38-Year-Old Female with High Calcium Levels

Olesya Krivospitskaya, MD

Endorama 02/28/2013

History of past illness:

- 38 y.o. female was referred by her PCP for evaluation and management of her elevated calcium levels.
- The pt has a history of primary hyperparathyroidism diagnosed in 1996 after she presented with c/o frequent headaches, muscle pain, difficulties sleeping.
- She underwent parathyroidectomy (one of her glands was removed) in 06/1996.
- She did not have parathyroid scan before the surgery.
- Her calcium levels normalized after the surgery, muscular pains and headaches improved after surgery.
- Calcium levels remained normal until 10/2012 when she was found to have calcium 10.6 on routine blood work, PTH was also elevated at 109.
- The pt was referred to endocrinology clinic for further evaluation.

Past medical history:

- Depression
- Fibromyalgia
- Primary hyperparathyroidsm, s/p partial parathyroidectomy in 06/1996
- Medications: biotin, sertraline, pregabalin, alprazolam, iron
- Family history: depression (mother), fibromyalgia (sister), galactorrhea (mother), pancreatic cancer (maternal grandfather)
- Social history: director`s assistant, does not smoke but smoked occasionally from the ages of 21 to 35. No drug use. Social alcohol. Single. Has a history of 2 sexual assaults in the past.
- Menstrual history: menarche at 13, menstrual cycles were always irregular and coming every other month. She has never been pregnant and never tried to get pregnant. Has a history of 2 sexual assaults as a teenager, not sexually active now.

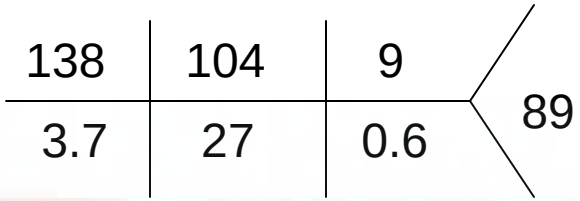
Review of systems:

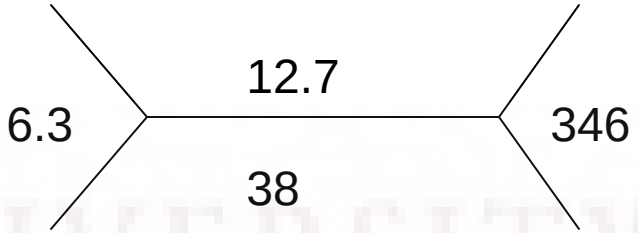
- Constitutional: No fevers. No weight loss. **+Fatigue.**
- HEENT: No vision changes. No hoarseness. Neck: No neck swelling or pain.
- Cardiovascular: No chest pain. No palpitations.
- Respiratory: No dyspnea. No orthopnea.
- Gastrointestinal: No diarrhea. No constipation.
- Genitourinary: **+ Galactorrhea for 6 years. + Menstrual cycles are irregular, every other month since menarche.**
- Musculoskeletal: **+ Myalgias.**
- Skin: No rash. No skin changes. No hair loss.
- Neurologic: No tremor. **+Headaches.** No weakness.
- Psychiatric: No depression. **+ Anxiety.**
- Endo: No polyuria. No polydypsia.

Physical exam:

- Constitutional: Well-developed and well-nourished, in no acute distress.
- Eyes: Conjunctivae are not injected. Sclerae anicteric. Pupils are equal, round, and reactive to light. Extraocular movements are intact. Visual fields are intact to confrontation.
- ENT: mucous membranes are moist.
- Neck: Supple. **Thyroid is palpable, upper limit of normal size.** No nodules palpated.
- Cardiovascular: Regular rhythm and rate. No murmurs appreciated. Intact distal pulses.
- Respiratory/Chest: Normal respiratory effort. No wheezes or crackles.
- Gastrointestinal/Abdomen: Normoactive bowel sounds. Soft, nontender, nondistended.
- Genitourinary: **+Expressible galactorrhea.**
- Musculoskeletal/extremities: No peripheral edema. Normal range of motion.
- Neurological: Alert and oriented to person, place, and date. Normal deep tendon reflexes.
- Skin: Skin is warm and dry. No acanthosis nigricans noted. +**Facial acne.**
- Psychiatric: Normal mood and affect
- Vitals: BP 127/80, HR 94, RR 16, height 162 cm, weight 67.6 kg, BMI 25.76.

Labs:





Ca 9.6 (8.4-10.2 mg/dL)
Actual Ca 4.83 (4.6-5.4 mg/dL)
PTH 99 (15-75 pg/ml)
25 hydroxy vitamin D 16 ng/mL

LFTs:
Total Protein 7.3 (6-8.3 g/dL)
Albumin 4.6 (3.5-6 g/dL)
Total Bilirubin 0.3 (0.1-1 mg/dL)
Alk Phos 111 (30-120 U/L)
AST 17 (8-37 U/L)
ALT 17 (8-35 U/L)

Prolactin 79.69 (4.8-23.3 ng/ml)
Repeated prolactin 98.59 (4.8-23.3 ng/ml)
Total testosterone 20 (20-60 ng/dL)
Free testosterone 5 (3-9 pg/ml)
Te binding globulin 34 (20-100 nmol/L)

Pregnancy test: negative

TSH 0.95 (0.3-4.0 mcU/ml)

Free T4 0.95 (0.9-1.7 ng/dL)

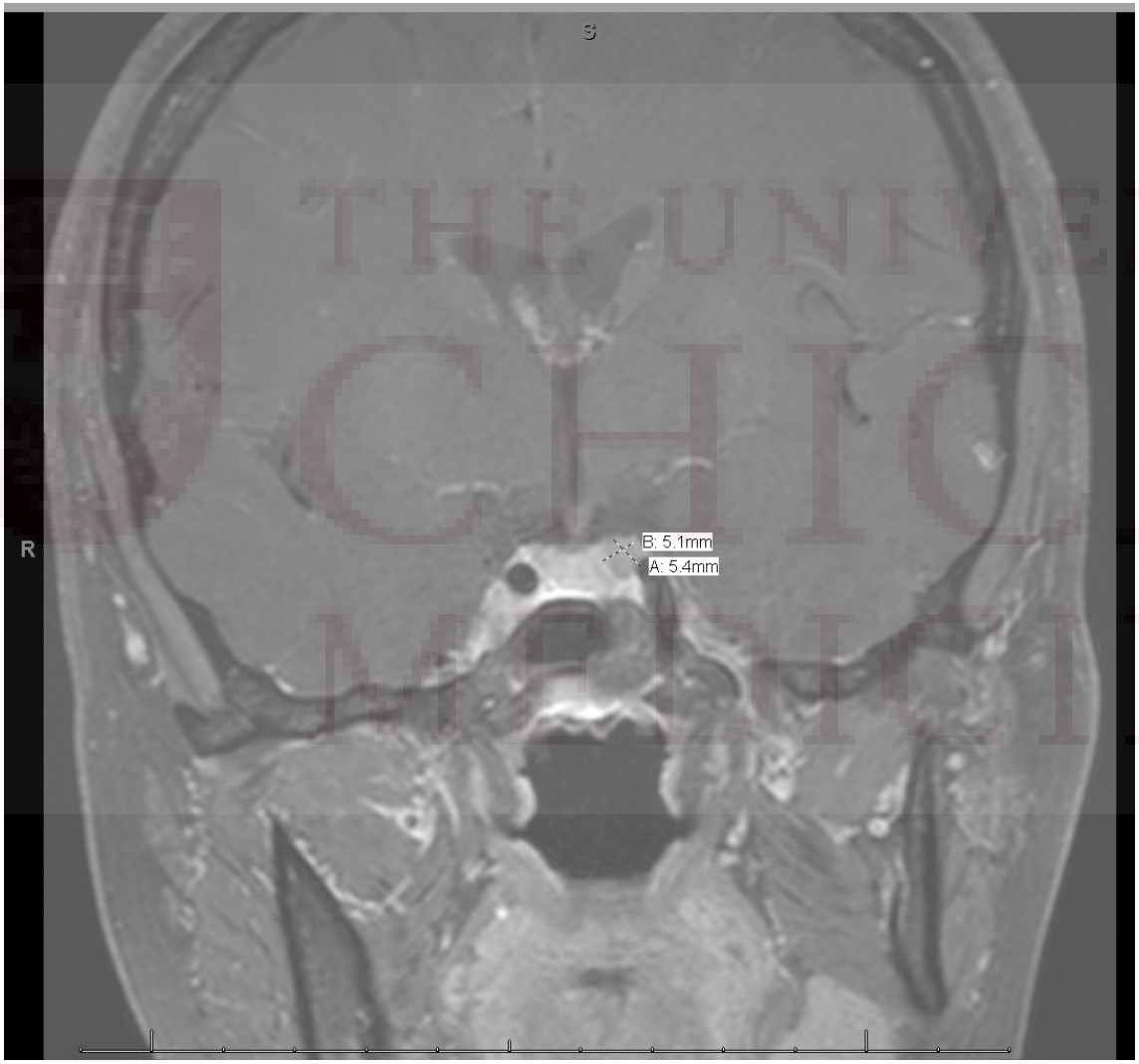
T3 110 (80-195 ng/dL)

Anti TPO AB neg

Anti TG AB neg

BMD: The Forearm (Radius 33%) BMD of 0.717 g/cm2 with a T-score of -1.8 and a Z-score of -1.8. The L1-L4 spinal BMD of 1.106 g/cm2 with a T-score of -0.6 and a Z-score of -0.7. The femoral neck BMD is 0.876 g/cm2 with a T-score of -1.2 and a Z-score of -0.8.

MRI:



There is a 5-mm mass in the left half of the pituitary gland. This most likely represents a microadenoma given the patient's clinical history.

Labs

ACTH 45.7 (<52 pg/mL)
Cortisol 18 mcg/dL
IGF1 146 (109-284 ng/mL)
LH 4.4 mIU/mL
FSH 5.7 mIU/mL
Estradiol 52 (30-400 pg/mL)
Midnight salivary cortisol <50 ng/dL (<100 ng/dL)

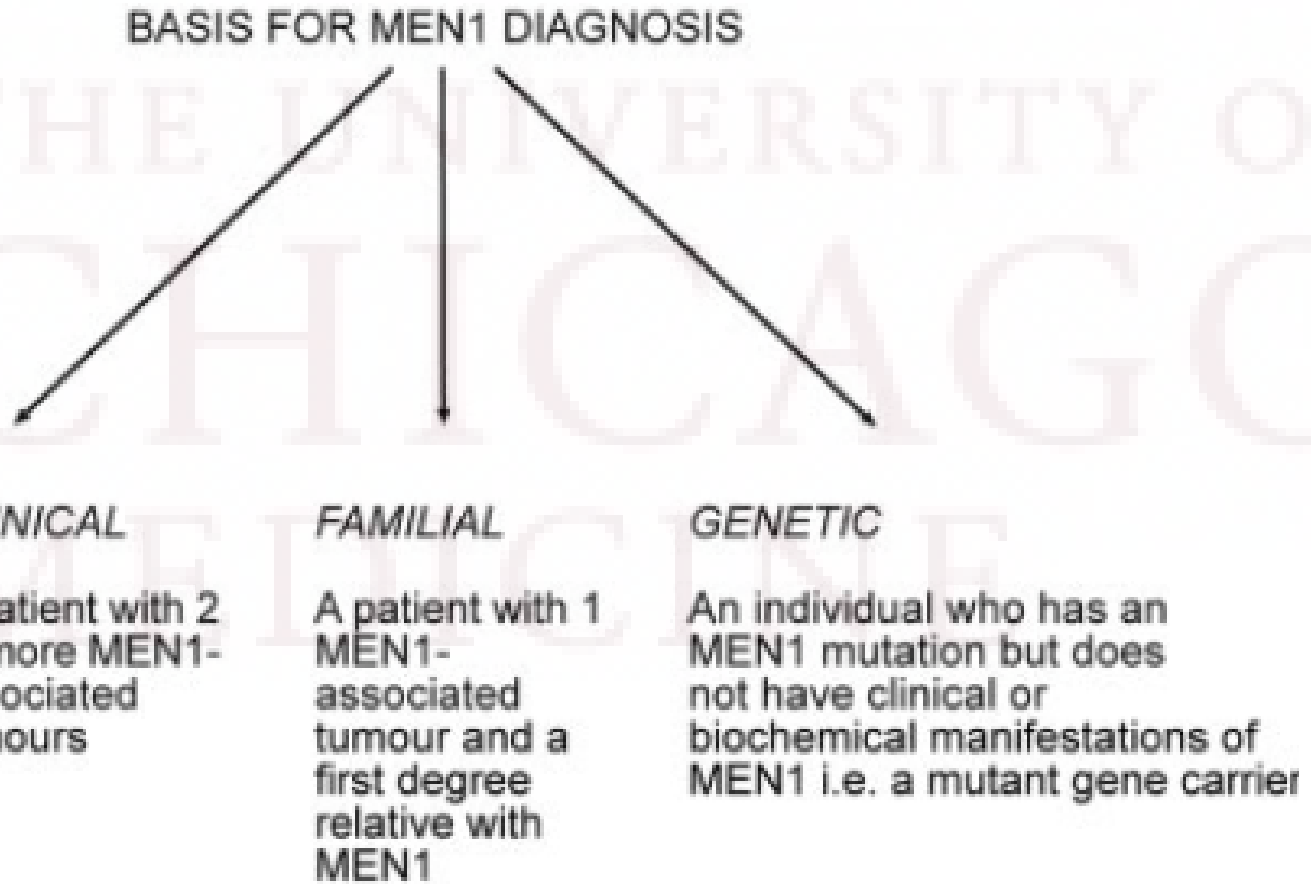
- What is MEN type 1
- Who should be screened
- What is the prognosis
- Is there any difference in management of primary hyperparathyroidism in MEN type 1 compare to idiopathic primary hyperparathyroidism

- Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant predisposition to tumors of the parathyroid glands (which occur in nearly all patients by age 50 years), anterior pituitary, and entero-pancreatic endocrine cells

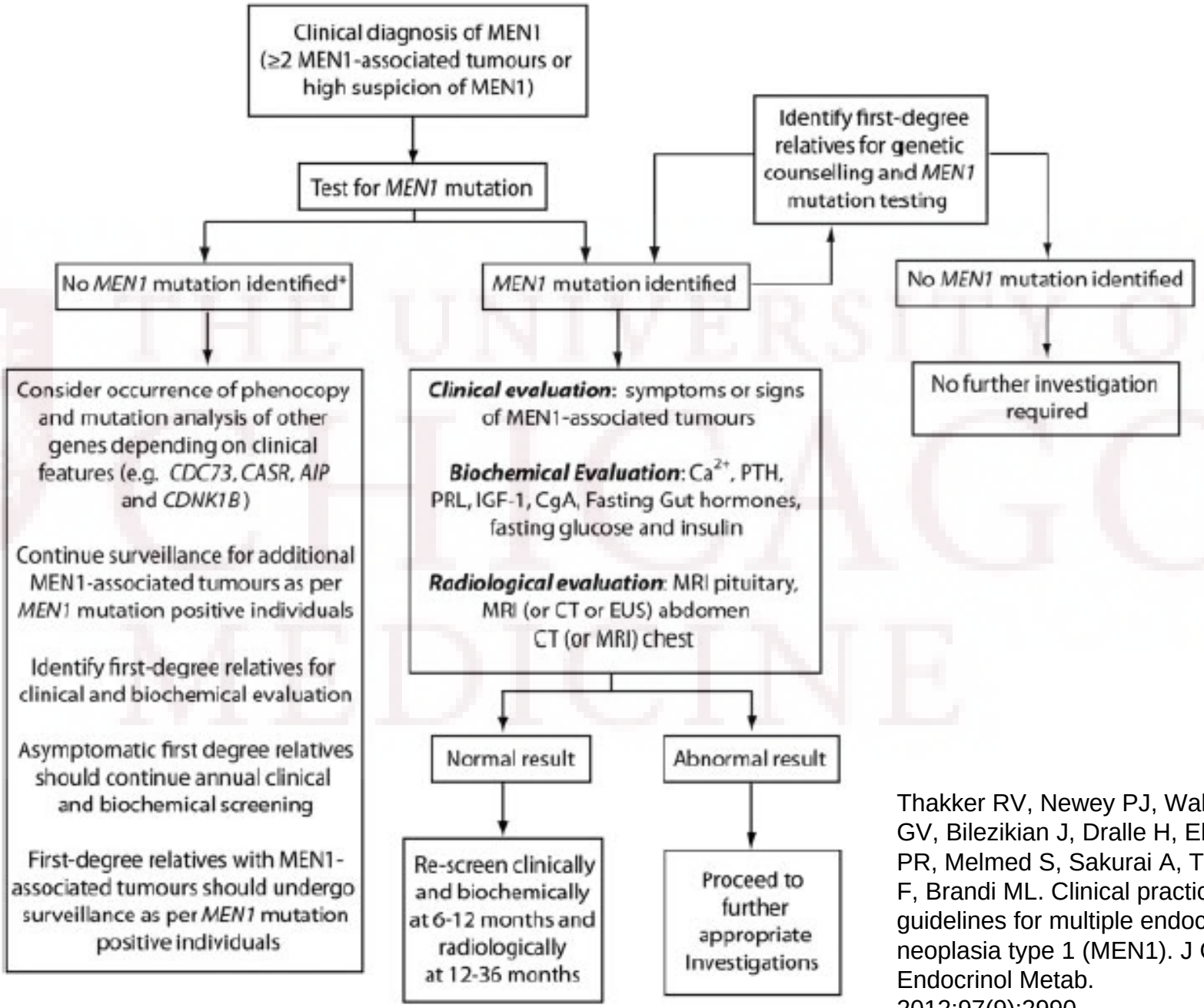
- MEN1 gene is located on a long arm of chromosome 11 (11q13), mutations in these gene are detected in about 75% cases of MEN type 1 syndrome and are inherited in autosomal dominant pattern

- Some other genes: cyclin-dependent kinase (CDK) inhibitor genes (CDKN1B, CDKN2B, CDKN2C, and CDKN1A)

Diagnosis:



Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, Melmed S, Sakurai A, Tonelli F, Brandi ML. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012;97(9):2990



Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, Melmed S, Sakurai A, Tonelli F, Brandi ML. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012;97(9):2990

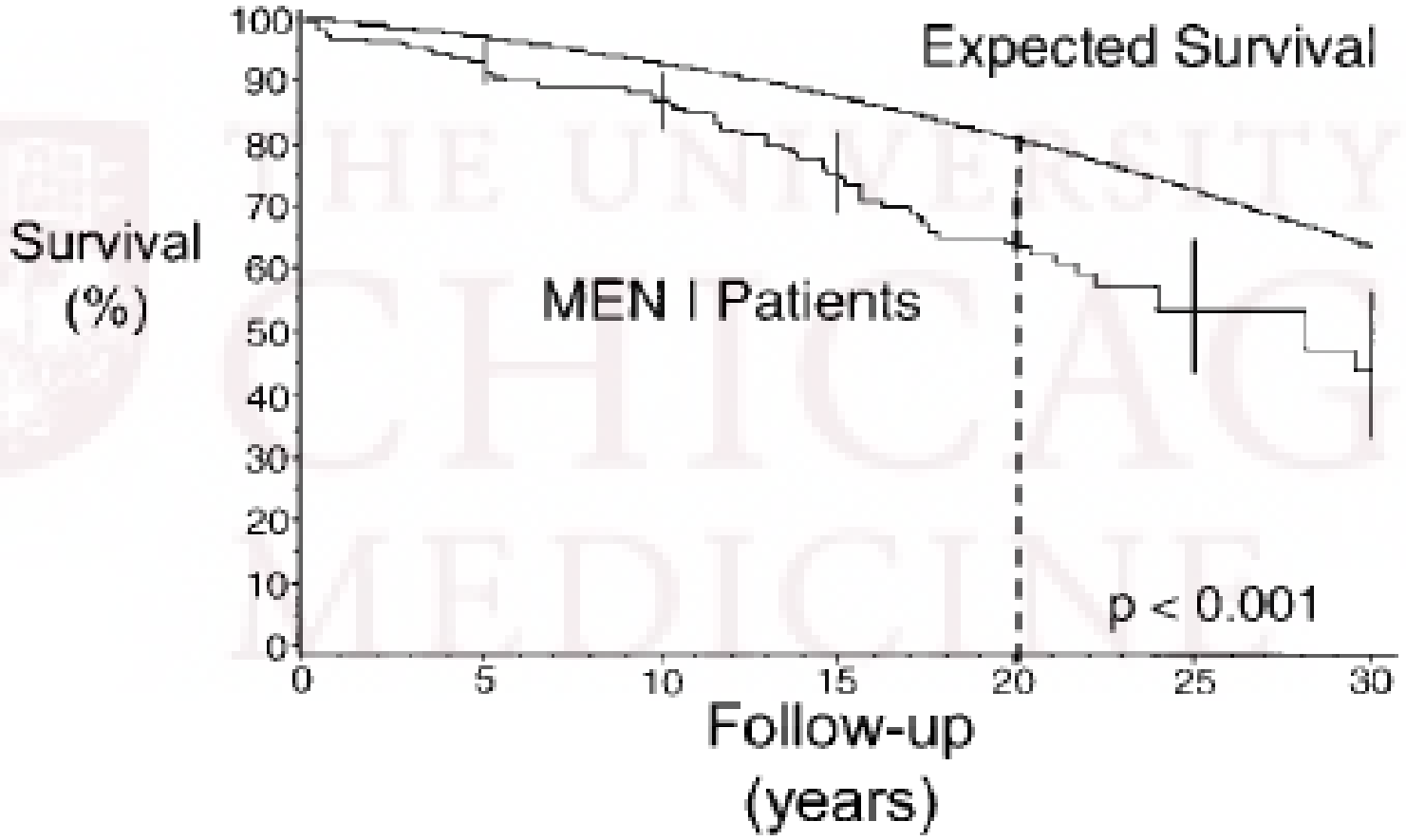
Suggested screening:

TABLE 2. Suggested biochemical and radiological screening in individuals at high risk of developing MEN1

Tumor	Age to begin (yr)	Biochemical test (plasma or serum) annually	Imaging test (time interval)
Parathyroid	8	Calcium, PTH	None
Pancreatic NET			
Gastrinoma	20	Gastrin (± gastric pH)	None
Insulinoma	5	Fasting glucose, insulin	None
Other pancreatic NET	<10	Chromogranin-A; pancreatic polypeptide, glucagon, VIP	MRI, CT, or EUS (annually)
Anterior pituitary	5	Prolactin, IGF-I	MRI (every 3 yr)
Adrenal	<10	None unless symptoms or signs of functioning tumor and/or tumor >1 cm are identified on imaging	MRI or CT (annually with pancreatic imaging)
Thymic and bronchial carcinoid	15	None	CT or MRI (every 1–2 yr)

Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, Melmed S, Sakurai A, Tonelli F, Brandi ML. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012;97(9):2990

Prognosis:



Dean PG, van Heerden JA, Farley DR, Thompson GB, Grant CS, Harmsen WS, Ilstrup DM. Are patients with multiple endocrine neoplasia type I prone to premature death? World J Surg. 2000;24(11):1437

Causes of death in MEN1 patients:

Table 1. Known causes of death (60 patients).

Causes of death	No.
MEN-I-related (28%)	
Metastatic islet cell tumor	10
Metastatic carcinoid tumor	3
Postoperative death	2
Gastrointestinal bleeding (ZES)	1
Refractory hypercalcemia (HPT)	1
Non-MEN-I-related (72%)	
Coronary artery disease	10
Nonendocrine malignancy	10
Pneumonia	6
Congestive heart failure	4
Accidental	2
Other	11
Total	60

Dean PG, van Heerden JA, Farley DR, Thompson GB, Grant CS, Harmsen WS, Ilstrup DM. Are patients with multiple endocrine neoplasia type I prone to premature death? World J Surg. 2000;24(11):1437

	Diagnosis before 1990	Diagnosis after 1990
Related to MEN1	53 (76.8%)	25 (71.4%)
Due to ulcerous disease (perforation or hemorrhage)	10 (14.5%)	1 (2.8%)
Due to local or metastatic progression	33 (47.8%)	23 (65.7%)
Zollinger–Ellison	12	6
Insulinoma	3	0
Glucagonoma–vipoma–somatostatinoma	2	2
Nonfunctioning pancreatic tumor	5	6
Thymic tumor	2	3
Bronchial tumor	5	0
Gastric tumor	0	1
Pituitary tumor	1	1
Adrenal tumor	2	1
Brain tumor	1	1
Unknown primary tumor	0	2
Other reasons related to	10 (14.5%)	1(2.8%)
Zollinger–Ellison	2 postoperative deaths 1 chemotherapy 1 septicemia	1 acute pancreatitis
Insulinoma	1 postoperative death 1 hypoglycemia-related suicide	0
Glucagonoma–vipoma–somatostatinoma	1 postoperative death	0
Hyperparathyroidism	2 acute hypercalcemias	0
Pituitary tumor	1 postoperative death	0
Unrelated to MEN1	13 (18.8%)	10 (28.6%)
Other cancers	8[a]	3[b]
Other medical causes	5[c]	7[d]
Unknown causes	3 (4.4%)	0 (0%)

Goudet P, Murat A, Binquet C, Cardot-Bauters C, Costa A, Ruszniewski P, Niccoli P, Ménégaux F, Chabrier G, Borson-Chazot F, Tabarin A, Bouchard P, Delemer B, Beckers A, Bonithon-Kopp C. Risk factors and causes of death in MEN1 disease. A GTE (Groupe d'Etude des Tumeurs Endocrines) cohort study among 758 patients. World J Surg. 2010;34(2):249

Management of hyperparathyroidism in MEN type 1:

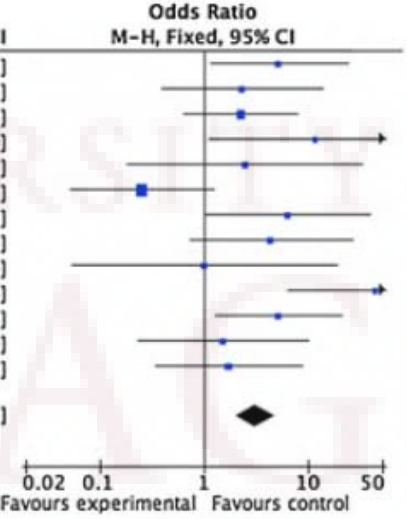
- Multiple gland involvement is common
- High risk of recurrent hyperparathyroidism after apparently successful subtotal parathyroidectomy
- The indications for surgical intervention are similar to those in patients with sporadic adenomas causing primary hyperparathyroidism
- Subtotal or total hyperparathyroidectomy should be considered

Surgical management of primary hyperparathyroidism in MEN 1:

A

Study or Subgroup	Experimental (<SPTX) Events	Total	Control (SPTX/TPTX) Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
current series	17	20	11	21	7.0%	5.15 [1.15, 23.01]
Dotzenrath	3	13	3	26	6.7%	2.30 [0.39, 13.42]
Elaraij	6	12	22	71	13.9%	2.23 [0.65, 7.68]
Hellman	16	17	7	12	2.1%	11.43 [1.12, 116.70]
Hubbard	1	4	3	25	2.7%	2.44 [0.19, 31.77]
Kraimps	4	26	5	12	25.3%	0.25 [0.05, 1.22]
Lambert	10	12	8	18	4.7%	6.25 [1.05, 37.07]
Langer	5	10	3	16	5.0%	4.33 [0.74, 25.29]
Lee	1	11	1	11	4.0%	1.00 [0.05, 18.30]
Malmeus	13	16	2	22	1.4%	43.33 [6.35, 295.76]
Norton	16	19	23	45	9.4%	5.10 [1.30, 19.97]
O Riordain	2	23	3	51	7.4%	1.52 [0.24, 9.80]
Rizzoli	6	20	3	15	10.5%	1.71 [0.35, 8.37]
Total (95% CI)		203		345	100.0%	3.11 [2.00, 4.84]
Total events	100		94			

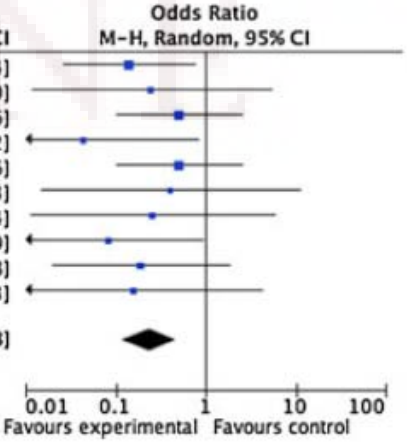
Heterogeneity: $Chi^2 = 22.03$, df = 12 (P = 0.04); $I^2 = 46\%$
Test for overall effect: Z = 5.04 (P < 0.00001)



B

Study or Subgroup	Experimental (<SPTX) Events	Total	Control (SPTX/TPTX) Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
current series	2	29	8	23	17.5%	0.14 [0.03, 0.74]
Dotzenrath	0	13	3	26	5.3%	0.25 [0.01, 5.19]
Elaraij	2	13	21	79	19.4%	0.50 [0.10, 2.46]
Hellman	0	26	7	24	5.7%	0.04 [0.00, 0.82]
Hubbard	2	13	21	79	19.4%	0.50 [0.10, 2.46]
Lambert	0	13	1	17	4.5%	0.41 [0.02, 10.83]
Langer	0	14	2	20	5.0%	0.26 [0.01, 5.74]
Lee	1	11	6	11	8.7%	0.08 [0.01, 0.89]
Malmeus	1	21	5	24	9.8%	0.19 [0.02, 1.78]
Norton	0	1	34	50	4.6%	0.16 [0.01, 4.13]
Total (95% CI)		154		353	100.0%	0.24 [0.12, 0.48]
Total events	8		108			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.36$, df = 9 (P = 0.89); $I^2 = 0\%$
Test for overall effect: Z = 4.03 (P < 0.0001)



Schreinemakers JM, Pieterman CR, Scholten A, Vriens MR, Valk GD, Rinkes IH. The optimal surgical treatment for primary hyperparathyroidism in MEN1 patients: a systematic review. World J Surg. 2011 Sep;35(9):1993-2005

Take home points:

- MEN type 1 is a rare genetic disorder (prevalence is 2 per 100,000), which however associated with reduced life expectancy

- Routine screening for MEN type 1 related tumors of all patients and first-degree relatives with MEN1 mutations is needed

References:

- Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, Melmed S, Sakurai A, Tonelli F, Brandi ML. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012;97(9):2990.

- Dean PG, van Heerden JA, Farley DR, Thompson GB, Grant CS, Harmsen WS, Ilstrup DM. Are patients with multiple endocrine neoplasia type I prone to premature death? World J Surg. 2000;24(11):1437.

- Goudet P, Murat A, Binquet C, Cardot-Bauters C, Costa A, Ruszniewski P, Niccoli P, Ménégaux F, Chabrier G, Borson-Chazot F, Tabarin A, Bouchard P, Delemer B, Beckers A, Bonithon-Kopp C. Risk factors and causes of death in MEN1 disease. A GTE (Groupe d'Etude des Tumeurs Endocrines) cohort study among 758 patients. World J Surg. 2010;34(2):249.

- Schreinemakers JM, Pieterman CR, Scholten A, Vriens MR, Valk GD, Rinkes IH. The optimal surgical treatment for primary hyperparathyroidism in MEN1 patients: a systematic review. World J Surg. 2011 Sep;35(9):1993-2005.