
</tr>
</tbody>
</table>
Dosimetric approach

Maxon HR, et al.
Radioiodine-131 therapy for well differentiated thyroid cancer - a quantitative radiation dosimetric approach: outcome and validation in 85 patients

Aim: 300 Gy delivered to the thyroid remnant

173–374 Gy

120 Gy Successful ablation
600 Gy Unsuccessful ablation
Post-therapy WBS after remnant ablation?

**ATA GL 2005** R32 - Recommendation B

- Recommended 5–8 days after $^{131}	ext{I}$ remnant ablation to visualize metastases
- Published data supporting this time interval are lacking

After high $^{131}	ext{I}$ activity

- Additional metastatic foci (most often in the neck, lungs and mediastinum) in 10%–26% of Pts compared to the diagnostic WBS
- Altered the disease stage in ~ 10% of the Pts
- Affected clinical management in 9%–15%
TSH elevations to provide sufficient thyroid stimulation

- >25 or 30 mIU/L (Schlumberger, 1998)
- ≥30–50 mIU/mL (McDougall & Weigel 2001)

**TH withdrawal and consequent hypothyroidism**

**vs**

rhTSH on L-T$_4$ therapy

preserving quality of life
Robbins
Dosimetric approach

% successful ablation

CR
PR
No ablation

L-T$_4$ Withdrawal
$N=42$
$^{131}I$ 128±74 mCi

rh-TSH
$N=45$
$^{131}I$ 110±65 mCi
rhTSH-aided ablation using a $^{131}$I activity of 100 mCi

A Randomized, Controlled, Multi-National Pilot Study

(Pacini F et al, JCEM 2006)

Ablation = no visible uptake or, if visible, <0.1% at the 8 mo rhTSH-WBS
rhTSH-aided ablation using a $^{131}$I activity of 100 mCi
A Randomized, Controlled, Multi-National Pilot Study
(Pacini F et al, J CEM 2006)

Ablation = no visible thyroid bed uptake at the 8 mo rhTSH-WBS

95% CI on Difference in Ablation Rate:
(-30.5% to 9.1%)
$\chi^2 p=0.30$
rhTSH-aided ablation using a 131I activity of 100 mCi
A Randomized, Controlled, Multi-National Pilot Study
(Pacini F et al, JCEM 2006)
**Remnant cumulated activity per unit administered activity (h)**

The thyroid-remnant absorbed dose can be calculated by equation (MIRD):

\[ D_R = \tilde{A}_R S_{T \leftarrow T} \frac{m_T}{m_R} \]

where \( \tilde{A}_R \) is the cumulated \(^{131}\text{I} \) activity in thyroid post-surgical remnant; \( S_{T \leftarrow T} \) is the MIRD-defined S-values for thyroid irradiating itself (constant); \( m_T \) is the reference man thyroid mass (constant) and \( m_R \) is the post-surgical remnant mass.

**TWO CONSEQUENCES:**
- The remnant absorbed dose depends strongly from the remnant mass
- For Pts whose remnant mass is the same the remnant absorbed dose depends on the cumulated activity in the remnant
Comparison between cumulated activities per unit administered activities

CONSEQUENCES: If one wants the same remnant absorbed dose for Pts with the same remnant mass, the administered activity must be \( \sim 1.5 \) times higher for rh-TSH Pts.
rhTSH-aided ablation using a $^{131}$I activity of 50 vs 100 mCi

A Randomized Pilot Study

(Pacini F et al)

Ablation = no visible thyroid bed uptake or, if visible, <0.1% at the 8 mo rhTSH-WBS

$\chi^2$

$p=0.83$
Post-surgical remnant uptake after rh-TSH

0.9 mg x 2 d vs 0.45 mg x 4 d

24 h uptake

3.2% 6.1%

Elisei R
Ablation = no visible uptake at the 8 mo rhTSH-WBS

Castagna 2005
**$^{131}$I ablation: indications**

- Surgery: complete?
- T1: $\leq 1 \text{ cm} > 1 \text{ cm}$?
- Unifocal? $\Leftrightarrow$ Assessment of Multifocality?
- Favorable histology
- Lymph node metastases? $\Leftrightarrow$ Level VI?
- Extrathyroidal extension?
$^{131}$I ablation: protocol

- Surgery: complete  YES
- T1: ≤1 cm  YES
- Unifocal  YES
  - $\iff$ Assessment of Multifocality  YES
- Favorable histology  YES
- Lymph node metastases  NO  $\iff$ Level VI  YES
- Extrathyroidal extension  NO

Very low-risk
\textbf{131I ablation: when indicated}

- Low-iodine diet \textit{YES/NO}
- \textit{131I} diagnostic WBS \textit{NO}
  \iff 
  Assessment of uptake for dosimetry \textit{YES/NO}
- \textit{rhTSH} \textit{YES}
- \textit{131I} activity \textit{the lowest useful}
- \textit{131I} posttherapy WBS \textit{YES}
Low Risk Differentiated Thyroid Cancer

What Kind of Follow-up?

Furio Pacini
Department of Endocrinology
University of Siena, Italy
Thyroid cancer

- Thyroid nodules may approach 20% of the population;

- 5-7% of thyroid nodules is cancer (the most frequent endocrine cancer);

- Thyroid cancer is among the three human cancers at increase;

- The clinical presentation has been changing in recent years: >80% are at low risk

- Long term survival is the rule, but recurrences may appear even 20 years from the diagnosis.

- Thus, it has strong socio-economical implication
CONSENSUS STATEMENT

European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium

Furio Pacini, Martin Schlumberger¹, Henning Drale², Rossella Elisei³, Johannes W A Smit⁴, Wilmar Wiersinga⁵
and the European Thyroid Cancer Taskforce

¹Section of Endocrinology and Metabolism, University of Siena, Via Bracci, 53100 Siena, Italy, ²Service de Médecine Nucléaire, Institut Gustave Roussy, Villejuif, France, ³Department of General, Visceral and Vascular Surgery, University of Halle, Germany, ⁴Department of Endocrinology, University of Pisa, Italy, ⁵Department of Endocrinology and Metabolic Disease, Leiden University Medical Center, The Netherlands and ⁶Department of Endocrinology and Metabolism, University of Amsterdam, The Netherlands
Definition of risk

- **Very low risk patients**: T1<1cm, unifocal and intra-thyroid; favorable histology; N0

- **High risk patients**: T2-4, N1, M1, persistent disease

- **Low risk patients**: all the other patients.
FOLLOW-UP

Depending from initial treatment:

**Lobectomy:**
- Serum Tg poorly sensitive
- Neck ultrasound: most sensitive

**Replacement**, not suppressive l-T4 therapy
FOLLOW-UP

Depending from initial treatment:

Total thyroidectomy:

Serum Tg highly sensitive
Neck ultrasound highly sensitive
13I diagnostic WBS poorly sensitive
FOLLOW-UP: 3 months after ablation

On I-T4 therapy: Measurements of

• Serum Tg and anti-Tg antibodies

• Thyroid hormones and TSH: to assess the appropriate dose of I-T4
SERUM Tg LEVELS SOON AFTER INITIAL TREATMENT

• Some months after initial treatment, detectable serum Tg (<5-10ng/mL) may be produced by:
  – irradiated cells that will disappear in 2/3 of cases (Baudin, Pacini, Torlontano, Toubeau), and serum Tg will decrease
  – neoplastic cells that will progress, and serum Tg will increase.

• A control TSH-stimulated Tg obtained some months (or years) later will differentiate these two groups of patients.

• The most relevant parameter is the trend of Tg level, rather than its level.
FOLLOW-UP: 8-12 MONTHS AFTER ABLATION

- Clinical examination: poorly sensitive
- Neck ultrasonography
- Serum Tg determination following TSH stimulation
- ($^{131}$I-total body scan)
NECK ULTRASONOGRAPHY

The most sensitive tool for detecting neck lymph node metastases. Benign lymph nodes are frequent, and specificity should be improved by:

– Careful definition of US criteria of suspicion
– FNA: cytology + Tg in the aspirate fluid

Strongly recommended
SERUM Tg DETERMINATION

- Serum Tg is a marker of disease \((\text{Van Herle, 1975})\), not a disease

- Measurement:
  - Immunometric assay (IMA)
  - Standardization: CRM-457
  - Functional sensitivity < 1ng/mL. Supersensitive methods (<0.1ng/mL): improved sensitivity but decreased specificity.
  - Search for interferences:
    - Measurement of anti-Tg antibodies.
USE OF rhTSH.

• The benefits in terms of QOL of rhTSH over withdrawal are obvious.

• Is the sensitivity of serum Tg similar following rhTSH and withdrawal?
The sensitivity of serum Tg determination is improved by 15-20% following TSH stimulation.
# SIGNIFICANCE OF DETECTABLE Tg/TSH AT 1 YEAR

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>n</strong></td>
<td>83</td>
<td>107</td>
<td>109</td>
<td>92</td>
<td>294</td>
<td>256</td>
</tr>
<tr>
<td><strong>Tg/TSH &lt;1 ng/ml (%)</strong></td>
<td>83</td>
<td>81</td>
<td>83</td>
<td>85</td>
<td>85</td>
<td>86</td>
</tr>
<tr>
<td><strong>No disease (%)</strong></td>
<td>98</td>
<td>98</td>
<td>92</td>
<td>99</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td><strong>Tg/TSH &gt;1 ng/ml(%)</strong></td>
<td>17</td>
<td>19</td>
<td>17</td>
<td>15</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td><strong>Disease detected</strong></td>
<td>6</td>
<td>8.4</td>
<td>8.2</td>
<td>3.3</td>
<td>7.8</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>Neck / Distant</strong></td>
<td>4.8/1.2</td>
<td>3.7/4.7</td>
<td>4.6/3.7</td>
<td>3.3/0</td>
<td>6.1/1.7</td>
<td>1.9/1.6</td>
</tr>
<tr>
<td><strong>NED</strong></td>
<td>9.6</td>
<td>10.3</td>
<td>9.2</td>
<td>12</td>
<td>7.1</td>
<td>10.9</td>
</tr>
</tbody>
</table>
OUTCOME OF LOW RISK PATIENTS WITH Tg ≤ 1ng/mL FOLLOWING THYROID HORMONE WITHDRAWAL

- 219 patients
- Mean follow-up: 10 years
- Neck lymph node recurrence at US: 1 (<0.5%).
- TSH in the normal range (0.5-2.5 µU/mL) in > 90%.
- Cailleux, JCEM, 2000

- 315 patients
- Mean follow-up: 12 years
- Neck lymph node recurrence at US: 2 (0.6%).
- Pacini, JCEM, 2002.

Excellent NPV of Tg/TSH
Diagnostic 131-I WBS useless
# DETECTION OF NECK RECURRENCES

## STUDY INFORMATION:

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pacini</th>
<th>Frasoldati</th>
<th>Torlontano</th>
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</thead>
<tbody>
<tr>
<td>N₁/Pts</td>
<td>27/340</td>
<td>51/494</td>
<td>38/456</td>
</tr>
</tbody>
</table>

## METHOD:

<table>
<thead>
<tr>
<th>Method</th>
<th>Pacini</th>
<th>Frasoldati</th>
<th>Torlontano</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tg/TSH</td>
<td>85% (rhTSH)</td>
<td>57% (WD)</td>
<td>82% (WD)</td>
</tr>
<tr>
<td>¹³¹I TBS</td>
<td>21%</td>
<td>45%</td>
<td>34%</td>
</tr>
<tr>
<td>Neck US</td>
<td>70%</td>
<td>94%</td>
<td>100%</td>
</tr>
<tr>
<td>Neck US+Tg/TSH</td>
<td>96%</td>
<td>99.5%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Combination of neck US and Tg/TSH determination.*
LOW RISK PATIENTS: UNDETECTABLE SERUM stimulated Tg AT 8-12 MONTHS

- False negative results are rare (excellent NPV)
- LT4 dose can be decreased to achieve a low-normal serum TSH level (0.5-2.5 µU/mL)
- Patients are followed up on a yearly basis on replacement L-T4 treatment.
- In the absence of abnormalities, no other testing is warranted.
- The need for another TSH stimulation test needs further studies.
Patients with positive anti-Tg antibodies

• Serum Tg unreliable if undetectable

• Follow the changes in anti-Tg antibodies

• Neck Ultrasound

• Diagnostic WBS may be informative
Total thyroidectomy
131I ablation and post-therapy WBS

3 months: Check for appropriate LT4 therapy
TSH, FT4, (FT3), on LT4

6–12 months: rhTSH-Tg* and neck US on LT4

80%
Undetectable Tg
No other abnormalities

10%
Detectable Tg
< institutional cut-off: no other abnormalities

10%
Detectable Tg
> institutional cut-off and/or other abnormalities

Decrease LT4 dose
Yearly evaluation
LT4 with TSH, FT3, FT4, Tg, neck US

Repeat rhTSH with Tg at > yearly interval

Withdraw LT4
Treatment with large activity of 131I and post-therapy WBS (and/or surgery)

Decreased but still detectable:
Continue TSH suppression, re-test in 1 year

Increased
“A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma”

Mazzaferri EL, Robbins RJ, Spencer CA, Braverman LE, Pacini F, Wartofsky L, Haugen BR, Sherman SI, Cooper DS, et al.

*J Clin Endocrinol Metab, 2003, 88: 1433-2003*

“Follow up of low risk patients with differentiated thyroid carcinoma: an European prospective”


*European Journal of Endocrinology, 2004, 150: 105-112*
CONCLUSIONS

• Follow up based on neck US and Tg/TSH
• Routine control $^{131}$I-TBS in most patients can be avoided: low uptake in the thyroid bed: no relevance
• Use of rhTSH improves the QOL and does not decrease the quality of follow up
• No interest of other scintigraphy markers
• FDG PET scanning in selected patients

• *Shift from suppressive to replacement therapy as soon as your patient is defined as complete remission*