1° CORSO NAZIONALE DI AGGIORNAMENTO
IPER[CORSI] **AME**

Iperparatiroidismo Primario
Approccio alla malattia multighiandolare

Indagini genetiche:
Quando e come?

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IPERPARATIROIDISMO PRIMARIO (PHPT)

90-95%

SPORADICO

5-10%

FAMILIARE

<1%

Adenoma

Carcinoma

MEN1 MEN2A HPT-JT FHH FIHP

Genes implicated in syndromic and sporadic parathyroid tumorigenesis, and related syndromes

Gene	Protein encoded	Associated hyperparathyroid syndrome: main syndromic manifestations	Features of syndromic parathyroid tumors	Defect in sporadic parathyroid tumors
MEN1	Menin	Multiple endocrine neoplasia type 1: anterior pituitary, parathyroid, enteropancreatic, foregut carcinoid tumors	Multiple, asymmetric tumors typical (> 99% benign)	Inactivation in ~25-35% of benign tumors; mutation exceedingly rare in cancer
HRPT2/CDC73	Parafibromin	Hyperparathyroidism-jaw tumor syndrome: fibro-osseous jaw, parathyroid, uterine tumors; renal cysts	Single tumor common (~15% malignant)	Inactivation in ~70% of cancers; mutation rare in sporadic adenomas
CASR	Calcium-sensing receptor	Familial hypocalciuric hypercalcemia (FHH) with heterozygous inactivation; neonatal severe hyperparathyroidism (NSHPT) with homozygous inactivation	FHH: near-normal size and surgical pathology; altered serum calcium set-point for PTH release NSHPT: Marked enlargement of multiple glands	Decreased expression common; mutation exceedingly rare
RET	c-Ret	Multiple endocrine neoplasia type 2A: medullary thyroid cancer, pheochromocytoma, parathyroid tumors	Single tumor common (> 99% benign)	Mutation exceedingly rare
CCND1/PRAD1	Cyclin D1	NA	NA	Overexpression results from DNA rearrangement involving PTH gene

NA, not applicable

J Clin Endocrinol Metab 94: 340–350, 2009

Diagnosis of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Third International Workshop

Conclusions

DNA sequence testing for mutations of *CASR*, *MEN1*, and *HRPT2* genes can provide clinically useful information, particularly in known or suspected cases of familial hyperparathyroidism. These studies are not recommended on a routine basis. Mutations in the *RET* gene are of particular value in the management of medullary thyroid carcinoma in MEN2A.

Symposium | Journal of INTERNAL MEDICINE

doi: 10.1111/j.1365-2796.2009.02105.x

DNA-based test: when and why to apply it to primary hyperparathyroidism clinical phenotypes

A. Falchetti[1], F. Marini[1], F. Giusti[1], L. Cavalli[1], T. Cavalli[1] & M. L. Brandi[2]

Genetic tests may be used for (i) diagnostic testing
the clinical diagnosis must be secure before predictive testing is used.
disorder in a symptomatic individual (proband); (ii)
predictive testing that can be offered to asymptomatic
individuals with a family history of a genetic disorder:

Iperparatiroidismo familiare: caratteristiche cliniche comuni

1) Età alla diagnosi anticipata
2) Coinvolgimento ghiandolare multiplo (iperplasia o adenomi multipli)
3) Anamnesi familiare e personale suggestiva per sindrome

Falchetti A, J In Med 2009

Table 2 Main clinical features of various forms of hereditary hyperparathyroidism

Syndrome	Elevated PTH (%)	Age of onset (year)	Parathyroid glands involvement	Pathology	Treatment
MEN1	90–100	20–25	Multiglandular	Hyperplasia/adenoma(s)	SPTX or TPTX with autologous reimplantation + transcervical thymectomy
MEN2A	15–30	>30	Single/ multiglandular	Multiple adenomas/ hyperplasia	Resection of only enlarged glands, SPTX, TPTX with autologous reimplantation
FHH/NSHPT-NHPT	12–14	All ages/ at birth or within the first 6 months	Multiglandular	Mildly enlarged parathyroid glands/ markedly hyperplastic parathyroid glands	FHH: patients do not benefit from surgery of parathyroid lesions, but subtotal parathyroidectomy can be performed in subjects developing symptomatic PHPT NSHPT: TPTX
ADMH	100 (inappropriate levels)	44.5 ± 3.9	Single/ multiglandular	Diffuse to nodular parathyroid neoplasia	Radical subtotal parathyroid resection with parathyroid remnants of 10–20 mg or TPTX with autologous reimplantation
HPT-JT	80	>30 (average age 32)	Single/ multiglandular (generally two glands)	Single or double adenoma (cystic parathyroid adenomatosis). Parathyroid carcinoma in approximately 10–15% of affected individuals	Single disease: parathyroid adenomectomy Multiglandular disease: SPTX or TPTX with autologous reimplantation Carcinoma: neck surgery, specifically an en bloc resection of primary tumour, as the only curative treatment
FIHPT	>Ca^{++} with inappropriate PTH levels	NR	Single/ multiglandular	Single, multiple adenoma(s)	Single disease: parathyroid adenomectomy Multiglandular disease: SPTX or TPTX with autologous reimplantation

SPTX, subtotal parathyroidectomy; TPTX, total parathyroidectomy; NR, not reported.

Falchetti A,
J In Med 2009

INDICAZIONI

- ClCa/ClCr > 0.010
- Età alla diagnosi anticipata
- Coinvolgimento ghiandolare multiplo (iperplasia o adenomi multipli)
- Anamnesi familiare e personale suggestiva per sindrome (litiasi renale, tumori neuroendocrini, adenomi ipofisari)

Indicazioni

- Conferma di diagnosi clinica o di una presentazione anomala (es, evidenza ad una età precoce).
- Identificazione di un soggetto a rischio
- Identificazione di carriers
- Cessazione di screening in familiari non portatori della mutazione

Falchetti A, J In Med 2009

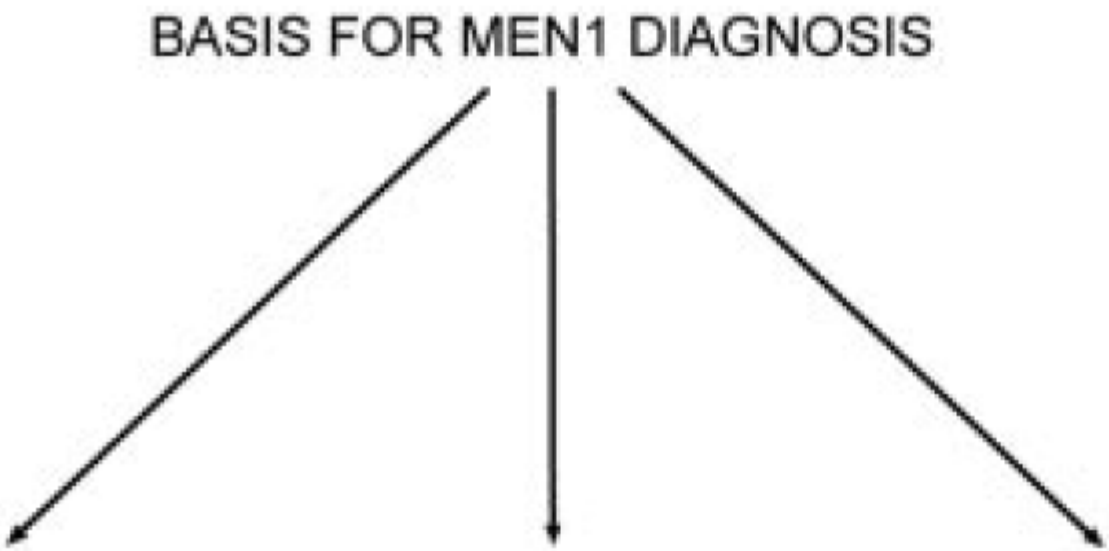
Prevalence of endocrine and nonendocrine tumors associated with MEN1

Tumor	Prevalence at 40 years
Endocrine	
Parathyroid adenomas	○90%
Enteropancreatic tumors	○Gastrinoma 40%, insulinoma 10% ○Others (VIPoma, glucagonoma) 2% ○Nonfunctioning 20%
Pituitary adenomas	○Prolactinoma 20%, GH 5% ○GH/PRL 5%, TSH <1%, ACTH secreting 2% ○Nonfunctioning 17%
Foregut carcinoids	○Thymic 2%, bronchial 2%, gastric 10%
Adrenal gland	○Nonfunctioning 20–40% (most bilateral hyperplasia)
Nonendocrine	
Cutaneous tumors	○Facial angiofibroma 85% ○Collagenoma 70% ○Lipoma 30%
Central nervous system lesions	○Meningioma 5–8% ○Ependymoma 1%

Almeida M and Stratakis C, Cancer Genetics and Cytogenetics 2010

TABLE 1. MEN syndromes and their characteristic tumors and associated genetic abnormalities

Type (chromosome location)	Tumors (estimated penetrance)	Gene, most frequently mutated codons
MEN1 (11q13)	Parathyroid adenoma (90%) Enteropancreatic tumor (30–70%): gastrinoma (40%), insulinoma (10%), nonfunctioning and PPoma (20–55%), glucagonoma (<1%), VIPoma (<1%) Pituitary adenoma (30–40%): prolactinoma (20%), somatotropinoma (10%), corticotropinoma (<5%), nonfunctioning (<5%) Associated tumors: adrenal cortical tumor (40%), pheochromocytoma (<1%), bronchopulmonary NET (2%), thymic NET (2%), gastric NET (10%), lipomas (30%), angiofibromas (85%), collagenomas (70%), meningiomas (8%)	*MEN1* 83/84, 4-bp del (≈4%) 119, 3-bp del (≈3%) 209–211, 4-bp del (≈8%) 418, 3-bp del (≈4%) 514–516, del or ins (≈7%) Intron 4 ss, (≈10%)
MEN2 (10 cen-10q11.2)		
MEN2A	MTC (90%) Pheochromocytoma (50%) Parathyroid adenoma (20–30%)	*RET* 634, missense *e.g.* Cys→Arg (~85%)
MTC only	MTC (100%)	*RET* 618, missense (>50%)
MEN2B (also known as MEN3)	MTC (>90%) Pheochromocytoma (40–50%) Associated abnormalities (40–50%) Mucosal neuromas Marfanoid habitus Medullated corneal nerve fibers Megacolon	*RET* 918, Met→Thr (>95%)
MEN4 (12p13)	Parathyroid adenoma[a] Pituitary adenoma[a] Reproduction organ tumors (*e.g.* testicular cancer, neuroendocrine cervical carcinoma)[a]	*CDKN1B* No common mutations identified to date



CLINICAL

A patient with 2 or more MEN1-associated tumours

FAMILIAL

A patient with 1 MEN1-associated tumour and a first degree relative with MEN1

GENETIC

An individual who has an MEN1 mutation but does not have clinical or biochemical manifestations of MEN1 i.e. a mutant gene carrier

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An approach to screening in MEN1

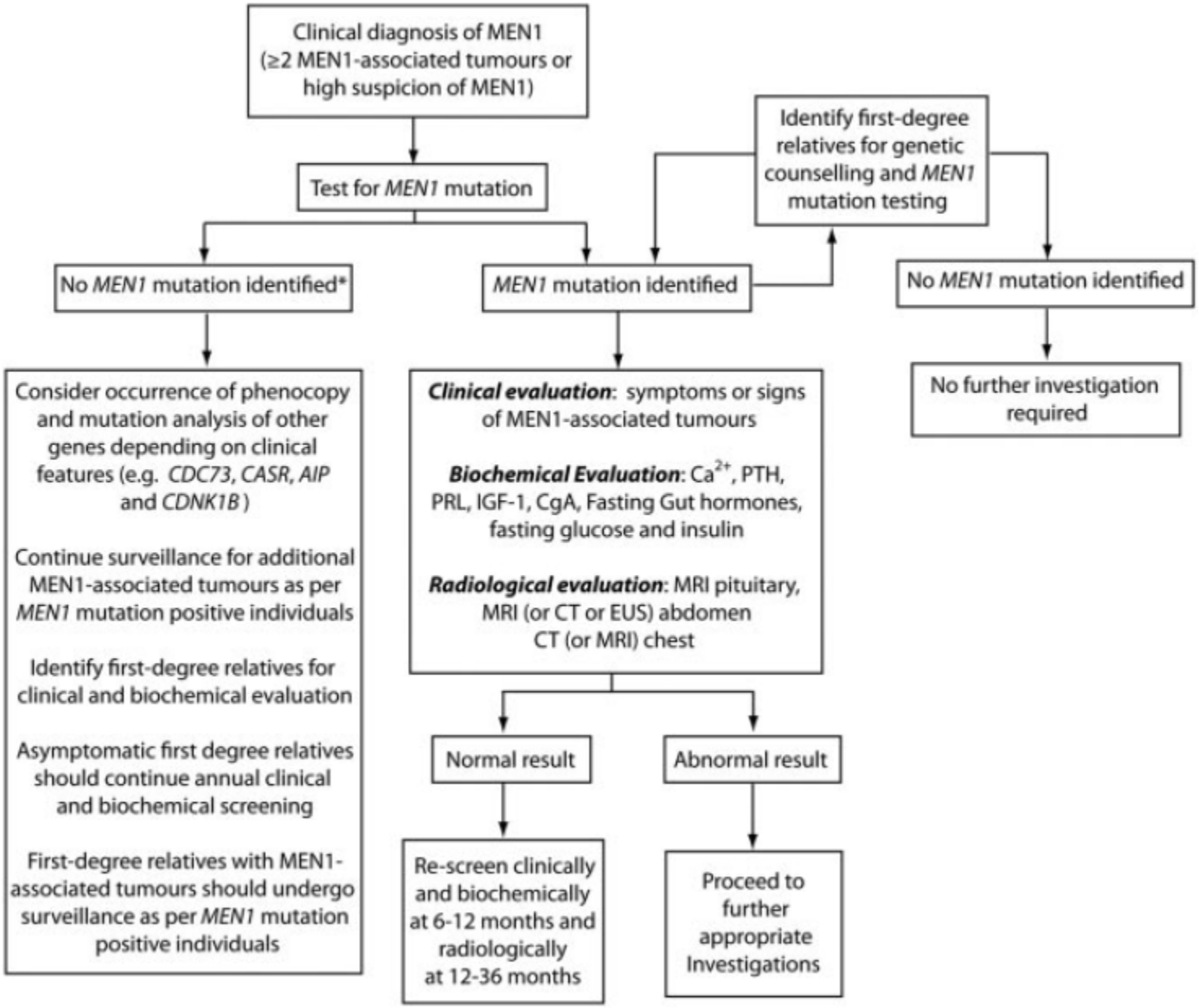

TABLE 2. Suggested biochemical and radiological screening in individuals at high risk of developing MEN1

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)

EUS, Endoscopic ultrasound. [Adapted from P. J. Newey and R. V. Thakker: Role of multiple endocrine neoplasia type 1 mutational analysis in clinical practice. *Endocr Pract* 17(Suppl 3):8–17, 2011 (21), with permission. © American Association of Clinical Endocrinologists. And from R. V. Thakker: Multiple endocrine neoplasia type 1 (MEN1). *Translational Endocrinology and Metabolism*, Vol 2. (edited by R. P. Robertson and R. V. Thakker), The Endocrine Society, Chevy Chase, MD, 2011, pp 13–44 (5), with permission.]

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Suggested approach for *MEN1 mutational* analysis in a clinical setting

Value in clinical setting

- Aid in confirming the diagnosis
- Identify mutation carriers in a family for screening and development of tumors, thereby facilitating early treatment
- Identify the 50% of family members who do not harbor the *MEN1 mutation, thereby alleviating the anxiety and* burden of disease from them and their progeny

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Suggested approach for *MEN1 mutational* analysis in a clinical setting

Who should be tested?

In an index case

Meeting the clinical criteria for MEN1 (*i.e. two or more* MEN1-associated tumors or a diagnosis of familial MEN1)

Suspicious (*i.e. multiple parathyroid adenomas before the* age of 40 yr; recurrent hyperparathyroidism; gastrinoma or multiple pancreatic NET at any age) or

atypical for MEN1 (*i.e. development of two nonclassical MEN1*- associated tumors, *e.g. parathyroid and adrenal tumor)*

A first-degree relative of family member with known *MEN1* mutation

Asymptomatic first-degree relative

First-degree relative with familial MEN1 (*i.e. one MEN1*- associated tumor)

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Suggested approach for *MEN1 mutational* analysis in a clinical setting

When should testing be undertaken?

As early as possible (*e.g. before 5 yr of age for asymptomatic* individuals)

Where should test be performed?

In accredited department/laboratory undertaking DNA testing of *MEN1 gene*

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MEN 1

- *MEN1 germline mutation testing should be offered to* **index patients** withMEN1and their **first-degree relatives**. This includes relatives who are either asymptomatic or who have clinical manifestations of MEN1 (lev 1).
- *MEN1 germline mutation testing of asymptomatic* relatives should be offered **at the earliest opportunity** because MEN1 manifestations may occur by the age of 5 yr (lev 2).
- *MEN1 germline mutation testing may be recommended* in individuals with an **atypical MEN1 phenotype** (*e.g. multigland hyperparathyroidism) (lev 2).*
- All individuals offered *MEN1 mutation testing should* be provided with genetic counseling before testing (lev 1).

MEN 1

- *MEN1 germline mutation testing should be undertaken* by a clinical genetics laboratory accredited in mutation analysis of the *MEN1 gene (lev 1).*
- *If a coding* region *MEN1 mutation is not identified, then testing for* partial or whole-gene deletion, or haplotype analysis of the *MEN1 locus, or analysis of other genes should be* considered (lev 1).

- Relatives of a patient with a known *MEN1 mutation* should be offered *MEN1 germline mutation analysis before* biochemical and radiological screening tests for the detection of MEN1 tumors, so as to avoid the burden of undergoing multiple tests involving different modalities and to reduce financial costs (lev 1).

Individuals who are found to have a *MEN1 germline* mutation should be screened regularly (*e.g. on an annual* basis) for development of MEN1-associated tumors (lev 1).

Ricerca di mutazioni nel gene CDC73

- Sindrome HPT-JT
- FIHP

- **Calcemia > 12 mg/dL + età alla diagnosi < 40 anni**
- **Carcinoma paratiroideo**

- Se non si identifica la mutazione con il sequenziamento diretto, ricercare la presenza di grosse delezioni

- Eseguire lo **screening nei parenti tra i 5 e 10 anni** e secondo alcuni alla nascita, per il potenziale maligno della malattia

HPT-JT

Iperparatiroidismo primitivo

Malattia uni o multighiandolare

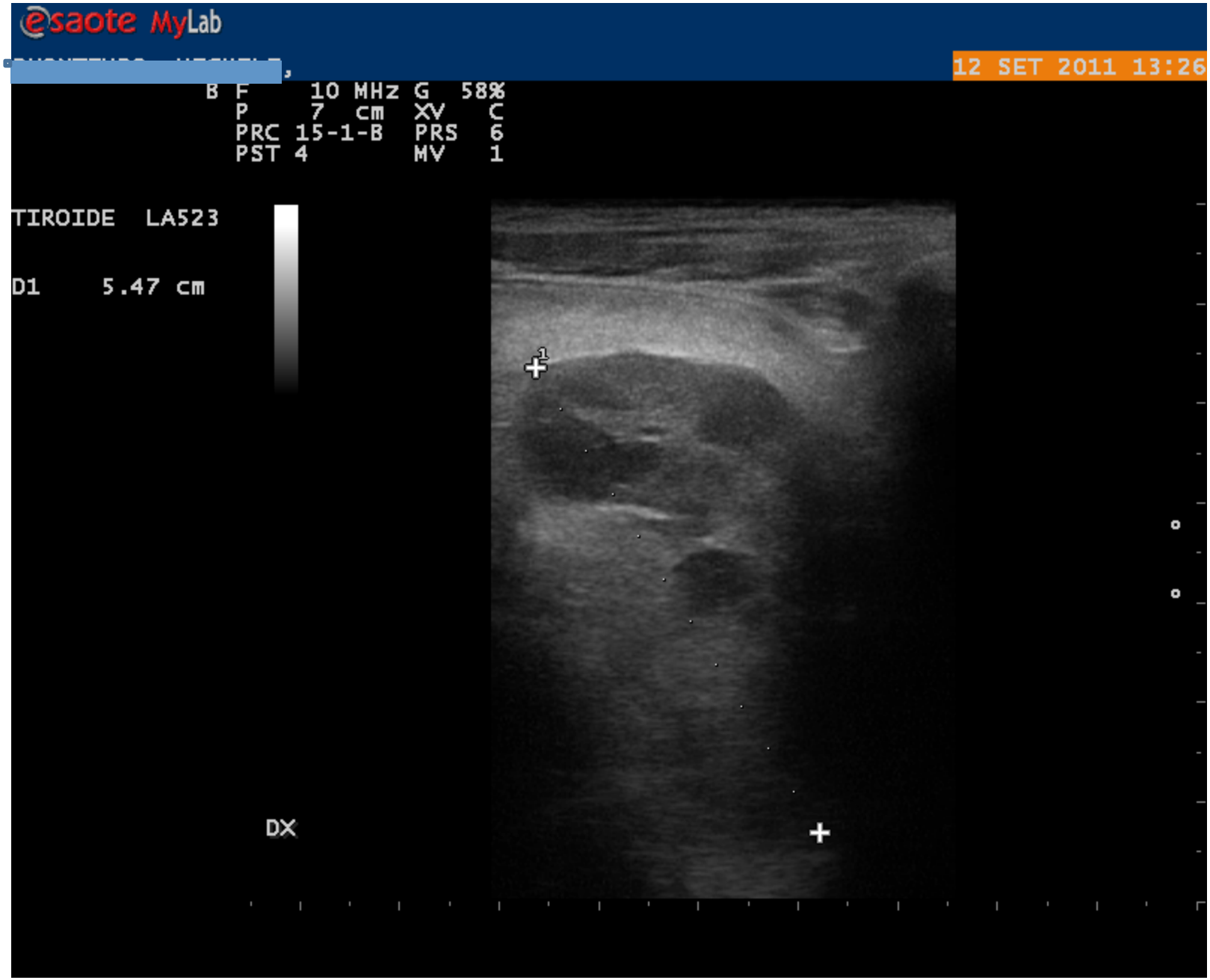
Carcinoma paratiroideo

Paratiroide con aspetti cistici all'istologia

Tumori fibro-ossei mandibola o della mascella (28%)

Lesioni renali (16%)

Lesioni uterine (74%)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