

Controversial Issues in Managing Locally Advanced Head and Neck Cancer

Thyroid Cancer

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Disclosures

- Grants and contracts: Eisai, Merck Sharp & Dome
- Honoraria and consultation fees: Merck Serono, Bristol-Myers Squibb, Eisai, Otsuka and Bayer

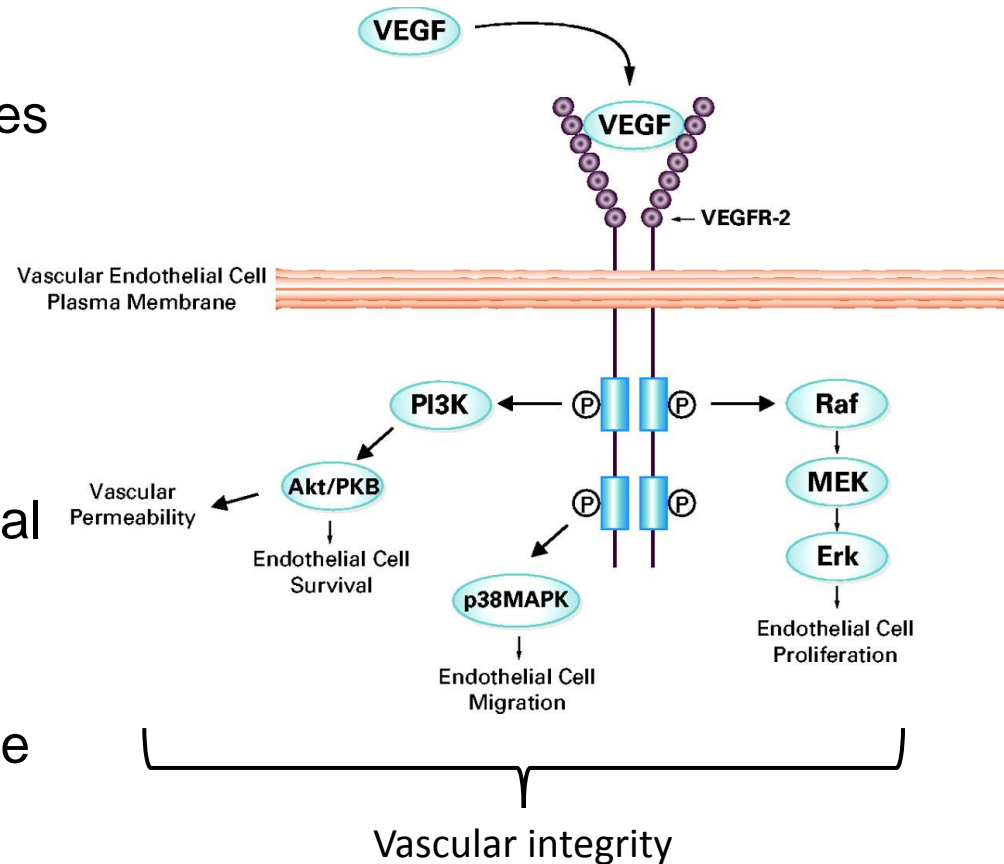
Controversial Issues in Managing Thyroid Cancer

- Risk of bleeding by VEGF-targeted TKI



Hemorrhagic complications

- One of the most severe and potentially life-threatening toxicities of anti-VEGF drugs
- Inhibition of VEGF
 - Interfere with the regenerative capacity of endothelial cells
 - Cause defects of the endothelial layer with exposure of the underlying matrix
 - Thrombosis and/or hemorrhage



Risk of bleeding with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials

- 23 trials were selected for the meta-analysis, yielding 6779 patients
- Incidence of bleeding events
 - All grades: 16.7% (95% CI 12.7–21.5)
 - High-grade events: 2.4% (1.6–3.9)
- Relative risk of all-grade bleeding events* was 2.0 (1.14–3.49; $p=0.015$)

*associated with sunitinib and sorafenib (for randomised controlled trials only)

Incidence of bleeding with VEGF-targeted TKI

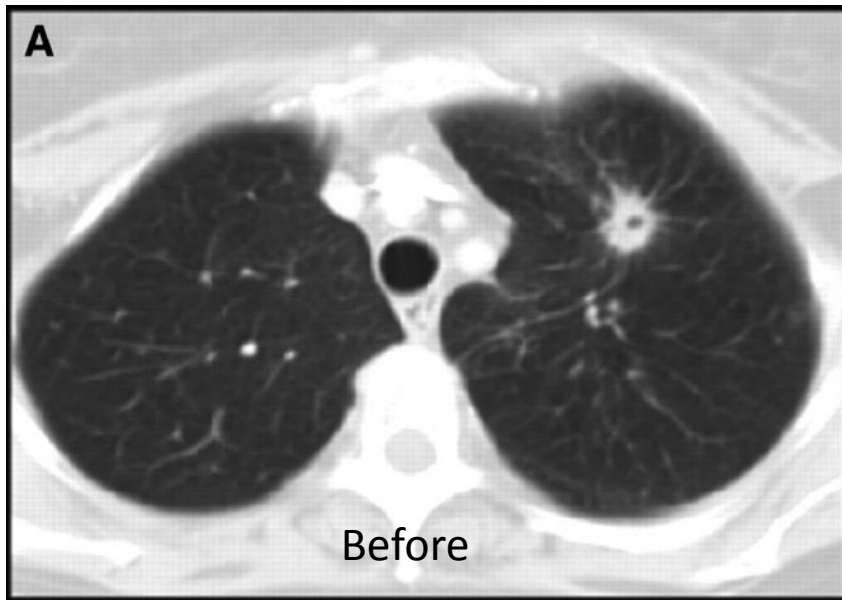
Therapy	Author	No.	Type of cancer	Rate of \geq grade 3 bleeding (grade 5)
Sunitinib	Demetri ¹	207	GIST	0%
	Socinski ²	63	NSCLC	(5%)
	Motzer ³	375	RCC	1%
	Machiels ⁴	38	SCCHN	5% (11%)
	Hui ⁵	13	NPC*	28.6%:4pts(14.3%:2pts)
Sorafenib	Ratain ⁶	202	RCC	4%
	Abou-Alfa ⁷	137	HCC	(1pt: intracranial hemorrhage)
	Escudier ⁸	451	RCC	3%
	Brose ⁹	207	DTC	(1pt: myocardial infarction)
Lenvatinib	Schlumberger ¹⁰	261	DTC	(1pt: pulmonary embolism) (1pt: hemorrhagic stroke)

*previously received high dose radiation

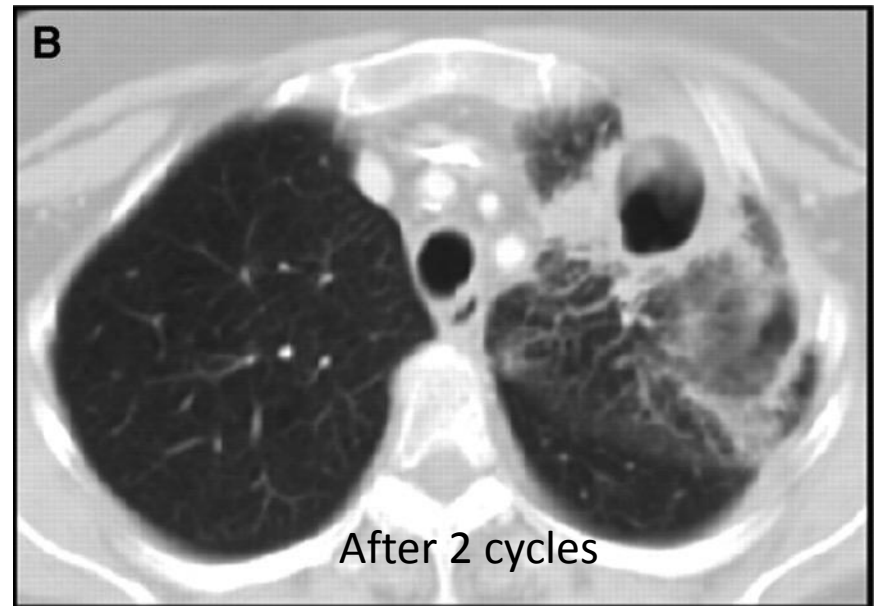
1. Lancet 2006;368(9544):1329–38
2. J Clin Oncol 2008;26(4):650–6
3. N Engl J Med 2007;356(2):115–24.
4. J Clin Oncol 2010;28:21-28
5. Annals of Oncol 2010;22(6):1280-87
6. J Clin Oncol 2006;24(16):2505–12
7. J Clin Oncol 2006;24(26):4293–300.
8. N Engl J Med 2007;356(2):125–34
9. Lancet. 2014 Jul 26;384(9940):319-28
10. N Engl J Med. 2015 Feb 12;372(7):621-30

Baseline tumor cavitation as a significant risk factor for severe hemorrhage

- Retrospective multivariate analysis of clinical or radiological risk factors for pulmonary hemorrhage in two trials of bevacizumab-contained regimens
- Only baseline cavitation was associated with an increased risk (OR, 4.5; 95% CI, 0.73 to 28.33), although not significant ($P = .063$)



A left upper lobe cavitating mass that did not contact any vascular structure...



...developed further cavitation, and became contiguous with a vascular structure

Phase II study of sunitinib in R/M SCCHN: GORTEC 2006-01 (N=38)

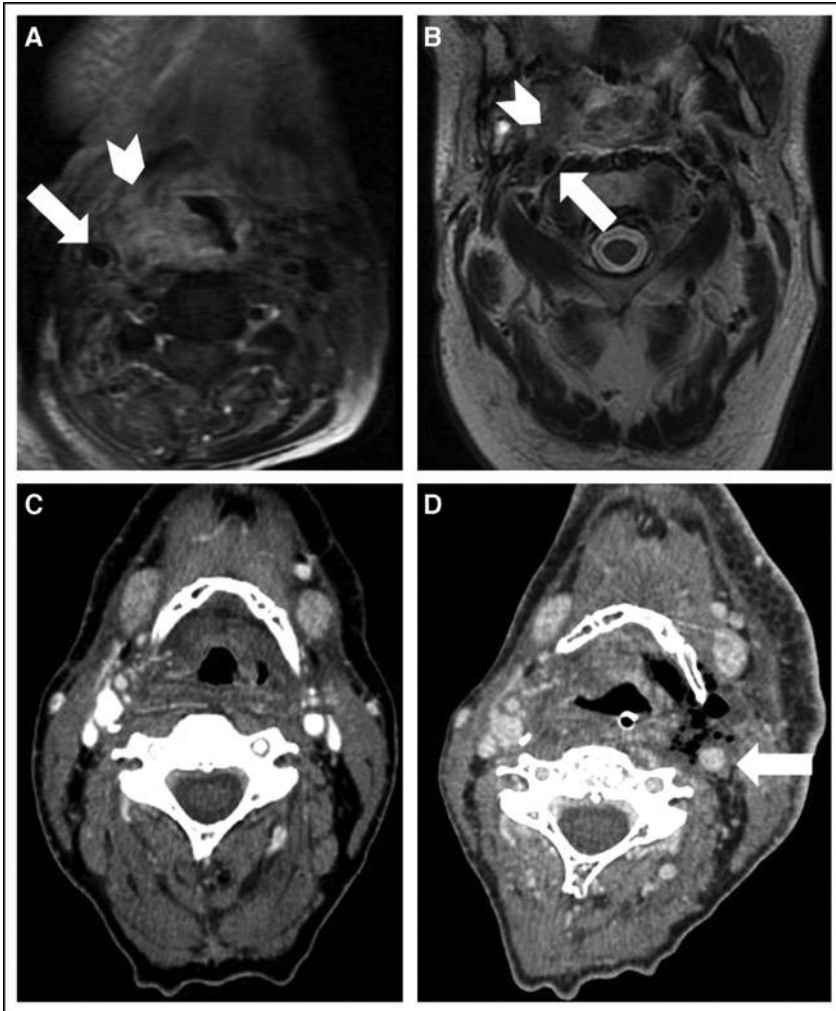
- Head and Neck Bleeding**

	No. of patients (%)		
	Gr 1-2	Gr-3-4	Gr5
Head and neck bleeding	7 (18)	2 (5)	4 (11)
with local relapse	7 (18)	2 (5)	3*(8)
with no local relapse	0	0	1 [#] (3)

- ***Tumor located less than 5 mm from carotid artery**
- **#A large ulcer with subsequent carotid rupture in an area that was previously irradiated**

Grade 5 bleeding complications

Tumor located less than 5 mm from carotid artery



A large ulcer with subsequent carotid rupture in an area that was previously irradiated



Risk of bleeding with VEGF-targeted TKI

- Should patients with the following risk factors avoid VEGFR-targeted therapy ?
 - Tumor located less than 5 mm from the carotid artery
 - Tumor located in an area that was previously irradiated
- Additional risk factors?

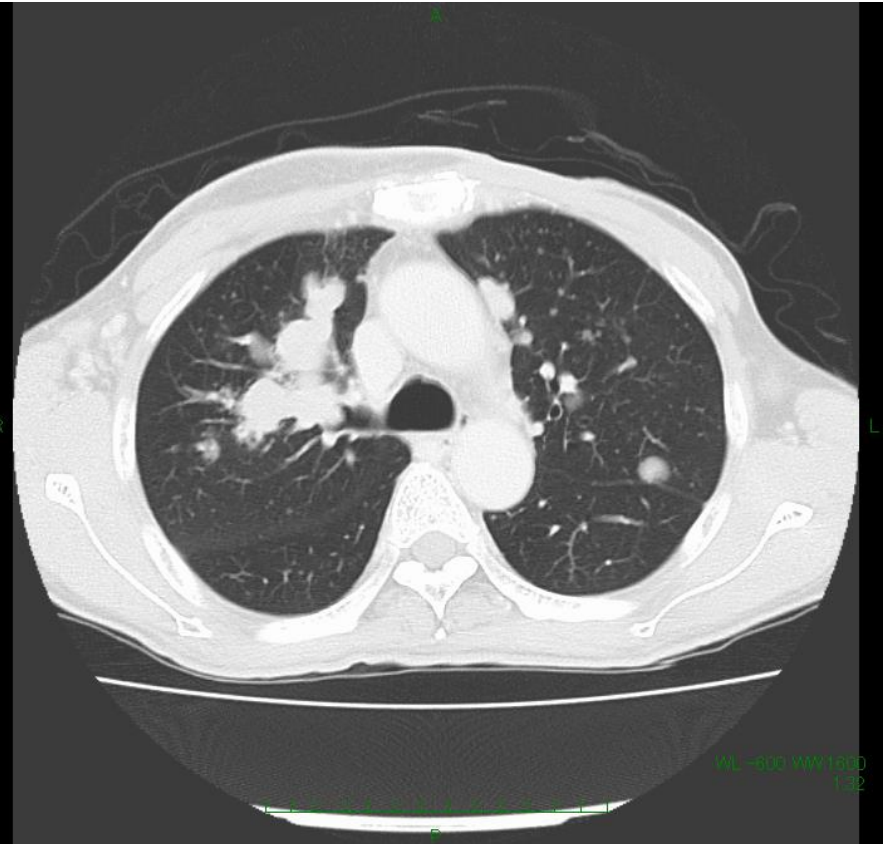
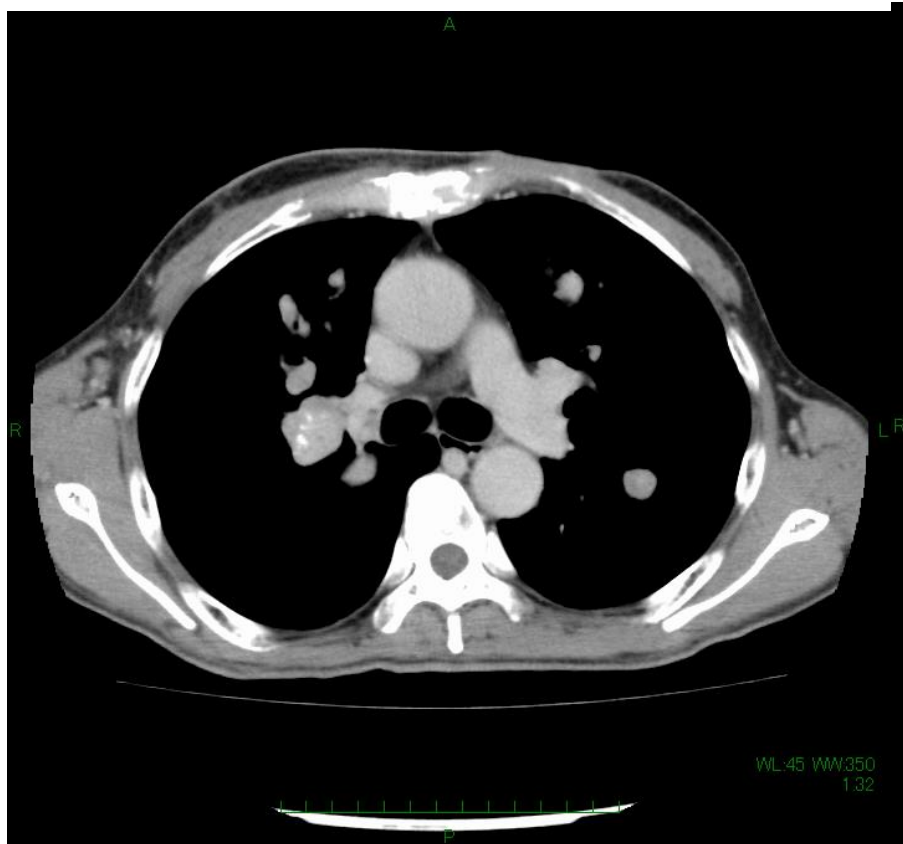
Case 1

- 59 yr male with recurrent PTC
- Prior treatment
 - Total thyroidectomy (1997)
 - RT for local recurrence (2004)
 - Total laryngectomy, ND (2007)
 - RT for bone metastasis (2008)
 - RAI for neck recurrence (2009)
- PS 1
- Symptoms: neck pain, bloody sputum
- No significant comorbidity
- No abnormal organ function



Protruding tumors that bleed easily in a part of the neck that was previously irradiated

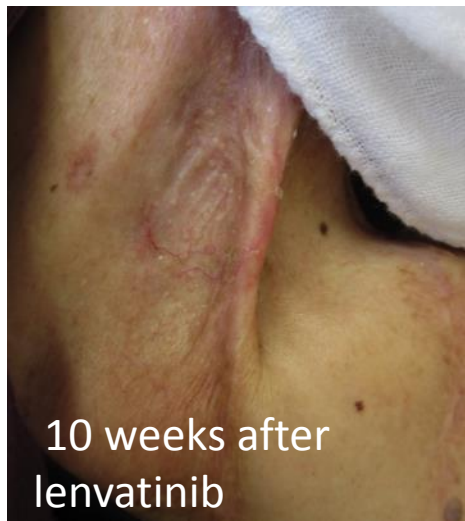
CT scan



Question 1

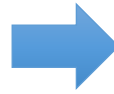
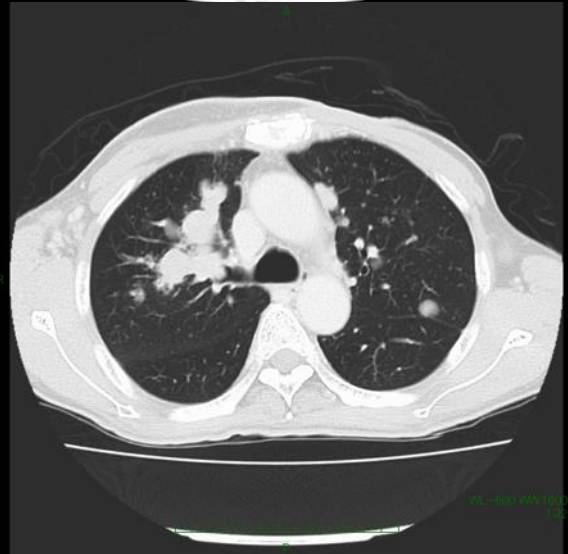
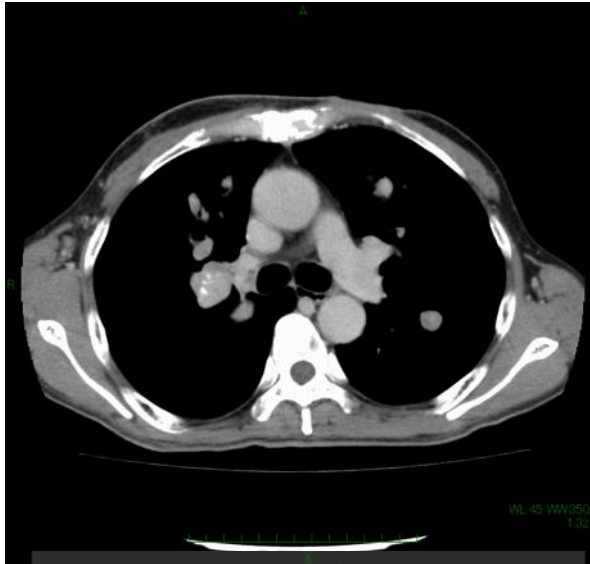
- Summary of Case 1
 - ✓ Tumor that bleeds easily in an area that was previously irradiated, but not located less than 5 mm from the carotid artery
 - ✓ Bloody sputum
- Does he have a high risk of bleeding?
- Should he avoid VEGFR-targeted TKI?

Clinical course after enrollment in the SELECT study

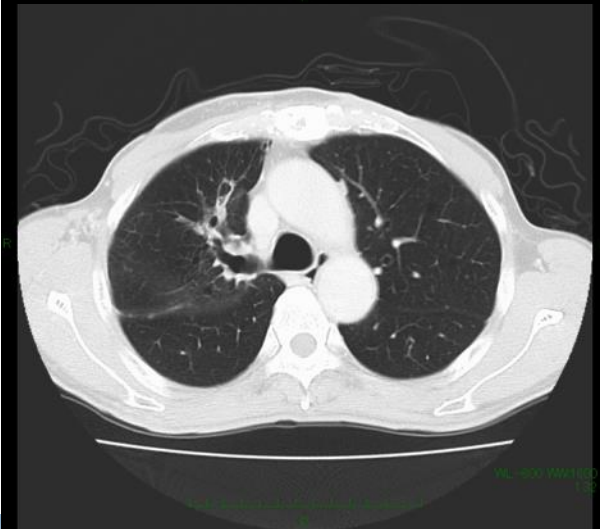


CT scan

Before study drug

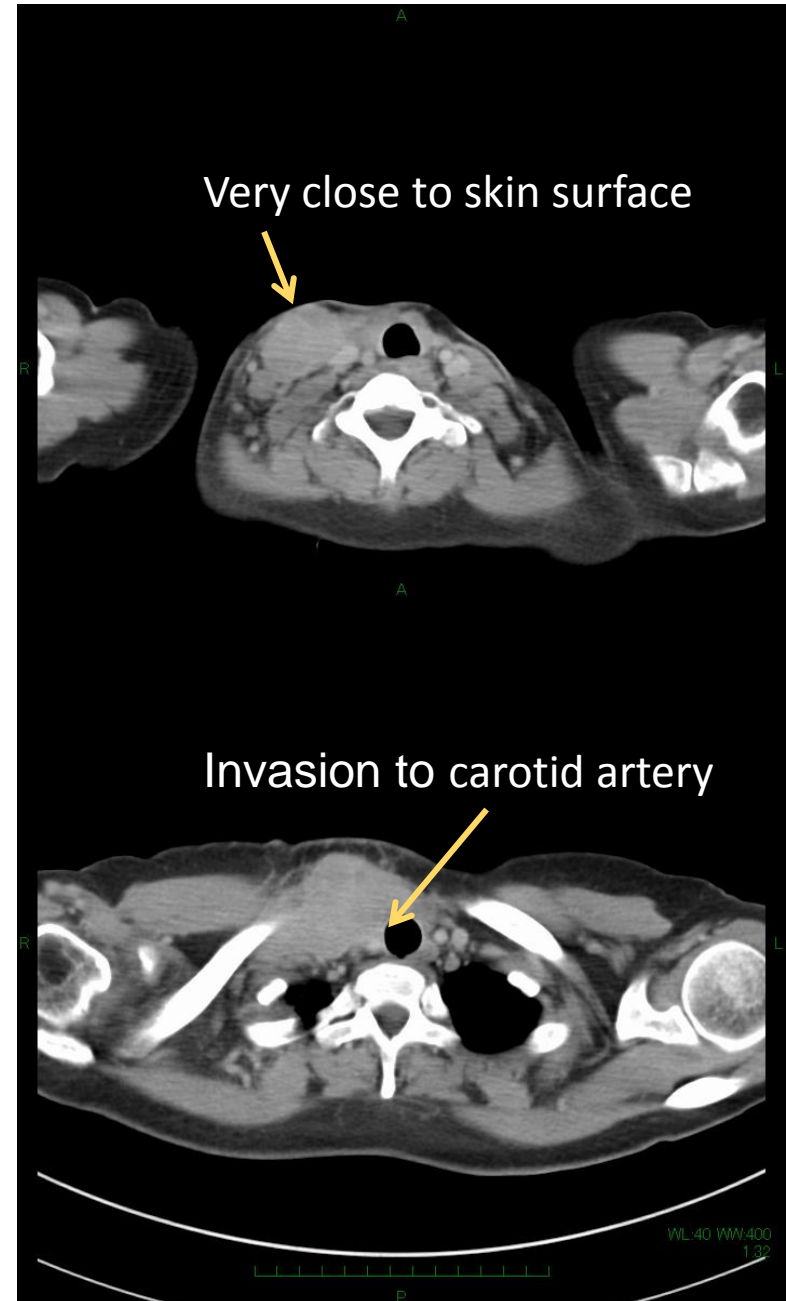


4 month after study drug



Case 2

- 44 yr female with ATC
- Prior treatment
 - Subtotal thyroidectomy for PTC(2011)
 - ND for lt neck LN meta (2012)
 - RAI 100mCi (2013)
 - ND for paratracheal LN meta (2014)
 - ND for subclavicular LN meta (2015/2)
 - ND for rt neck LN meta (2015/8)
 - ATC transformation
- PS 1
- Symptoms: neck swelling
- No significant comorbidity
- No abnormal organ function



Question 2

- Summary of case 2
 - ✓ Tumor invasion to the carotid artery
 - ✓ Tumor reached very close to the skin surface
 - ✓ No clear evidence of skin invasion
- Does she have a high risk of bleeding?
- Should she avoid VEGFR-targeted TKI?

CT scan

Before Lenvatinib



28 days after lenvatinib



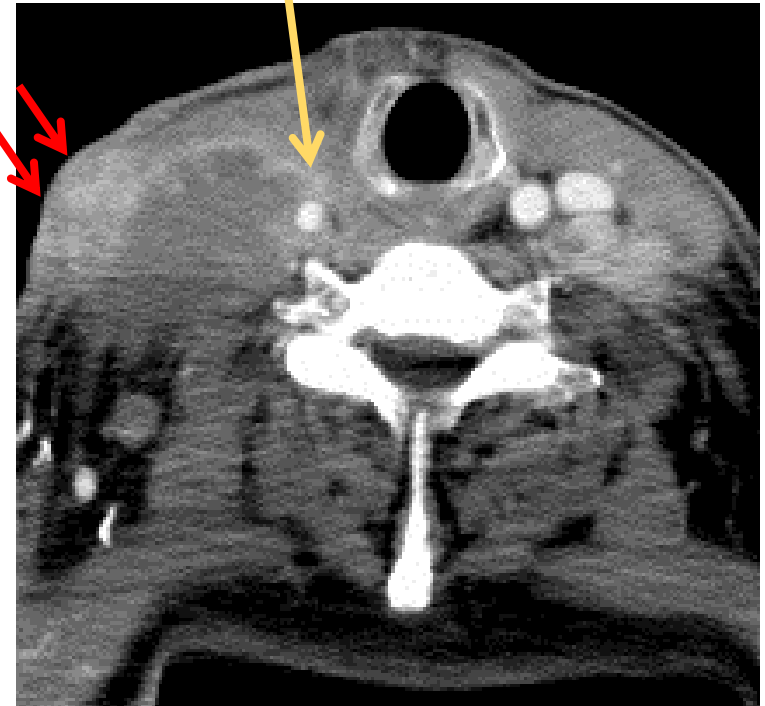
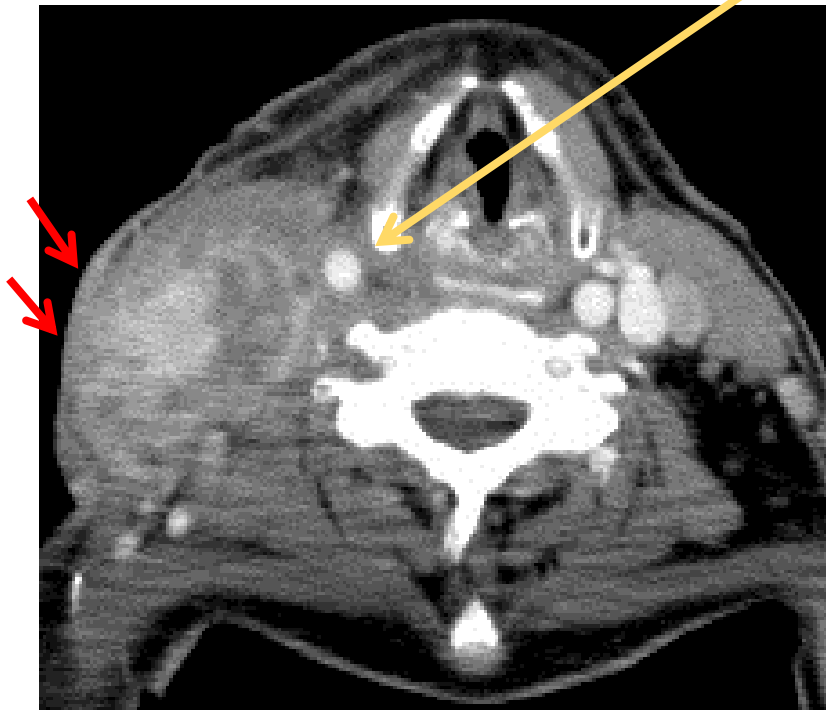
Case 3

- A 73 yr male with recurrent PTC
- Prior treatment
 - Total thyroidectomy and ND (2005)
 - RAI 100mCi (2005)
 - Sorafenib(2014/7) for neck LN meta
 - Discontinued due to neck tumor bleeding (2014/10)
 - RT (30Gy/10Fr) for neck LN meta (2015/3)
 - Mohs paste for neck bleeding (2015/3/27)
- PS 1
- Symptoms: neck swelling
- Comorbidity
 - ✓ DM (HbA1c: 8.4%)
- No abnormal organ function



CT scan

carotid artery



Question 3

- Summary of Case 3
 - ✓ Tumor invaded the carotid artery in an area that was previously irradiated
 - ✓ Skin invasion
 - ✓ History of neck bleeding due to sorafenib
 - ✓ Poor control of diabetes
- Does he have a high risk of bleeding?
- Should he avoid VEGFR-targeted TKI?
- If he had no history of neck bleeding due to sorafenib, would you change your decision?

Clinical course

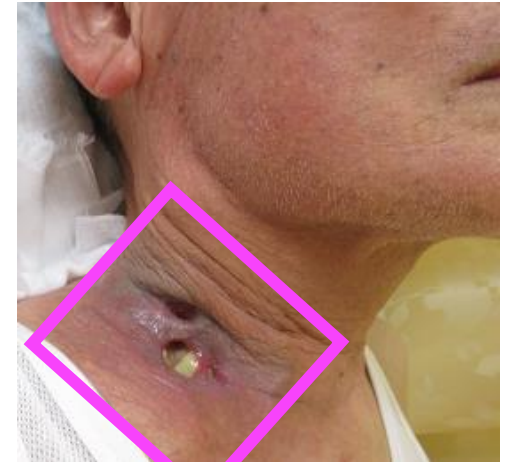
Before LEN



Day 11 after LEN



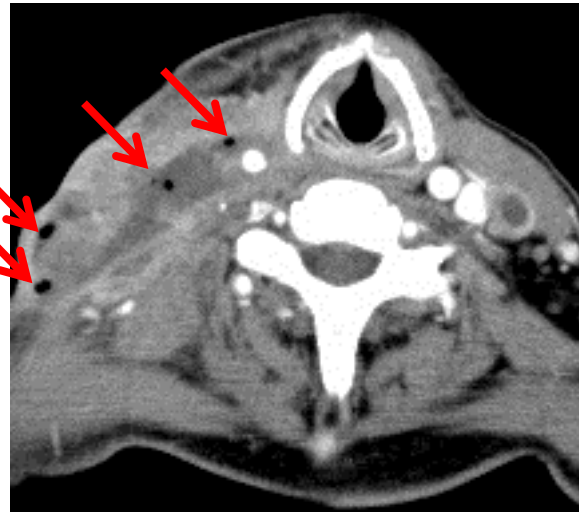
Day 24 after LEN



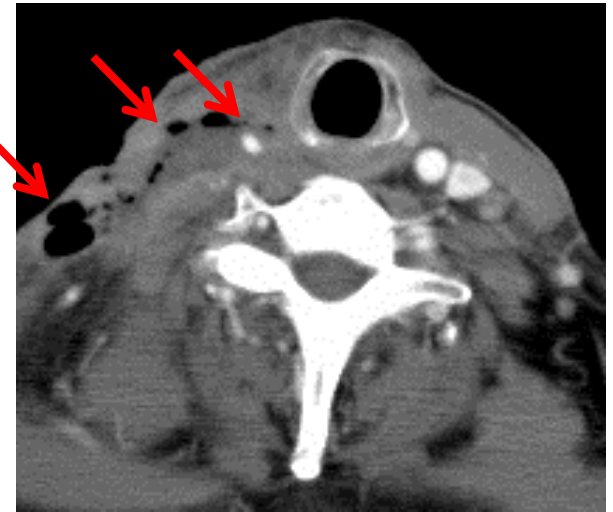
CT scan



Before LEN



Day 10 after LEN



Day 25 after LEN

Skin invasion and disintegration, like an ulcerative tumor, is a major high risk factor for bleeding

Risk of bleeding with VEGFR-targeted TKI

- High risk of bleeding with VEGFR-targeted TKI
 - Tumor located less than 5 mm from the carotid artery
 - Tumor located an area that was previously irradiated
- Major risk of bleeding
 - Skin invasion and disintegration
 - Avoid VEGFR-targeted TKI
 - Air infiltration (cavitation) around the carotid artery
 - Discontinuation of VEGFR-targeted TKI