

Oncogenes/Growth Factors & Environment

8th Postgraduate Course in
Endocrine Surgery

Crete, Greece

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Thyroid Cancer

- Thyroid cancer is the 8th most common and most rapidly increasing cancer in women
- An estimated 30,000 cases will occur in the United States in 2006
- It frequently affects individuals under 50 years of age
- There are about 300,000 survivors of thyroid cancer in the USA

Thyroid Cancer

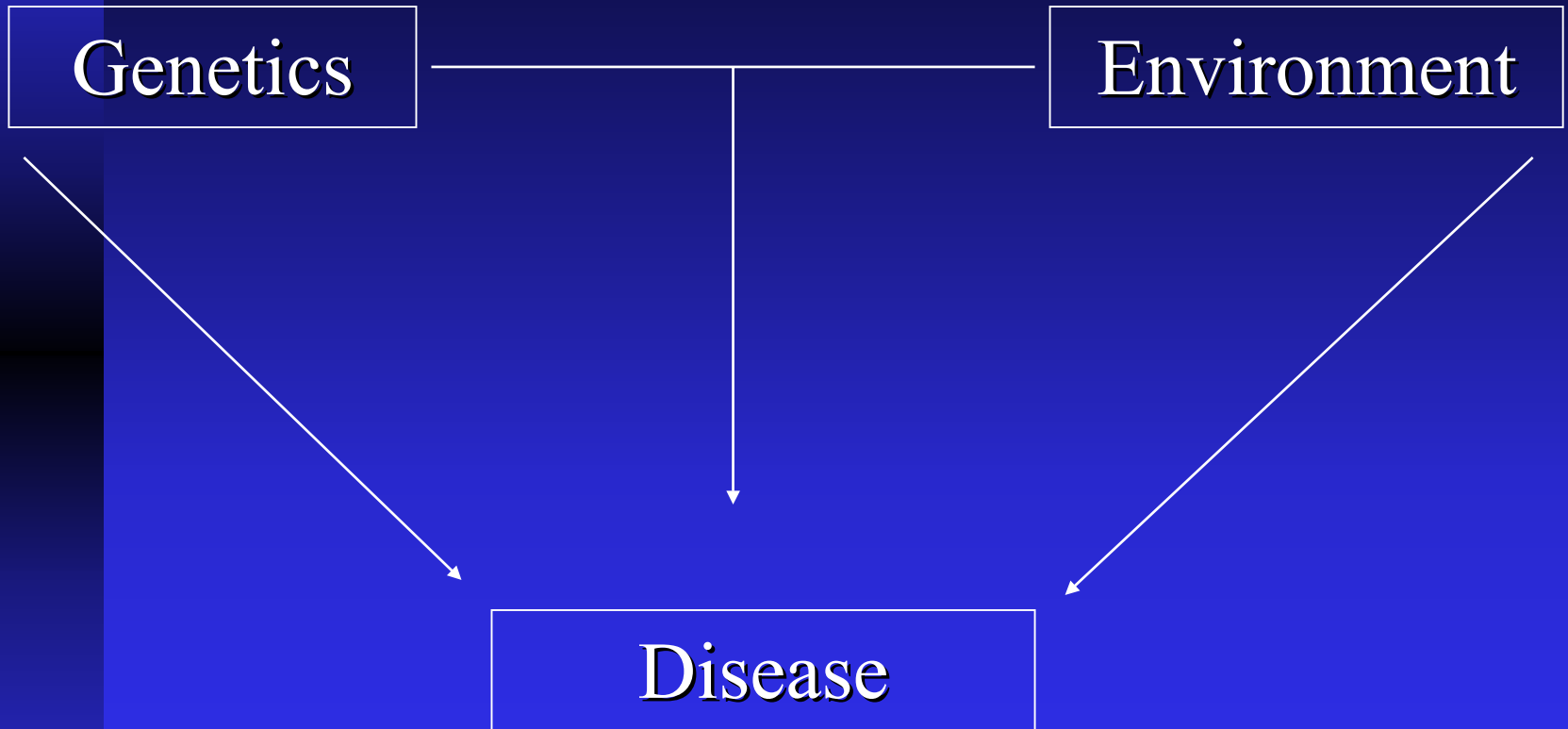
- There are 5 major types of thyroid cancers: (Papillary 80% / Follicular 9% / Hurthle Cell 3% / Medullary 7% / Anaplastic 1%)
- Familial thyroid cancer occurs in about 25% of patients with medullary thyroid cancer and 5 % of those with papillary and Hurthle cell cancer
- Familial Non Medullary thyroid cancer is defined as thyroid cancer affecting at least two first degree relatives (roughly 90% are papillary)



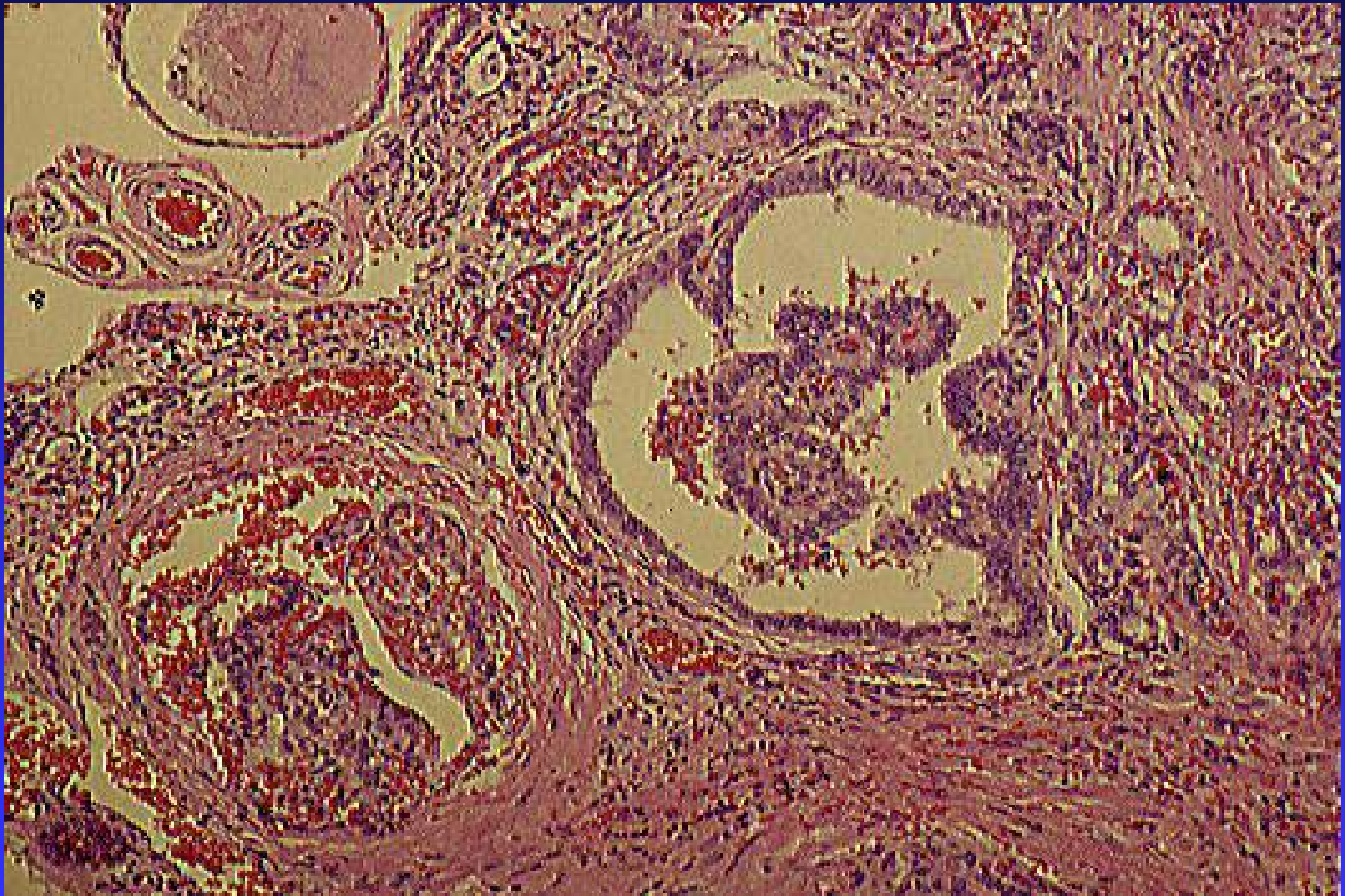
Thyroid Cancer Epidemiology

- Ron et al (1991): 5 fold increased risk of thyroid cancer when another family member has thyroid cancer
- Goldgar et al. (1994): 9 fold increase of thyroid cancer in association with breast cancer

Environment and Genetics



Histogram – Occult PTC



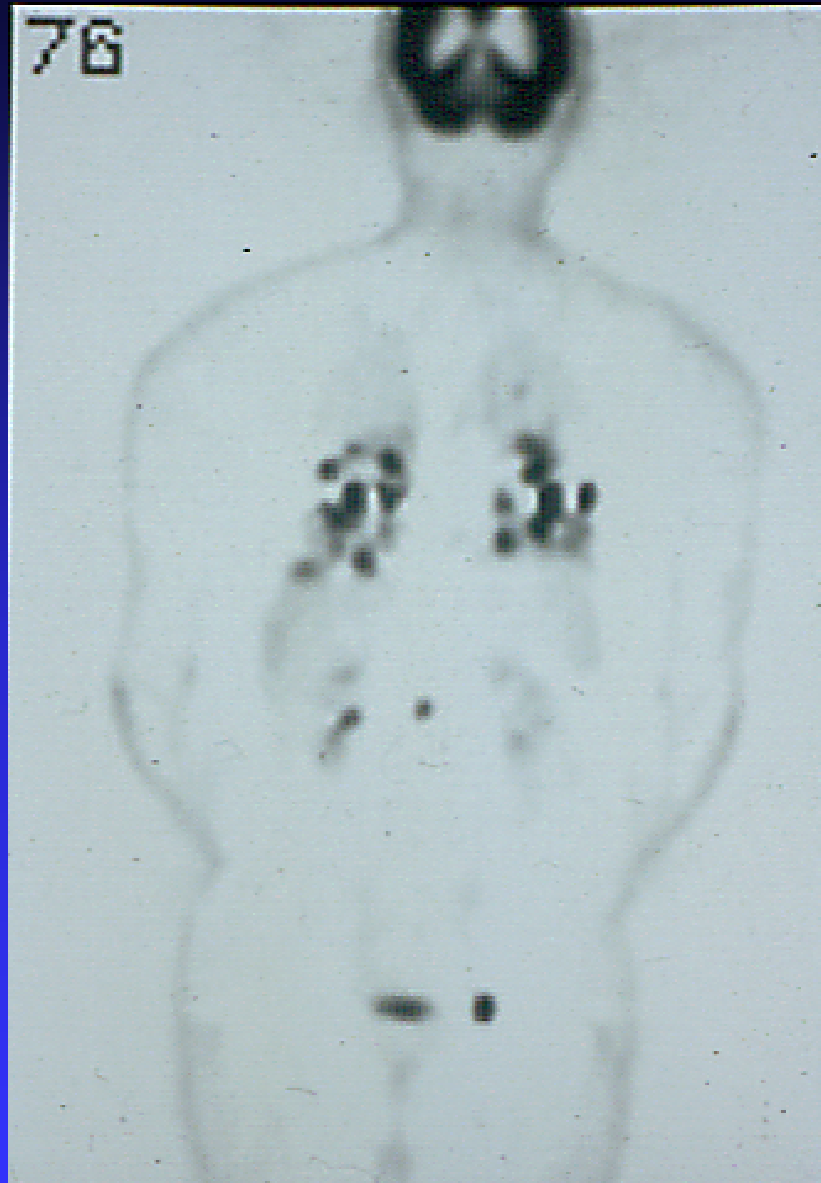
Patient with large PTC



CT of PTC



PET Scan



Thyroid Cancer: A Lethal Endocrine Neoplasm

(NIH Conference)

Although the mortality rate from thyroid cancer is low, it is the highest among cancers affecting the endocrine glands (excluding the ovary).

(Robbin J et al. Ann Intern Med 115:133-147, 1991)

Death from Thyroid Cancer

UCSF 1965-1995

Patient Characteristics (102 patients)

Mean age 58 years (range 12 to 90 years)

31 less than 45 years of age

Tumor size ranged from 0.6 to 13.0 cms

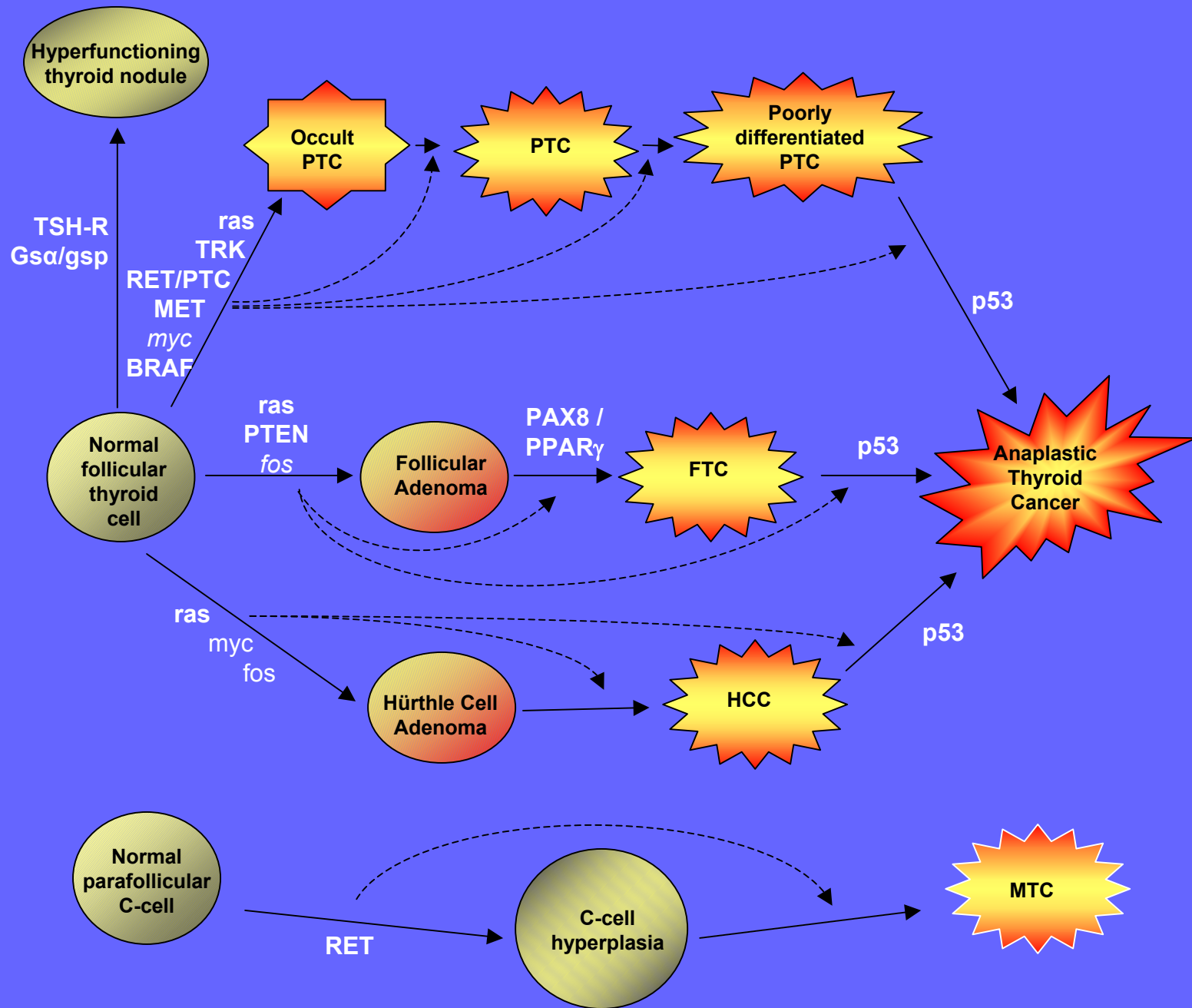
Metastases in 46% (regional) and 18% distant

50% of patients with PTC & HTC verses
11% of FTC died of locally advanced disease

(Wu HS et al, JACS 191:600-606, 2000)

Genes Implicated in Sporadic Papillary Thyroid Cancer

<u>Gene</u>	<u>Comment</u>
RET/PTC	More frequent in children and after radiation (Tyrosine Kinase)
BRAF	Most common mutation in PTC- Appears to be associated with more aggressive tumors
ras	Early in tumor development and more frequent in follicular thyroid cancer
TRK	Activated in about 15% of PTC (Tyrosine Kinase)
MET	Over expressed Tyrosine Kinase
p53	Dedifferentiated or undifferentiated tumors



Inherited Thyroid Cancer Syndromes

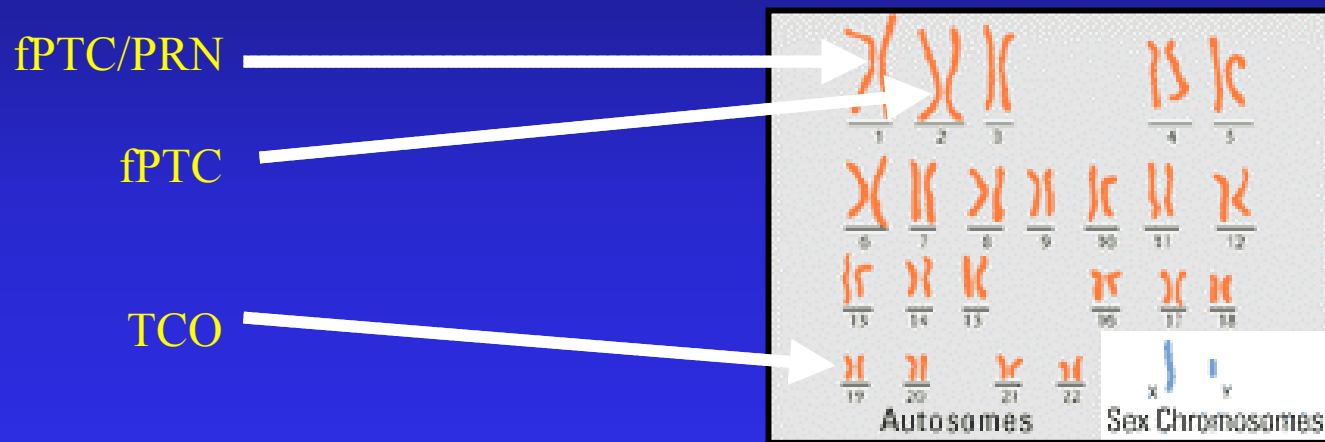
Syndrome	Chromosome Location	Gene
Multinodular goiter (MNG)	14q31	?
Trabecular, oxyphilic & MNG	19p 13.2	?
PTC-Renal neoplasia	1q 21	?
PTC – Follicular variant PTC	2q21	?
Familial adenomatous polyposis	5q21-22	APC*
Cowden's Syndrome	10q23.3	PTE N



* > 80% of these thyroid cancers have ret/PTC somatic mutations.

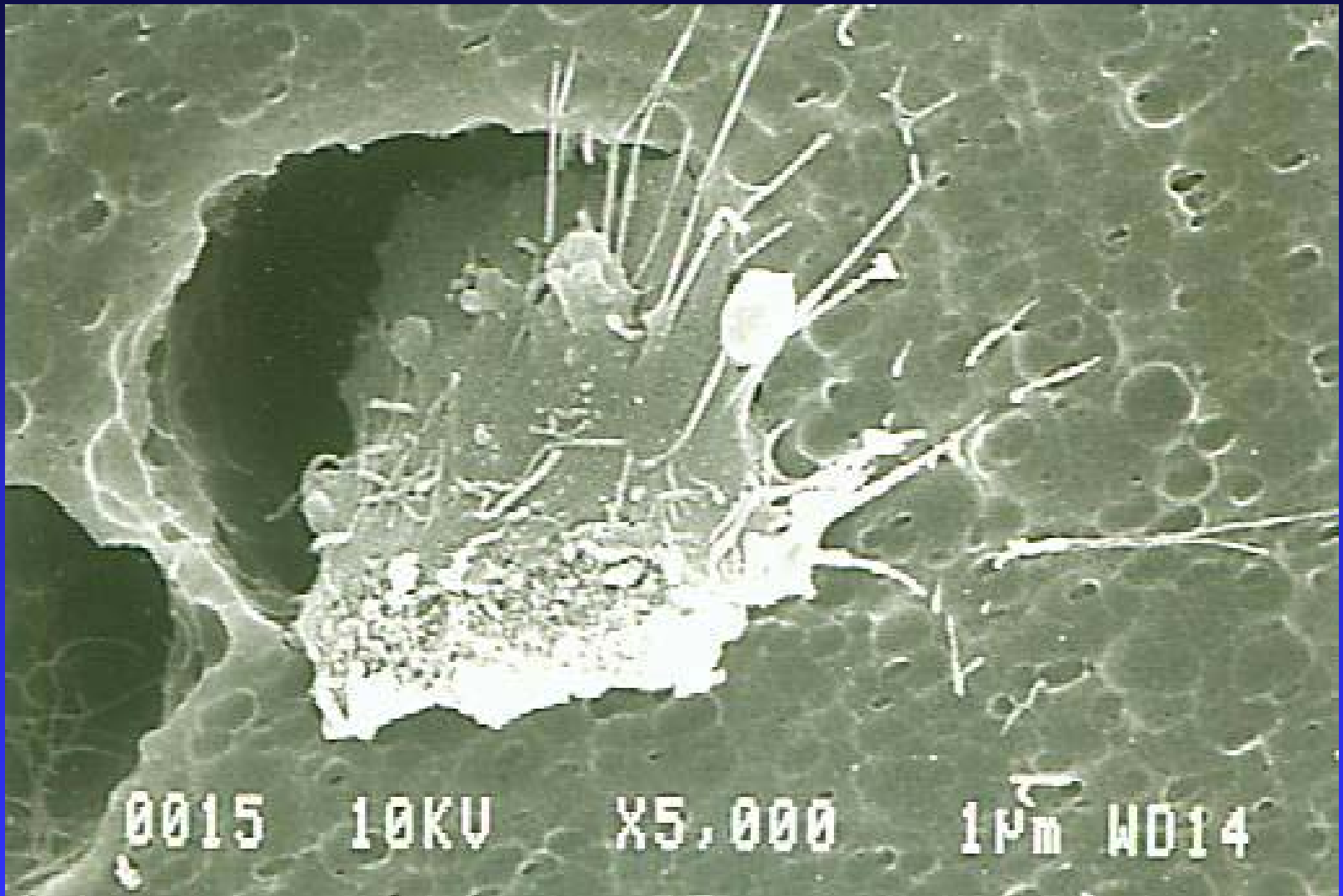
Familial Non-Medullary Thyroid Cancer

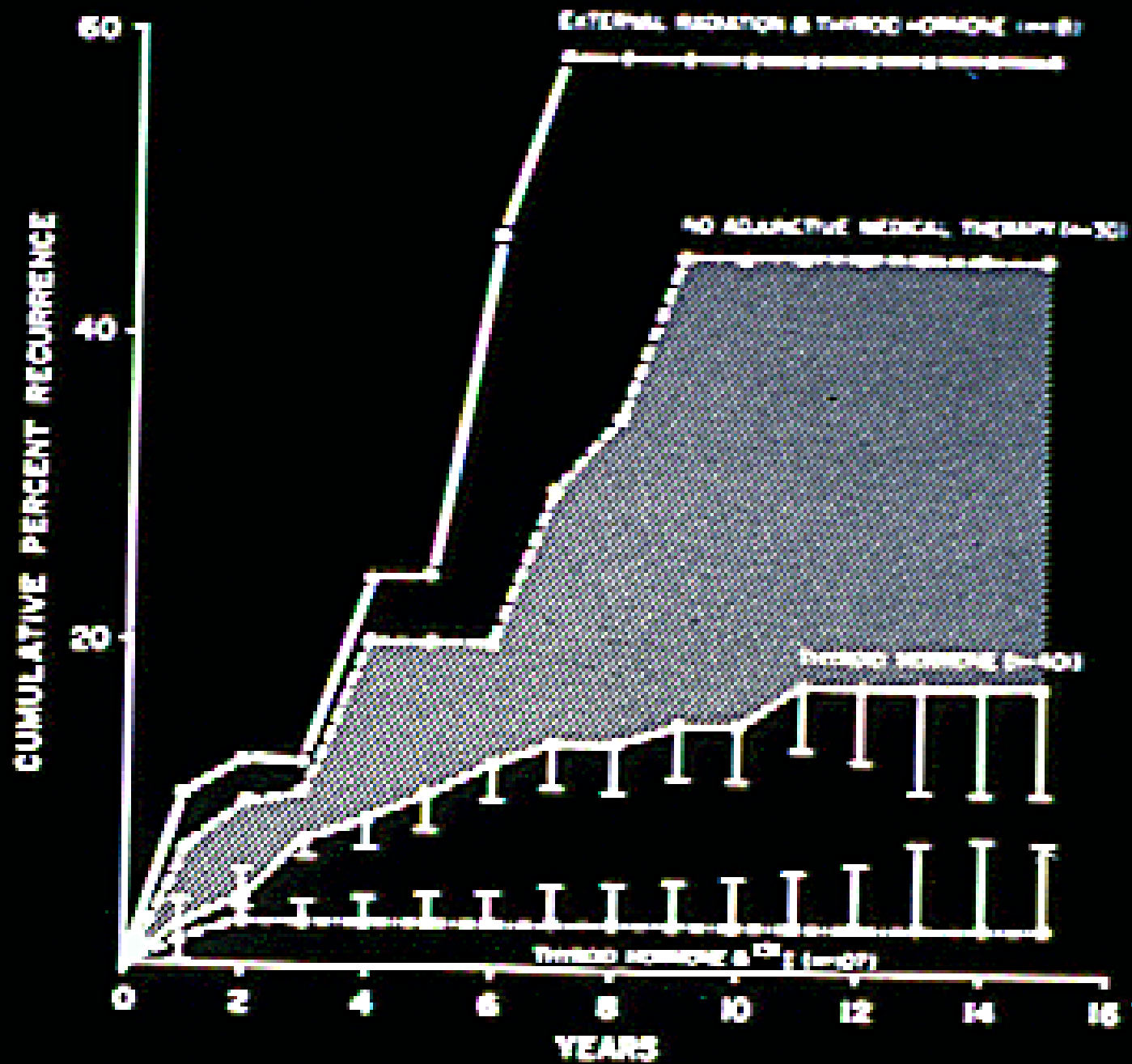
- Familial Hürthle cell (TCO): 19p13.2¹
- Familial papillary thyroid cancer with papillary renal neoplasia (fPTC/PRN): 1q21²
- Familial papillary thyroid cancer in Tas1 (fPTC): 2q21³



1. Canzian *et al.* Am J Hum Genet. 63:1743, 1998.
2. Malchoff *et al.* JCEM. 85(5):1758, 2000.
3. McKay *et al.* Am J Hum Genet. 69(2):440, 2001

Photo of Thyroid Cancer Cell





TSH Suppression and Thyroid Cancer

“After 30 years’ follow-up, we found that there were 25% fewer recurrences in patients treated with T_4 as compared with no adjunctive therapy ($p < .01$), and there were fewer cancer deaths in the T_4 group (6% versus 12%; $p < 0.0001$).”

(Mazzaferri EL, Jhiang, SM: *Am J Med* 73:424, 1994)

TSH Suppression and Thyroid Cancer

- Relapse-free survival was longer in patients with TSH <0.05 or < 0.1 than in those with non-suppressed TSH values
- The level of TSH suppression was an independent prognostic factor using multivariate analysis

(Pujol P, et al. JCEM, 1996)

Outcome of Children Treated for Thyroid Cancer

“Thyroid stimulating hormone suppression was the only intervention shown to reduce the recurrence rate.”

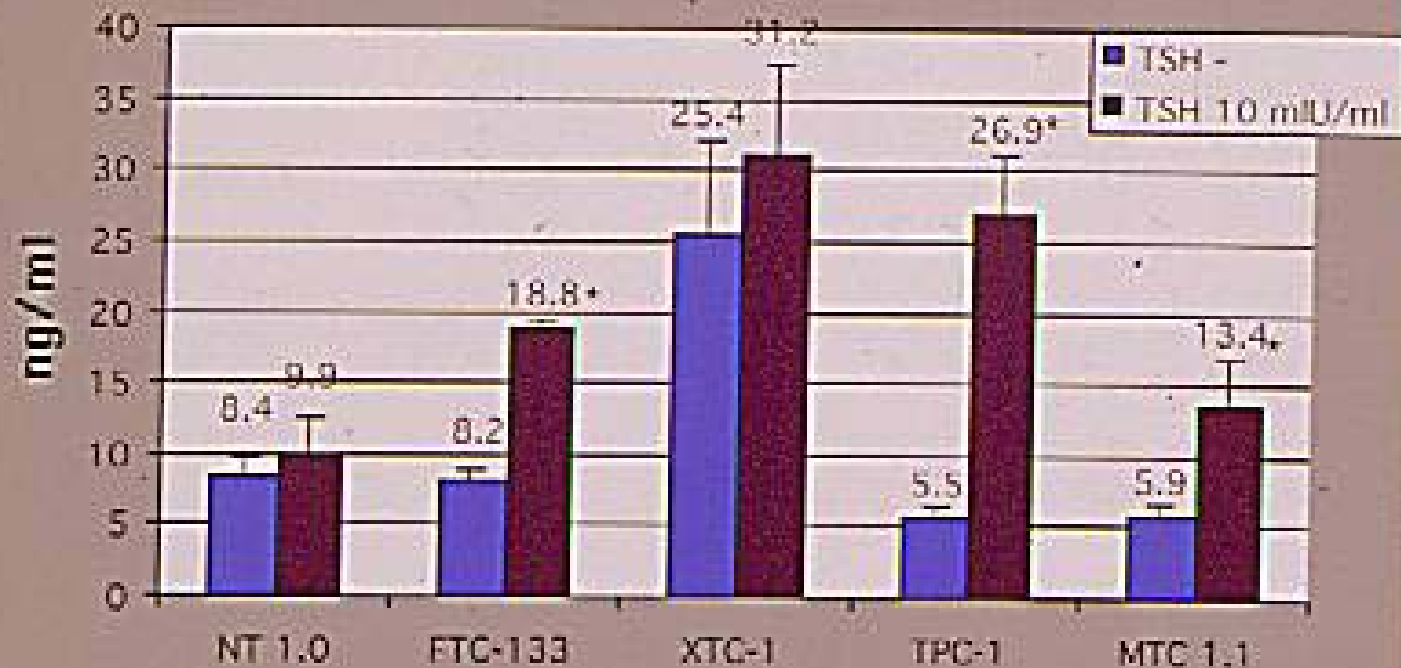
(Landau D *et al* European J Cancer 36: 214-220, 2000)

Thyroid Cancer

- ret PTC (Tg - PTC - 1) transgenic mice
 - ◆ develop thyroid cancer
 - ◆ are responsive to TSH suppression (grow slower but still grow)

(S. Jhiang, PhD – ATA, 2002)

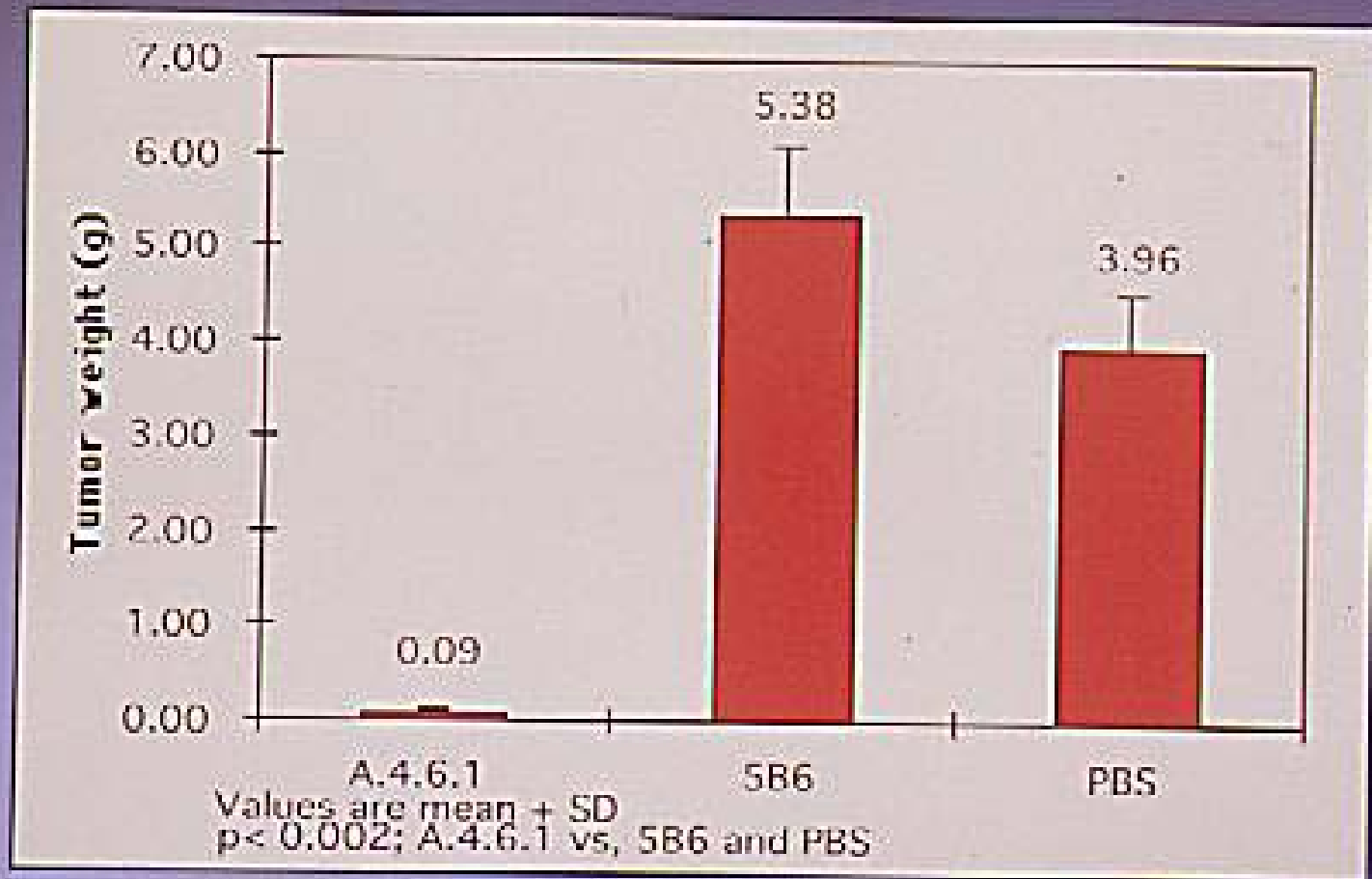
TSH stimulates VEGF secretion in some thyroid cancers



Mean + SD

* $p < 0.01$ vs, TSH -

Effects of anti-VEGF antibody on Tumor Weight (FTC-133)





Thyroid Cancer: Potential New Methods of Therapy

- Anti-angiogenesis agents
- Redifferentiation agents
 - ◆ Retinoids
 - ◆ Aromatic fatty acids (phenylacetate/phenylbutrate)
 - ◆ PPAR gamma agonists
 - ◆ Histone deacetylase (HDAC) inhibitors (Tricostatin A/Depsipeptide)
 - ◆ COX 2 inhibitors
- Gene therapy
 - ◆ P53/TTF₁/PAX8/NIS
- Anti invasion (metalloproteinase inhibitors)