

# **Carcinoma tiroideo: overdiagnosis?**

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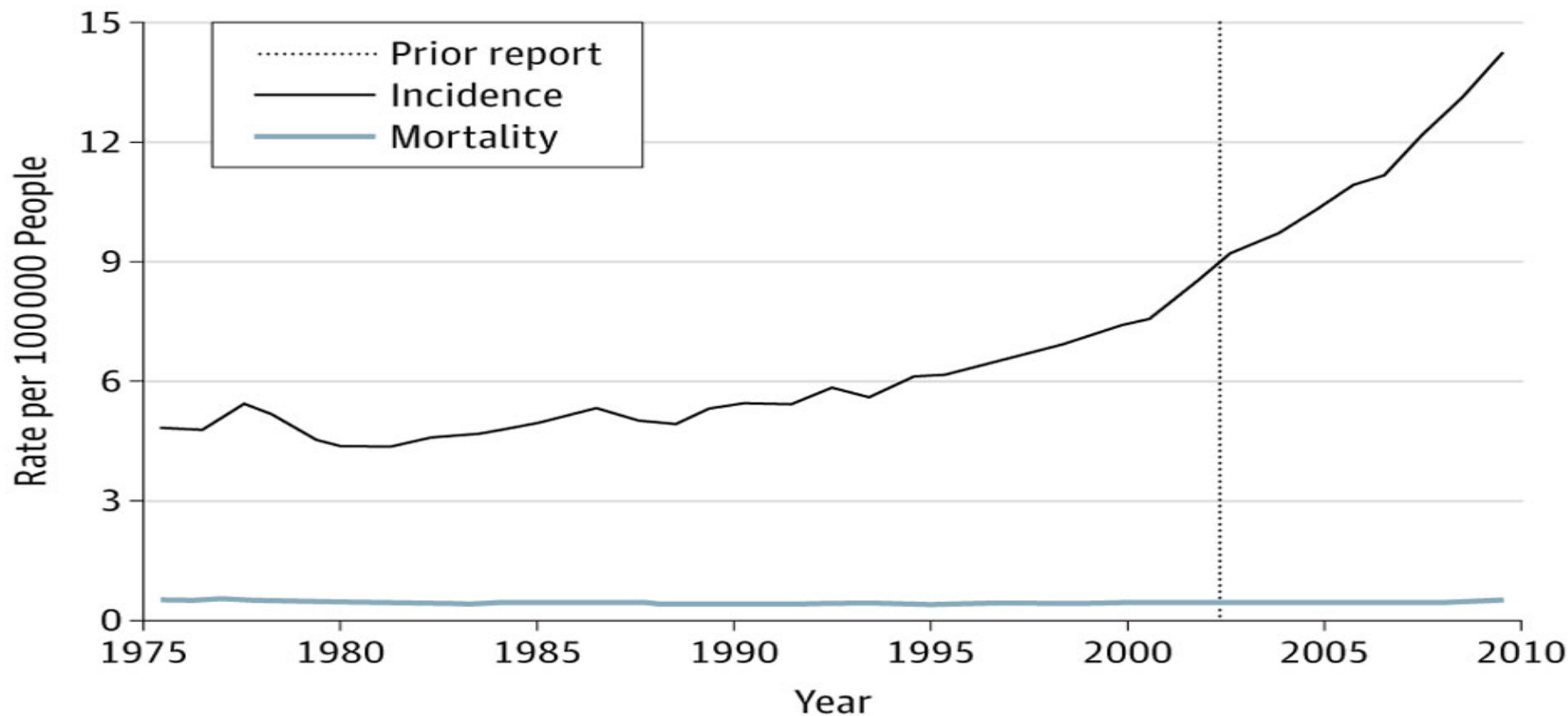


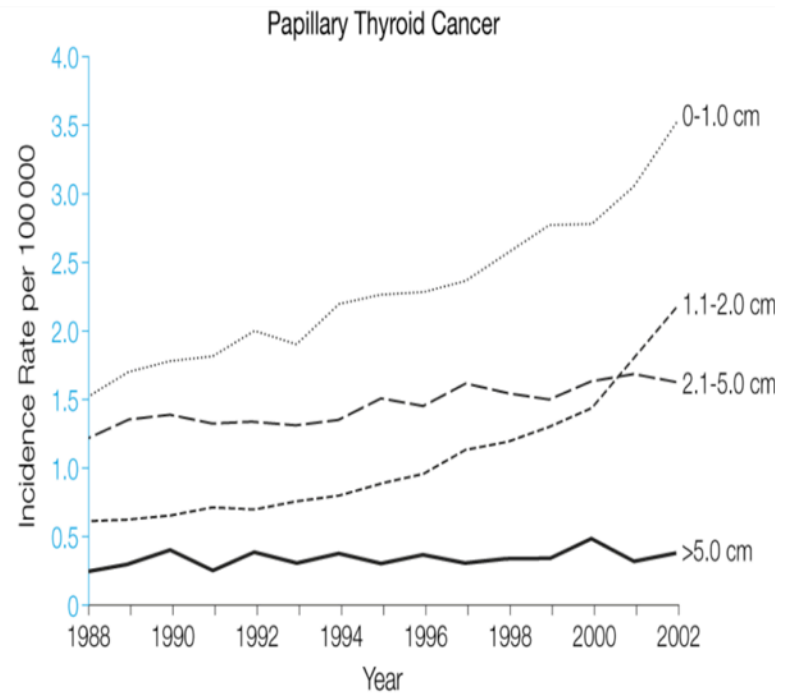
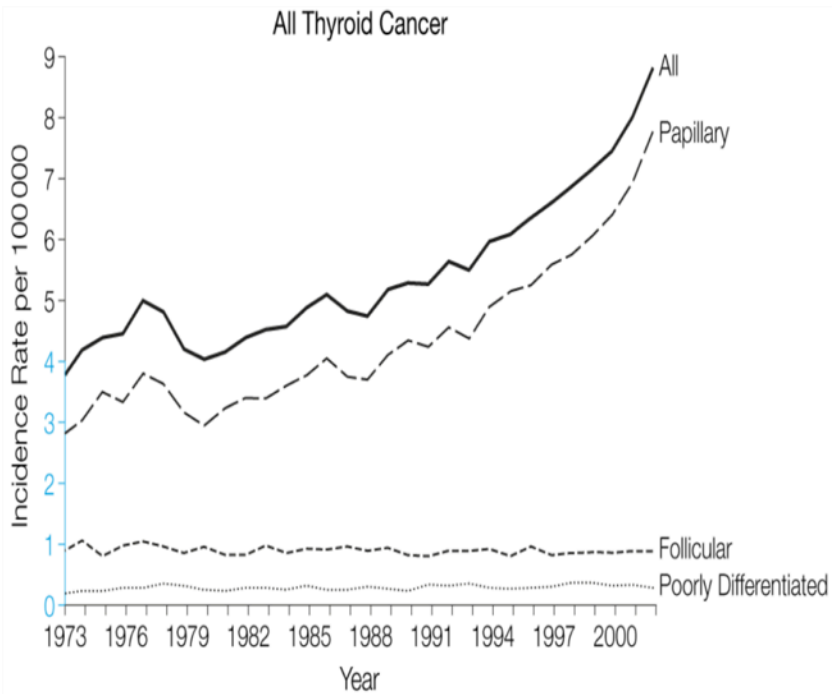
Table 1. Absolute and Relative Changes in Thyroid Cancer Incidence in the United States by Sex, 1975, 2002, and 2009<sup>a</sup>

Group	Thyroid Cancer Incidence, Age-Adjusted Rate per 100 000 Individuals			Change From 1975 Baseline, No. (Range)		Change From 2002 Prior Report, No. (Range)	
	Baseline 1975 (a)	Prior Report 2002 (b)	Current 2009 (c)	Absolute (c - a)	Relative (c/a)	Absolute (c - b)	Relative (c/b)
<b>Any thyroid cancer</b>							
Both sexes	4.9	9.2	14.3	9.4 (8.9-9.9)	2.9 (2.7-3.1)	5.1 (4.5-5.6)	1.6 (1.5-1.6)
Women	6.5	13.4	21.4	14.9 (14.0-15.8)	3.3 (3.0-3.6)	8.0 (7.0-9.0)	1.6 (1.5-1.7)
Men	3.1	4.9	6.9	3.8 (3.2-4.4)	2.2 (1.9-2.6)	2.0 (1.4-2.6)	1.4 (1.3-1.6)
<b>Papillary thyroid cancer</b>							
Both sexes	3.4	7.9	12.5	9.1 (8.6-9.6)	3.7 (3.4-4.0)	4.6 (4.1-5.1)	1.6 (1.5-1.7)
Women	4.6	11.6	19.0	14.4 (13.6-15.2)	4.1 (3.7-4.6)	7.4 (6.5-8.3)	1.6 (1.5-1.7)
Men	2.2	4.0	5.9	3.7 (3.2-4.2)	2.7 (2.3-3.2)	1.9 (1.4-2.4)	1.5 (1.3-1.7)

<sup>a</sup> Data are from Surveillance, Epidemiology, and End Results (SEER) 9, 1975-2009, maintained by the National Cancer Institute, National Institutes of Health, released April 2012, based on the November 2011 submission.

From: **Increasing Incidence of Thyroid Cancer in the United States, 1973-2002**

JAMA. 2006;295(18):2164-2167. doi:10.1001/jama.295.18.2164

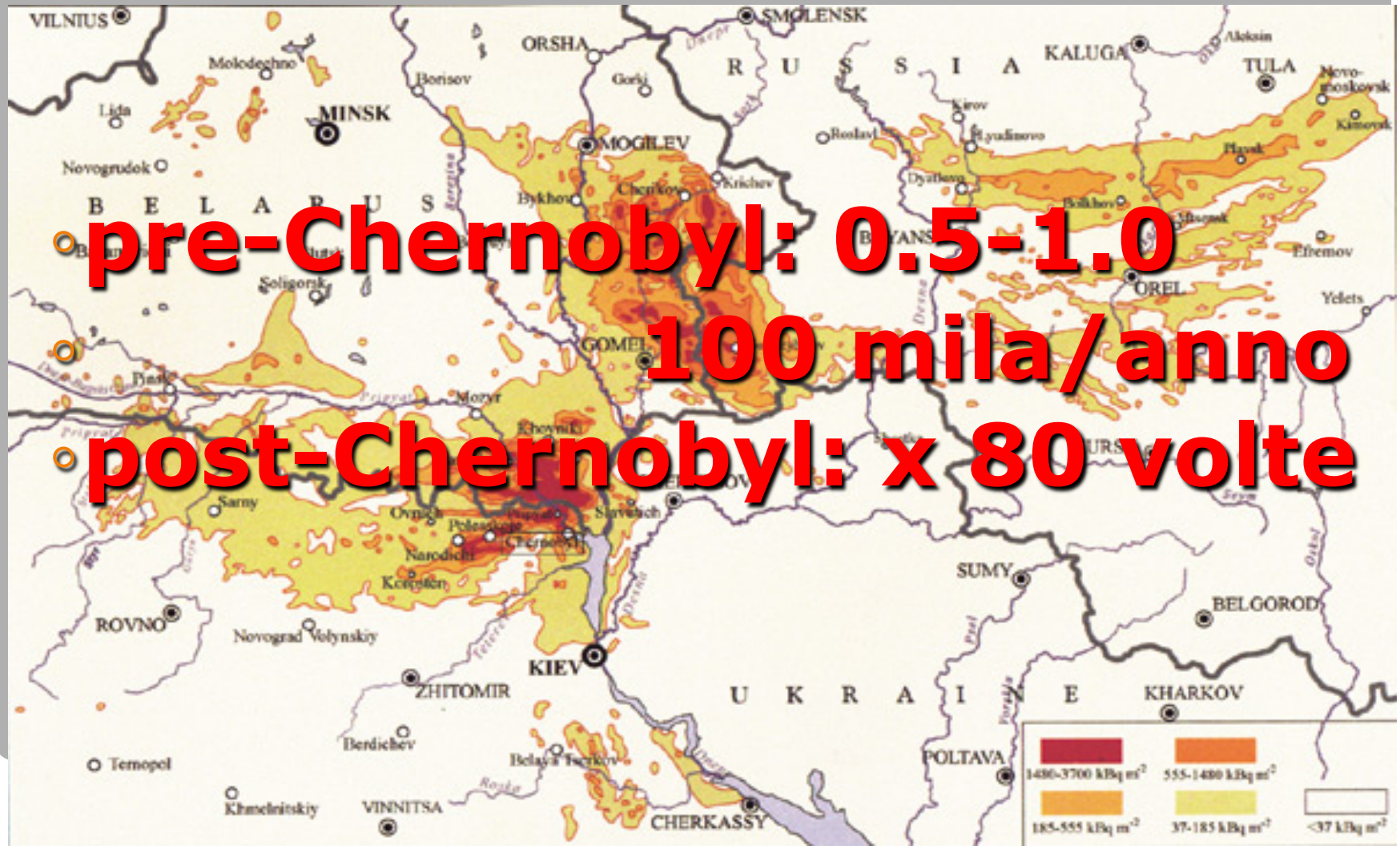


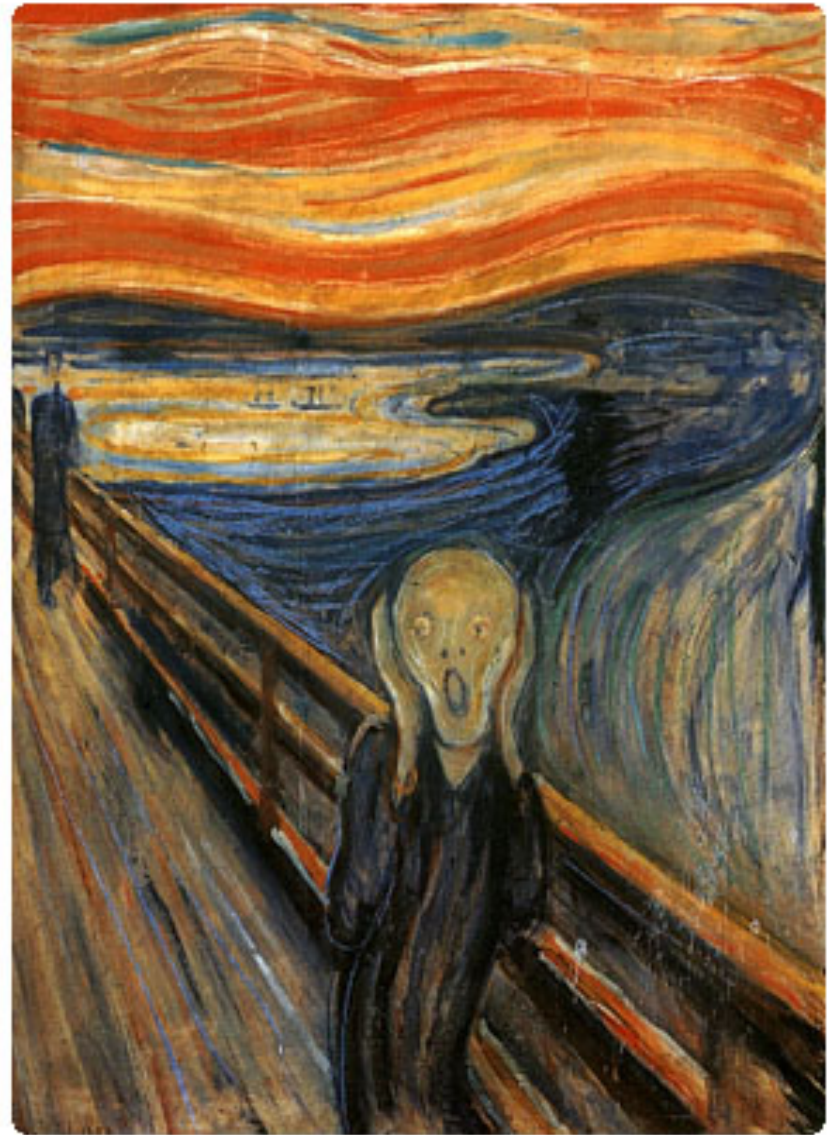
**Figure Legend:**

Poorly differentiated indicates anaplastic and medullary cancers.

**Davies & Welch, 2006**

# Incidenza nei bambini ucraini





**Pellegriti et al 2009**

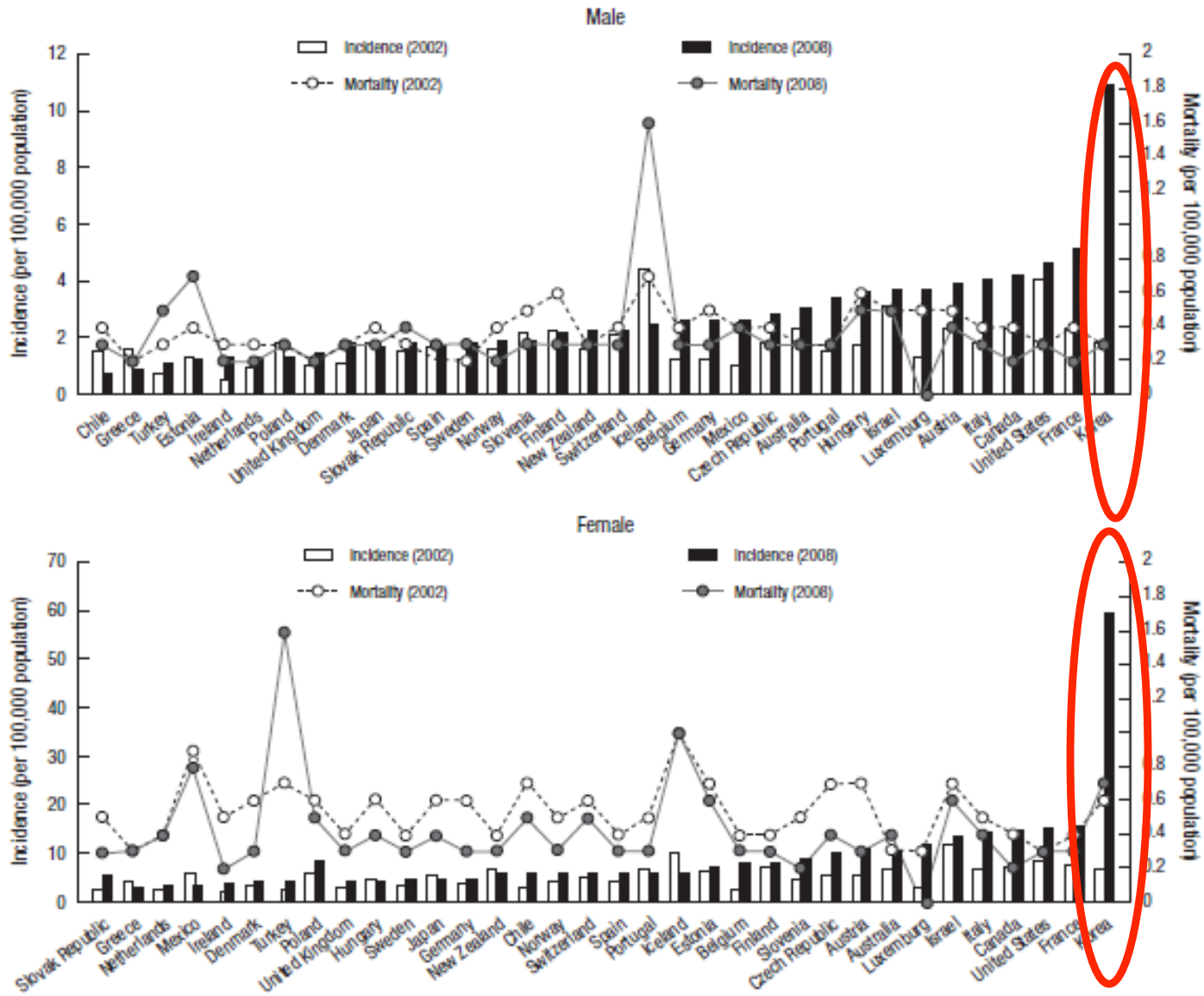


Fig. 1. Incidence and mortality of thyroid cancer in OECD countries (2002, 2008). Incidence and mortality of thyroid cancer denote age-standardized rates per 100,000 population in OECD countries in 2002 and 2008. About three fourths of the countries experienced increases in the incidence of thyroid cancer from 2002 to 2008 while most countries maintained a low mortality or even experienced decreases in mortality during this period. Sources: GLOBOCAN 2002 and 2008.



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# Thyroid cancer: zealous imaging has increased detection and treatment of low risk tumours

This article is part of a series on overdiagnosis looking at the risks and harms to patients of expanding definitions of disease and increasing use of new diagnostic technologies

Thyroid cancer is the most common endocrine malignancy.<sup>1</sup> Worldwide, its incidence has increased substantially over the past 50 years. The Cancer Incidence in Five Continents report showed that the age standardised incidence of thyroid cancer in women rose from 1.5 cases/100 000 population in 1953 to 7.5 cases/100 000 in 2002, with a similar relative increase in men (fig 1).<sup>2</sup> Behind these averages hide important and surprising differences between and within countries. In the US, the incidence of thyroid cancer has tripled in the past 30 years, increasing from 3.6 cases/100 000 in 1973 to 11.6 cases/100 000 in 2009,<sup>3</sup> making it one of the fastest growing diagnoses. By contrast, in Sweden, Japan, and China, the increase in incidence has been minimal.<sup>2</sup>

## Not all thyroid cancers are equal

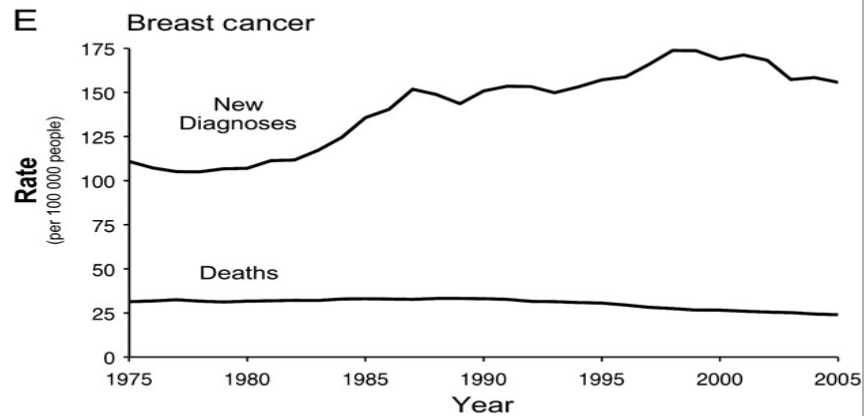
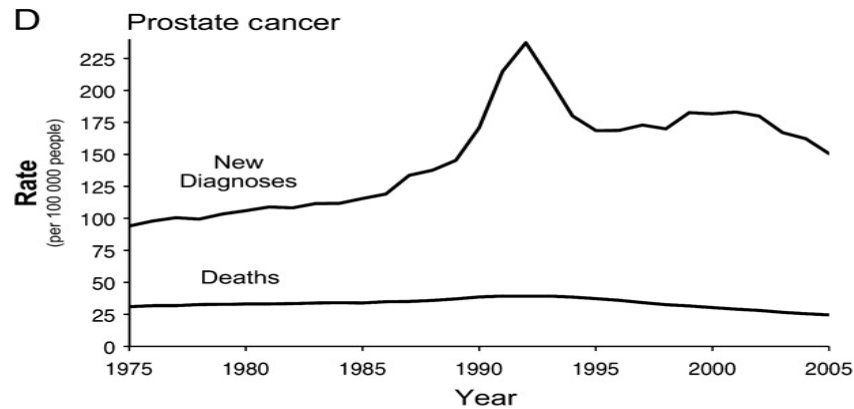
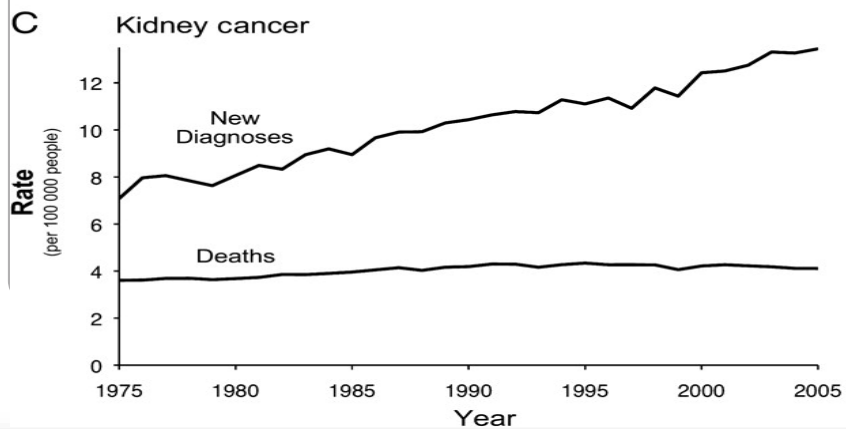
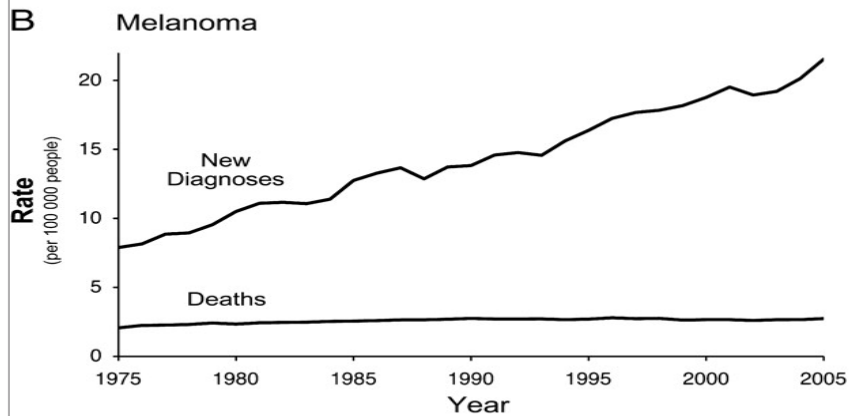
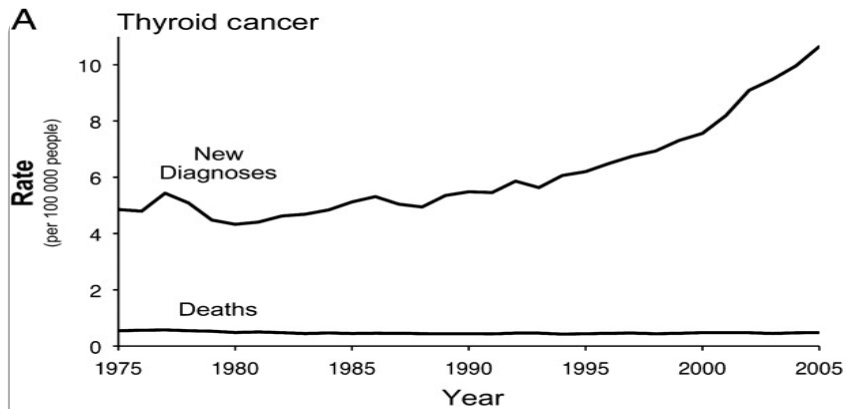
Malignant cells are detected in only 10% of patients who present with thyroid nodules.<sup>4</sup> To identify which nodules are malignant, current guidelines recommend that patients with thyroid nodules have thyroid ultrasonography followed by fine needle aspiration biopsy if ultrasonography shows suspicious features (microcalcifications, hypoecogenecity, infiltrative margins) or if the patient has a family history of thyroid cancer or has had significant radiation exposure (box).

The histology of malignant thyroid nodules provides the most important prognostic information. Thyroid cancer is divided into four types: papillary (comprising 85% of the total detected), follicular (11%), medullary (3%), and anaplastic (1%).<sup>5-6</sup> Anaplastic thyroid can-

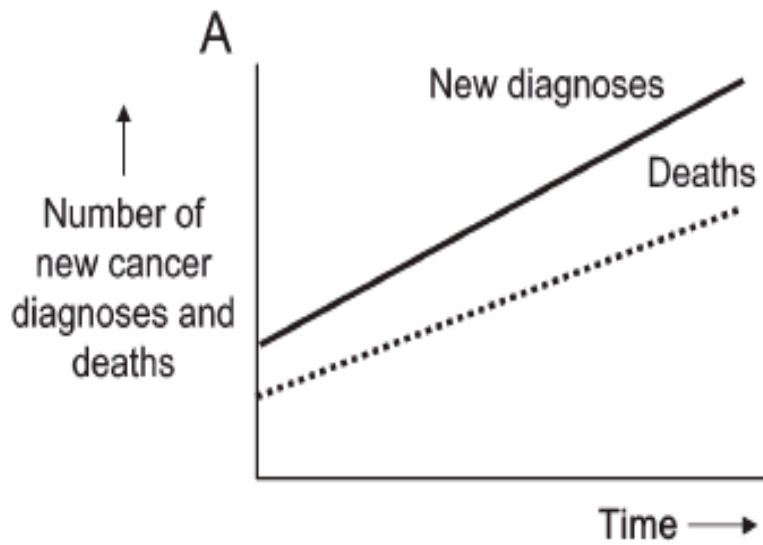
cer is associated with the worst prognosis, with most patients dying within a year of diagnosis (table).<sup>7</sup> This contrasts with the excellent prognosis of papillary cancers, especially in patients with nodules <20 mm in diameter: 99% of these patients will be alive at 20 years.<sup>8</sup> Patients with small (<15-20 mm) lesions, no family history of thyroid cancer or personal history of radiation exposure, and no evidence of extraglandular invasion on ultrasonography are considered to be at low risk of progression.<sup>9-10</sup>

Autopsy series have shown a large reservoir of subclinical papillary thyroid cancers. One study found that a third of people who died from other causes had this type of thyroid cancer. These tumours (most <1 mm) were discovered through interval sectioning even though the possibility that many were missed between interval cuts. The presence of this subclinical reservoir is consistent with the

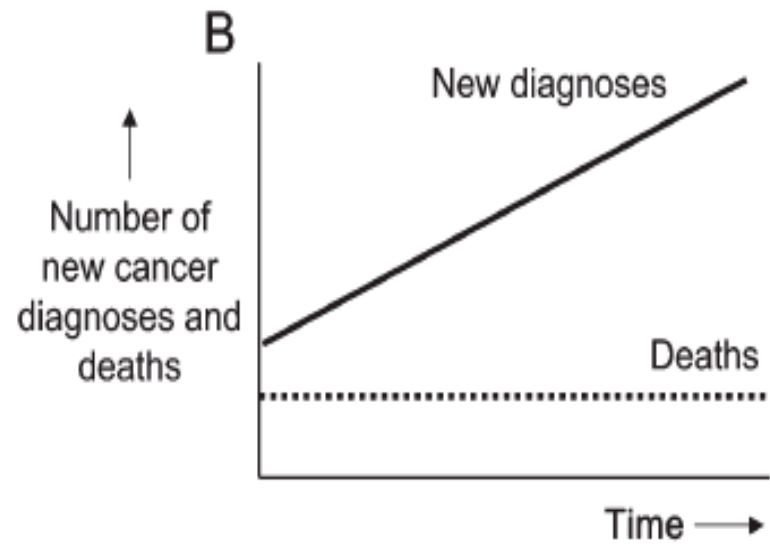




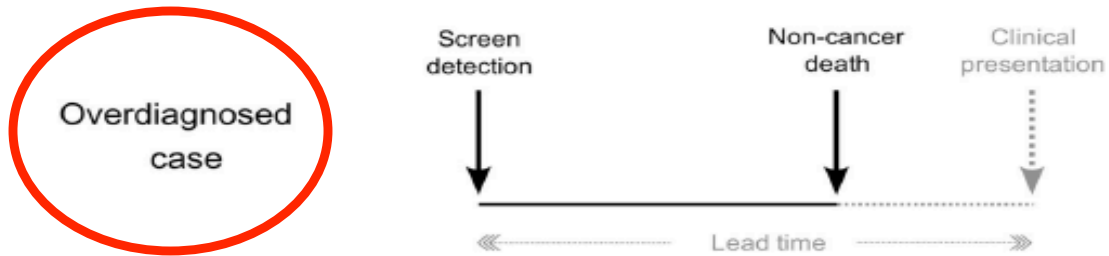
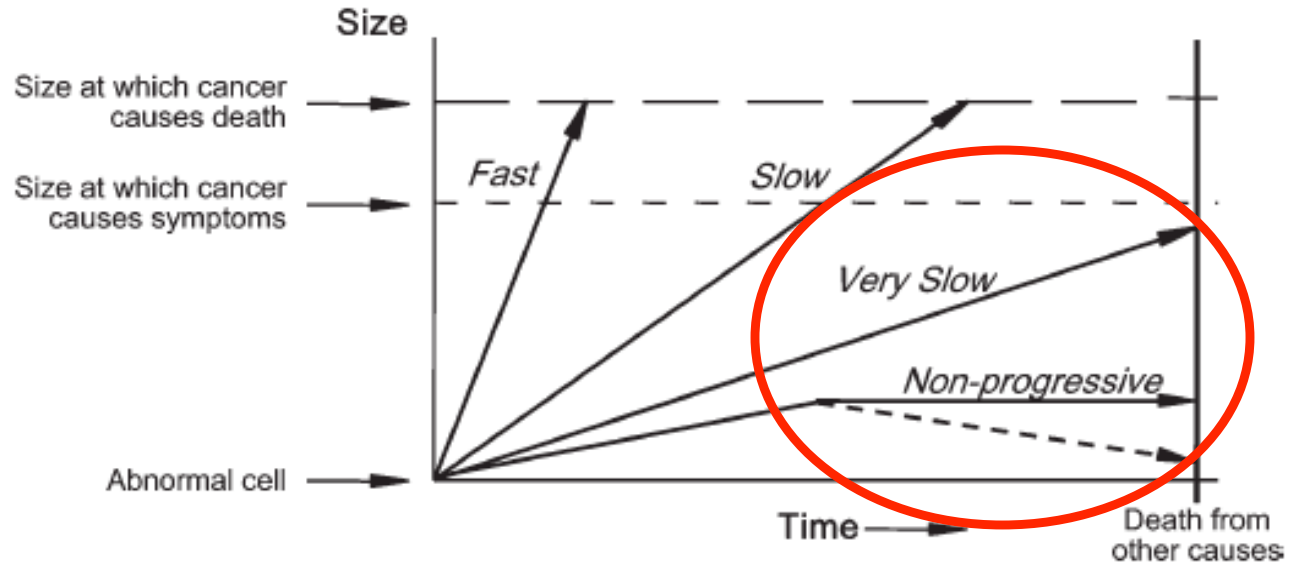





Suggests a true increase in the amount of cancer



Suggests overdiagnosis of cancer



# overdiagnosis

- **Quando in soggetti asintomatici viene diagnosticata una malattia che non sarà mai sintomatica né causa di mortalità precoce**
- 
- Eccesso di medicalizzazione
  - Possibile overtreatment
  - Labeling effect
  - Spreco di risorse economiche che potrebbero essere più appropriatamente utilizzate
  - Sovrastima dell'efficacia dei trattamenti in oncologia

# Driver dell' overdiagnosis

- Evoluzione tecnologie diagnostiche
- Interessi commerciali e professionali
- Gruppi di esperti in conflitto di interesse che espandono continuamente le definizioni di malattia e definiscono nuove entità patologiche
- Orientamento dell' autorità giudiziaria a condannare l' underdiagnosis ma non l' overdiagnosis
- Sistemi sanitari che incentivano la medicalizzazione
- Percezione socio-culturale che “more is better” e che la diagnosi precoce non comporti alcun rischio



25 Maggio 2013

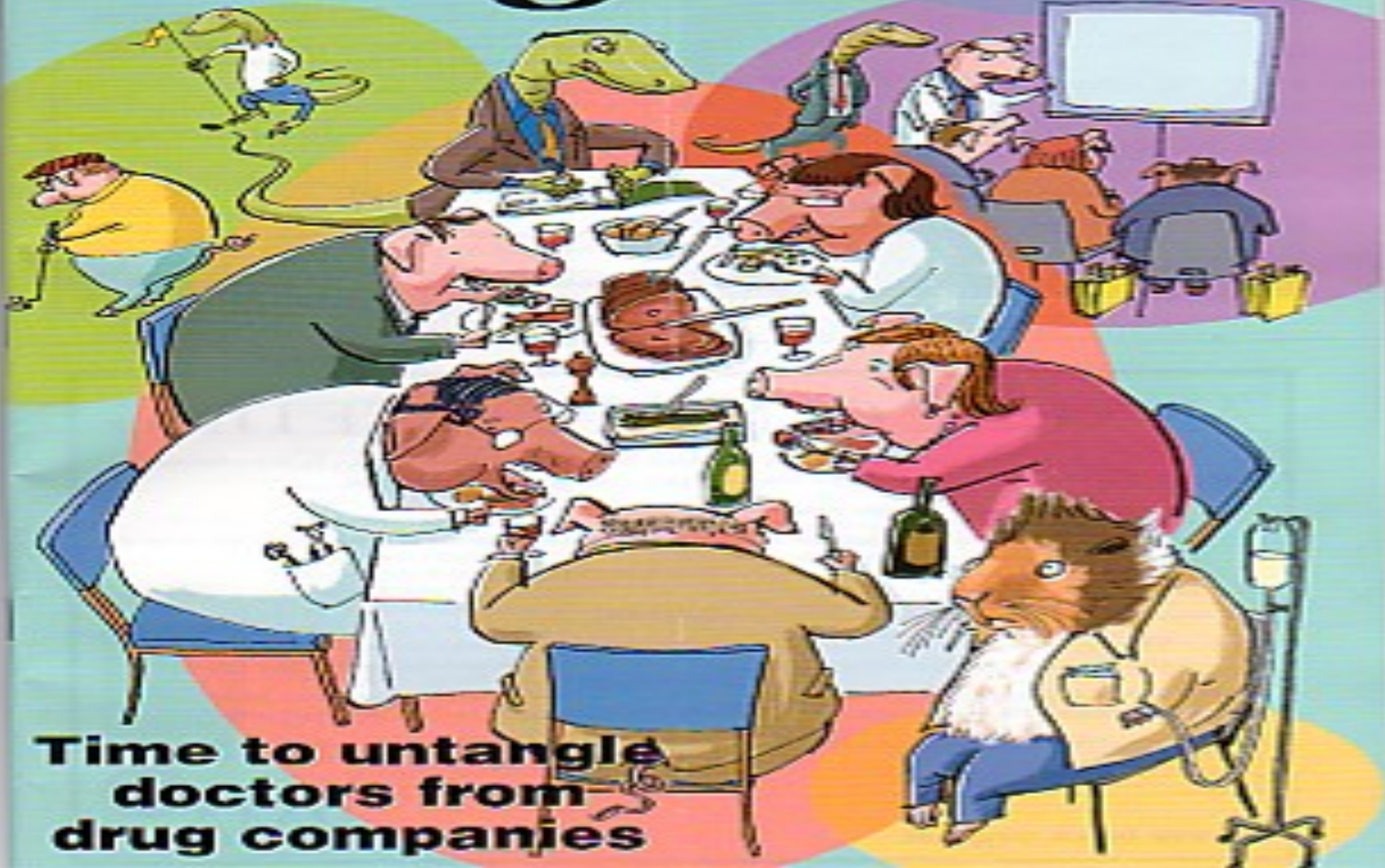
# Giornata Mondiale della **TIROIDE**



**TIROIDE:**  
meglio prevenire  
che curare

# BMJ

No 7800 31 May 2003



**Table 2. Draft balance sheet for screening mammography in 50-year-old women\***

<b>Benefits</b>	<b>Harms</b>
One woman will avoid a breast cancer death (36)	Between two and 10 women will be overdiagnosed and treated needlessly Between five and 15 women will be told that they have breast cancer earlier than they would otherwise yet have no effect on their prognosis Between 200 and 500 women will have at least one "false alarm" (50–200 will be biopsied)

\* Among one thousand 50-year-old women undergoing annual mammography for 10 years. See Supplementary Technical Appendix (available online).

US Preventive Service Task Force. *Effectiveness of Mammography in Reducing Breast Cancer Mortality*. Rockville, MD: Agency for Healthcare Research and Quality. <http://www.ahrq.gov/clinic/3rduspstf/breastcancer/bcscrnsu1.htm#results>.

# Prevenire overdiagnosis e suoi effetti

- Conferenze internazionali
- Archives of Internal Medicine: “less is more”
- BMJ: serie di articoli
- National Cancer Institute: O. tra le priorità
- Nuove linee Guida: atteggiamento meno aggressivo per incidentalomi e alcune lesioni neoplastiche
- Escludere dai gruppi di lavoro i professionisti con rilevanti conflitti di interesse
- Definire regole più rigide per i rapporti con le aziende
- Evitare gli screening sulla popolazione asintomatica
- “Relabeling”: limiti...



# microcarcinoma tiroideo

Prevalence of mPTC in autoptic studies with >200 cases.

Authors (Ref.)	Year	City/Country	Cases	mPTC	Prevalence (%)	Sectioning Techniques
Lang et al <sup>11</sup>	1988	Hannover	1020	63	6.2	1-2mm
Silverberg and Vidone <sup>13</sup>	1966	New Haven	300	8	2.7	2-3mm
Sampson et al <sup>14</sup>	1969	Hiroshima & Nagasaki	1096	196	17.9	2-3mm
Fukunga and Yatani <sup>16</sup>	1975	Columbia	607	34	5.2	2-3mm
Bondeson and Ljungberg <sup>17</sup>	1981	Sweden	500	43	8.6	1-2mm
Furmanchuk et al <sup>18</sup>	1993	Minsk	215	19	8.8	2-3mm
Martinez-Tello et al <sup>19</sup>	1993	Spain	625	33	5.2	3mm
Sobinho-Simoes et al <sup>21</sup>	1979	Portugal	600	39	6.5	3mm
Yamamoto et al <sup>23</sup>	1990	Japan	408	46	11.3	3mm
Arellano and Ibarra <sup>25</sup>	1984	Chile	274	10	3.6	2-3mm
Autelitano et al <sup>26</sup>	1990	Italy	507	37	7.5	2-3mm
Total			6142	528	7.62	

Prevalence of mPTC surgical series with >200 cases.

Authors (Ref.)	Year	City/Country	Cases	mPTC	Prevalence (%)
Sakorafas et al <sup>29</sup>	2007	Greece	380	27	7.1
De Matos et al <sup>30</sup>	2006	Brazil	261	19	7.2
Fink et al <sup>31</sup>	1996	Canada	425	71	16.7
Yamashita et al <sup>32</sup>	1997	Japan	835	137	16.4
Pelizzo et al <sup>34</sup>	1990	Italy	227	24	10.5
Lokey et al <sup>35</sup>	2005	USA	738	28	3.8
Park et al <sup>36</sup>	1988	Korea	1095	56	5.1
Delides et al <sup>38</sup>	1987	Greece	611	11	1.8
Olen and Klinck <sup>39</sup>	1966	USA	2114	53	1.3
Mean			6686	426	7.76

# microcarcinoma tiroideo

Pathological features of mPTC in different series.

Authors (ref)	Year	Series	Multicentricity	Bilaterality	Extrathyroidal invasion	Lymphnode metastases	Distant metastases
Baudin et al <sup>46</sup>	1998	281	112 (40%)	46 (16%)	42 (15%)	121 (43%)	8 (3%)
Hay et al <sup>47</sup>	1992	535	107 (20%)	54 (10%)	10 (2%)	172 (32%)	1 (0.2%)
Roti et al <sup>48</sup>	2006	243	78 (32%)	45 (19%)	42 (17%)	32 (13%)	4 (1.6%)
Chow et al <sup>49</sup>	2003	203	63 (31%)	–	42 (20.7%)	50 (24.6%)	2 (1.0%)
Ito et al <sup>50</sup>	2003	626	269 (42.8%)	–	10 (1.6%)	300 (50.5%)	0 (0%)
Noguchi et al <sup>51</sup>	1996	867	48 (5.5%)	44 (5%)	72 (8.3%)	75 (8.6%)	0 (0%)

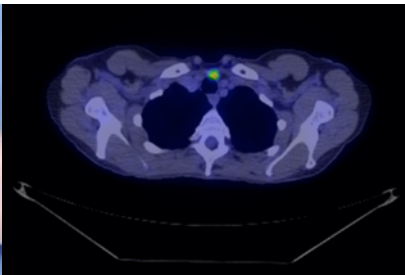
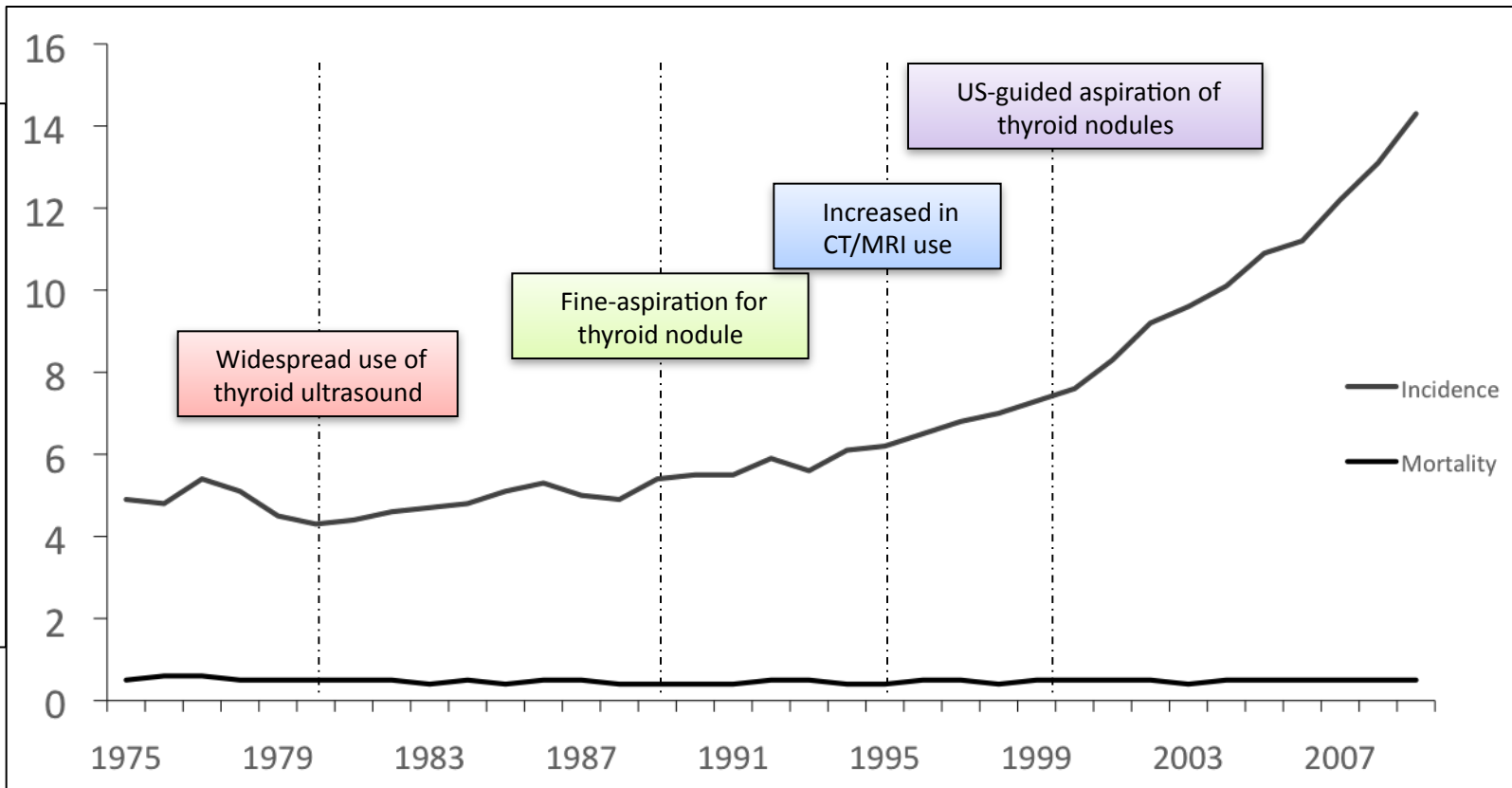
Outcome of mPTC and its prognostic factors.

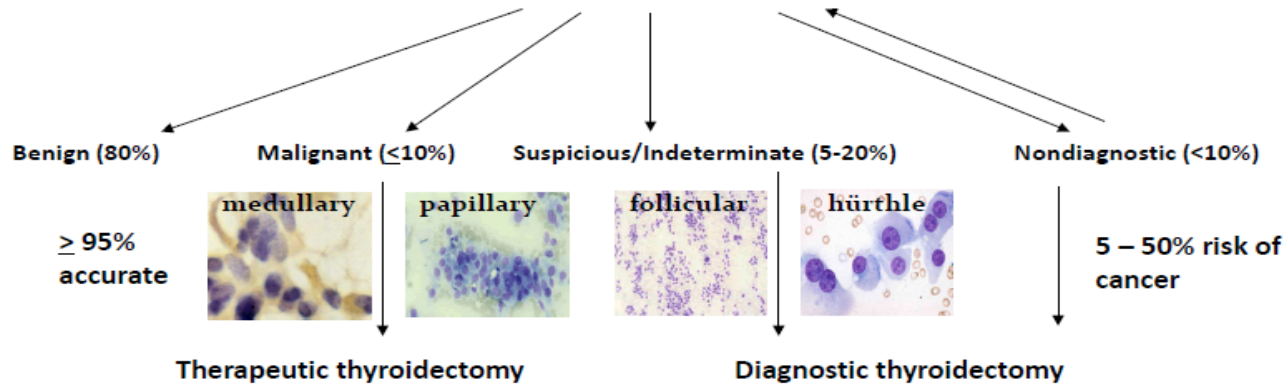
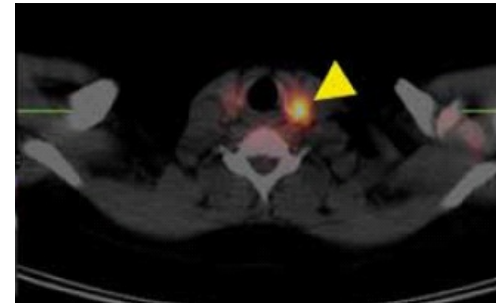
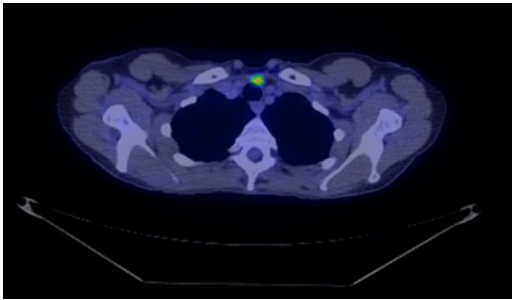
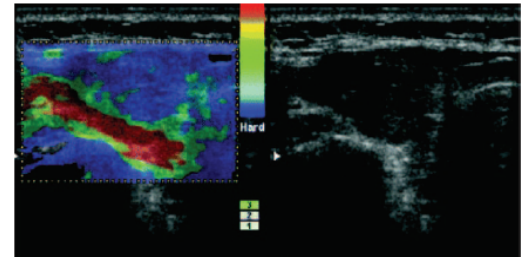
Authors (ref)	Follow-up	Year	Series	Recurrence	Mortality	Prognostic factors
Baudin et al <sup>46</sup>	7.3	1998	281	3.9%	0%	Multifocality Lobectomy
Hay et al <sup>47</sup>	60	1992	535	6%	0.4%	Lymph node mets. Lobectomy
Chow et al <sup>49</sup>	10	2003	203	7.3%	1%	Multifocality Limited surgery
Ito et al <sup>50</sup>	10	2003	626	5.0%	0%	ND
Noguchi et al <sup>51</sup>	10	1996	867	1.4%	0.2%	ND
Yu et al <sup>65</sup>	15	2011	18445	ND	0.5%	Age >45, Male Sex, Lymph node mets. Extrathyroidal invasion
Yamashita et al <sup>32</sup>	11	1997	1743	1.5	0.2%	Lymph node mets.

Clinical-pathological features of mPTC incidental or not incidental in different series.

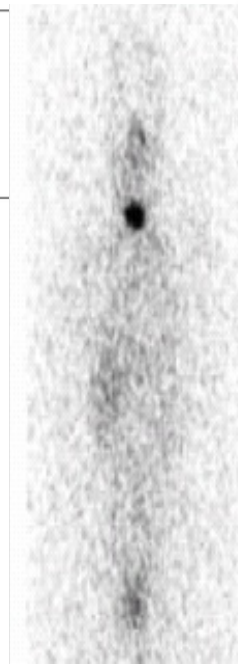
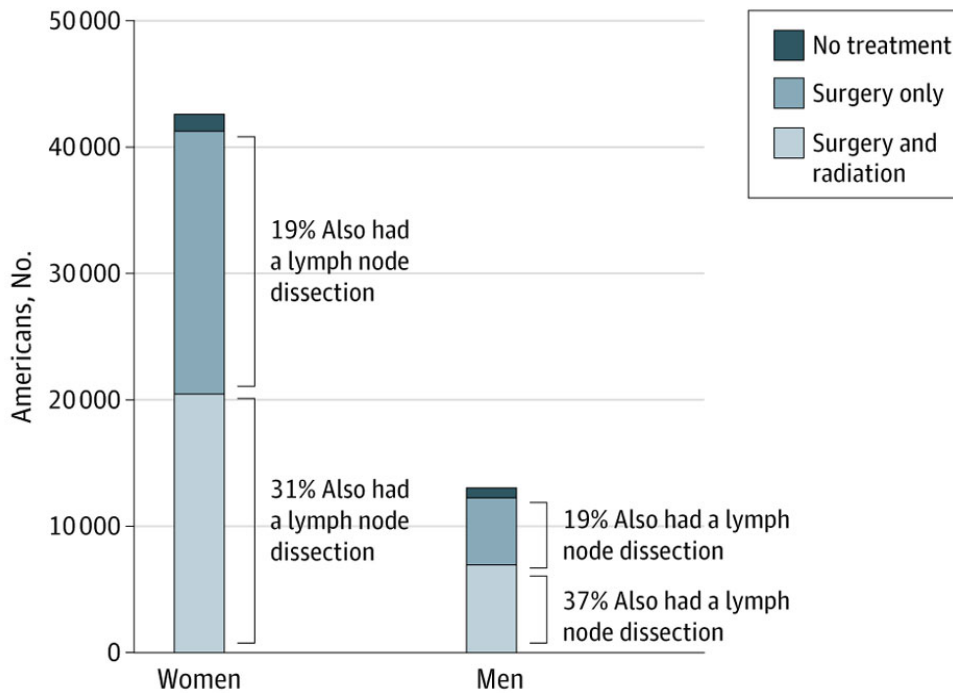
Author (ref)	Diagnosis	Patients	Multicentric	Bilateral	Invasive	Lymph node metastases	Distant metastases
Baudin et al <sup>46</sup>	Incidental	189	56 (30%)	25 (13%)	21 (11%)	41 (22%)	0 (0%)
	Not incidental	92	56 (61%) <sup>a</sup>	21 (23%) <sup>a</sup>	21 (23%) <sup>a</sup>	89 (91%) <sup>a</sup>	8 (8.6%) <sup>a</sup>
Pellegriti et al <sup>66</sup>	Incidental	151	37 (24.5%)	22 (14.6%)	16 (10%)	24 (15.9%)	1 (0.7%)
	Not incidental	148	58 (39.2%) <sup>a</sup>	33 (22.3%)	38 (25%) <sup>a</sup>	66 (44.6%) <sup>a</sup>	7 (4.7%)
Roti et al <sup>48</sup>	Incidental	52	10 (19%)	6 (11%)	8 (15%)	2 (4%)	0 (0%)
	Not incidental	191	68 (36%)	39 (20%)	34 (18%)	30 (16%)	4 (2%)
Chung-Yau et al <sup>67</sup>	Incidental	75	9 (12%)	n.d	0 (0%)	0 (0%)	0 (0%)
	Not incidental	110	35 (32%) <sup>a</sup>	n.d	21 (19%) <sup>a</sup>	43 (39%) <sup>a</sup>	3 (2.7%)

<sup>a</sup> Significantly different.



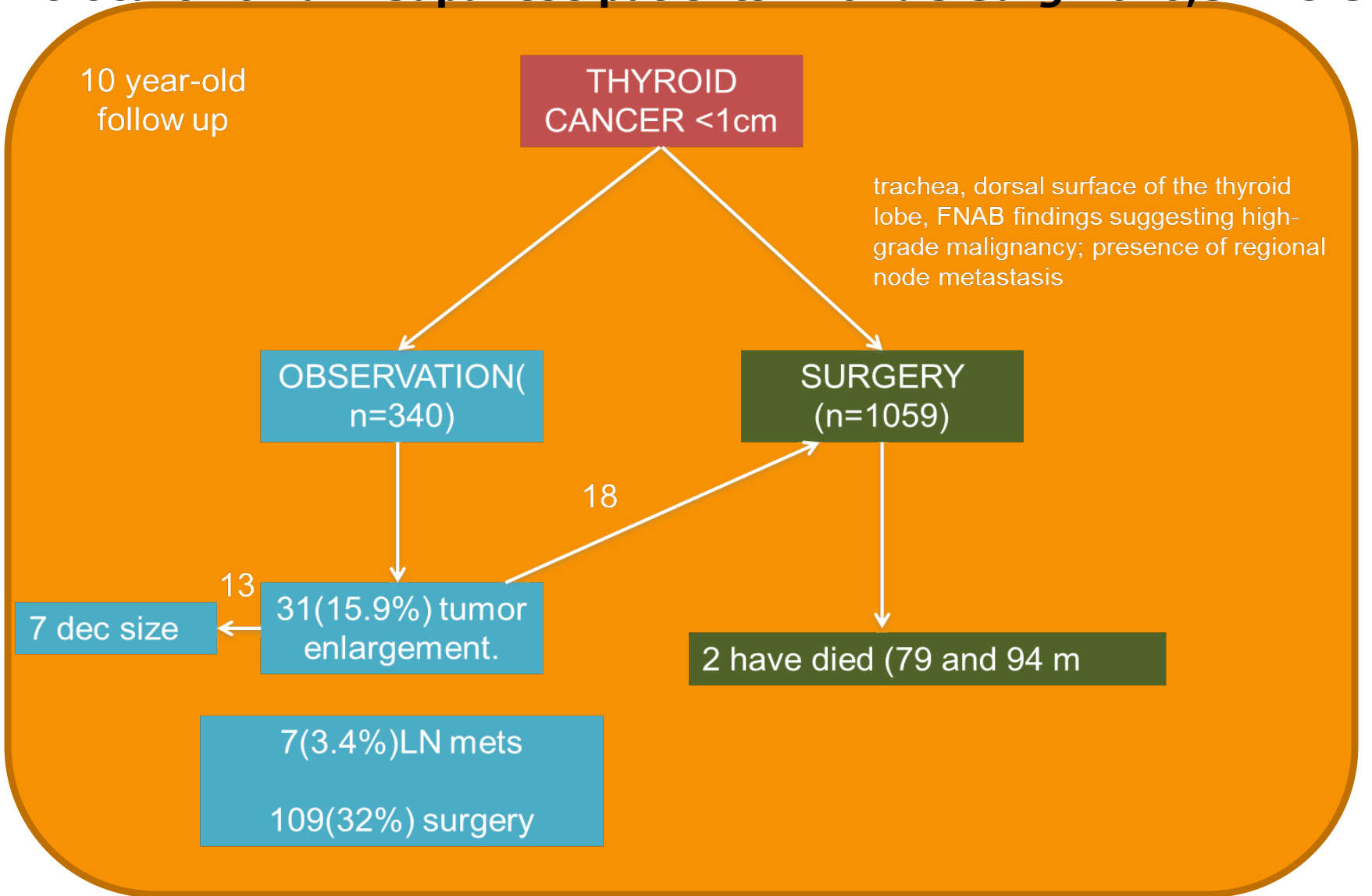


# Thyroidectomies has risen by 60% over the past 10 years



Permanent hypoparathyroidism in 10 per 1000 patients  
 Laryngeal nerve injury 60 per 1000 patients  
 Cost  
 Follow up

**Ito Y et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J Surg* 2010;34:28-35**

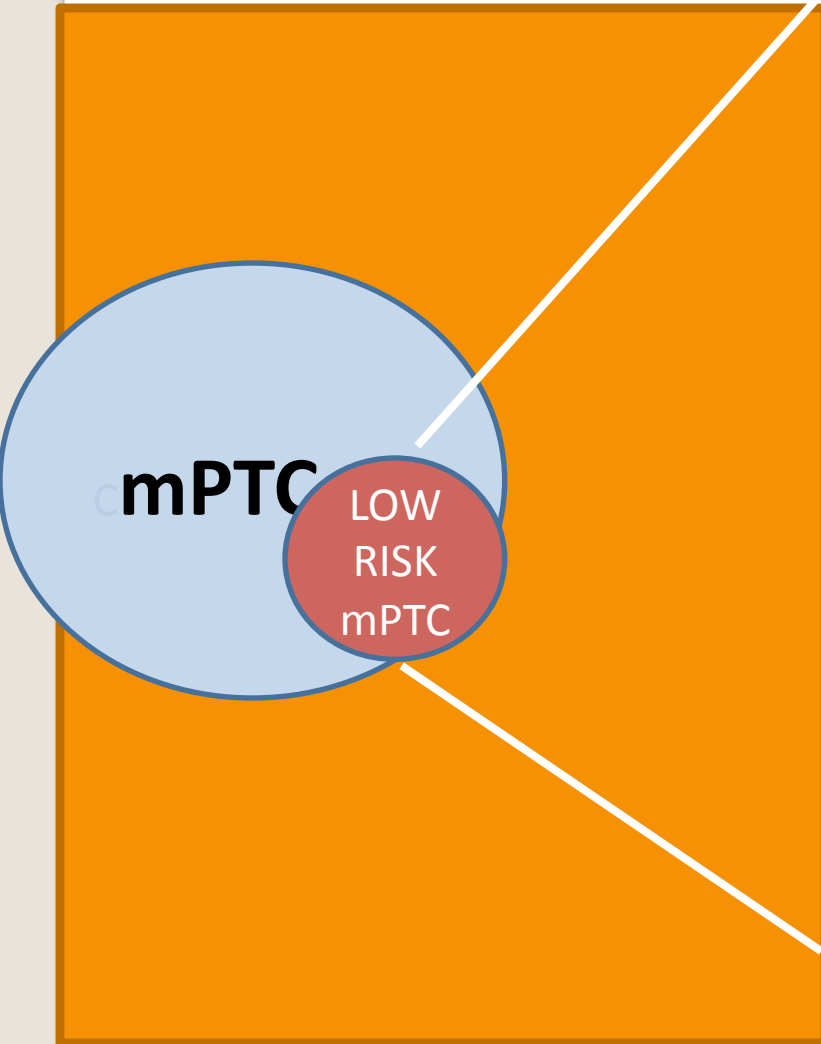


# ENGAGING PATIENTS TO AVOID OVERTREATMENT



Need for lifelong thyroid replacement	Rare	Always	No
Cost of therapy	\$16,000-35,000 + f/u		\$ 0 + f/u
Follow up	Yearly with blood test and thyroid ultrasound		US every 6 -12m
Complications	laryngeal nerve injury in 10 per 1000 patients	Permanent hypoparathyroidism in 10 per 1000 patients; laryngeal nerve injury 60 per 1000 patients	Silent cancer growth of >3 mm in 70 per 1000 patients, and a lymph node metastasis in 15 per 1000 patients
Mortality	1 per 1000 patients		From 0 to 3 per 1000 patients

# IDENTIFICATION OF PATIENTS AT LOW RISK



No family history of thyroid cancer

No personal history of radiation exposure

<1.5 cm lesion compatible with papillary thyroid cancer on cytology

No evidence of extraglandular extension or lymph node metastasis



# CHANGING THE LABEL

Papillary

Lesion

Mass

Tumor

microPLIC

course

Non-lethal

prognosis

indolent

# Problemi relabeling (microPLIC)

- Corretta informazione del paziente
- Non è possibile a priori sapere se si tratta di un' overdiagnosis
- Non è possibile con il solo es. citologico definire "indolent" una lesione. Senza istologico non sappiamo :
  - se è multifocale e il numero dei foci
  - L' esatta misura
  - L' eventuale estensione extratiroidea
  - Il pattern di crescita (invasivo vs incapsulato)
  - Se è una variante più aggressiva (es. a cellule alte)
  - Se presente reazione desmoplastica
  - Se presenti metastasi linfonodali (se linfectomia)

# Classificazione TNM dei DTC

## Tumore primitivo (T)

- TX: Il tumore primitivo non può essere valutato
- T0: Non evidenza di tumore primitivo
- T1: Tumore di 2 cm o meno nella dimensione maggiore, limitato alla tiroide
  - T1a Tumore di 1 cm o meno nella dimensione maggiore, limitato alla tiroide
  - T1b Tumore maggiore di 1 cm ma meno di 2 cm nella dimensione maggiore, limitato alla tiroide
- T2: Tumore maggiore di 2 cm ma non più di 4 cm nella dimensione maggiore, limitato alla tiroide
- T3: Tumore maggiore di 4 cm nella dimensione maggiore, limitato alla tiroide o qualsiasi tumore con estensione extratiroidea minima (per es. estensione nel muscolo sternotiroideo o nei tessuti molli peritiroidei)
- T4a: Tumore esteso oltre la capsula tiroidea con invasione di una qualsiasi delle seguenti strutture: tessuti molli sottocutanei, laringe, trachea, esofago, nervi ricorrenti
- T4b: Il tumore invade la fascia pre-vertebrale, i vasi mediastinici o ingloba le arterie carotidee

## Linfonodi regionali (N)

- NX: I linfonodi regionali non possono essere valutati
- N0: Assenza di metastasi nei linfonodi regionali
- N1: Metastasi nei linfonodi regionali
  - N1a: Metastasi nel livello VI ( linfonodi pretracheali, paratracheali, e perilaringei/delfici)
  - N1b: Metastasi nei linfonodi latero-cervicali unilaterali, bilaterali, controlaterali (Livelli I, II, III, IV or V) o retrofaringei o del mediastino superiore

## Metastasi a distanza (M)

- M0: Assenza di metastasi a distanza
- M1: Presenza di metastasi a distanza

## Sotto 45 anni

- |             |       |       |    |
|-------------|-------|-------|----|
| • Stadio I  | Any T | Any N | M0 |
| • Stadio II | Any T | Any N | M1 |

## 45 anni o più

- |              |            |        |    |
|--------------|------------|--------|----|
| • Stadio I   | T1a, T1b   | N0     | M0 |
| • Stadio II  | T2         | N0     | M0 |
| • Stadio III | T3         | N0     | M0 |
|              | T1, T2, T3 | N1a    | M0 |
| • Stadio IVA | T1, T2, T3 | N1b    | M0 |
|              | T4a        | N0, N1 | M0 |
| • Stadio IVB | T4b        | Any N  | M0 |
| • Stadio IVC | Any T      | Any N  | M1 |

# Stratificazione rischio di recidiva dei DTC

- **Rischio bassissimo**

Microcarcinoma unifocale ( $\leq 1$  cm) + tutte le altre caratteristiche del basso rischio

- **Rischio basso**

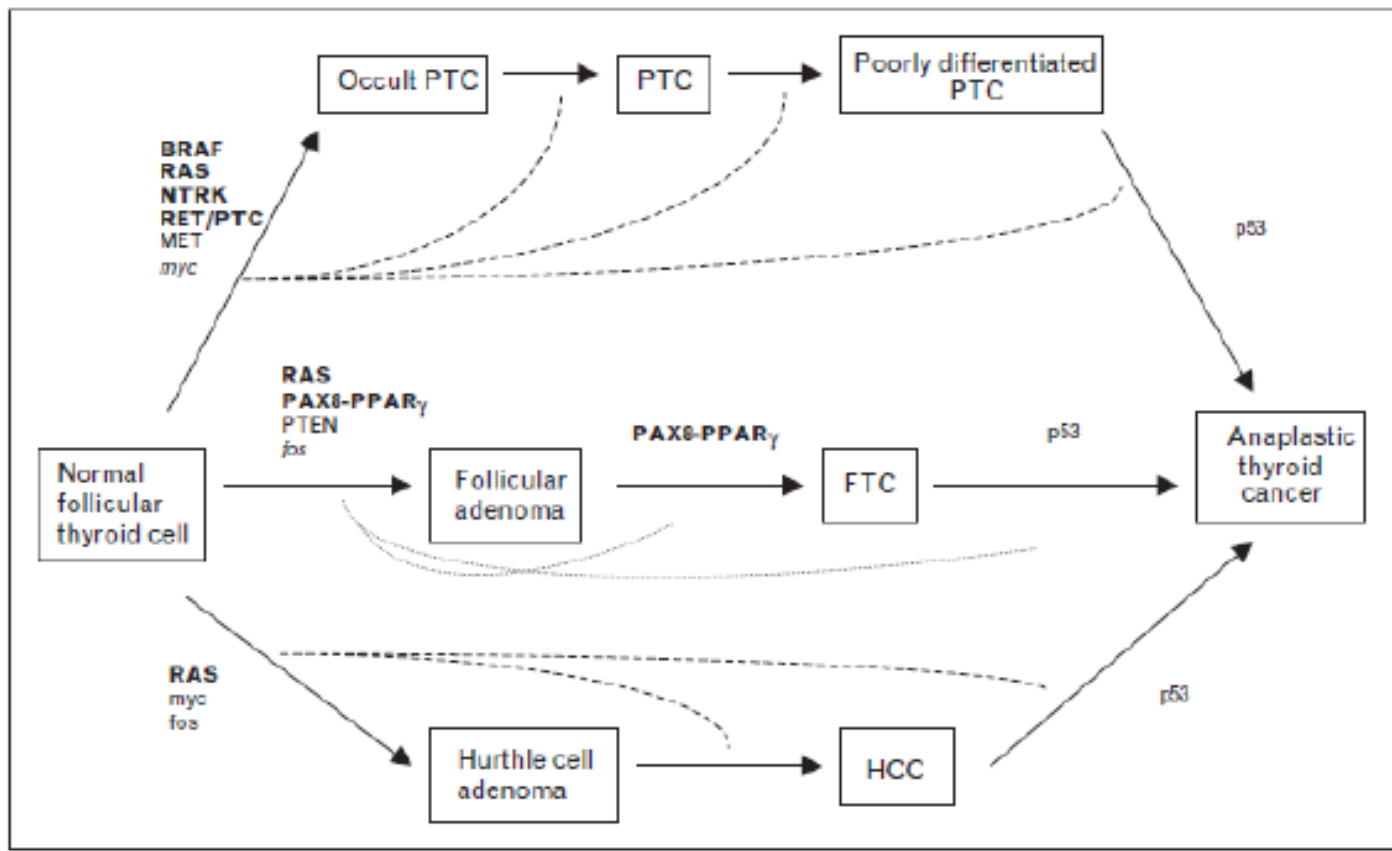
1) assenza di metastasi locali o a distanza; 2) resezione macroscopica di tutto il tumore; 3) assenza di invasione di tessuti o strutture loco-regionali; 4) istologia non aggressiva e assenza di invasione vascolare; 5) assente up-take dello  $^{131}\text{I}$  al di fuori del letto tiroideo al primo RxWBS

- **Rischio intermedio**

1) invasione microscopica del tumore nei tessuti molli peri-tiroidei; 2) metastasi linfonodali cervicali o up-take dello  $^{131}\text{I}$  al di fuori del letto tiroideo al primo RxWBS; 3) istologia aggressiva o invasione vascolare

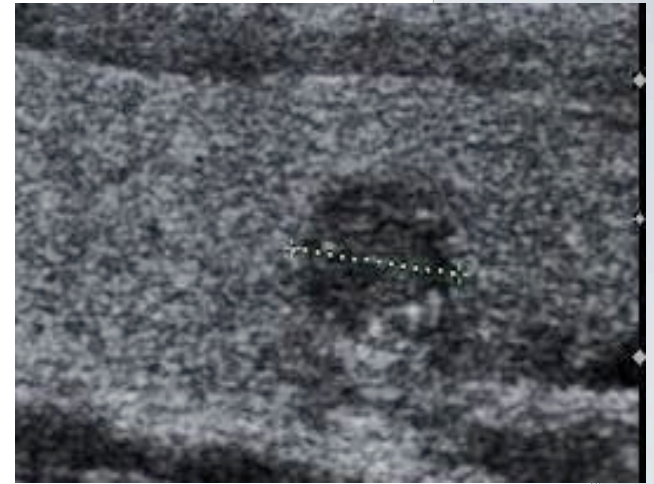
- **Rischio alto**

1) invasione macroscopica del tumore; 2) resezione incompleta; 3) metastasi a distanza; 4) Tg sproporzionatamente alta rispetto a quanto si vede nel RxWBS



# Limitare l'overdiagnosis di carcinoma tiroideo e relativi danni

- Evitare screening su persone asintomatiche /senza fattori di rischio
- Linee guida nodulo tiroideo (agoaspirato)
- “Relabeling” dei piccoli K PAP: limiti!
- Identificazione marcatori di comportamento più aggressivo
- Condivisione scelte con il paziente (adeguatamente informato). Possibile sorveglianza attiva
- Evitare l' overtreatment (LG)
- Opzioni terapeutiche alternative: interventi parziali, imaging-guided therapies (radiofrequenze, microonde, laser, cryo, high-intensity focused ultrasound...)
- Gruppo di lavoro dedicato al problema overdiagnosis nell' ambito delle società scientifiche



**Vantaggi diagnosi precoce**      **Rischi overdiagnosis**

**Grazie per l'attenzione**