Non Surgical Treatment of Thyroid Goiter

Where are we?

Verona, October 28, 2006

THERMAL ABLATION:
FROM BASIC PRINCIPLES TO CLINICAL USE

Enrico Papini & Claudio M Pacella

Background (1): Cold Nodules

- only a small group of benign nodules is responsive to L-T4 suppressive therapy
- most nodules are clinically controlled on a long-term basis
- when the nodule shows a progressive growth and is a cause of compressive symptoms or concern surgery is usually recommended

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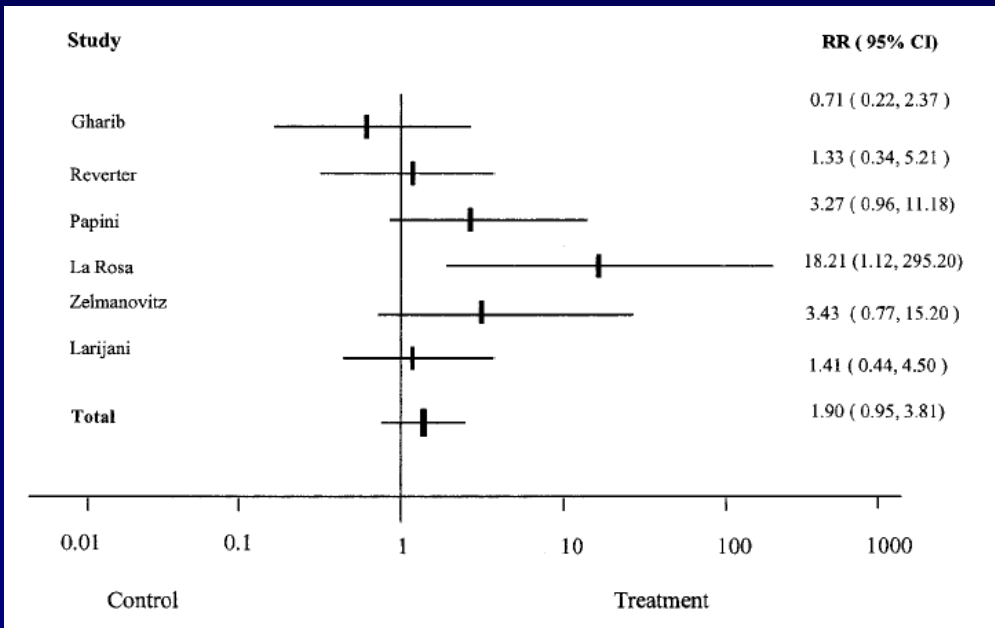
The Journal of Clinical Endocrinology & Metabolism 87(9):4154–4159

doi: 10.1210/jc.2001-011762

Effectiveness of Thyroid Hormone Suppressive Therapy in Benign Solitary Thyroid Nodules: A Meta-Analysis

M. REGINA CASTRO, PEDRO J. CARABALLO, AND JOHN C. MORRIS

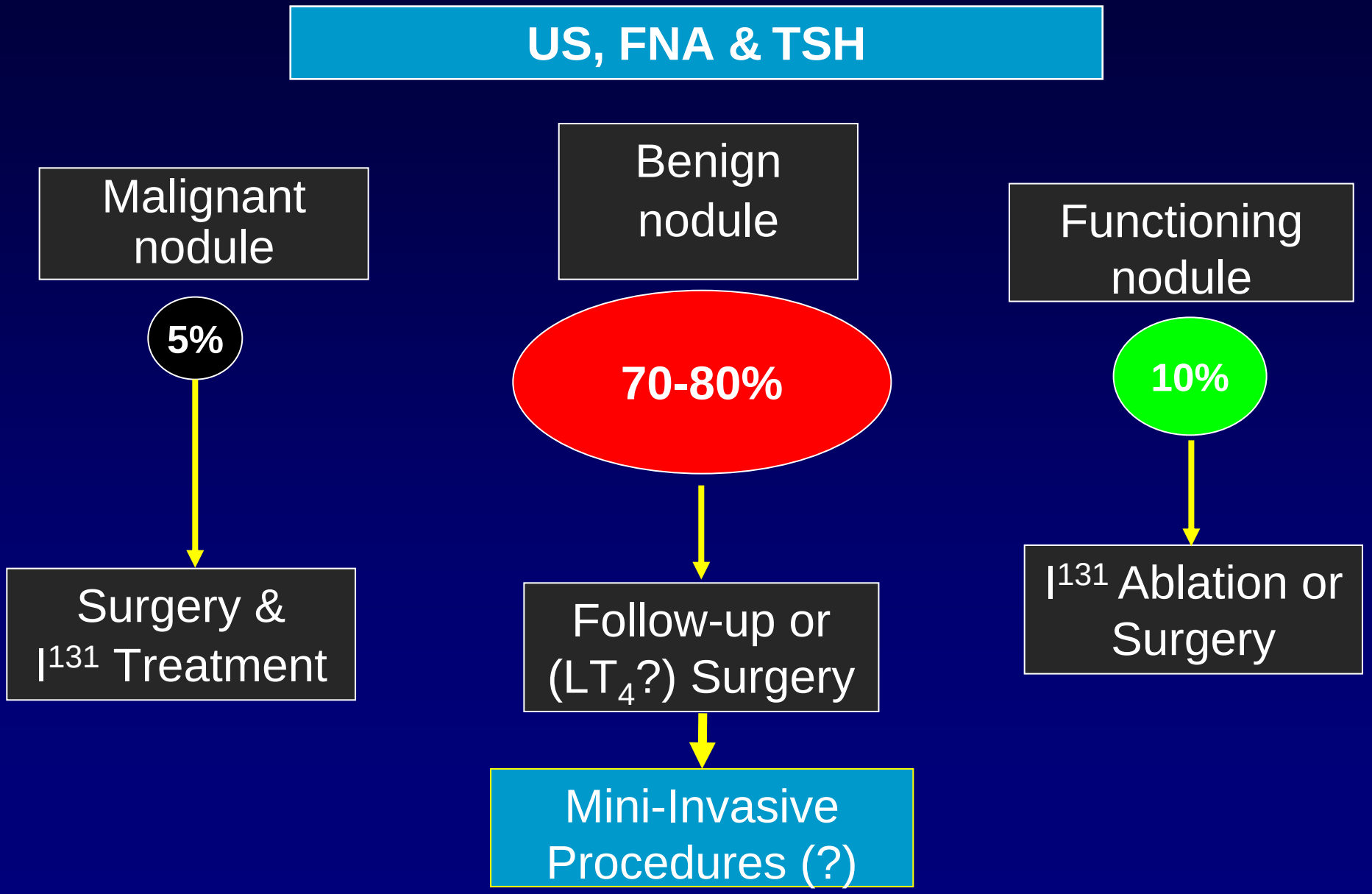


Background (2)

Surgery is an expensive procedure not devoid of complications or side-effects:

- Subclinical hypothyroidism
- Cosmetic damage
- Hypoparathyroidism
- Recurrent nerve damage
- Neck bleeding

Current Management of Thyroid Nodules



When an ablation procedure may be useful for thyroid gland lesions?

Benign Lesions at Risk of Surgery:

- Relapsing cystic lesions
- Benign thyroid nodules which cause local symptoms
- Hyperfunctioning thyroid nodules requiring large activities of ^{131}I

Nonsurgical debulking of malignancy (?)

Who may benefit from a minimally invasive procedure?

- Previous thyroid surgery
- Poor surgical risk
- Fear of surgical complications or cosmetic damage
- Tumor recurrence not amenable to traditional thyroid cancer treatments

Minimally Invasive Ablation Techniques

Injective

Localized Hyperthermia

Chemical Injection (Ethanol: PEI)

Percutaneous Laser Ablation (PLA)

Radio Frequency

HIFU (***Not*** *Invasive*)

Micro-Wave

International Working Group on Image-Guided Tumor Ablation. J Vasc Interv Radiol, 2005

Key Recommendation
Percutaneous Ethanol Injection

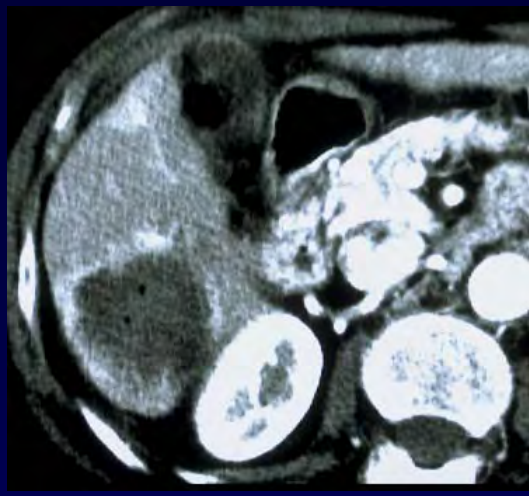
- PEI is highly effective in the treatment of thyroid cysts and complex nodules with a large fluid component
- Because the only alternative to PEI for recurrent and enlarging cysts is surgical resection, PEI is the first line nonsurgical treatment for cystic nodules if US-FNA has ruled out a malignant lesion

Key Recommendation
Percutaneous Ethanol Injection 2.

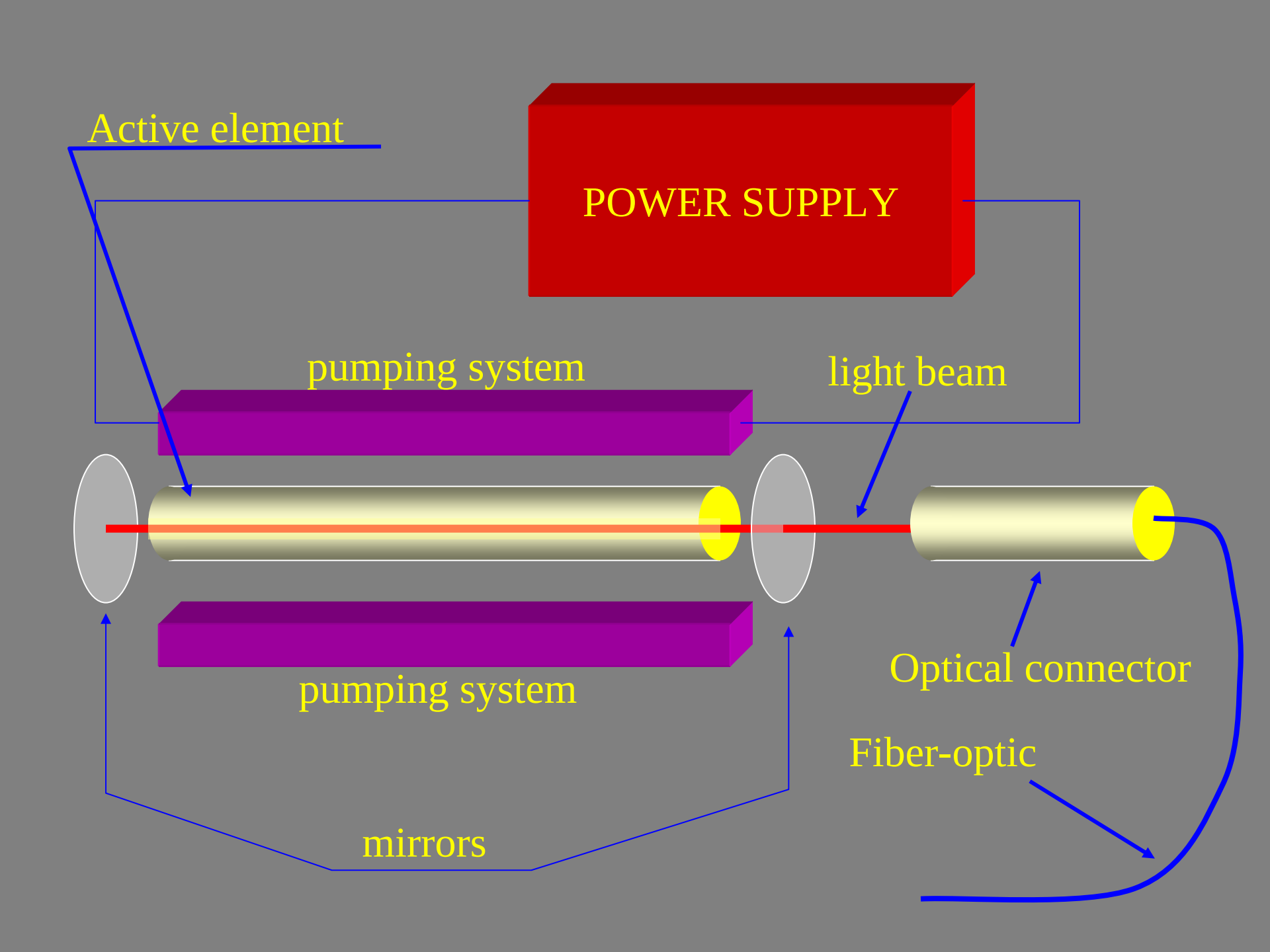
PEI should NOT be performed:

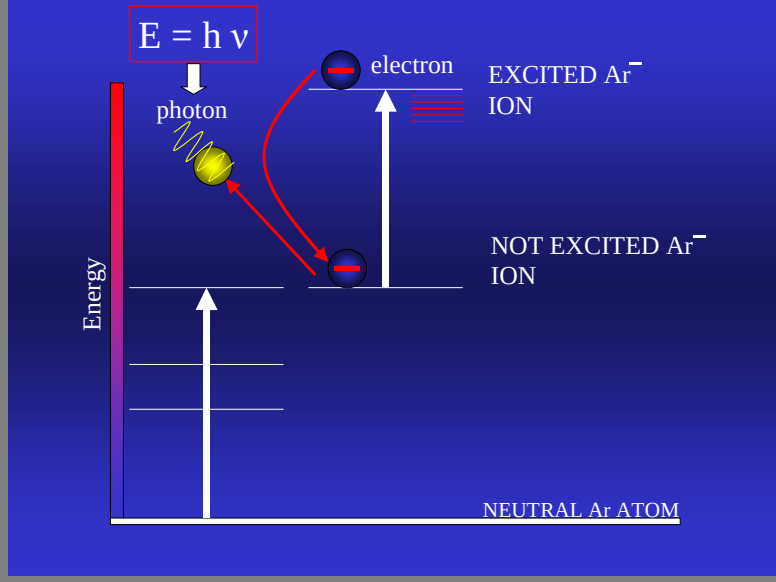
- On solid cold nodules unless surgical treatment is contraindicated
- On large or toxic AFTN – the rate of cure is too low and relapse is frequent
- On toxic MNG

The **hypertermic methods** have been used for the palliative treatment in a variety of tumors and benign lesions



• primary tumors (hepatocellular ca., renal cell ca., brain tumors, lung cancer, nasopharingeal tumors)	• ILP, RF, MW
• hepatic, cerebral, lung, and retroperitoneal metastases	• ILP,RF
• osteoid osteoma	• ILP,RF
• **hot and cold thyroid nodules**	• ILP,RF
• **thyroid anaplastic carcinoma**	• ILP
• benign prostatic hyperplasia	• ILP,RF
• uterine leiomyomas	• ILP
• hyperfunctioning parathyroid adenoma*	• ILP,RF


Active element
POWER SUPPLY
pumping system
light beam
pumping system
Optical connector
Fiber-optic
mirrors



argon

He-Ne

CO_2

Nd-YAG

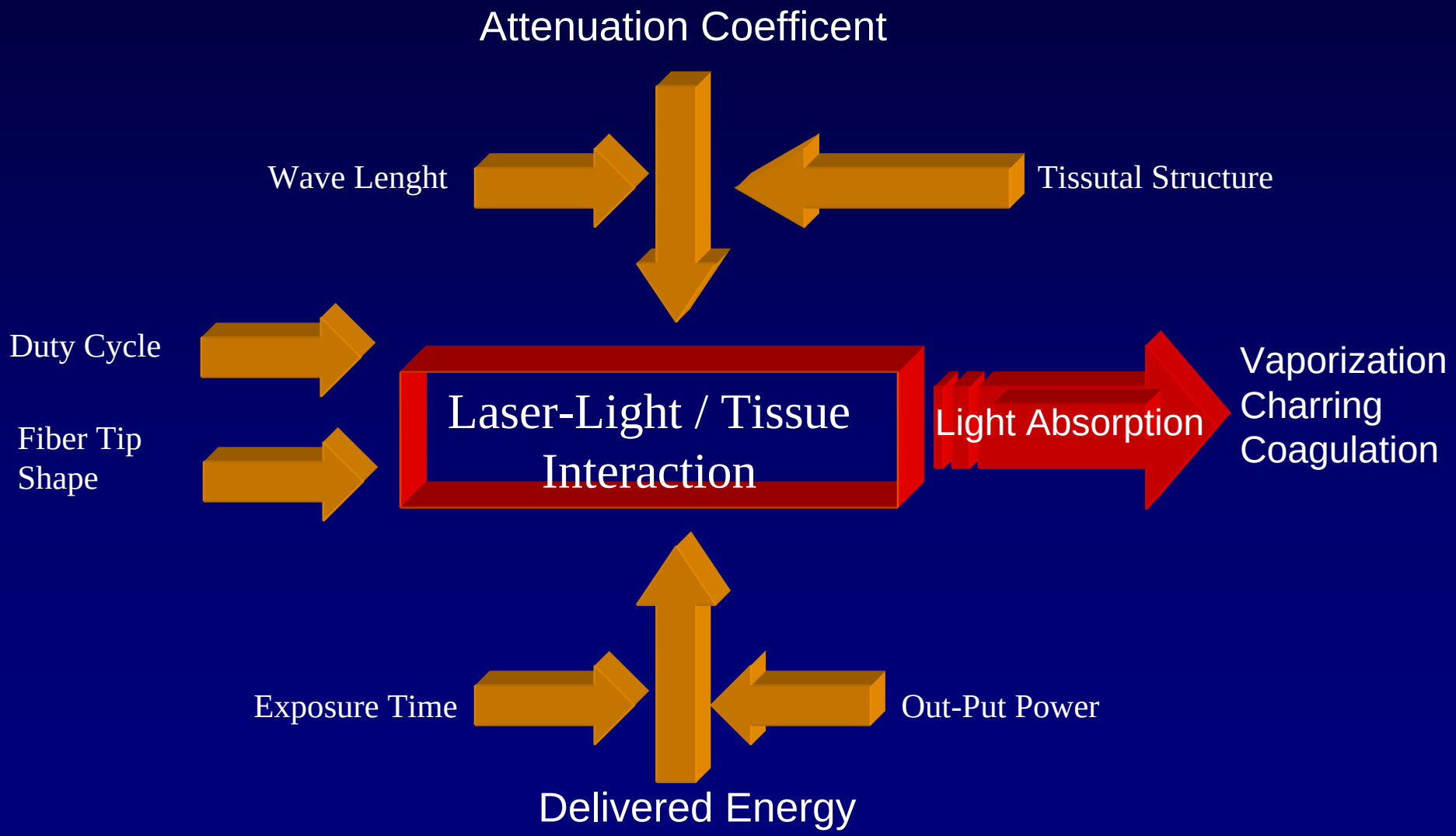
Diode

300 500 700 1000 2 5 10 20

nm μm

visible near infrared far infrared

Physical Parameters and Laser-Light/Tissue Interaction



Problems in Heat Tissue Ablation

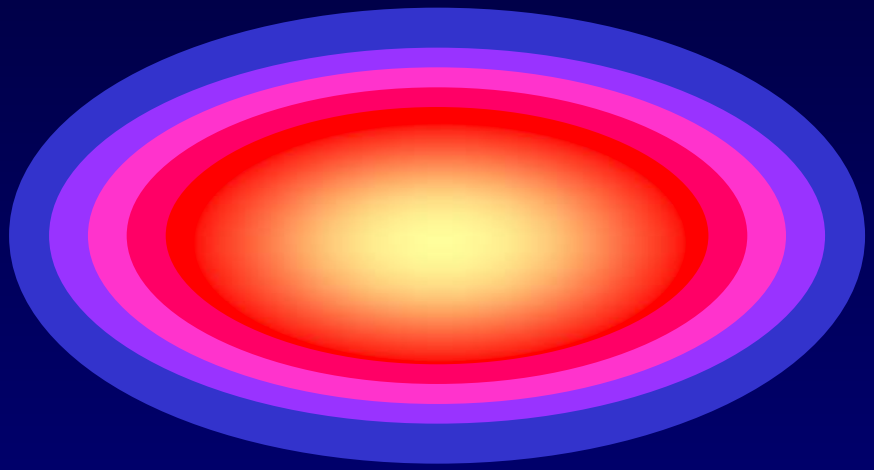
- *Local temperature between 40 and 45°C*

  ➔ damages are reversible if the exposure time is less than 30 – 60 minutes
- *Local temperature between 45 and 99°C*

  ➔ tissue coagulates at different times depending on temperature (1 second at 60° C)
- *Local temperature greater than 100°C*

  ➔ tissue is vaporized and charred, a cavity is created and thermal diffusion is hampered

single ablation with point-like source



8-10 mm*

16-18 mm.*

Eur. Radiol. 3, 26–32 (1993)

European Radiology

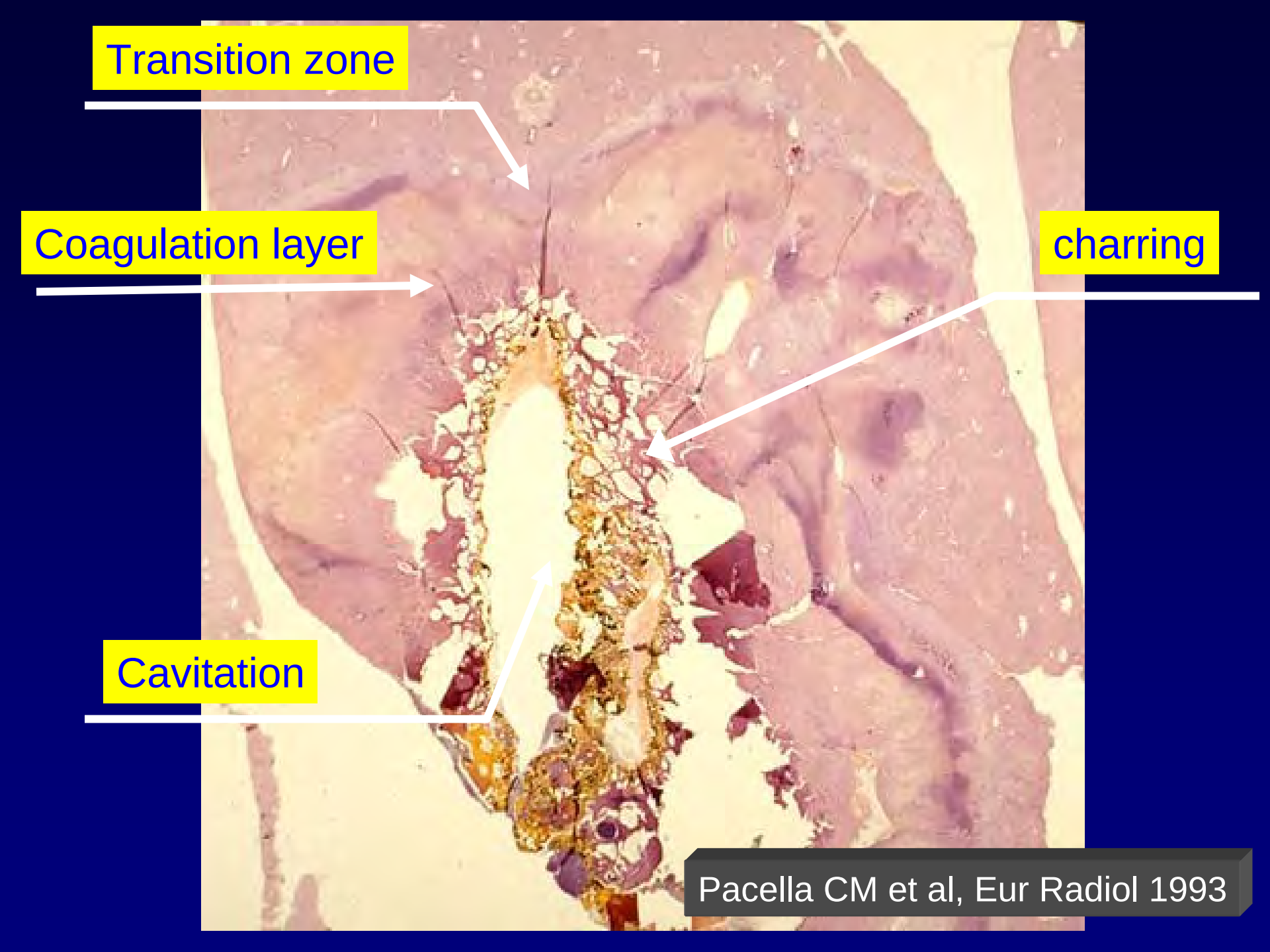
Ultrasound radiology

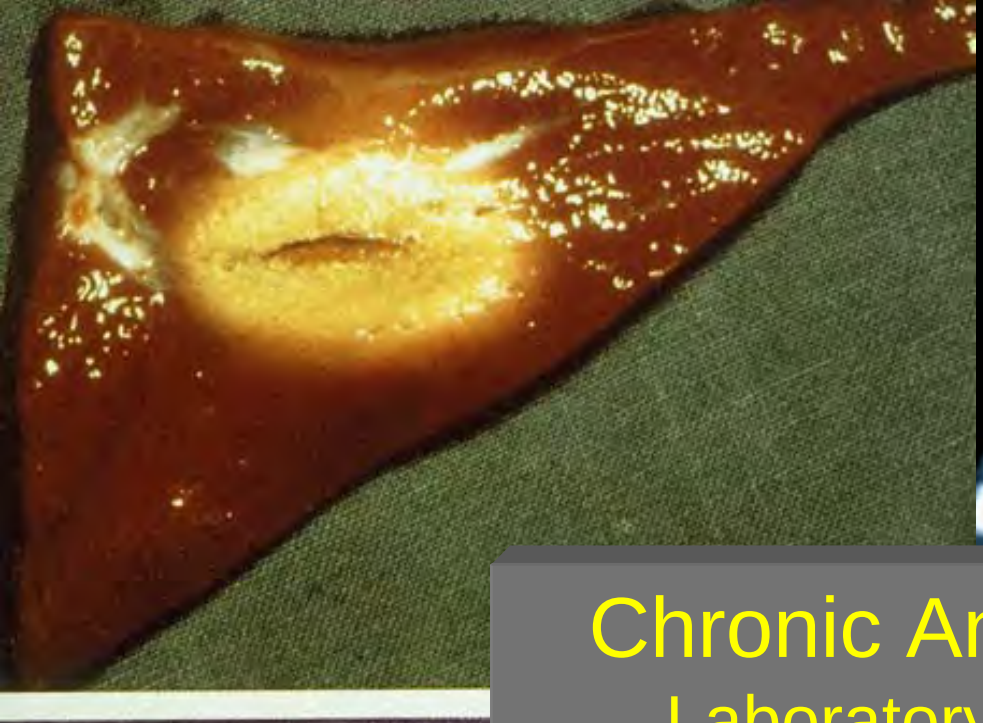
Ultrasound-guided percutaneous laser ablation of liver tissue in a rabbit model

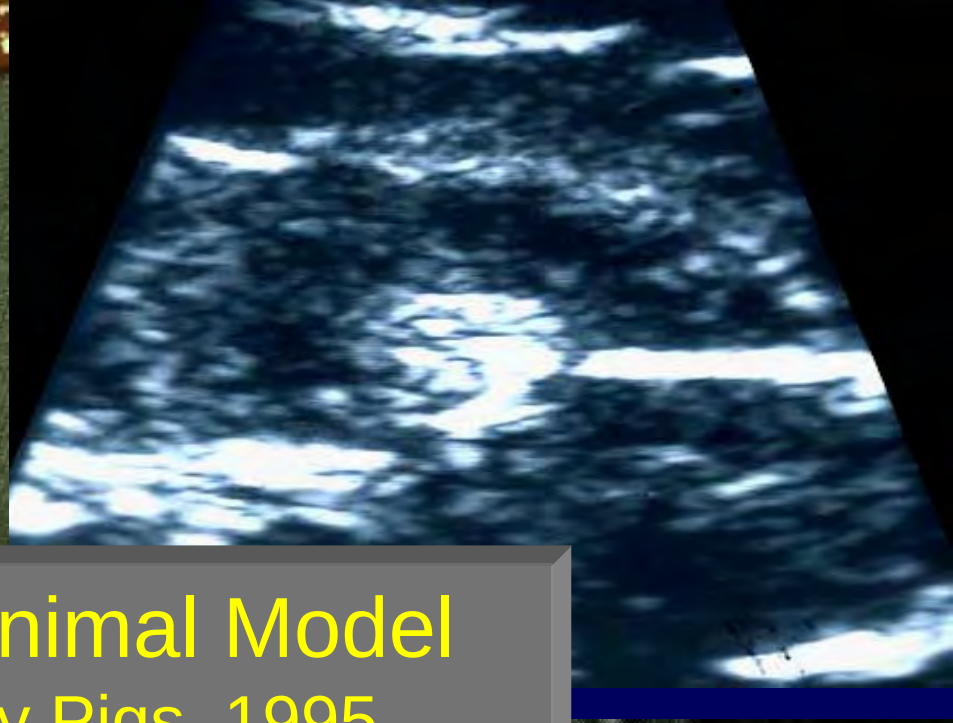
C. M. Pacella[1], Z. Rossi[1], G. Bizzarri[1], E. Papini[1], V. Marinozzi[2], D. Paliotta[2], P. Castaldo[3], V. Ziparo[3], F. Garosi[4], M. Cinti[4], and F. Muzzi[5]

One of the first experimental contributes

- nine New Zealand rabbits
- Nd:YAG laser coupled to a 600 nm quartz fibreoptic guide
- the fibre and a thermocouple were placed in the lumen of two Chiba needles (18 G) and these were inserted into the liver 10 mm apart under ultrasound guidance
- laser was fired for 5 minutes at 1, 3 and 5 W power
- all the rabbits survived for the full extent of the study

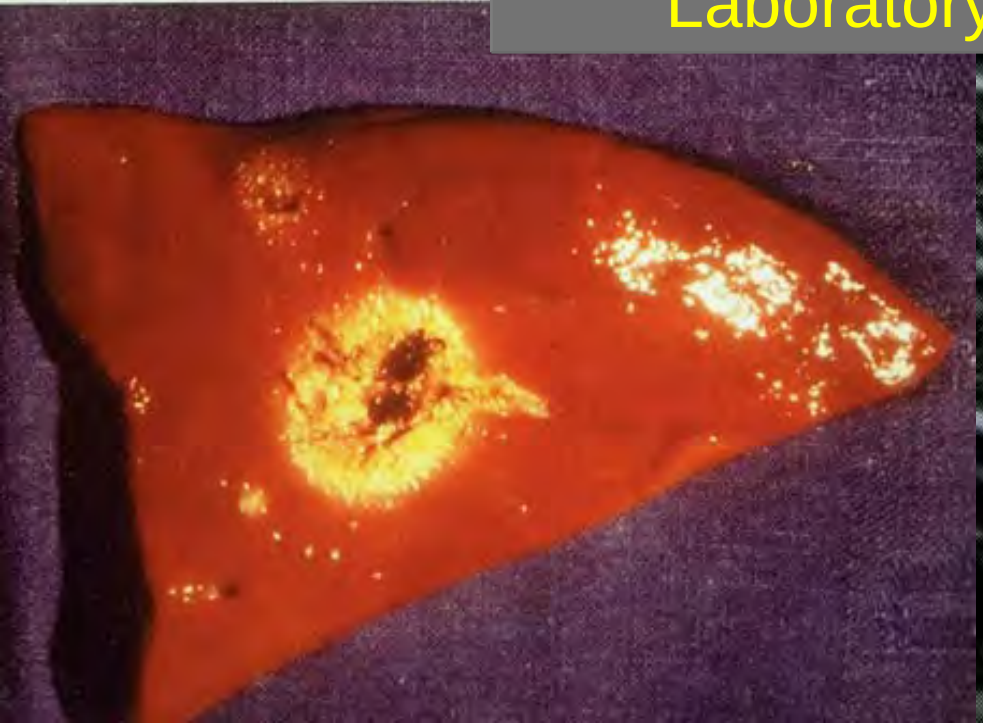

Transition zone
Coagulation layer
charring
Cavitation
Pacella CM et al, Eur Radiol 1993

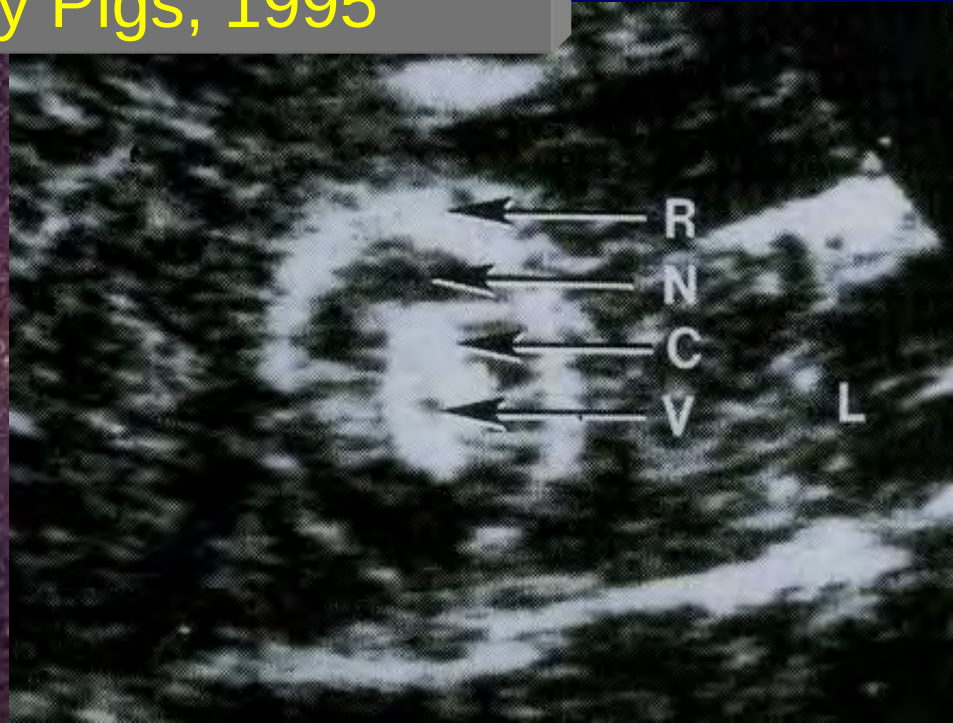




Chronic Animal Model

Laboratory Pigs, 1995



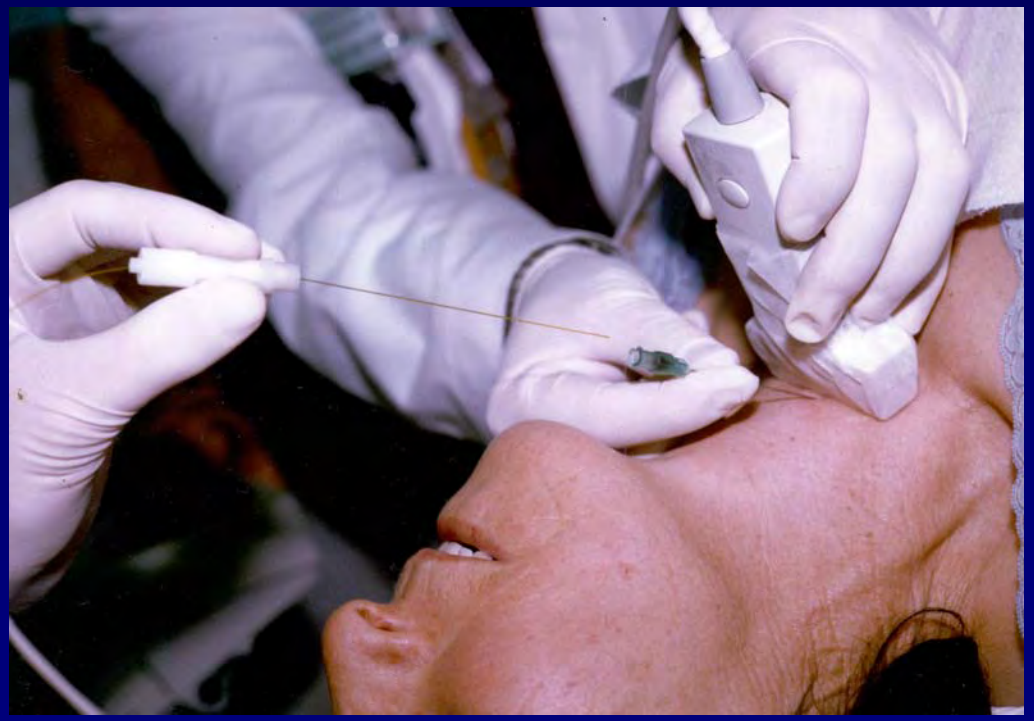


PLA as an interventional procedure for the treatment of thyroid lesions.Thyroid Glands. Ex vivo and in vivo Study

Claudio M. Pacella, MD
Giancarlo Bizzarri, MD
Rinaldo Guglielmi, MD
Vincenzo Anelli, MD
Antonio Bianchini, MD
Anna Crescenzi, MD
Sara Pacella, MD

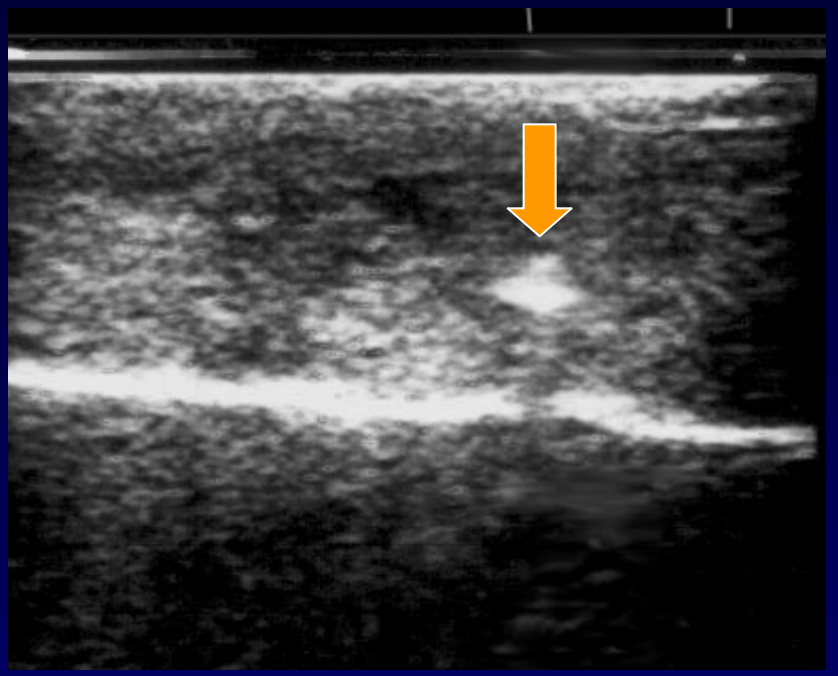
Thyroid Tissue: US-guided Percutaneous Interstitial Laser Ablation—A Feasibility Study[1]

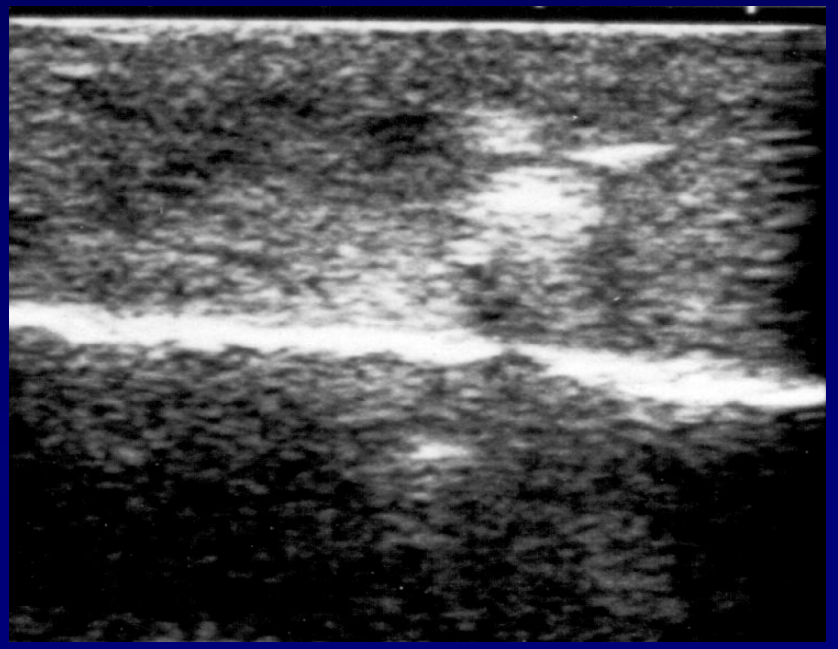
Radiology, 2000



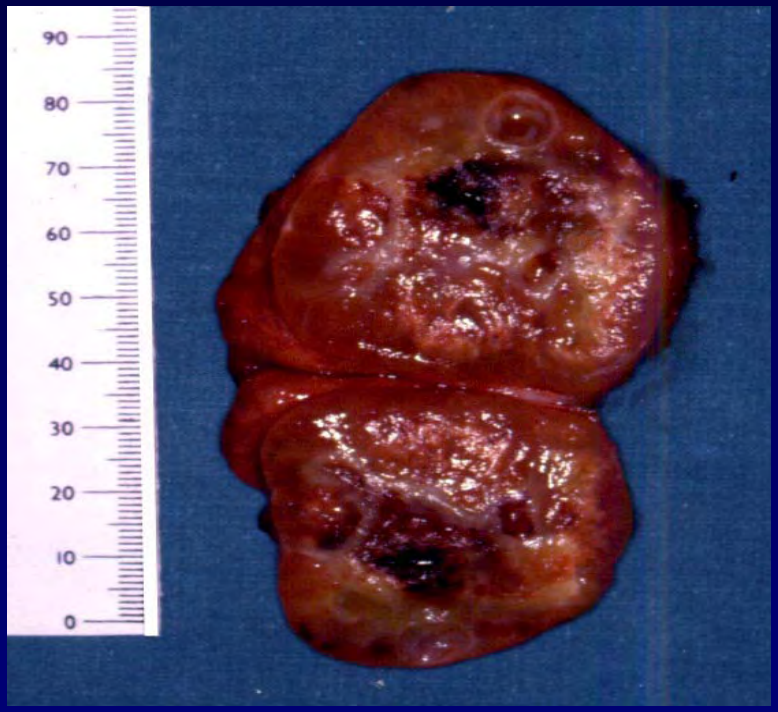
Resected glands

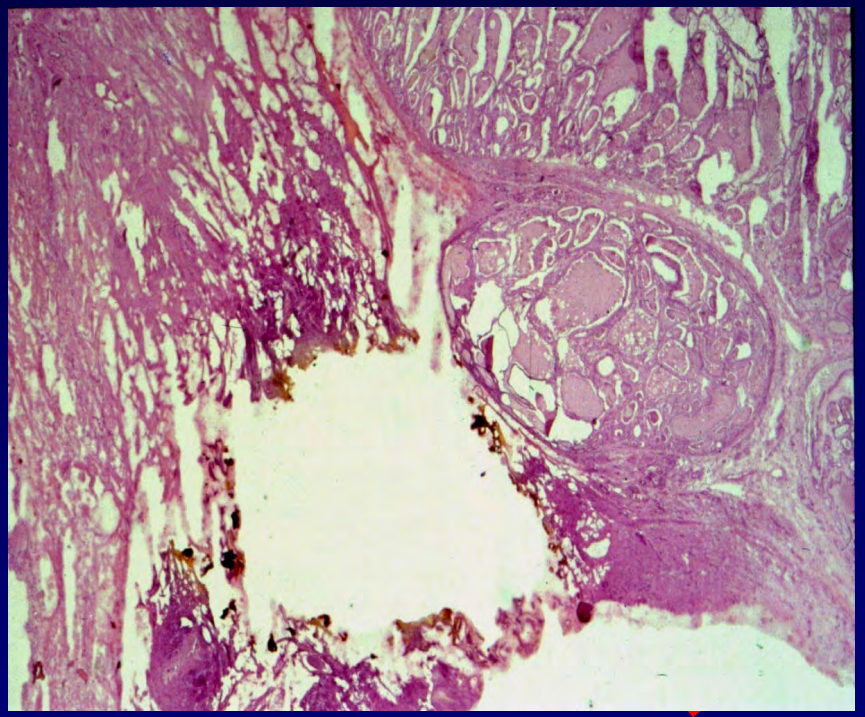
- at US monitoring the tip of the optical fiber was clearly visualized as a hyperechoic spot
- during PLA an irregular highly echogenic area slowly enlarged over time





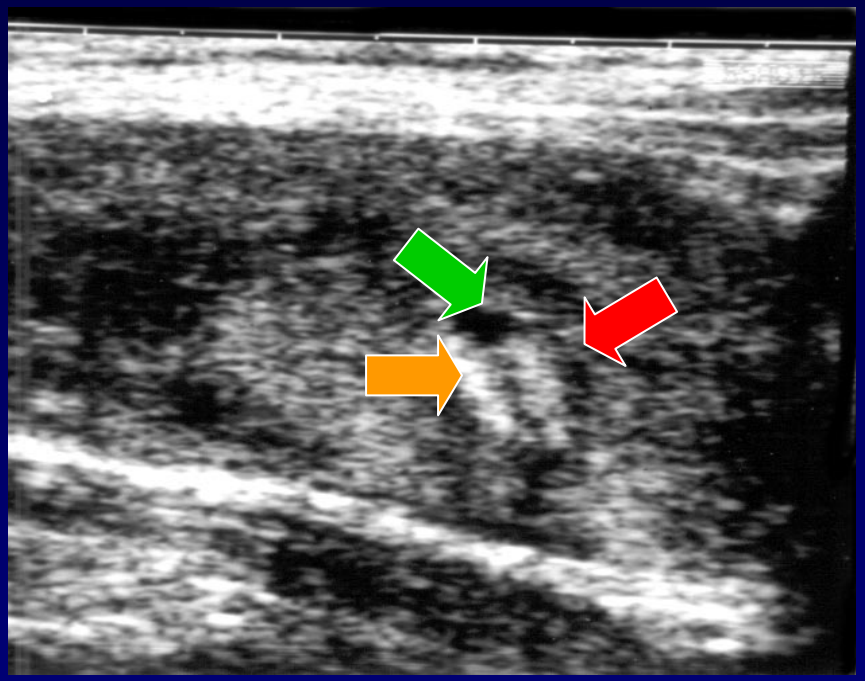
In vivo study: Surgical Specimens



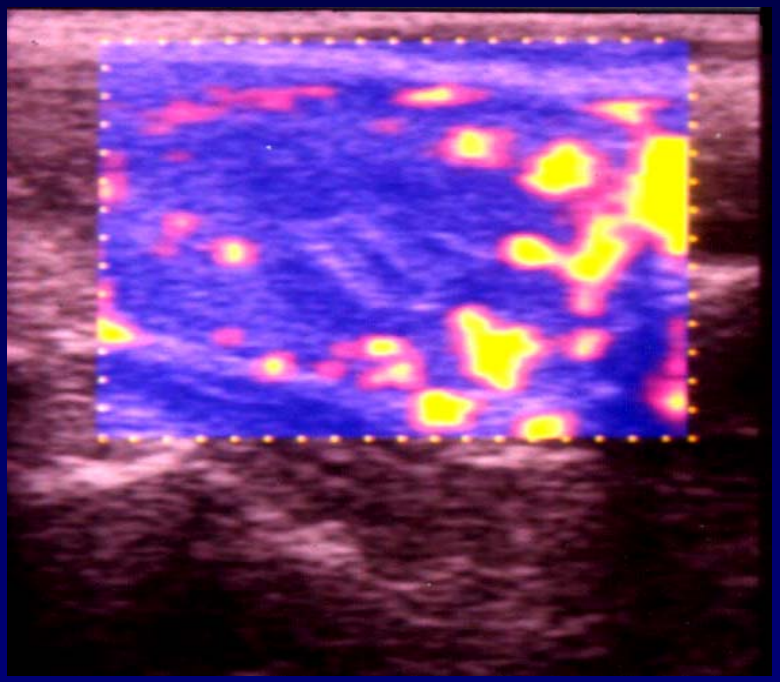


Macroscopic examination: cavitation area, rim of carbonization, coagulative necrosis, peripheral edema

US Changes after 1 week



- a small central hypoechoic area surrounded by a hyperechoic rim



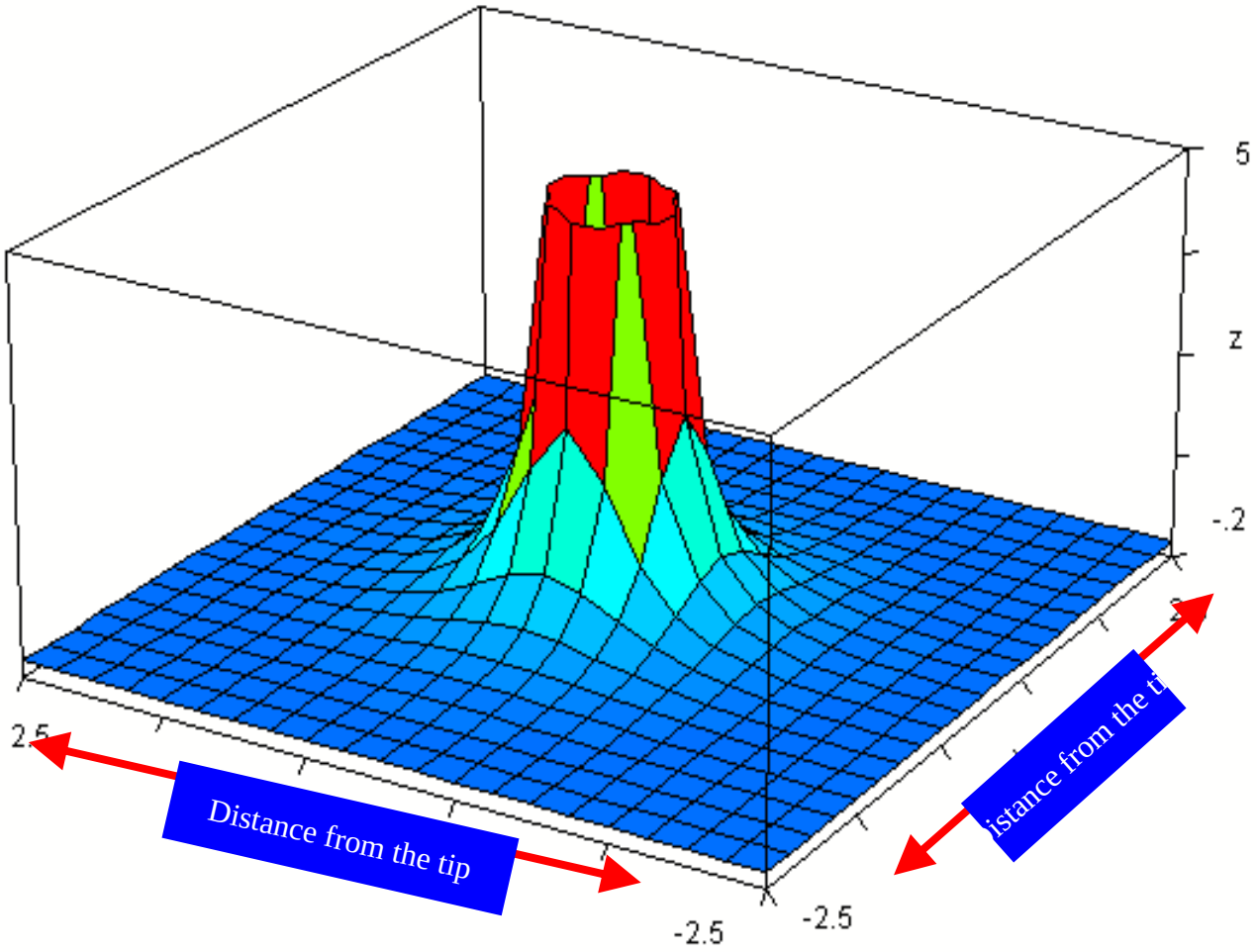
- an outer hypoechoic zone
- the loss of vascular signals at power-doppler evaluation

Clinical Studies Using PLA for Thyroid Nodules Ablation

	Cases	Follow-up (m)	Reduction
Dossing, et al (2002)	16	6	46%
Spiezia, et al (2003)	12	12	61%
Dossing, et al (2003)	1	9	59%
Pacella, et al (2004)	25	6	47%
Papini, et al (2004)	20	6	63% *
Dossing, et al (2005)	30	6	44% °
Amabile et al (2006)	23	3	36%
Dossing, et al (2006)	10	12	57%
Dossing, et al (2006)	30	6	45/58%

* multiple treatments; °randomized trial

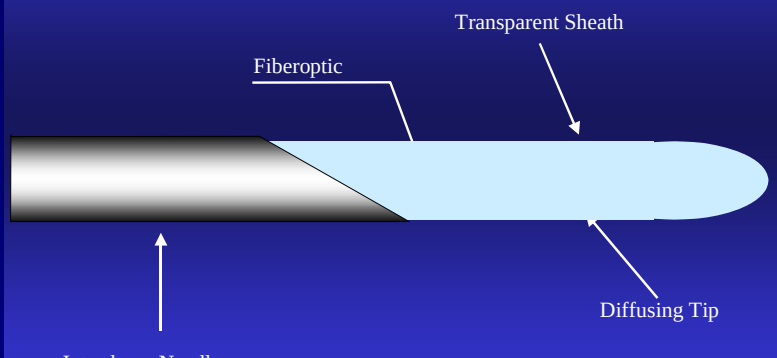
Energy Density as Function of the Attenuation Coefficient (K) and Spatial Decay



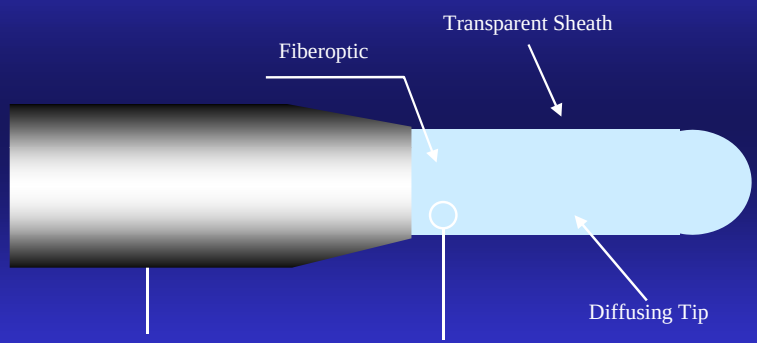
LASER Ablation: Possible Solutions

Multifiber Technique

Hot Cylindrical Tip



Cooled Cylindrical Tip



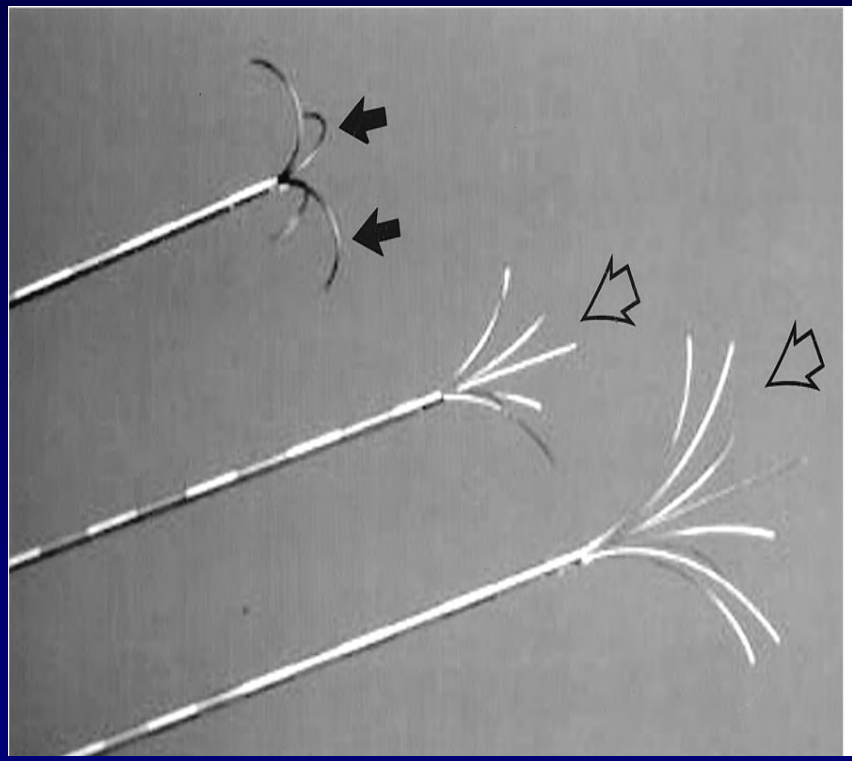
Mini-Invasive Thermal Ablation
Still unresolved problems

- Patient's compliance
- Geometric shape of thermal-induced damage and of the surrounding cervical structures
- Real-time assessment of the extension of thyroid tissue damage

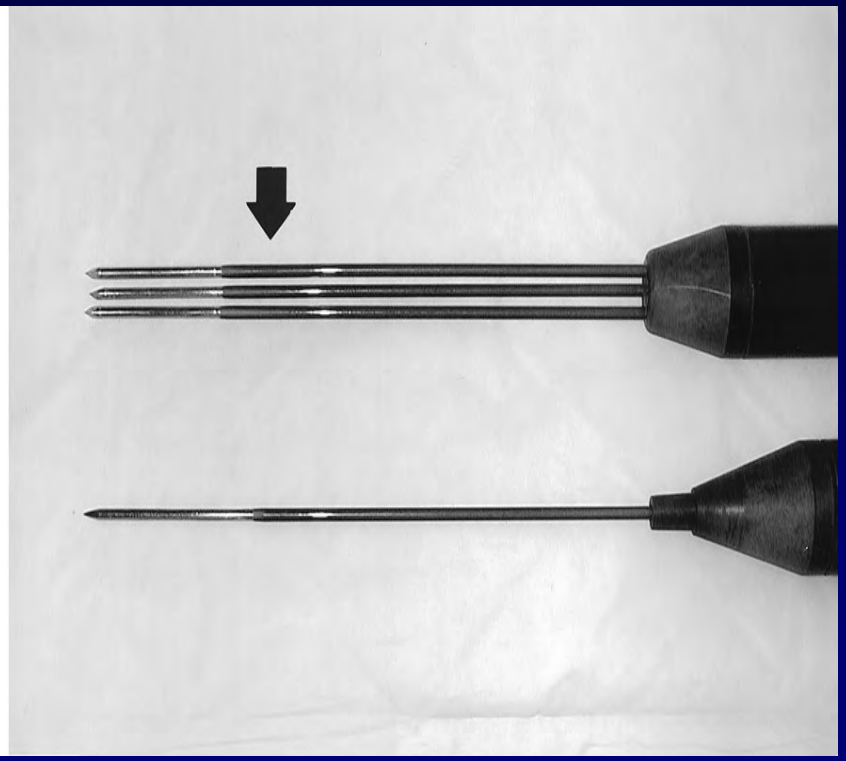
Radiofrequency Ablation

- A high-frequency alternating electrical current moves from the electrode into the tissue and causes ions to follow the changes in the direction of the alternating current
- The movement of the ions results in frictional heating of the tissue
- Monopolar probes are able to heat by ionic agitation within 2 mm of their surface, and tissue heating beyond this is due to heat conduction.

Radiofrequency: multiple sources technique



14-15G hook or umbrella needles



18G internally cooled needle

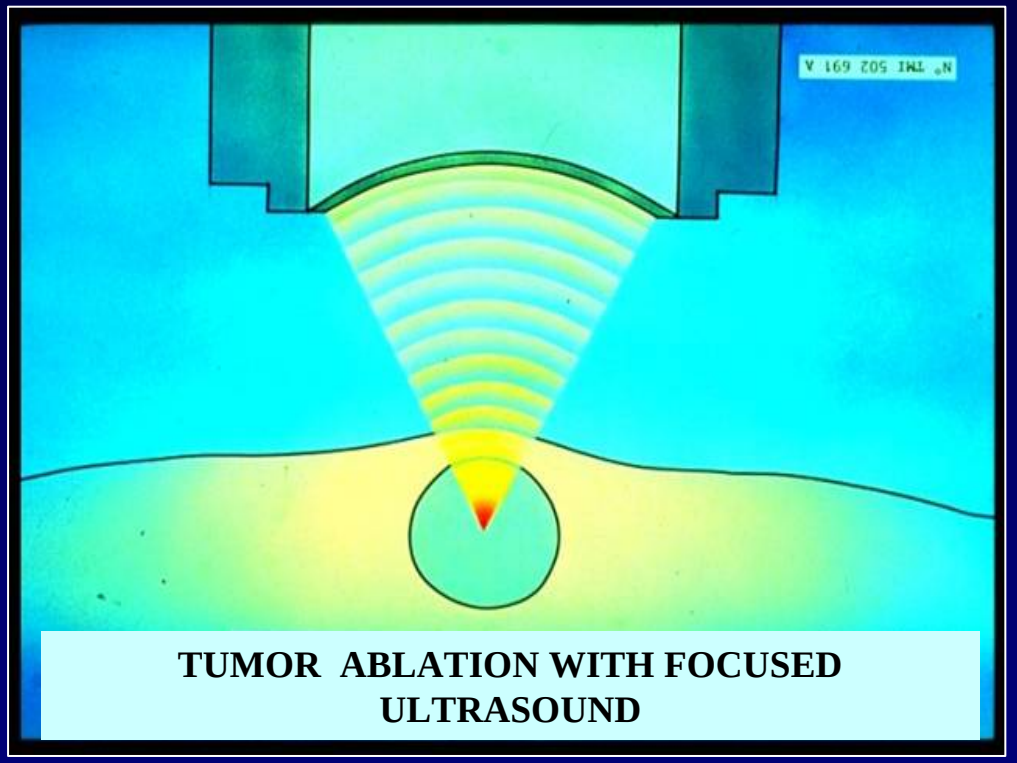
Radiofrequency Ablation of Benign Cold Thyroid Nodules: Initial Clinical Experience

- 35 cold nodules in 30 euthyroid patients
- RG ablation with a 1 cm-internally cooled electrode (17 gauge-needle, 8-25 minutes)
- 77% of cases treated with conscious sedation
- Median follow-up: 6.4 months
- Volume change: from 23.8 to 45.8%
- One case of vocal cord palsy (permanent?)

Kim Y-S et al, Thyroid 2006; 16: 361-7

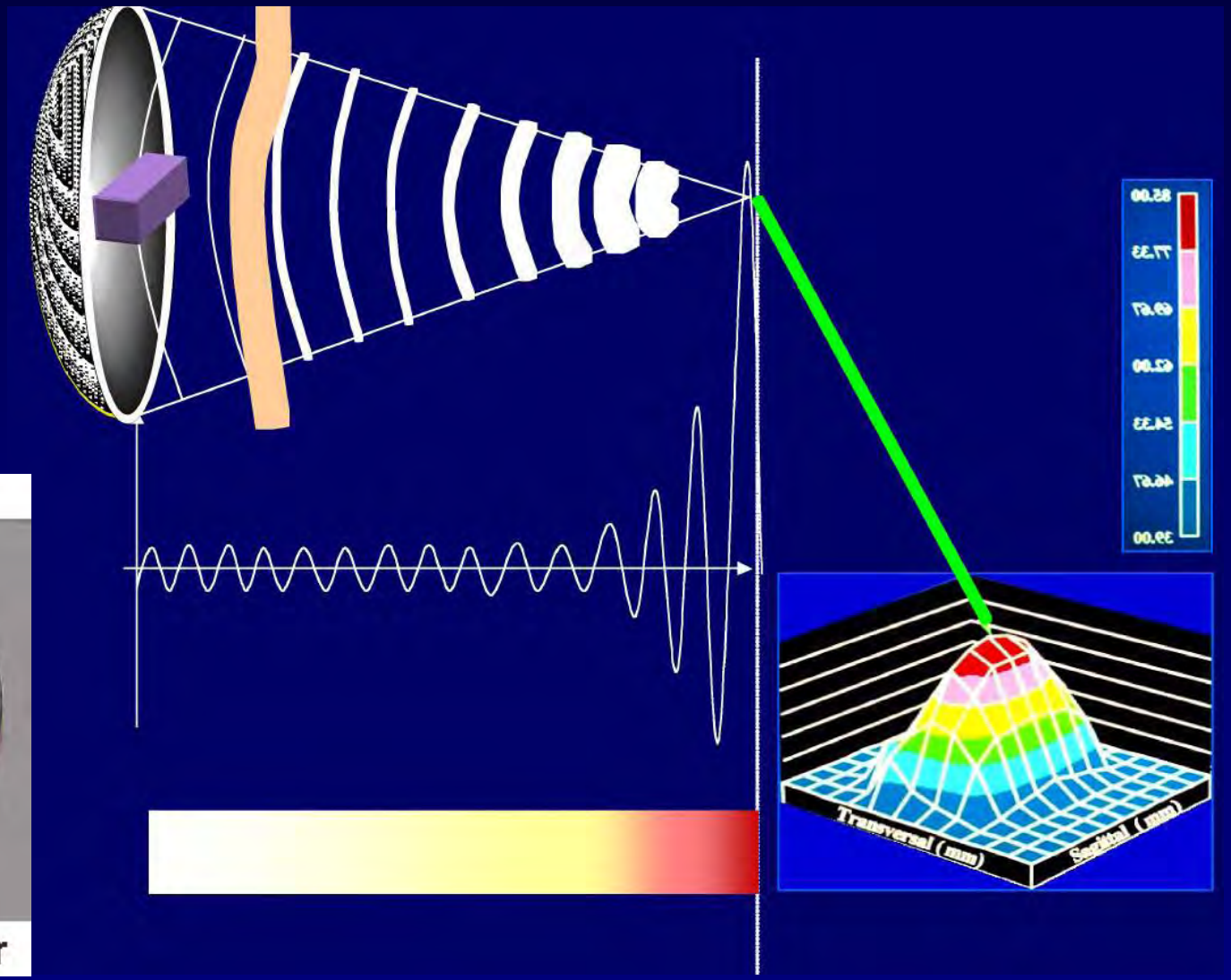
Highly Focused Ultrasound

- Ultrasound tightly focused into the body
- Production of regions of high energy density
- Tissue destroyed without damage to overlying or intervening structures



Courtesy of O. Esnault, 2005

HIFU: Principles of Action



Requirements for a Nonsurgical Ablation of Thyroid Nodules

- Non-invasive or minimally invasive
- Possibility of repeated treatment
- Reproducible
- Other treatment options still possible in case of failure
- Rapid and Inexpensive
- Safe & Effective

State of the Art

- Currently, no available method satisfies all the requirements of an ideal ablation system
- Among thermal methods, only PLA has been extensively tested on both experimental and clinical grounds on thyroid lesions
- In the near future, new imaging and targeting systems will probably improve the safety, efficacy and reproducibility of mini-invasive procedures

Verona, Oct 27-29 2006 – 3 rd AME-AACE Joint Meeting

Laser Thermal Ablation in Clinical Practice

Roberto Valcavi

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Past President, Italian Association of Clinical Endocrinologists (AME)

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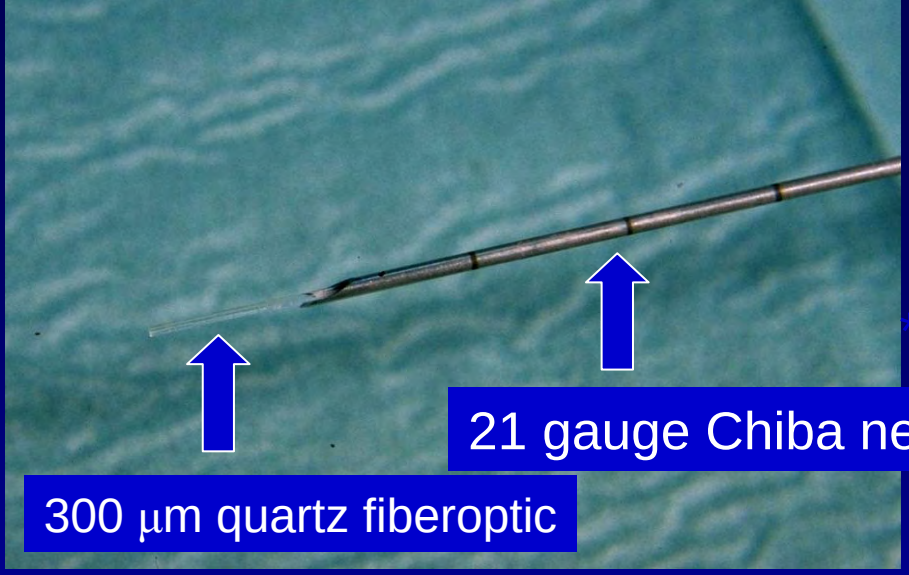
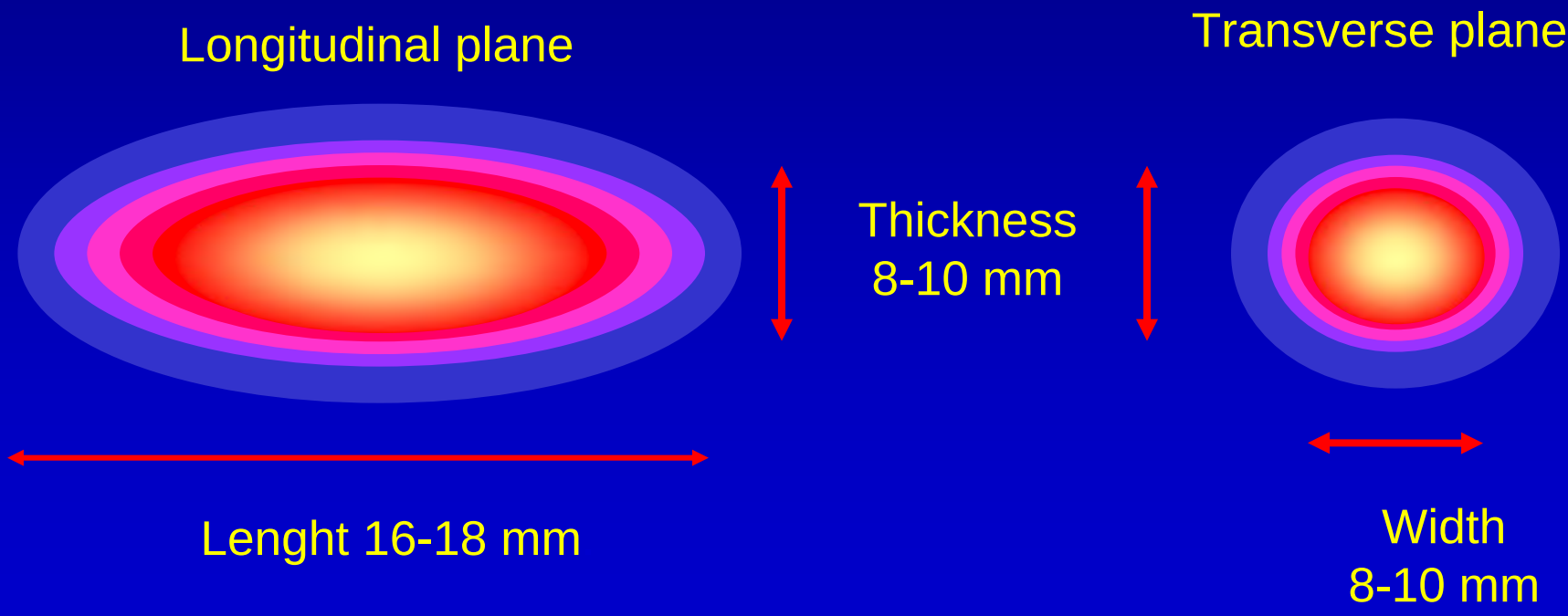
Flat Tip Technique

Single Ablation Diameters

* Continuous operating Nd:YAG LASER 3 W, 1800 J.





Modified, from C.M. Pacella

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Clinical Research

Low-Energy Interstitial Laser Photocoagulation for Treatment of Nonfunctioning Thyroid Nodules: Therapeutic Outcome in Relation to Pretreatment and Treatment Parameters

Gerardo Amabile,[1*] Mario Rotondi,[4*] Giovanni De Chiara,[2] Antonio Silvestri,[1] Bruno Di Filippo,[1] Antonio Bellastella,[3] and Luca Chiovato[4]

Published online before print July 5, 2006
The British Institute of Radiology, doi: 10.1259/bjr/40698061

The British Journal of Radiology

Beneficial effect of combined aspiration and interstitial laser therapy in patients with benign cystic thyroid nodules: a pilot study

[1]H DØSSING, MD, [2]F N BENNEDBÆK, MD, PhD and [3]L HEGEDÜS, MD, DSc

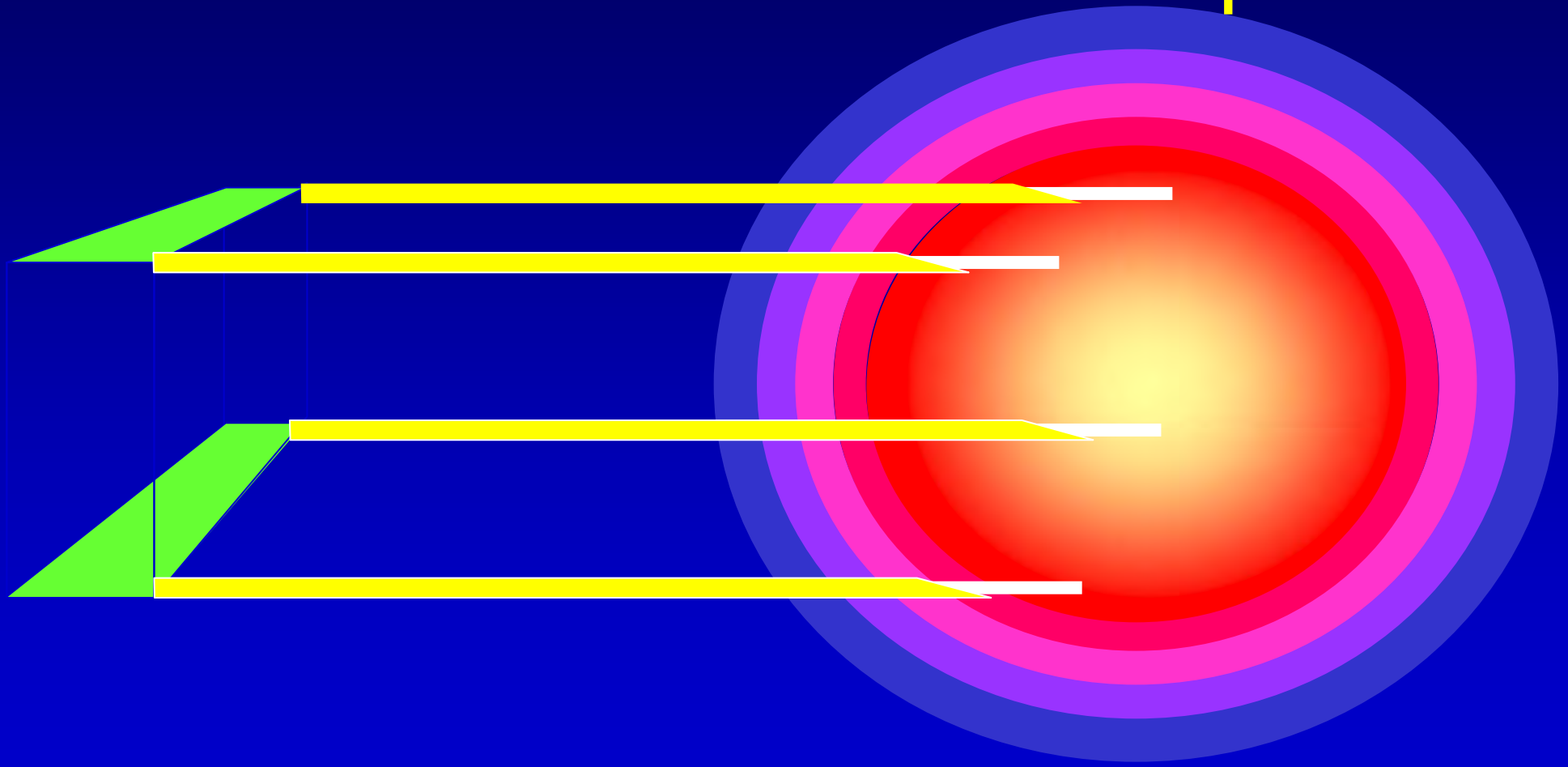
[1]*Department of Oto-rhino-laryngology and Neck Surgery, Odense University Hospital,* [2]*Department of Endocrinology and Metabolism, Herlev University Hospital and* [3]*Department of Endocrinology and Metabolism, Odense University Hospital, Denmark*

THYROID
Volume 16, Number 8, 2006

Effect of Ultrasound-Guided Interstitial Laser Photocoagulation on Benign Solitary Solid Cold Thyroid Nodules: One versus Three Treatments

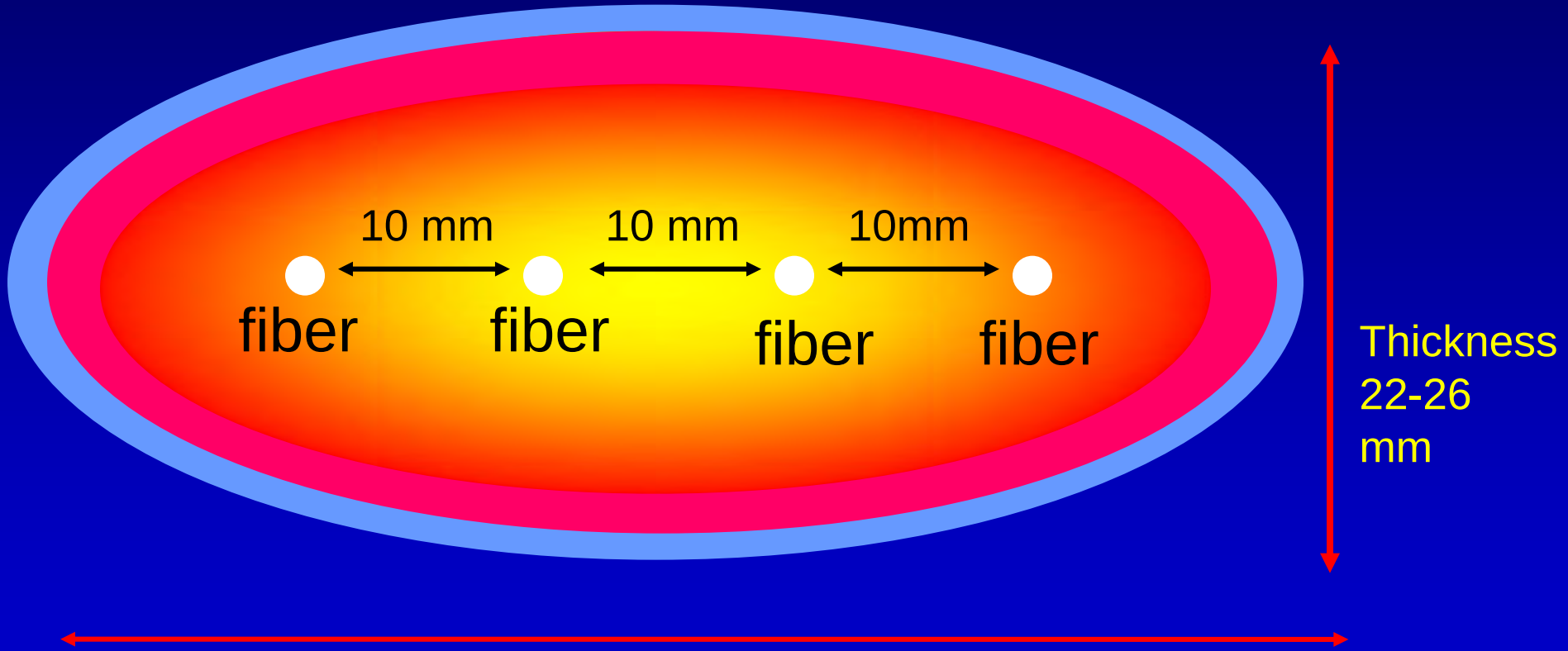
Helle Døssing,[1] Finn Noe Bennedbæk,[2] and Laszlo Hegedüs[2]

How to Increase Ablation Volume
LTA : Multifiber Technique



C.M. Pacella

PLA: Ellipsoid Multiple fiber technique



Continuous operating Nd:YAG LASER 3-4 W, up to 6000 J/fiber

Roberto Valcavi

Percutaneous Laser Ablation (PLA) in benign thyroid nodules

Valcavi R, Pesenti M, Bertani A, Frasoldati A, Formisano D

Endocrine Unit & Thyroid Disease Center, Arcispedale Santa Maria Nuova,
42100 Reggio Emilia, Italy.

Aim: evaluation of feasibility, efficacy and safety of PLA on benign thyroid nodule size reduction and thyroid function

- **with the multiple-fibers technique**
- **in a single shot-single procedure**

Methods 1*

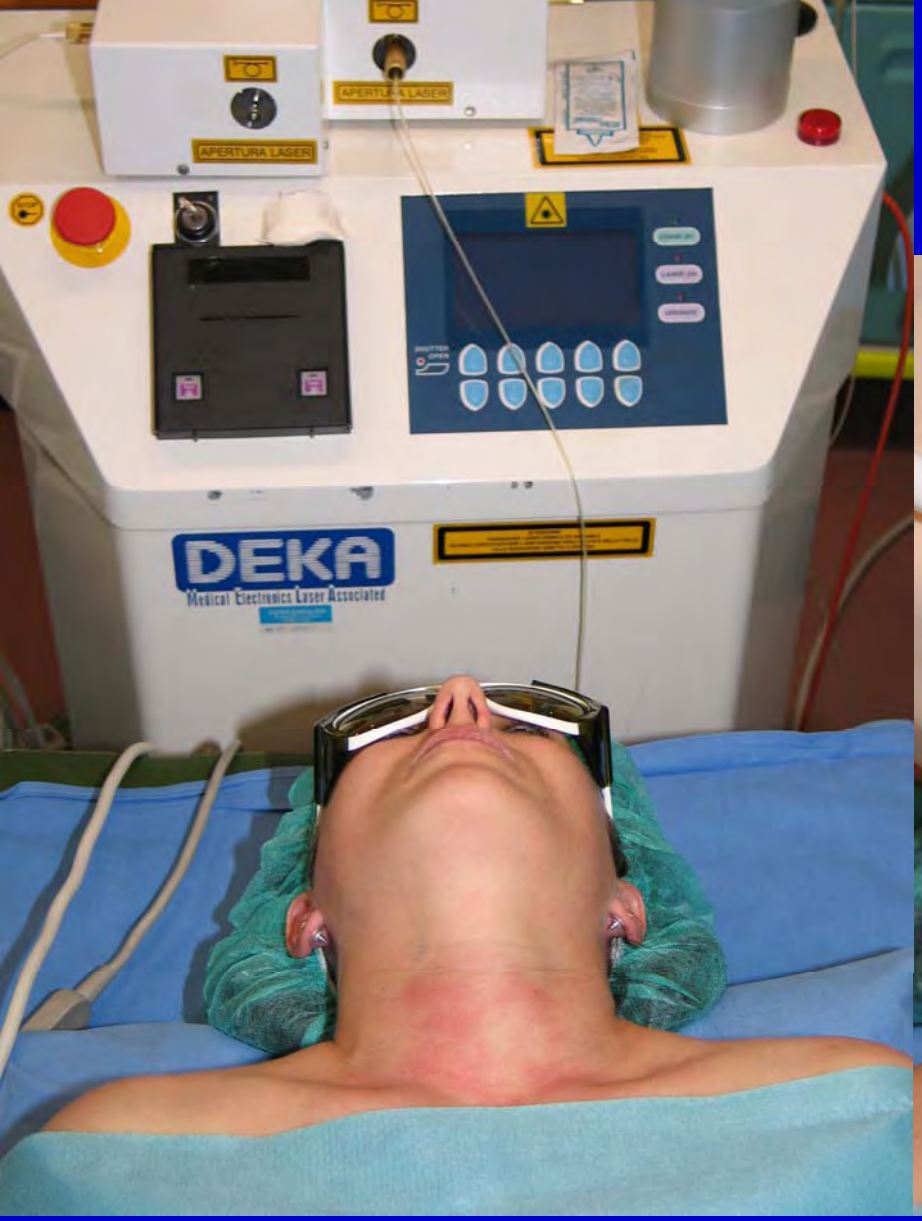
Patients	119 (M 23 F 96)
Age	55.8 ± 13.3 years
Cytology	benign hyperplasia
No. of PLA session	single
No. of optic fibers	1-4
Energy delivered	7060 ± 4299 J (1062–22200 J)
Energy delivered/ml	420 ± 334 J (105-2705 J)
Output power	2-4 Watts (2.9 ± 0.5 W)
Treatment time	19 ± 8 min
Pre-treatment vol	24.8 ± 21.1 ml (1.3-104 ml)

**mean ± SD*

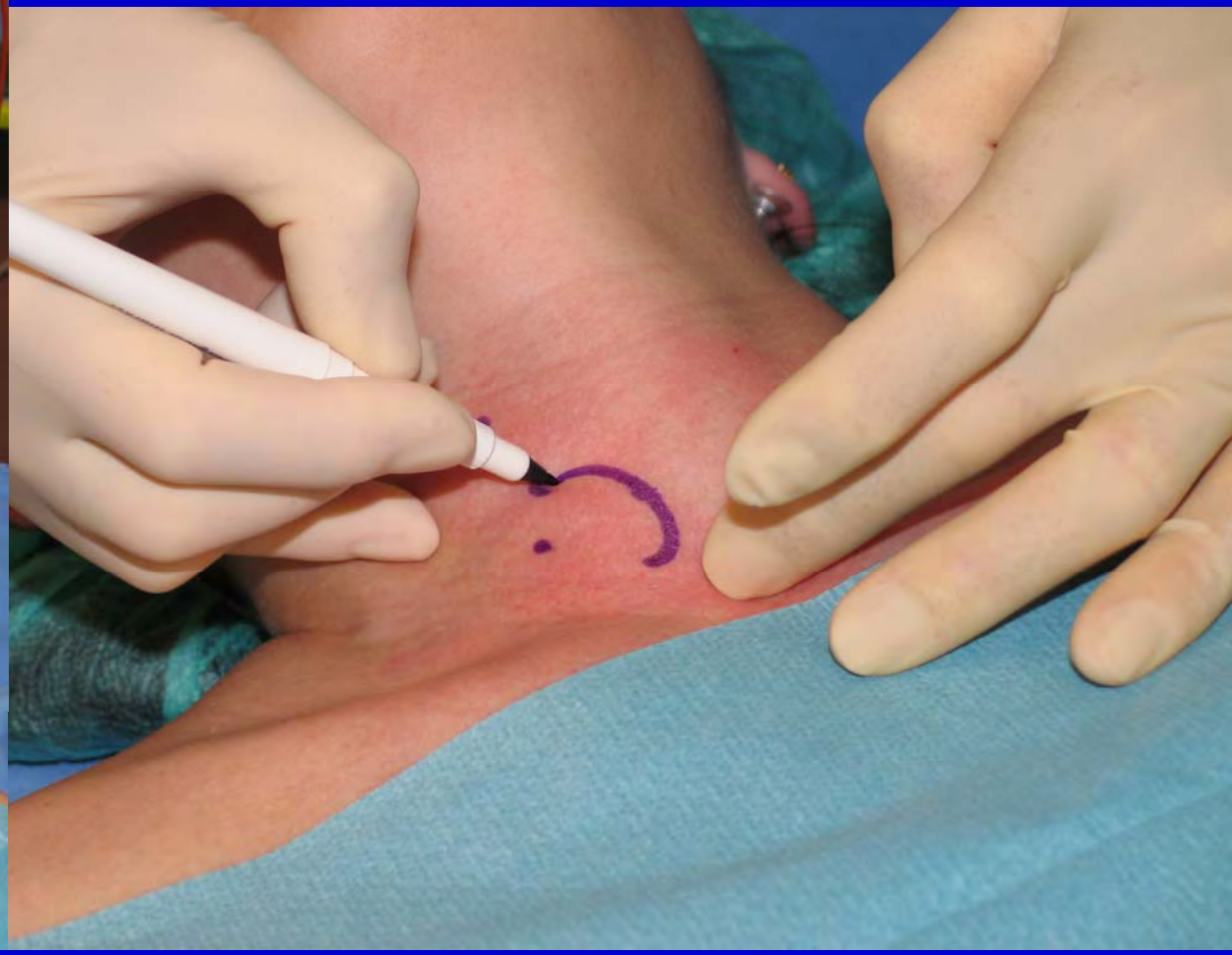
Methods 2

- **Nodule** US features
  size (ml)
  necrosis (ml)
- **Lab tests** TSH, fT3, fT4, Tg, antiTg & antiTPO ab
- **Side effects** pain, others
- **Symptom score** (1-3)
- **Cosmetic score** (1-3)

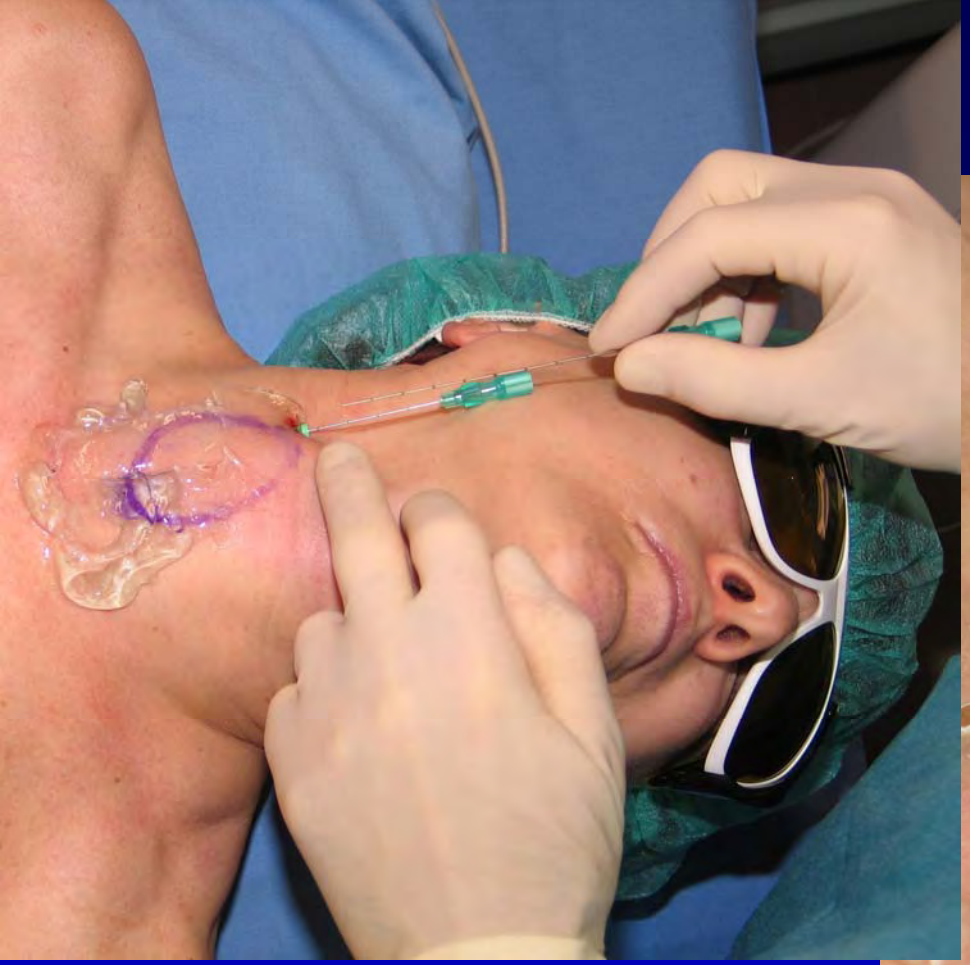
were recorded at baseline and during 1 year follow-up (days 1-7-30-90-180-360)

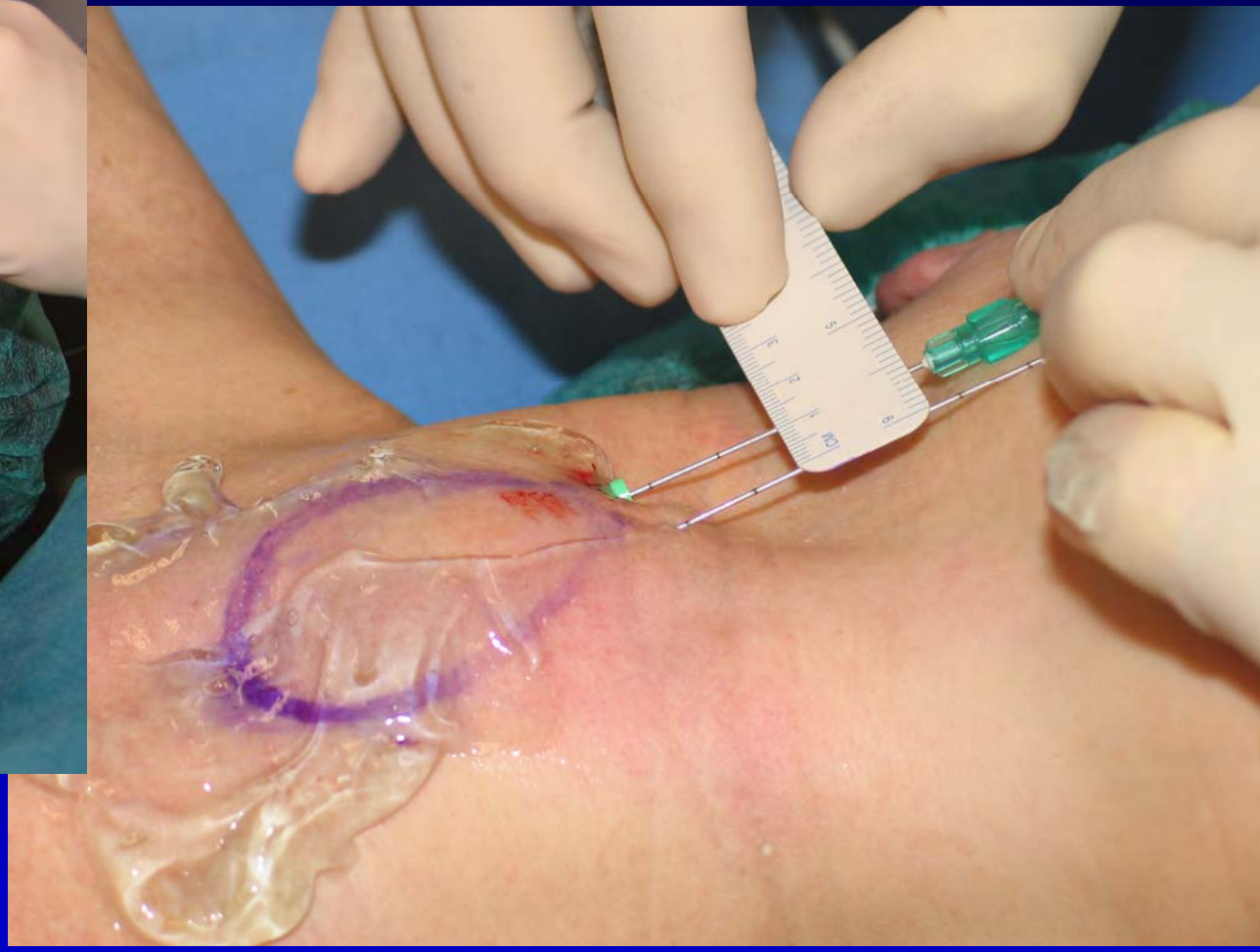


Patient placement

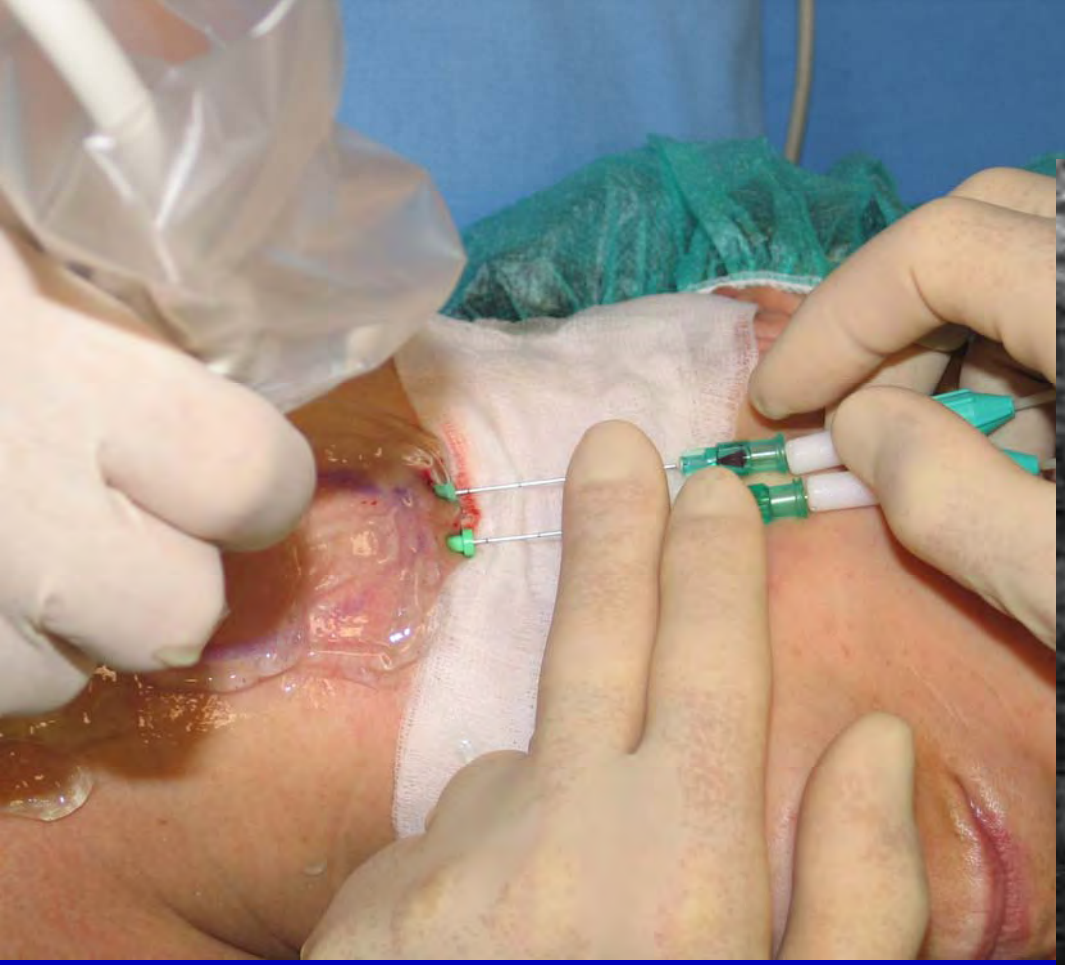


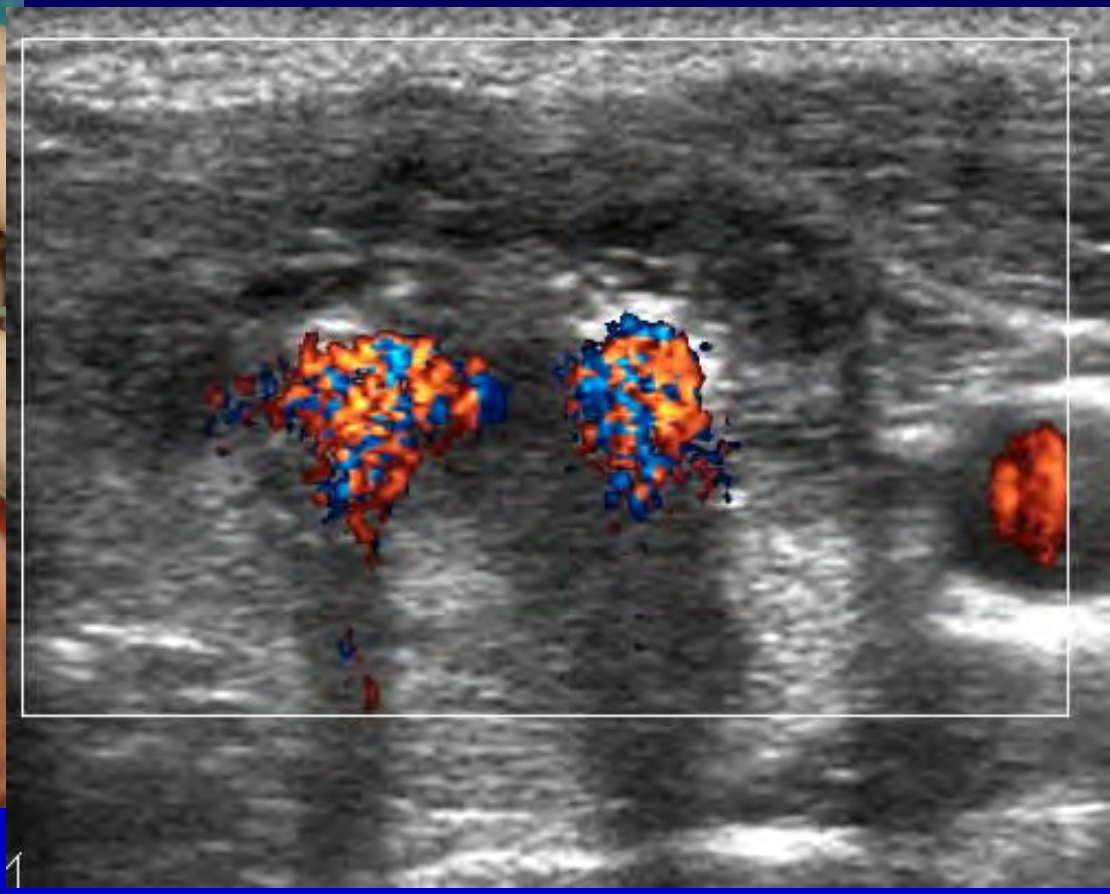
Nodule delimitation





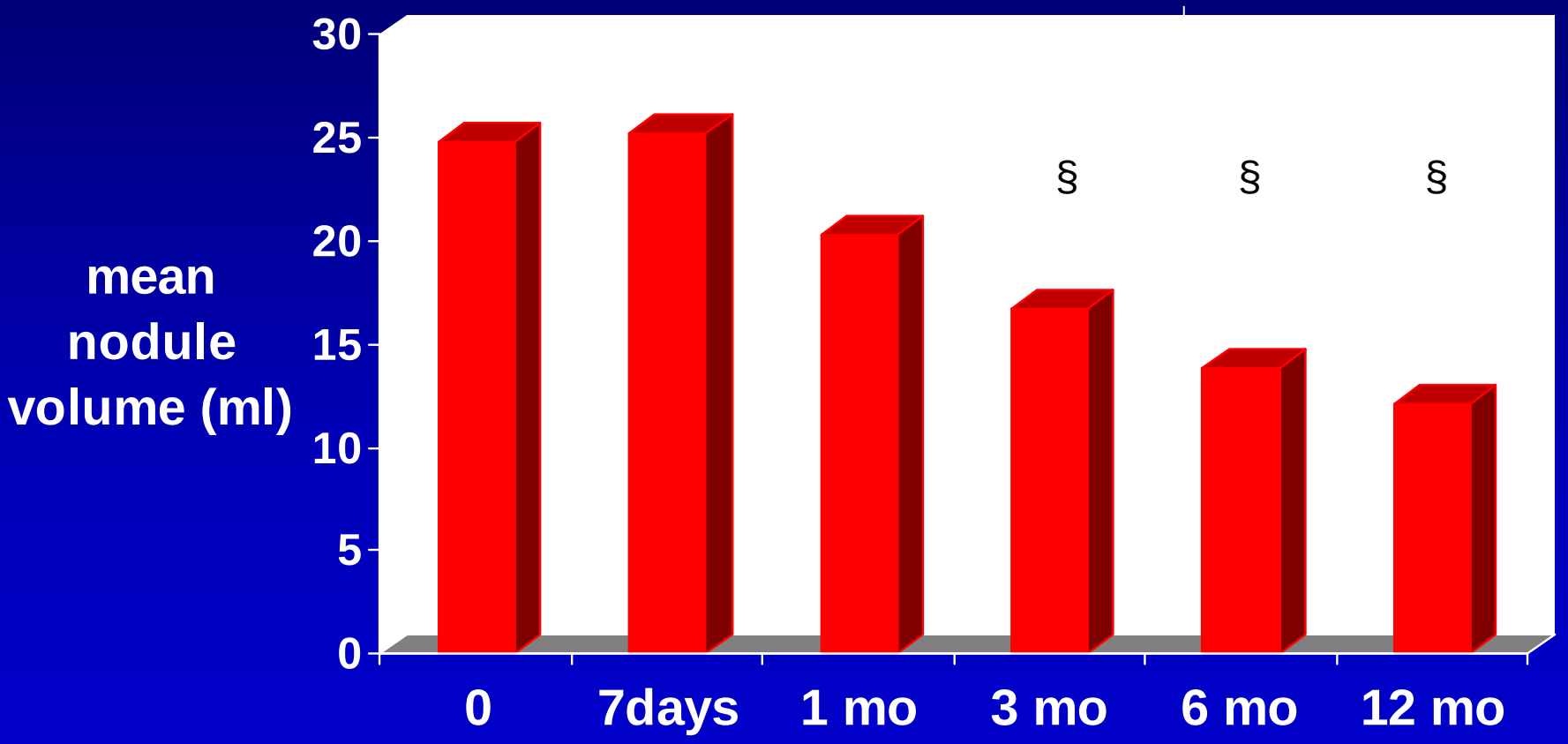
Needle manual placement at 10 mm distance





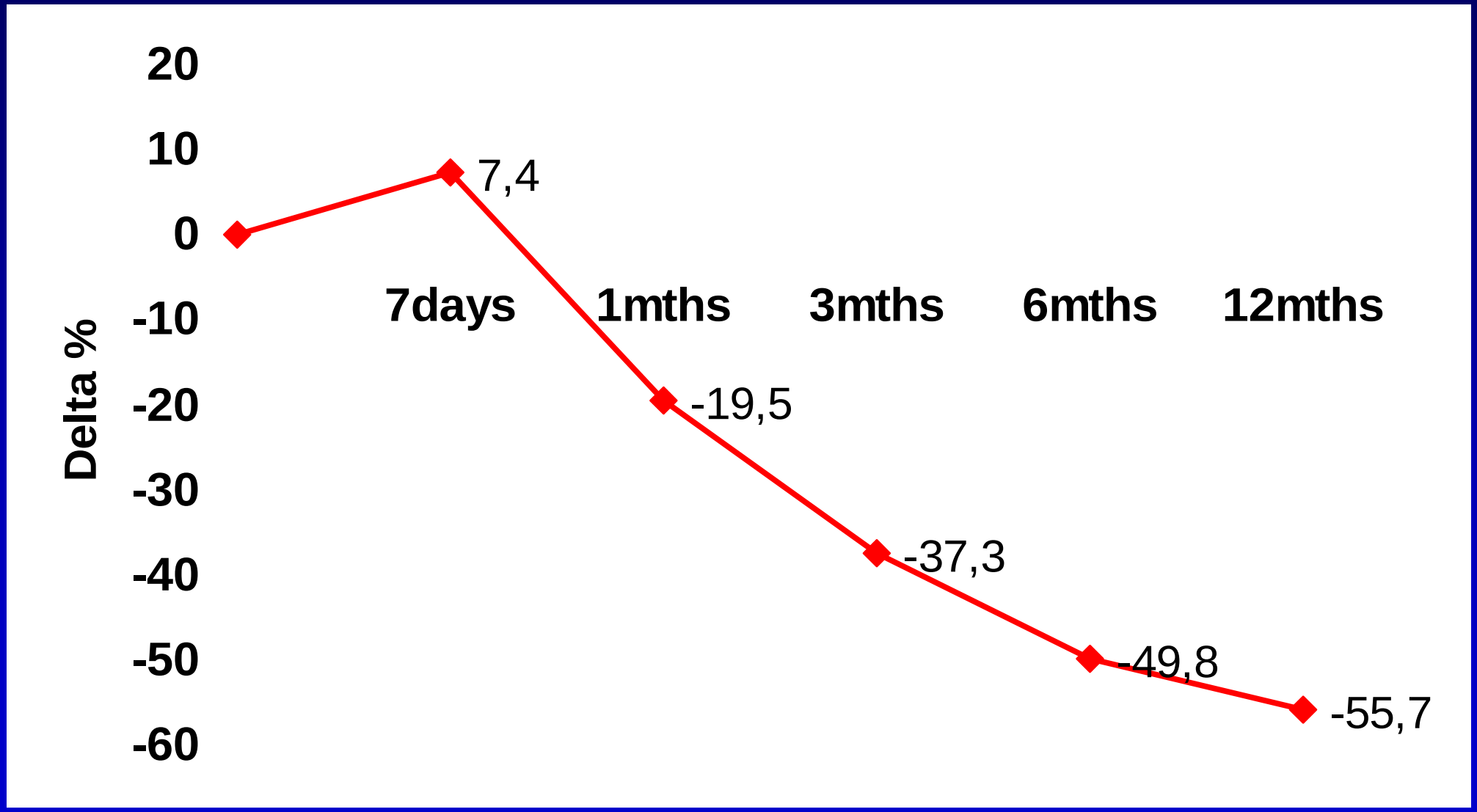
Fibers insertion and US image of laser firing

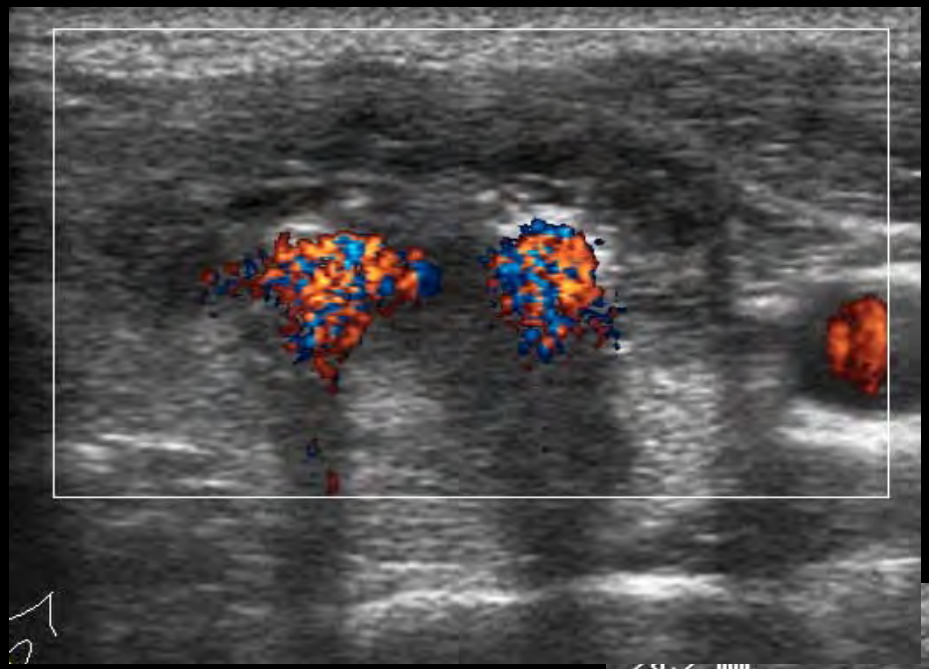
Mean nodule volume after PLA



T test Paired Samples § p =0.001 vs baseline

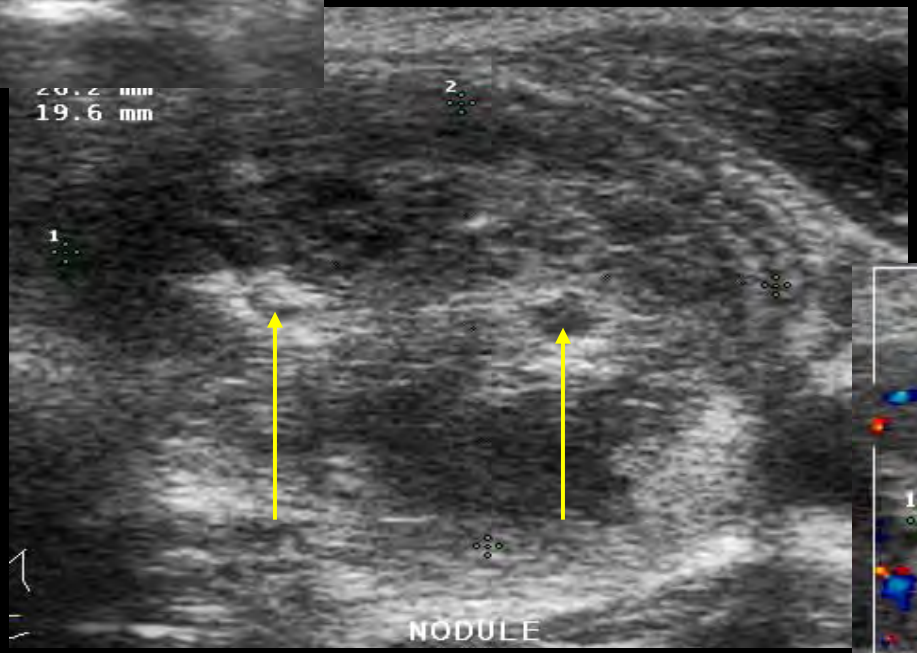
% volume reduction (Delta Δ %) after PLA





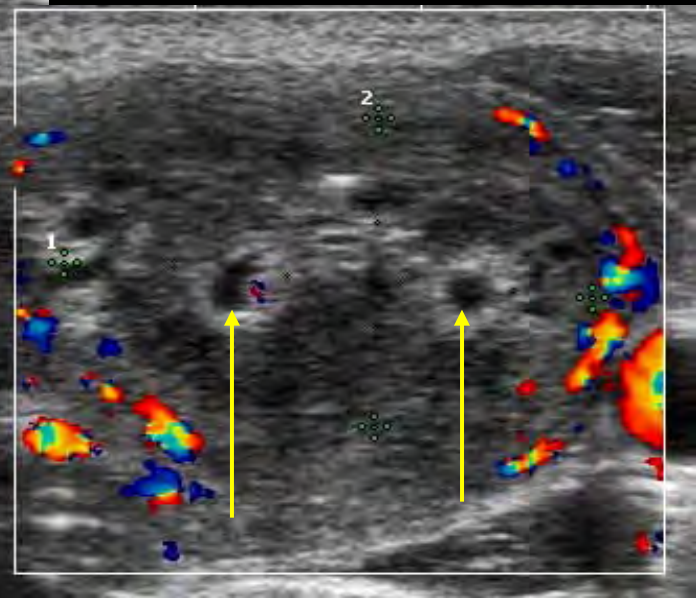
LTA session

12000, 3 W, 2 fibres
27 x 17 x 40 mm
Volume 9.5 ml

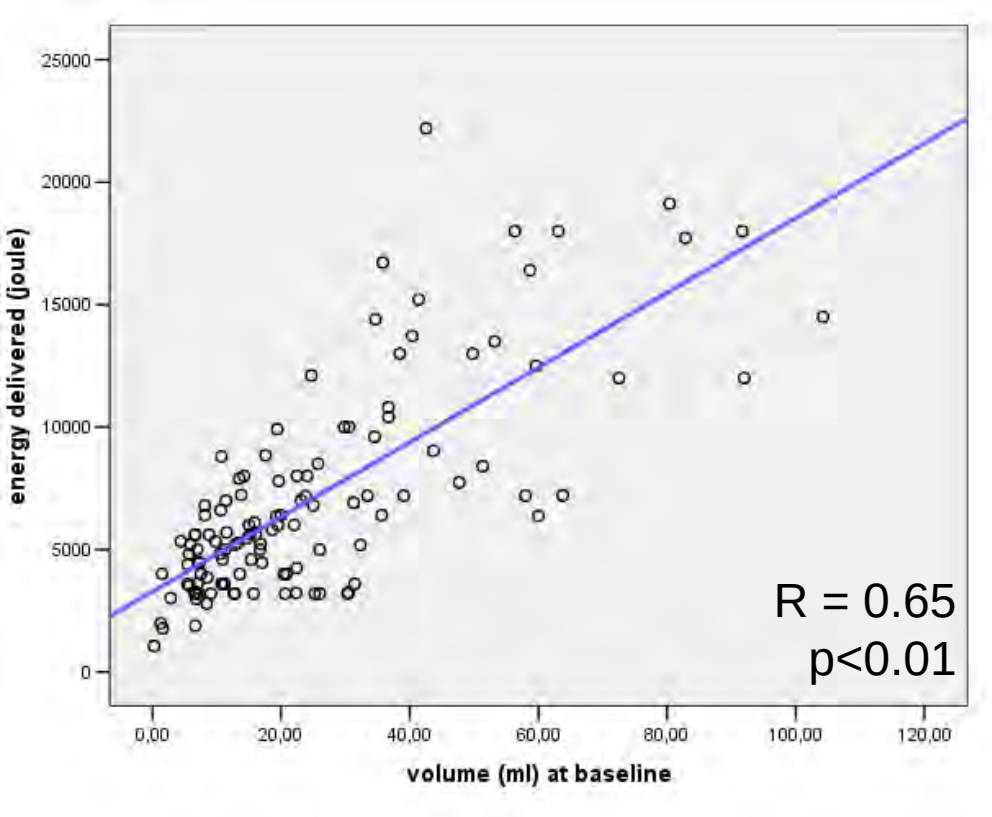


7 days
Ablation : 73%

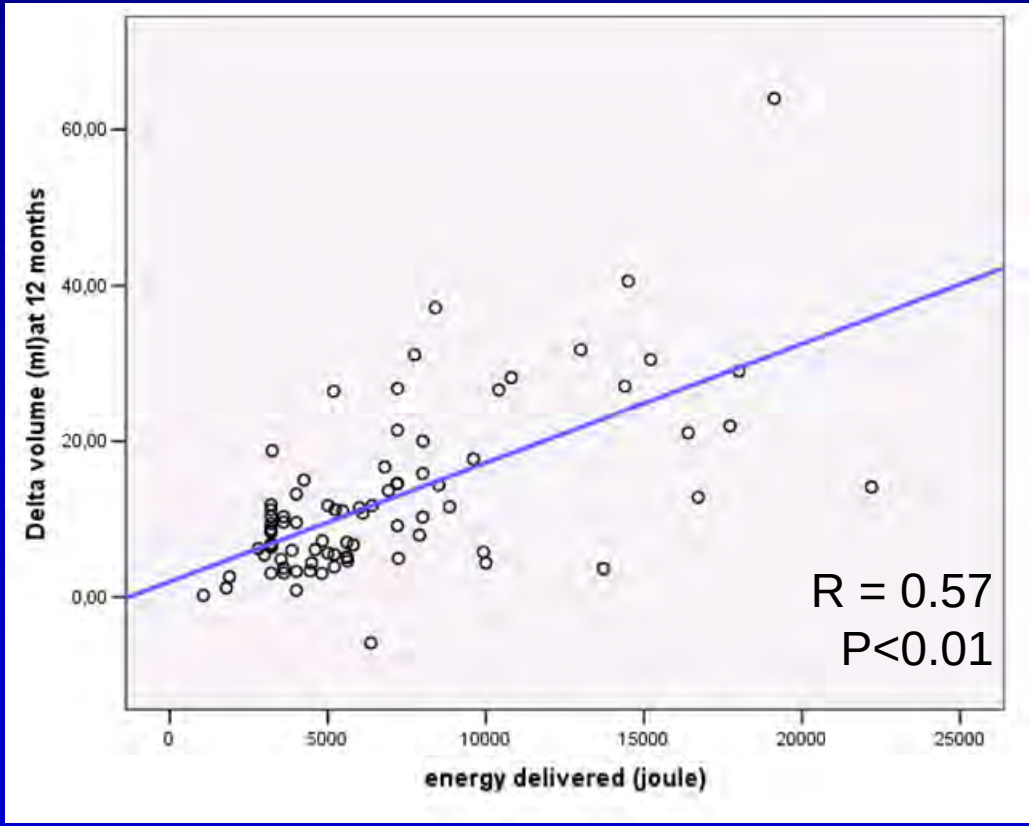
1 month



Correlation b/t energy delivered (J) and initial volume (ml)



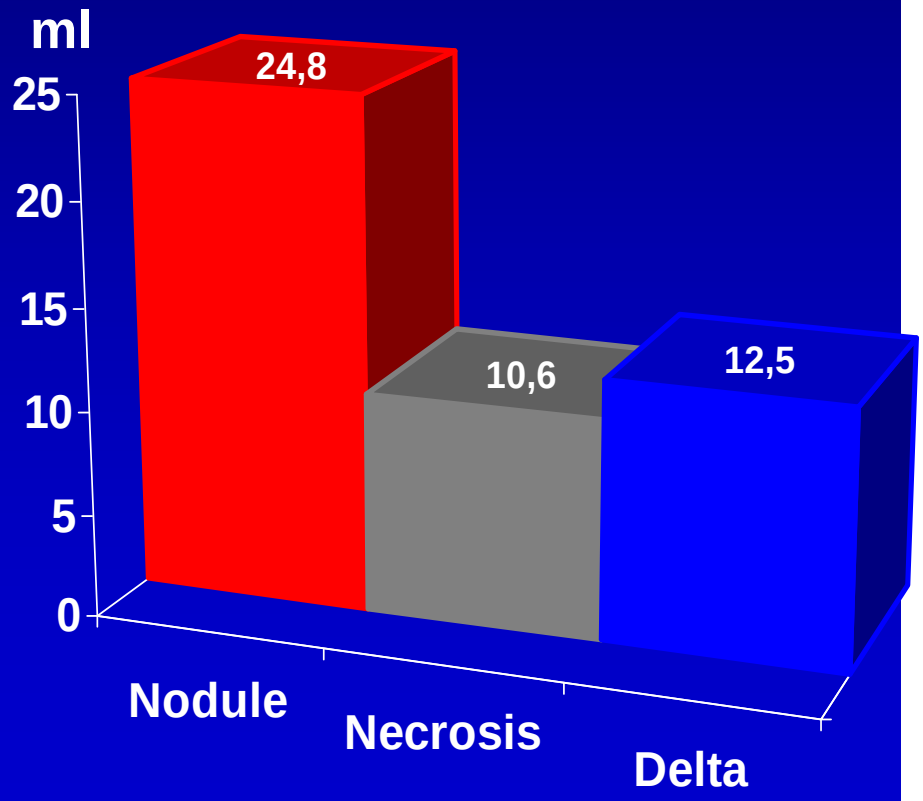
Correlation b/t energy delivered (J)and ∆ ml volume at 12 months

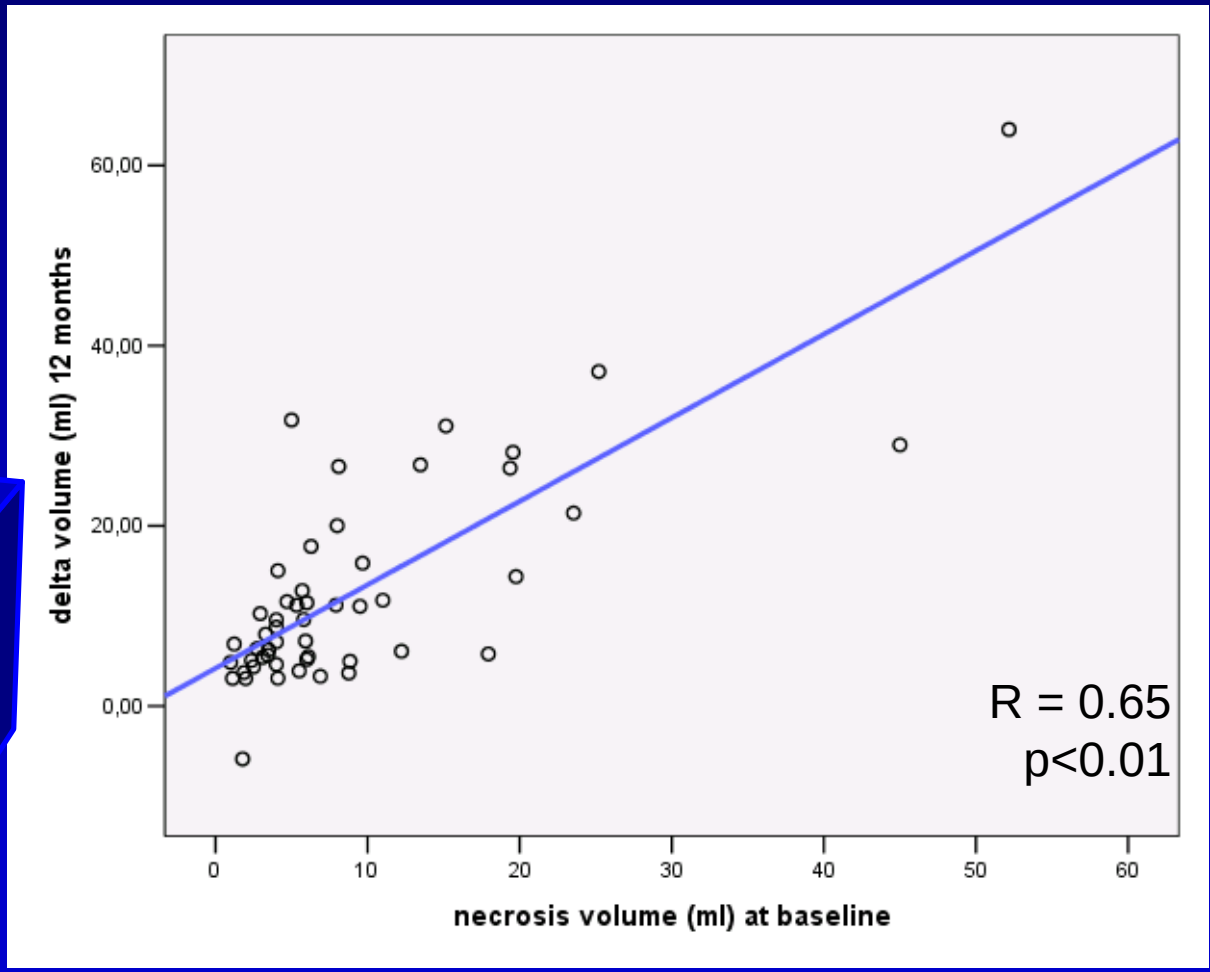


Δ% at 12 months according to US features

Variable	Mean Δ %	p
Hypo	57,02	0.78
Iso	55,67	
Solid	53,9	0,6
Mixed	65,1	
Elipse	61,08	0,001
Irreg	40,11	
Calcif.	51,65	0,32
None	57,76	

Correlation between Necrosis volume at baseline (ml) and Nodule reduction (Δ ml) at 12 months





Baseline volume distribution

n° 119; mean 24.8ml ± SD 21,1

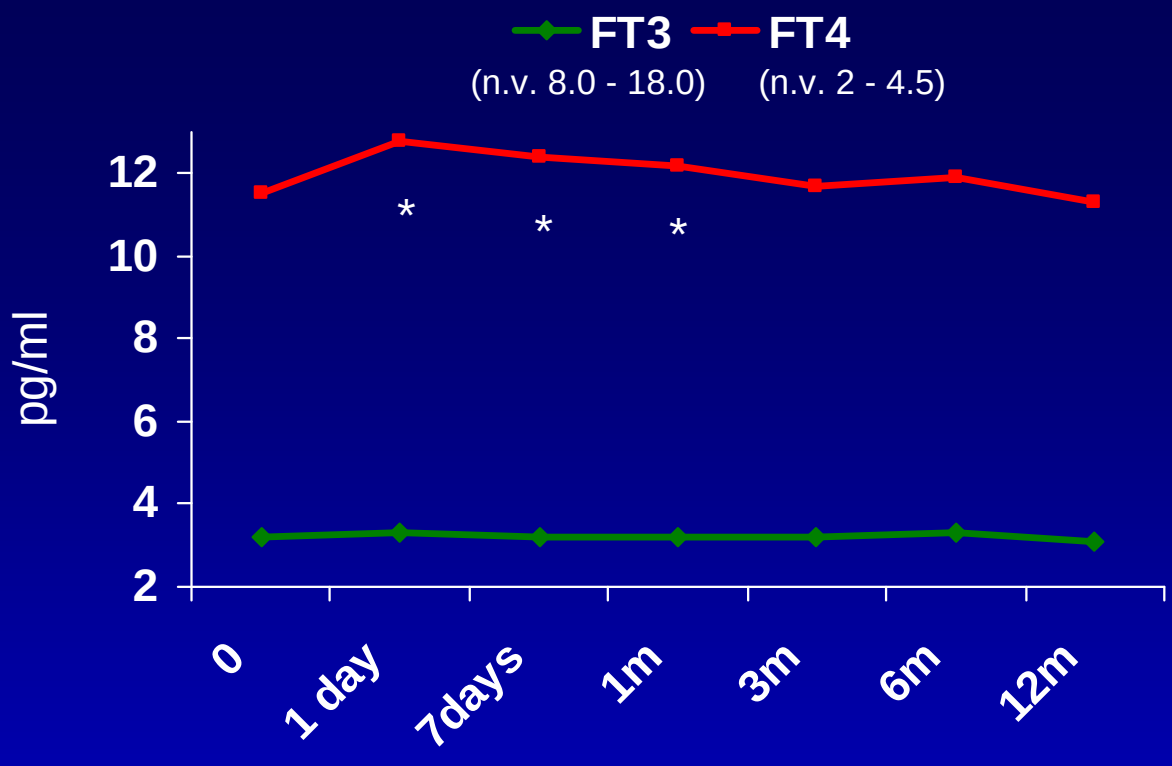
		Baseline
Class 1 small	**25 % n.29**	1.25 - 9.66 ml **mean 6.3 ml**
Class 2 medium-small	**50 % n.30**	9.67 - 18.09 ml **mean 13.4 ml**
Class 3 medium-large	**75 % n.30**	18.1 - 33.7 ml **mean 24.6 ml**
Class 4 large	**>75% n.29**	33.8 - 104.2 ml **mean 55.3 ml**

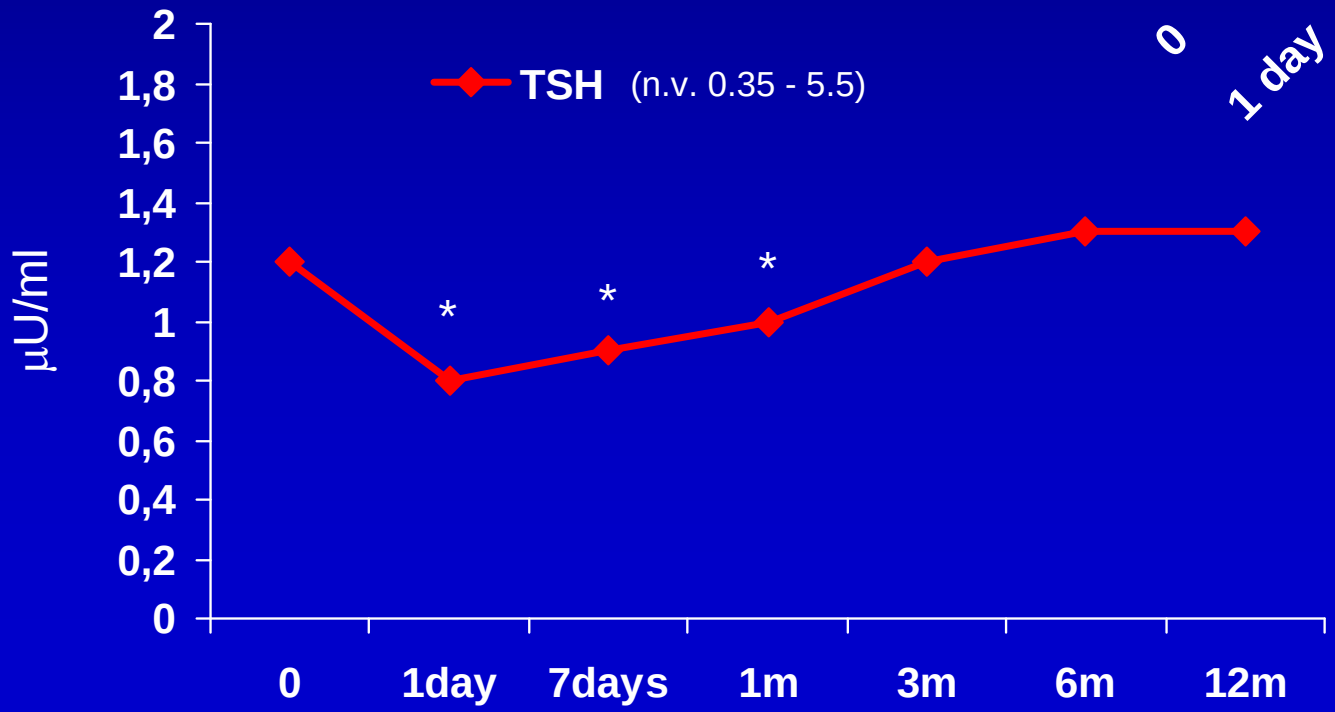
Mean Delta (Δ ml and Δ %) volume changes over time

	Baseline		6 months		12 months	
	Nodule ml	Necrosis ml	Δ ml	Δ %	Δ ml	Δ%
Class 1 25°	6.3	3.7	3.7	59.0	4.3	66.0
Class 2 50°	13.4	7.2	7.3	55.4	8.7	61.3
Class 3 75°	24.6	10.2	10.9	44.0	11.9	46.8
Class 4 >75°	55.3	23.4	21.8	40.6	25.3	49.9

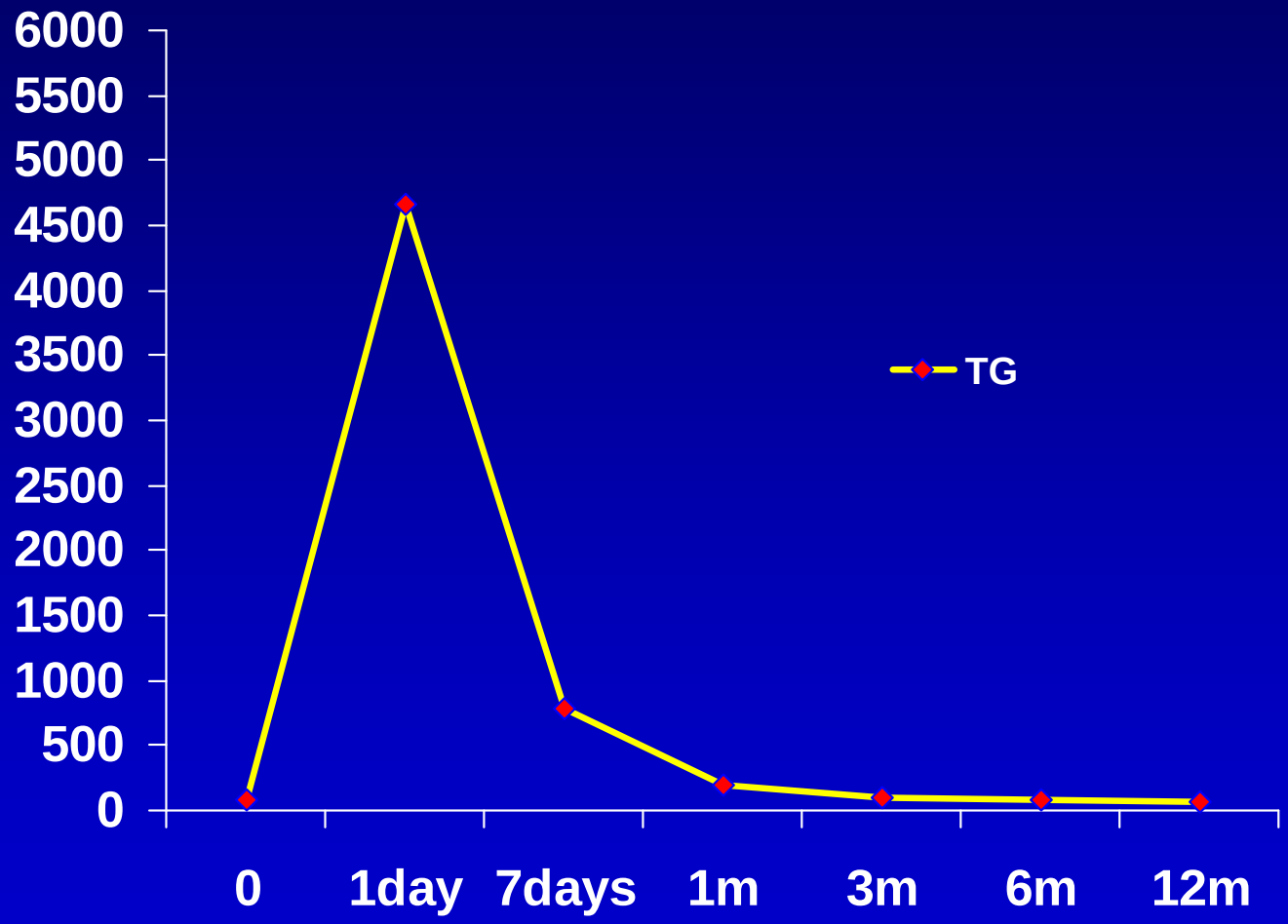
TSH, FT3, FT4 after PLA

T test Paired Samples
* p =0.001 vs baseline

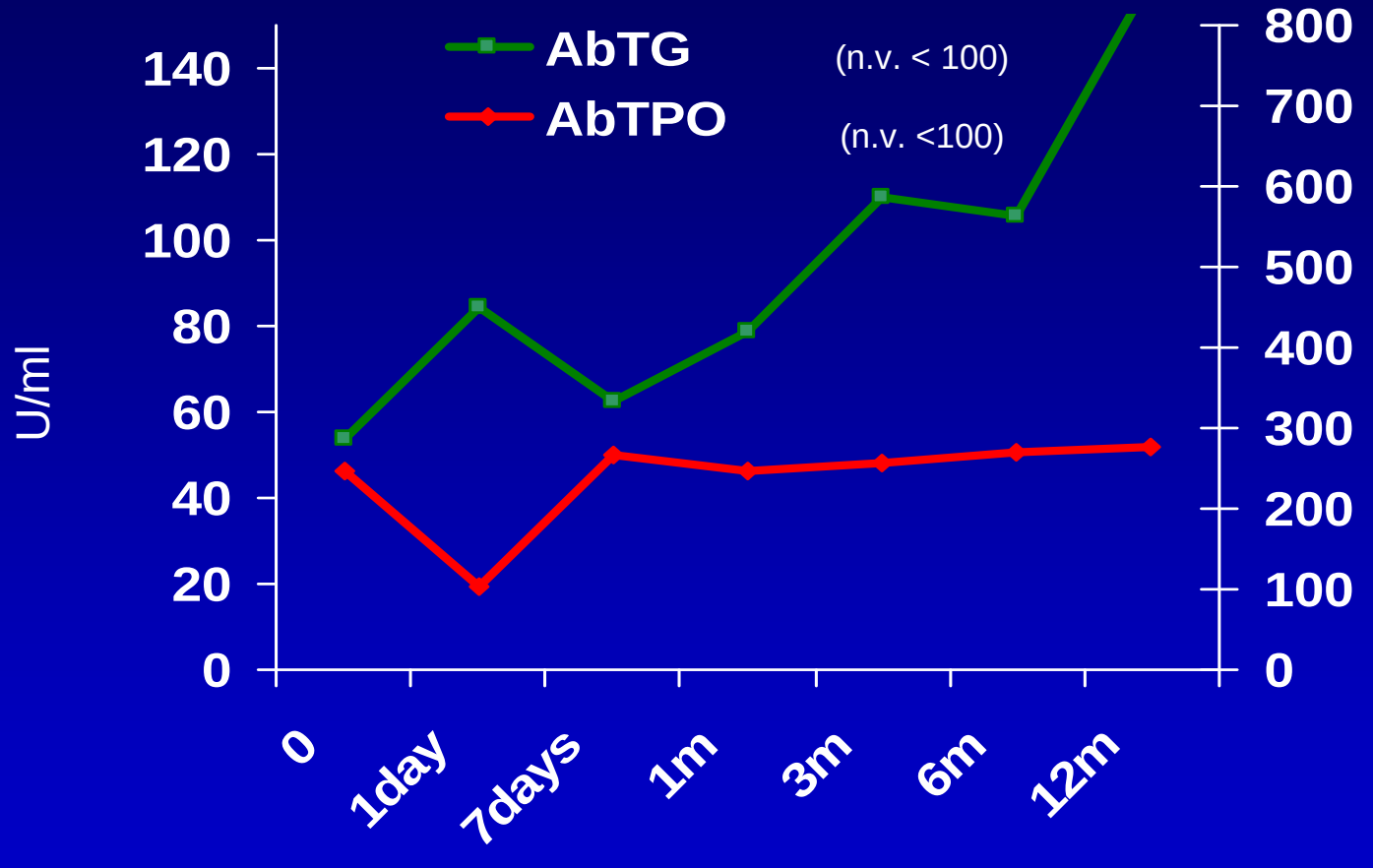




Plasma Tg levels

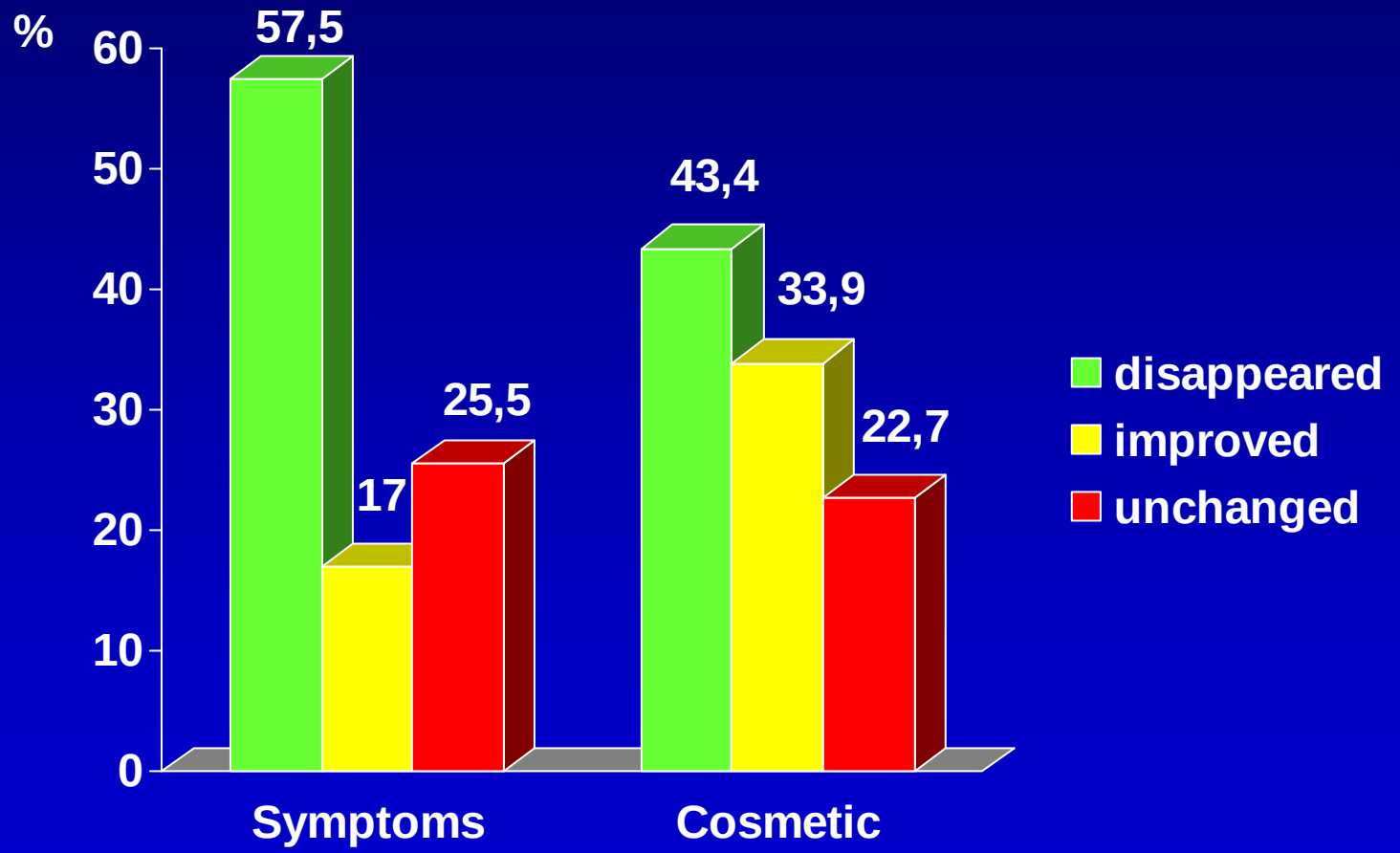


AbTg e AbTPO afer PLA



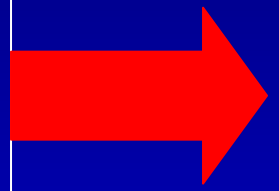
- Negative AbTg at baseline → 5.5% pos at 12 months
- Negative AbTPO at baseline → 0% pos at 12 months

Symptom and cosmetic score at baseline *vs* 12 months



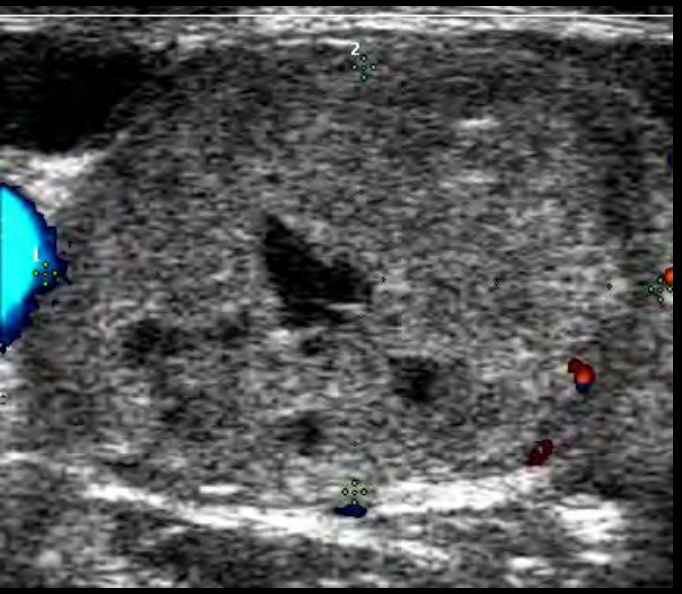
Side effects

- **none n. 76 (63.9%)**
- **cervical pain n.36 (30.3%)**
- fever n. 4
- hematoma n.1
- skin burn n.1



- **slight n.33 (91.7%)**

- **intense n. 3 (8.3%)**



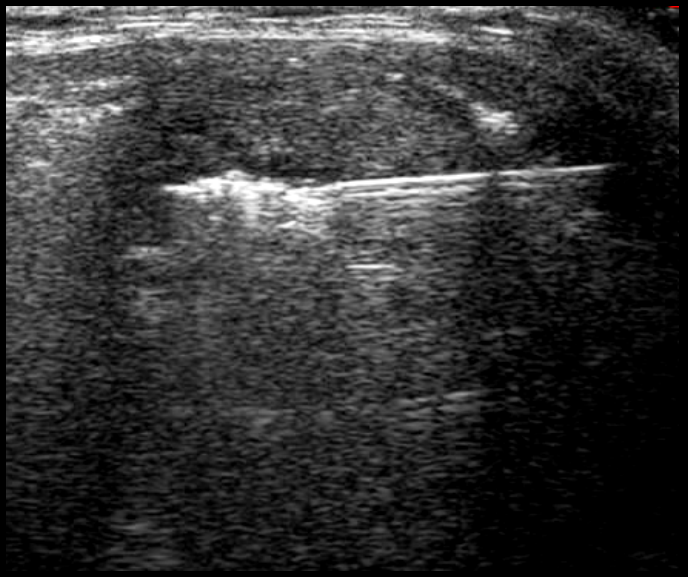
Transverse sections

Pre-treatment

Ø T x AP x L =

25 x 19 x 27 mm

Volume: ml 6,66

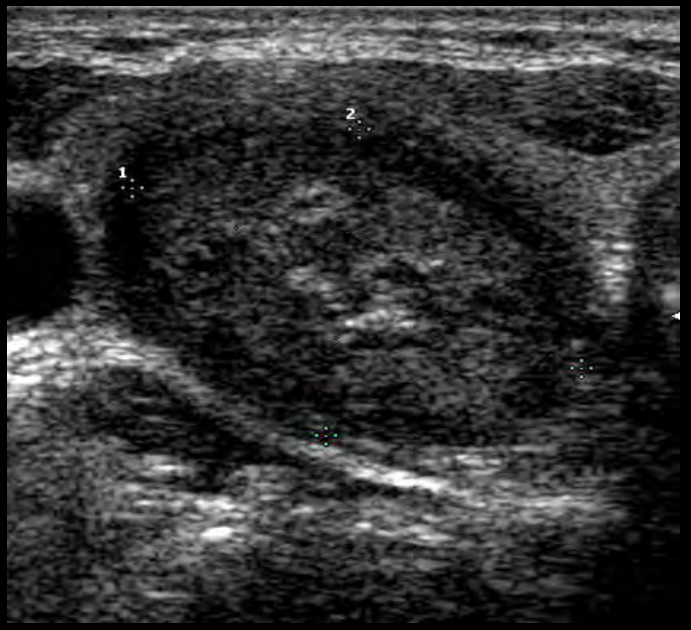


Laser

3 W, 2 Fibres,

6000 Joules

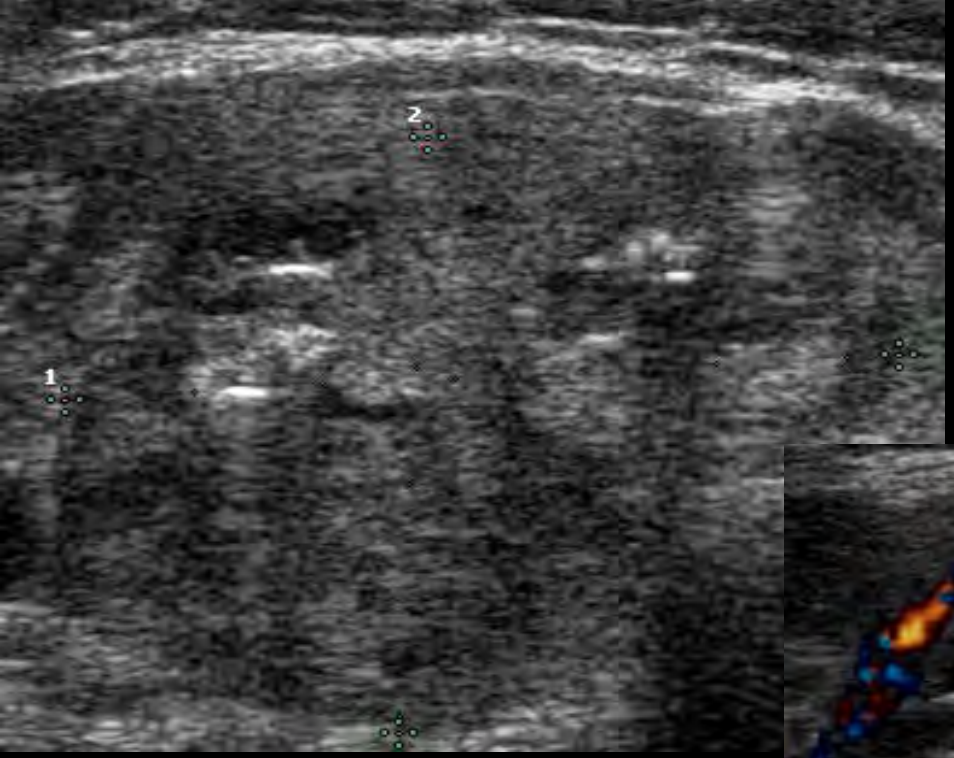
Ablation 92 %



2 Months

Volume: ml 3,5

Reduction 48%

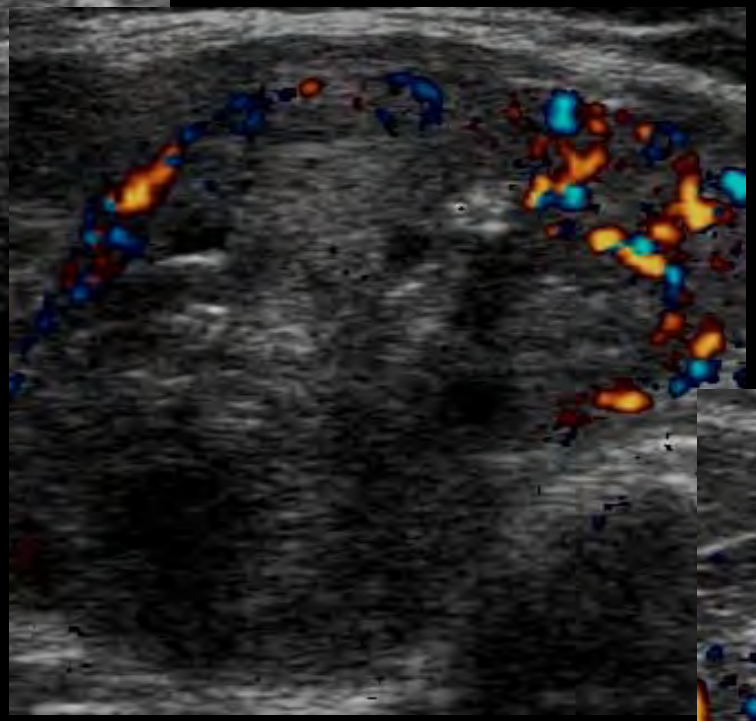


PLA

30x35x44mm

volume 24 ml

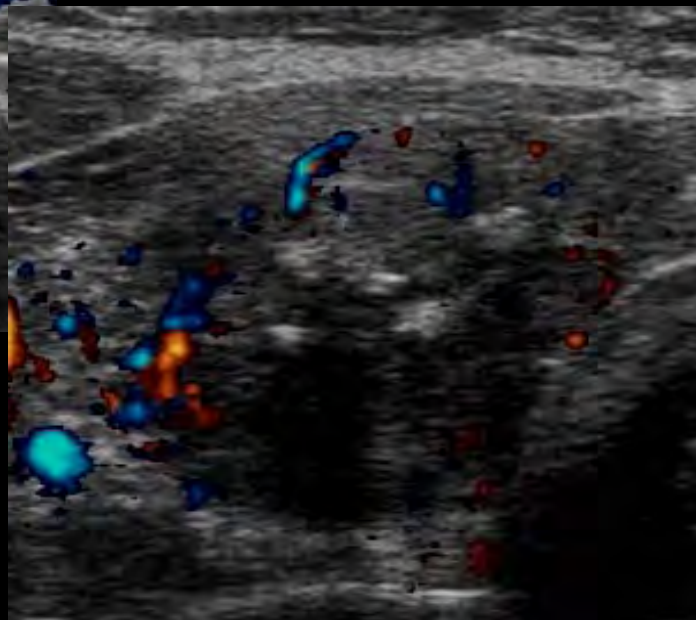
8000 J, 4 W, 2 fibres



12 months

19x17x2 mm

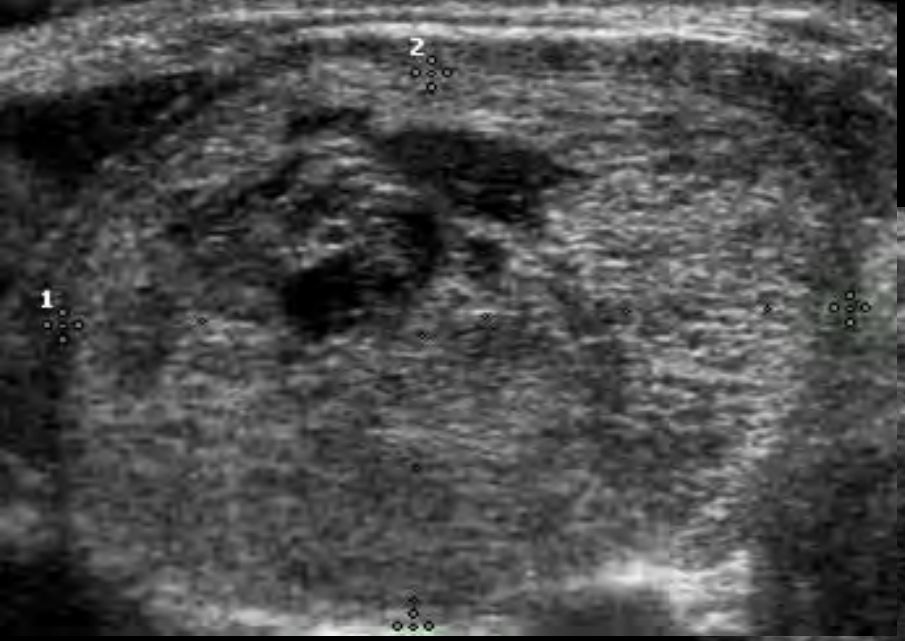
volume 3.7 ml, -85%



1 month

27 x 25 x 45 mm

Volume 15.7 (-34.6 %)



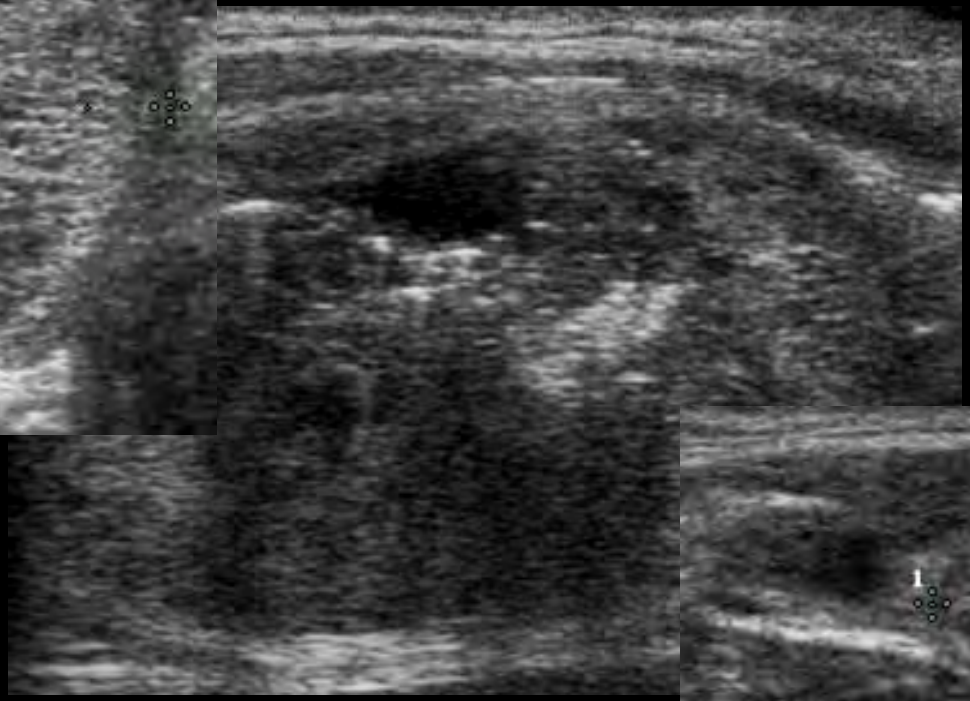
PLA

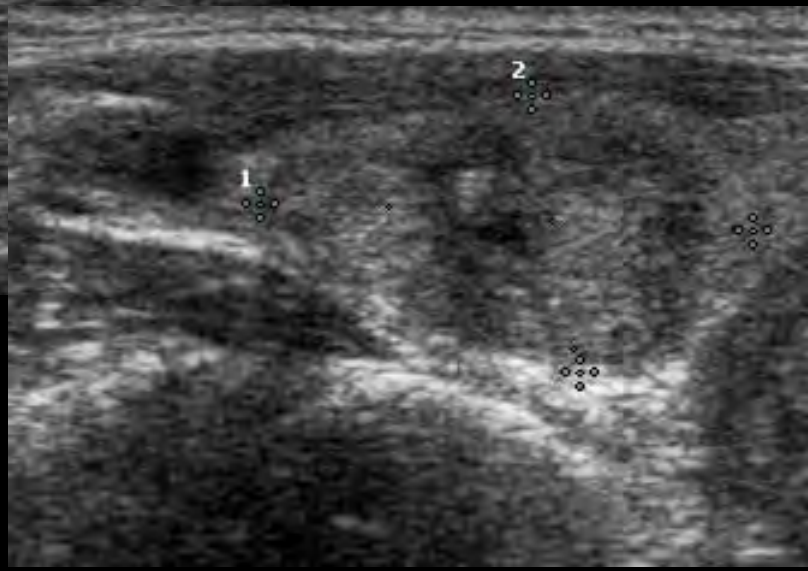
28x21x35mm

volume 10.7 ml

3600 J, 3 W, 2 fibres

Immediate post-PLA

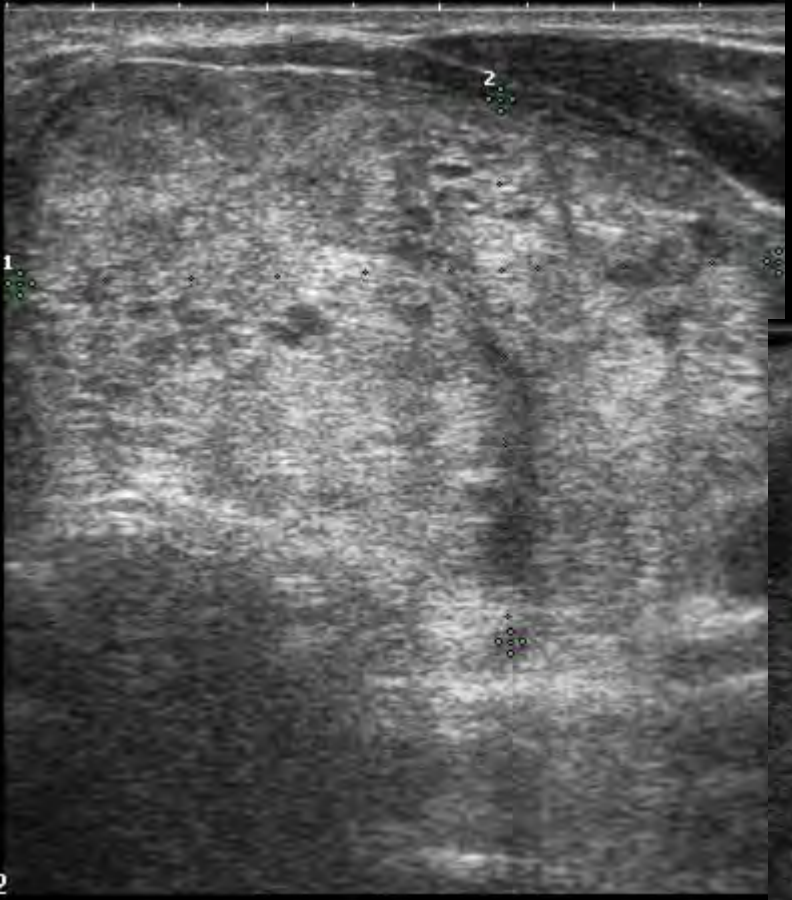




12 months

19x10x21mm

volume 2.0 ml, -81%



PLA

43x31x50 mm

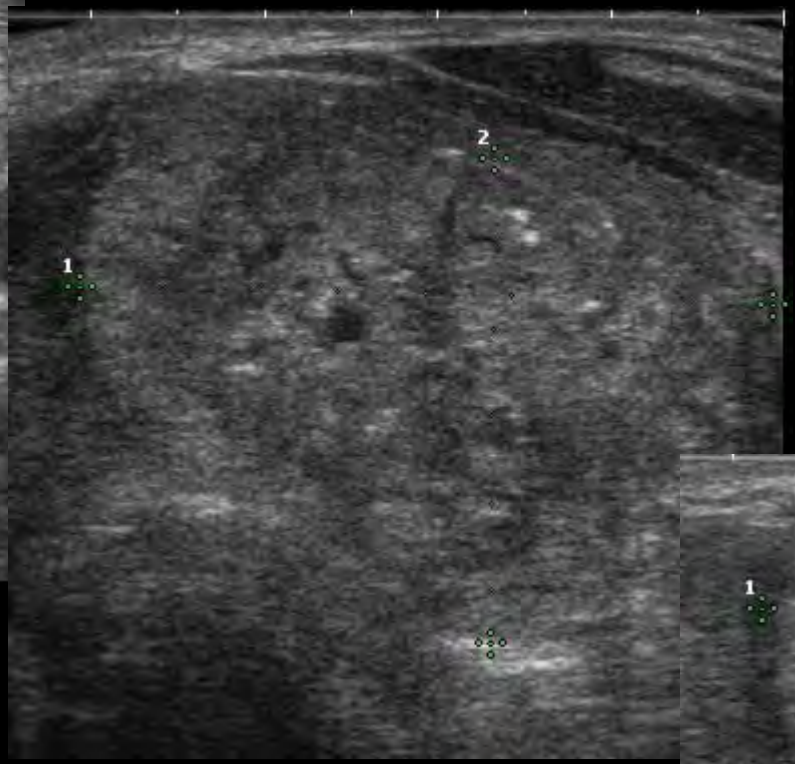
volume 34,6 ml

14400 J, 4 W, 2 fibres

1 month

40x20x37 mm

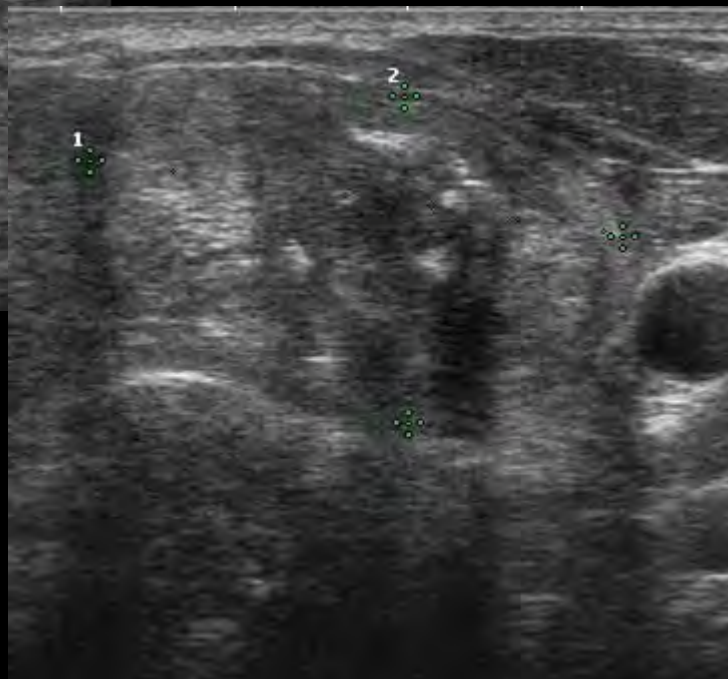
Volume 21,9 (-37 %)



12 months

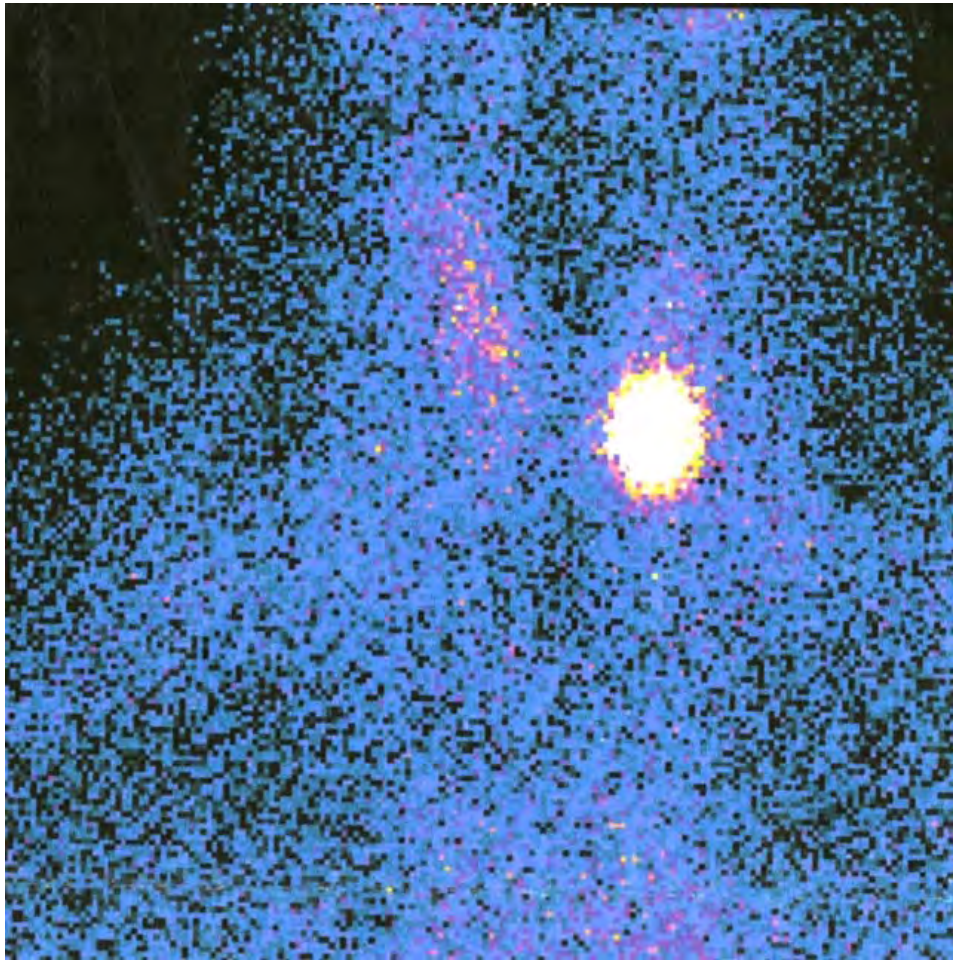
28x18x29

volume 7,6 ml, -78%

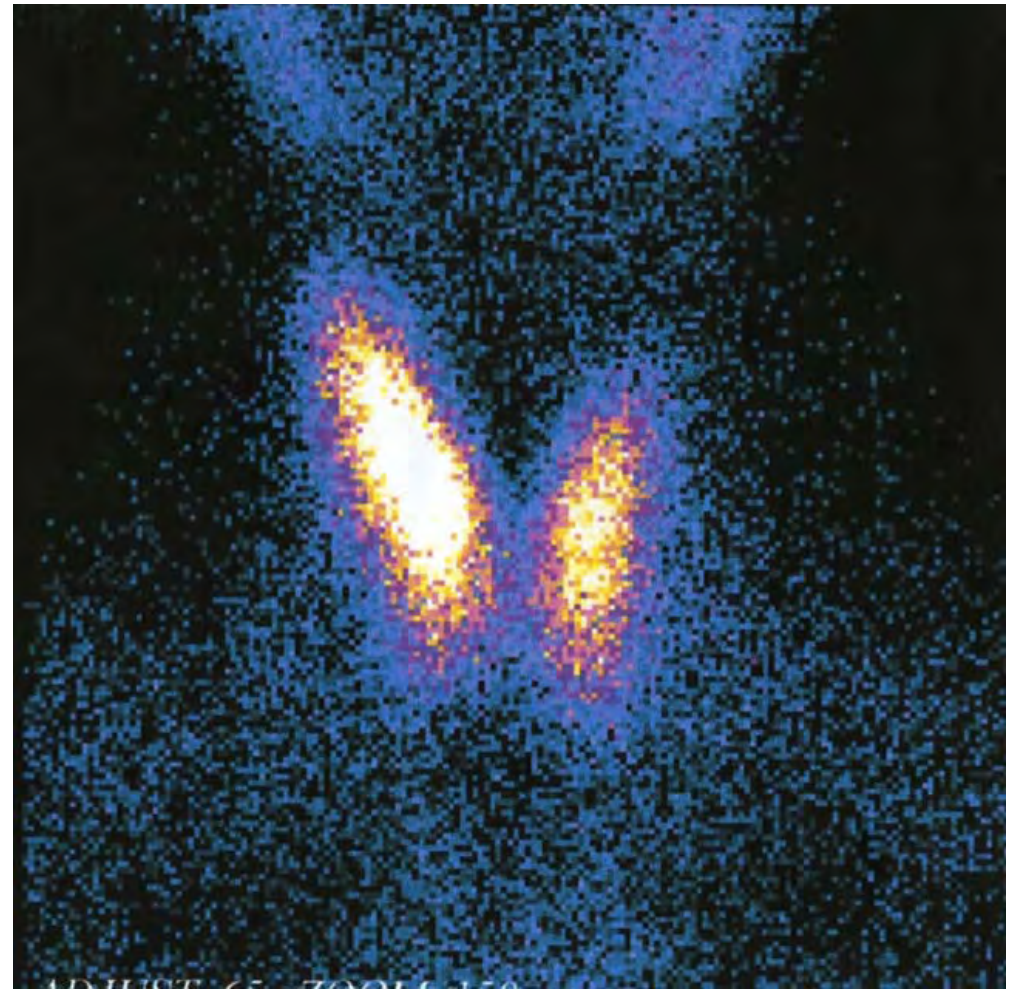


PLA of toxic adenoma of the left thyroid lobe

Before



After



PLA - CONCLUSIONS

Advantages

1. **Effective:** thyroid nodule shrinkage > 50% in a single PLA session
2. **Safe**
3. **Office-based setting**
4. **New therapeutic option** in management of benign thyroid nodules

Limitations

1. Restricted to specialized centers
2. Operator dependent
3. Long-term effects unknown

The Ultrasound-Guided PLA team, Reggio Emilia, Italy

- Roberto Valcavi, MD, FACE, Operator
- Angelo Bertani, MD, Ultrasonographer
- Marialaura Pesenti, MD, Clinical Management
- Raifa Al Jandali ‘Y Laura, MD, Clinical Management
- Deborah Formisano, Statistical Analysis
- Monica Frattini, Assistant Nurse

Arcispedale Santa Maria Nuova
Azienda Ospedaliera - Reggio Emilia

Utility of Recombinant Human Thyrotropin (rhTSH) for Augmentation of the Radioiodine Uptake (RAIU) in Multinodular Goiter (MNG) Therapy

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AME/AACE – Verona, Italy

MULTINODULAR GOITER = MULTIPLE

POTENTIAL PROBLEMS

PROBLEMS. . .

- MNG patients often have serious comorbid diseases (ie cardiovascular, chronic CHF, COPD, chronic renal insufficiency, diabetes, etc)
- Symptomatic MNG patients are frequently poor surgical candidates due to older age and high risk for anesthesia and surgery
- Antithyroid drugs (ATDs) are variably effective in hyperthyroid MNG patients and occasionally exacerbate compressive or obstructive symptoms
- Radioiodine therapy for MNG is usually less effective in iodine sufficient countries (frequently there is a low or normal RAIU)
- Radioiodine scans for MNG demonstrate increased isotopic concentration in “warm”/“hot” versus “cold” nodules/regions and I-131 therapy is less efficacious in “cold” nodules/areas of the goiter
- There is the potential for malignant neoplasms within MNG (4-7%)

OBSERVATIONS

- In vitro studies have shown that adding TSH to incubating thyroid follicular cells is associated with an increase in iodide transport after 12-24 h (Weiss, 1984)
- During thyroid cell incubation, iodide transport reaches a maximum at 72 hours (Kogai, 1997):
  - mRNA concentration of the sodium iodide symporter (NIS) maximizes @ 24 h
  - NIS protein levels increase by 36 h and maximize @ 72 h

RAIU Stimulation with rhTSH

- 1999 - rhTSH (Thyrogen, Genzyme) introduced in USA.

- May, 2003 - We reported the **OFF LABEL** use of rhTSH, in a non-randomised, non-controlled, intention to treat study in 16 symptomatic MNG patients who were US and 123-I scan screened and underwent UGFNA when indicated.
- 16 pts received either rhTSH 0.9 mg and 30 mCi of 131-I after **24 hours** (N=10); or, rhTSH 0.3 mg and 30 mCi of 131-I after **72 hours** (N=6)
- All 16 pts experienced no serious side effects and resolution of all signs and symptoms by 1 month; at 4-7 (mean of 5.5 months), 15/16 patients experienced 35% reduction in goiter size and 9/16 treated patients developed hypothyroidsim.

(Duick DS and Baskin HJ - Endocrine Practice 2003;9:204)

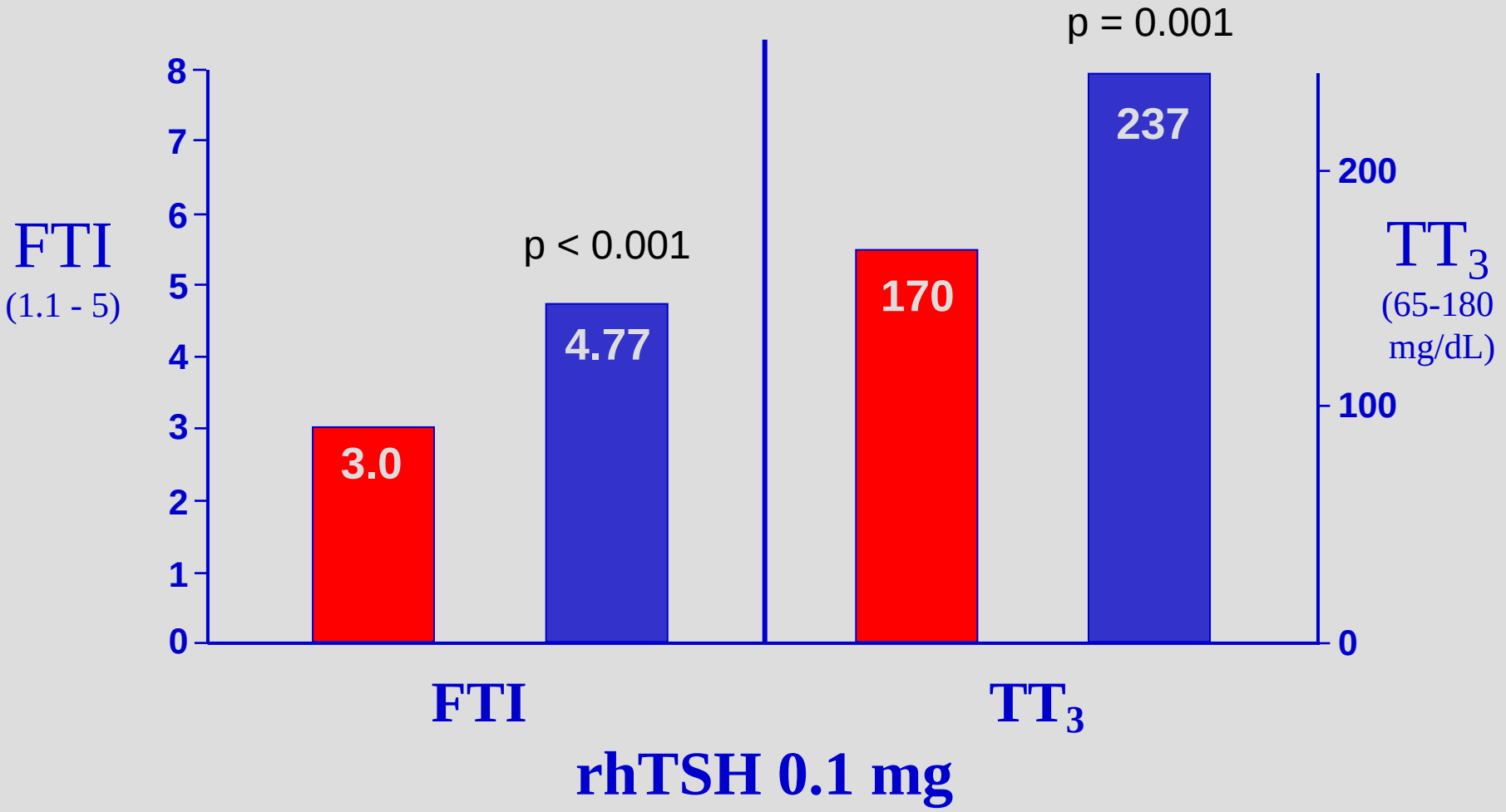
SECOND STUDY
RAIU Augmentation with rhTSH, 0.1 mg vs 0.3 mg with 131-I Rx @ 72 Hours

- Study Design: **OFF LABEL**, non-randomised, non-controlled, intention to treat study of 30 **symptomatic MNG patients*** utilizing rhTSH 0.1 mg (N =21) and rhTSH 0.3mg (N=9)
- rhTSH and 123-I (100 microcuries) were administered and RAIU and scans were performed @4 and 24 hrs; 123-I was readministered @ 48 hrs post rhTSH and repeat RAIU and scans were performed @ 52 and 72 hours
- Thyroid function tests were obtained at 0 and 72 hours and both patient groups received 30 mCi of 131-I @72 hours
- All patients were carefully monitored and some received or continued beta blockers or calcium channel blockers

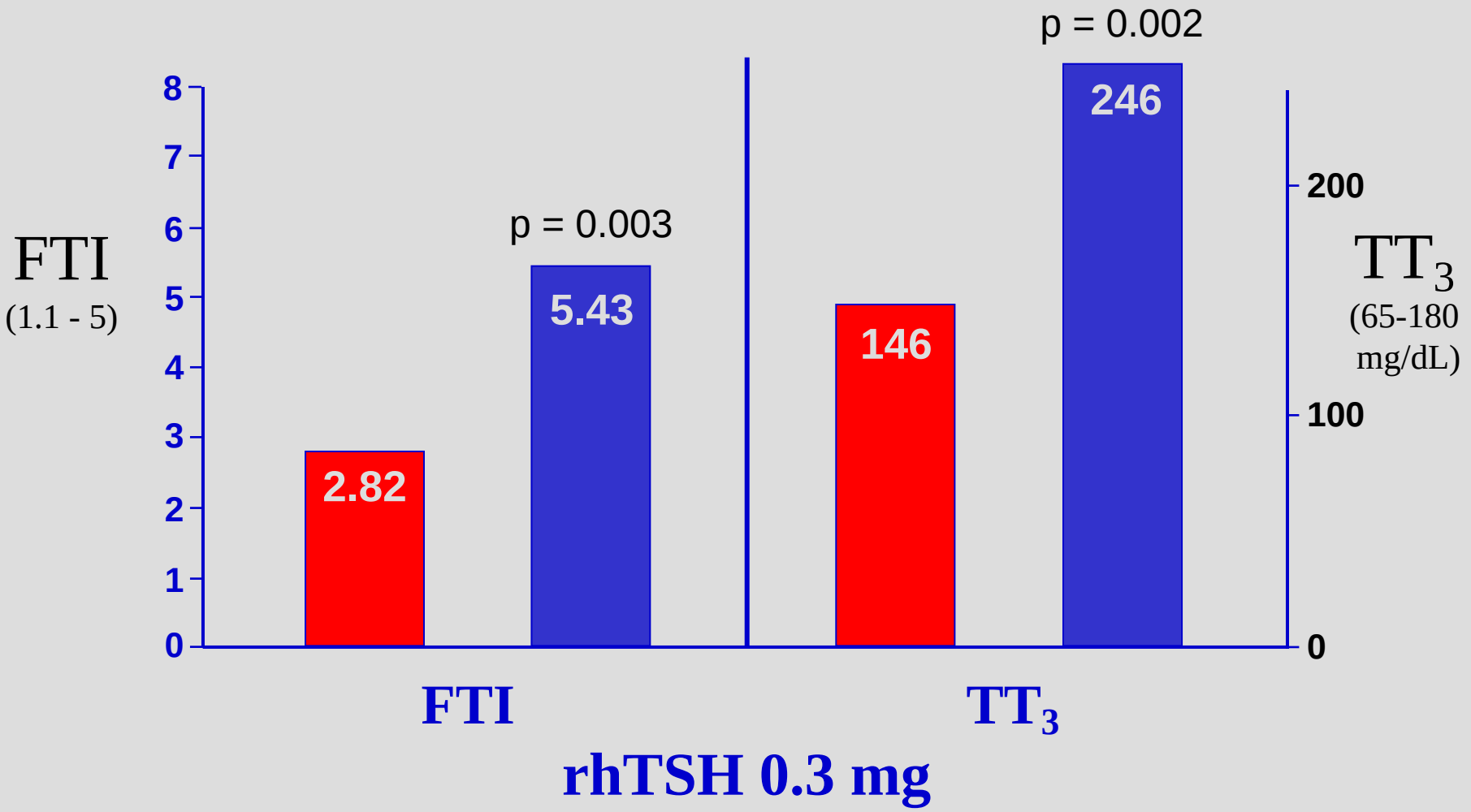
*All symptomatic MNG patients had one or more symptoms and signs: weight loss, palpitations, atrial fibrillation, clinical or subclinical thyrotoxicosis, compression (neck tightness or fullness), dysphagia w/o obstruction or progressive dyspnea

(Duick DS and Baskin HJ – Endocrine Practice 2004; 10:253)

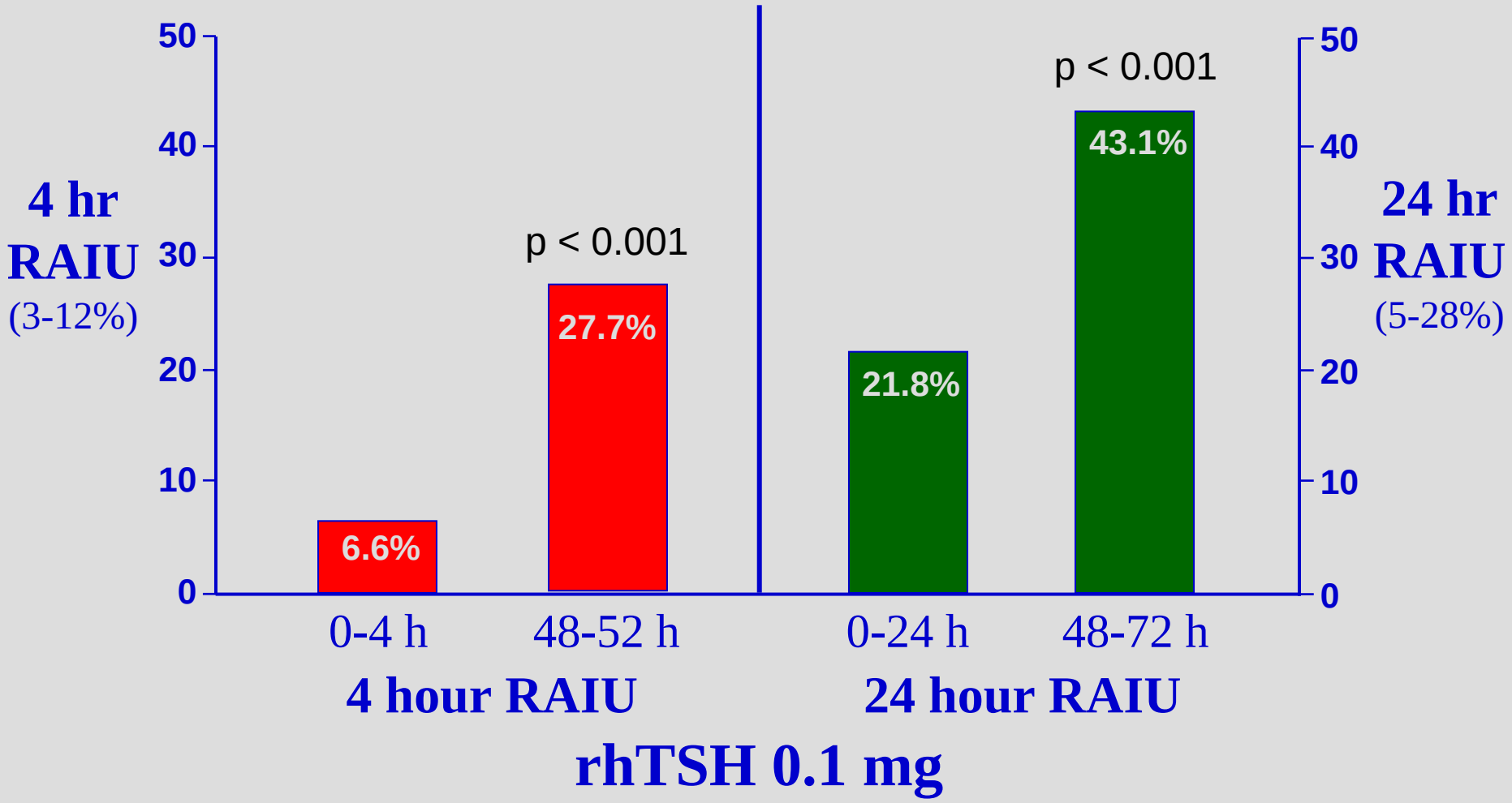
FTI and TT_3 **Pre** and **Post** rhTSH 0.1 mg at 72 Hours



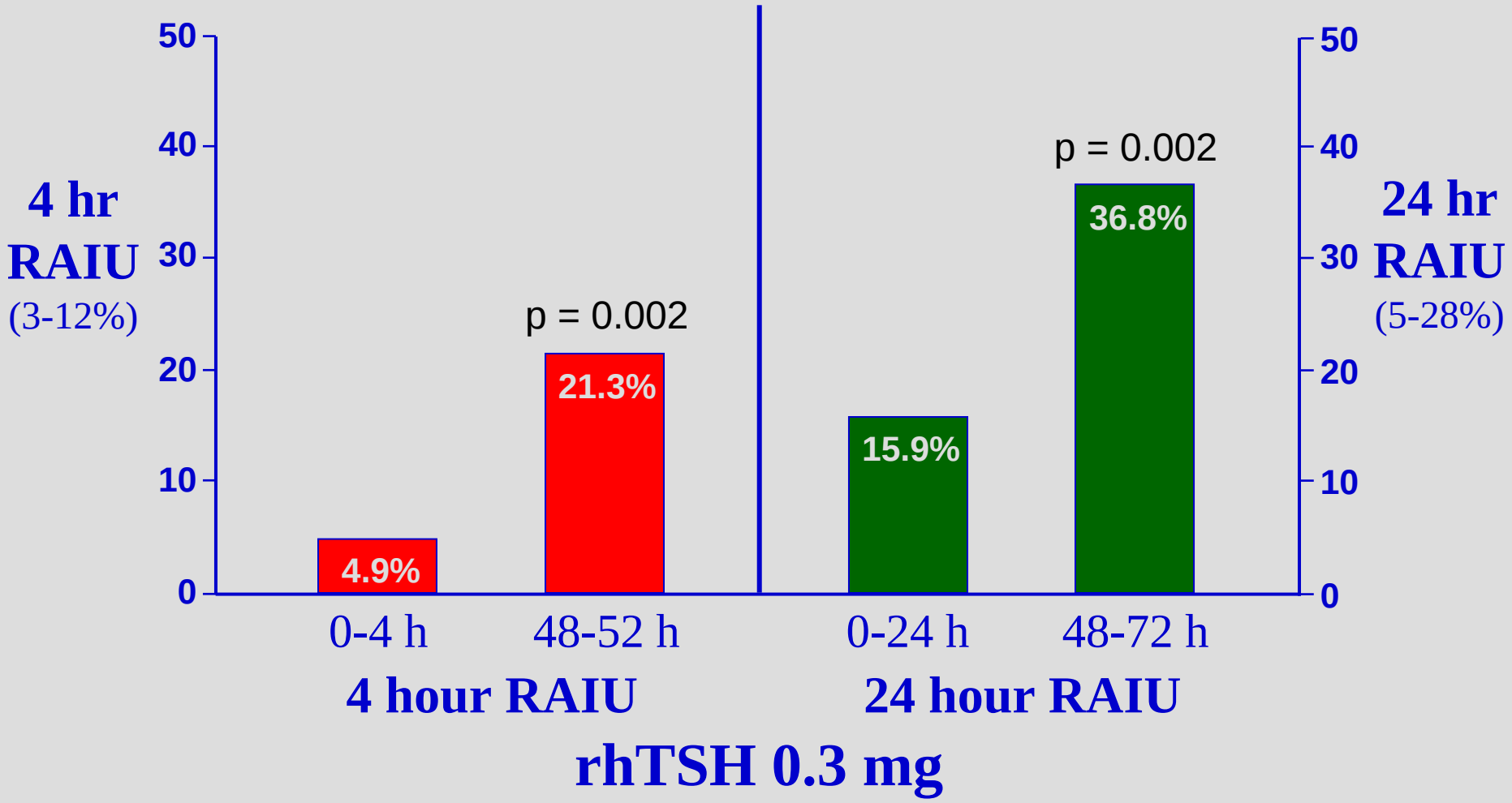
FTI and TT_3 **Pre** and **Post** rhTSH 0.3 mg at 72 Hours



4 Hr RAIUs @ 4 and 52 hrs and 24 Hr RAIUs @ 24 and 72 Hrs post rhTSH 0.1 mg



4 Hr RAIUs @ 4 and 52 hrs and 24 Hr RAIUs @ 24 and 72 Hrs post rhTSH 0.3 mg



THYROID 10-7-03
THYROGEN 0.1

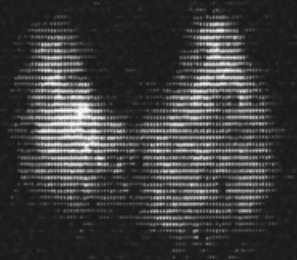
RT

STER

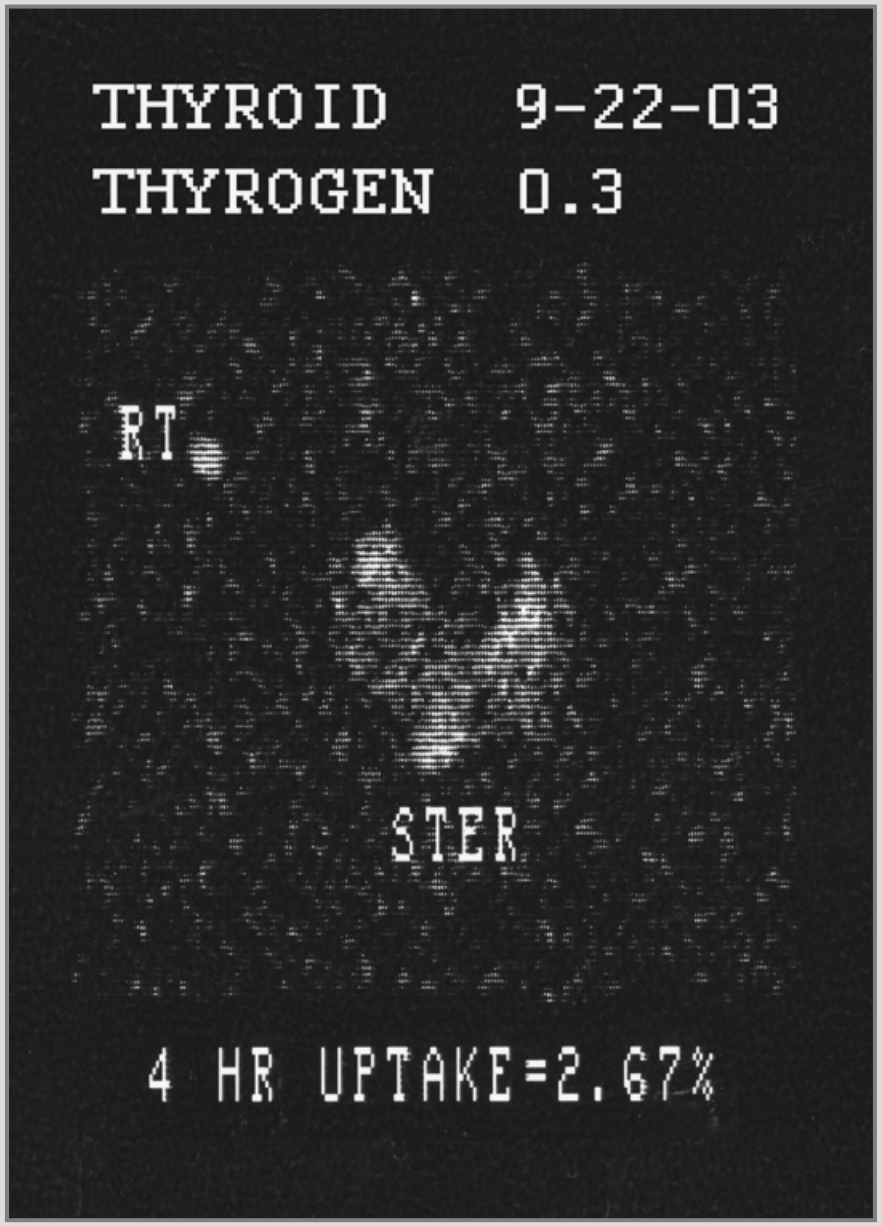
24 HR UPTAKE=31.64%

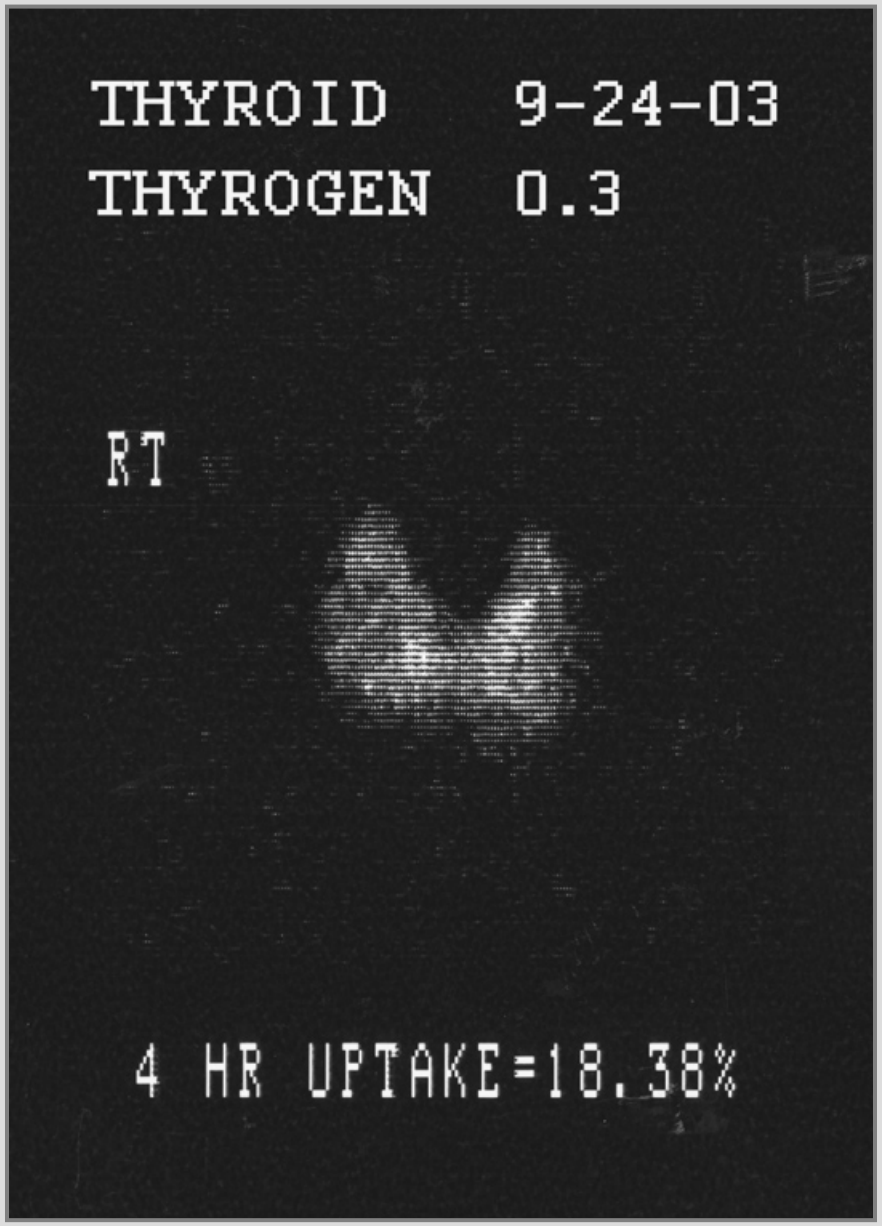
THYROID 10-9-03
THYROGEN 0.1

RT



24 HR UPTAKE=59.08%


THYROID 9-22-03
THYROGEN 0.3
RT
STER
4 HR UPTAKE=2.67%


THYROID 9-24-03
THYROGEN 0.3
RT
4 HR UPTAKE=18.38%

SUMMARY

- Symptomatic MNG patients pretreated with either rhTSH 0.1 mg or 0.3 mg resulted in no significant difference on the stimulation of thyroid hormone levels or RAIU
- There is a 2 fold rise in the 24 hr RAIU post 0.1 or 0.3 mg rhTSH (compared to patients unstimulated or historical RAIU controls) and a 4 fold+ rise in the 72 hr RAIU (a doubling of the 24 hr RAIU).
- The 4 Hr RAIU study at 48-52 hours is associated with a 4 fold rise over the baseline study with both rhTSH doses and suggests that this 48 hour time interval may be used for radioiodine therapy
- Both rhTSH 0.1mg and 0.3mg doses when followed by 131-I Rx at 72 hours are well tolerated and effective for the treatment of MNG
- No significant difference between rhTSH 0.1 vs 0.3 mg but “trend” toward better outcomes with 0.3 mg dose.

What Did We Learn From These 2 Off Label, Observational And Intention To Treat Studies?

1. In symptomatic MNG patients, Recombinant Human TSH (0.1 or 0.3 mg) is an excellent stimulator of a normal or suppressed RAIU, hypofunctioning thyroid nodules and goitrous tissue. Subsequent 131-I Rx resulted in a 35% goiter reduction at 6 mos and 46% reduction at 12 mos.
2. Hormone release post rhTSH is modest with 0.1 and 0.3 mg pretreatment and side effects related to increased circulating thyroid hormones (lasting 1-3 weeks) can be observed or medically managed according to symptoms or signs
3. Induction of compressive airway symptoms occurred transiently post rhTSH in one patient and post radiation thyroiditis ocurred in one patient; 1 patient (TRAB was NEGATIVE at beginning of study) also developed overt hyperthyroidism due to Graves disease at 2 months after 131-I Rx (TRAB was now POSITIVE) and was retreated with 131-I Rx.
4. 67% of all treated patients from both our first and second studies evolved hypothyroidism.

To Date, What Have We Learned From Subsequent Studies?

1. **Brazil** (Silva MN, et al. Clin Endocrinol 2005;60:300)

   Group 1 (17 MNG pts) RAI Rx only; Group 2 (17 MNG pts) rhTSH 0.45mg and RAI Rx (variable doses) at 24 afterward; pre Rx with 4-6 mos of low iodine diet for all and 7 pts Rx'd with methimazole to euthyroidism: goiter reduction at 12 mos was 40% in Group 1 and 60% in Group 2 @ 12 mos; hypothyroidism in 21% and 60%, respectively @12 mos

2. **Brazil** (Albino CC, et al. JCE&M 2005;90:2775)

   18 MNG pts: rhTSH 0.1mg x day 1 and day 2 with 30 mCi RAI Rx on day 3: 50% goiter reduction at 6 mos

3. **Israel** (Cohen O, et al. Euro J of Endocrinology 2006; 154:243)

   17 MNG pts pretreated with rhTSH 0.03 mg and 30mCi of I-131 24 hrs later; 34% goiter reduction and 18% hypothyroidsm.

To Date, What Have We Learned From Subsequent Studies?

4. **Denmark** (Nielsen VE, et al. Arch Intern Med 2006;166:1476) is the current hallmark rhTSH clinical trial - prospective, placebo controlled, randomized, double-blinded study: 57 non-toxic nodular goiter patients (no significant symptoms and inclusion criteria included baseline 24 hr RAIU > 20%) were randomized – 29 pts saline injected and 28 pts received rhTSH 0.3mg - both Rx'd 24 hrs later with 131-I, dose adjusted based on goiter size by US and RAIU

Results:

- at 12 mos goiter reduction was 46% in controls vs 62% in rhTSH subjects -
-in both groups, there was no correlation between goiter reduction and retained RAI dose (70% higher in rhTSH treated subjects)
- hypothyroidism incidence of 11% in placebo and 62% in rhTSH treated subjects
- no difference between groups regarding patient satisfaction
- most serious side effects were in rhTSH subjects: induction of hyperthyroid symptoms in 10 vs 6; cervical pain/discomfort (1st week) 8 vs 2 and NONE experienced any respiratory or compressive symptoms

To Date, What Have We Learned From Subsequent Studies?

4. **Denmark** (Nielsen VE, et al) continued:

   Recommendations: “Future studies should focus on including patients with large goiters and low RAIU because they may benefit the most from recombinant human thyrotropin prestimulation. Finally, the optimal dose and timing of recombinant human thyrotropin in relation to 131-I therapy remains to be determined…..”

   NOTE: This group is currently registering goiter patients for a clinical trial utilizing 131-I Rx to be given at 3 different time intervals: 24, 48 and 72 hrs post rhTSH 0.1 mg

Our Follow-up and Current Data of Symptomatic MNG patients Pretreated with **Off Label** rhTSH for Radioiodine Therapy

As of August, 2006, 97 symptomatic MNG patients (low or normal 24 hr RAIU) have received rhTSH 0.3mg (41) or 0.1mg (56) followed by 30 mCi of 131-I Rx at **72 hrs:**

Data for 83/97 patients (2001 thru 8/2005, mean of 2.8 years):

- average goiter reduction at 12 mos (63/83 based on ultrasound studies both pre and post goiter therapy) is 46%
- complete relief symptoms and signs in 80/83 patients; 3/83 required repeat 131-I therapy within 24 mos
- hypothyroidism has developed in 68% (57/83) of pts - average time interval post Rx = 6.5 mos
- no serious AEs: 4/83 patients received methyl prednisolone for cervical pain

GRAZIE

GRAND CANYON, ARIZONA