
**III SESSIONE**

**TUMORI DIFFERENZIATI DELLA TIROIDE: PROBLEMI APERTI**

# • Terapia sempre TSH-soppressiva e quale?

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# La triade della terapia del carcinoma tiroideo

- Terapia chirurgica
- Terapia radiometabolica ($^{131}I$) dell'eventuale residuo tiroideo e delle metastasi
- Terapia soppressiva con L-tiroxina.

1. TSH stimola la proliferazione delle cellule tiroidee, l'uptake dello Iodio e la produzione della Tireoglobulina
2. Tuttavia è stato documentato che l'espressione del R-TSH può essere parzialmente o totalmente persa dai carcinomi tiroidei
3. Ci sono funzioni cellulari che non dipendono dal TSH ed è ora nota l'implicazione nello sviluppo tumorale di fattori di crescita e di oncogeni attivati come RET/PTC, BRAF e RAS.

# Treatment With Thyroid Hormone

Bernadette Biondi and Leonard Wartofsky*

Department of Clinical Medicine and Surgery (B.B.), University of Naples Federico II, 80131 Naples, Italy; and Washington Hospital Center (L.W.), Washington, D.C. 20010

**Table 10.** Starting L-$T_4$ Dose According to the Age of the Patients and Physiological and Pathological Conditions

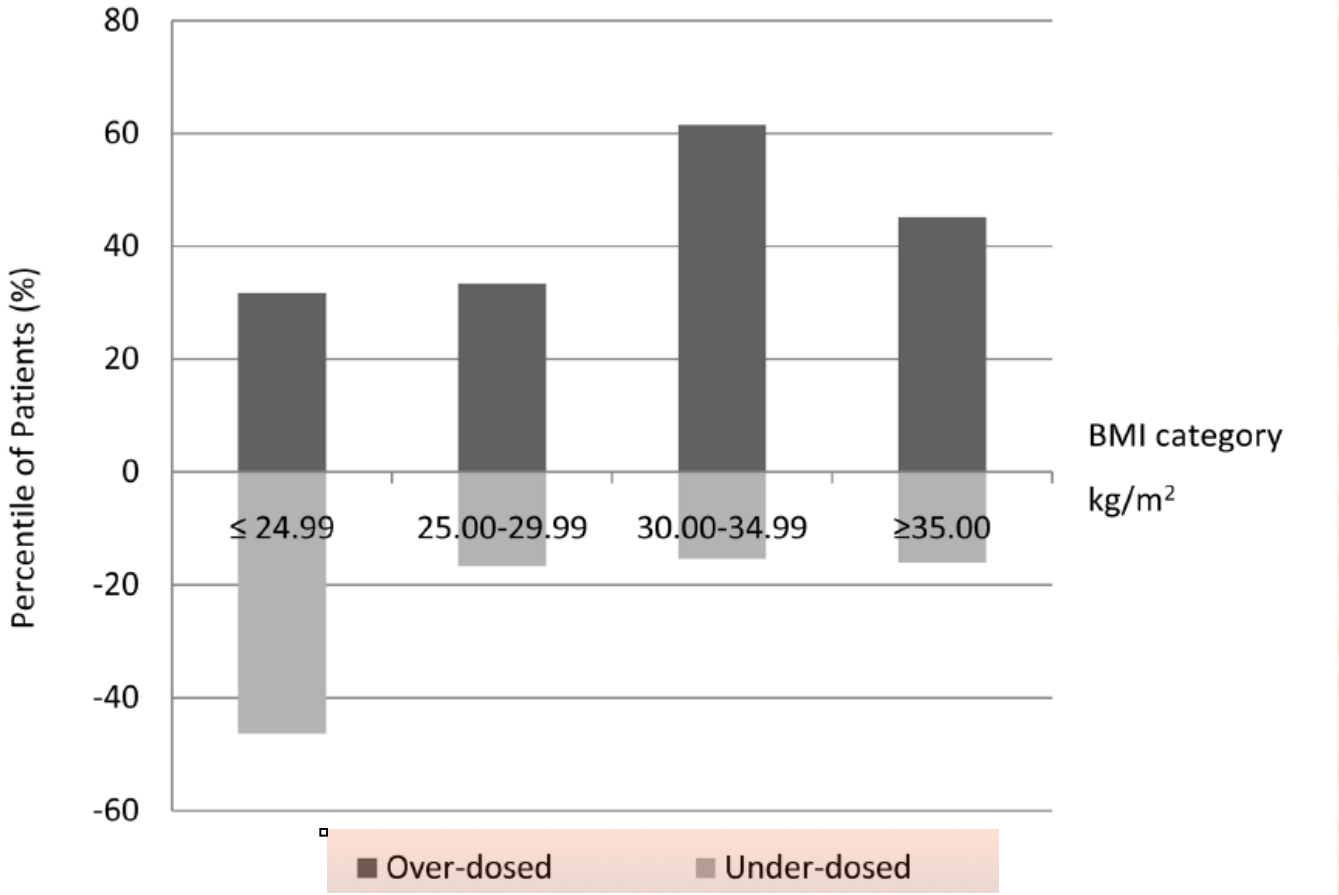
| Age/Condition | Starting L-$T_4$ Dose |
|---|---|
| Adults with primary hypothyroidism | 1.6–1.8 μg/kg/d for replacement doses<br>2.0–2.5 μg/kg/d for TSH suppressive doses of L-$T_4$ |
| Elderly patients | 25–50 μg/d with 25–50 μg/d incremental dose every 3–4 wk |
| Very elderly patients | 12.5–25 μg/d with 12.5–25 μg/d incremental dose every 3–4 wk |
| Patients with CHD | 12.5 μg/d with 12.5 μg/d incremental dose every 3–4 wk |
| Pregnancy | 30–50% increment in dosage (~2.0–2.4 μg/kg/d) |
| Congenital hypothyroidism | 10–15 μg/kg/d (~37.5–50 μg/d) |
| Hypothyroidism during the first 6 mo of age | 8–10 μg/kg/d (~25–37.5 μg/d) |
| Hypothyroidism after 6 mo of age | |
| 6–12 mo | 6–8 μg/kg/d (~50–75 μg/d) |
| 1–5 y | 5–6 μg/kg/d (~75–100 μg/d) |
| 6–12 y | 4–5 μg/kg/d (~75–125 μg/d) |
| 12 y to adults | 1–3 μg/kg/d (~100–200 μg/d) |
| Infantile CH | 8–10 μg/kg/d (~25–37.5 μg/d) |
| Juvenile and adult CH | 1.3 μg /kg/d |

La dose correla con il BMI e in particolare con la massa magra, più che con peso, età e sesso

## Using BMI to Predict Optimal Thyroid Dosing Following Thyroidectomy

*J Am Coll Surg.* 2013 March : 216(3): 454–460.

Kristin A. Ojomo, PA[1], David F. Schneider, MD, MS[1], Alexandra E. Reiher, MD[2], Ngan Lai, BA[1], Sarah Schaefer, NP[1], Herbert Chen, MD, FACS[1], and Rebecca S. Sippel, MD, FACS[1]



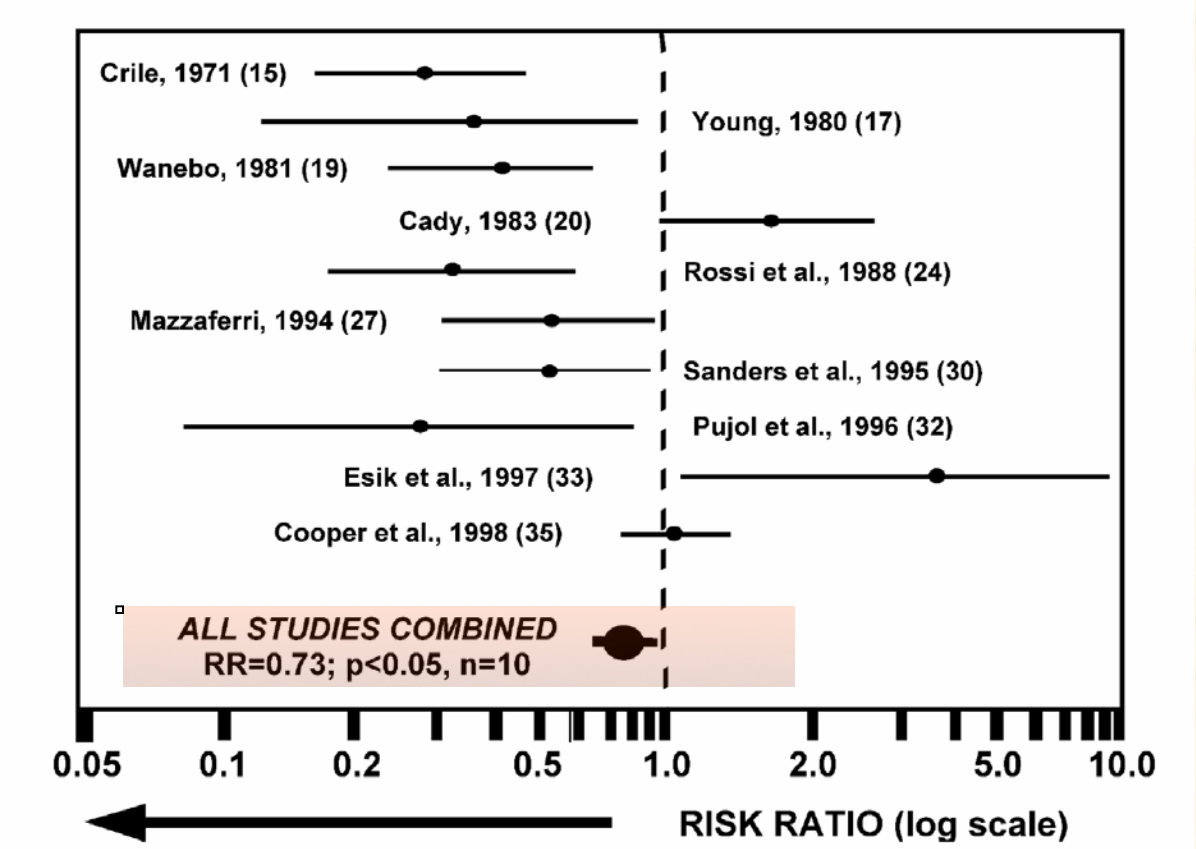

Mcg/kg/day= -.018*BMI +2.13

# Effects of thyroid hormone suppression therapy on adverse clinical outcomes in thyroid cancer

*Nayahmka J McGriff*[1], *Gyorgy Csako*[2], *Loukas Gourgiotis*[3], *Lori C Guthrie*[3] *Frank Pucino*[1] *and Nicholas J Sarlis*[4].

*Ann Med* 2002; 34: 554–564

| Primary study (First author and publication year (reference no.) |
|---|
| Mazzaferri, 1994 (27) |
| Pujol, 1996 (32) |
| Cooper, 1998 (35) |
| Crile, 1971 (15) |
| Young, 1980 (17) |
| Wanebo, 1981 (19) |
| Cady, 1983 (20) |
| Rossi, 1988 (24) |
| Sanders, 1995 (30) |
| Esik, 1997 (33) |




Limiti metodologici:
Casistiche vecchie
Trattamenti non omogenei
Casistiche piccole
Manca la valutazione di aggressività

THTS: riduce il rischio di eventi clinici avversi maggiori

# Outcomes of Patients with Differentiated Thyroid Carcinoma Following Initial Therapy*

Jacqueline Jonklaas,[1] Nicholas J. Sarlis,[2‡] Danielle Litofsky,[2] Kenneth B. Ain,[3] S. Thomas Bigos,[4] James D. Brierley,[5] David S. Cooper,[6] Bryan R. Haugen,[7] Paul W. Ladenson,[8] James Magner,[9] Jacob Robbins,[10] Douglas S. Ross,[11] Monica Skarulis,[10] Harry R. Maxon,[12] and Steven I. Sherman[2]

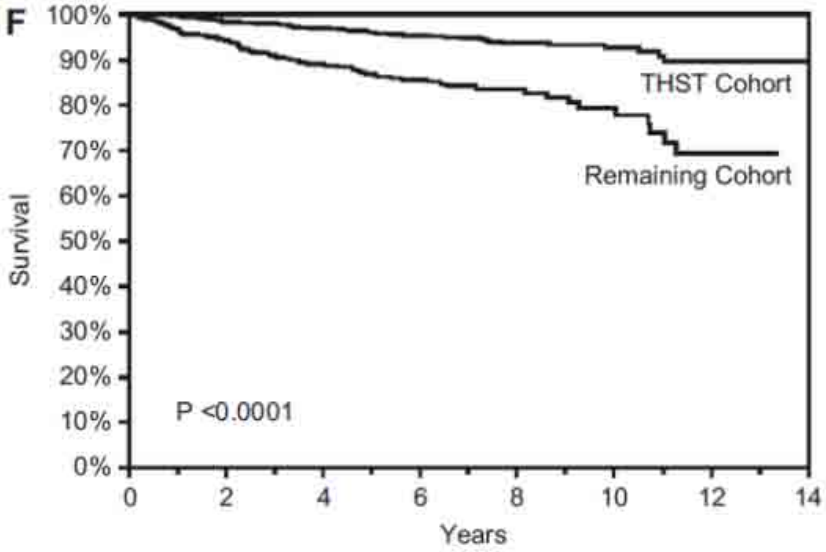
THYROID
Volume 16, Number 12, 2006

| | | *Overall Survival* | | | *Disease-Specific Survival* | | | *Disease-Free Survival* | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *TSH score group* | *RR* | *95% CI* | *p*** | *RR* | *95% CI* | *p*** | *RR* | *95% CI* | *p*** |
| Stage I | 3/(1&2) | $6\times10^{-6}$ | * | 0.65 | 1.00 | * | 1.00 | 0.47 | 0.077–1.54 | 0.24 |
| Stage II | 3/(1&2) | 101 | 10–2300 | 0.0001 | $1.6\times10^{-6}$ | * | 0.89 | 1.03 | 0.17–3.43 | 0.97 |
| Stages III & IV | (3&2)/1 | 2.04 | 1.18–3.64 | 0.011 | 4.07 | 1.32–10.5 | 0.017 | 1.27 | 0.77–2.11 | 0.35 |

N: 2936 DTC
Mean TSH score: gruppo 1: 1-1.9 mUI/L
gruppo 2: 2-2.9
gruppo 3: 3-4

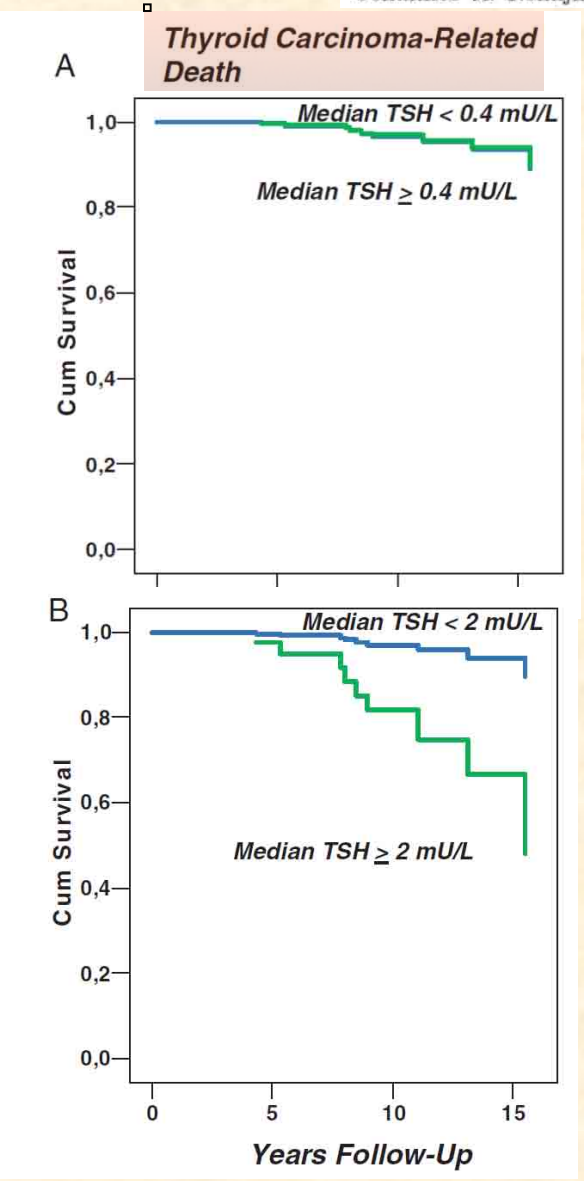
Stratifica efficacia:
Stadio I (basso rischio): nessun effetto
Stadio II, III, IV: correlazione chiara tra THST e sopravvivenza

TSH > 3 mUI/L: riducono sopravvivenza



# Associations of Serum Thyrotropin Concentrations with Recurrence and Death in Differentiated Thyroid Cancer

Guido C. Hovens, Marcel P. Stokkel, Job Kievit, Eleonora P. Corssmit, Alberto M. Pereira, Johannes A. Romijn, and Johannes W. A. Smit

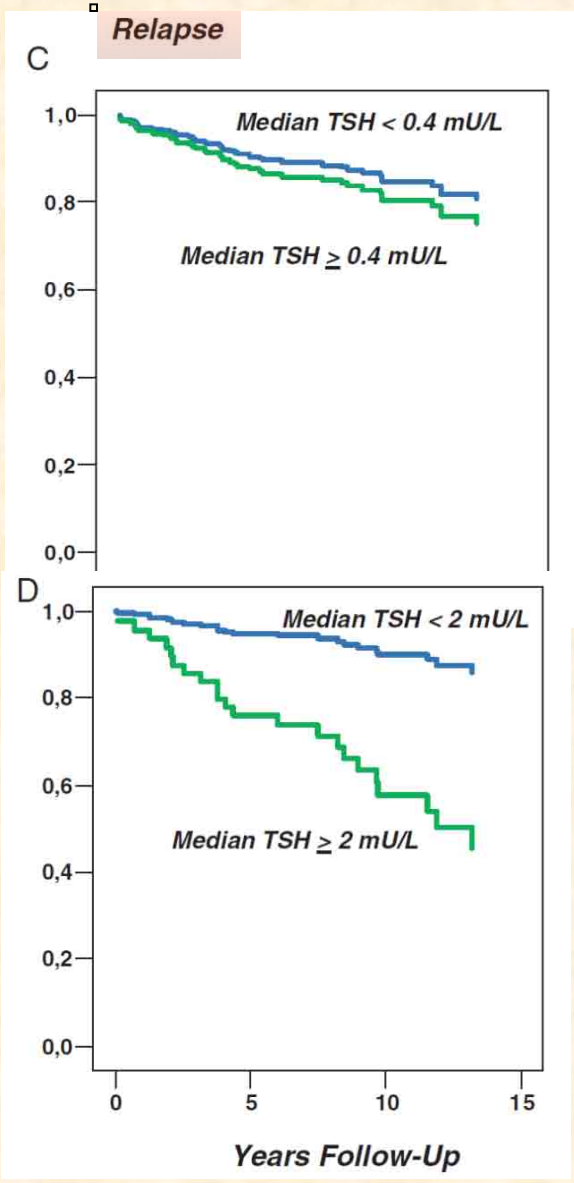



Nessuna differenza nei pz con TSH < 0.1 o < 0.4 mUI/L.

**N: 366 DTC**, Olanda

TSH >2 mUI/L si associa con rischio aumentato di morte specifica e recidiva.

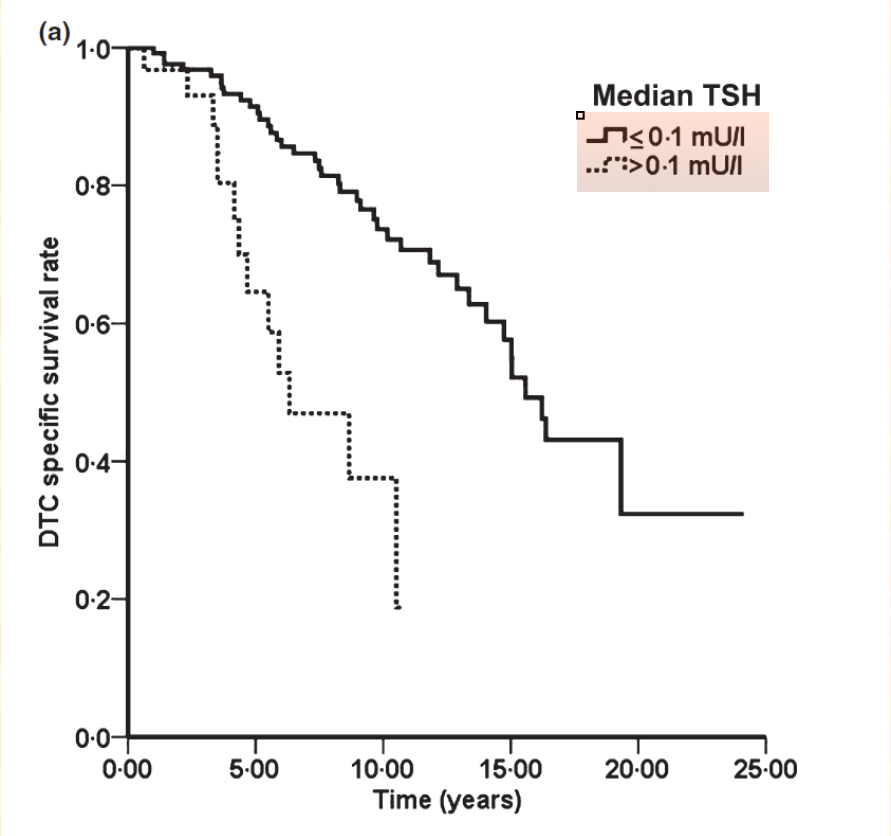
TSH > 4.5 mUI/L è un predittore indipendente di mortalità.

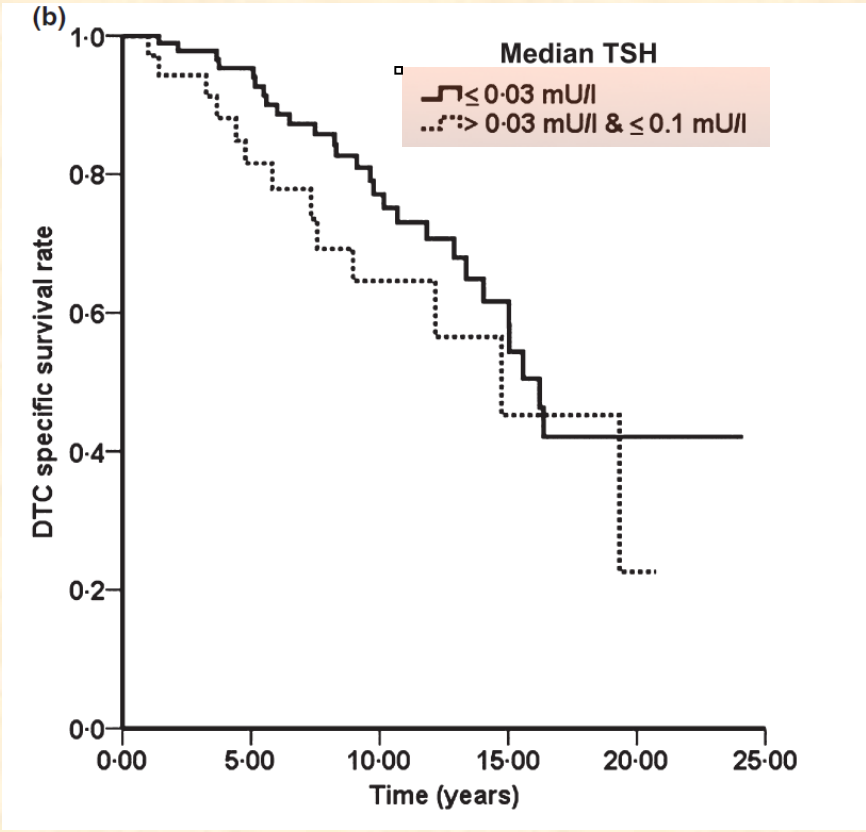



(*J Clin Endocrinol Metab* 92: 2610–2615, 2007)

# Impact of moderate *vs* stringent TSH suppression on survival in advanced differentiated thyroid carcinoma

Stefanie Diessl*, Barbara Holzberger*, Uwe Mädert, Inge Grelle*, Johannes W. A. Smit‡, Andreas K. Buck*, Christoph Reiners* and Frederik A. Verburg*·§



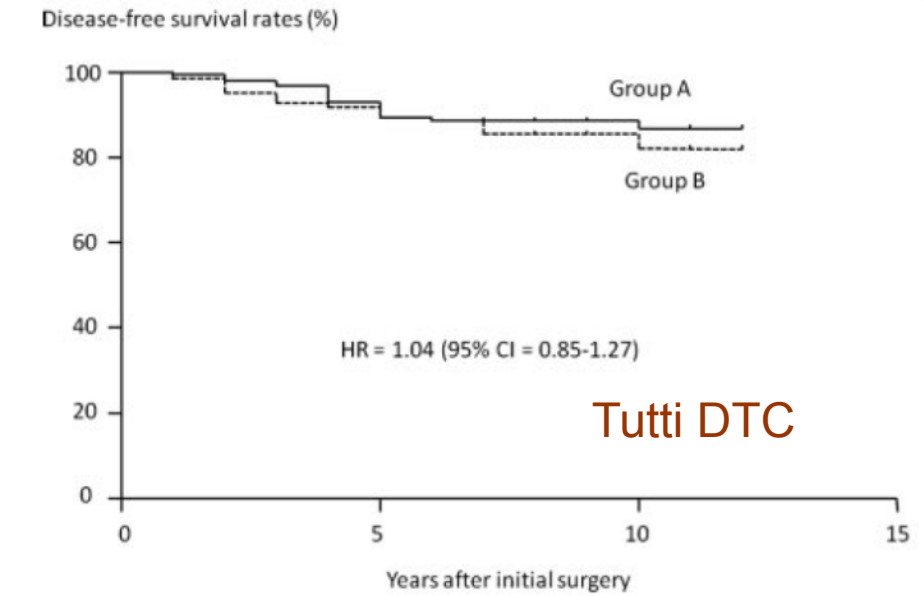

Nei pz DTC con M+ migliora la prognosi per TSH < 0.1 mUI/L.
Non ulteriori benefici per TSH < 0.1 mUI/L.

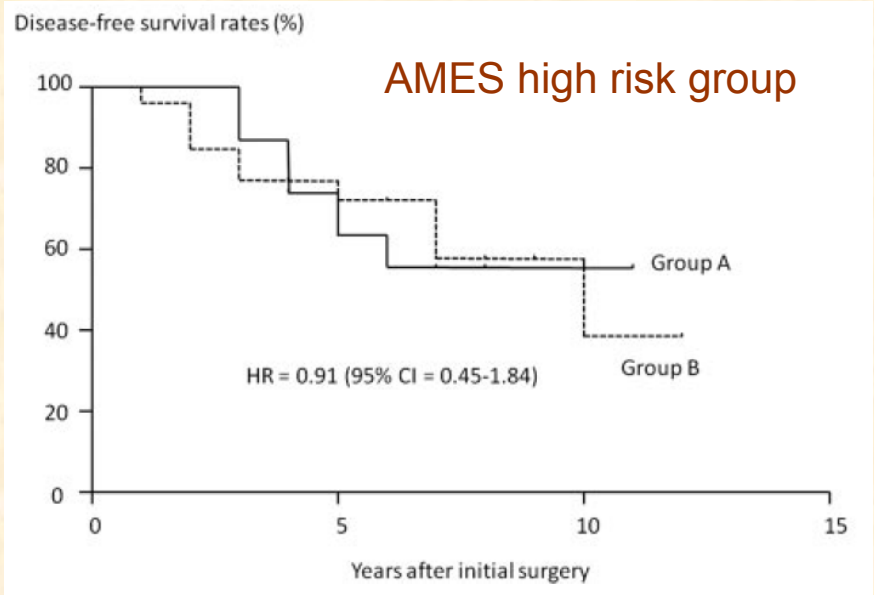
Clinical Endocrinology (2012) **76**, 586–592

# Does Postoperative Thyrotropin Suppression Therapy Truly Decrease Recurrence in Papillary Thyroid Carcinoma? A Randomized Controlled Trial

Iwao Sugitani and Yoshihide Fujimoto

Studio prospettico, randomizzato, 218 (T4 soppressiva) vs 215 (T4 sostitutiva) DTC
Follow-up 7 anni. Nessuna differenza per recidive, tempo libero da malattia, metastasi, mortalità generale e specifica.

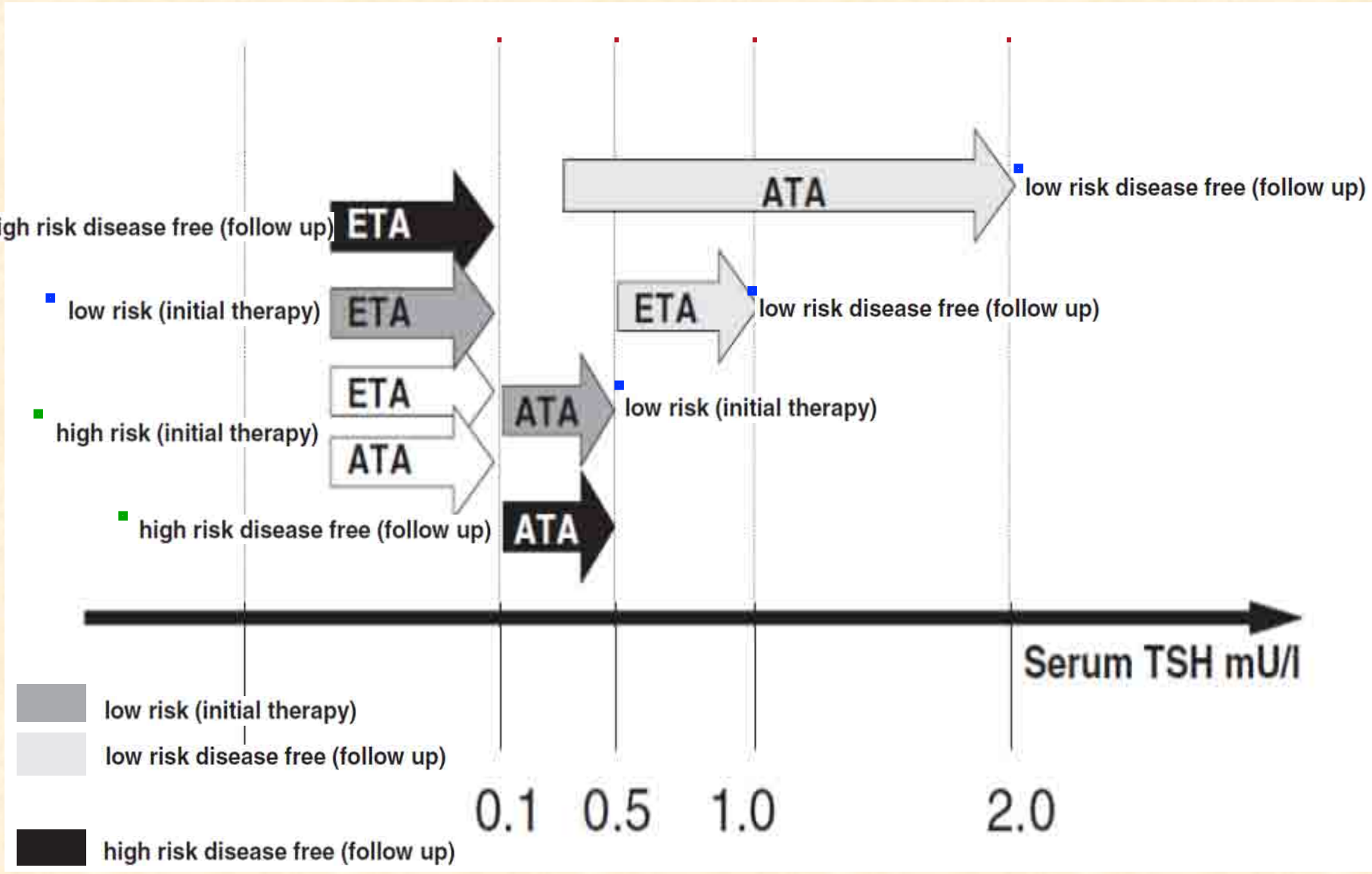



| | | | |
|---|---|---|---|
| TSH (μU/ml) | 0.07 ± 0.13 (range, <0.01–6.55) | 3.19 ± 1.74 (range, 0.01–39.90) | <0.0001[a] |

(*J Clin Endocrinol Metab* 95: 4576–4583, 2010)

# *Differenze nella terapia con L-T4 nei DTC tra le principali linee guida (ATA 2009-ETA 2006)*



# Potenziali effetti avversi della ST con LT4

- Sistema cardiovascolare (alterazioni elettrofisiologiche e strutturali miocardiche)
- Osso (riduzione della BMD e aumento rischio frattura)
- Quality of life
- SNC (demenza e Alzheimer)
- Immunità
- Emostasi (stato protrombotico)

Gli effetti avversi sono strettamente legati all'età del paziente.
I pazienti più anziani hanno un rischio più elevato di svilupparli e sono spesso meno sintomatici

# Thyroid Function and Cancer Risk: A Prospective Population Study

Alf Inge Hellevik, Bjørn Olav Åsvold, Trine Bjøro, et al.

*Cancer Epidemiol Biomarkers Prev* 2009;18:570-574.

N: 29.691 pz, Norvegia, follow-up 9 yr

**Table 1. HRs for total cancer and specifically, for cancer of the colon, lung, breast, and prostate, by categories of thyrotropin measured at baseline**

| Thyrotropin (mU/L) | Persons (*n*) | Cancers (*n*) | HR* | HR (95% CI)† |
|---|---|---|---|---|
| Total cancer | | | | |
| <0.50 | 674 | 76 | 1.36 | 1.34 (1.06-1.69) |
| 0.50-1.4 | 12,389 | 1,010 | 1.0 (Reference) | 1.0 (Reference) |
| 1.5-2.4 | 10,882 | 914 | 0.95 | 0.98 (0.90-1.08) |
| 2.5-3.5 | 3,597 | 313 | 0.89 | 0.95 (0.83-1.08) |
| >3.5 | 2,149 | 198 | 0.90 | 0.96 (0.82-1.12) |
| Colon cancer | | | | |
| <0.50 | 674 | 9 | 1.42 | 1.38 (0.70-2.73) |

**Table 3. HRs of total cancer and cancer of the lung and prostate among people with overt and subclinical hyperthyroid function, compared with the euthyroid reference group (0.50-1.4 mU/L)**

| | Overt hyperthyroid function* | | | Subclinical hyperthyroid function† | | |
|---|---|---|---|---|---|---|
| | Cancers (*n*) | Persons (*n*) | HR (95% CI)‡ | Cancers (*n*) | Persons (*n*) | HR (95% CI)‡ |
| With follow-up starting at baseline | | | | | | |
| Total cancer | 12 | 75 | 1.96 (1.11-3.47) | 64 | 599 | 1.27 (0.98-1.63) |
| Lung cancer | 2 | 75 | 4.65 (1.14-19.04) | 9 | 599 | 2.11 (1.06-4.20) |
| Prostate cancer | 1 | 8 | 4.08 (0.57-29.36) | 9 | 163 | 1.87 (0.95-3.68) |
| With follow-up starting 2 years after baseline | | | | | | |
| Total cancer | 11 | 70 | 2.35 (1.29-4.26) | 56 | 578 | 1.42 (1.08-1.86) |
| Lung cancer | 2 | 70 | 6.80 (1.65-28.09) | 8 | 578 | 2.55 (1.22-5.35) |
| Prostate cancer | 1 | 6 | 5.47 (0.76-39.55) | 9 | 154 | 2.46 (1.24-4.87) |
| 0.50-1.4 | | 4,362 | 135 | 1.0 (Reference) | | 1.0 (Reference) |
| 1.5-2.4 | | 3,764 | 121 | 0.94 | | 0.93 (0.73-1.20) |
| 2.5-3.5 | | 1,121 | 37 | 0.79 | | 0.78 (0.54-1.13) |
| >3.5 | | 563 | 23 | 0.87 | | 0.86 (0.55-1.35) |

**Integrin $\alpha_V\beta_3$ Contains a Cell Surface Receptor Site for Thyroid Hormone that Is Linked to Activation of Mitogen-Activated Protein Kinase and Induction of Angiogenesis**

2005 Endocrinology 146(7):2864–2871

Joel J. Bergh, Hung-Yun Lin, Lawrence Lansing, Seema N. Mohamed, Faith B. Davis, Shaker Mousa, and Paul J. Davis

L'integrina alfavBeta3, proteina eterodimerica di membrana ha siti specifici che agiscono come R degli ormoni tiroidei.

Ha locus specifici in grado di legare alcuni T4, altri T3 e sosterrebbe l'azione non-genomica degli ormoni tiroidei.

Viene espressa sulla superficie di cellule endoteliali e muscolari lisce
e sulla membrana cellulare di numerosi tumori (inclusi polmone e prostata).

E' stato dimostrato che la sua attivazione, a concentrazioni fisiologiche di T4, provoca proliferazione e riduce apoptosi in linee cellulari di PTC e FTC.

E' stato postulato che la sua attivazione da parte degli TH possa essere responsabile della promozione dell'angiogenesi attraverso l'attivazione di vie protein-chinasiche (MAPK).

*High risk from tumor recurrence or death*

- Increased age (>45–50 years)
- Increased size (>4 cm)
- Macroscopic tumor invasion
- Incomplete tumor resection
- Distant metastases
- Radioiodine uptake outside the thyroid bed after a posttreatment radioiodine scan performed after ablation of remnant thyroid

## *Risk from $T_4$ therapy*

- Patients with a history of paroxysmal or persistent atrial fibrillation (71,72,78), especially in the presence of left atrial enlargement (78);
- Patients with previous history of stroke or transient ischemic attack (78);
- Other comorbidities (e.g., diabetes, renal failure) (80);
- Left atrial dilatation (78);
- Increased risk factors for stroke (78);
- Patients with a history of congestive heart failure (81);
- The presence of valvular heart disease (78);
- Known or suspected vascular disease (coronary or peripheral arterial disease) (80–83);
- Evidence of osteoporosis or a previous fragility fracture (69,107).

## *Risk of cancer recurrence and progression*

# Grazie per l'attenzione!