Topics in Thyroid Cancer: Insular Carcinoma and Tyrosine Kinase Inhibitors

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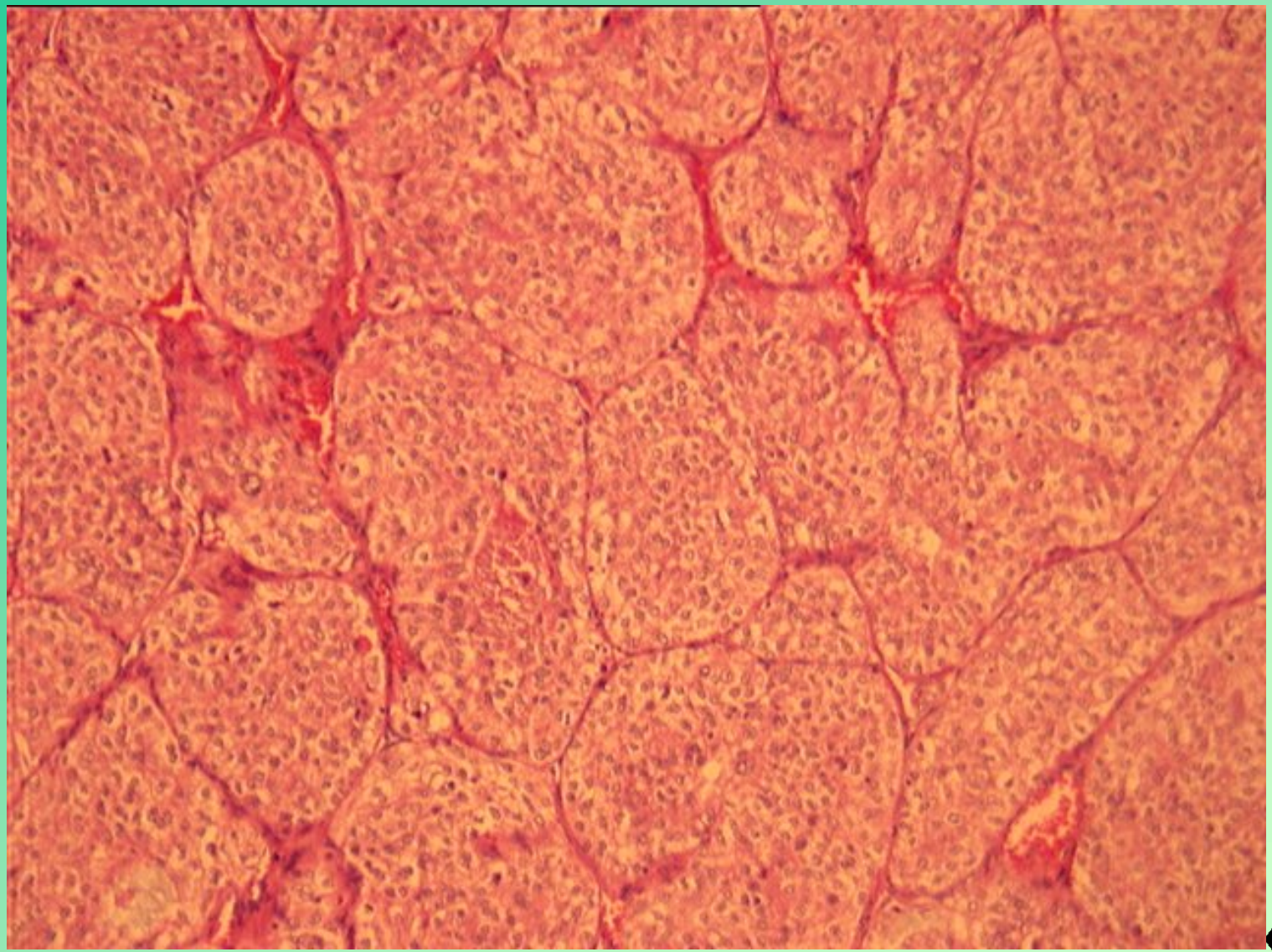
Insular Carcinoma of Thyroid



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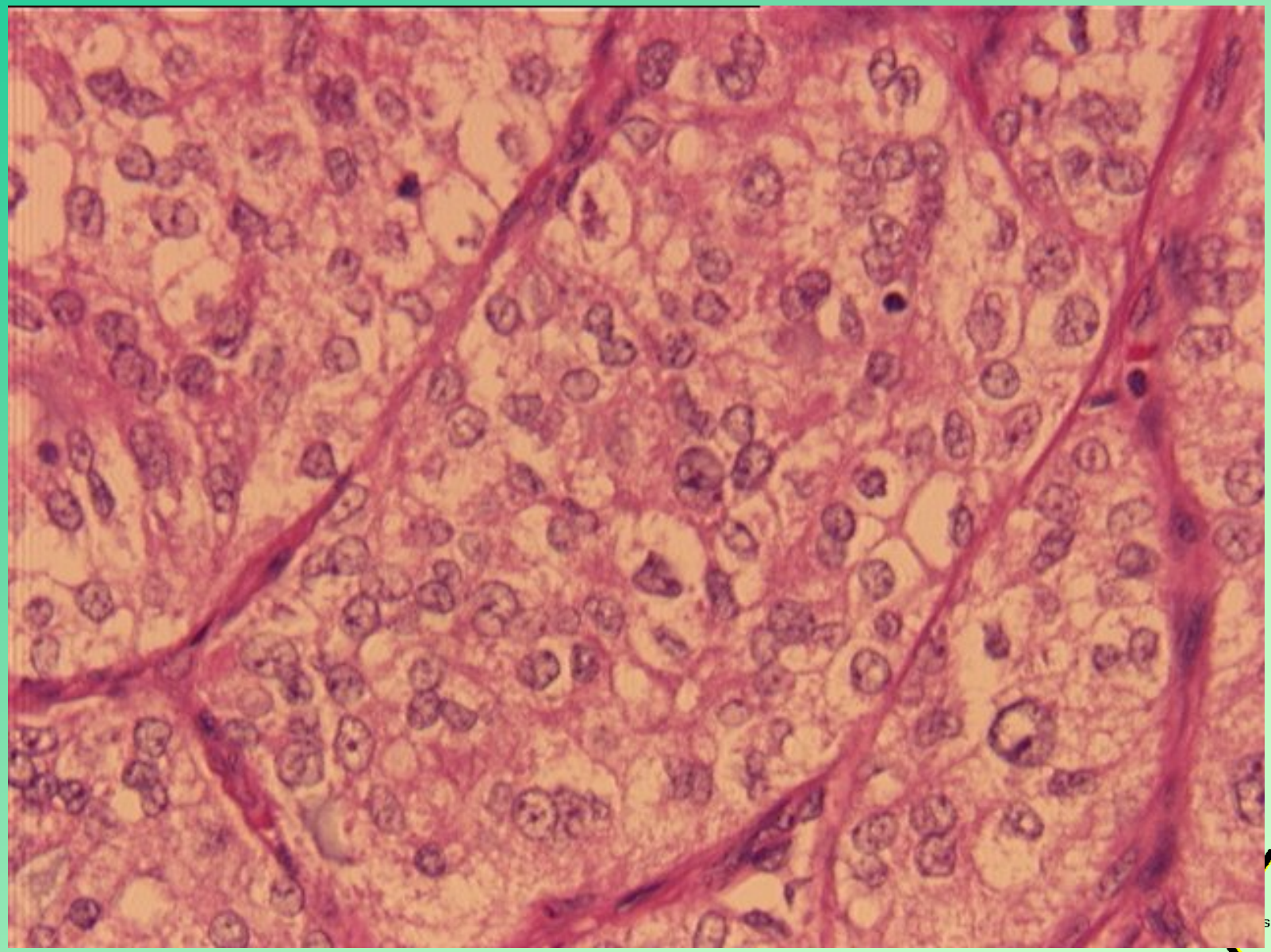
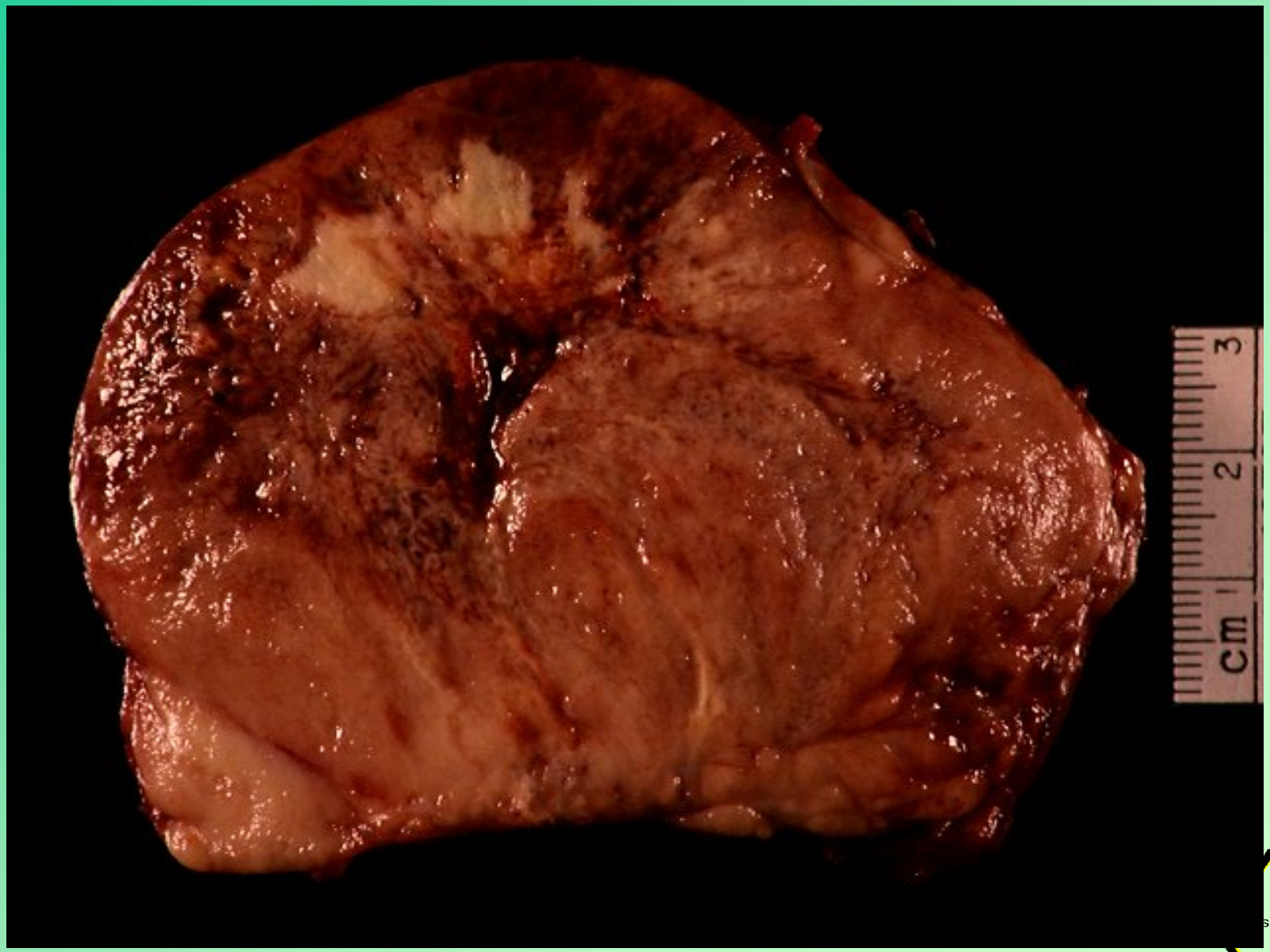
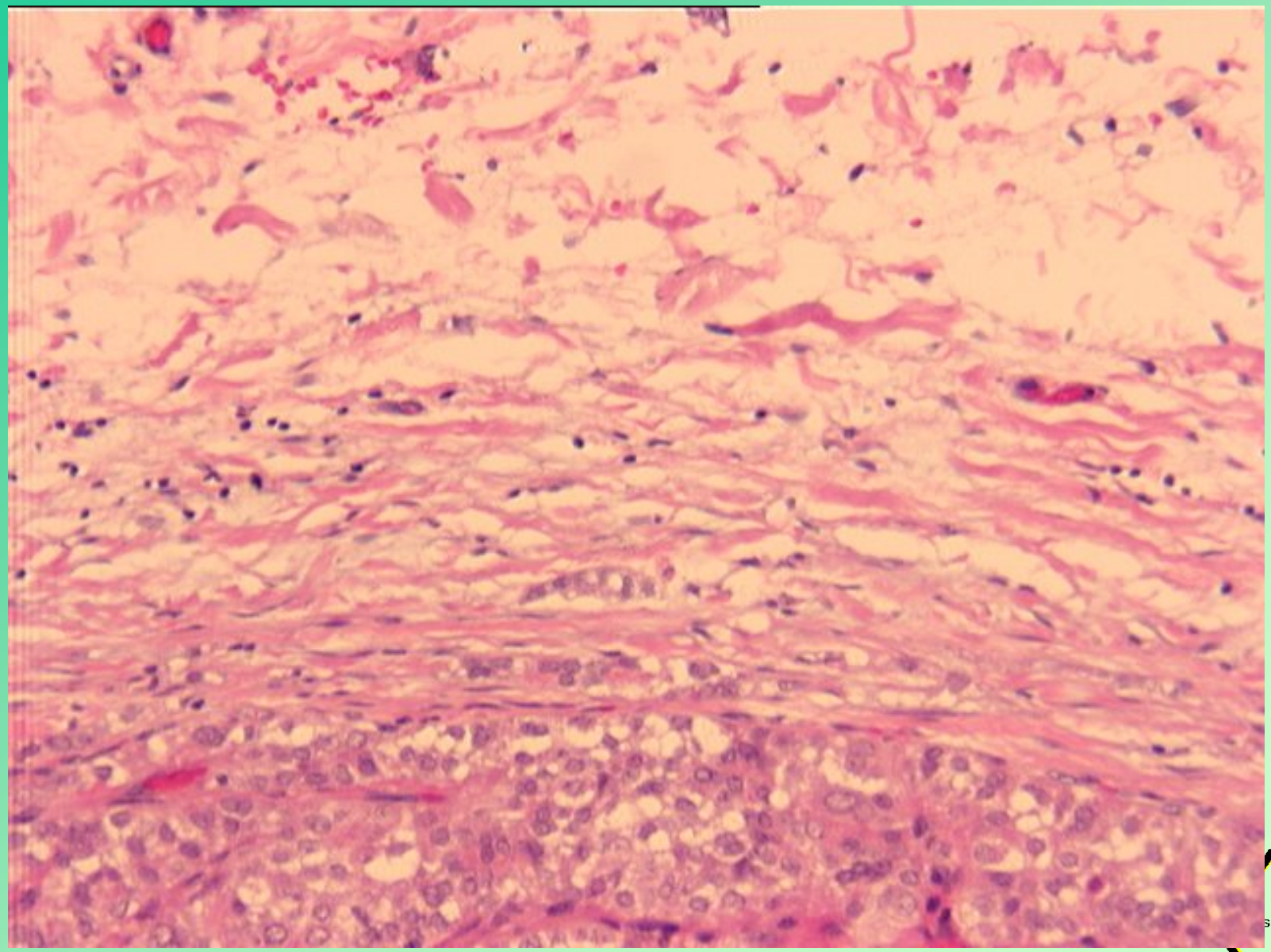
Magnified View



Gross View of Tumor



Invasive Portion of Tumor



Insular Carcinoma

- Aggressive Variant of Thyroid Cancer
- Case reports and review from Taipei*:
  - 82 cases collected (1% of all thyroid cancers)
  - Median follow-up 7 years
  - 68% women
  - 49% had lymph-node metastases
  - 57% had distant metastases (!!)
  - Disease-specific death rate 38% (some not followed long enough or died of something else)
  - Radioiodine use had no impact on survival

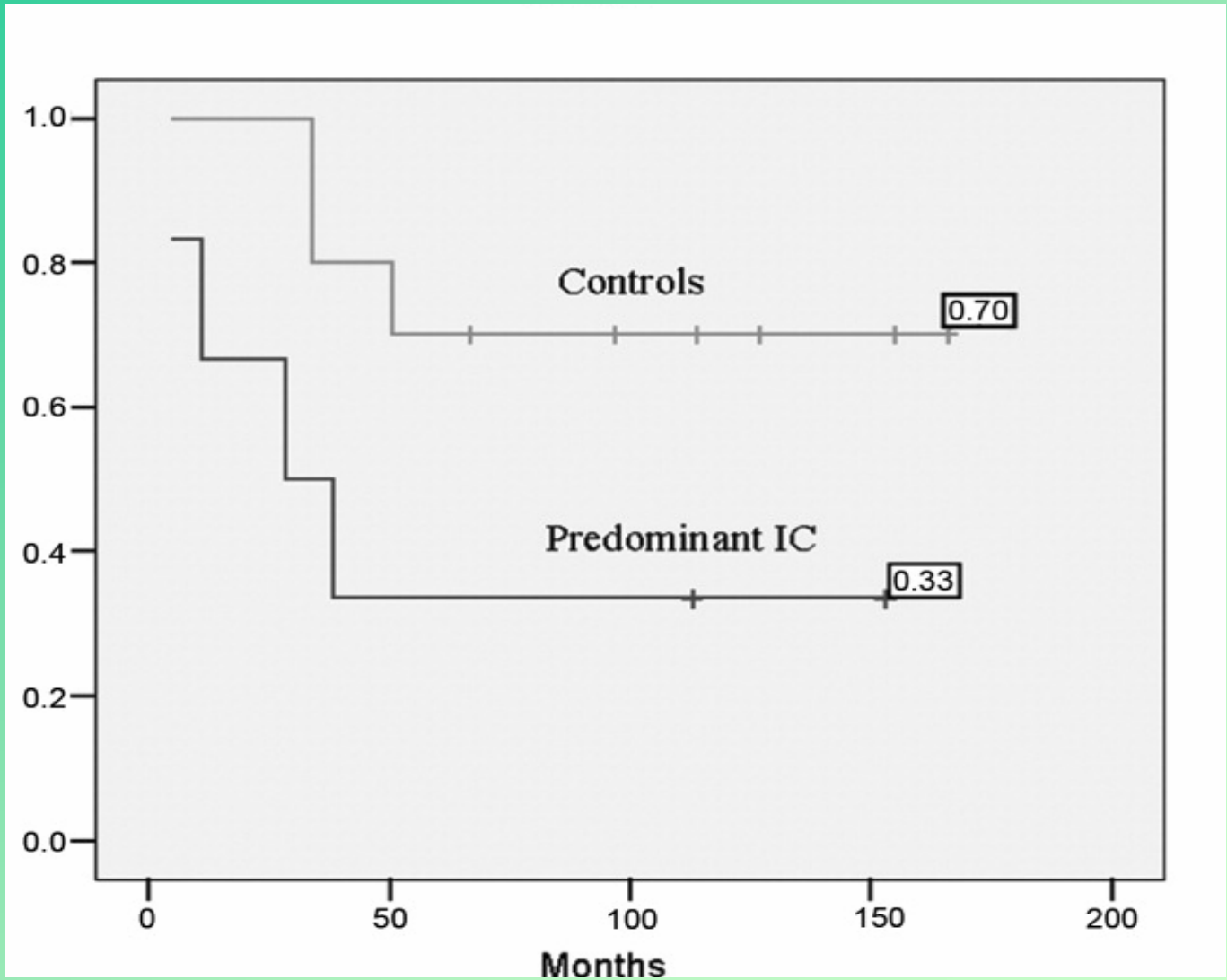
***Lai et al *J Amer Coll Surg* 203:715, 2006**

Insular Carcinoma, cont.

- Italian Study*: 33 patients in their series (0.4% of their total) compared to matched group of 66 with garden-variety thyroid cancer from their database – matched for age, size of primary and degree of differentiation
- Results of comparison…

***Rufini et al *CANCER* 110: 1209, 2007**

Italian Insular Series: Overall Survival



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Follow-up and Outcome of Patients With IC (Either Focal IC or Predominant IC) and Patients in the Control Group

	Focal IC	Predominant IC	Control group	*P*
Follow-up, mo				
Range	55-142	5-163	15-188	
Mean	108 ± 21	87 ± 52	100 ± 45	
Median	106	103	100.4	
Disease free	12 (75%)	4 (24%)	45 (68%)	.002
Alive with disease	2 (12.5%)	6 (35%)	11 (17%)	NS
Dead of disease	1 (6.25%)	7 (41%)	6 (9%)	.002
Dead of unrelated causes	1 (6.25%)	0 (0%)	4 (6%)	NS

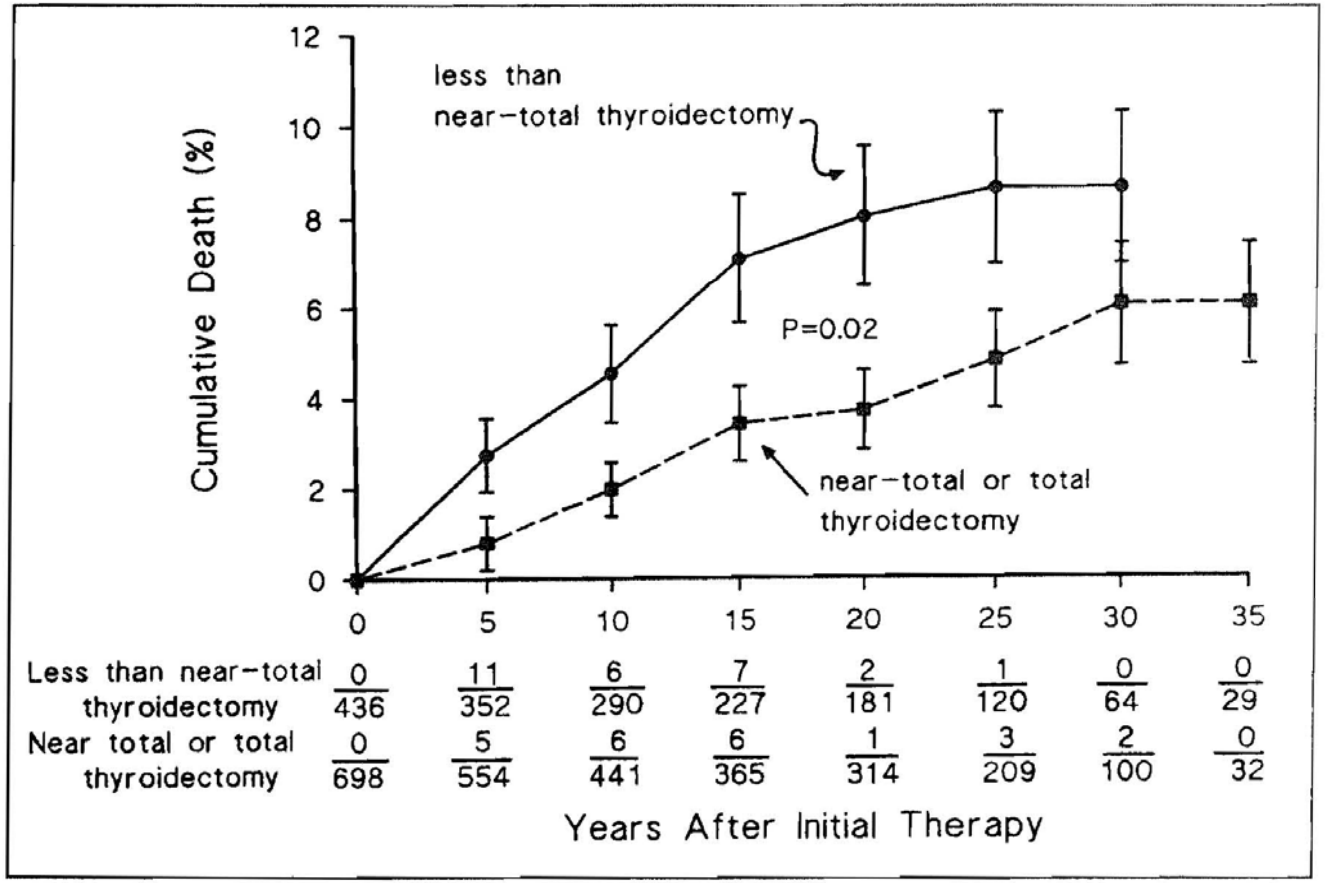
Major difference in survival

Thyroid Cancer: Role of Tyrosine Kinase Inhibitors

- Role of RAI in treating thyroid cancer still paramount
- Abundance of outcomes data to support its use as a post-operative adjuvant
- What happens when the tumor recurs and no longer responds to RAI is a big problem in a small minority of patients

- But first…some basics of thyroid cancer therapy

Impact of type of surgery* -- Value of total thyroidectomy



*Mazzaferri et al *Am J Med* 97:418, 1994

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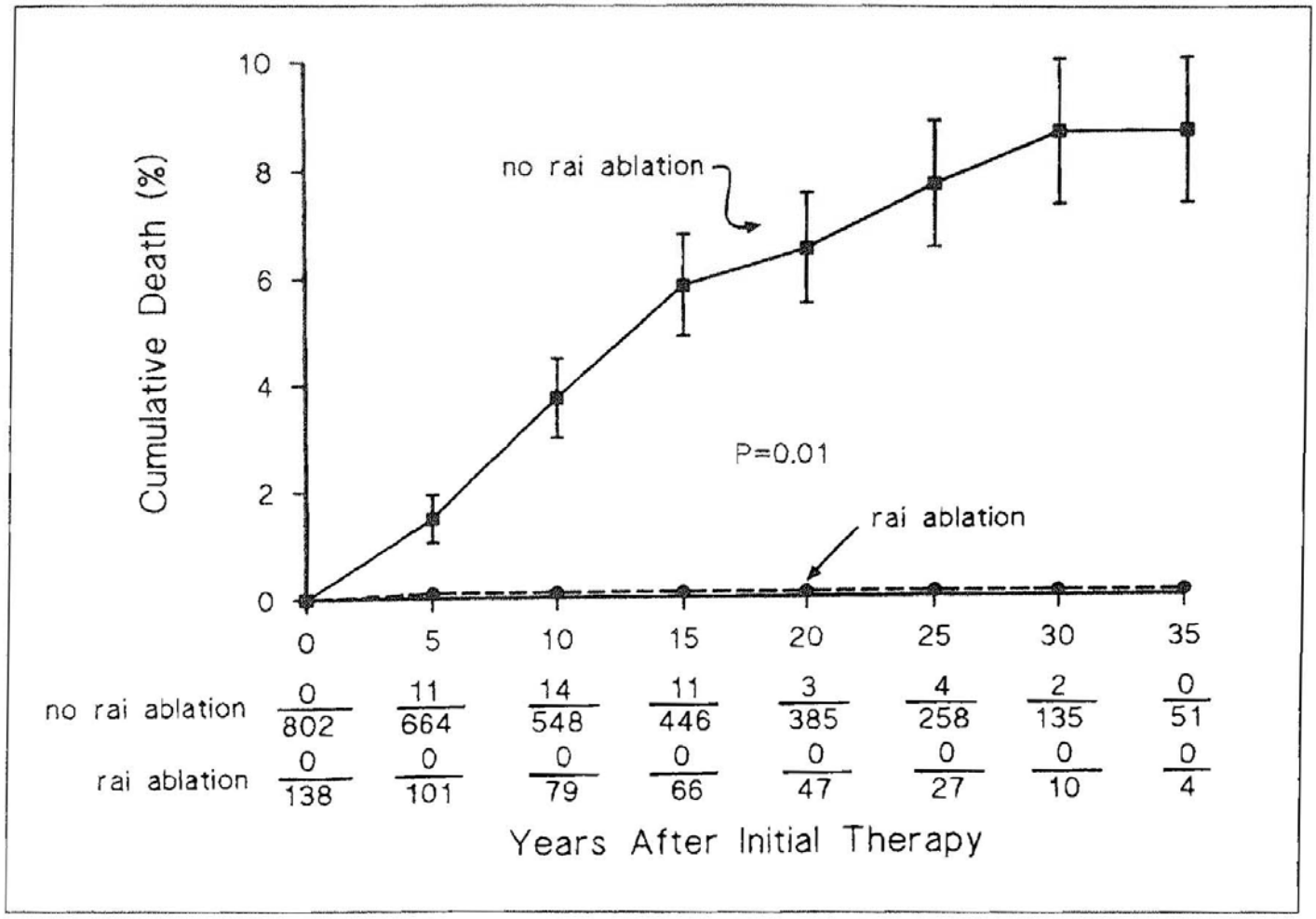
Impact of RAI after Thyroidectomy



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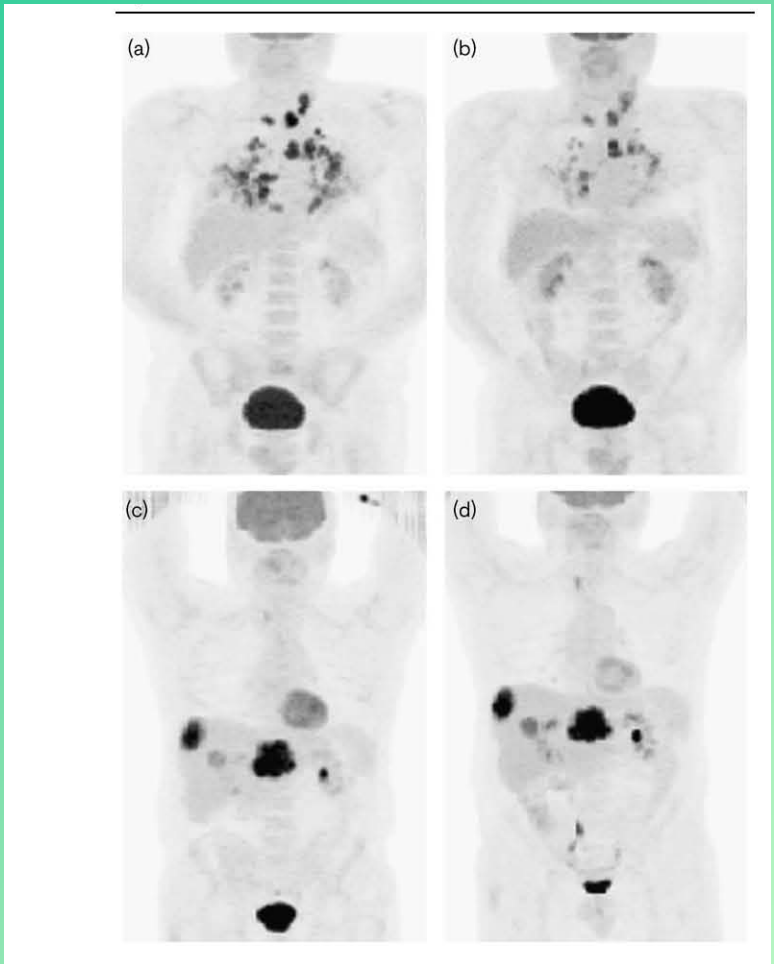
What happens when RAI doesn't work any more?

- Chemotherapy has been tried and is ineffective
- External beam radiation is not very effective
- Tyrosine kinase inhibitors are newly arrived on the scene and have just been tried
- Rationale: alteration in RET signaling pathway leading to altered transmembrane tyrosine kinases resulting in a new target for treatment

Tyrosine Kinase Inhibitors

- Sunitinib (Sutent): active in renal cell carcinoma and hepatocellular carcinoma
- Attaches to extracellular portion of tyrosine kinase
- Tried in thyroid cancer…

Two cases of metastatic thyroid cancer resistant to RAI treated with Sutent: one responded, the other did not*



Partial Response (a) vs. (b)

Has lasted for four years

No response

***Dawson et al *Anti-Cancer Drugs* 19:547, 2008**

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Other tyrosine kinase inhibitors

- Sorefanib (Nexavar) has limited record in thyroid cancer
- Extensive in vitro experience with thyroid tumor models suggesting it should be active

Axitinib – a new VEGF inhibitor

- Not commercially available yet
- Very interesting recent study* looking at efficacy and mechanism of action in thyroid cancer

*Cohen et al J Clin Oncol 26:4708, 2008

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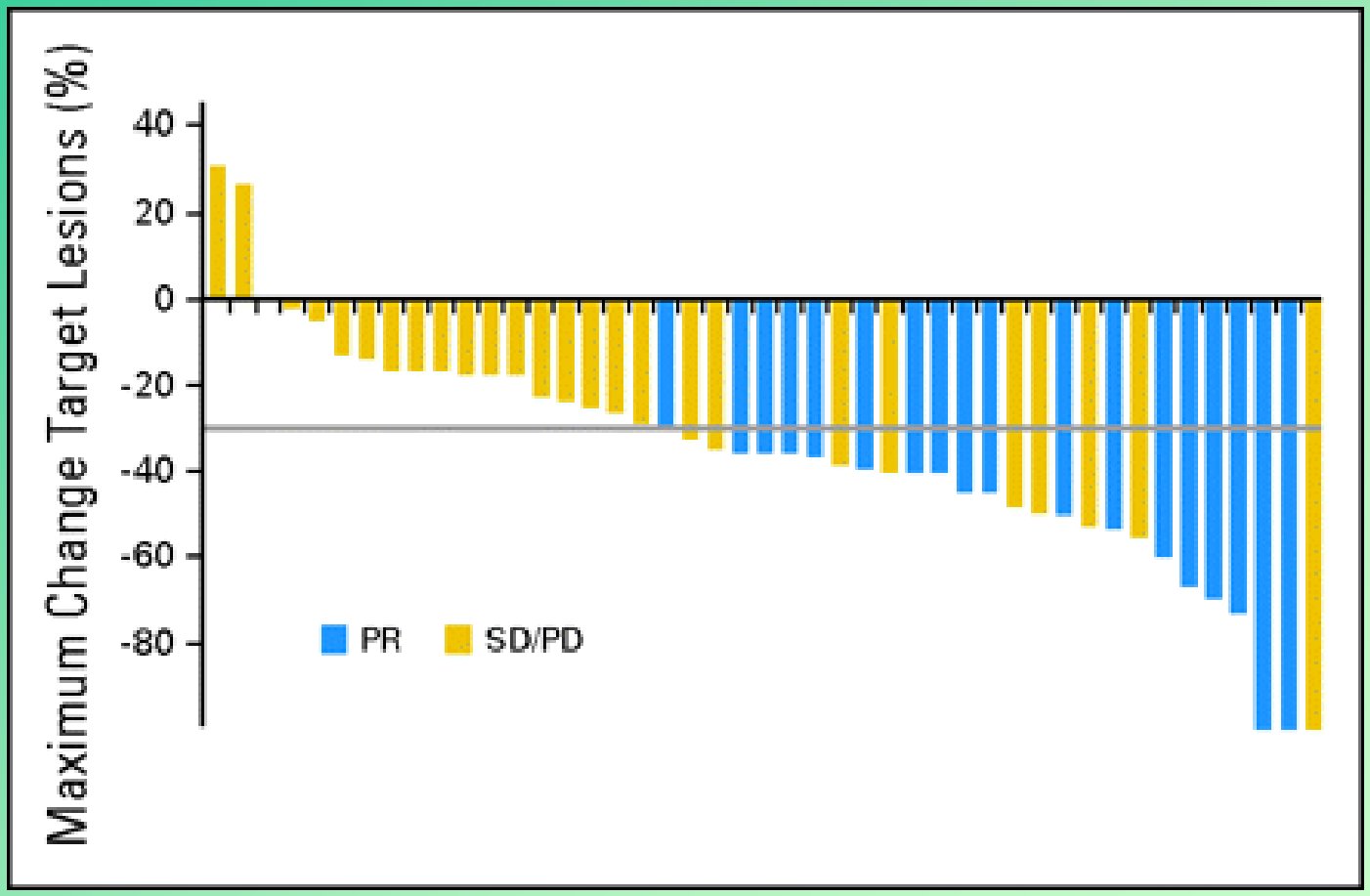
Maximum percentage of tumor reduction for target lesions by Response Evaluation Criteria in Solid Tumors



Very effective drug: only two patients progressed over the life of the study

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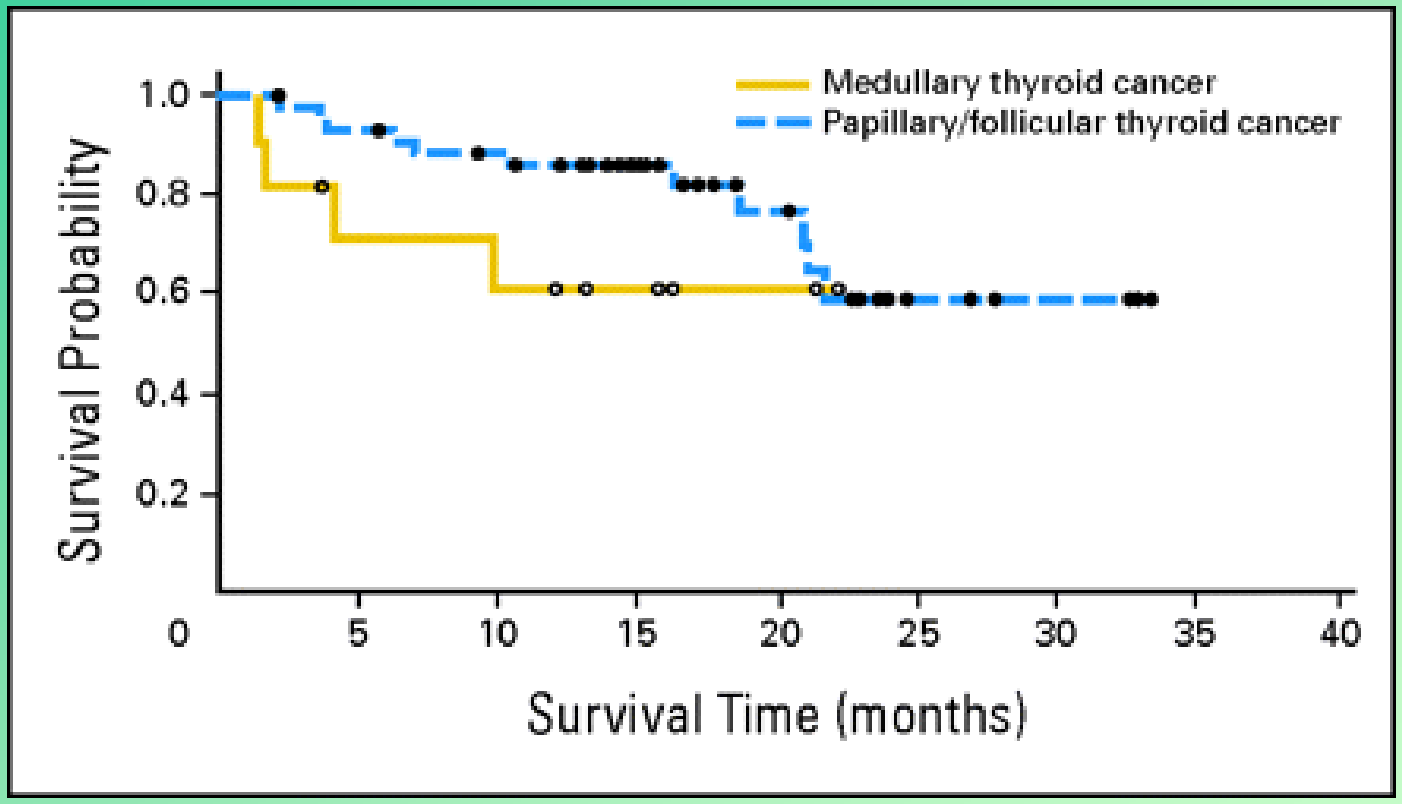
Kaplan-Meier curve for overall survival in patients with medullary thyroid cancer (solid line) and differentiated thyroid cancer (dashed line) – all after conventional therapy has failed



Substantial survival in high-risk group of patients

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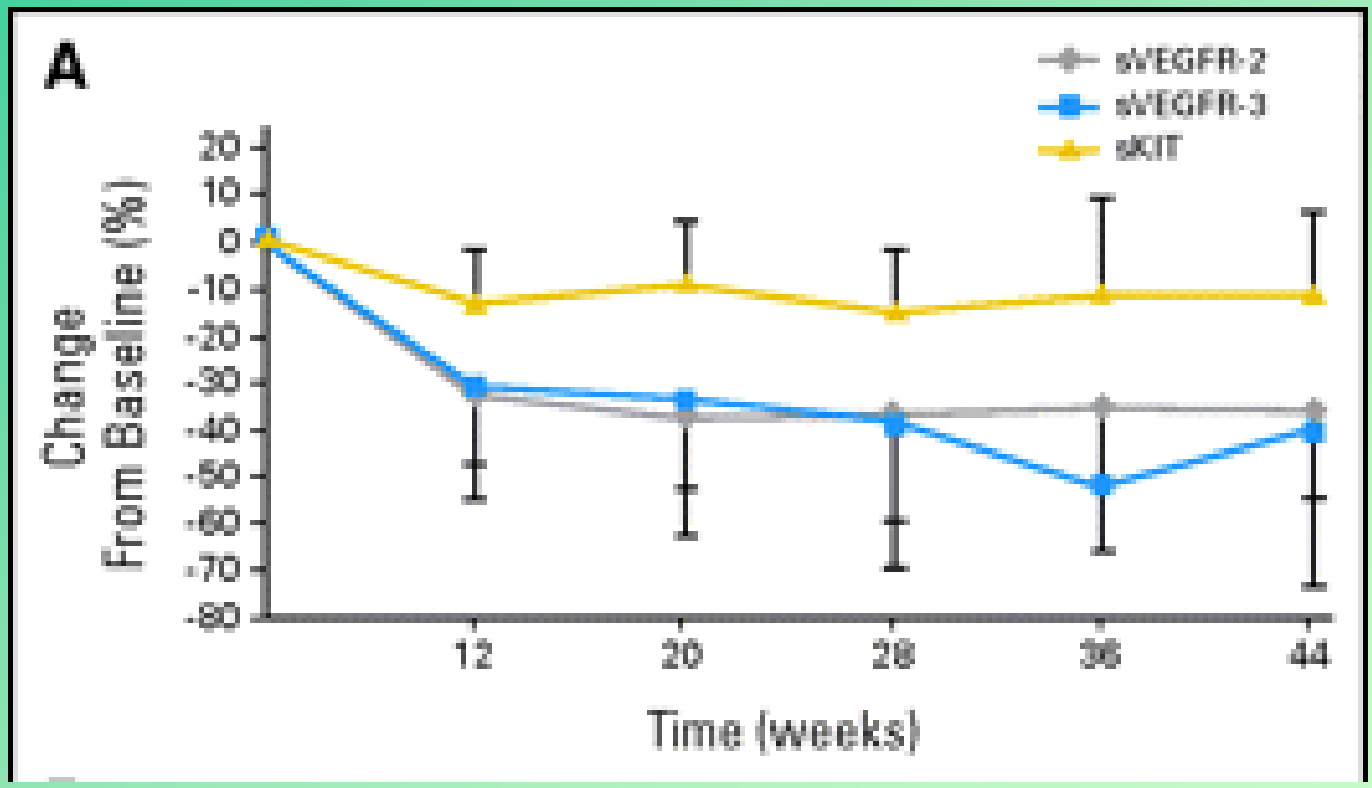
Preferential suppression of soluble vascular endothelial growth factor receptor sVEGFR-2 and sVEGFR-3 by axitinib in patients with thyroid cancer



Change in growth-factor receptor levels probably correlates with suppressive effect of drug on tumor; s-Kit used as control

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Summary

- Insular thyroid cancer is aggressive variant of adenocarcinoma of thyroid

- Substantial data to suggest that TKI's can produce clinically meaningful remissions in metastatic iodine-resistant thyroid cancer
- Much work needs to be done, possibly including TKI's in up-front high-risk situations
- Relative rarity of disease and lack of organized multi-institution trials make progress slow