

A case of tumor-induced osteomalacia in which recurrence and bilateral lung metastases occurred following tumor resection

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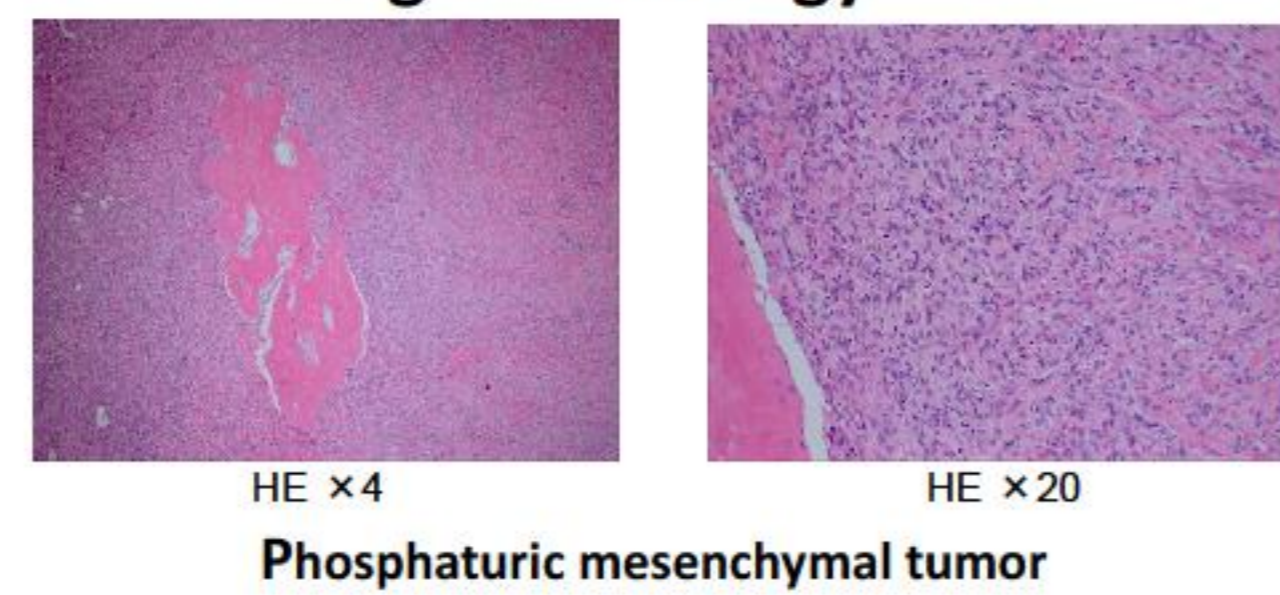
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CASE: 32-years-old female Japanese

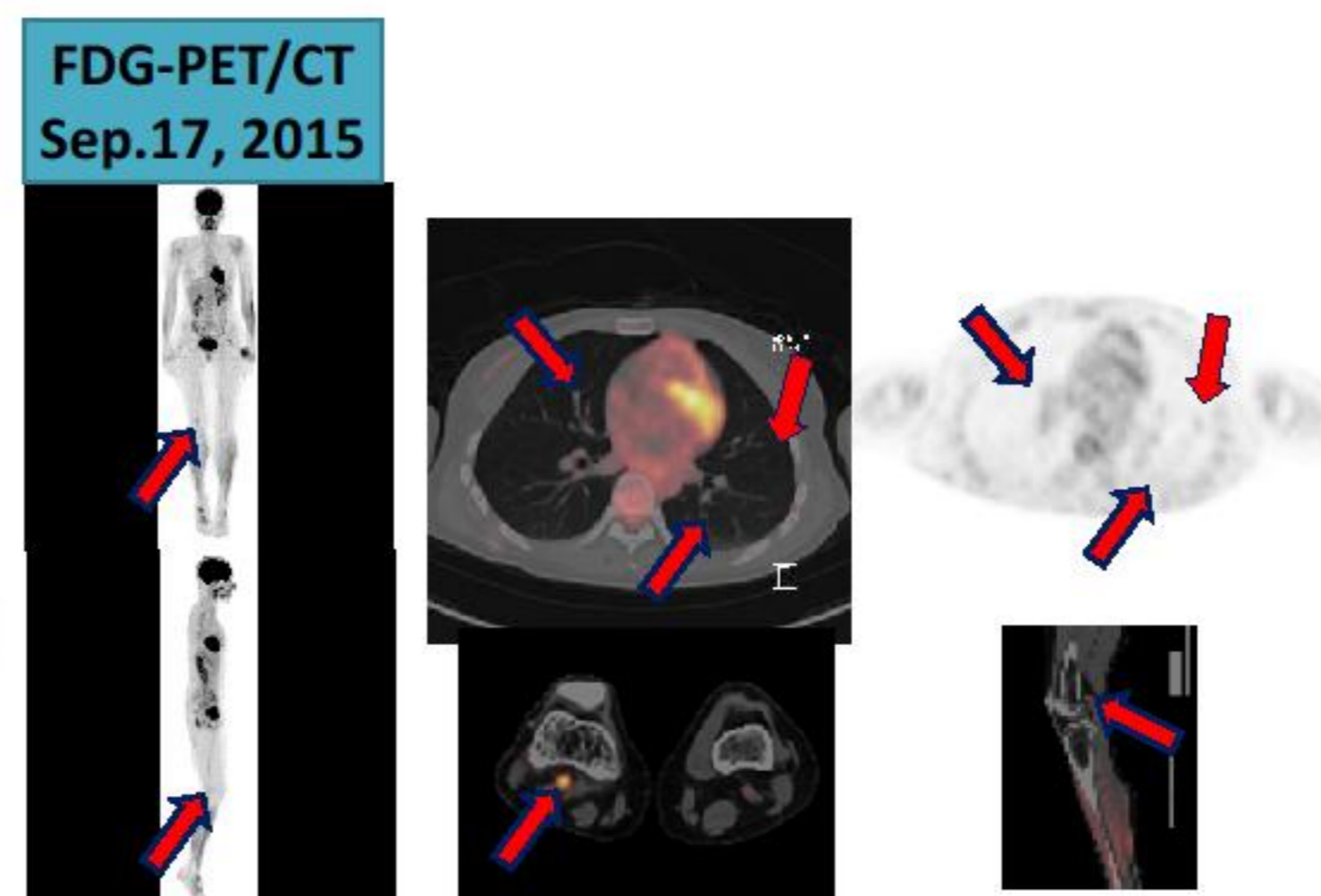
Chief Complaint: General fatigue and walking difficulty
 Past medical problems: No significant
 Family History: No osteomalacia

Fig.4 Pathology



The tumor primarily comprised spindle-shaped cell proliferation interposed with collagen fibers. A disarray of fiber bundles as well as small, thin-walled blood vessels that were dilated or showed a cleft-like form were also present, representing findings suggestive of hemangiopericytoma.

Fig.8 FDG-PET/CT



Treatment for Tumor-Induced Osteomalacia

- Surgical treatment
- Medical treatment
 - Neutral phosphorus formulation and active vitamin D formulation
 - Treatment with octreotide**
 - Treatment with anti-FGF23 antibody (currently undergoing trial)
 - Anti-cancer drug therapy using molecularly targeted drugs

History of Present Illness 1: up to first surgery

The patient began experiencing right hip pain around 2007 and became unable to walk. In 2009, osteomalacia and hypophosphatemia were identified at a local orthopedic surgery department, and the patient was referred and admitted to our hospital.

Marked hypophosphatemia was observed (serum Ca, 9.5 mg/dl; **IP, 1.4 mg/dl**), and tumor-induced osteomalacia (TIO) was diagnosed due to high levels of intact PTH (29 pg/ml), TmP/GFR (1.14 mg/dl), and **Fibroblast growth factor 23 (FGF23) (713 pg/ml)**; normal, 10-50 pg/ml). A high level of FGF23 (1600 pg/ml) was detected from the right femoral vein with systemic venous sampling (fig.1), and a 26-mm mass was evident at the posterior right knee on right leg MRI (fig.2)

Resection of the right knee tumor was performed in June 2011. Hypophosphatemia promptly improved postoperatively and FGF23 also normalized to 23 pg/ml (fig.3) The patient regained the ability to walk independently and returned to work and activity.

The pathological diagnosis was phosphaturic mesenchymal tumor (fig.4)

History of Present Illness 2: process from post-1st surgery to 2nd surgery

However, serum IP (1.8 mg/dl) began to decrease and FGF23 again increased since October 2013, reaching 221 pg/ml. Oral neutral phosphorus formulation and active vitamin D₃ formulation were restarted, as a result, malaise was improved. (fig.5)

In May 2014, right knee MRI was performed with consideration of recurrent TIO, but no significant findings were found. **In June 2014, multiple nodules were detected in the left upper lung on chest CT.** (fig.6) In July 2015, right knee MRI was performed again, showing that a 25-mm tumor was detected in the posterior right knee. (fig.7) Furthermore, **FDG-PET/CT** showed a tumor in the posterior right knee and chest CT showed uptake into both lung fields corresponding to multiple nodules. (fig.8) **Recurrence of TIO was then diagnosed.**

On September 18, 2015, we performed right knee tumor resection. The pathological diagnosis was recurrent phosphaturic mesenchymal tumor. However, high levels of FGF23 continued postoperatively at 950 pg/ml, as compared with 1500 pg/ml preoperatively. Hypophosphatemia did not improve, suggesting that it was due to residual tumor and lung metastasis. Since **somatostatin receptor (SSTR)2** was expressed in the resected specimen on RT-PCR (fig.9) The patient was admitted to the hospital for the treatment of somatostatin analog. (fig.10-12)

Fig.9 RT-PCR shows expression of SSTR2 mRNA



Fig.12 FGF23 could not be suppressed with octreotide treatment.

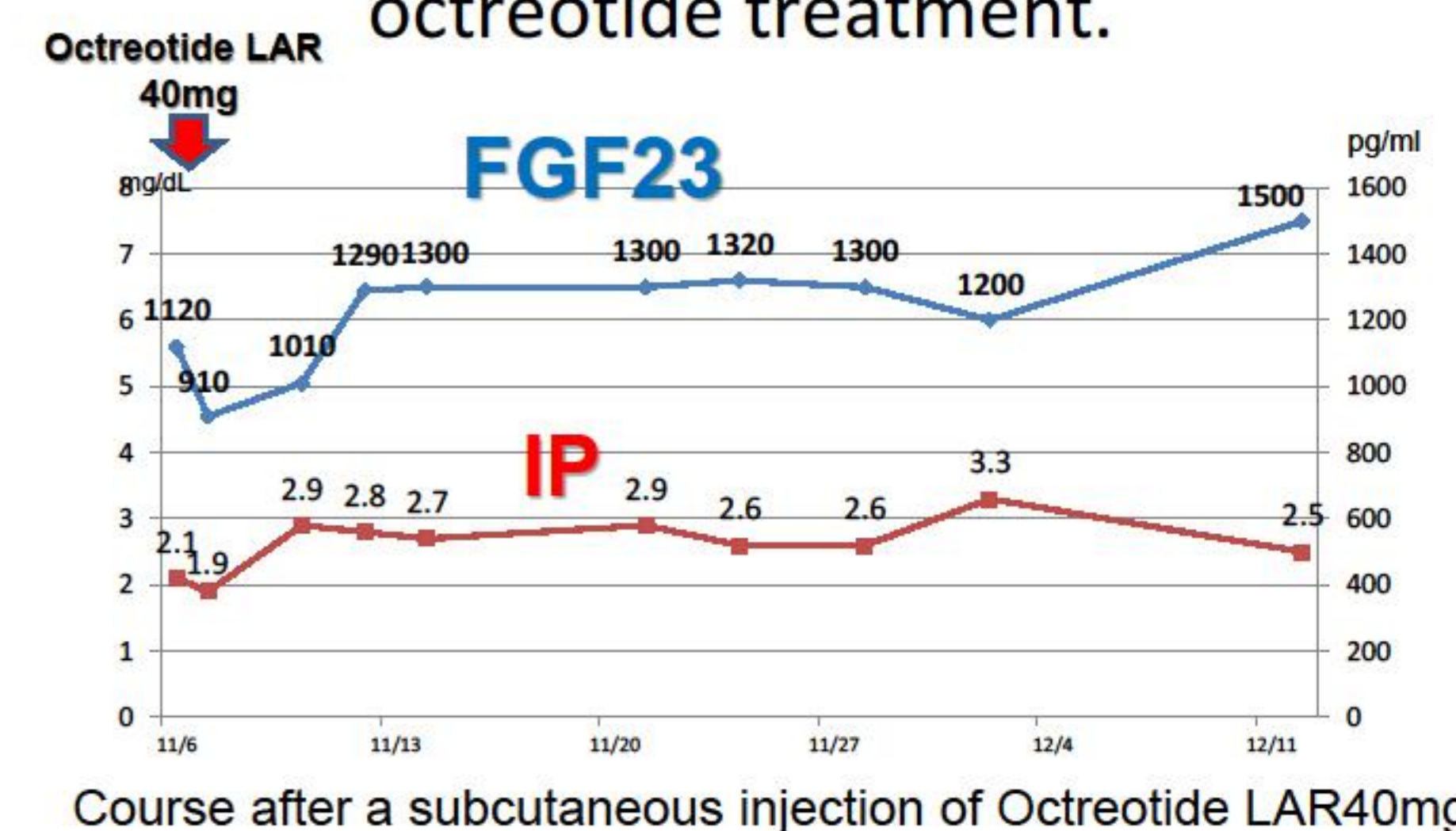


Fig.1 Venous sampling for FGF23 in patient with suspected TIO.

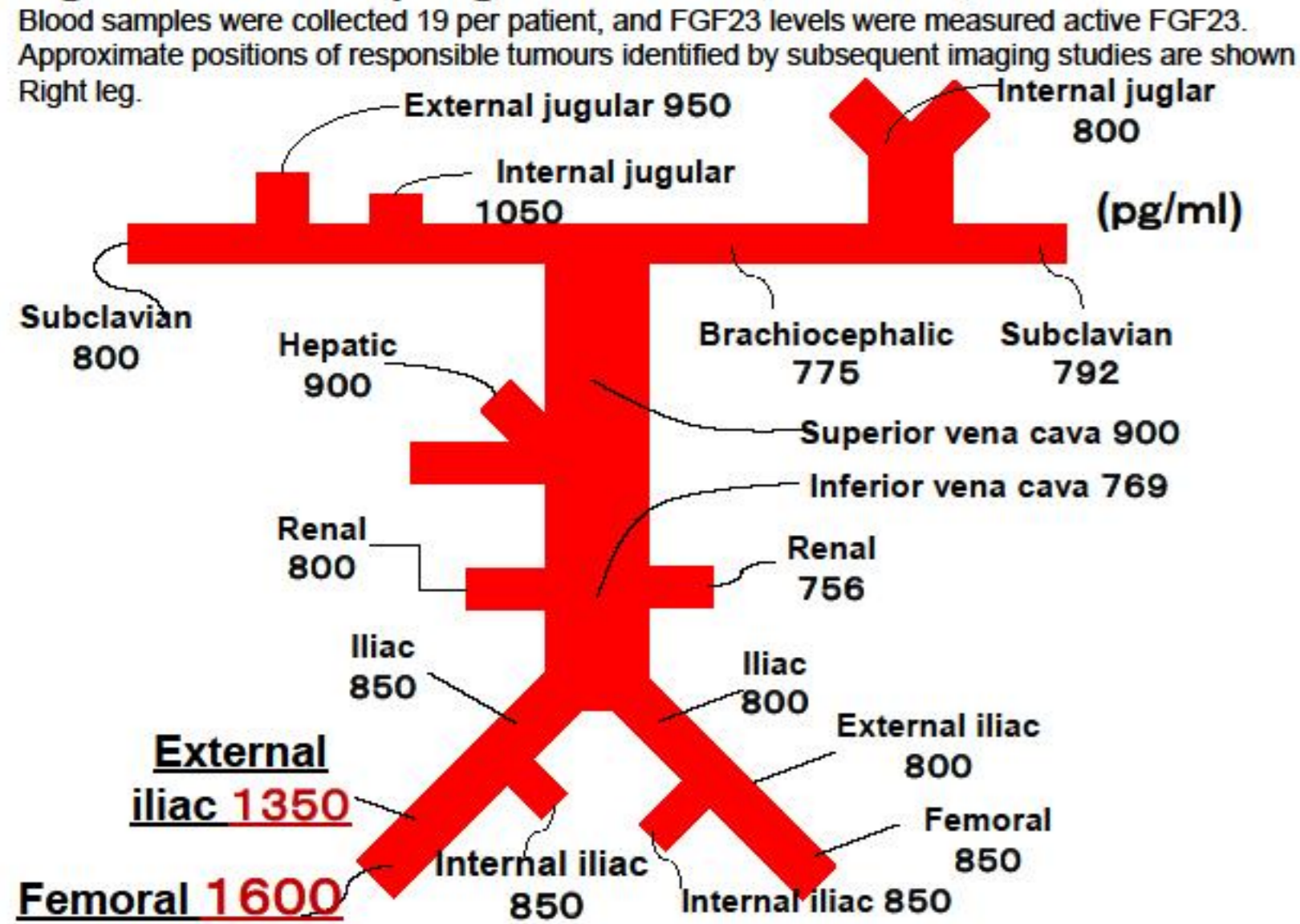


Fig.5 Up to second surgery

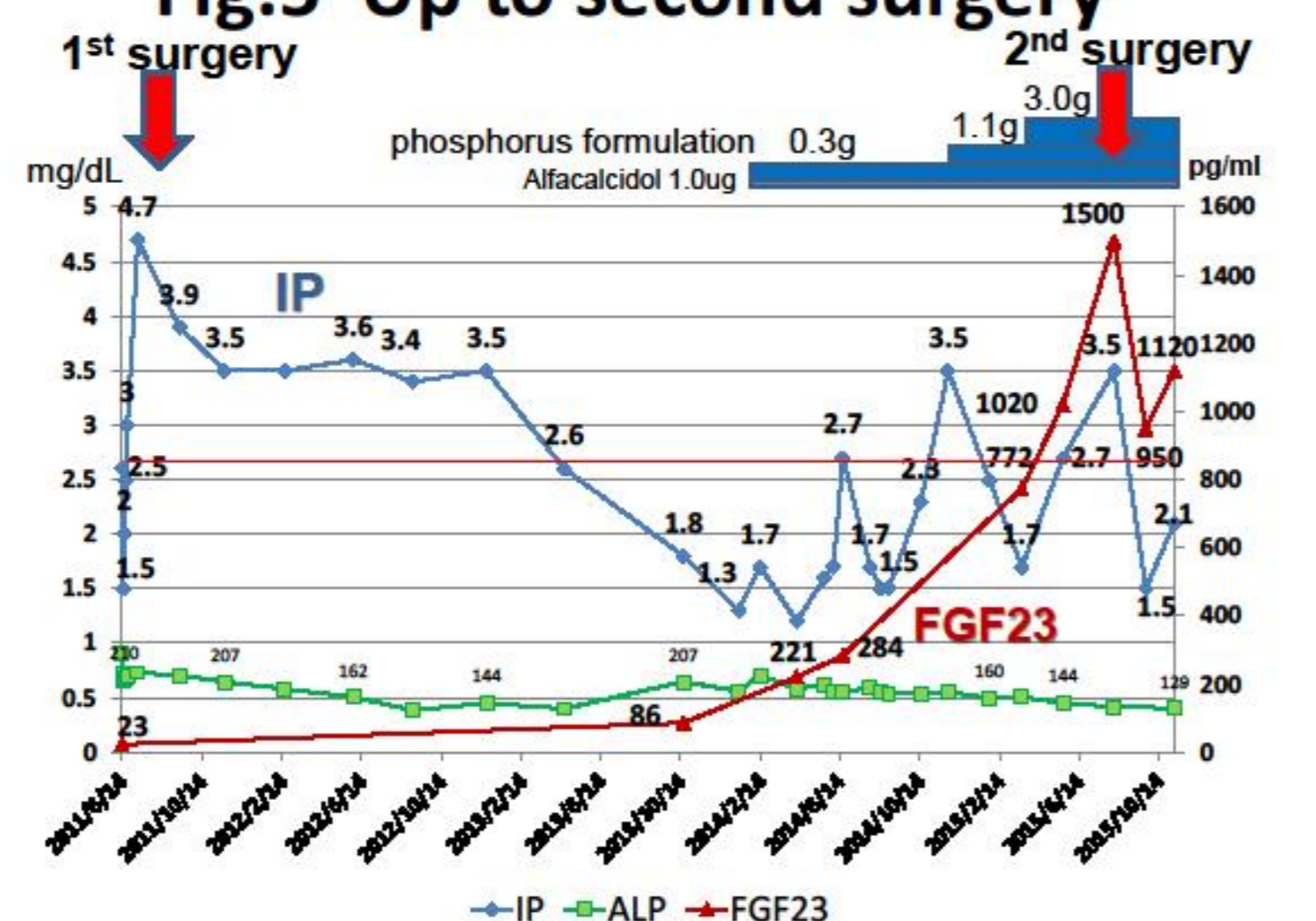


Fig.10 Laboratory finding on admission

< Hematology >		< Urinalysis >	
WBC 4300 /µl	TP 6.7 g/dl	Na 177 mmol/l	
Hb 11.7 g/dl	ALB 4.4 g/dl	K 50.5 mmol/l	
Ht 35.9 %	ALP 129 IU/l	Cl 115 mmol/l	
RBC 405 × 10 ³ /µl	γ-GTP 10 IU/l	Ca 6.0 mg/dl	
PLT 19.6 × 10 ³ /µl	AST 16 IU/l	IP 288.8 mg/dl	
	ALT 12 IU/l	Cr 105 mg/dl	
	LDH 192 IU/l	PH 6.0	
	CK 66 IU/l	Density 1.020	
Na 139 mmol/l	TC 145 mg/dl	Protein(-)	
K 3.6 mmol/l	LDL-C 74 mg/dl	Glucose(-)	
Cl 106 mmol/l	HDL-C 61 mg/dl	Oculta(-)	
Ca 9.3 mg/dl	TG 55 mg/dl		
IP 2.1 mg/dl ↓	BUN 14.3 mg/dl		
	Cr 0.51 mg/dl		
	CRP 0.01 mg/dl		
	UA 4.1 mg/dl		
	FGF23 1120 pg/ml		
	(normal 10-50)		

Hormonal regulation → Reduce the tumor

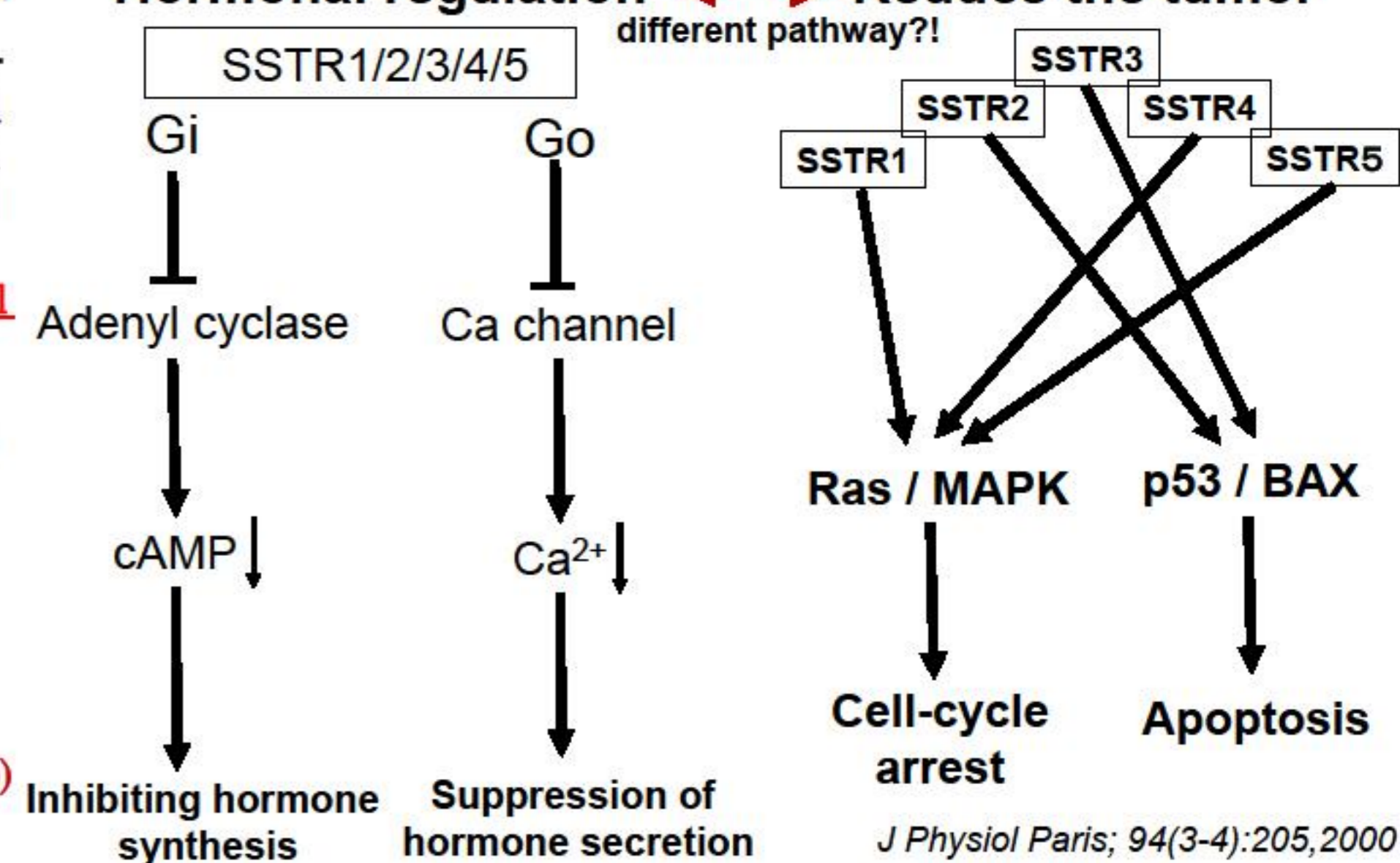


Fig.2 Primary tumor of TIO

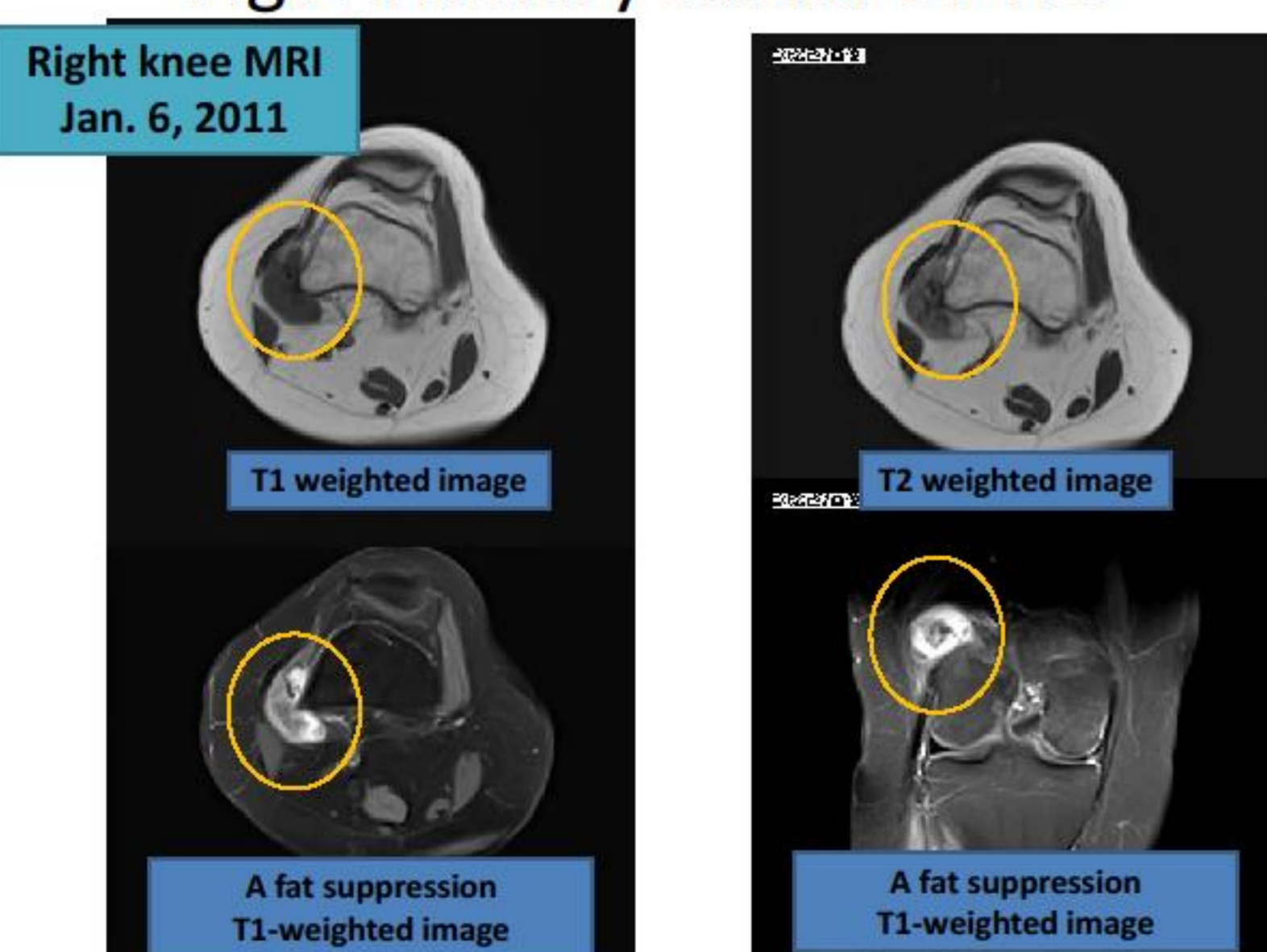


Fig.6 Bilateral lung metastases

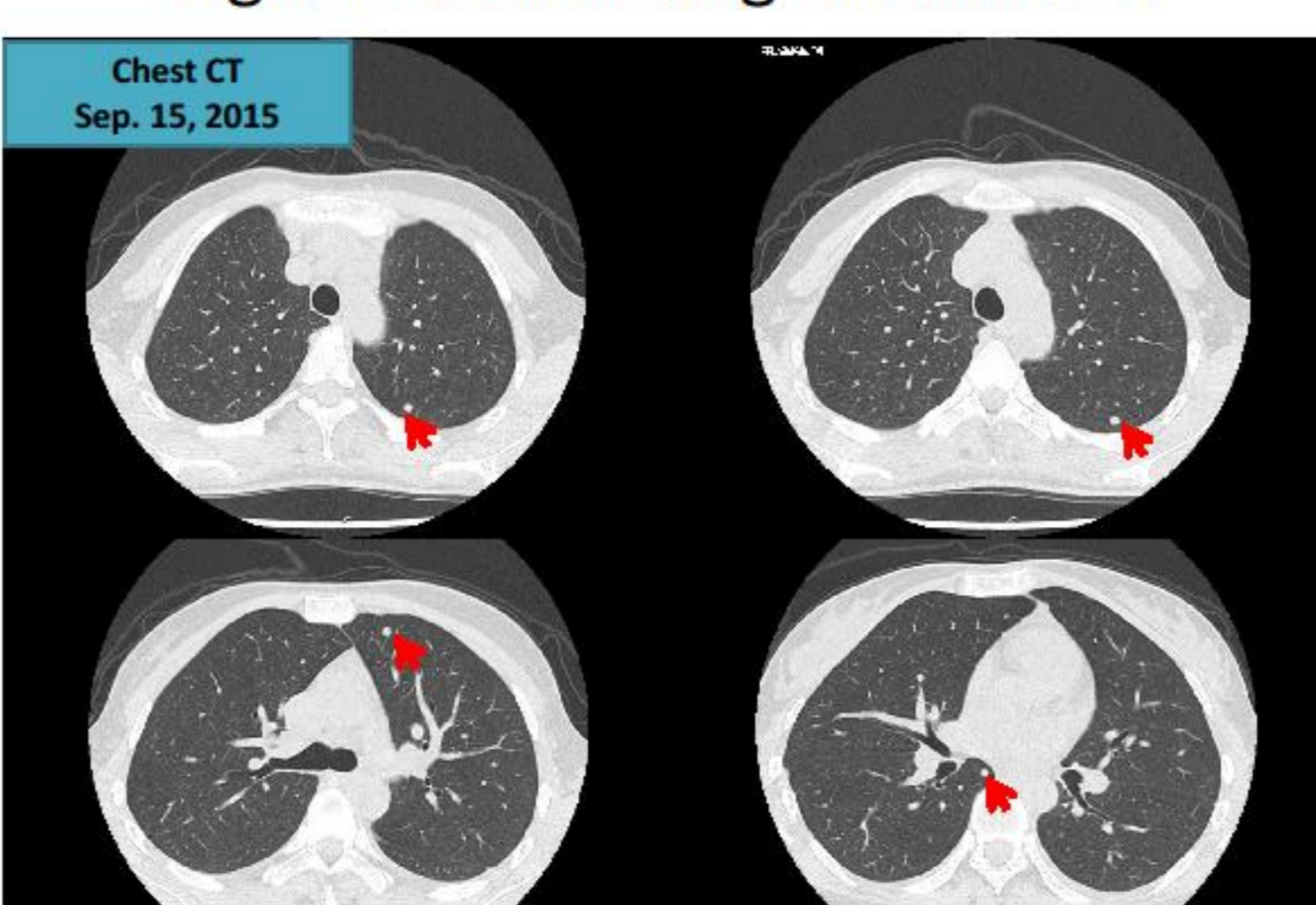


Fig.11 Endocrinological examination

< Pituitary >		< Parathyroid >	
ACTH 13.5 pg/ml	GH 1.49 ng/ml	intact PTH 58 pg/ml	
IGF-I 176 ng/ml	LH 4.9 mIU/ml	%TRP 47.08% ↓ (n.81~90%)	
FSH 5.3 mIU/ml	PRL 32.3 ng/ml	TmP/GFR 0.99 mg/dl ↓ (n. 2.5~4.5 mg/dl)	
< Thyroid >		< Adrenal >	
FT4 0.99 ng/dl	FT3 2.13 pg/ml	Cortisol 11.4 µg/dl	
TSH 2.551 µIU/ml		PRA 0.3 ng/ml/h	
		PAC 98.8 pg/ml	
		DHEA-S 260 ng/ml	
		Adrenaline 14 pg/ml	
		nor Ad. 263 pg/ml	
		Dopamine 13 pg/ml	

Conclusions

- We encountered a case of malignant tumor-induced osteomalacia that recurred and metastasized to both lungs.
- Although SSTR2 was detected in the tumor, FGF23 could not be suppressed with octreotide treatment.
- Only symptomatic therapy is available in cases of metastasis, and no definitive method of treatment has yet been established.

Fig.3 Process from first visit to first surgery

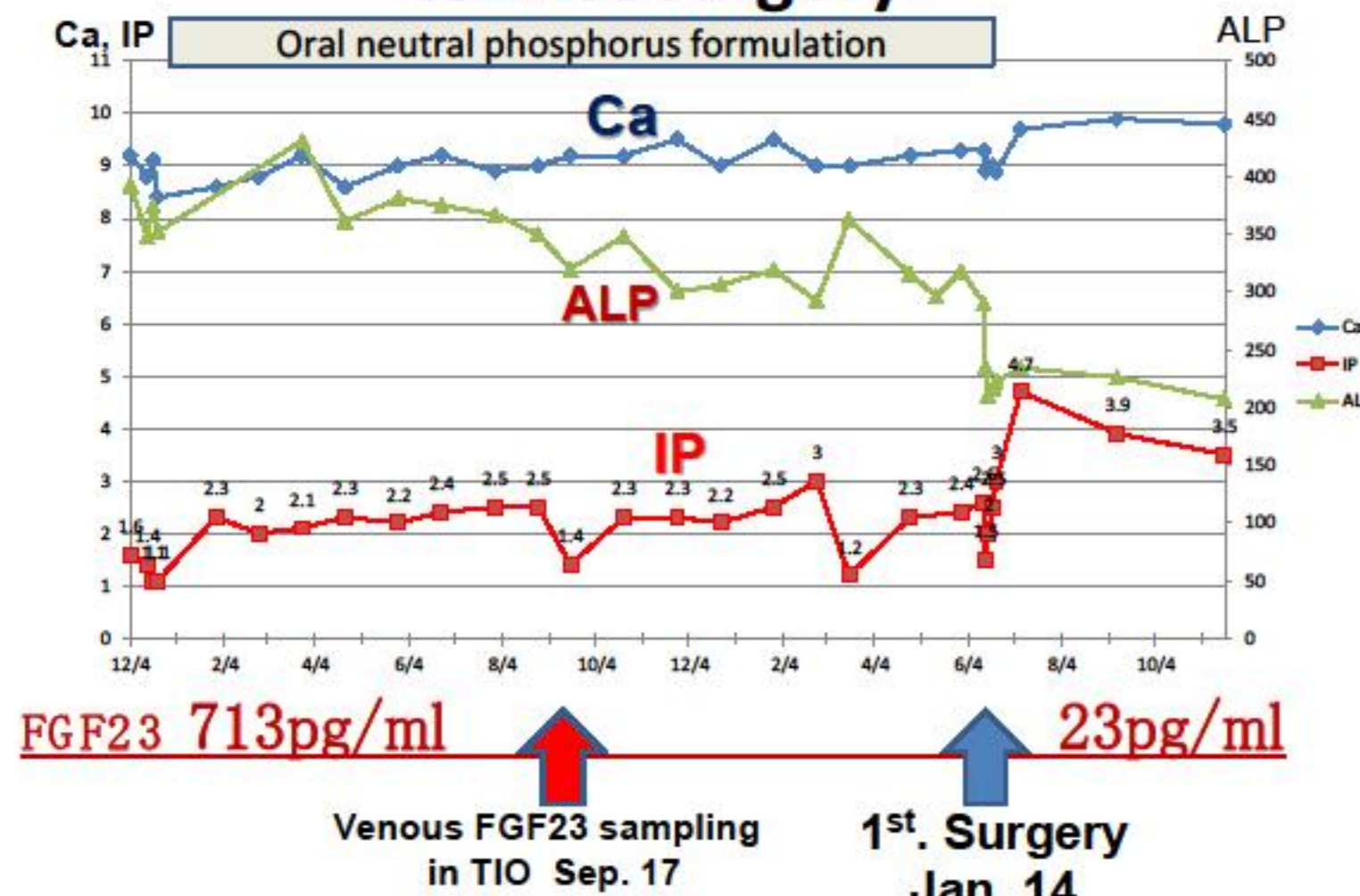


Fig.7 Recurrence of malignant TIO

