# ENDORAMA

## 'A 10-YEAR HISTORY OF RECURRENT HYPERPARATHYROIDISM'

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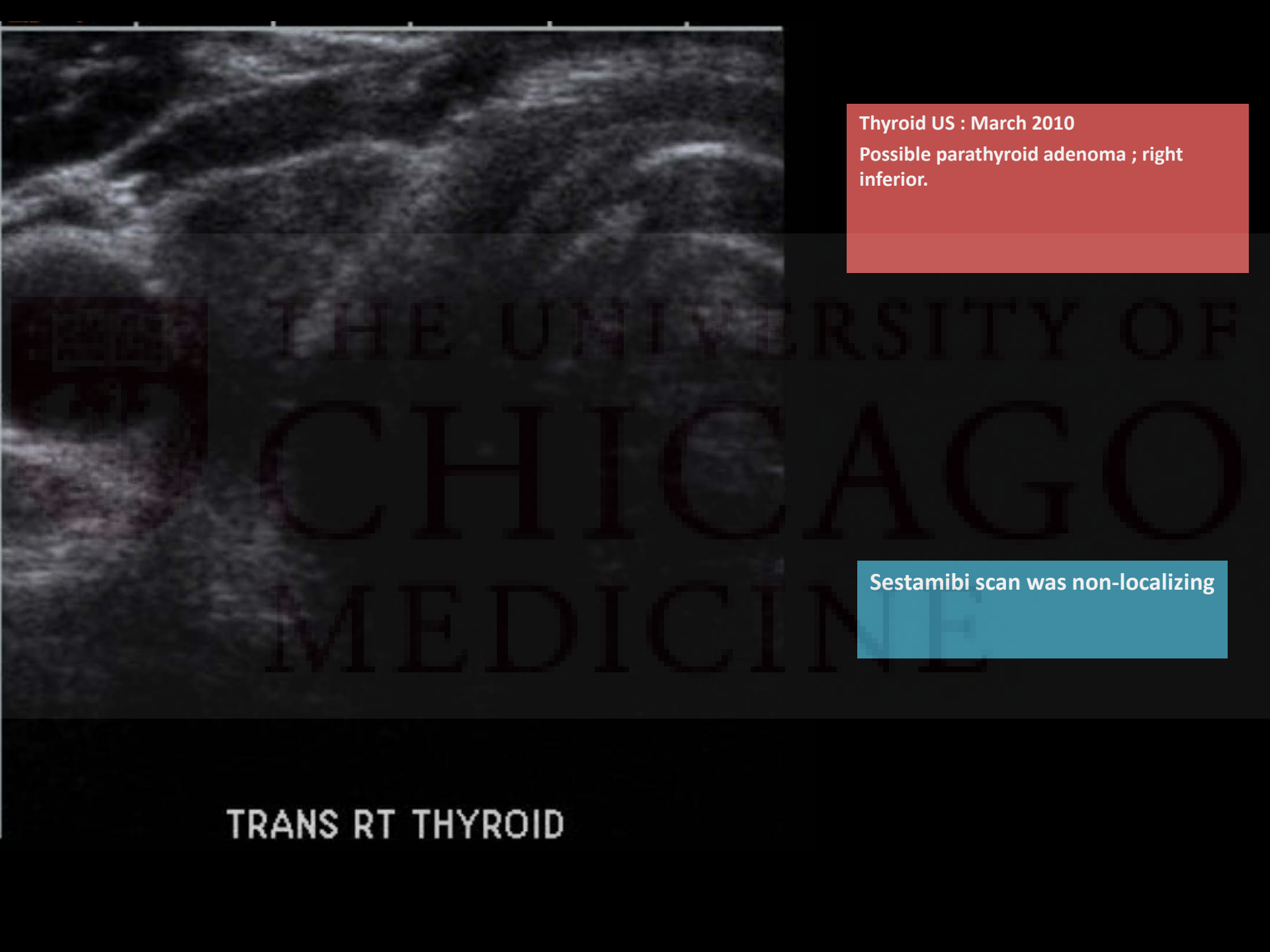
THE UNIVERSITY OF CHICAGO
ENDOCRINE SURGERY

# LEARNING OBJECTIVES

- Review differential diagnosis of recurrent hyperparathyroidism
- Review of risk factors of recurrent hyperparathyroidism after parathyroidectomy.
- Treatment options for parathyroid cancer

# Case: History

- 73 year old lady initially evaluated in 2010 for primary hyperparathyroidism (PHPT).
  - Noted to have elevated calcium on routine labs. Calcium : 12.1, PTH: 145.
- No family history of endocrine disorder
- No previous neck surgery




**Thyroid US : March 2010**

**Possible parathyroid adenoma ; right inferior.**

**Sestamibi scan was non-localizing**

# CASE: HISTORY

- She underwent a 4- gland exploration starting on the right side.
- Right parathyroidectomy (PTX) with appropriate drop in IOPTH.
  - Pre: 350, 10 mins post excision: 20
- Post operative levels
  - Calcium: 8.6
  - PTH : 13
- Final path : Enlarged and hypercellular parathyroid gland( 300mg)

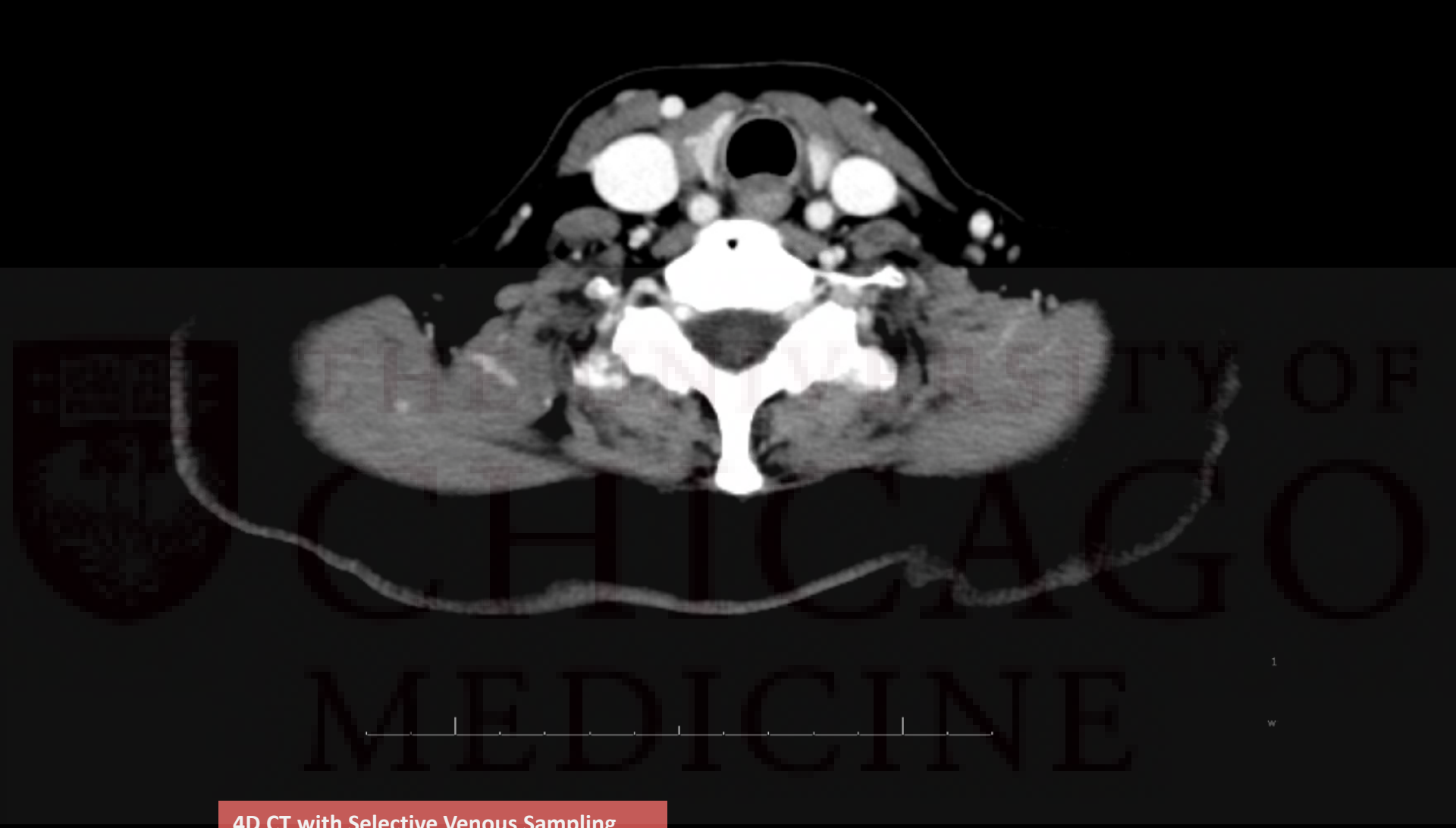
# CASE: HISTORY

- She returned 3 years later( July 2013) with biochemical features of PHPT.

  - Calcium: 11.9 (8.7 - 10.7)

  - PTH: 168.3

- Non-localizing US and Sestamibi



4D CT with Selective Venous Sampling Suggested :

- Possible right intra-thyroid adenoma
- Lateralized to the right on Venous sampling

# CASE: HISTORY

- Removal of **right upper parathyroid:**

- Pre: 279
- 5 min: 52
- 10 min: 45
- 15 min: 59
- 25 min: 118

- Removal of **left upper parathyroid:**

- 5 min: 82
- 10 min: 116

- **Right IJ stick**
- Right IJ PTH level : 214
- Left IJ PTH level : 87

- Removal of **right thyroid lobe**:
- 5 min: 86
- 10 min: 74
- 20 min: 70

# CASE: HISTORY

- Final path:

-Right and left superior Parathyroid adenomas

- Right thyroid lobe with adenomatoid nodules

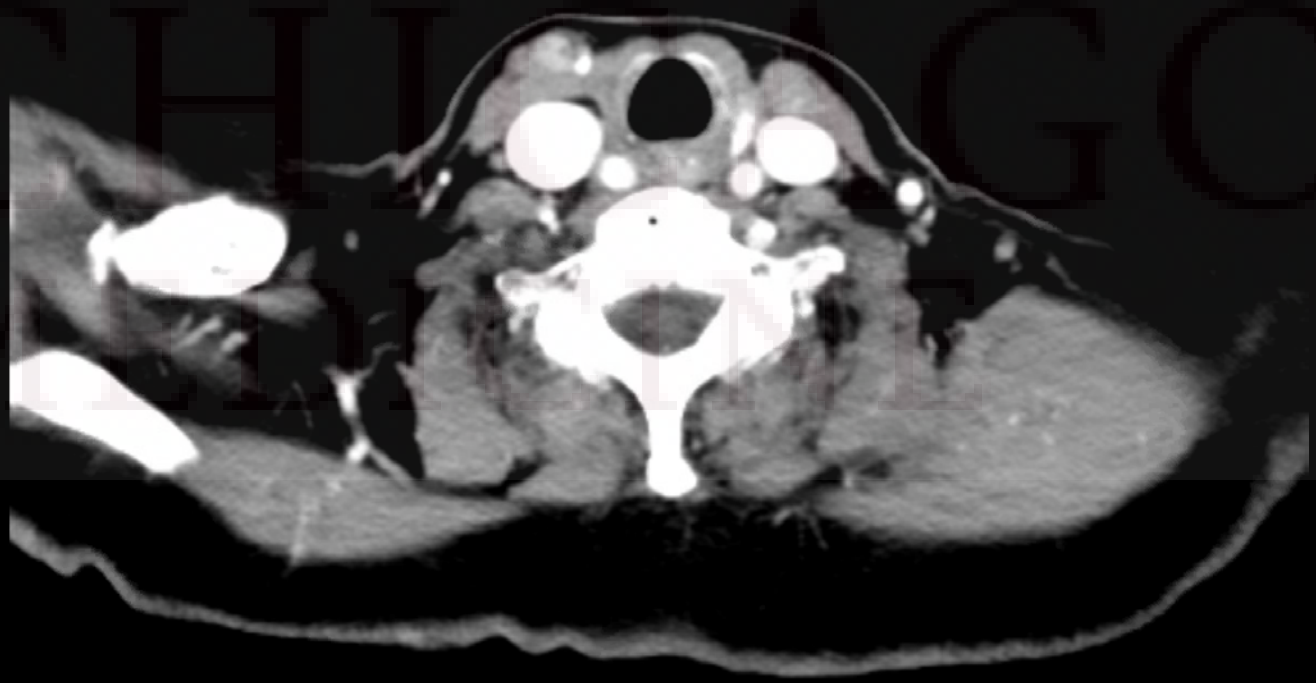
# Case: History

- In 2014 noted to have high normal PTH with Calcium 11.
- Followed by Endocrinologist and re-started on sensipar.
- 2015: worsening hypercalcemia( 13) and elevated PTH ( 325) with new neck masses.

**4D CT with Selective Venous Sampling**

**Sugessted :**

- **Multiple enhancing nodules anterior the right SCM**
- **Lateralized to the right on Venous sampling**



- Biopsy→ parathyroid tissues

- Attempt to control her symptoms with Sensipar failed.

- Neck was re-explored with en-bloc resection of all 3 nodules, portions of SCM, strap and platysma.

- IOPTH dropped appropriately.
- Post op labs
- Calcium 10.2
- PTH 33

# CASE: HISTORY

- Final pathology

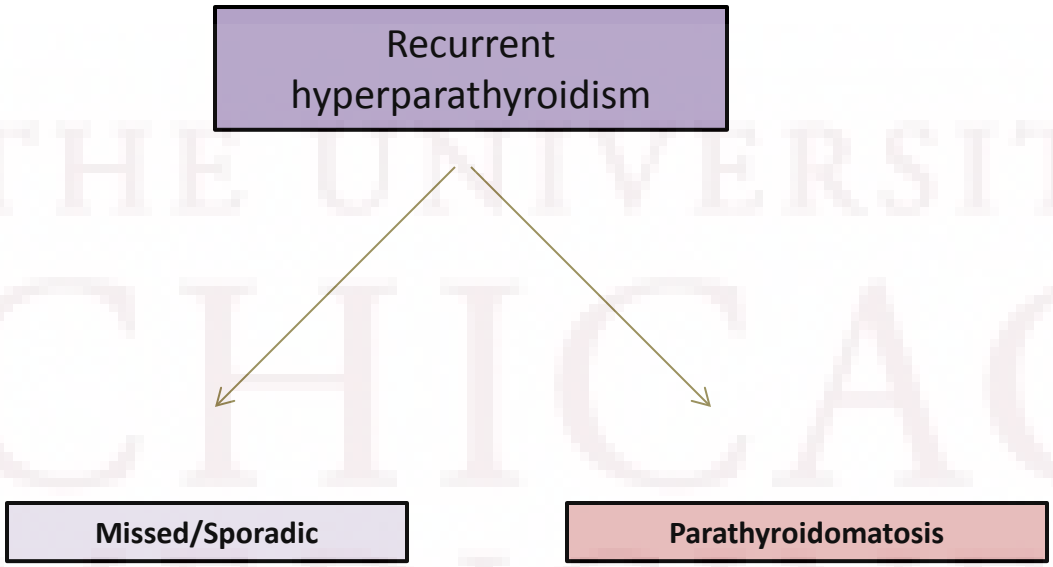
- Multiple parathyroid nodules (1.2, 1.1 and 0.3 cm) within fibro-adipose tissue and adjacent to skeletal muscle

- Consistent with parathyromatosis

# CASE: SUMMARY

- Initial presentation: Parathyroid adenoma
- 2nd presentation: Parathyroid adenoma
- 3rd Presentation: Parathyroidomatosis.

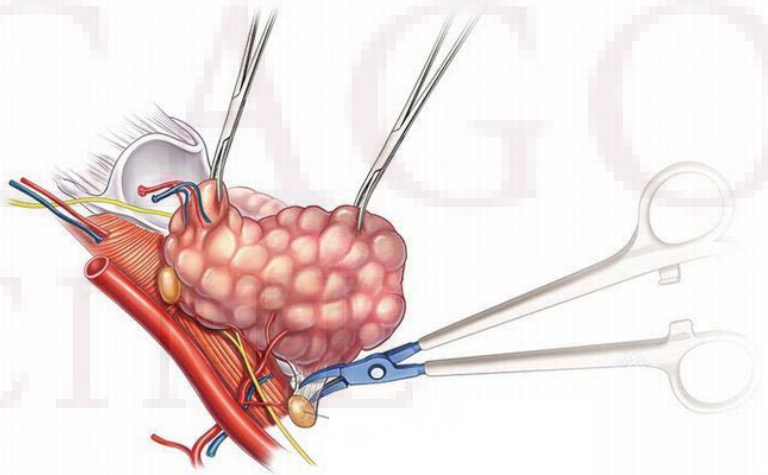
# Discussion



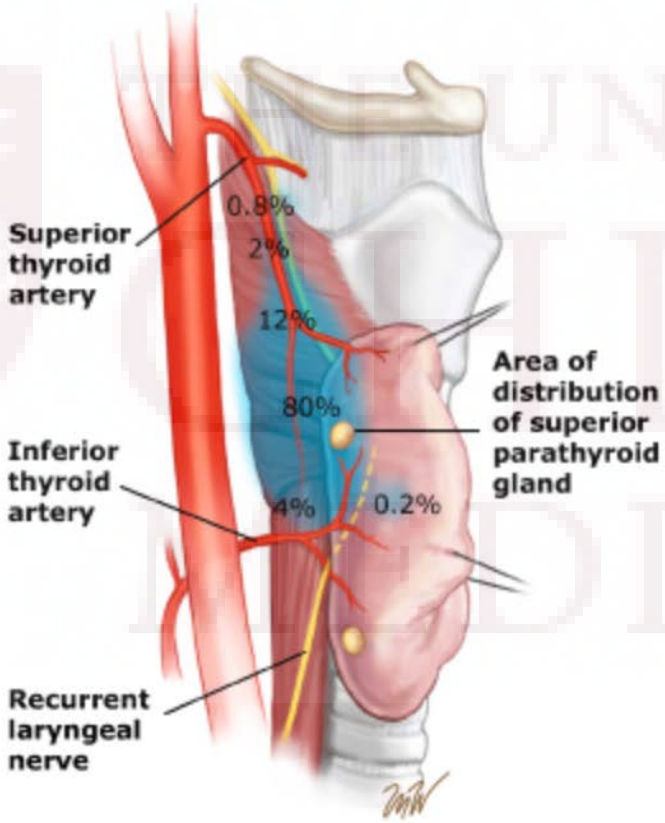
# RECURRENT PRIMARY HPT - CAUSES

- Sporadic recurrence

- Missed parathyroid adenoma
  - Abnormal location; ectopic
  - Index multi-gland disease
    * double adenoma



# PARATHYROID GLAND - SURGICAL ANATOMY



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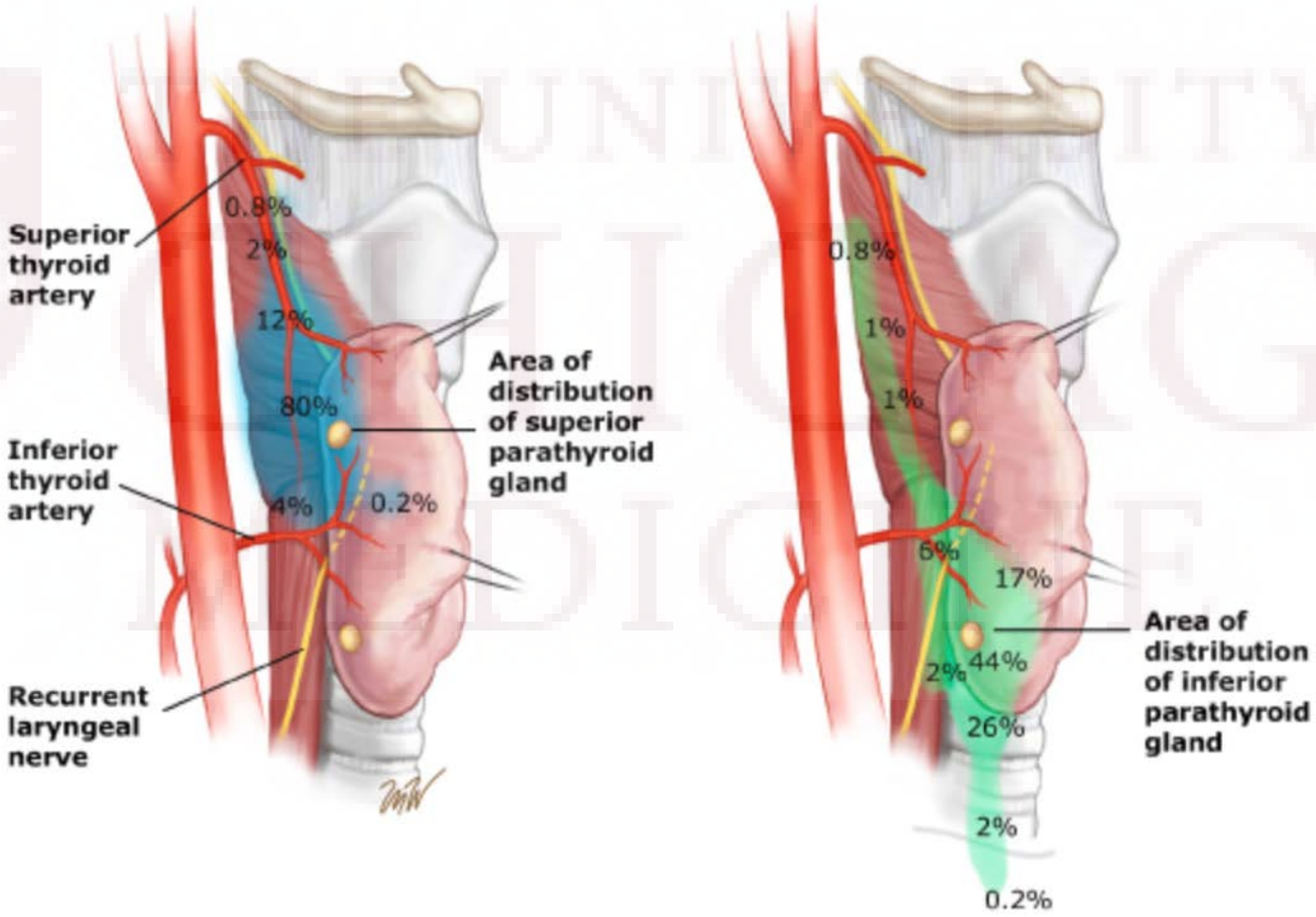


# RECURRENT PRIMARY HPT – MISSED/SPORADIC

**HYPERPARATHYROIDISM: AN ANALYSIS OF 1,386 CASES**

**David F. Schneider, MD, MS**, **Haggi Mazeh, MD**, **Herbert Chen, MD, FACS**, and **Rebecca S. Sippel, MD, FACS**
Section of Endocrine Surgery, Department of Surgery, University of Wisconsin, Madison, WI

- 1386 patients operated on over a 10 year period
- 1006 MIP, 380 bilateral neck exploration( BNE)
- Mean Age 61 years, Calcium 11, PTH 127.
- 70% of patients had positive Sestamibi scan
- Median follow up 9.6 months
- Recurrence = 40 patients( 2.8%): 2.5% MIP, 2.1% BNE ( p= 0.68)

# RECURRENT PRIMARY HPT – MISSED/SPORADIC

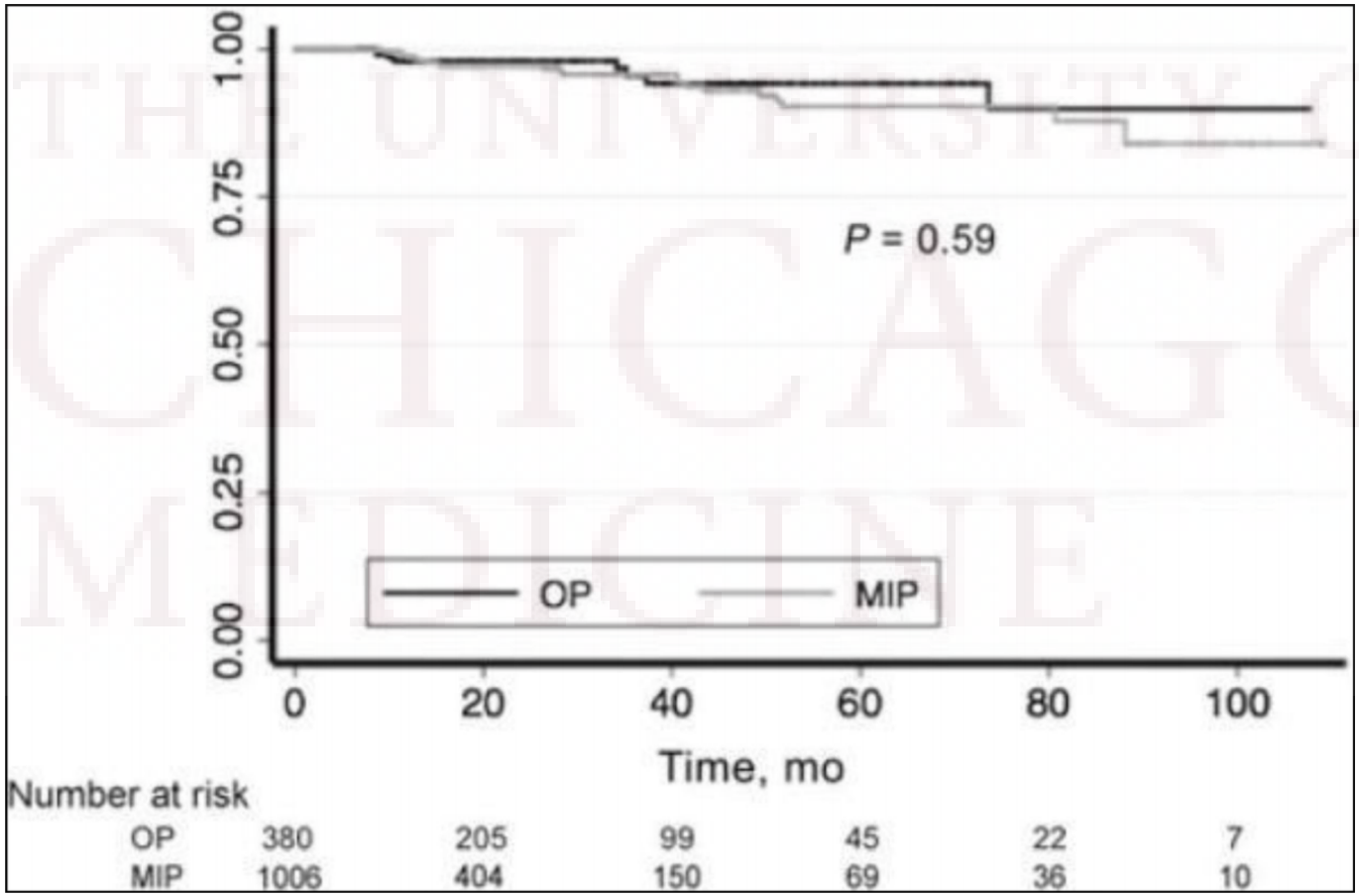
- MVA for predictors of recurrence :

  - Rate of decrease in IOPTH 63% (PPV 3.8%, NPV 98.9%).

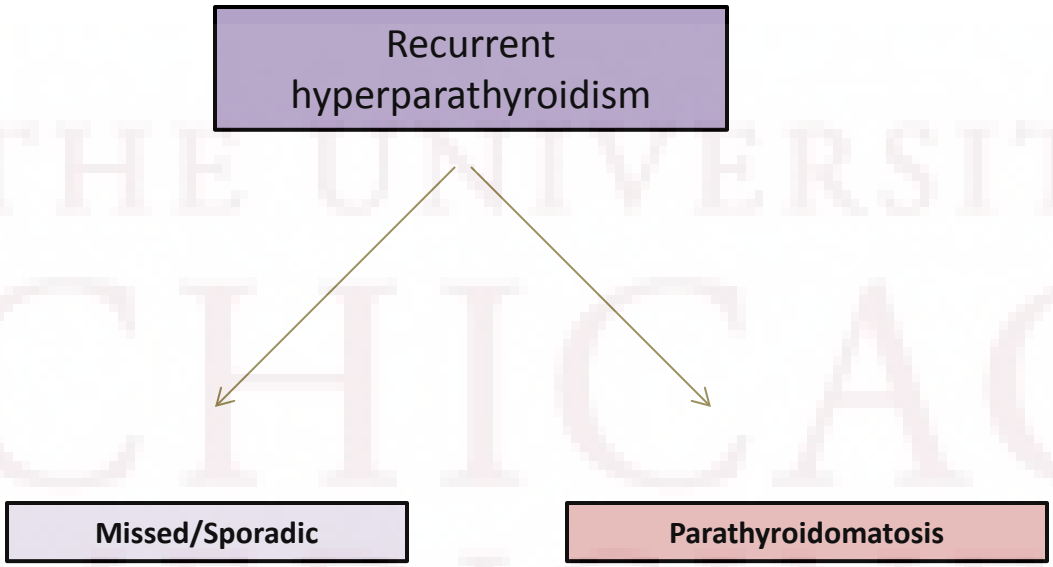
  - Post op PTH <48pg/ml ( PPV 6%, NPV 99%)

- Technique of exploration ( bilateral neck exploration vs MIP) did not influence recurrence of primary HPT

# BNE vs MIP


1.00
0.75
0.50
0.25
0.00
P = 0.59
OP
MIP
0
20
40
60
80
100
Time, mo
Number at risk
OP 380 205 99 45 22 7
MIP 1006 404 150 69 36 10

# Discussion



# PARATHYROMATOSIS

- Parathyromatosis is a rare cause of hyperparathyroidism characterized by multiple nodules of hyperfunctional parathyroid tissues scattered in the neck and mediastinum
- First described by Palmer et al in 1975
- About 50 cases reported in literature to date
- Occurrence anywhere from 5 months to 19 years post op.
- Slightly more common in females( F: M – 1.5:1)
- More common in patients with chronic kidney disease( CKD)

# PARATHYROMATOSIS

- Classified into two types by Riddick et al
- Type 1(Ontogenous): congenital development of remnant nest of parathyroid tissues scattered all over the adipose tissues of the neck and mediastinum

- Type 2 : spillage of parathyroid cell during parathyroidectomy.

  *more common

- The persistent stimulation of the parathyroid gland as seen in CKD is attributed as the trigger.

# PARATHYROMATOSIS

**Diagnosis**

- No unique laboratory and imaging feature.

- High index of suspicion in post-parathyroidectomy patients presenting with ↑PTH, ↑Calcium and

- US: multiple hypoechoic nodules in soft tissue of the neck with no definitive parathyroid adenoma.

- Sestamibi: foci of activity outside the normal path of parathyroid descent.

- Most cases will be diagnosed intra-op or post op on final path

# PARATHYROMATOSIS

**Operative management**

- Cytoreductive procedure guided by imaging and intra-operative finding.
- Complete resection of all visible nodules, fibrous scar and soft tissues around area of activity on the Sestamibi scan.
- Resection of residual parathyroidectomy in cases of prior subtotal parathyroidectomy , and then auto-transplant.
- En-bloc resection of auto-transplanted tissue.
- Routine thymectomy? (ectopic inf. parathyroid gland, up to 8% incidence of thymic supranumarary parathyroid gland)

# PARATHYROMATOSIS

- Intra-operative adjuncts

- Use of intra-operative PTH monitoring.
  * may not be applicable in Parathyromatosis.

- Use of intra-operative US.

- Use of intra-operative radio-guided parathyroid gland localization using a gamma probe after $^{99m}$Tc-sestamibi injection may be useful

- No studies have reported post op hypoparathyroidism even in cases of en-bloc resection of parathyroid auto-transplant.

- Pathology:

- scattered collections of parathyroid cells outside the parathyroid capsule or embedded within the surrounding soft or scar tissue of the neck .

- Normal nuclear features.

- No LN or capsular or vascular invasion.

# PARATHYROMATOSIS

**Medical management**

- Cinacalcet : should be tried for normalization of PTH and Calcium levels
- Bisphosphonate: stabilized changes in BMD in some report.

# BACK TO OUR PATIENT

# Case: History

- Slowly increasing PTH an calcium over the next 5 years( 2014 to 2019)
- Sensipar was started in 2015 with initial good control, but increasing since Jan 2019
- Oct 2019:  PTH of 1075, calcium of 11.7 and developed worsening dysphagia. Did not tolerate increase dos of sensipar.
- US and 4DCT showed two right neck masses and one central neck mass.
- Mass biopsy → hyperplastic parathyroid gland

# CASE: HISTORY

- Neck masses were resected.

- right recurrent laryngeal nerve sacrificed: encased by the central neck mass which was compressing the esophagus.

- Post op injection laryngoplasty was performed with good result.

- Discharged home on POD 2

# CASE: HISTORY

- Final path

- All 3 masses were parathyroid carcinoma

right anterior 2.2 cm, 1.92 g

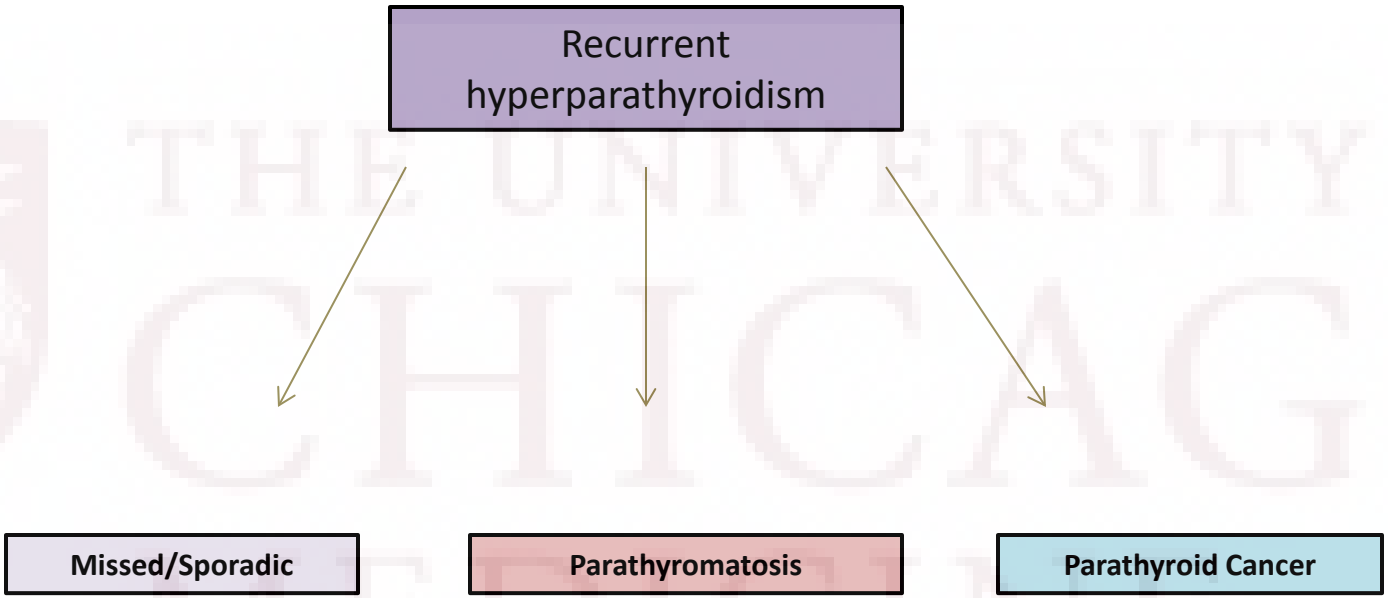
right lateral 1.7 cm, 1.7g

central 2.3 cm, 2.66g with perineural and perivascular invasion

Ki 67 > 20%, Mitotic index of 10/10 hpf

- 1/2 Level IV LN positive for parathyroid cancer

# Discussion



# PARATHYROID CANCER

- Rare : 0.3 to 1% of primary HPT; overall incidence decreasing.
- More common in age 44 to 54 years.
- Slightly more common in men (1.2 : 1).
- A single gland is far more common. Multi-gland disease is rare
- Most all cases are sporadic
  - *only 3 cases of parathyroid cancer reported in MEN 1 patients.*
  - *15% of patients with HPT-JT syndrome will develop parathyroid cancer.*

# PARATHYROID CANCER

- HRPT2 ( aka CDC73):

  - Tumor suppressor gene.

  - located on chromosome 1 and encodes parafibromin protein

  - parafibromin may be involved in regulation of gene expression and inhibition of parathyroid cell proliferation.

# Parathyroid Cancer

| Manifestation | Incidence |
|---|---|
| Serum Calcium > 14mg/dl | 65 – 75% |
| Serum PTH > 5 fold upper limit of normal | ≈ 100% |
| Neck mass( more common in asymptomatic normocalcemic pts) | 34- 52% |
| Bone disease (osteopenia/ostoporosis, pathological #s) | 34- 73% |
| Renal disease (polyuria, stones, ↓GFR) | 32- 72% |
| Pancreatitis | Up to 15% |
| Parathyroid crisis | 10 – 12% |
| Asymptomatic | Up to 7% |
| LN Mets | Up to 30% |
| Distant Mets (typically liver , bone) | ” |

# Parathyroid Cancer

**Compared to benign Primary HPT**

- More likely to be symptomatic
- Larger tumor size
- Marked hypercalcemia

**Atypical presentation of parathyroid cancer**

- Normocalcemia
- Neck mass
- More aggressive tumor
- Mortality typically from mass effect or tumor burden rather than from hypercalcemia

# PARATHYROID CANCER

**Diagnosis**

- Based on clinical presentation and intra-op findings.

- Highly suggestive path features:
  - trabecular pattern and high mitosis
  - capsular and vascular invasion

- Two definitive path criteria:
  - Local invasion of contiguous structures and/or
  - Lymph node or distant metastases

PTH < 4x upper ,limit of normal and tumor size <1.9g almost always excluded parathyroid cancer

Robert JH, Trombetti A, Garcia A, et al. **Primary hyperparathyroidism: can parathyroid carcinoma be anticipated on clinical and biochemical grounds? Report of nine cases and review of the literature.** *Ann Surg Oncol*. 2005;12(7):526–532

**Staging**

- AJCC 2017 TNM proposed staging
- Poorly correlated to prognosis or extent/type of treatment

# PARATHYROID CANCER

**Treatment**

- Resectable disease :surgery is main modality.

- Clinical scenarios determines extent and intent of resection

- Pre-op/Intra-op suspicion: Enbloc resection of the parathyroid and adjacent structure including ipsilateral thyroid lobectomy.

- Post op diagnosis: re-exploration and resection of adjacent tissues.

  * debate in cases of only histological features without invasion.

- Recurrent disease : most occur in the neck. Surgical resection mainstay at least for palliation

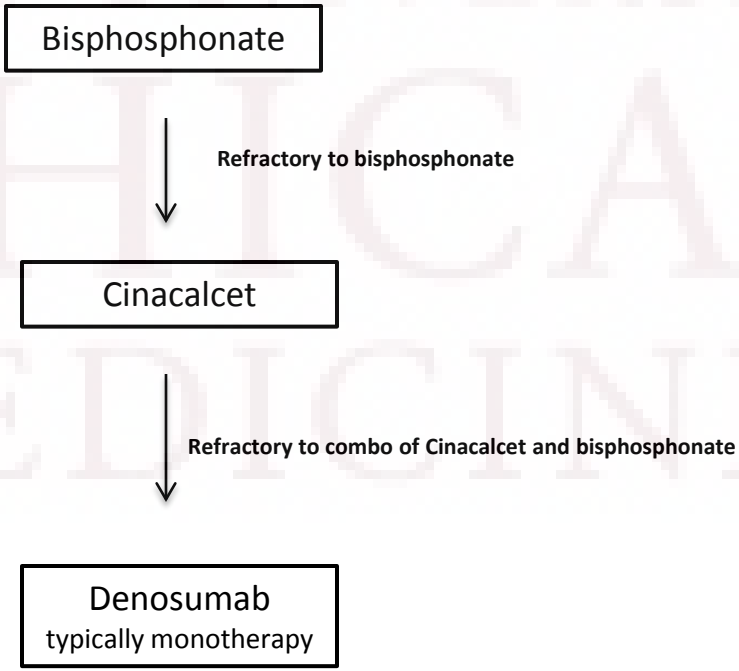
- Metastatic disease: Palliative resection for hypercalcaemic symptom control + use of Calcimimetic

# PARATHYROID CANCER

**Treatment**

- Unresectable disease : disseminated disease beyond surgical resection.

- Goal is to control symptoms and effect of hypercalcemia



# PARATHYROID CANCER

Course/Prognosis

- Generally a slow disease process.
- A few patients may have aggressive and short clinical course.

- one-third of patients are cured at initial or follow-up surgery,
- one-third recur after a prolonged disease-free survival but may be cured with reoperation,
- one-third of patients experience a short and aggressive clinical course.


- Hoelting T, Weber T, Werner J, Herfarth C. **Surgical treatment of parathyroid carcinoma (Review)**. *Oncol Rep*. 2001;8(4):931–934

# THANK YOU

**TEXT CODE:** BEDGUW to 773-245-0068

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# THANK YOU