UNIVERSITA' DEGLI STUDI DI GENOVA

Dipartimento DI Medicina Interna e Specialità Mediche (DiMI)

Dottorato di Ricerca in "Medicina Interna Clinico-Sperimentale"

XXX Ciclo

Curriculum:

Fisiopatologia e Clinica delle Malattie Endocrino-Metaboliche

Coordinatore: Chiar.mo Prof. Marcello Bagnasco

PERCUTANEOUS THERMAL ABLATIONS

OF BENIGN THYROID NODULES

Relatore: Chiar.mo Prof. Massimo Giusti

Candidata: Dott.ssa Silvia Oddo

INDEX

4. Discussion
5. Conclusions
6. References

CHAPTER 4

A comparison of laser with radiofrequency ablation for the treatment of benign thyroid nodules: a propensity score matching analysis.

Pacella CM, Mauri G, Cesareo R, Paqualini V, Cianni R, De Feo P, Gambelunghe G, Raggiunti B, Tina D, Deandrea M, Limone PP, Mormile A, Giusti M, **Oddo S**, Achille G, Di Stasio E, Misischi I, Papini E. Int J Hyperthermia. 2017 Jun 12:1-9.

1. Introduction
2. Material and Methods
3. Results
4. Discussion
5. References

CHAPTER 5

A case of thyroid cancer on the track of the radiofrequency electrode 30 months after percutaneous ablation.

Oddo S, Spina B, Vellone VG, Giusti M. J Endocrinol Invest. 2017; 40: 101-102.

1. Introduction
2. Material and Methods
3. Results

4. Discussion
5. References

CHAPTER 6

A benign thyroid nodule unresponsive to radiofrequency ablation treated with laser ablation.

Oddo S, Balestra M, Vera L, Giusti M. Journal of Medical Case Reports. *Accepted in 21th February 2018.*

1. Background
2. Case presentation
3. Discussion
4. Conclusions
5. References

CHAPTER 7

Other papers

1. **Five-year longitudinal evaluation of mild primary hyperparathyroidism - medical treatment versus clinical observation.**

   Vera L, Accornero M, Dolcino M, **Oddo S**, Giusti M. Endokrynol Pol. 2014; 65: 456-463.

2. **Primary hyperparathyroidism in pregnancy treated with cinacalcet: a case report and review of the literature.**

Vera L, **Oddo S**, Di Iorgi N, Bentivoglio G, Giusti M. J Med Case Rep. 2016; 10: 361.

CHAPTER 8

Conclusions

PREFACE

The thesis contains the results of the clinical researches carried out during my three years of PhD training.

Chapter 1 is a brief introduction of the main field of my research, minimally invasive percutaneous thermal ablation of benign thyroid nodules by means of radiofrequency and laser sources.

Chapter 2 to 6 report clinical researches in the field of percutaneous thermal ablation of benign thyroid nodules.

Chapter 2 describes our experience in thermal ablation of benign thyroid nodule with radiofrequency.

Chapter 3 describes our experience in thermal ablation of benign thyroid nodule with laser.

Chapter 4 illustrates a multicenter study of comparison of radiofrequency and laser ablation of benign thyroid nodule that involved some italian centers that perform minimally invasive procedures on thyroid.

Chapter 5 documents a rare adverse events of radiofrequency ablation.

Chapter 6 reports a case of a thyroid nodule that didn't respond to radiofrequency ablation and that responded to laser ablation.

Chapter 7 report clinical researches in other fields like primary hyperparathyroidism.

All this works are published on indexed journals or in course of revision in indexed journals.

CHAPTER 1

Introduction

In 2010 and in 2015 AACE-AME-ETA guidelines recommended mini-invasive thermal ablation as possible terapeutical choice for benign thyroid nodules in patients that refuse thyroidectomy or that have comorbilities that contraindicated surgery [1, 2]. These techniques arrived in Italy in the last 10 years, thus in 2015 the Italian opinion statement was written [3].

Not-invasive techniques as TSH suppression with levo-tiroxine in the euthyroid patient could reduce the nodule growth and prevent new nodules formation[4], but many evidences suggest that this treatment in efficient just in single solid nodules; only 20% of nodules reduces significantly in volume (>50%) and it often regrowth after L-T4 suspension [5].

Other possibility is radioiodine therapy after recombinant TSH, that reduces goiter volume from 35 to 56% but causes hypothyroidism in majority of patients [6].

The basic principle of minimally invasive techniques on benign thyroid nodules, by mean of laser ablation (PLA) or radiofrequency ablation (RFA), is to create a thermal damage to the nodules resulting in an irreversible coagulative necrosis. Temperatures between 60-100°C create irreversible tissue damage, temperatures above 100-110°C result in carbonization which reduces the effectiveness of the procedure [7].

Other minimally invasive thyroid nodule procedures include percutaneous alcoholization that was initially used in benign solid nodules, but now is the first choice in the treatment of recurrent cystic nodules [1, 2]. The success of alcoholization

(volume reduction> 50%) is high (about 83%) and it improves neck symptoms in 78% of patients and benefit persists at least 24 months after the procedure [8]. For cystic nodules other minimally invasive techniques are to be considered in case of regrowth after alcoholization [3].

In agreement with the Korean Society of Thyroid Radiology Consensus [7], laboratory tests (thyroid function and autoimmunity and calcitonin) should be evaluated before the procedures; morphology and cytology of the nodule (at least twice), cordal and heart functional state.

These data are necessary to identify the correct indications to the procedure and to avoid possible adverse events [7]. In particular, if anti-thyroid antibodies are positive, the patient should be informed of the increased risk of hypothyroidism after RFA [7]. Before the procedure it's necessary to suspend antiplatelet and anticoagulants [7]. The patient should be informed of the possibility of repetition of the procedure in a second time [7].

The RFA is started with a power of 30-50 W and increased by 10 W if an echogenic zone is not formed near the electrode tip after 5-10 seconds, up to a maximum power of 80-120 W. The power is reduced or the generator is switched off for a few seconds if the patient complains pain [9]. The electrode should be well visualized with US scan throughout its length and throughout the procedure to exclude damage to the "danger triangle" (recurrent laryngeal nerve, trachea and esophagus). The electrode should be placed in the deepest and most distant region of the nodule and then moved back to the most superficial and close to exclude visual disturbances due to echogenic bubbles

[9, 10]. There is the possibility of using a "virtual track" system to visualize the tip of the electrode even when the tip is obscured by vapor bubbles [11].

PLA is performed by inserting into the nodule, under ultrasound guidance, one or more optical fibers of 300 μm in diameter through some guides of 16-21 gauge diameter. The fibers then form an ellipsoidal shape which covers most of the area of the nodule. The patient is placed on an operating table in a supine position with the neck hyperextended [10].

The guides are inserted in cranio-caudal section. The energy is supplied at 1200-1800 J/fiber starting at 1 cm from the bottom of the lesion. From the vaporization result an ecogenic area that increases in size. It is possible to perform one to two pull-backs of 1 cm. The number of fibers, of pull-back, of released energy are evaluated according to the size of the nodule and the shape. The duration varies from 6 to 30 minutes and depends on the size. The generator must be switched off in case of pain, cough or the occurrence of adverse events [10].

In PLA and in RFA complications are rare (3-5%) and may be [10, 12]:

- pain (most common) which decreases rapidly when the generator is turned off; it can persist even after the end of the procedure and is treated with analgesics;
- changes in the tone of the voice, which may be due to a recurrent laryngeal nerve injury;
- hematoma, which can be controlled with a compressive bendage;
- skin burn, generally of first grade; treated with application of ice on the electrode insertion site;

- rupture of the nodule, secondary to sudden expansion due to haemorrhage, treated with antibiotics and analgesics or with surgery in case of abscess;
- transient thyrotoxicosis, which usually normalizes after one month, which can be treated with steroids;
- hypothyroidism, more frequent in patients with functioning thyroid nodules or in in patients with positive autoimmunity.

The cost of minimally invasive procedures is lower of a total thyroidectomy and of a hemithyroidectomy; the cost of a radiofrequency generator is about 25,000 dollars (often it is given in free loan); the cost of electrodes is 750 dollars per session. The average time of the procedure is about 30 minutes [13]. An Italian study compares the efficacy, tolerability and cost of RFA and hemithyroidectomy: the cost for a session of RFA was 1661.5 euro, the cost of a hospitalization for hemithyroidectomy was 4139.4 euro and for a short hospitalization (< 24h) [14]. The cost for an ultrasound equipment with laser source to perform PLA is high (about 120,000 dollars), but the cost of fibers per session are low (about $ 400); the treatment can be practiced as a day-hospital in 30 minutes.

After PLA, an intranodular cavitation confined by carbonized tissue can be seen few weeks after procedure. After few weeks a not vascularized hypoechoic area, compatible with the area of necrosis, with much more regular margins than the RFA can be seen at US scan. Consistency with qualitative elastosonography increases proportionally to fibrosis [15].

After the RFA the nodular tissue changes ultrasonographic characteristics and may erroneously appear with suspicious characteristics. Immediately after the procedure

the released gas makes the nodule less evaluable. In RFA, carbonization of the tissue is a rare event; in that case the nodules appear more homogeneous and the margins of the necrotic area can be irregular. Consistency with qualitative elastosonography increases proportionally to fibrosis [15].

Analysis of the operative samples after thyroidectomy in nodules subjected to PLA showed the presence of necrosis, fibrotic degeneration without extrathyroid damage or cervical fibrosis [16].

Microwave and ultrasound ablations is less used and not yet approved by international guidelines [17, 18].

Radiofrequency ablation: clinical outcomes in patients with symptomatic benign thyroid nodules (in major series).

Author	Nodules number	Randomized-controlled trials	Radioisotope scan	Ultrasound pattern	Fluid component (%)	Baseline volume (mL)	Electrode type	Energy load J/mL	Number of sessions (mean)	Follow up months (mean)	Volume reduction (%)	Serum hormone changes	Local symptoms changes
												Thyroid-stimulating hormone normalization (%)	Improvement (%)
De Andrea et al. 2008	33		Hot	Cystic-solid	<30	23	14G multitined electrodes		1	6	53	3/23 (13)	
Spiezia et al., 2009	94		Hot			33	14G multitined electrodes		1	24	79	15/15 (100)	75/75 (100)
Faggiano et al., 2012	20		Hot			13	14G multitined electrodes		1	12	85 *v* 0	4/10 (40)	
Kim et al., 2006	35		Cold	Cystic-solid	>80	6	17G cooled electrode		1	6	73	22/25 (88)	
Spiezia et al., 2007	39		Cold	Solid	<30		14G multitined electrodes		1.4	6	74	39/39 (100)	
Jeong et al., 2008	302		Cold	Cystic-solid	>80	6	17G cooled electrode		1.4	6	85		
Deandrea et al., 2008	33		Cold	Cystic-solid	<30	39	14G multitined electrodes		1	6	46	13/14 (93)	
Spiezia et al., 2009	94		Cold	Cystic-solid	<30	21	14G multitined electrodes		1	24	79	88/88 (100)	75/75 (100)
Baek et al., 2010	15 *v* 15	Yes	Cold	Cystic-solid	>50	7	18G cooled electrode	4966	1	6	80		
Sung et al., 2011	44		Cold	Cystic	>90	10	18G cooled electrode		1.7	12	95		
Huh et al., 2012	15		Cold	Cystic-solid	>50	13/13	18G cooled electrode	4377 *v* 6157	1	6	70 *v* 78		
Faggiano et al., 2012	10		Cold	Cystic-solid	<30	13	14G multitined electrodes		1	12	85 *v* 0		
Lim et al., 2013	126		Cold	Cystic-solid	65	10	17/18 cooled electrode	2936	2.2	49	93		
Sung et al., 2013	25 *v*25	Yes	Cold	Cystic	>90	9	18G cooled electrode		1	6	98/94		

laser ablation: clinical outcomes in patients with symptomatic benign thyroid nodules (major series).[a]

Author	Nodule number	Randomized-controlled trial	Radioisotope scan	Ultrasound pattern	Baseline volume (mL)	Laser source	Energy load Joules/mL	Number of sessions (mean)	Volume reduction (%)	Serum hormone changes	Local symptoms changes	Follow up months (mean)
										Thyroid-stimulating hormone normalization[a] (%)	Improvement (%)	
Pacella et al., 2004	24		Hot	Solid	8.0	Nd:YAG	816	2.7	62		12/14 (86)	6
Barbaro et al., 2007	18		Hot	Solid	21.0	Nd:YAG		3	59	N		12
Dossing et al., 2007	14 *v* 15	Yes	Hot	Solid	11/11	820 diode	217	1/1	44	7/14 (50)		6
Amabile et al., 2011	26		Hot	Solid	55.3	980 diode	379	3.2 cycle	77	(87)		12
Dossing et al., 2002	16		Cold	Solid	10.0	820 diode	761	1	46			6
Spiezia et al., 2003	12		Cold	Solid	11.0	Nd:YAG		2.2	61	5/5 (100)		12
Pacella et al., 2004	24		Cold	Solid	23.0	Nd:YAG	788	4.1	63	12/14 (86)		6
Papini et al., 2004	20		Cold	Solid	24.0	Nd:YAG	300	2.2	64	16/18 (89)		6
Dossing et al., 2005	15 *v* 15	Yes	Cold	Solid	8.0	820 diode	224	1	44	10/13 (77)		6
Amabile et al., 2006	23		Cold	Solid	15.0	980 diode	33	1.2	36	5/23 (65)		3
Dossing et al., 2006	15 *v* 15	Yes	Cold	Solid	10.1/11.0	820 diode	262 *v* 412	1	45 *v* 58	6/13 (47)	9/10 (90)	6
Papini et al., 2007	21 *v* 21 *v* 20	Yes	Cold	Solid	12.0/14.0/12.0	Nd:YAG	1221	1	>40	13/16 (81)	13/16 (81)	12
Valcavi et al., 2008	119		Cold	Solid	25.0	Nd:YAG		1	56	(72)	(86)	12
Valcavi et al., 2010	122		Cold	Solid	23.0	Nd:YAG	484	1	48	89 (73)	87 (71)	36
Dossing et al., 2011	78/78	Yes	Cold	Solid	8.0	820 diode	242	1	51	62/74 (84)	33/46 (72)	67
Amabile et al., 2011	51		Cold	Solid	54.0	980 diode	391	3.2 cycle	80			12
Gambelunghe et al., 2013	20		Cold	Solid	15/14	Nd:YAG	71/579[b]	1	11/57	17/20 (85)	14/20 (70)	36
Gambelunghe et al., 2013	50		Cold	Solid	21/21	Nd:YAG	502/499	1	55/56			6
Dossing et al., 2013	22 *v* 22	Yes	Cold	Solid	10.0/12.0	820 diode	83	1	26 *v* 73			6

[a] After a time ranging from 3–6 weeks to 2–3 months, all patients with single autonomously functioning nodules had improvement of serum levels of FT3 and FT4 and a complete normalization of thyroid-stimulating hormone that remained unaltered during follow up.

[b] Median energy/mL delivered.

Primary hyperparathyroidism (PHPT) is a disorder characterized by inappropriately high secretion of parathyroid hormone (PTH). PHPT has become a common disease, with an estimated prevalence of 1% of the general population and 3% in postmenopausal women [19], and an increasing incidence over the last few decades.

PHPT is usually the result of a single over-active parathyroid gland as a result of adenoma, hyperplasia or cancer [20]. The clinical presentation has changed over the years: today, 80–85% of cases are asymptomatic [21].

A National Institutes of Health consensus panel has recognized two forms of the disease: asymptomatic and symptomatic [22]. The diagnosis is based on the clinical and objective picture, evaluation of serum calcium (S-Ca) and PTH. Preoperative localization studies are required.

Therapy may involve medical or surgical treatment, and many guidelines have been proposed over the years. Although parathyroidectomy (PTX) is regarded as the treatment of choice for patients with symptomatic hypercalcaemia or evidence of target organ damage [23], conservative management has been favored in asymptomatic patients. In addition, in some cases surgery fails, in some it is contraindicated, and in others it is refused [24]. At the most recent International Workshop [25], the guidelines pointed out that there was no data to support the medical treatment of patients with mild PHPT. In general, it is recommended that patients who do not meet surgical criteria [25] be monitored closely. However, the validity of medical treatment is unanimously recognised.

The decision to employ a pharmacological approach depends also upon the goal of treatment, to reduce the serum calcium level and/or to increase BMD [26].

Cinacalcet hydrochloride is a calcimimetic agent that binds to the calcium-sensing receptor (CaR) of parathyroid cells, resulting in diminished S-Ca, but has only a modest effect to reduce the PTH level and BMD does not change. Cinacalcet is generally well-tolerated. The most common side effect is dose dependent and is nausea [27].

Data from randomized controlled studies have consistently demonstrated that oral alendronate decreases bone turnover and increases BMD in patients with mild PHPT, although the effects on serum calcium PTH have been inconsistent [26].

Moreover, for most drugs, long-term data are insufficient regarding benefit and safety. There are limited data on the combination of bisphosphonate and cinacalcet in PHPT. The use of any of these pharmacological agents should be dictated by the goal. To increase BMD, bisphosphonate therapy would be the choice. If there is concern about the level of the serum calcium concentration, cinacalcet would be the choice to reduce it. If there is no intention to improve the BMD or to lower the serum calcium concentration, pharmacological agents are not used [25].

References

1. *Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, Hegedüs L, Vitti P; AACE/AME/ETA Task Force on Thyroid Nodules American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: Executive Summary of recommendations. J Endocrinol Invest. 2010; 33: 287-291.*
2. *R. Haugen, Erik K. Alexander, Keith C. Bible, Gerard M. Doherty, Susan J. Mandel, Yuri E. Nikiforov, Furio Pacini, Gregory W. Randolph, Anna M. Sawka, Martin Schlumberger, Kathryn G. Schuff, Steven I. Sherman, Julie Ann Sosa, David L. Steward, R. Michael Tuttle and Leonard Wartofsky. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer Bryan. Thyroid. 2016; 26: 1-149.*
3. *Garberoglio R, Aliberti C, Appetecchia M, Attard M, Boccuzzi G, Boraso F, Borretta G, Caruso G, Deandrea M, Freddi M, Gallone G, Gandini G, Gasparri G, Gazzera C, Ghigo E, Grosso M, Limone P, Maccario M, Mansi L, Mormile A, Nasi PG, Orlandi F, Pacchioni D, Pacella CM, Palestini N, Papini E, Pelizzo MR, Piotto A, Rago T, Riganti F, Rosato L, Rossetto R, Scarmozzino A, Spiezia S, Testori O, Valcavi R, Veltri A, Vitti P, Zingrillo M. Radiofrequency ablation for thyroid nodules: which indications? The first Italian opinion statement.J Ultrasound. 2015 Jun 19; 18: 423-430.*

4. *Hegedüs L, Bonnema SJ, Bennedbaek FN. Management of simple nodular goiter: current status and future perspectives. Endocr Rev. 2003; 24: 102-132.*
5. *Gharib H, Mazzaferri EL. Thyroxine suppressive therapy in patients with nodular thyroid disease. Ann Intern Med. 1998; 128: 386-394.*
6. *Graf H, Fast S, Pacini F, Pinchera A, Leung A, Vaisman M, Reiners C, Wemeau JL, Huysmans D, Harper W, Driedger A, de Noemberg Souza H, Castagna MG, Antonangeli L, Braverman L, Corbo R, Duren C, Proust-Lemoine E, Edelbroek A, Mariott C, Rachinsky I, Gruppe P, Watt T, Magner J, Hegedus L. Modified-Release Recombinant Human TSH (MRrhTSH) augments the effect of 131I therapy in benign multinodular goiter; results from a multicenter international, randomized, placebocontrolled study. J Clin Endocrinol Metab. 2011; 96: 1368–1376.*
7. *Na DG, Lee JH, Jung SL, Kim JH, Sung JY, Shin JH, Kim EK, Lee JH, Kim DW, Park JS, Kim KS, Baek SM, Lee Y, Chong S, Sim JS, Huh JY, Bae JI, Kim KT, Han SY, Bae MY, Kim YS, Baek JH; Korean Society of Thyroid Radiology (KSThR); Korean Society of Radiology. Radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: consensus statement and recommendations. Korean J Radiol. 2012;13: 117-125.*
8. *Shin JH, Baek JH, Ha EJ, Lee JH. Radiofrequency ablation of thyroid nodules: basic principles and clinical application. Int J Endocrinol. 2012; 2012: 919650.*
9. *Papini E, Pacella CM, Misischi I, Guglielmi R, Bizzarri G, Døssing H, Hegedus L. The advent of ultrasound-guided ablation techniques in nodular thyroid disease:*

towards a patient-tailored approach. Best Pract Res Clin Endocrinol Metab. 2014; 28: 601-618.

10. *Baek JH, Lee JH, Valcavi R, Pacella CM, Rhim H, Na DG. Thermal ablation for benign thyroid nodules: radiofrequency and laser. Korean J Radiol. 2011;12: 525-540.*
11. *Turtulici G, Orlandi D, Corazza A, Sartoris R, Derchi LE, Silvestri E, Baek JH. Percutaneous radiofrequency ablation of benign thyroid nodules assisted by a virtual needle tracking system. Ultrasound Med Biol. 2014; 40: 1447-1552.*
12. *Baek JH, Lee JH, Sung JY, Bae JI, Kim KT, Sim J, Baek SM, Kim YS, Shin JH, Park JS, Kim DW, Kim JH, Kim EK, Jung SL, Na DG; Korean Society of Thyroid Radiology. Complications encountered in the treatment of benign thyroid nodules with US-guided radiofrequency ablation: a multicenter study. Radiology. 2012; 262: 335-342.*
13. *Gharib H, Hegedüs L, Pacella CM, Baek JH, Papini E. Clinical review: Nonsurgical, image-guided, minimally invasive therapy for thyroid nodules. J Clin Endocrinol Metab. 2013; 98: 3949-3957.*
14. *Bernardi S, Dobrinja C, Fabris B, Bazzocchi G, Sabato N, Ulcigrai V, Giacca M, Barro E, De Manzini N, Stacul F. Radiofrequency ablation compared to surgery for the treatment of benign thyroid nodules. Int J Endocrinol. 2014; 2014: 934595.*
15. *Andrioli M, Valcavi R. The peculiar ultrasonographic and elastographic features of thyroid nodules after treatment with laser or radiofrequency: similarities and differences. Endocrine. 2014; 47: 967-968.*

16. *Cakir B, Topaloglu O, Gul K, Agac T, Aydin C, Dirikoc A, Gumus M, Yazicioglu K, Ersoy RU, Ugras S. Effects of percutaneous laser ablation treatment in benign solitary thyroid nodules on nodule volume, thyroglobulin and anti-thyroglobulin levels, and cytopathology of nodule in 1 yr follow-up. Journal of Endocrinological Investigation. 2006; 29: 876–884.*
17. *Yue W, Wang S, Wang B, Xu Q, Yu S, Yonglin Z, Wang X. Ultrasound guided percutaneous microwave ablation of benign thyroid nodules: safety and imaging follow-up in 222 patients. Eur J Radiol. 2013; 82: e11-16.*
18. *Esnault O, Franc B, Ménégaux F, Rouxel A, De Kerviler E, Bourrier P, Lacoste F, Chapelon JY, Leenhardt L. High-intensity focused ultrasound ablation of thyroid nodules: first human feasibility study. Thyroid. 2011; 21: 965-973.*
19. *Yu N, Leese GP, Smith D et al. The natural history of treated and untreated primary hyperparathyroidism: the Parathyroid Epidemiology and Audit Research Study. Quart J Med 2011; 104: 513–521.*
20. *Fraser WD. Hyperparathyroidism. Lancet 2009; 374: 145–158.*
21. *Rubin MR, Bilezikian JP, McMahon DJ et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. J Clin Endocrinol Metab 2008; 93: 3462–3470.*
22. *Bilezikian JP, Potts JTJr, Fuleihan Gel-H et al. Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. J Clin Endocrinol Metab 2002; 87: 5353–5361.*

23. *Macfarlane DP, Yu N, Donnan PT et al. Should 'Mild Primary Hyperparathyroidism' be reclassified as 'insidious': is it time to reconsider? Clinical Endocrinol 2011; 75: 730–737.*
24. *Faggiano A, Di Somma C, Ramundo V et al. Cinacalcet hydrochloride in combination with alendronate normalizes hypercalcemia and improves bone mineral density in patients with primary hyperparathyroidism. Endocr 2011; 39: 283–287.*
25. *Bilezikian JP, Khan AA, Potts JTJr. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. J Clin Endocrinol Metab 2009; 94: 335–339.*
26. *Sociedade Brasileira de Endocrinologia e Metabologia, Bandeira F, Griz L, Chaves N, Carvalho NC, Borges LM, Lazaretti-Castro M, Borba V, Castro LC, Borges JL, Bilezikian J. Diagnosis and management of primary hyperparathyroidism--a scientific statement from the Department of Bone Metabolism, the Brazilian Society for Endocrinology and Metabolism. Arq Bras Endocrinol Metabol. 2013; 57: 406-424.*
27. *Bollerslev J, Marcocci C, Sosa M, Nordenström J, Bouillon R, Mosekilde L. Current evidence for recommendation of surgery, medical treatment and vitamin D repletion in mild primary hyperparathyroidism. Eur J Endocrinol. 2011; 165: 851-864.*

CHAPTER 2:

Quality of life in patients treated with radiofrequency ablation for thyroid nodules.

Oddo S, Felix E, Repetto A, Mussap M, Giusti M.

Res J Endocrinol Metab. 2016; 4: 1

Background

The greater availability of diagnostic techniques, together with an increase in attention to thyroid diseases, has led to a significant rise in diagnoses of thyroid cancer [1]. Consequently, the number of thyroidectomies for malignant disease is destined to grow. It is therefore essential to use minimally invasive techniques, such as thyroid radiofrequency ablation (RFA), in order to reduce the number of surgical procedures for benign diseases. Percutaneous thyroid RFA procedures are less expensive than thyroidectomy, whether total or partial, do not require hospitalization and cause only mild and rare adverse events. Moreover, they can be undertaken in patients with contraindications for surgery due to comorbidities.

Since 2010, the AACE-AME-ETA guidelines have recommended thyroid RFA as a possible therapeutic option for the treatment of benign thyroid nodules [2]. Indications for RFA in thyroid nodules are: symptomatic benign disease (discomfort or pain in the neck, dysphagia, foreign body sensation, coughing or discomfort), aesthetic problems or autonomous functioning nodules [3]. Thyroid RFA can also be used to treat autonomous nodules if radiometabolic therapy is refused or not practicable [2]. For cystic nodules, mini-invasive therapy is considered in the case of regrowth after percutaneous ethanol ablation [3].

While many studies have reported reductions in treated nodules and improvements in the sense of pressure and aesthetic symptoms [**4**], only one study has described changes in quality of life (QoL).

The aim of our study was to evaluate QoL changes in a cohort of patients treated with RFA for benign thyroid nodules from 2012 to 2015 in our department. QoL was monitored by means of a 13-scale questionnaire validated for thyroid diseases, namely Thyroid-specific Patient Reported Outcome (ThyPRO) [**5**]. Moreover, we assessed the efficacy of the procedure in correlation with certain features of the treated nodules and of patients, and recorded the frequency of adverse events and improvement in neck discomfort.

Materials and methods

Subjects

From January 2012 to March 2015, patients with a benign thyroid nodule or a single predominant benign thyroid nodule (> 30 mm in diameter) in the context of a multi-nodular goitre were evaluated in our department with a view to undergoing percutaneous thyroid RFA. These patients had either refused total or subtotal thyroidectomy or had comorbidities that contraindicated surgery. All patients signed an informed consent form that included a detailed explanation of the procedure and its purpose. The study was performed in compliance with the Helsinki Declaration and was approved by University of Genoa Ethics Committee.

From January 2012 to March 2014, we enrolled 32 patients (24 females and 8 males) aged between 36 and 80 years (mean 56 ± 14 years) with a single thyroid nodule or a predominant thyroid nodule (> 30 mm in diameter) in a multi-nodular goitre; 11 patients (34%) had a single nodule, while 21 (66%) had a prevalent nodule (> 30 mm in diameter) in the context of a goitre. These nodules, which had been discovered 9±11 years earlier, were located in the right lobe in 13 patients (41%), in the left lobe in 18 patients (56%) and in the isthmus in 1 patient (3%). Two patients had undergone ethanol ablation of the nodule approximately one year earlier, without significant benefit. One patient had undergone radioiodine therapy, without apparent benefit. Seven patients were on L-T4 replacement therapy for hypothyroidism at a mean dose of 329±156 mcg/week. Another patient was taking methimazole (2.5 mg/day) for a pre-toxic goitre, which displayed no hot areas on scintigraphy.

After retrospective subdivision of patients into two groups (n=16 each group), no differences were observed in terms of sex, age, BMI, time since diagnosis, functional status of thyroid, nodule volume on enrolment, Joules administered during thyroid RFA, symptomatic visual analogic scale (VAS) (table 1) or ThyPRO score (table 2).

Protocol

To perform thyroid RFA, we followed the indications of the Consensus Statement of the Korean Society of Thyroid Radiology [3]. Before procedures, patients underwent complete anamnesis and physical examination, routine blood tests and thyroid function tests (f-T3, f-T4, TSH), evaluation of thyroid autoimmunity, calcitonin and thyroglobulin, ECG and phoniatric examination.

The volume (ml) of the nodule undergoing thyroid RFA was evaluated by means of the ellipsoid formula: antero-posterior diameter x latero-lateral diameter x cranio-caudal diameter x 0.52 /1000. This formula was also used to calculate the total volume of each thyroid lobe [6].

Before thyroid RFA, patients underwent FNAB cytology on the nodule on two separate occasions, to confirm benignity (Thy 2 in accordance with the British Thyroid Association [7]). Only patients with a finding of benignity on both occasions underwent thyroid RFA.

Patients filled out both a VAS that rated neck discomfort and a 13-scale Thyroid-specific Patient Reported Outcome (ThyPRO) QoL questionnaire validated for patients with thyroid disease [5].

Clinical examinations, assessments of thyroid function and thyroid autoimmunity and VAS evaluation were repeated after 1 week and 1, 3 and 6 months, and then annually.

ThyPRO and ultrasound thyroid volume were evaluated after 1, 3 and 6 months, and then annually. Phoniatric examination was repeated if symptoms related to chordal dysmotility appeared after the procedure.

Subsequently, according to the percentage reduction of the treated nodule at the last evaluation, patients were divided into two groups: those with ≥30% reduction (group 1) and those with <30% reduction (group 2). We looked for possible correlations between the degree of nodule reduction and some parameters: baseline volume nodule, Joules administered during thyroid RFA, time since diagnosis, hormonal status (TSH, f-T3, f-T4, thyroglobulin on enrolment and 1 week after the procedure) and patient age. The value of 30% was chosen in accordance with the mean percentage of nodule volume reduction recorded in our centre.

Procedures

Procedures were carried out in a day-hospital regimen. Antiplatelet and anticoagulant therapies were suspended for an appropriate time before the procedure. On the day of the procedure, patients were in a fasting state. After placement of a venous catheter, patients underwent intravenous infusion of ketorolac (20 mg) and ranitidine (50 mg) diluted in 100 ml of 0.9% saline solution for 30 minutes. Subsequently, intravenous ketorolac (40 mg) and ranitidine (50 mg) were administered in 500 ml of 0.9% saline for about 5 hours (during and after thyroid RFA). In subjects allergic to ketorolac or in patients with moderate-to-severe renal impairment, premedication with intravenous paracetamol (500 mg) was carried out before and during the procedure. After thyroid RFA, a compressive bandage and ice were applied to the

neck. Patients were allowed a light meal before being discharged in the early afternoon. All subjects received a domiciliary prescription for steroid administration (prednisone 25 mg for 3 days, 12.5 mg for 3 days, 6.25 for 3 days) and gastric protection, if not already ongoing.

Methods

Thyroid RFA was performed by means of 7 cm, 18 Gauge electrodes with a 1 cm active tip (Starmed, Seoul, Korea). Procedures were performed with the support of an ultrasound echo-Laser XVG (Esaote, Genoa, Italy) with a 7.5 MHz linear probe (LA523).

Follow-up ultrasound examinations were performed by means of a MyLab Five (Esaote, Genoa, Italy) ultrasound scanner with a 7.5 MHz linear probe (LA523) (Esaote, Genoa, Italy).

The radiofrequency generator used was an RF System Viva VRS01 (Starmed, Seoul, Korea). The peristaltic pump was an R4S100 (Starmed, Seoul, Korea).

Thyroid RFA was performed in a single session by a single operator with 3 years' experience by means of a moving-shot technique and trans-isthmic access.

Laboratory tests

TSH, f-T3 and f-T4 were measured by means of ultra-sensitive chemiluminescence immunoassay (Cobas® e602, Roche Diagnostics, Milan, Italy). The normal ranges are: 0.27-4.2 mIU/L for TSH, and 2.76-7.07 pmol/L and 11.97-21.88 pmol/L for f-T3 and f-T4, respectively. TPOAb and TgAb were evaluated by means of DiaSorin (Saluggia, Italy), concentrations <100 mU/L being regarded as negative. Calcitonin was measured

by chemiluminescence immunoassay (DiaSorin); in our laboratory the normal value is <10 ng/L. Automated complete blood counts were taken by an ADVIA 2120 automated counter (Siemens Healthcare, Milan, Italy); coagulation tests were performed by means of an automated BCS analyzer (Siemens Healthcare, Milan, Italy), and biochemical tests for the routine assessment of hepatic and renal function on the fully-automated Cobas® c701 platform (Roche Diagnostics, Milan, Italy).

Questionnaires

The subjective benefits of thyroid RFA were evaluated several times during the study by means of a VAS questionnaire with a score ranging from 0 (no symptoms/discomfort) to 10 (highest level of symptoms/discomfort).

QoL was assessed before the procedure, after 1, 3 and 6 months and then annually, by means of ThyPRO, a validated questionnaire for thyroid diseases which consists of 13 scales with multiple-choice answers (0 = "none"; 1 = "slight"; 2 = "moderate"; 3 = "severe"; 4 = "very severe"). The ThyPRO scales concern the following aspects: goitre symptoms, hyperthyroid symptoms, hypothyroid symptoms, eye symptoms, tiredness, cognitive problems, anxiety, depressivity, emotional susceptibility, impaired social life, impaired daily life, impaired sexlife, cosmetic complaints.

We also evaluate a further scale, present in the questionnaire that answer to the question "in the last 4 weeks thyroid disease has had a negative effect on your quality of his life?", that we call "general score". Lastly we consider also the mean values of 13-scales score.

Statistical analysis

All data were analysed by means of GraphPad Prism for Windows (Version 6.0, GraphPad Software, San Diego, CA, USA). The data are presented as means ± SD, unless otherwise indicated. Continuous data were compared by means of the Mann-Whitney test, while percentages were compared by means of the Fisher test. Correlations between variables were assessed by means of the Spearman correlation. A P value <0.05 was deemed to indicate significance.

Results

Procedure effects

Procedures were stopped when all portions of the nodule had been ablated, with particular attention being paid to danger triangle and the nodular capsule. Procedures lasted 7 ± 3 minutes on average (range: 2:45 – 15:00 min), with a mean delivery of 1575 ± 767 J/ml (range: 13607 – 43459 J; 349 – 3171 J/ml) at a mean power of 42 ± 5 W (range: 40 - 50 W). On enrolment, the mean volume of the nodules was 22 ± 14 ml (range: 7 - 38 ml) and the total gland volume was 39 ± 16 ml (range: 14 - 76 ml) (table 3). Table 3 reports the reduction in nodular and thyroid volumes at each time-point of the study. The percentage volumetric reductions in the RFA-treated thyroid nodules and in the thyroid volume were statistically significant at 1, 3, 6, 12 and 24 months (table 3).

There was no significant correlation between percentage volume reduction and joules administered during the procedure, baseline nodule volume or years since diagnosis. A significant correlation between better reduction and patient age ($P = 0.039$; $r = 0.365$; CI 95% = 0.008-0.639) was found (figure 1).

Changes in thyroid parameters

Parameters of thyroid function at the baseline and at the various time-points are reported in table 4. One week after thyroid RFA, F-T4 levels were significantly ($P=0.02$) increased, although in the normal range. By the month-1 follow-up examination, they had returned to baseline levels (table 3). In one case (3%) f-T4 increased beyond the

normal range, probably owing to iatrogenic destructive thyrotoxicosis, but spontaneously returned to the normal range about 1 month after thyroid RFA. During follow-up, one patient developed overt hypothyroidism, which required L-T4 replacement therapy; this patient had previously displayed TSH and f-T4 values suspicious for overt hypothyroidism. F-T3 and TSH levels did not exhibit significant changes (table 4). None of the subjects on L-T4 therapy on enrolment had to increase the dosage. Thyroid autoantibody positivity was observed in 28% of patients (n= 9); this percentage was the same at the last evaluation. Thyroglobulin levels were significantly increased 1 week after thyroid RFA (P = 0.049) and returned to values comparable to the baseline approximately one month after thyroid RFA (P = 0.77) (table 4). No significant correlation was found between percentage volume reduction and hormonal data (TSH, f-T3, f-T4, thyroglobulin on enrolment and after procedure).

Subjective complaints

During the procedure, 28 patients (88%) experienced discomfort in the neck, 12 patients (38%) experienced pain which required a reduction in the voltage of the source of radiofrequency, 4 (13%) suffered slight haemorrhage from the site of electrode insertion and 1 patient (3%) had neck oedema. Twelve patients (38%) did not experience any problems.

One week after the procedure, 12 patients (38%) did not have any problems, 9 (28%) felt discomfort in the neck, 3 (9%) felt pain (mean VAS score: 2), 3 (9%) had a haematoma, and 1 (3%) had oedema in the neck. These symptoms did not require any

kind of medication and resolved spontaneously during the 1st month. No patient suffered hoarseness, dysphagia, nodule rupture, major bleeding or infections.

The VAS score was 3±3 at the baseline; at the last evaluation, it was lower, but not significantly so (p = 0.06) (table 5). Specifically, it decreased significantly from the 1st month to the 6th month after thyroid RFA, but then seemed to worsen at 12, 24 and 36 months (table 5).

In patients with VAS >0 on recruitment (n=23), 74% (n=17) reported an improvement in symptoms, 17% (n=3) stability of symptoms and 17% (n=3) worsening of neck symptoms.

The score on each single scale of the ThyPRO questionnaire was unchanged after thyroid RFA (figure 2). By contrast, the "general scale" of ThyPRO showed a significant improvement in scores (P=0.02) from the baseline to the 3rd month; this QoL improvement persisted over time (figure 3). Likewise, analysis of the ThyPRO scores of group 1 patients (nodule reduction>30%) revealed that single scores on the 13 scales did not change significantly.

Discussion

We performed all thyroid RFA procedures according to the consensus statement of the Korean Society of Thyroid Radiology [3]. The duration of thyroid RFA in our hands was much lower than that reported in the literature [8]. This difference can be ascribed to the personal choice of the operator, whose main objective was to prevent severe side effects. Indeed, the appearance of transient hyperechoic zone during thyroid RFA may hinder visualization of the electrode, thus jeopardizing the safety of the procedure. It is therefore not surprising that the mean reduction in nodular volume was slightly lower in our hands than in other centres [4]. However, the reduction in volume remained stable over time, at least up to the 24^{th} month after the procedure, as reported in other studies [4, 9].

To our knowledge, there are no data on the relationship between thyroid RFA efficacy and nodule echogenicity or the presence of UNG or MNG; this issue was addressed in our study, but no significant results emerged. Similarly, no study in the literature has analysed the response to thyroid RFA as a factor of patient age, sex, BMI, time since diagnosis, L-T4 therapy and hormonal status; our evaluation did not yield a significant correlation between thyroid RFA efficacy and any of these features, apart from age. Indeed, in our cohort, older patients displayed a better reduction in thyroid nodule volume; we do not know the reason for this finding, but we might hypothesize a different intracellular content in older patients, which could facilitate necrosis after thyroid RFA.

In two of our patients, thyroid RFA was performed approximately one year after percutaneous ethanol ablation. In these two patients, there was no significant

reduction in volume even after thyroid RFA; in a study by Sung et al. (2013), both thyroid RFA and percutaneous ethanol ablation of cystic thyroid nodules seemed to be effective, achieving similar volume reductions[10].

Thyroid RFA-treated patients did not have any serious complications during or after the procedure; no patient reported symptoms or showed signs of complications of severity comparable to those cited in the literature, which reports a percentage of around 3-5% [11].

In our study, thyroid RFA did not lead to significant changes in thyroid function or thyroid autoimmunity. The levels of thyroglobulin and f-T4 increased significantly a week after the procedure, but returned to their previous values about one month after the treatment. These data have not been reported in any other study.

Many studies have reported improvements in neck discomfort and aesthetic symptoms after thyroid RFA. In the literature, aesthetic issues have been assessed by means of a score (generally from 1 to 4 or from 0 to 3) [12]. In our study, we used the aesthetic scale of ThyPRO, which did not reveal any improvement after thyroid RFA. However, it should be noted that all our patients had very low baseline scores on this scale. In many studies, neck discomfort has been evaluated by means of a score (usually from 1 to 4 or from 0 to 3) [3]. Like us, Baek et al. [9] used a 10 cm VAS analogue scale [9]. A recent study by Valcavi et al. (2015) reported an improvement in VAS from 5.6 ± 3.1 cm to 1.9 ± 1.3 cm [14] after 2-year follow-up of benign thyroid nodules treated with thyroid RFA.

Our patients displayed a significant improvement in VAS at the 1^{st}, 3^{rd} and 6^{th} month follow-up examinations; however, the significance seemed to shrink with time. Thus,

at 12 months, the improvement in neck discomfort was at the limit of significance; this borderline significance was lost after the 12th month, probably because of the decrease in the number of patients at the subsequent time-points of the study.

QoL is defined as a person's perception of his/her position in life, in the context of the culture and system of values in which he/she lives and in relation to its objectives, expectations, standards and concerns [14].

In the case of thyroid diseases, QoL is often assessed by means of various inventories (e.g. SF-36, Hamilton scale and the Kellner Symptoms Questionnaire). Questionnaires for QoL evaluation have been used in numerous benign and malignant thyroid diseases, such as benign goitre treated with RAI following rhTSH premedication, autoimmune hypothyroidism and chronic autoimmune thyroiditis [14-23]. Only one study has reported changes in QoL in patients treated with RFA for benign thyroid nodules; Valcavi et al. (2015) reported a significant improvement in QoL in 40 patients treated with RFA for benign thyroid nodules, as assessed by means of the Physical Component Summary (from 50.4 ± 8.9 to 54.5 ± 5.3) and Mental Component Summary (from 36.0 ± 13.3 to 50.3 ± 6.3) after 2 years of follow-up [13]. This questionnaire consists of 8 scales, 3 of which concern physical health (physical functioning, limitation of specific activities due to physical problems, pain), 2 reflect general health (general health and vitality), and the remaining 3 measure aspects of psychological and emotional health (social activities, limitation of specific activity due to emotional problems, mental health). The Physical Component Summary and Mental Component Summary are two synthetic indexes that summarize the results of the 8 scores in just two numbers: the higher the score, the better the level of health perceived [13].

In our study, none of the scores on the single ThyPRO scales changed significantly from the baseline to the last evaluation. However, the overall score was significantly lower at the month-3 evaluation, and this reduction persisted over time. To our knowledge, no data on QoL evaluated by means of ThyPRO in patients treated with RFA for thyroid nodules have been reported.

Some studies in the literature have evaluated QoL by means of ThyPRO after other therapies for goitre. Fast et al. (2014) found that the majority of patients treated with rhTSH for goitre reported an improvement in symptoms on the specific ThyPRO scale concerning goitre, and that the improvement persisted at least up to the 36^{th} month [19]. Moreover, according to studies conducted by two groups of surgeons on patients who had undergone thyroidectomy for goitre, QoL improved significantly after surgery, whether total thyroidectomy or hemithyroidectomy had been performed [24, 25].

Conclusions

In conclusion, our study shows that thyroid RFA can be effective both in reducing the volume of the nodule and in alleviating neck symptoms. In our study, the efficacy of thyroid RFA correlated with patient age. The procedure proved to be safe; adverse events were few and mild in comparison with surgery or radioiodine therapy. Thyroid RFA was well tolerated by patients and VAS scores improved a few months after the procedure. However, in our cohort of patients, scores on the 13 individual ThyPRO scales did not improve after RFA for benign non-functioning thyroid nodules. By contrast, the "general scale" of ThyPRO, which answers the question "In the last 4 weeks, has thyroid disease had a negative effect on your quality of his life?", showed a significant improvement in scores, and this QoL improvement persisted over time.Further studies will be necessary in order to confirm or contradict our data, especially in a cohort of patients with a better response to thyroid RFA in terms of nodule volume reduction.

References

1. Shah JP. Thyroid carcinoma: epidemiology, histology and diagnosis. Clin Adv Hematol Oncol. 2015; 13:3-6.

2. Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, Hegedus L and Vitti P.American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: Executive Summary of recommendations. J Endocrinol Invest. 2010; 33:287-291.

3. Na DG, Lee JH, Jung SL, Kim JH, Sung JY, Shin JH, Kim EK, Kim DW, Park JS,Kim KS, Baek SM, Lee Y, Chong S, Sim JS, Huh JY, Bae JI, Kim KT, Han SY,Bae MY, Kim YS and Baek JH. Radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: consensus statement and recommendations. Korean J Radiol. 2012; 13:117-125.

4. Papini E, Pacella CM, Misischi I, Guglielmi R, Bizzarri G, Dossing H and Hegedus L. The advent of ultrasound-guided ablation techniques in nodular thyroid disease: towards a patient-tailored approach. Best PractRes Clin Endocrinol Metab. 2014; 28:601-618.

5. Watt T, Hegedus L, Groenvold M, Bjorner JB, Rasmussen AK, Bonnema SJ and Feldt-Rasmussen U. Validity and reliability of the novel thyroid specific quality of life questionnaire, ThyPRO. Eur J Endocrinol. 2010;162:161-167.

6. Le Moli R, Wesche MF, Tiel-Van Buul MM and Wiersinga WM. Determinants of longterm outcome of radioiodine therapy of sporadic non-toxic goitre. Clin Endocrinol (Oxf). 1999; 50:783-789.

7. Agarwal A and Kocjan G. FNAC thyroid reporting categories: value of using the British Thyroid Association (Thy 1 to Thy 5) thyroid FNAC reporting guidelines. Cytopathology. 2009; 20:133-134.

8. Gharib H, Hegedus L, Pacella CM, Baek JH and Papini E. Clinical review: Nonsurgical, image-guided, minimally invasive therapy for thyroid nodules. J Clin Endocrinol Metab. 2013; 98:3949-3957.

9. Baek JH, Kim YS, Lee D, Huh JY and Lee JH. Benign predominantly solid thyroid nodules: prospective study of efficacy of sonographically guided radiofrequency ablation versus control condition. AJR Am J Roentgenol. 2010; 194:1137-42.

10. Sung JY, Baek JH, Kim KS, Lee D, Yoo H, Kim JK and Park SH. Single session treatment of benign cystic thyroid nodules with ethanol versus radiofrequency ablation: a prospective randomized study. Radiology. 2013; 269:293-300.

11. Baek JH, Lee JH, Sung JY, Bae JI, Kim KT, Sim J, Baek SM, Kim YS, Shin JH, Park JS, Kim DW, Kim JH, Kim EK, Jung SL and Na DG. Complications encountered in the treatment of benign thyroid nodules with US-guided radiofrequency ablation: a multicenter study. Radiology. 2012; 262:335-342.

12. Wong KP and Lang BH. Use of radiofrequency ablation in benign thyroid nodules: a literature review and updates. Int J Endocrinol. 2013;2013:428363.

13. Valcavi R and Tsamatropoulos P. Health-Related Quality of Life after Percutaneous Radiofrequency Ablation of Cold, Solid, Benign Thyroid Nodules: A 2-Year Follow-up Study in 40 Patients. Endocr Pract. 2015;21:887-896.

14. Crevenna R, Zettinig G, Keilani M, Posch M, Schmidinger M, Pirich C, Nuhr M, Wolzt M, Quittan M, Fialka-Moser V and Dudczak R. Quality of life in patients with non-

metastatic differentiated thyroid cancer under thyroxine supplementation therapy. Support Care Cancer. 2003; 11:597-603.

15. Giusti M, Sibilla F, Cappi C, Dellepiane M, Tombesi F, Ceresola E, Augeri C, Rasore E and Minuto F. A case-controlled study on the quality of life in a cohort of patients with history of differentiated thyroid carcinoma. J Endocrinol Invest. 2005; 28:599-608.

16. Giusti M, Melle G, Fenocchio M, Mortara L, Cecoli F, Caorsi V, Ferone D, Minuto F and Rasore E. Five-year longitudinal evaluation of quality of life in a cohort of patients with differentiated thyroid carcinoma. J Zhejiang Univ Sci B. 2011; 12:163-173.

17. Hoftijzer HC, Heemstra KA, Corssmit EP, van der Klaauw AA, Romijn JA and Smit JW. Quality of life in cured patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2008; 93:200-203.

18. Tan LG, Nan L, Thumboo J, Sundram F and Tan LK. Health-related quality of life in thyroid cancer survivors. Laryngoscope. 2007; 117:507-510.

19. Hirsch D, Ginat M, Levy S, Benbassat C, Weinstein R, Tsvetov G, Singer J, Shraga-Slutzky I, Grozinski-Glasberg S, Mansiterski Y, Shimon I and Reicher-Atir R. Illness perception in patients with differentiated epithelial cell thyroid cancer. Thyroid. 2009; 19:459-465.

20. Fast S, Hegedus L, Pacini F, Pinchera A, Leung AM, Vaisman M, Reiners C, Wemeau JL, Huysmans DA and Harper W et al. Long-term efficacy of modified-release recombinant human thyrotropin augmented radioiodine therapy for benign multinodular goiter: results from a multicenter, international, randomized, placebo-controlled, dose-selection study. Thyroid. 2014; 24:727-735.

21. Watt T, Hegedus L, Bjorner JB, Groenvold M, Bonnema SJ, Rasmussen AK and Feldt-Rasmussen U. Is Thyroid Autoimmunity per se a Determinant of Quality of Life in Patients with Autoimmune Hypothyroidism? Eur Thyroid J. 2012; 1:186-192.

22. Giusti M, Caorsi V, Mortara L, Caputo M, Monti E, Schiavo M, Bagnara MC, Minuto F and Bagnasco M. Long-term outcome after radioiodine therapy with adjuvant rhTSH treatment: comparison between patients with non-toxic and pre-toxic large multinodular goitre. Endocrine. 2014; 45:221-229.

23. Winther KH, Watt T, Bjorner JB, Cramon P, Feldt-Rasmussen U, Gluud C, Gram J, Groenvold M, Hegedus L, Knudsen N, Rasmussen AK and Bonnema SJ. The chronic autoimmune thyroiditis quality of life selenium trial (CATALYST): study protocol for a randomized controlled trial. Trials. 2014; 15:115.

24. Mishra A, Sabaretnam M, Chand G, Agarwal G, Agarwal A, Verma AK and Mishra SK. Quality of life (QoL) in patients with benign thyroid goiters (pre- and post-thyroidectomy): a prospective study. World J Surg. 2013; 37:2322-2329. 25. Schmitz-Winnenthal FH, Schimmack S, Lawrence B, Maier U, Heidmann M, Buchler MW and von Frankenberg M. Quality of life is not influenced by the extent of surgery in patients with benign goiter. Langenbecks Arch Surg. 2011; 396:1157-1163.

Table 1: data on group 1 and 2 patients.

(NS= not significant; MNG: multinodular goitre; UNG: uninodular goitre)

	Group 1	Group 2	*P*
Males / Females	03 / 13	05 / 11	0.6
Age (years; mean ± SD)	60 ± 12	52 ± 14	0.71
BMI (kg/m^2; mean ± SD)	25 ± 3	27 ± 5	0.95
Time since diagnosis (years; mean ± SD)	13 ± 13	7 ± 8	0.64
VAS score (mean ± SD)	3 ± 3	3 ± 3	1
MNG / UNG	12 / 04	10 / 06	0.74
Location (right / left)	09 / 07	10 / 06	0.87
TSH (mIU/L; mean ± SD)	1.55 ± 1.13	1.24 ± 0.85	0.63
Nodule volume at baseline (ml; mean ± SD)	19 ± 10	26 ± 16	0.89
Joules administered (J/ml; mean ± SD)	1819 ± 712	1346 ± 767	0.72
Follow-up (months; mean ± SD)	15 ± 11	14 ± 9	0.85
Volume reduction (%)	45 ± 9	11 ± 17	*P*<0,0001

Table 2: ThyPRO scores at baseline in groups 1, in group 2 and total patients (mean ± SD).

Significant *P* scores are in italic form.

	Total patients			Group 1			Group 2		
	Baseline	Last Evaluation	*P*	Baseline	Last Evaluation	*P*	Baseline	Last Evaluation	*P*
Goiter symptoms	16 ± 15	18 ± 13	0,87	16 ± 16	18 ± 2	0,71	17 ± 15	14 ± 12	0,6
Hyperthyroidism symptoms	13 ± 13	10 ± 9	0,74	11 ± 13	10 ± 7	0,87	14 ± 13	11 ± 14	0,94
Hypothyroidism symptoms	15 ± 14	19 ± 10	0,71	15 ± 13	19 ± 0	0,68	16 ± 15	17 ± 19	0,85
Eye symptoms	7 ± 8	19 ± 22	0,09	8 ± 9	19 ± 16	0,19	7 ± 7	6 ± 7	0,88
Tiredness	33 ± 17	25 ± 10	0,53	28 ± 17	25 ± 7	0,69	34 ± 17	32 ± 14	0,6
Cognitive problems	12 ± 18	13 ± 12	0,96	15 ± 22	13 ± 9	0,9	9 ± 8	8 ± 9	0,84
Anxiety	19 ± 18	25 ± 35	0,66	13 ± 12	25 ± 25	0,19	24 ± 21	20 ± 16	0,64
Depressivity	26 ± 18	24 ± 8	0,95	23 ± 17	24 ± 6	0,97	28 ± 18	20 ± 18	0,37
Emotional susceptibility	22 ± 17	24 ± 18	0,9	20 ± 17	24 ± 13	0,79	27 ± 17	19 ± 16	0,5
Impaired social life	8 ± 13	16 ± 22	0,44	5 ± 9	16 ± 16	0,2	11 ± 15	5 ± 8	0,45
Impairmed daily life	9 ± 13	17 ± 23	0,44	8 ± 12	17 ± 17	0,41	10 ± 14	7 ± 11	0,63
Impaired sexlife	9 ± 20	32 ± 26	0,14	7 ± 21	32 ± 19	0,15	12 ± 19	8 ± 11	0,66
Cosmetic complaints	10 ± 13	11 ± 15	0,95	8 ± 13	11 ± 11	0,78	12 ± 13	4 ± 7	0,19
General score	29 ± 7	0 ± 0	*0*	26 ± 27	0 ± 0	*0,02*	25 ± 26	13 ± 21	0,07
Mean values	16 ± 2	19 ± 6	0,72	14 ± 11	19 ± 11	0,7	17 ± 12	13 ± 11	0,44

Table 3: reduction (mean ± SD in ml and %) of nodule and thyroid with significances.

(N= number of patients; *[1]= *P*=0.55; *[2]= *P*=0.16; *[3]= *P*=0.0017; *[4]= *P*=0.0012; *[5]= *P*=0.0006; *[6]= *P*<0.0001)

	N	Nodule volume (ml)	Nodule volume (%)	Thyroid volume (ml)	Thyroid volume (%)
Baseline	32	22 ± 14	-	39 ± 16	-
1st month	32	18 ± 11	- 18 ± 18 *[6]	34 ± 15	- 10 ± 18 *[3]
3rd month	30	16 ± 10	- 27 ± 21 *[6]	31 ± 15	- 16 ± 21 *[6]
6th month	26	16 ± 11	- 30 ± 24 *[6]	33 ± 18	- 13 ± 21 *[5]
12th month	22	16 ± 10	- 27 ± 22 *[6]	31 ± 15	- 14 ± 24 *[4]
24th month	10	17 ± 11	- 26 ± 24*[1]	31 ± 14	- 17 ± 19 *[6]
36th month	2	12 ± 6	- 45 ± 5 *[6]	40 ± 25	- 5 ± 30 *[2]

Table 4: changes in thyroid function.

(N= number of patients; *[1]=*P*=0.03; *[2]= *P*=0.04)

	N	TSH (mIU/L)	f-T3 (pmol/L)	f-T4 (pmol/L)	Thyroglobulin (µg/L)
Baseline	32	1.4 ± 0.99	4.88 ± 0.65	15.4 ± 2.29	399.15 ± 778.28
1st week	32	1.36 ± 1.22	4.88 ± 0.52	17.13 ± 3.56 *1	1243.70 ± 2254.49 *2
1st month	32	1.27 ± 0.76	4.82 ± 0.60	14.80 ± 3.41	343.82 ± 779.13
3rd month	30	1.26 ± 0.86	4.96 ± 0.60	15.70 ± 2.33	325.06 ± 686.08
6th month	26	1.34 ± 0.75	4.73 ± 0.49	14.54 ± 3.27	494.48 ± 1114.1
12th month	22	1.33 ± 0.92	4.72 ± 0.66	15.02 ± 1.21	280.55 ± 523
24th month	10	1.35 ± 0.94	4.98 ± 0.55	14.67 ± 2.39	297.17 ± 759.51
36th month	2	1.08 ± 0.5	6.03 ± 0.28	14.48 ± 0.09	67 ± 91.2

Table 5: changes in VAS score (mean ± SD).

(N= number of patients; *= *P*=0.02)

	N	score
Baseline	32	3 ± 3
1st week	32	2 ± 2
1st month	32	1 ± 2 *
3rd month	30	1 ± 2 *
6th month	26	1 ± 2 *
12th month	22	1 ± 2
24th month	10	3 ± 2
36th month	2	3 ± 4

Figure 1: correlation between nodule reduction (%) and age of patients.

The x-axis indicates the age of the patients; the y-axis indicates the volume reduction of thyroid nodules. In our study, there was a significant correlation between percentage nodule reduction and patient age: older patients had a greater reduction.

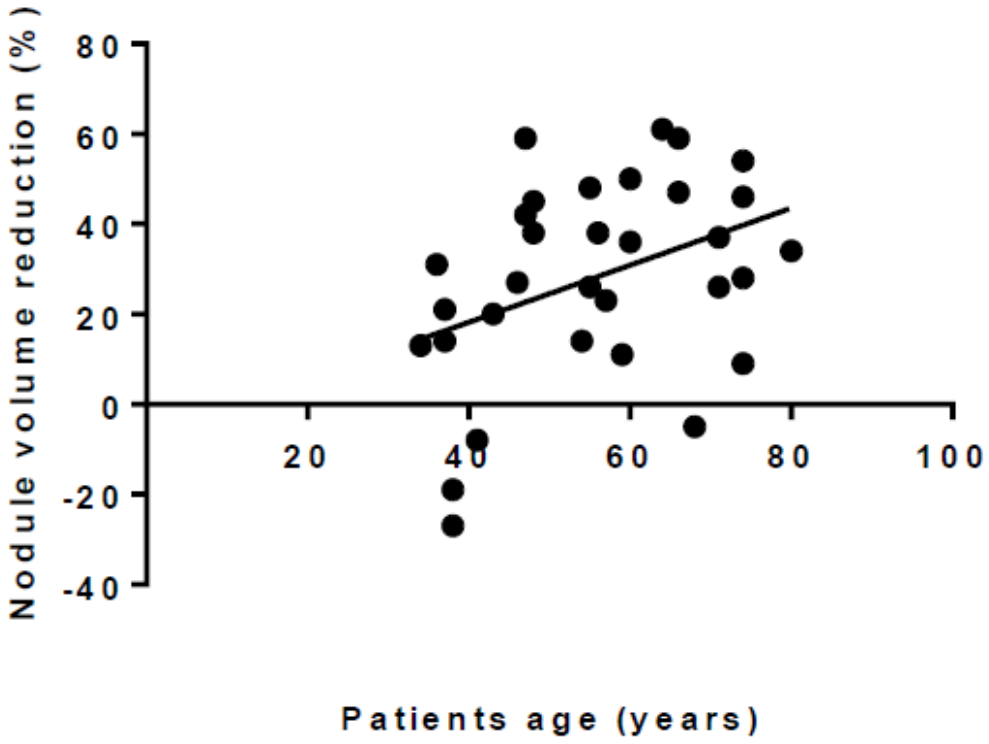


Figure 2: changes in ThyPRO score.

The six graphs show the scores on the 13 scales of ThyPRO at different times of the study (1 month, 3 months, 6 months, 12 months, 24 months and 36 months) compared with the baseline. None of the 13 scales significantly changed from the baseline at any time of the study.

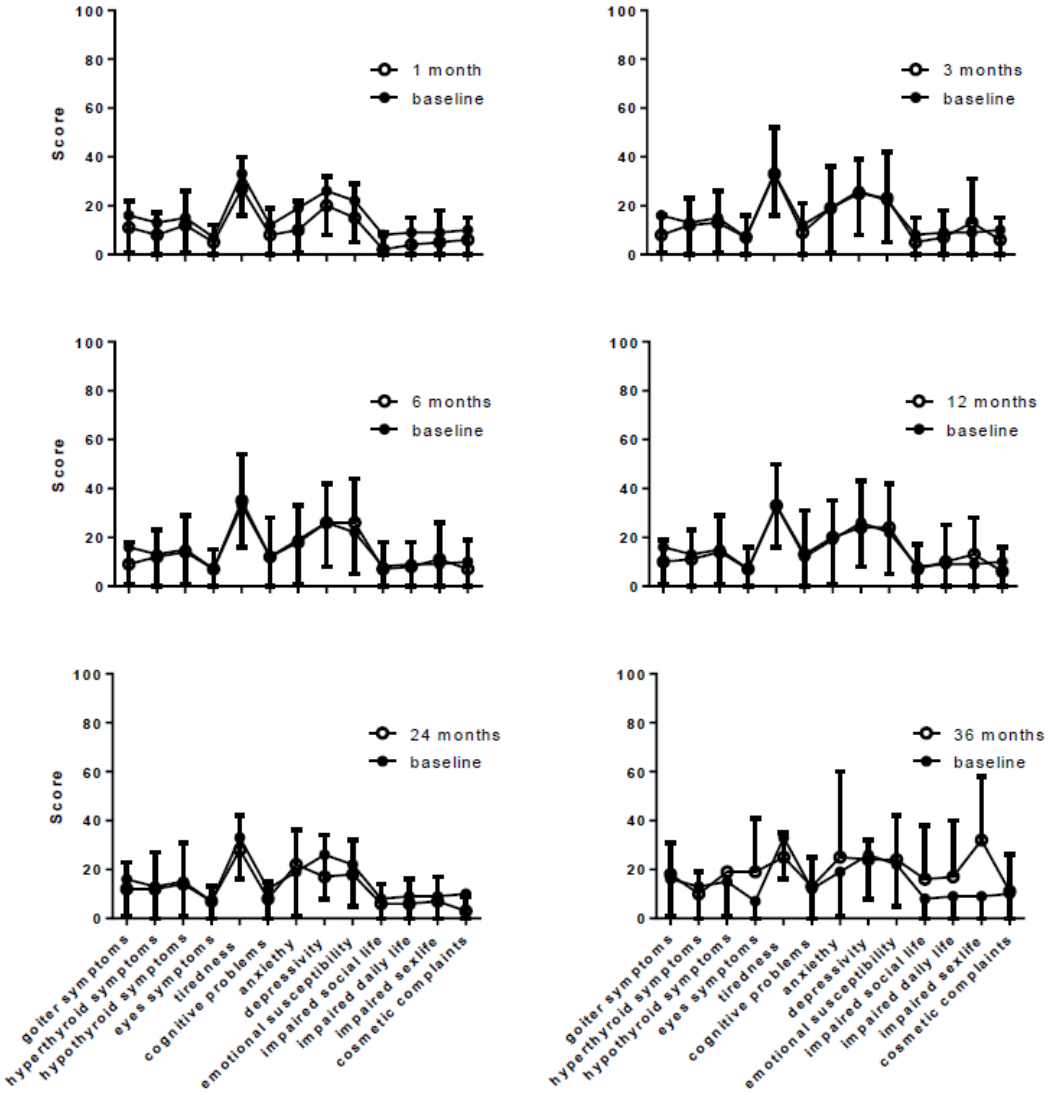
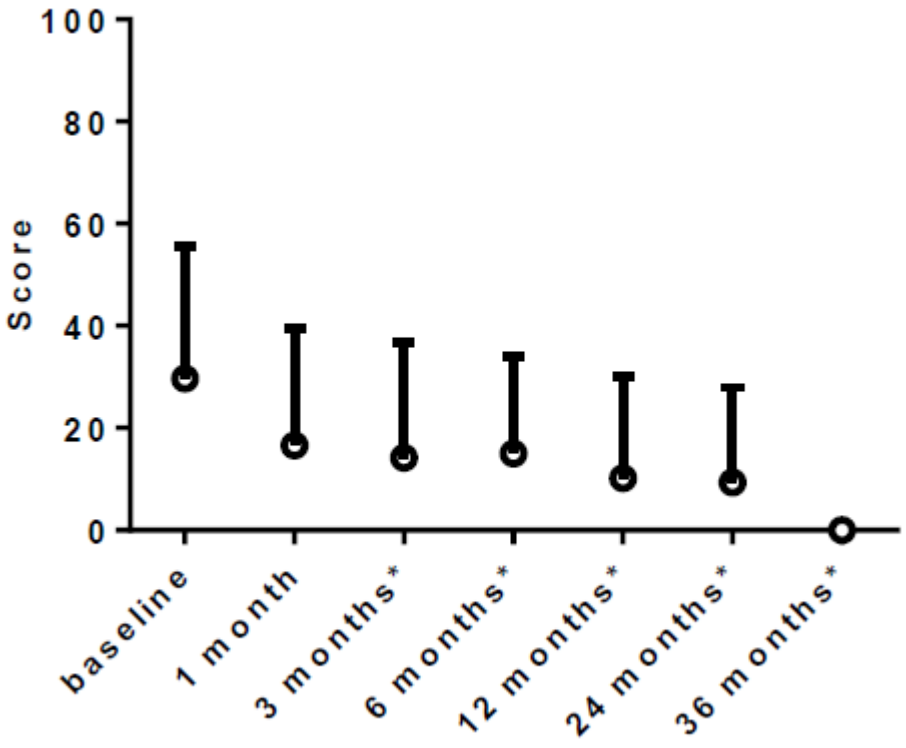


Figure 3: "general score" of ThyPRO.

The "general score" of ThyPRO, which answers the question "In the last 4 weeks, has thyroid disease had a negative effect on your quality of life?", improved from the 3rd month onwards. * = *P* <0.05



CHAPTER 3:

Quality of life in patients treated with percutaneous laser ablation for non-functioning benign thyroid nodules: a prospective single-center study.

Oddo S, Felix E, Mussap M, Giusti M.

Korean Journal of Radiology. 2018; 19: 175-184.

Background

Since 2010, the American Association of Clinical Endocrinologists-Associazione Medici Endocrinologi-European Thyroid Association (AACE-AME-ETA) guidelines have recommended laser ablation (LA) as a possible therapeutic option for the treatment of benign symptomatic thyroid nodules in patients who refuse thyroidectomy, or in those with comorbidities that contraindicate surgery [1]. LA tends to be less expensive than thyroidectomy, whether total or partial. LA also does not require hospitalization, and causes only mild and rare adverse events. Thus, it can be undertaken in patients with contraindications for surgery or in those who refuse surgery. Moreover, compared with surgery, minimally invasive procedures for benign thyroid nodules preserve normal thyroid function [2].

Other non-surgical treatments for benign thyroid nodules include other percutaneous techniques, such as ethanol ablation, microwave or radiofrequency, and high-intensity focused ultrasound [3]. LA, radiofrequency ablation (RFA), and ethanol ablation are also utilized for recurrent thyroid cancer [3].

Other non-invasive techniques for reducing benign thyroid nodules are radioiodine with recombinant thyroid-stimulating hormone (TSH) [4] or suppressive levothyroxine (L-T4) therapy [5].

While many studies have reported reductions in treated nodules and improvements in the sense of pressure and in esthetic symptoms [3] after LA, none have described changes in quality of life (QoL). The aim of our study was to therefore evaluate QoL changes in a cohort of patients treated with a single session of LA for benign thyroid nodules.

Materials and methods

We conducted this prospective single-center study at the endocrinology department of IRCSS AOU San Martino University-IST of Genoa (Italy) from September 2014 to September 2015. All patients signed an informed consent form that included a detailed explanation of the LA procedure and its purpose. Our Ethics Committee approved the LA treatment protocol.

Subjects

We evaluated patients with benign thyroid nodules, solid or nearly completely solid (with a liquid component not exceeding 30%), single or clearly detectable in a multinodular goiter, with a view to undergoing percutaneous LA [3]. These patients had either refused total or subtotal thyroidectomy, or had comorbidities that contraindicated surgery.

We enrolled 14 patients (12 females and 2 males) aged between 38 and 72 years (mean ± standard deviation [SD], 55 ± 10 years) with a single thyroid nodule (n = 8, 57%) or a predominant thyroid nodule in a goiter (n = 6, 43%).

These nodules, which had been discovered 7 ± 8 years earlier, were located in the right lobe in 10 patients (71%) and in the left lobe in six patients (29%). No patient had undergone ethanol ablation of the nodule or radioiodine therapy. Two patients were on L-T4 replacement therapy for hypothyroidism at a mean dosage of 616 ± 124 μg/weekly. Table 1 reports on patients' features.

Pre-ablation assessment and procedures

Before performing LA, we excluded contraindications for the procedures, as recommended in the Consensus Statement of the Korean Society of Thyroid Radiology for RFA [6]. Before LA, patients underwent the following: a review of clinical data and physical examination; routine blood tests and thyroid function tests (free T3 [f-T3], free T4 [f- T4]; TSH); evaluation of anti-thyroid peroxidase antibodies (TPOAbs), calcitonin, thyroglobulin, electrocardiography; and a phoniatric examination. We evaluated the volume (mL) of the nodule undergoing LA by means of the ellipsoid formula: antero-posterior diameter x latero-lateral diameter x cranio-caudal diameter in millimeter (mm) x 0.52 / 1000. We also used this formula to calculate the total volume of each thyroid lobe [7].

Before LA, patients underwent fine needle aspiration of the nodule on two separate occasions, to confirm benignity cytologically (Thy 2 in accordance with the British Thyroid Association [8]). Only patients with a finding of benignity on both occasions underwent LA.

Patients filled out both a symptomatic visual analogic scale (VAS) that rated discomfort in the neck and a 13-scale Thyroid-specific Patient Reported Outcome (ThyPRO) QoL questionnaire validated for patients with thyroid disease [9].

Clinical examinations, assessments of thyroid function and thyroid autoimmunity, and VAS scores were repeated after one week and 1, 3, 6, and 12 months. ThyPRO and ultrasound thyroid volume were evaluated after 1, 3, 6, and 12 months. We performed follow-up ultrasound examinations using a MyLab Five (Esaote®, Genoa, Italy) ultrasound scanner with a 7.5 MHz linear transducer (LA 523, Esaote®). We repeated

phoniatric examination if symptoms related to chordal dysmotility appeared after the procedure.

Procedures and Methods

Laser ablation was performed in an out-patient regimen. Antiplatelet and anticoagulant therapies were suspended a week before the procedure. On the day of the procedure, patients were in a state of 8-hour fasting. After placement of a venous catheter, patients underwent intravenous infusion for over 30 minutes of ketorolac 20 mg (Tora-dol®, Recordati Spa, 10 mg/mL, Milan, Italy) and ranitidine 50 mg (Ranitidina®, 50 mg/5mL, S.A.L.F. Spa, Cenate Sotto, Italy) diluted in 100 mL of 0.9% saline solution. Subsequently, intravenous ketorolac 40 mg (Tora-dol® Recordati Spa, 10 mg/mL) and ranitidine 50 mg (Ranitidina® 50 mg/5 mL, S.A.L.F Spa) were administered in 500 mL of 0.9% saline for about five hours (during and after LA). In subjects allergic to ketorolac or in patients with moderate-to-severe renal impairment, premedication with intravenous paracetamol (500 mg) (Perfalgan®, 10 mg/mL, 50 mL, Bristol-Myers Squibb Srl, Roma, Italy) was carried out before and during the procedure. We placed patients on an operating table in the supine position with the neck hyperextended. Before LA, we performed a careful US examination to evaluate neck anatomy and ensure preservation of the “danger triangle” during procedures (10). Local anesthesia with 2% lidocaine (Lidocaina Cloridrato®, 20 mg/mL, Monico Spa, Mestre, Italy) was carried out at the puncture site. If the patient did not tolerate pain during ablation, we reduced the power or turned it off for several seconds.

In three patients, we performed percutaneous drainage of cystic intranodular fluid before the procedure. LA was performed in a single session by a single operator. The operator had one year of experience with LA, four years of experience of thyroid RFA, and 22 years of experience with fine-needle aspiration biopsy, by means of 300 µm diameter fibers and a 21-Gauge Chiba-needle (ELESTA®, Calenzano, Italy). Procedures were performed by means of a commercially available US scanner (Echo-laser X4®, Esaote®) equipped with a 7.5 MHz linear transducer (LA 332, Esaote®) with a 1064 µm diode laser unit with a maximum of four laser sources, each with an individual energy emission setting and independent activation.

The operator was positioned at the patient's side and inserted from one to two fibers into the longitudinal length of the nodule, forming a shape matching the ellipsoid of thyroid nodule. The initial energy was delivered at 1200–1800 Joules per fiber with an output power of 2−4 W, starting at one centimeter from the bottom of the lesion. One or two 1-cm pull-backs were programmed to maximize the ablation volume in a single LA session. The number of fibers, their placement, the number of pull-backs and total energy delivered were tailored to the shape and volume of each thyroid nodule, as described by Baek et al. (11). LA lasted 16 ± 2 minutes on average (range: 13−19 minutes), with a mean delivery of 4459 ± 1525 J (range: 1713−6203 J), one or two fibers (mean 1.7) and one or two pull-backs (mean 1.3). The energy load in J/mL was 340 ± 196 (range: 87−742 J/mL). Light irradiation was continuous, but was suspended in the event of pain or in order to reposition the fibers.

After LA, patients received a compressive bandage and ice to apply to the neck. Patients were allowed a light meal before being discharged in the early afternoon. All

subjects received a domiciliary prescription for steroid administration (prednisone 25 mg for three days, 12.5 mg for three days, 6.25 mg for three days) and gastric protection, if not already ongoing.

Laboratory tests

We measured TSH, f-T3, and f-T4 by ultra-sensitive chemiluminescence immunoassay (Cobas® e602, Roche Diagnostics, Milan, Italy). The normal ranges are: 0.27−4.2 mIU/L for TSH, and 2.76−7.07 pmol/L and 11.97−21.88 pmol/L for f-T3 and f-T4. We evaluated TPOAbs by means of DiaSorin (Saluggia, Italy); we regarded concentrations < 100 mU/L as negative. We measured calcitonin by chemiluminescence immunoassay (DiaSorin); in our laboratory, the normal value is < 10 ng/L. We performed automated complete blood counts using an ADVIA 2120 automated counter (Siemens Healthcare, Milan, Italy); coagulation tests on an automated BCS analyzer (Siemens Healthcare); and biochemical tests for the routine assessment of hepatic and renal function on the fully-automated Cobas® c701 platform (Roche Diagnostics).

Questionnaires

We evaluated the subjective benefits of LA several times during the study through a VAS with a score ranging from 0 (no symptoms/discomfort) to 10 (highest level of symptoms/discomfort). We assessed QoL before the procedure (baseline), and after 1, 3, 6, and 12 months, by means of ThyPRO, a validated questionnaire for thyroid diseases (9), which consists of 13 scales with multiple-choice answers (0 = “none”; 1 = “slight”; 2 = “moderate”; 3 = “severe”; 4 = “very severe”). The ThyPRO scales concern

the following aspects: goiter symptoms, hyperthyroid symptoms, hypothyroid symptoms, eye symptoms, tiredness, cognitive problems, anxiety, depression, emotional susceptibility, impaired social life, impaired daily life, impaired sex life, and cosmetic complaints.

We also evaluated a further scale, dubbed “general score”. It assesses answers to the question, “In the last 4 weeks, has thyroid disease had a negative effect on your QoL?” Lastly, we considered the mean values of the 13-scale score [9].

Statistical analysis

All data were analysed by means of GraphPad Prism for Windows (Version 6.0, GraphPad Software, San Diego, CA, USA). The data are presented as means ± SD, unless otherwise indicated. Continuous data were compared by means of the Mann-Whitney test, while percentages were compared by means of the Fisher test. Correlations between variables were assessed by means of the Spearman correlation. A P value <0.05 was deemed to indicate significance.

Results

Procedure effects

On enrolment, the mean volume of the nodules was 19 ± 14 mL (range: 5−55 mL) and the total gland volume was 32 ± 16 mL (range: 13−59 mL). Table 2 reports the mean volume of nodules and thyroid at each time-point of the study. Figure 1 reports on the mean volumetric changes at different time-points.

After LA, we found a progressive reduction in nodule volume: -37 ± 23%, -55 ± 22%, -53 ± 25%, -58 ± 25% at the first, third, sixth and twelfth month, respectively ($p < 0.01$ vs. baseline at the first, third, and sixth month, and $p < 0.05$ at the twelfth month). The percentage reductions in thyroid volume were significant at 3, 6, and 12 months ($p < 0.01$, < 0.05, < 0.05, respectively) (Fig. 1). At the 12-month follow-up, we observed a reduction of > 50% in 86% of the patients treated ($p < 0.01$). In two patients (14%), however, LA resulted in a nodule volume reduction of < 20%.

Figure 2 shows a nodule at the baseline of the study (Fig. 2A) and the same nodule 12 months after LA (Fig. 2B).

Changes in thyroid parameters

Table 3 depicts the parameters of thyroid function at the baseline and at the various time-points. f-T4, f-T3, thyroglobulin, and TSH levels did not exhibit significant changes (Table 3). None of the patients developed hypothyroidism. None of the subjects on L-T4 therapy on enrolment had to increase the dosage. TPOAbs were positive in 21% of patients (n = 3); this percentage was the same at the last evaluation.

Subjective complaints

During the procedure, four patients (26%) experienced discomfort in the neck, and three patients (21%) experienced pain. Seven patients (50%) did not experience any problems. One week after the procedure, five patients (36%) did not have any problems, four (26%) felt discomfort in the neck, three (21%) felt pain (mean VAS score was 3 ± 2), three (21%) had edema in the neck and one (7%) had a hematoma. These symptoms did not require any kind of medication and resolved spontaneously during the first month. No patient developed hoarseness, dysphagia, nodule rupture, major bleeding or infections.

The VAS score at the baseline was 5 ± 3, and was significantly lower at each subsequent evaluation: from the first week after LA until the last evaluation at the twelfth month (Fig. 3). The VAS score improved in 100% of patients.

Table 4 shows the mean score on each ThyPRO scale at each time-point of the study. The data shows a significant improvement on the scale of “goiter symptoms” from the first month onwards, and on the scale of “general score” from the sixth month onwards. The mean values of the 13 scales also improved significantly from the sixth month onwards (Fig. 4). These improvements persisted over time. By contrast, no significant changes in the other scales were recorded.

Discussion

The present paper reports our preliminary data on the use of a single session of LA to treat 14 benign thyroid nodules in 14 patients recruited over 12 months and followed up for 12 months.

We used standard procedures recommended by the Korean RFA Guidelines [7, 11], and we performed LA after excluding contraindications.

The mean reduction in the volume of our nodules appears to be similar or slightly lower than those observed in other centers: 58 ± 25%. At 12 months, the mean nodule volume reduction was -72 ± 11% in a study by Pacella et al. [12], -84 ± 13% in a study by Achille et al. [13], -59 ± 22% in a study by Papini et al. [14], - 51 ± 11% in a study by Døssing et al. [15], and -70 ± 16% in a study by Mauri et al. [16].

The mean reduction in the volume of our nodules appears to be similar or slightly lower than that observed after a single session of RFA: -74 ± 12% in a study by Mauri et al. [16], -69 ± 14% in a study by Cesareo et al. [17], and 77 ± 3% in a study by Faggiano et al. [18], -79.7% in a study of Baek et al. [19], -84 ± 15% in a study of Jeong et al. [20]. We achieved more than 50% volume reduction at the 12 months in 86% of nodules. This result is comparable to, or better than, the data presented in a three-year multicenter prospective study (67.3%) [14].

Laser ablation can lead to normalization of TSH in patients with hyperthyroidism with “hot” nodules [21]. The literature reports a change in thyroid function (hypo-or hyperthyroidism) in 2% of patients after LA [12]. By comparison, in our study that enrolled only euthyroid patients, LA did not lead to significant changes in thyroid function and preserved euthyroidism. This data confirms the safety of this procedure

and may prompt percutaneous techniques to be preferred to surgery, which causes hypothyroidism in 100% of cases after total thyroidectomy and in 22% of cases after hemithyroidectomy [2]. In comparison studies between RFA and surgery, there were also no hypothyroidism patients after RFA [22, 23].

Most of our patients did not experience any problems either during or after LA. In our study, adverse events were few and mild; indeed, the main complaints were “discomfort in the neck” and “pain” during and after LA. If these symptoms started after LA, they resolved spontaneously in a few weeks; if they arose during LA, they were alleviated by reducing the energy delivered or turning off the fibers for several seconds. In any case, pain was mild, with the mean VAS score being 3.

Other adverse events in our experience were asymptomatic edema of the neck in one patient and a superficial hematoma in another patient; however, these resolved spontaneously. Our patients did not suffer other major adverse events, such as dysphagia, nodule rupture, pericapsular bleeding, vagal symptoms with bradycardia, or infections, which were reported in 0.5% of cases in a study by Pacella et al. [12] on 1280 nodules treated with LA. In that study, the rate of major complications was lower in patients treated without local anesthesia or with no conscious sedation than in patients managed with local anesthesia and conscious sedation. Conversely, complaints of side effects were more frequent in subjects treated without local anesthesia [12]. In our protocol, we did not use conscious sedation, which probably explains why we observed no major complications and few adverse events. In our cohort of patients, we did not administer local sub-capsular anesthesia, but subcutaneous tissue anesthesia. Furthermore, we infused analgesic and anti-

inflammatory drugs before and during the procedures and prescribed steroids for some days after discharge, in order to minimize complications. While these precautions probably helped to minimize complications, they did not completely alleviate pain and discomfort in the neck.

It should be borne in mind that proximity of the light to the capsule cause pain and discomfort in the neck. If patients complain of these symptoms during the procedure, the patients can thereby help the operator not to exceed the capsule of the treated nodule and minimize adverse events [12]. In any case, the complications of LA, and of other minimally invasive procedures, such as RFAs [11], are fewer and milder than those of thyrodectomy, whether total or partial. The types and frequencies of adverse events of thyroid surgery are described in a recent review by a group of Indian surgeons (24). A study by Wang et al. [25] describes the prevalence of complications after conventional and endoscopic thyroidectomies as follows: transient laryngeal nerve palsy in 5.4%, transient hypocalcemia in 3.6%, bleeding in 0.5% and hematoma in 0.5% of cases. Furthermore, discomfort in the neck and chest was reported in 80% of patients on the third day, and pain in the neck and chest in 10% of patients one month after thyroidectomy [25].

Many studies have reported improvements in neck discomfort and esthetic symptoms after LA. In a study by Valcavi et al. [21], neck symptoms improved in 73% of patients, were unchanged in 23%, and worsened in only 4%; esthetic symptoms improved in 71% of patients, were unchanged in 24%, and worsened in 5%. Moreover, in a study by Pacella et al. [12], neck symptoms improved in 10−49% of cases, and esthetic symptoms improved in 8−86% of cases. In addition, in a study by Achille et al. [13],

esthetic problems were completely resolved in 87% of treated patients, reduced in 9%, and unchanged in 2%, and pressure symptoms were resolved in 88% of cases. In our study, esthetic complaints were assessed by means of the cosmetic scale of ThyPRO, which revealed no improvement after LA. However, it should be noted that the baseline scores on this scale were very low in all our patients.

Quality of life is defined as a person's perception of his/ her position in life, in the context of the culture and system of values in which he or she lives and in relation to his or her objectives, expectations, standards, and concerns [26]. In thyroid diseases, besides ThyPRO, QoL is often calculated by means of various questionnaires: the Short Form-36 [27], the SF-12 Health Survey [28], the Hamilton Depressive Scale [29], and the Kellner Symptoms Questionnaire [9, 30].

While the Hamilton Depressive Scale (24-scale multiple-choice questionnaire) and the Kellner Symptoms Questionnaire (92-item questionnaire with Yes/No answers) focus more on the psychological aspects of QoL, the Short Form-36 (11-scale multiple-choice questionnaire), the slimmer SF-12 Heath Survey (12-item multiple-choice questionnaire), and ThyPRO analyze both physical and mental health [9, 27-30]. We chose to utilize ThyPRO because it has been validated for thyroid diseases and could therefore provide a more detailed analysis of QoL in patients undergoing thyroid LA. Indeed, the 13 scales of ThyPRO investigate several aspects of life that may be impaired by goiter-related compression symptoms or discomfort in the neck, by esthetic alterations and by an altered thyroid function (both hypo- and hyper-thyroidism). As of this writing, no literature has reported on changes in QoL in patients treated with LA. However, ThyPRO has been used to assess QoL in numerous benign

and malignant thyroid diseases. Regarding the use of questionnaires to evaluate changes in QoL in patients treated with thermal ablation for thyroid nodules, a study by Valcavi et al. [31] reported a significant improvement in QoL. The study assessed QoL using the Physical Component Summary and Mental Component Summary of Short Form-12 after two years of follow-up and in 40 patients treated with RFA for benign thyroid nodules. In the that study, both the Physical Component Summary and the Mental Component Summary significantly improved after one year, and remained stable from year one to year two.

Our group recently published a study on changes in QoL, as assessed by means of ThyPRO after RFA of benign thyroid nodules. In that study, we did not find a significant improvement in ThyPRO scales, except for the "general score," which improved after three months [32]. The cause of less improvement of ThyPRO scales in this study [32] was probably induced by low volume reduction: the majority of patients showed less than a 50% volume reduction. Moreover, four patients showed increased nodule volume after RFA. The mean volume reductions of nodule was -18 ± 18%, -30 ± 24% and -27 ± 22% after RFA vs. -37 ± 23%, -53 ± 25% and -58 ± 25% in LA at 1, 6, and 12 months, respectively, although the features of nodules and inclusion criteria were the same in the two studies. In the present study, scores on the "goiter symptoms" and "general score" scales of the ThyPRO questionnaire showed a significant improvement from the first month and from sixth month onwards, respectively. The mean values of the scores on all 13 scales displayed a significant reduction from the sixth month onwards. In the present study, scores on each of the other scales did not change significantly. This could be due to LA does not affecting thyroid function. Indeed,

changes in hyperthyroid symptoms, hypothyroid symptoms, eye symptoms, tiredness, cognitive problems, anxiety, depression and emotional susceptibility scales could be more closely related to changes in thyroid hormonal status.

Our study yielded more short-term data on changes in QoL than that of Valcavi et al. [31]. However, our cohort of patients was smaller and follow-up was shorter.

The main limitation of our study is its small population (n = 14) and short follow-up. Further studies, especially in a larger cohort of patients and over several years of follow-up, are necessary in order to confirm or disprove our data.

In conclusion, LA is effective in reducing both nodule volume and neck symptoms. Moreover, the procedure is safe. In comparison to surgery, adverse events are few and mild. LA is well-tolerated by patients and the VAS score improves significantly in all patients. In our cohort of patients, the goiter scale, the general score and the mean value of ThyPRO scores improved significantly a few months after LA for benign non-functioning thyroid nodules.

References

1. *Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26:1-133*
2. *Verloop H, Louwerens M, Schoones JW, Kievit J, Smit JW, Dekkers OM. Risk of hypothyroidism following hemithyroidectomy: systematic review and meta-analysis of prognostic studies. J Clin Endocrinol Metab 2012;97:2243- 2255*
3. *Papini E, Pacella CM, Misischi I, Guglielmi R, Bizzarri G2, Døssing H, et al. The advent of ultrasound-guided ablation techniques in nodular thyroid disease: towards a patient-tailored approach. Best Pract Res Clin Endocrinol Metab 2014;28:601-618*
4. *Fast S, Nielsen VE, Bonnema SJ, Hegedüs L. Time to reconsider nonsurgical therapy of benign non-toxic multinodular goitre: focus on recombinant human TSH augmented radioiodine therapy. Eur J Endocrinol 2009;160:517-528*
5. *Bandeira-Echtler E, Bergerhoff K, Richter B. Levothyroxine or minimally invasive therapies for benign thyroid nodules. Cochrane Database Syst Rev 2014 Jun 18;(6):CD004098*
6. *Shin JH, Baek JH, Chung J, Ha EJ, Kim JH, Lee YH, et al. Ultrasonography diagnosis and imaging-based management of thyroid nodules: Revised Korean society of thyroid radiology consensus statement and recommendations. Korean J Radiol 2016;17:370-395*

7. *Na DG, Lee JH, Jung SL, Kim JH, Sung JY, Shin JH, et al. Radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: consensus statement and recommendations. Korean J Radiol 2012;13:117-125*
8. *Agarwal A, Kocjan G. FNAC thyroid reporting categories: value of using the British Thyroid Association (Thy 1 to Thy 5) thyroid FNAC reporting guidelines. Cytopathology 2009;20:133-134*
9. *Watt T, Hegedüs L, Groenvold M, Bjorner JB, Rasmussen AK, Bonnema SJ, et al. Validity and reliability of the novel thyroid-specific quality of life questionnaire, ThyPRO. Eur J Endocrinol 2010;162:161-167*
10. *Ha EJ, Baek JH, Lee JH. Ultrasonography-based thyroidal and perithyroidal anatomy and its clinical significance. Korean J Radiol 2015;16:749-766*
11. *Baek JH, Lee JH, Valcavi R, Pacella CM, Rhim H, Na DG. Thermal ablation for benign thyroid nodules: radiofrequency and laser. Korean J Radiol 2011;12:525-540*
12. *Pacella CM, Mauri G, Achille G, Barbaro D, Bizzarri G, De Feo P, et al. Outcomes and risk factors for complications of laser ablation for thyroid nodules: a multicenter study on 1531 patients. J Clin Endocrinol Metab 2015;100:3903-3910*
13. *Achille G, Zizzi S, Di Stasio E, Grammatica A, Grammatica L. Ultrasound-guided percutaneous laser ablation in treating symptomatic solid benign thyroid nodules: Our experience in 45 patients. Head Neck 2016;38:677-682*
14. *Papini E, Rago T, Gambelunghe G, Valcavi R, Bizzarri G, Vitti P, et al. Long-term efficacy of ultrasound-guided laser ablation for benign solid thyroid nodules.*

Results of a three-year multicenter prospective randomized trial. J Clin Endocrinol Metab 2014;99:3653-3659

15. *Døssing H, Bennedbæk FN, Hegedüs L. Long-term outcome following interstitial laser photocoagulation of benign cold thyroid nodules. Eur J Endocrinol 2011;165:123-128*
16. *Mauri G, Cova L, Monaco CG, Sconfienza LM, Corbetta S, Benedini S, et al. Benign thyroid nodules treatment using percutaneous laser ablation (PLA) and radiofrequency ablation (RFA). Int J Hyperthermia 2016 Nov 15 [Epub ahead of print]. https://doi.org/10.1080/02656736.2016.1244707*
17. *Cesareo R, Pasqualini V, Simeoni C, Sacchi M, Saralli E, Campagna G, et al. Prospective study of effectiveness of ultrasound-guided radiofrequency ablation versus control group in patients affected by benign thyroid nodules. J Clin Endocrinol Metab 2015;100:460-466*
18. *Faggiano A, Ramundo V, Assanti AP, Fonderico F, Macchia PE, Misso C, et al. Thyroid nodules treated with percutaneous radiofrequency thermal ablation: a comparative study. J Clin Endocrinol Metab 2012;97:4439-4445*
19. *Baek JH, Kim YS, Lee D, Huh JY, Lee JH. Benign predominantly solid thyroid nodules: prospective study of efficacy of sonographically guided radiofrequency ablation versus control condition. AJR Am J Roentgenol 2010;194:1137-1142*
20. *Jeong WK, Baek JH, Rhim H, Kim YS, Kwak MS, Jeong HJ, et al. Radiofrequency ablation of benign thyroid nodules: safety and imaging follow-up in 236 patients. Eur Radiol 2008;18:1244-1250*

21. *Valcavi R, Riganti F, Bertani A, Formisano D, Pacella CM. Percutaneous laser ablation of cold benign thyroid nodules: a 3-year follow-up study in 122 patients. Thyroid 2010;20:1253-1261*
22. *Che Y, Jin S, Shi C, Wang L, Zhang X, Li Y, et al. Treatment of benign thyroid nodules: comparison of surgery with radiofrequency ablation. AJNR Am J Neuroradiol 2015;36:1321-1325*
23. *Bernardi S, Dobrinja C, Fabris B, Bazzocchi G, Sabato N, Ulcigrai V, et al. Radiofrequency ablation compared to surgery for the treatment of benign thyroid nodules. Int J Endocrinol 2014;2014:934595*
24. *Padur AA, Kumar N, Guru A, Badagabettu SN, Shanthakumar SR, Virupakshamurthy MB, et al. Safety and effectiveness of total thyroidectomy and its comparison with subtotal thyroidectomy and other thyroid surgeries: a systematic review. J Thyroid Res 2016;2016:7594615*
25. *Wang YC, Zhu JQ, Liu K, Xiong JJ, Xing TF, Han QQ, et al. Surgical outcomes comparison between endoscopic and conventional open thyroidectomy for benign thyroid nodules. J Craniofac Surg 2015;26:e714-e718*
26. *Crevenna R, Zettinig G, Keilani M, Posch M, Schmidinger M, Pirich C, et al. Quality of life in patients with non-metastatic differentiated thyroid cancer under thyroxine supplementation therapy. Support Care Cancer 2003;11:597-603*
27. *McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short- Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31:247-263*

28. *Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220-233*
29. *Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62*
30. *Kellner R. A symptom questionnaire. J Clin Psychiatry 1987;48:268-274*
31. *Valcavi R, Tsamatropoulos P. Health-related quality of life after percutaneous radiofrequency ablation of cold, solid, benign thyroid nodules: a 2-year follow-up study in 40 patients. Endocr Pract 2015;21:887-896*
32. *Oddo S, Felix E, Repetto AM, Mussap M, Giusti M. Quality of life in patients treated with radiofrequency ablation for thyroid nodules. Res J Endocrinol Metab 2016 November 1 [Epub]. http://doi.org/10.7243/2053-3640-4-1*

Table 1: patients demographic data.

BMI = body mass index, L-T4 = levothyroxine ; MNG= multinodular goiter; UNG= uninodular goiter.

Males / Females	2 / 12
Age (years) (mean ± SD)	55 ± 10
BMI (kg/m2) (mean ± SD)	25 ± 4
L-T4 therapy (yes / no)	2 / 12
Time since diagnosis (years) (mean ± SD)	7 ± 8
MNG / UNG	6 / 8
Location of the nodule (right lobe / left lobe)	10 / 6

Table 2: volume of nodules and thyroid (mean ± SD) and volume reduction ratio of nodules and thyroid at each time-point of the study.

	Nodule volume (ml)	Nodule volume reduction ratio (%)	Thyroid volume (ml)	Thyroid volume reduction ratio (%)
Baseline	19 ± 14	-	32 ± 16	-
1st month	11 ± 9	-42	28 ± 13	-12
3rd month	9 ± 10	-57	23 ± 11	-28
6th month	10 ± 11	-47	24 ± 12	-25
12th month	9 ± 12	-57	24 ± 13	-25

Table 3: thyroid function at each time-point of the study (mean ± SD).

f-T3 = free T3, f-T4 = free T4, TSH = thyroid-stimulating hormone.

	TSH (mIU/L)	f-T3 (pmol/L)	f-T4 (pmol/L)	Thyroglobulin (µg/L)
Baseline	1.76 ± 1.31	5.07 ± 0.74	14.69 ± 2.4	104.9 ± 83.5
1st week	1.33 ± 0.97	5.24 ± 0.63	15.30 ± 1.8	452.2 ± 658.8
1st month	1.25 ± 0.85	5.24 ± 0.55	14.95 ± 2.28	99.8 ± 93.7
3rd month	1.28 ± 1.30	5.42 ± 0.54	15.37 ± 2.11	103.9 ± 228.9
6th month	1.57 ± 1.29	5.07 ± 0.72	14.97 ± 1.71	107.9 ± 178
12th month	1.07 ± 0.55	5.01 ± 0.64	15.24 ± 2.11	73.0 ± 57.8

Table 4: ThyPRO scores (mean ± SD) on each scale at each time-point of the study.

*= p<0.05 vs baseline; **= p<0.01 vs baseline

	Baseline	1st month	3rd month	6th month	12th month
Goiter symptoms	23 ± 13	10 ± 8 *	9 ± 9 **	8 ± 5 **	7 ± 4 **
Hyperthyroidism symptoms	13 ± 14	8 ± 14	9 ± 14	8 ± 9	2 ± 3
Hypothyroidism symptoms	9 ± 9	6 ± 6	8 ± 9	9 ± 10	7 ± 4
Eye symptoms	9 ± 9	5 ± 7	6 ± 9	3 ± 5	1 ± 2
Tiredness	34 ± 13	32 ± 13	31 ± 16	26 ± 10	21 ± 5
Cognitive problems	11 ± 13	7 ± 12	13 ± 12	10 ± 8	6 ± 4
Anxiety	17 ± 13	12 ± 11	13 ± 17	18 ± 13	17 ± 7
Depression	26 ±15	19 ± 12	23 ± 15	17 ± 14	19 ± 9
Emotional susceptibility	20 ±17	15 ± 13	14 ± 18	12 ± 10	10 ± 4
Impaired social life	3 ±5	5 ± 9	3 ± 6	0 ± 2	0 ± 0
Impaired daily life	5 ± 10	6 ± 8	4 ± 10	2 ± 4	0 ± 0
Impaired sex life	6 ± 11	4 ± 8	3 ± 6	1 ± 4	3 ± 6
Cosmetic complaints	6 ± 8	6 ± 11	4 ± 8	2 ± 4	1 ± 3
General score	14 ± 19	7 ± 12	4 ± 13	0 ± 0 **	0 ± 0 *
Mean values	14 ± 7	10 ± 7	11 ± 9	9 ± 5 *	7 ± 1 *

Figure 1: mean changes (columns) with SD (error bars) in nodule (full columns) and thyroid (empty columns) volume in milliliters (a) and percentage (b).

Significance vs. baseline: *= p<0.05; **= p<0.01

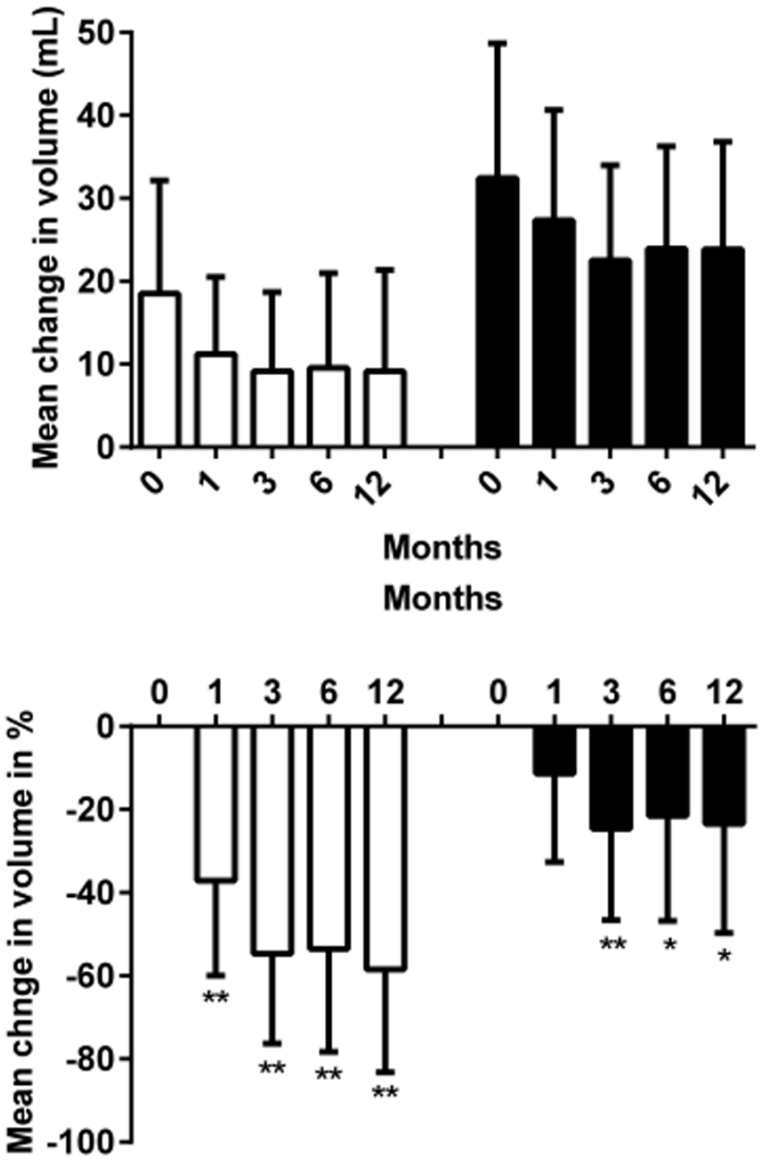


Figure 2: changes in the volume of a nodule at ultrasound scan at baseline (a, b); 12 months after LA (c, d). Transverse (a, c) and longitudinal images (b, d).

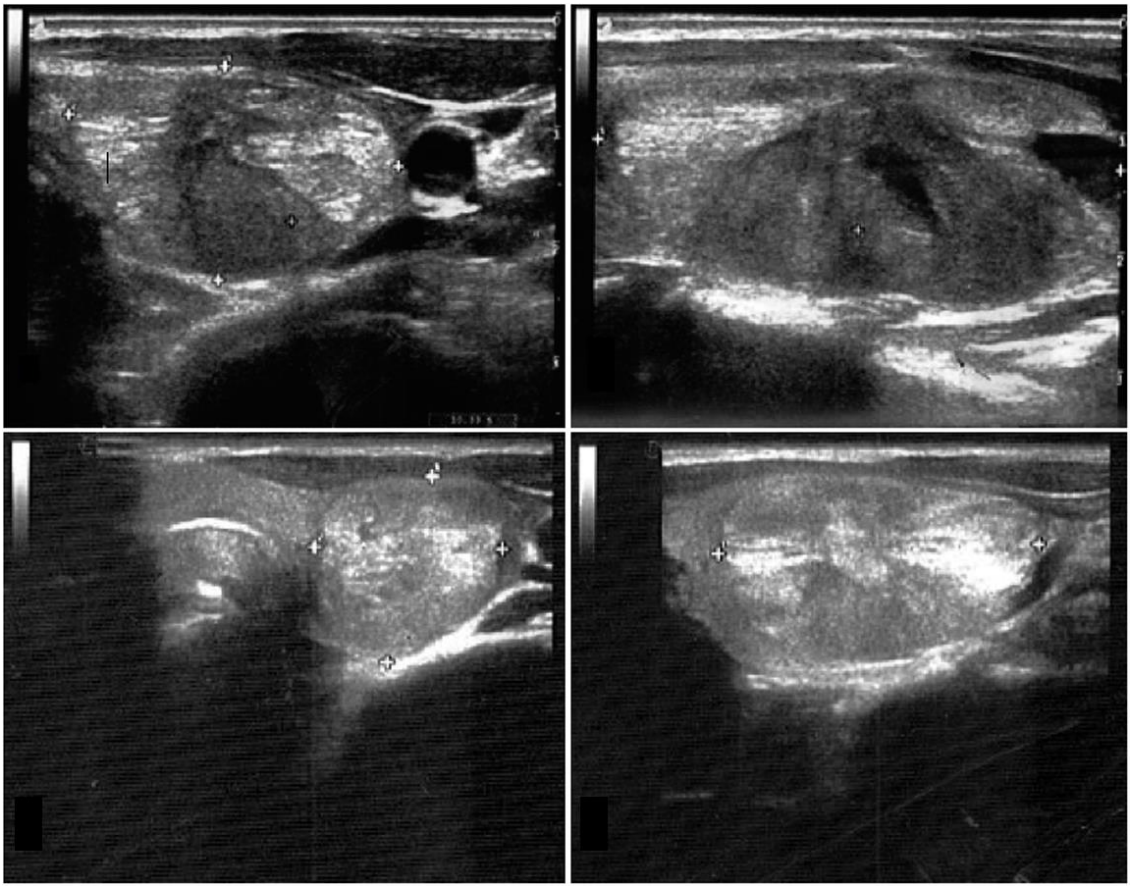


Figure 3: changes in VAS score, with mean score (squares) and SD (error bars). Significance vs. baseline: *= p<0.05; **= p<0.01

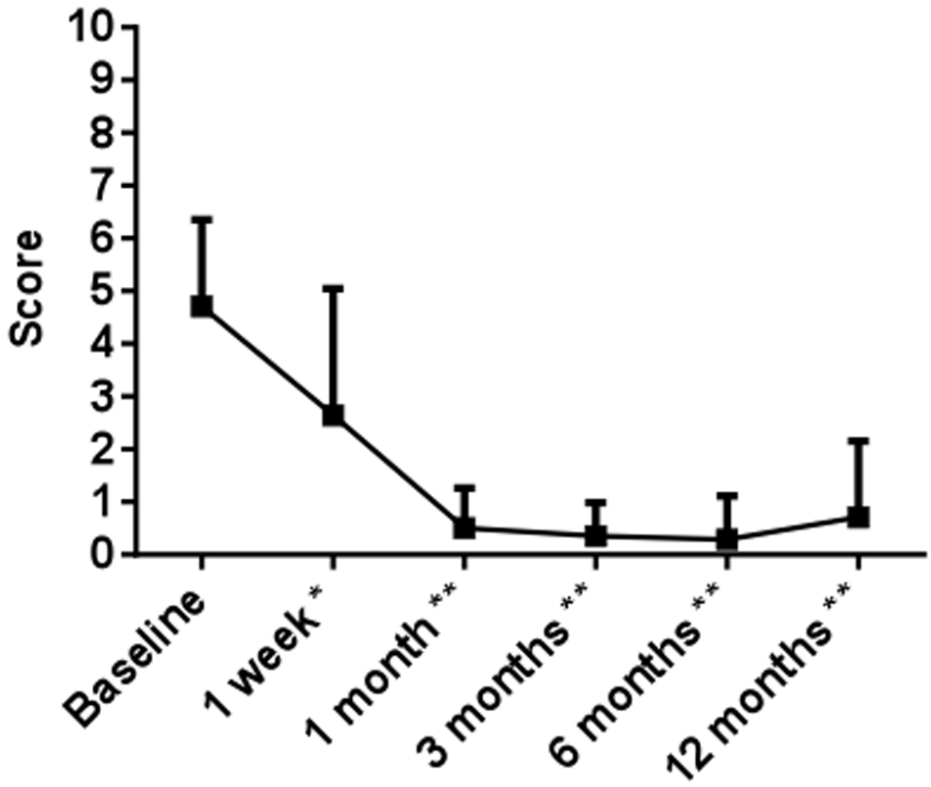
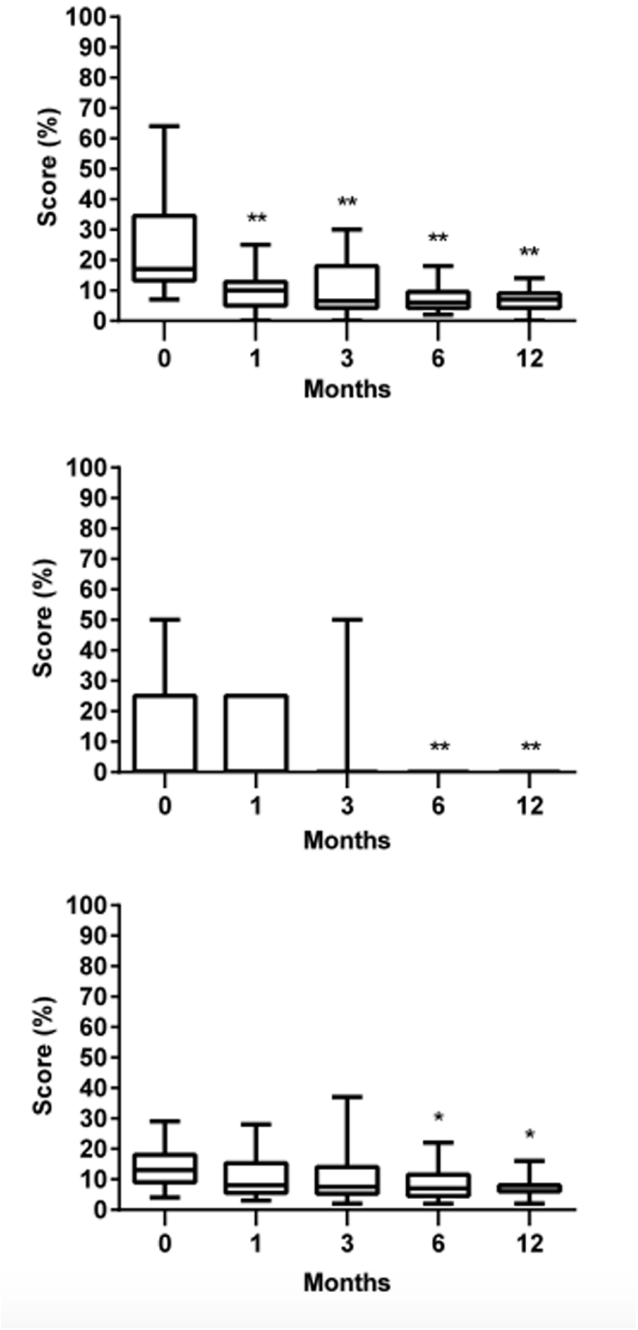


Figure 4: significant changes in ThyPRO scale scores, expressed in mean percentages (boxes) and SD (error bars): a) goiter symptoms scale, b) general score scale, c) mean values.

Significance vs. baseline: *= p<0.05; **= p<0.01



CHAPTER 4

A comparison of laser with radiofrequency ablation for the treatment of benign thyroid nodules: a propensity score matching analysis.

Pacella CM, Mauri G, Cesareo R, Paqualini V, Cianni R, De Feo P, Gambelunghe G, Raggiunti B, Tina D, Deandrea M, Limone PP, Mormile A, Giusti M, Oddo S, Achille G, Di Stasio E, Misischi I, Papini E.

Int J Hyperthermia. 2017 Jun 12:1-9.

Introduction

Over the last years, image-guided minimally-invasive techniques have been proposed to treat clinically relevant benign thyroid nodules (BTNs) [1,2]. Ultrasound-guided (US-g) thermal ablation with laser or radiofrequency energy is increasingly being used for non-surgical management of symptomatic non-functioning thyroid nodules that are benign at cytological assessment [3]. Due to their debulking efficacy, substantial safety and low-cost as outpatient procedures, both laser ablation (LA) and radiofrequency ablation (RFA) are currently used in several thyroid referral centres. Microwave ablation (MWA) technique, on the other hand, represents an emerging but still not thoroughly assessed and well established ablative method for BNTs [4–6]. Numerous uncontrolled and prospective randomised controlled trials with different treatment algorithms have confirmed the clinical effectiveness and safety of LA [7–19] and of RFA in both solid thyroid nodules and in lesions with variable fluid component [20–27]. However, the reported series of LA usually included patients with larger thyroid nodules and the series of RFA included patients with a higher cyst component [2].

Thus, the results are difficult to be compared [28]. To date, only one review including meta-analysis [29] and a more recent paper on a small case series [30] have reported direct comparisons between the two techniques with contradictory conclusions. While the first study concludes that RFA is superior to LA, the second highlights a substantial equivalence of the two techniques when performed by operators with the same expertise. Thus, pending prospective comparative studies, we retrospectively compared LA and RFA outcomes in the treatment of benign thyroid nodules in a large cohort of patients treated at different centres in Italy. In order to minimise the effect of potential confounders or selection bias, patients of each group were matched by applying the one-to-one propensity score matching [31,32]. The aim of our study was to compare in real clinical practice the efficacy and safety of LA and RFA in the treatment of benign thyroid nodules.

Methods

Patients

The institutional review board of each participating centre approved this retrospective study and waived the requirement for informed consent. All patients undergoing percutaneous thermal ablation for symptomatic BTNs from May 2009 to December 2014 at eight thyroid referral centres were retrospectively considered for the study. Four of these centres had specific expertise in RF technique while four of them used laser technology. Then, four centres have only used RFA technique and four laser technology. In four centres the procedures were performed by endocrinologists, in three by interventional radiologists, and in one by surgeons. The patients had refused surgery or had poor surgical indications because of age, cardiovascular risk, respiratory failure or because they were not eligible for general anaesthesia. No patient had undergone ethanol sclerotherapy or other percutaneous minimally invasive therapies.

Inclusion criteria were as follows: solid nodule (uniformly compact or nearly completely solid, with a liquid component not exceeding 30%); evidence at ultrasound examination of a single or of a dominant nodule, clearly detectable in a multinodular goitre; serum TSH and thyroid hormones within normal range; benign cytological examination (class II of the Bethesda classification system) [33] assessed by two separate FNAs; and presence of either local pressure symptoms or cosmetic concern. Patients were excluded from the treatment in case of suspicious or cytologically proven malignancy, altered serum TSH and thyroid hormones or coagulation disorders.

Preoperative patient management

A general consensus among centres for clinical, ultrasound and laboratory assessment was based on the international guidelines criteria [34,35]. Thyroid sonographic evaluation was conducted in all centres by means of a commercially available US scanner, equipped with a 7.5–13.0 MHz linear transducer. The nodule volume was calculated with the ellipsoid formula (V¼length_width_depth_0.525). Serum TSH, FT4 and other laboratory controls were determined with commercially available immunoradiometric assay kits. Routine coagulation tests were performed before the procedure and included INR and platelet count. All centres operated according to the guidelines used for interventional procedures in other organs, such as liver, kidney or lung [36,37]. Only one session of treatment was scheduled for each nodule.

Technique

The treatment procedures followed those previously applied and published elsewhere [7]. Briefly, in the case of laser technique, the number of 21 gauge (G) applicators (up to four) to be inserted is based on nodule size. Under US-g the introducer needles, and subsequently the optic fibres, are inserted into the target thyroid nodule along its longest axis. Each treatment is performed using diode lasers with a fixedpower protocol (3 W). Each illumination time ranges from a minimum of 400 s to a maximum of 600 s to achieve a total energy delivery between 1200 and 1800 Joules per fibre. Depending on the size of the nodule, one to three consecutive illuminations are performed with a pullback technique during the same treatment session. For the radiofrequency technique, the procedure is based on the moving-shot technique as

described elsewhere [21]. Under US-g electrode-needles with a caliber ranging from 17 G to 19 G are inserted into the thyroid nodule along its short axis by using a trans-isthmic approach. Different zones of the lesion were ablated sequentially by moving the position of the electrode tip. The electrode was initially positioned in the deepest part of the nodule and was moved into the central and finally the superficial areas of the lesion. During the manoeuvre, the output power ranges from 40 to 80 W, and the exposure time was calculated mainly on the appearance of a transient hyperechoic area in each of the different zones undergoing ablation [26,27]. The number of insertions depends on the nodule size. In different centres, the RFA procedures were performed by two endocrinologists with 4 and 6 years of experience, respectively, and by two interventional radiologists with 3 and 5 years of experience in the movingshot technique, respectively. Laser procedures were performed by three endocrinologists with 1, 6 and 10 years of experience, respectively, and by a surgeon with 7 years of experience.

Data analysis

The nodule population was classified, in agreement with the available data in the literature [11,14,27], into three groups according to the baseline volume. Nodules with initial volume _13 ml were defined as small, those between 13.1 to 30.0 ml as medium, and those >30.0 ml as large [38]. Preoperative characteristics, age, sex, ablation time, energy deployed per nodule and results in terms of percentage volume reduction (PVR) at 6 and 12 months in RFA and LA groups were compared overall and according to the baseline nodule volume. In each centre, operators performing the ablation were

involved in the assessment of the results and data collection. Previous clinical evidence consistently demonstrated that the major volume reduction of nodules occurs within the first six months after treatment (with significant improvement of local symptoms), followed by a minor reduction from the sixth to the twelfth month [2,39]. On the basis, technical success was defined as a _50% volume reduction at 6 months after a single treatment session. Three treatment variables were considered and correlated with a successful outcome: baseline nodule volume, total ablation time (from the initial targeting of applicator(s) into thyroid nodule to the final assessment after treatment) and total energy delivered per treatment session. Finally, we compared major and minor complications of the two treatment modalities, classifying them according to the time of occurrence as intraprocedural (during the thermal session), postprocedural (within 24 h), periprocedural (within 30 days) and late complications [36,37]. To minimise the effect of potential confounders on selection bias, propensity scores were generated by using binary logistic regression to estimate the probability that a patient would undergo RFA instead of LA. Independent variables that entered into the propensity model included sex, age and baseline nodule volume.

Statistical analysis

Statistical analyses were performed using statistical software (SPSS, version 22.0 for Windows; SPSS, Chicago, Ill). All data were first analysed for normality of distribution using the Kolmogorov–Smirnov test of normality. One-to-one matching between the treatment groups was accomplished by using the nearest-neighbour matching method [31,32,40]. Briefly, the distribution of propensity scores was evaluated by treatment

group to examine for sufficient overlap among the groups to ensure comparability. Continuous variables were expressed as mean ± SD, categorical variables displayed as frequencies and the appropriate parametric (student t-test) or non-parametric test (Mann–Whitney U-test or v2 test) was used to assess significance of the differences between subgroups. A p value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics of LA and RFA groups Six hundred and one nodules in 601 euthyroid patients were ablated percutaneously through US-g thermal therapy. Four hundred and forty-nine (mean age 57 ± 14) underwent LA while 152 (mean age, 57 ± 14) underwent RFA. The baseline characteristics of all patients are shown in Table 1. A number of cases treated in each centre are reported in Figure 1(A,B). The mean total baseline volume of the nodules treated with LA did not show statistically significant differences (21.5 ± 16.5 vs. 24.6 ± 17.9 ml, respectively; p¼0.065) compared with nodules treated with RFA. Patients with baseline nodule volume>30 ml who underwent RFA were significantly older (65 ± 14 vs. 58 ± 15 years, respectively; p¼0.028) than those who underwent LA. The mean baseline nodule volume in group of patients with nodules_13 ml was significantly greater in patients who underwent RFA than in patients who underwent LA (9.9 ± 2.9 vs. 7.4 ± 3.1 ml, respectively; p<0.001) (Table 1).

Volume reduction according to baseline nodule volume

Mean nodule volume decreased from 21.5 ± 16.5 at baseline to 8.7 ± 7.7 (p <0.001) and to 8.0 ± 7.2 ml (p<0.001) at 6 and 12 months, respectively, after treatment in patients who underwent LA. Mean nodule volume decreased from 24.5 ± 17.9 ml at baseline to 11.3 ± 10.7 (p<0.001) and to 9.9 ± 9.5 ml (p<0.001) at 6 and 12 months, respectively, after treatment (p<0.001) in patients who underwent RFA. There were no statistically significant differences between the two treatment groups. Volume

reduction in nodules >30 ml at both 6 and 12 months was significantly higher (p¼0.003 and p¼0.033, respectively) in LA group (from mean 45.1 ± 16.6 ml baseline volume to 17.6 ± 9.8 ml and to 16.0 ± 9.3 ml, respectively) than in RFA group (from mean 49.0 ± 20.3 ml baseline volume to 24.6 ± 13.3 ml and to 21.5 ± 11.5 ml, respectively). The total energy delivered per treatment/session was significantly higher in nodules treated with RFA than in nodules treated with LA (64.6 ± 58 vs. 5.8 ± 2.7 kJ, p¼0.001). There was no statistically significant difference in ablation time between the two techniques. All results are summarised in Table 1.

Technical results

Although not statistically significant, the rate of technical success was higher in LA- than in RFA-treated patients (75% vs. 69%; p¼0.197). The baseline volume was higher in PVR _50% group than in PVR <50% group (p¼0.006) in the LA-treated while this finding was not observed in the RFA treated patients. Total energy delivered was higher in PVR _50% group than in PVR <50% group, both in LA-treated patients (p¼0.033) and in RFA-treated patients (p¼0.010). Finally, ablation time was longer in the PVR _50% than in PVR <50% group, both in all study patients (p ¼0.001) and in only RFA treated-patients (p ¼0.002). Table 2 summarises all these data. Figure 1(A,B) shows the distribution of the number of patients with a nodule volume reduction higher or lower than 50% at 6 months in the LA (panel A) and in the RFA (panel B) groups according to the different centres/operators. In both groups, operators with interventional training (surgeons or interventional radiologists) had the highest rate of >50% volume reduction.

Comparison of volume reduction rates between LA group and RFA group after one-to-one propensity score matching

We trimmed the sample by removing 325 patients (RFA, n¼14; LA, n¼311) with non-overlapping propensity score distribution. Therefore, adjusted comparisons by propensity scores were based on data from 138 patients for each treatment arm. Confounding factors were well matched between the LA and RFA groups: mean age 57 ± 14 vs. 57 ± 13 (p¼0.932), baseline nodule volume 21.9 ± 13.3 vs. 21.5 ± 11.5 (p¼0.760), and female subjects 69% vs. 72% (p ¼0.572), respectively. Therefore, after this matching the resulting two patient groups had similar baseline characteristics. After this adjustment, mean nodule reduction at 6 and 12 months was _67 ± 19% (mean volume 7.5 ± 6.6 ml) vs. _57 ± 21% (9.6 ± 7.5 ml) (p<0.001) and _70 ± 19% (6.6 ± 6.2 ml) vs. _62 ± 22% (8.6 ± 7.8 ml) (p¼0.001) in LA vs. RFA group. Nodules with volume>30 ml had significantly higher percentage volume reduction at 6 and 12 months in the LA group than in the RFA group (_70 ± 19% vs. 62 ± 22, p¼0.001). No difference in total ablation time was detected (17.7 ± 6.3 vs. 18.7 ± 13.6 min (p¼0.436), while a lower release of energy in the LA group compared to the RFA group was confirmed (6.1 ± 2.7 vs. 61.6 ± 51.4kJ, respectively; p¼0.001) (Table 3). According to the PVR_50% response, the rate of volume reduction was greater in LA than in RFA group (86% vs. 70% and 92% vs. 78%) at 6 and 12 months, respectively. In Figure 2, we report the mean nodule reduction at 6 and 12 months according to baseline nodule volume group in all patients before (A) and after (B) propensity score adjustment. Again, in both groups the propensity score-matching analysis confirmed the operators' role in determining a volumetric reduction greater than 50% at six months.

Complications

No immediate or late changes in thyroid function were observed. Thyroid-stimulating hormone, (TSH) free triiodothyronine (FT3) and free thyroxine (FT4) serum levels remained stable. No significant changes were observed in anti-thyroglobulin (TgAb) and anti-thyroperoxidase (TPOAb) antibodies titres during follow up, except for a single patient with a large nodule who developed autoimmune hyperthyroidism six months after RF ablation. Table 4 reports the incidence of major and minor complications and side effects in both groups.

Discussion

Several case reports and prospective randomised trials have established the clinical effectiveness of US-g thermal ablation procedures for the management of symptomatic BTNs [39]. Presently, a still unresolved issue concerns the comparison of the two mainly used techniques – laser and RF – in terms of technique efficacy and safety in real clinical practice. One recent systematic review tried to compare the results of RFA and LA from the data of the published literature, and concluded that RFA appears to be superior to LA in reducing benign solid thyroid nodule volume [29]. However, in this paper, the considered studies had very small number of patients (range 10–21), papers regarding LA were all significantly older than paper regarding RFA, and 6 out of 8 considered papers on LA were performed by the same author. A more recent paper compared results of LA and RFA performed by the same equipe of operators, and found no significant differences among the two techniques, suggesting that the two techniques might be similarly effective when performed by operators with the same expertise. However, this study was based on a limited experience of a single equipe of operators [30]. For this reason, our comparative study was performed on a consecutive population of patients treated in thyroid referral centres and its outcomes reflect the clinical findings of the everyday activities of well-trained operators working in this field. To our knowledge, this is the first large retrospective cohort study to date which compares safety and technique efficacy of RFA and LA in the percutaneous treatment of benign solid thyroid nodules by using propensity score

matching with power analysis and statistically simulating randomised controlled trials [31].

This study leads to some interesting considerations. The first is that both percutaneous thermal ablation procedures were highly effective in inducing a significant decrease in thyroid nodule volume. Both techniques were equally effective in small and medium size nodules, while the laser technique showed a slightly greater efficacy than RFA in nodules larger than 30 ml (Table 1 and Figure 2(A,B)). Based on previous studies on thyroid tissue and in other organs [13,41–43], this different outcome could be due to the simultaneous use of multiple (up to four) laser sources in large nodules, with a more homogeneous distribution of heat energy in the target area and thus with greater treatment efficacy. Moreover, with the trans-isthmic approach it might be more difficult to treat the deeper part of large nodules, which can be conversely easily reached by a direct puncture of the nodule on its long axis. After adjustment by the propensity score matching, the higher rate of PVR in the LA group for large thyroid nodules was confirmed (as represented in Figure 2(B) and in Table 3). Notably, both techniques produced a rather wide variability in nodule volume reduction (Figure 3(A,B)). This results in a relevant overlap between the two procedures. Although the statistical analysis shows a significant difference between LA and RFA, in clinical practice the different efficacy of the two techniques seems to be of minor importance. A randomized controlled trial (RCT) could confirm this specific finding. To this end, we are currently conducting an ongoing Phase III trial and we are recruiting patients to prospectively assess the effectiveness and safety of LA compared to RFA

(ClinicalTrials.gov identifier: NCT02714946) in order to avoid the potentially confounding bias present in this retrospective study.

A second and the most relevant finding, as shown in Figure 1, is the role of the operator in determining the efficacy and the extent of nodule volume reduction. The influence of the operator experience on the treatment outcome was confirmed, regardless of whether laser light or radiofrequency energy was used. The proper targeting of nodules in close proximity to vital structures such as neck vessels, trachea and laryngeal nerve requires a good manual skill in placing the devices correctly in an anatomical region as small as the neck. This problem underscores the importance of appropriate training and learning curve, which should be longer for operators who are not confident with minimally invasive procedures. This issue should be better clarified by a study addressed to the learning curve of individual operators for thyroid minimally invasive techniques.

Thirdly, we observed that to achieve a comparable volume reduction in small and medium size nodules, the operators used more energy (about ten times more) with the radiofrequency technique than with laser technology (Table 2 and Figure 2). This finding could be explained by the different modalities of production and distribution of thermal energy within the tissue to be ablated by means of the two techniques. The last data, however, do not seem to be relevant in clinical practice because they are inherent to the technique used but do not cause the undesired effects on thyroid tissue that are described in hepatic thermal ablation [44–46].

The two procedures appeared both safe and well tolerated, with a similar complications rate (Table 4). The easiness of use of techniques seems to be subjective

and in most cases is dependent on the clinical circumstances and on the devices available in the institution where the operators work.

Finally, since costs are becoming more and more important in decision making, may be useful to consider the costs of the two techniques. Taking into account the rental of generators in both techniques, the cost of a single laser applicator is about U.S.$250 per session (in most cases two applicators are needed) while the cost of an RFA electrode is about U.S.$800 per session. Both treatments may be performed on outpatients by an operator and a nurse. In both procedures, the cost of dressings, including local anaesthetics and pain-killers, is quite low.

Our study has some limitations. First, we used a retrospective approach; therefore, inherent selection bias was unavoidable, even with the propensity score analysis.

Second, this was a multicentre study with only eight participating centres, even if each of them had a large volume of percutaneous RFA or LA ablation. Moreover, operators were involved in the results assessment and data collection, and some possible bias should be taken into account. Therefore, we believe that careful consideration is needed before generalizing our results to other settings.

In summary, this study confirms the efficacy and safety in different clinical settings of US-g thermal ablation procedures consistently with previous reports. RFA and LA techniques seem to provide similar results, with a high success rate and low risk of major complications. The only difference was observed in the efficacy of LA in comparison with RFA in treatment of large size nodules. This finding seems to be, at least in part, due to the variable skill and experience of the operators.

References

1. Gharib H, Hegedus L, Pacella CM, et al. (2013). Clinical review: nonsurgical, image-guided, minimally invasive therapy for thyroid nodules. J Clin Endocrinol Metab 98:3949–57.

2. Papini E, Pacella CM, Hegedus L. (2014). Thyroid ultasound (US) and US-assisted procedures: from the shadows into an array of applications. Eje 170:R1–R15.

3. Gharib H, Papini E, Garber JR, et al. (2016). American Association of Clinical Endocrinologists, American College of Endocrinology,and Associazione Medici Endocrinologi Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules–2016 update. Endocr Pract 22:622–39.

4. Feng B, Liang P, Cheng Z, et al. (2012). Ultrasound-guided percutaneous microwave ablation of benign thyroid nodules: experimental and clinical studies. Eur J Endocrinol 166:1031–7.

5. Yue W, Wang S, Wang B, et al. (2013). Ultrasound guided percutaneous microwave ablation of benign thyroid nodules: safety and imaging follow-up in 222 patients. Eur J Radiol 82:e11–16.

6. Yang YL, Chen CZ, Zhang XH. (2014). Microwave ablation of benign thyroid nodules. Future Oncol 10:1007–14.

7. Pacella CM, Bizzarri G, Spiezia S, et al. (2004). Thyroid tissue: USguided percutaneous laser thermal ablation. Radiology 232:272–80.

8. Papini E, Guglielmi R, Bizzarri G, Pacella CM. (2004). Ultrasoundguided laser thermal ablation for treatment of benign thyroid nodules. Endocr Pract 10:276–83.

9. Dossing H, Bennedbaek FN, Hegedus L. (2006). Effect of ultrasound-guided interstitial laser photocoagulation on benign solitary solid cold thyroid nodules: one versus three treatments. Thyroid 16:763–8.

10. Cakir B, Topaloglu O, Gul K, et al. (2006). Effects of percutaneous laser ablation treatment in benign solitary thyroid nodules on nodule volume, thyroglobulin and anti-thyroglobulin levels, and cytopathology of nodule in 1 yr follow-up. J Endocrinol Investig 29:876–84.

11. Valcavi R, Riganti F, Bertani A, et al. (2010). Percutaneous laser ablation of cold benign thyroid nodules: a 3-year follow-up study in 122 patients. Thyroid 20:1253–61.

12. Gambelunghe G, Fede R, Bini V, et al. (2013). Ultrasound-guided interstitial laser ablation for thyroid nodules is effective only at high total amounts of energy: results from a three-year pilot study. Surg Innov 20:345–50.

13. Pacella CM, Mauri G, Achille G, et al. (2015). Outcomes and risk factors for complications of laser ablation for thyroid nodules: a multicenter study on 1531 patients. J Clin Endocrinol Metab 100:3903–10.

14. Achille G, Zizzi S, Di Stasio E, et al. (2016). Ultrasound-guided percutaneous laser ablation in treating symptomatic solid benign thyroid nodules: our experience in 45 patients. Head Neck 38:677–82.

15. Dossing H, Bennedbaek FN, Hegedus L. (2005). Effect of ultrasound-guided interstitial laser photocoagulation on benign solitary solid cold thyroid nodules – a randomised study. Eur J Endocrinol 152:341–5.

16. Gambelunghe G, Fatone C, Ranchelli A, et al. (2006). A randomized controlled trial to evaluate the efficacy of ultrasound-guided laser photocoagulation for treatment of benign thyroid nodules. J Endocrinol Investig 29:RC23–6.

17. Papini E, Guglielmi R, Bizzarri G, et al. (2007). Treatment of benign cold thyroid nodules: a randomized clinical trial of percutaneous laser ablation versus levothyroxine therapy or follow-up. Thyroid 17:229–35.

18. Dossing H, Bennedbaek FN, Hegedus L. (2011). Long-term outcome following interstitial laser photocoagulation of benign cold thyroid nodules. Eur J Endocrinol 165:123–8.

19. Negro R, Salem TM, Greco G. (2016). Laser ablation is more effective for spongiform than solid thyroid nodules. A 4-year retrospective follow-up study. Int J Hyperthermia 32:822–8.

20. Kim YS, Rhim H, Tae K, et al. (2006). Radiofrequency ablation of benign cold thyroid nodules: initial clinical experience. Thyroid 16:361–7.

21. Jeong WK, Baek JH, Rhim H, et al. (2008). Radiofrequency ablation of benign thyroid nodules: safety and imaging follow-up in 236 patients. Eur Radiol 18:1244–50.

22. Sung JY, Kim YS, Choi H, et al. (2011). Optimum first-line treatment technique for benign cystic thyroid nodules: ethanol ablation or radiofrequency ablation? AJR Am J Roentgenol 196:W210–14.

23. Lim HK, Lee JH, Ha EJ, et al. (2013). Radiofrequency ablation of benign non-functioning thyroid nodules: 4-year follow-up results for 111 patients. Eur Radiol 23:1044–9.

24. Baek JH, Kim YS, Lee D, et al. (2010). Benign predominantly solid thyroid nodules: prospective study of efficacy of sonographically guided radiofrequency ablation versus control condition. AJR Am J Roentgenol 194:1137–42.

25. Huh JY, Baek JH, Choi H, et al. (2012). Symptomatic benign thyroid nodules: efficacy of additional radiofrequency ablation treatment session-prospective randomized study. Radiology 263:909–16.

26. Deandrea M, Sung JY, Limone P, et al. (2015). Efficacy and safety of radiofrequency ablation versus observation for nonfunctioning benign thyroid nodules: a randomized controlled international collaborative trial. Thyroid 25:890–6.

27. Cesareo R, Pasqualini V, Simeoni C, et al. (2015). Prospective study of effectiveness of ultrasound-guided radiofrequency ablation versus control group in patients affected by benign thyroid nodules. J Clin Endocrinol Metab 100:460–6.

28. Wong KP, Lang BH. (2013). Use of radiofrequency ablation in benign thyroid nodules: a literature review and updates. Int J Endocrinol 2013:428363.

29. Ha EJ, Baek JH, Kim KW, et al. (2015). Comparative efficacy of radiofrequency and laser ablation for the treatment of benign thyroid nodules: systematic review including traditional pooling and bayesian network meta-analysis. J Clin Endocrinol Metab 100:1903–11.

30. Mauri G, Cova L, Monaco CG, et al. (2017). Benign thyroid nodules treatment using percutaneous laser ablation (PLA) and radiofrequency ablation (RFA). Int J Hyperthermia 33:295–9.

31. McDonald RJ, McDonald JS, Kallmes DF, Carter RE. (2013). Behind the numbers: propensity score analysis-a primer for the diagnostic radiologist. Radiology 269:640–5.

32. Haukoos JS, Lewis RJ. (2015). The Propensity Score. Jama 314:1637–8.

33. Bongiovanni M, Spitale A, Faquin WC, et al. (2012). The Bethesda system for reporting thyroid cytopathology: a meta-analysis. Acta Cytol 56:333–9.

34. Cooper DS, Doherty GM, Haugen BR, et al. (2009). Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 19:1167–214.

35. Gharib H, Papini E, Paschke R, et al. (2010). American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: executive summary of recommendations. J Endocrinol Investig 33:51–6.

36. Sacks D, McClenny TE, Cardella JF, Lewis CA. (2003). Society of Interventional Radiology clinical practice guidelines. J Vasc Interv Radiol 14:S199–S202.

37. Ahmed M, Solbiati L, Brace CL, et al. (2014). Image-guided tumor ablation: standardization of terminology and reporting criteria–a 10-year update. J Vasc Interv Radiol 25:1691–705 e1694.

38. Livraghi T, Goldberg SN, Lazzaroni S, et al. (2000). Hepatocellular carcinoma: radio-frequency ablation of medium and large lesions. Radiology 214:761–8.

39. Papini E, Pacella CM, Misischi I, et al. (2014). The advent of ultrasound-guided ablation techniques in nodular thyroid disease: towards a patient-tailored approach. Best Pract Res Clin Endocrinol Metab 28:601–18.

40. Takuma Y, Takabatake H, Morimoto Y, et al. (2013). Comparison of combined transcatheter arterial chemoembolization and radiofrequency ablation with surgical

resection by using propensity score matching in patients with hepatocellular carcinoma within Milan criteria. Radiology 269:927–37.

41. Pacella CM, Stasi R, Bizzarri G, et al. (2008). Percutaneous laser ablation of unresectable primary and metastatic adrenocortical carcinoma. Eur J Radiol 66:88–94.

42. Pacella CM, Francica G, Di Lascio FM, et al. (2009). Long-term outcome of cirrhotic patients with early hepatocellular carcinoma treated with ultrasound-guided percutaneous laser ablation: a retrospective analysis. J Clin Oncol 27:2615–21.

43. Mauri G, Cova L, Tondolo T, et al. (2013). Percutaneous laser ablation of metastatic lymph nodes in the neck from papillary thyroid carcinoma: preliminary results. J Clin Endocrinol Metab 98:E1203–7.

44. Rozenblum N, Zeira E, Bulvik B, et al. (2015). Radiofrequency ablation: inflammatory changes in the periablative zone can induce global organ effects, including liver regeneration. Radiology 276:416–25.

45. Rozenblum N, Zeira E, Scaiewicz V, et al. (2015). Oncogenesis: an "off-target" effect of radiofrequency ablation. Radiology 276:426–32.

46. Velez E, Goldberg SN, Kumar G, et al. (2016). Hepatic thermal ablation: effect of device and heating parameters on local tissue reactions and distant tumor growth. Radiology 281:782–92.

Table 1. Baseline characteristics and results in all study patients according to baseline nodule volume group before propensity score matching.

Table 1. Baseline characteristics and results in all study patients according to baseline nodule volume group before propensity score matching.

	LA group nodule volume (ml)				RFA group nodule volume (ml)				*p* Value			
	≤13 (*n* = 151)	13.1–30 (*n* = 195)	>30 (*n* = 103)	Total (*n* = 449)	≤13 (*n* = 35)	13.1–30 (*n* = 80)	>30 (*n* = 37)	Total (*n* = 152)	≤13 (*n* = 186)	13.1–30 (*n* = 275)	>30 (*n* = 140)	Total (*n* = 601)
Age (yrs)	55 ± 13	57 ± 14	58 ± 15	57 ± 14	53 ± 13	56 ± 13	65 ± 14	57 ± 14	0.410	0.611	0.028	0.526
Female	77%	67%	61%	69%	77%	69%	76%	71%	0.968	0.882	0.112	0.642
Baseline volume	7.4 ± 3.1	20.0 ± 4.7	45.1 ± 16.6	21.5 ± 16.5	9.9 ± 2.9	19.7 ± 4.7	49.0 ± 20.3	24.6 ± 17.9	<0.001	0.677	0.304	0.065
Volume reduction at 6th month (%)	−58 ± 19	−59 ± 19	−61 ± 17	−59 ± 18	−59 ± 25	−59 ± 19	−50 ± 19	−57 ± 21	0.791	0.960	0.003	0.210
Volume reduction at 12th month (%)	−62 ± 19	−62 ± 18	−64 ± 16	−63 ± 18	−69 ± 24	−63 ± 19	−56 ± 21	−62 ± 21	0.174	0.848	0.033	0.830
Total energy (kJ)[a]	3.5 ± 1.9	6.6 ± 2.1	7.8 ± 2.3	5.8 ± 2.7	46.2 ± 30.2	59.6 ± 40.9	93.6 ± 92.6	64.6 ± 58.2	<0.001	<0.001	<0.001	<0.001
Ablation time (min)	11.9 ± 4.3	18.9 ± 5.3	21.7 ± 5.7	17.1 ± 6.4	14.2 ± 8.0	18.1 ± 10.6	26.9 ± 24.8	19.4 ± 15.5	0.111	0.680	0.221	0.086

Values are reported as mean ± SD.
[a]kJ: Kilojoules.

Table 2. Predictive factors for percentage volume reduction (PVR) at 6th month in all study patients and according to LA or RFA treatment before propensity score matching.

	All patients			LA group			RFA group		
	PVR <50% (n = 161) 27%	PVR ≥50% (n = 440) 73%	p Value	PVR <50% (n = 114) 25%	PVR ≥50% (n = 335) 75%	p Value	PVR <50% (n = 47) 31%	PVR ≥50% (n = 105) 69%	p Value
Age (yrs)	55 ± 14	57 ± 14	0.193	55 ± 14	57 ± 14	0.087	58 ± 16	57 ± 13	0.871
Female (%)	74	68	0.160	75	67	0.140	72	70	0.815
Baseline volume	21.4 ± 17,2	22.6 ± 16.8	0.412	18.3 ± 13.5	22.6 ± 17.3	0.006	28.8 ± 22.3	22.7 ± 15.3	0.095
Total energy (kJ)[a]	17.4 ± 33.8	21.8 ± 40.4	0.177	5.4 ± 2.6	6.0 ± 2.7	0.033	47.1 ± 52.4	72.3 ± 59.1	0.010
Ablation time (min)	15.5 ± 9,7	18.5 ± 9,5	0.001	16.2 ± 6.7	17.4 ± 6.3	0.101	13.6 ± 14.5	21.9 ± 15.3	0.002

Values are reported as mean ± SD.
[a]kJ: Kilojoules.

Table 3. Results in all study patients according to baseline nodule volume group after propensity score matching.

	LA group nodule volume (ml)				RFA group nodule volume (ml)				*p* Value			
	≤13 (*n* = 34)	13.1–30 (*n* = 74)	>30 (*n* = 30)	Total (*n* = 138)	≤13 (*n* = 34)	13.1–30 (*n* = 74)	>30 (*n* = 30)	Total (*n* = 138)	≤13 (*n* = 68)	13.1–30 (*n* = 148)	>30 (*n* = 60)	Total (*n* = 276)
Volume reduction at 6th month (%)	−67 ± 22	−65 ± 17	−69 ± 19	−67 ± 19	−57 ± 25	−59 ± 19	−50 ± 21	−57 ± 21	0.071	0.026	0.001	<0.001
Volume reduction at 12th month (%)	−70 ± 22	−69 ± 18	−73 ± 18	−70 ± 19	−67 ± 24	−63 ± 19	−54 ± 23	−62 ± 22	0.646	0.047	0.001	0.001
Total energy (kJ)[a]	4.0 ± 2.0	6.6 ± 2.2	7.1 ± 3.1	6.1 ± 2.7	44.8 ± 30.5	59.9 ± 41.0	88.0 ± 83.3	61.6 ± 51.4	<0.001	<0.001	<0.001	<0.001
Ablation time (min)	12.6 ± 4.8	18.9 ± 4.8	20.5 ± 7.3	17.7 ± 6.2	13.9 ± 8.1	18.2 ± 10.7	25.8 ± 21.8	18.7 ± 13.6	0.435	0.623	0.238	0.437

Values are reported as mean ± SD.
[a]kJ: Kilojoules.

Table 4. Major, minor complications and side effects in each group of 138 patients.

Type of complications (SIR Class)[a]		Complications and side effects no. (%)[b] time of detection												
		Intra-procedural		Immediate post-procedural (within 24 h)		Peri-procedural (within 30 days)		Delayed (after 30 days)		Time to recovery (days)				
		LA	RFA	LA	RFA	LA	RFA	LA	RFA			*p*	LA	RFA
Major														
Voice change[c]	(C)			4 (1.2)	3 (2.7)					28–84	2-permanent[d]	NS		
Hyperthyroidism	(C)								1 (0.6)			NS		
Minor														
Hematoma	(B)	3 (0.9)	5 (4.5)							5–10	5–10	0.044		
Side effects														
Pain	(A)													
Mild		18 (5.5)	12 (10.9)									NS		
Moderate		4 (1.3)[e]								1–4		NS		
Severe		2 (0.6)[e]	1 (0.9)	2 (0.6)[f]						1–3	1	NS		
Vasovagal reaction	(A)	4 (1.2)										NS		
Fever (37.5 °C–38.5 °C)	(A)	6 (1.8)								1–4		NS		

[a]Society of Interventional Radiology (SIR) guidelines criteria; Minor complications: A: No therapy, no consequence; B: Nominal therapy, no consequence; includes overnight admission for observation only. Major Complications: C: Require therapy, minor hospitalisation (<48 h); D: Require minor therapy, unplanned increase in level of care, hospitalisation >48 h; E: Permanent adverse sequelae; F: Death.

[b]Value calculated per LA sessions.

[c]Transient or permanent cord paralysis.

[d]One case with permanent stridor.

[e]With discomfort.

[f]With swelling.

Figure 1: The figure shows the operator's role in determining the extent of nodule volume reduction using laser light (A) or radiofrequency energy (B).

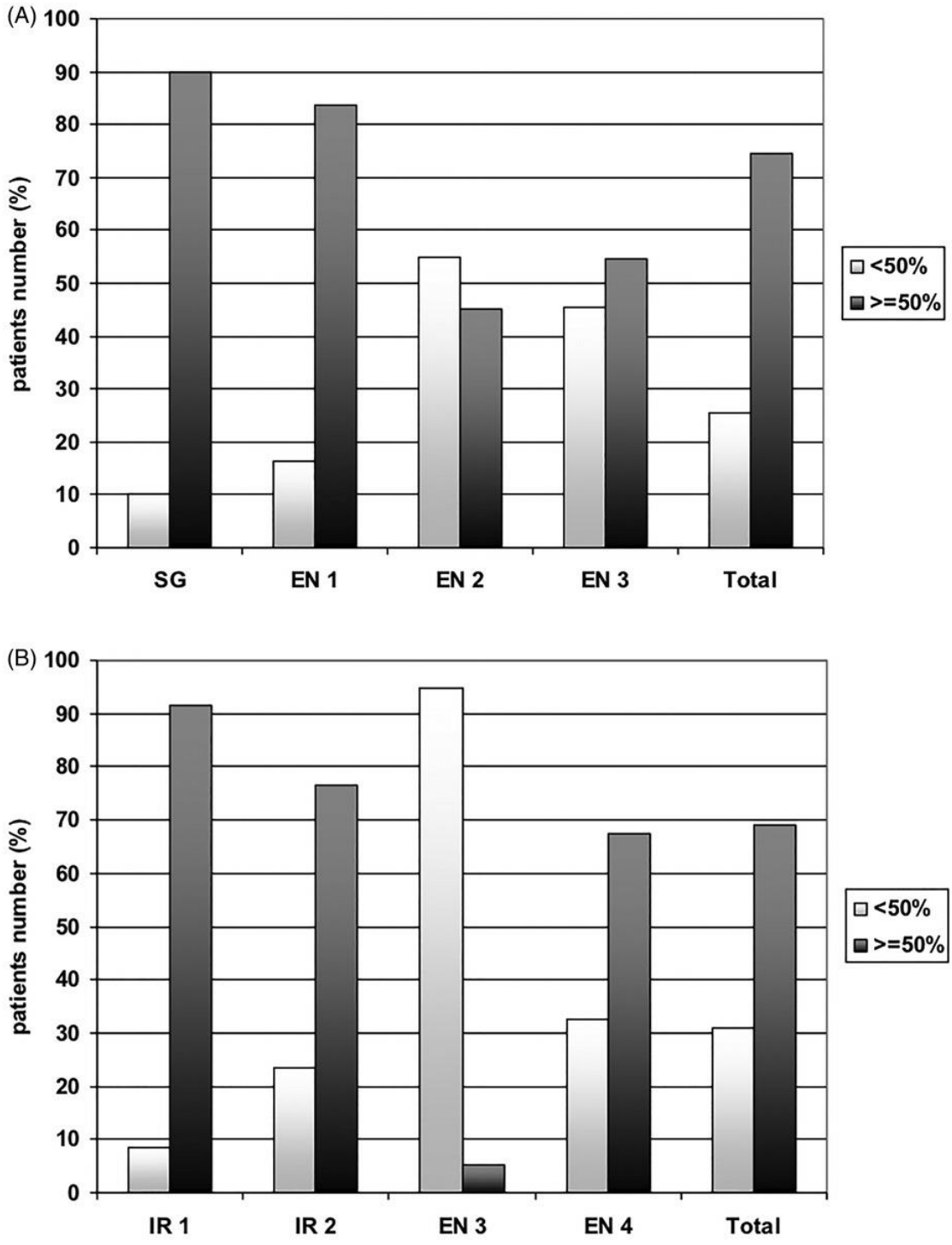


Figure 2: The figure shows the mean nodule reduction at 6 months according to baseline nodule volume group in all patients before (A) and after (B) propensity score adjustment. After propensity score-matching analysis, the higher rate of PVR in LA group in comparison with RFA group, appears confirmed in large nodules (>30 ml) thyroid nodules, appears clearly confirmed.

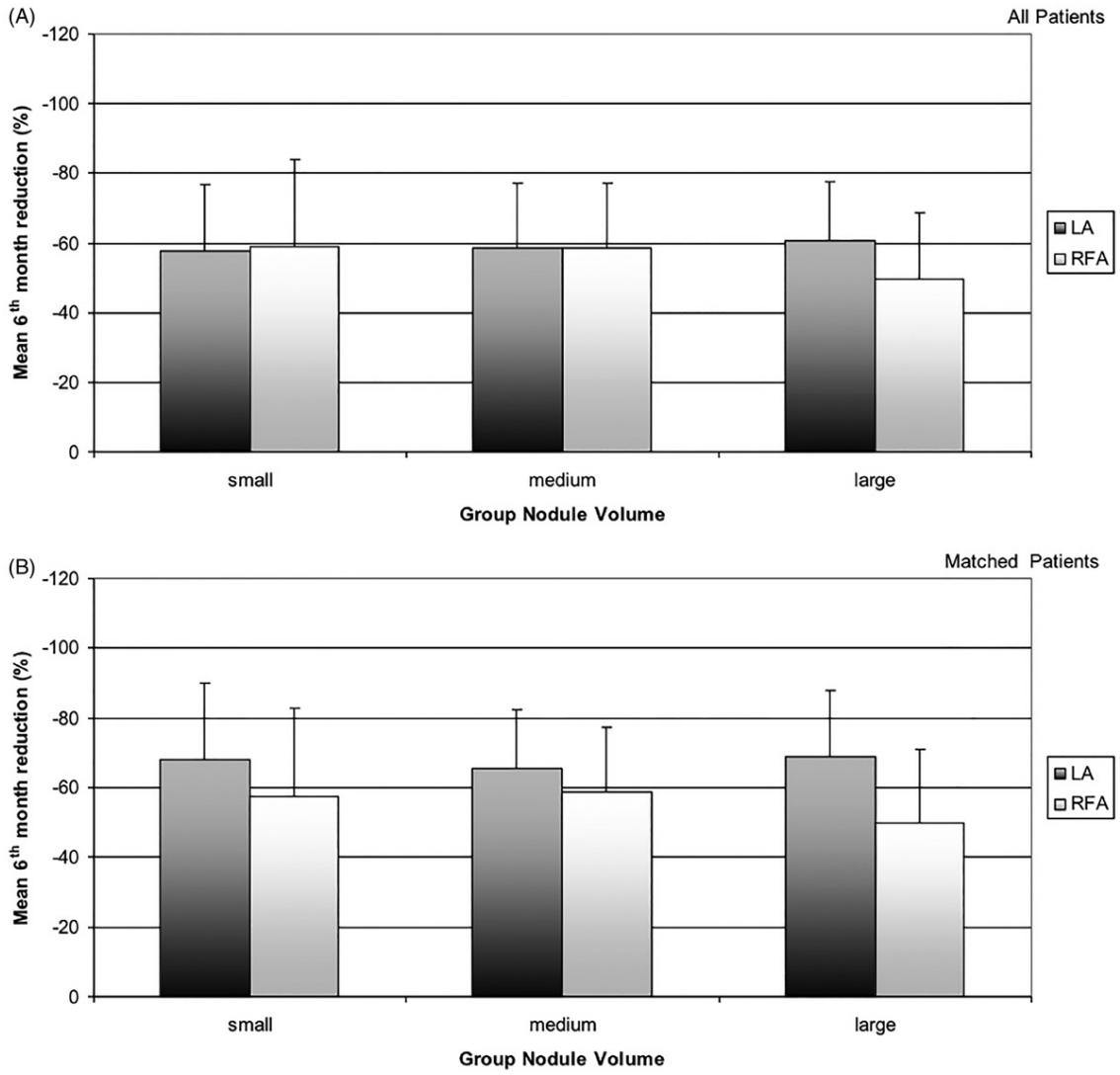
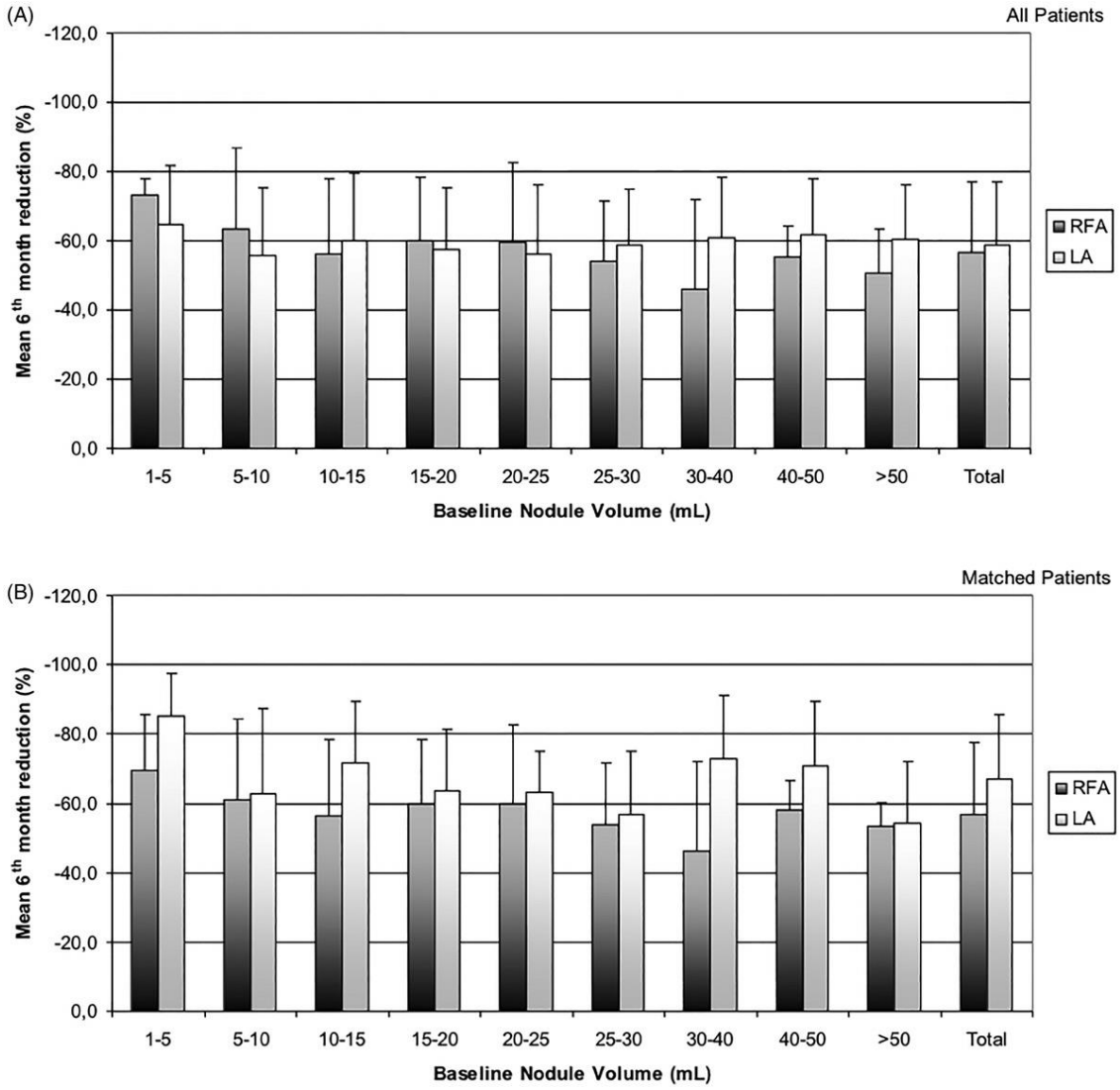


Figure 3: The figure shows the wide variability in volume reduction with both the techniques according to baseline nodule volume, both before (A) and after (B) propensity score adjustment.



CHAPTER 5

A case of thyroid cancer on the track of the radiofrequency electrode 30 months after percutaneous ablation.

Oddo S, Spina B, Vellone VG, Giusti M.

J Endocrinol Invest. 2017; 40: 101-102

Dear Editor,

a recent publication described a case of a full-thickness skin burn of the neck as a severe complication of percutaneous radiofrequency ablation (RFA) for a benign thyroid nodule [1]. We report what we believe is the second case of needle-track tumor seeding after RFA of a thyroid nodule [2].

This case involved a 74-year-old woman with negative oncological history and a symptomatic multi-nodular goiter: the predominant nodule (APxLLxCC diameters: 37x37x45 mm; 34 mL) was solid, isoechoic and localized in the right lobe. Thyroid function was normal, calcitonin and thyroid autoimmunity were negative. The patient underwent a fine-needle aspiration biopsy (FNAB), which revealed a colloid nodular hyperplasia (Thy 2). As the woman refused thyroidectomy, we proposed RFA of the predominant nodule. After a second FNAB (Thy 2), RFA was performed by means of a 7 cm, 19-Gauge electrode with a 1 cm active tip (Starmed, Seoul, Korea) and a moving-shot technique with a delivered energy of 14151 Joules.

Follow-up examination did not show any reduction of the nodule and, 30 months after RFA, an ultrasound scan revealed a hypoechoic extra-thyroid jugular median supra-fascial lesion of about 14 mL (APxLLxCC diameters: 26x30x34 mm). FNAB on that lesion

showed an hyperplastic, hypercellular with focal cytologic atypia (Thy 4), without BRAF, K-RAS or N-RAS mutations. Thyroidectomy, with excision of the extra-thyroid lesion, was performed.

The histologic diagnosis of the RFA-treated nodule was of a follicular carcinoma with a minority component of papillary carcinoma (collision tumor). Immunohistochemistry proved positive for galectin-3 and cytokeratin 19 in the papillary component; these were negative in the follicular component; the extra-thyroid lesion was a medium-differentiated follicular carcinoma; galectin-3 and cytokeratin 19 were negative. Revision of pre-RFA FNAB confirmed the Thy 2 diagnosis.

As suggested by Lee et al. [2], there are three possibilities: an incidental malignant potential of the benign thyroid nodule, the RFA-induced transformation of cells, or a sampling error.

Whether the risk of malignancy in thyroid nodules increases with size is debated, and the presence of cancer in Thy 2 has been described in about 6% of cases [3]. Moreover, 2% of Thy 2 transform into carcinomas.

We suppose that the extra-thyroid lesion was a dissemination of the follicular component of the thyroid carcinoma for the following reasons: (I) atypical site for metastasis; (II) it could not have been the canceration of an ectopic thyroid (not seen on US scan; histological examination revealed no residual normal tissue around the neoplasm); (III) tumor development corresponded to the insertion site of the electrode (trans-isthmic access); (IV) the moving-shot technique may increase the risk of seeding. Seeding of malignant cells after FNAB on thyroid nodules has been anedoctally reported in the literature; in agreement with Lee et al. [2], we suppose that RFA, as

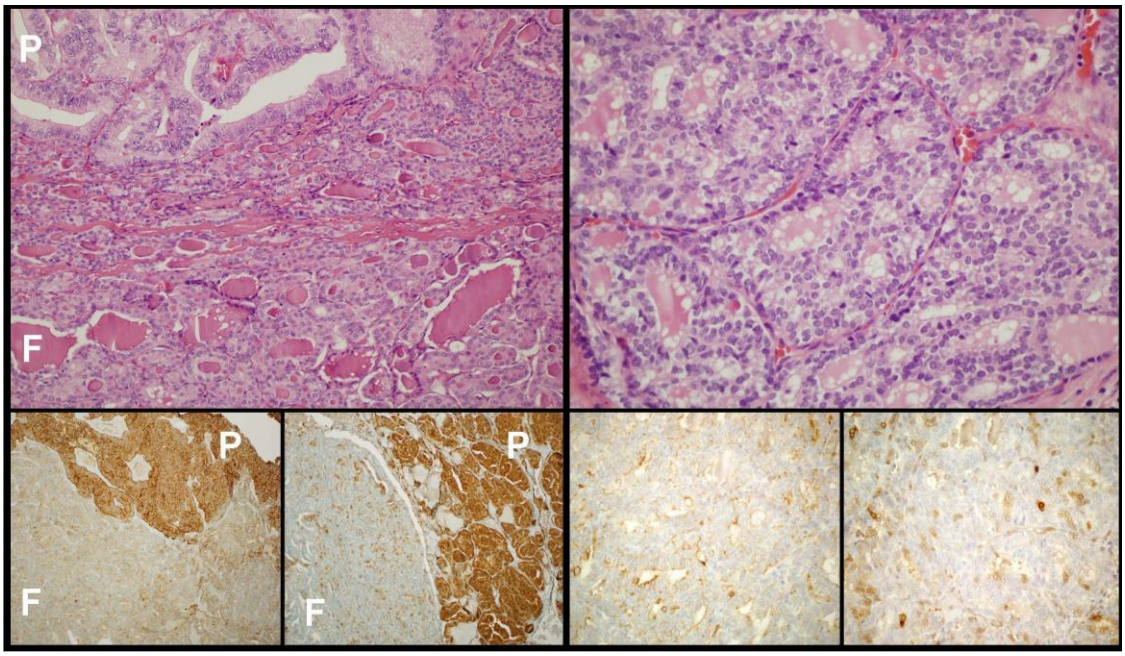
already described in liver and kidney, could cause seeding of malignant cells in the thyroid.

In conclusion, RFA is effective and safe, though in rare cases it can cause seeding of malignant cells from the nodule.

References

1. *Bernardi S, Lanzilotti V, Papa G, Panizzo N, Dobrinja C, Fabris B, Stacul F (2016) Full-Thickness Skin Burn Caused by Radiofrequency Ablation of a Benign Thyroid Nodule. Thyroid 26: 183-184. doi: 10.1089/thy.2015.0453*
2. *Lee CU, Kim SJ, Sung JY, Park SH, Chong S, Baek JH (2014) Needle track tumor seeding after radiofrequency ablation of a thyroid tumor. Jpn J Radiol. 32:661-663.*
3. *Wang CC, Friedman L, Kennedy GC, Wang H, Kebebew E, Steward DL, Zeiger MA, Westra WH, Wang Y, Khanafshar E, Fellegara G, Rosai J, Livolsi V, Lanman RB (2011) A large multicenter correlation study of thyroid nodule cytopatology and histopathology. Thyroid. 21:243-251.*

LEFT: histology of thyroid collision tumor of the right lobe: P) papillary component that is positive for cytokeratin 19 (left) and galectin-3 (right), F) follicular component that is negative for cytokeratin 19 (left) and galectin-3 (right); RIGHT: histology of extra-thyroid nodule: only follicular pattern that is negative for cytokeratin 19 (left) and galectin-3 (right).



CHAPTER 6

A benign thyroid nodule unresponsive to radiofrequency ablation treated with laser ablation.

Oddo S, Balestra M, Vera L, Giusti M.

Journal of Medical Case Reports. Under review

Background

Since 2010, practical guidelines have approved radiofrequency ablation (RFA) and laser ablation (LA) as possible therapeutic options for the treatment of benign symptomatic thyroid nodules in patients who refuse thyroidectomy or in those with comorbidities that contraindicate surgery [1, 2].

RFA and LA are safe and effective techniques for reducing nodule volume, neck symptoms and cosmetic complaints [3, 4].

Therapeutic success is defined as a nodule reduction >50% from the baseline volume 6-12 months after the procedure and is reportedly achieved in 67% and 81% of cases of LA and RFA, respectively, on 6-12-month follow-up [3, 4]. However, for unknown reasons, a percentage of nodules do not respond to thermal ablation.

Our paper describes the first case in literature of a benign thyroid nodule treated unsuccessfully with RFA and afterwards treated with LA with a significant reduction of volume and symptoms at the neck.

Case presentation

A 41-year-old Caucasian female discovered the presence of a mass at the neck palpation. Her family history was negative for thyroid illnesses, and she stated that she had no significant past medical history. The physical examination confirmed the presence of a soft mass in the right portion of the neck, mobile with swalling acts. The patient underwent a ultrasound (US)-scan, which showed a single, solid, isoechoic nodule of 12 mL (antero-posterior x latero-lateral x cranio-caudal diameters: 20 x 30 x 40 millimeters) in the right lobe of the thyroid (figure 1a). The patient was symptomatic for neck discomfort, with a score of 6/10 on the visual analogic scale (VAS). Thyroid function was normal (TSH 1.81 mIU/L, f-T3 5.0 pmol/L, f-T4 14.12 pmol/L); calcitonin was normal (<1 ng/L) and thyroid autoimmunity was negative (TPO-Abs 18 U/mL).

The patient underwent a fine-needle aspiration biopsy (FNAB), which revealed a colloid nodular hyperplasia with hyperplastic thyrocites and fluid colloid (Thy 2 according to the British Thyroid Association). The patient refused lobectomy for fear about surgery, so we proposed RFA of the nodule. After a second FNAB (Thy 2 according to the British Thyroid Association), a phoniatric evaluation, which excluded anomalies of vocal cord motility, and an electrocardiogram, which excluded arrhythmias, as suggested by the Korean consensus statement [5], a single session of RFA was performed with trans-isthmic access and moving-shot technique [5], with a delivered energy of 41868 Joules (3489 J/mL) in a day-hospital regimen. RFA was performed by means of 7 cm, 18 Gauge electrodes with a 1 cm active tip, with the support of an ultrasound MyLab Five (Esaote, Genoa, Italy) with a 7.5 MHz linear probe

(LA523). The radiofrequency generator used was an RF System Viva VRS01 (Starmed, Seoul, Korea) and the peristaltic pump was an R4S100 (Starmed, Seoul, Korea).

Before RFA the patient underwent intravenous infusion of ketorolac (20 mg) and ranitidine (50 mg) diluted in 100 ml of 0.9% saline solution for 30 minutes. Subsequently, intravenous ketorolac (40 mg) and ranitidine (50 mg) were administered in 500 ml of 0.9% saline for about 5 hours (during and after thyroid RFA). A pre-procedural local anesthesia with 2% lidocaine was carried out at the puncture site. The procedure was well-tolerated by the patient and there were no adverse events; after thyroid RFA, a compressive bandage and ice were applied to the neck and the patient received a domiciliary prescription for steroid administration (prednisone 25 mg for 3 days, 12.5 mg for 3 days, 6.25 for 3 days) and gastric protection,At the time of the RFA, our operator had 1-year experience of this technique.

During follow-up, the nodule displayed only a modest and fugacious volume reduction and from the sixth month the nodule regrowth (figure 1b and 2a). The patient's neck discomfort persisted (figure 2a).

Twenty-four months after RFA, as the patient again refused to undergo lobectomy, we proposed a single session of LA. This was performed by the same operator, who had with 1-year experience of this technique, by means of 2 fibres of 300 µm diameter inserted by means of a 21-Gauge Chiba-needle (ELESTA®, Calenzano, Italy), with one pull-back of 1 centimetre and a delivered energy of 5489 Joules (457 J/mL). LA was performed by means of a commercially available US scanner (Echo-laser X4®; Esaote, Genoa, Italy) equipped with a 7.5 MHz linear transducer (LA 332, Esaote®, Genoa, Italy)

with a 1064 µm diode laser unit with an individual energy emission setting and an indipendent activation. The pre-procedural modalities were the same of RFA.

The procedure was well-tolerated by the patient and there were no adverse events. At the time of the LA, our operator had 1-year experience of this technique. The patient referred a progressive improvement in neck symptoms and cosmetic complaints, and follow-up examinations showed a marked, progressive reduction in nodule volume (figure 1c and figure 2b). Thyroid function and thyroid autoimmunity remained unchanged after RFA and LA (table 1).

Discussion

Both RFA and LA are percutaneous techniques, and their efficacy in reducing thyroid nodule volume is reported to be similar [6]. Therapeutic success (nodule volume reduction >50%) is achieved in the majority of cases by both techniques [3, 4].

Some studies have identified factors that might predict a good response to RFA, though these are controversial: the small volume (<12 mL) of the nodule at the baseline [7], the absence of vascularization [8] the presence of a fluid component [9], the non-functioning status [10], and the presence of well-defined margins [4]. By contrast, a study by Papini et al. [3] found that baseline size, presence of goiter or US findings (like fluid component, halo, vascularization and calcifications) were not predictive factors of a volume decrease > 50% in thyroid nodules treated with LA.

Our patient's thyroid nodule was smaller than 13 mL, non-functioning, well-defined, and free from vascularization; thus, there were no parameters that could predict the inefficacy of RFA.

When therapy is not successful, another session of ablation may be proposed; in the second session, the same ablation procedure is generally performed [11]. This choice is probably determined by the availability of LA or RFA in each centre.

In our centre, however, we had the possibility to perform both RFA and LA. We chose to perform LA after unsuccessful RFA because in our cohort of patients, we had already observed two cases in which the repetition of RFA had failed to yield significant results in nodules that had previously undergone an unsuccessful RFA procedure so we conjectured that certain nodules might be intrinsically resistant to necrosis when one ablation technique is undertaken, but might respond to the other ablation technique.

Other possibility could be the inexperience of the operator in performing RFA compared to LA, but he performed RFA and LA with the same time of experience in both the procedures.

In our case, the thyroid nodule, which had not responded to a single session of RFA, displayed an optimal response to a single session of LA. We excluded the possibility that the better response of the nodule to LA might have been due to greater operator experience of this technique, as our operator had the same length of experience of both techniques at the time when they were performed.

Conclusions

In our opinion, LA may be a viable option in patients with a thyroid nodule that does not respond to RFA and who refuse surgery or have comorbilities that contraindicate it. It would be useful to conduct a study on a large cohort of patients with an inefficient response to RFA or to LA who are subsequently treated with the other technique.

References

1. *Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, Hegedüs L, et al. Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: executive summary of recommendations. J Endocrinol Invest 2010;33:287-291.*
2. *Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26:1-133.*
3. *Papini E, Rago T, Gambelunghe G, Valcavi R, Bizzarri G, Vitti P, et al. Long-term efficacy of ultrasound-guided laser ablation for benign solid thyroid nodules. Results of a three-year multicenter prospective randomized trial. Clin Endocrinol Metab. 2014;99:3653-3659.*
4. *Ahn HS, Kim SJ, Park SH, Seo M. Radiofrequency ablation of benign thyroid nodules: evaluation of the treatment efficacy using ultrasonography. Ultrasonography. 2016;35:244-252.*
5. *Na DG, Lee JH, Jung SL, Kim JH, Sung JY, Shin JH, et al. Radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: consensus statement and recommendations. Korean J Radiol. 2012;13:117-125.*
6. *Mauri G, Cova L, Monaco CG, Sconfienza LM, Corbetta S, Benedini S, et al. Benign thyroid nodules treatment using percutaneous laser ablation (PLA) and radiofrequency ablation (RFA). Int J Hyperthermia 2016;15:1-5.*

7. *Cesareo R, Pasqualini V, Simeoni C, Sacchi M, Saralli E, Campagna G, et al. Prospective study of effectiveness of ultrasound-guided radiofrequency ablation versus control group in patients affected by benign thyroid nodules. J Clin Endocrinol Metab. 2015;100:460-466.*
8. *Kim YS, Rhim H, Tae K, Park DW, Kim ST. Radiofrequency ablation of benign cold thyroid nodules: initial clinical experience. Thyroid.2006;16:361-367.*
9. *Baek JH, Kim YS, Lee D, Huh JY & Lee JH. Benign predominantly solid thyroid nodules: prospective study of efficacy of sonographically guided radiofrequency ablation versus control condition. Am J of Roentgenology. 2010;194:1137–1142.*
10. *Spiezia S, Garberoglio R, Di Somma C, Deandrea M, Basso E, Limone PP et al. Efficacy and safety of radiofrequency thermal ablation in the treatment of thyroid nodules with pressure symptoms in elderly patients. J Am Geriatr Soc. 2007; 55:1478-1479.*
11. *Huh JY, Baek JH, Kim JK, Lee JH. Symptomatic benign thyroid nodules: efficacy of additional radiofrequency ablation treatment session-prospective randomized study. Radiology.2012; 263:909-916.*

Table 1: thyroid function and autoimmunity at each time-point of the study.

	TSH (mIU/L) (0.27-4.2)	f-T3 (pmol/L) (2.76-7.07)	f-T4 (pmol/L) (11.97-21.88)	Calcitonin (ng/L) (<10)	TPO-Abs (U/mL) (<100)
Baseline RFA	1.81	5.00	14.12	<1	18
3rd month	1.60	4.98	15.30	-	19
6th month	1.43	5.20	14.35	-	25
12th month	1.57	5.05	15.07	-	15
24th month / Baseline LA	1.61	5.30	14.78	-	26
3rd month	1.47	5.12	15.03	-	30
6th month	1.36	4.97	14.99	-	24
12th month	1.89	5.00	15.12	-	19

Figure 1. Ultrasound images of thyroid nodule.

Figure “a” shows the thyroid nodule at the baseline; Figure “b” shows the thyroid nodule 24 months after radiofrequency ablation; Figure “c” shows the thyroid nodule 12 months after laser ablation.

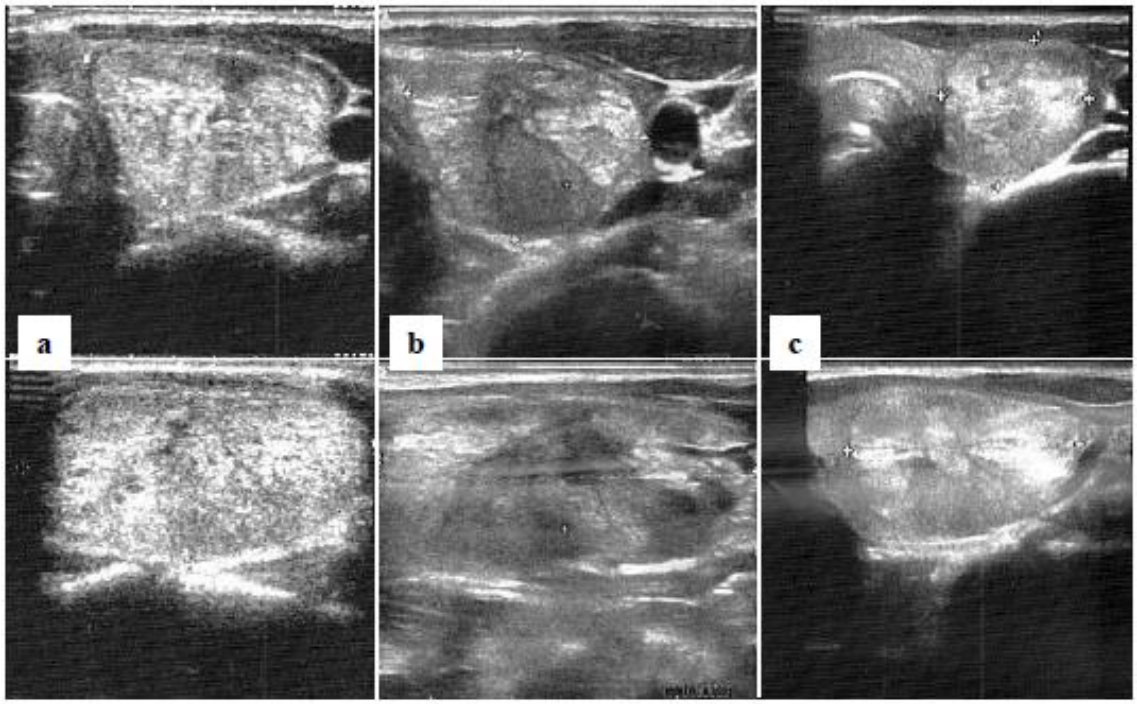
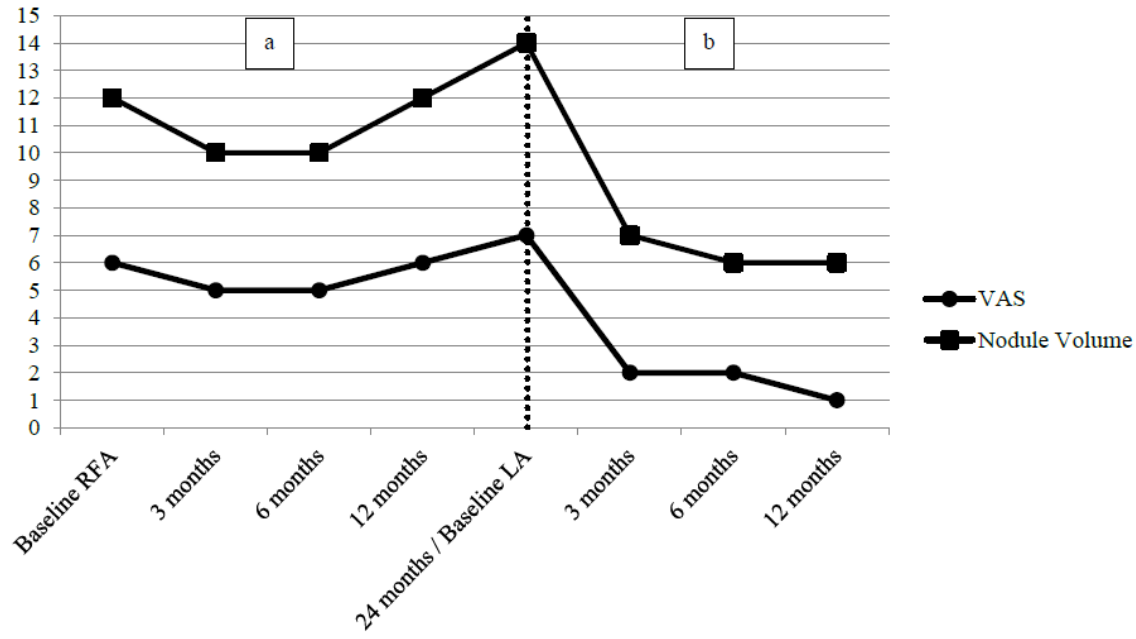


Figure 2. Changes in volume of the nodule and in symptoms at the neck of the patient.

Graph “a” shows changes in the thyroid nodule volume and symptoms at the neck by mean of the visual analogic scale (VAS) from baseline to 24 months after radiofrequency ablation (RFA); Graph “b” shows changes in the thyroid nodule volume and symptoms at the neck by mean of VAS from baseline of laser ablation (LA) (24 months after RFA) to 12 months after



CHAPTER 7

Other papers

Five-year longitudinal evaluation of mild primary hyperparathyroidism - medical treatment versus clinical observation.

Vera L, Accornero M, Dolcino M, Oddo S, Giusti M.

Endokrynol Pol. 2014; 65: 456-463.

Introduction

Primary hyperparathyroidism (PHPT) is a disorder characterised by inappropriately high secretion of parathyroid hormone (PTH). PHPT has become a common disease, with an estimated prevalence of 1% of the general population and 3% in postmenopausal women [1], and an increasing incidence over the last few decades.

PHPT is usually the result of a single over-active parathyroid gland as a result of adenoma, hyperplasia or cancer [2]. The clinical presentation has changed over the years: today, 80–85% of cases are asymptomatic [3].

A National Institutes of Health consensus panel has recognised two forms of the disease: asymptomatic and symptomatic [4]. The diagnosis is based on the clinical and objective picture, evaluation of serum calcium (S-Ca) and PTH. Preoperative localisation studies are required.

Therapy may involve medical or surgical treatment, and many guidelines have been proposed over the years. Although parathyroidectomy (PTX) is regarded as the treatment of choice for patients with symptomatic hypercalcaemia or evidence of

target organ damage [5], conservative management has been favoured in asymptomatic patients. In addition, in some cases surgery fails, in some it is contraindicated, and in others it is refused [6]. At the most recent International Workshop [7], the guidelines pointed out that there was no data to support the medical treatment of patients with mild PHPT. In general, it is recommended that patients who do not meet surgical criteria [7] be monitored closely. However, the validity of medical treatment is unanimously recognised. The prognosis of PHPT patients depends on the time-line of the diagnosis.

The aims of our five-year study were: 1) to evaluate patients with PHPT during the course of different types of treatment; and 2) to evaluate quality of life (QoL) in PHPT subjects by means of several instruments, both self-rated and physician-administered.

Material and methods

Patients

We longitudinally evaluated all patients (aged 22–90 years) with a history of PHPT in our endocrine unit from 2007–2011. Over the years, the number of patients progressively increased. Patients (N = 18) on cinacalcet were excluded from the study owing to their small number. The remaining study population was divided into three groups: 52 patients were on anti-resorptive therapy (bisphosphonate-treated group: alendronate 70 mg/week N = 22, risedronate 150 mg/month N = 13, ibandronate 150 mg/month N = 11, clodronate 100 mg/week N = 6); 37 were not on any treatment (untreated group); and 50 were disease-free after surgery (surgery group). When required, patients underwent supplementation with vitamin D (< 25mmol/L = 2,000 U/day, 25–50 mmol/L = 1,000 U/day, 50–75 mmol/L = 800 U/day, as reported in the guidelines SIOMMMS). Written informed consent was obtained from all participants.

Study design

Evaluation was based on clinical examination, neck ultrasonography, bone mineral density (BMD) and blood tests. S-Ca and PTH levels were recorded on each occasion. Serum phosphorus, 25hydroxy-vitaminD (25OHD) and 1.25dihydroxy-vitaminD (1.25OHD), creatinine, total and bone-specific alkaline-phosphatase (ALP), urinary cross-links and osteocalcin were measured annually. Finally, an Italian ad hoc parathyroid questionnaire (PQ) was administered to all patients, to evaluate their QoL. On entry to the study, a semistructured clinical interview was conducted by a psychiatrist. All subjects were then asked to complete the Italian version of the self-rated Kellner symptom questionnaire (KSQ) [8].

Laboratory evaluations

PTH was analysed by means of two chemiluminescence immunoassays (2007-2008: Immunolite2000, Diagnostic Products, San Juan Capistrano, CA, USA; from 2009: LIASON N-tactPTH, DIASorin, Saluggia, Italy). Reproducibility of the data yielded by the two methods was excellent. The reference range (r.r.) is 15–65 ng/L or < 36.8 ng/L. Creatinine (r.r., 44.0–115.0 µmol/L), S-Ca (2.1–2.7 mmol/L), phosphorus (0.8–1.4 mmol/L), and ALP (98.0–280.0 U/L) levels were determined by means of fully automatic equipment (ModularP800, Roche Diagnostics). Evaluation of 25OHD was performed by means of a chemiluminescence method (LIAISON, DIASorin). A range of 75–250 nmol/L was considered indicative of adequate vitamin D intake. Evaluation of 1.25OHD (r.r. 47.6–150 pmol/L) was performed by radioimmunoassay (Immunodiagnostic Systems). Osteocalcin (r.r. 0.5–7.0 ng/mL) was measured by means of an immunochemiluminescence method (Nichols).

Urinary cross-links (expressed as the molar ratio of creatinine) were measured by high-performance liquid chromatography (BioRad, Milan, Italy).

Imaging

Colour-Doppler neck ultrasonography (AU5Idea and MyLabFive; Esaote, Genoa, Italy) was performed by means of a device equipped with a linear 7.5–10 MHz probe. When indicated, fine-needle aspiration was performed and PTH was evaluated in fine-needle washing in order to locate hyperfunctioning parathyroid tissue [9, 10]. BMD (gr/cm2) in the lumbar spine and total hip was measured in the antero-posterior direction by means of a dual-energy X-ray absorptiometry technique (DXA) using Hologic instruments (QDR1500 and DQR4500, Bedford, MA). BMD was expressed as a T-score.

The so-called standard deviation (SD) scores were calculated from the following equation: T-score = (BMD measured–BMD of a sex- and age-matched population)/SD. DXA was also evaluated at the baseline and each year.

Survey measurements

The ad hoc PQ was prepared as a simplified version of the medical outcome study 36-item short-form survey (SF-36), which is a well-validated measure of general health status [11]. PQ comprised 39 questions, grouped into eight items designed to explore changes in general health perception, physical function, presence/absence of physical pain, social relations, mental health, osteoarticular pain, tiredness or vitality, and specific symptoms.

PQ was scored by assigning one point for each negative reply (no physical or mental changes) and two points for each positive reply (physical or mental changes). The total score ranges from 39-78 [12].

The self-rated KSQ had already been used by us [12] and others [13] in similar studies. KSQ comprises eight subscales. The items anxiety, depression, somatization and hostility evaluate the degree of psychological discomfort or lack of well-being on a numerical scale ranging from 0–23 for each item. The higher the score, the lower the QoL.

Statistical analysis

In accordance with the classification of the WHO, osteoporosis was defined as a T-score < –2.5 and osteopenia as a T-score between –2.5 and –1.0. Data was analysed by means of GraphPad Prism for Windows (Version4.0; GraphPad Software, San Diego, CA, USA). All values are expressed as mean ± standard error of mean (SEM) unless

indicated otherwise. To evaluate changes in experimental parameters during the five-year study, the non-parametric Kruskal-Wallis analysis of variance (ANOVA), followed by Dunn's Multiple Comparison test, was used. To compare absolute and percentage data, Mann-Whitney and Chi-square tests were used.

Correlation analyses between variables were carried out by means of the Spearman correlation. Data below the functional sensitivity or above the standard curve of the assays were analysed for statistical purposes by using the functional sensitivity value or the maximal value of the standard curve. Significance was taken as P-value ≤ 0.05.

Results

Clinical data

In total, 157 patients with PHPT were followed up. Inter-group comparison by means of ANOVA revealed no significant differences in age (65.2 ± 14.0 years ± SD; P = 0.07), female:male ratio, or smoking.

In the study population, mean body mass index (BMI) was 28.8 ± 5.2 kg/m2. Similar numbers of patients were overweight (BMI = 25–30 kg/m2) in the three study groups (patients with/without therapy, N = 38, 44%, and surgery group, N = 26, 52%). Eighty-three patients underwent one or more PTX. Histology revealed parathyroid adenoma in most cases (N = 66; 79.5%) or hyperplasia (N = 7; 8.4%), and parathyroid carcinomas in three patients; histopathology data from the remaining (N = 10) patients could not be retrieved. About 50% of no-PTX patients (N = 37) were already symptomatic at the time of diagnosis, while 48% (N = 40) of those who had undergone surgery were symptomatic. At the time of diagnosis, 83 patients were symptomatic for kidney stones (N = 37), bone and joint pains (N = 24), osteoporosis (N = 23), pathological fractures (N = 5), and pancreatitis (N = 2).

Laboratory data

The untreated group and the bisphosphonate-treated group showed similar reductions in S-Ca and PTH concentrations over the five-year follow-up. However, both groups differed significantly from the surgery group: PTH levels (P = 0.05) in the untreated group (P = 0.01) were significantly higher than in the surgery group; S-Ca levels (P = 0.0001) were lower in the surgery group than in the other two groups (Fig. 1).

In all PTX patients, there was a significant difference ($P < 0.001$) between pre-surgical and post-surgical S-Ca levels. However, while PTH levels remained essentially unchanged in the bisphosphonate-treated group before and after the initiation of drug therapy, serum levels of the hormone were significantly ($P < 0.001$) reduced after PTX.

Over the five-year study period, a significant reduction in PTH levels was seen only in the surgery group ($P < 0.01$); in the bisphosphonate-treated group, PTH levels tended to remain stable. A slight, non-significant increase in PTH levels was found in the untreated group. Similarly, S-Ca levels showed a significant reduction only in the surgery group ($P < 0.05$).

On final evaluation, other biochemical indices did not differ significantly among the three groups. Finally, 48 (28.9%) patients showed Vitamin D deficiency (VDD) (25OHD < 50 nmol/L). These subjects received replacement treatment with cholecalciferol (bisphosphonate treated group N = 33, mean dose 822.5 ± 158.6 U/day; surgery group N = 27, mean dose 737.5 ± 181.3 U/day; untreated group N = 16, mean dose 896.1 ± 296.1 U/day). Only the surgery group showed significantly lower 1.25OHD levels than the untreated group ($P = 0.001$).

Instrumental data

Each year, ultrasonography was used to search for any sites of parathyroid tissue (Table I).

BMD at the spinal level was not significantly different among the three groups of subjects ($P = 0.1$).

T-scores were mildly, but not significantly, increased in the lumbar spine and unchanged at the femur level five years after observation or therapy.

Quality of life

No significant differences in QoL scores emerged among the three groups of subjects (score: bisphosphonate- treated group 60.3 ± 8.9; untreated group 53.7 ± 17.9; surgery group 48.0 ± 6.7; ANOVA, P = 0.06). In the surgery group, however, QoL improved significantly after PTX (Wilcoxon, P = 0.05) (Fig. 2). Among PTX patients, 76% were satisfied with their PTX.

In semi-structured interviews of 28 subjects (21 females/seven males, age 63.4 ± 15.7 years), the psychiatric evaluation performed did not detect any improvement in psychopathology. In the majority of cases in which psychopathology was present, this was minor (anxiety, anxiety-depression, reactive depression); it was major in four (3%) patients (N = 1 potomania or psychogenic polydipsia; N = 1 panic attacks, N = 2 major depression). Concomitant psychopathological events proved to be more frequent in women (males N = 2, females N = 14). The overall scores of the items on the self-rated KSQ were: anxiety 7.7 ± 3.5, depression 7.2 ± 5.3, somatisation 9.9 ± 6.1, and hostility 4.9 ± 4.8. The correlations between age and KSQ scores, and between PTH and KSQ scores, were not statistically significant, nor was the correlation between KSQ and the duration (in months) of disease. No significant difference in KSQ scores emerged between females and males.

Discussion

Epidemiological considerations

The mean age of PTX patients was lower than that of the other groups. This is compatible with the fact that older people tend to have more co-morbidities (contraindications for surgery) and with the guidelines [7], which state that operable patients should be < 50 years old.

In our study, as in numerous epidemiological studies [10], PHPT was seen to be more frequent in females (N = 126, 77%) than in males (23%). Adenomas accounted for the majority of cases. These findings reflect the normal histological distribution of PHPT, which is supported by a solitary adenoma in 85-90% of cases [14].

BMI was higher in PTX patients. The reason for this is unclear. Finally, although smoking is a risk factor for osteoporosis, there was no significant difference between the number of smokers/past-smokers and non-smokers in our study.

Considerations on treatments

In the PTX patients, in agreement with previous evidence [15], we recorded a high surgical success rate.

However, in many patients, PTH concentration remained elevated (Fig. 3); these findings are in line with those of the literature, although this is usually only seen in 20% of patients or less. It is also possible that some of these patients may have been suffering from VDD: vitamin D supplementation after PTX can reduce the incidence of increased PTH. In our series, the untreated patients had higher than average S-Ca values over time, while in the majority of our patients PTH remained stable or decreased over the five-year follow-up. As previously demonstrated [6],

bisphosphonates do not normalise the levels of S-Ca and PTH. Likewise, in our series, all indices of bone metabolism differed only slightly in the bisphosphonate-treated group**.** Bisphosphonates are known to be effective in reducing bone turnover in PHPT patients [16]. However, we did not detect a significant difference in BMD in the subgroup treated. More recent data suggests that patients who have normal S-Ca levels after PTX, but elevated PTH, show no improvement in BMD comparatively [17]. This could explain why patients in all three groups displayed the same BMD changes.

Thus, medical management is a helpful alternative to PTX in patients for whom surgery is contraindicated or refused and in those patients with PHPT that relapses after surgery. Medical treatment is based on the use of bisphosphonates, oestrogens, modulators of oestrogen receptors and calciomimetics [18]. Antiresorptive therapy may be an effective therapeutic approach in those patients with low BMD, in order to prevent further bone loss and to reduce the risk of fracture [19]. Moreover, a recent meta-analysis concluded that the effects of PTX and bisphosphonates were similar in mild PHPT [20]. Furthermore, PHPT patients have slightly lower 25OHD levels than controls, despite supplementation.

Indeed, PTH induces renal conversion of 25OHD to 1.25OHD; integration may therefore require higher doses than in healthy subjects.

However, we recommend vitamin D substitution before a final decision on treatment is made. Evidence that treatment with vitamin D reduces PTH levels and bone turnover in mild PHPT has been provided by case studies and uncontrolled/controlled cohort studies.

Quality of life

The clinical presentation of mild PHPT may include non-specific symptoms [21] that may affect QoL. In recent years, interest in QoL has grown in some endocrinological fields. Randomised studies have indicated beneficial effects of surgery on QoL, as surveyed by the SF-36; however, these effects have been minor and inconsistent, and the potential placebo effect of the surgery can never be ruled out [22]. One obstacle to evaluating illness perception in patients with PHPT is the current lack of developed questionnaires.

With regard to the outcome of PHPT patients, it has not been specified that ad hoc SF-36 and Hamilton tests should be administrated before and after PTX. Our ad hoc PQ had been prepared to measure general health status and specific symptoms of PHPT.

Our data shows that persistence of the disease was variable in the different groups. However, we noted that QoL only improved in the surgery group. Indeed, over five years, we documented an improvement in somatic and psychological symptoms related to the presence of disease.

Limitations

Several limitations of our study have to be carefully considered, the first being the number of patients, which was somewhat lower than in other studies in the literature. However, over the years, the number of patients progressively increased and follow-up has now reached five years.

A second major limitation is related to the difficulty of randomising patients, as several types of treatment overlapped in the same subjects.

From a technological point of view, BMD was compared at the spine. Although the wrist is the first site of osteoporosis in PHPT, wrist assessment was rarely performed in most patients.

Conclusions

This study provided up-to-date information in terms of biochemical progression on the natural history of PHPT patients. No significant differences emerged between anti-resorptive therapy and observation only. It is not yet possible to assess the effect of pharmacological treatments on QoL in statistical terms, although QoL appeared to worsen in our bisphosphonate-treated patients. However, the number of medically treated PHPT patients is increasing as a result of the review of surgical indications, the increased incidence of diagnose in asymptomatic patients, and the development of new drug therapies.

References

1. Yu N, Leese GP, Smith D et al. The natural history of treated and untreated primary hyperparathyroidism: the Parathyroid Epidemiology and Audit Research Study. Quart J Med 2011; 104: 513–521.

2. Fraser WD. Hyperparathyroidism. Lancet 2009; 374: 145–158.

3. Rubin MR, Bilezikian JP, McMahon DJ et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. J Clin Endocrinol Metab 2008; 93: 3462–3470.

4. Bilezikian JP, Potts JTJr, Fuleihan Gel-H et al. Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. J Clin Endocrinol Metab 2002; 87: 5353–5361.

5. Macfarlane DP, Yu N, Donnan PT et al. Should 'Mild Primary Hyperparathyroidism' be reclassified as 'insidious': is it time to reconsider? Clinical Endocrinol 2011; 75: 730–737.

6. Faggiano A, Di Somma C, Ramundo V et al. Cinacalcet hydrochloride in combination with alendronate normalizes hypercalcemia and improves bone mineral density in patients with primary hyperparathyroidism. Endocr 2011; 39: 283–287.

7. Bilezikian JP, Khan AA, Potts JTJr. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. J Clin Endocrinol Metab 2009; 94: 335–339.

8. Fava GA, Kellner R. Versione Italiana del Symptoms Questionnaire di Kellner. In: Canestrari R (ed.). Nuovi metodi in Psicometria. Firenze 1982: 51–64.

9. Giusti M, Dolcino M, Vera L et al. Institutional experience of PTH evaluation on fine-needle washing after aspiration biopsy to locate hyperfunctioning parathyroid tissue. J Zhejiang Univ Sci B 2009; 10: 323–330.

10. Abdelghani R, Noureldine S, Abbas A et al. The diagnostic value of parathyroid hormone washout after fine-needle aspiration of suspicious cervical lesions in patients with hyperparathyroidism. Laryngoscope 2013; 123: 1310–1313.

11. Ware JE, Sherbourne CD. The MOS 36-item short-form healthy survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30: 473–483.

12. Giusti M, Melle G, Fenocchio M et al. Five-year longitudinal evaluation of quality of life in a cohort of patients with differentiated thyroid carcinoma. J Zhejiang Univ Sci B 2011; 12: 163–173.

13. Lee J, Yun MJ, Nam KH et al. Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal, and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. Thyroid 2010; 20: 173–179.

14. Ruda JM, Hollenbeak CS, Stack BC. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. Otoryngol Head Neck Surg 2005; 132: 359.

15. Udelsman R, Pasieka JL, Sturgeon C et al. Surgery for asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. J Clin Endocrinol Metab 2009; 94: 366–372.

16. Khan A, Grey A, Shoback D. Medical management of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. J Clin Endocrinol Metab 2009; 94: 373–381.

17. Ambrogini E, Cetani F, Cianferotti L et al. Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective randomized clinical trial. J Clin Endocrinol Metab 2007; 92: 3114–3121.

18. Marcocci C, Cetani F. Clinical practice. Primary hyperparathyroidism. N Engl J Med 2011; 365: 2389–2397.

19. Bollerslev J, Marcocci C, Sosa M et al. Current evidence for recommendation of surgery, medical treatment and vitamin D repletion in mild primary hyperparathyroidism. Eur J Endocrinol 2011; 165: 851–864.

20. Sankaran S, Gamble G, Bolland M et al. Skeletal effects of interventions in mild primary hyperparathyroidism: a metaanalysis. J Clin Endocrinol Metab 2010; 95: 1653–1662.

21. Silverberg SJ, Lewiecki EM, Mosekilde L et al. Presentation of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. J Clin Endocrinol Metab 2009; 94: 351–365.

22. Perrier ND, Balachandran D, Wefel JS et al. Prospective, randomized, controlled trial of parathyroidectomy versus observation in patients with ‘‘asymptomatic’’ primary hyperparathyroidism. Surgery 2009; 146: 1116–1122.

Table 1: Clinical, biochemical and instrumental parameters in all groups of patients on initial evaluation and on last follow-up evaluation (5 years).

Data are expressed as mean ± SD unless otherwise specified. SD — standard deviation; BMI — body mass index; S-Ca — serum calcium; PTH — parathyroid hormone; ALP — alkaline phosphatase; 25OHD — 25-hydroxyvitamin D; 1,25OHD — 1.25dihydroxy-vitamin D; Tx — thyroidectomy; UNG — uninodular goitre; MNG — multinodular goitre; NS — not significant.

Parameter	Surgery-group		Bisphosphonate-treated group		Untreated-group	
	Initial	Final	Initial	Final	Initial	Final
Number of patients	30	50	22	52	12	37
Female/male	21/9	31/19	19/3	40/12	10/2	31/6
Age (mean years)	61.5 ± 12.3	62.2 ± 1.9	71.7 ± 9.2	68.3 ± 1.6	62.1 ± 17.5	63.2 ± 1.9
BMI [kg/m^2]	27.3 ± 4.3	27.4 ± 5.4	25.9 ± 4.3	26.2 ± 4.8	25.6 ± 5.5	26.2 ± 2.6
Smoking (%)	25	16	8	7	0	5
Time since diagnosis (years)	4.1 ± 5.8	7.0 ± 5.9	2.7 ± 3.0	5.4 ± 4.0	3.2 ± 4.9	5.6 ± 5.3
Creatinine [μmol/L]	79.6 ± 17.7	79 ± 18	61.9 ± 17.7	88 ± 35	70.7 ± 17.7	79 ± 9
S-Ca [mmol/L]	2.4 ± 0.7	2.4 ± 0.0	2.5 ± 0.2	2.5 ± 0.2	2.4 ± 0.2	2.6 ± 0.2
PTH [ng/L]	158.9 ± 29.1	76.1 ± 9.3	204.6±56.9	112.7 ± 111.7	109.9 ± 74.4	152.5 ± 26.3
Total ALP [U/L]	180.8 ± 61.5	144.0 ± 42.0	206.6 ± 56.4	158.3 ± 58.5	173.2 ± 54.0	185.2 ± 73.4
25OHD [nmol/L]	43.7 ± 24.2	64.2 ± 27.2	39.0 ± 20.2	50.2 ± 22.7	48 ± 24.7	40.7 ± 25.2
1.25OHD [pmol/L]	224.0 ± 115.9	255.2 ± 110.9	291.4 ± 151.5	278.3 ± 144.8	299.5 ± 102.4	311.0 ± 130.3
Lumbar spine (T-score)	–1.99 ± 0.9	–1.75 ± 1.2	–2.08 ± 1.4	–2.18 ± 1.7	–1.80 ± 1.6	–1.54 ± 1.2
Total femur (T-score)	–1.33 ± 0.8	–1.50 ± 0.3	–1.88 ± 0.9	–0.19 ± 1.8	–1.98 ± 1.2	–2.96 ± 0.9
Ultrasound TX	30% (N = 9)	36% (N = 18)	9.1% (N = 2)	13.5% (N = 7)	8.3% (N = 1)	8.1% (N = 3)
UNG/MNG	30% (N = 9)	42% (N = 21)	63.6% (N = 14)	53.8% (N = 28)	41.7% (N = 5)	46% (N = 17)
Normal ultrasound pattern	40% (N = 12)	22% (N = 11)	13.6% (N = 3)	21.2% (N = 11)	41.7% (N = 5)	29.7% (N = 11)
Parathyroid pathological	–	–	13.6% (N = 3)	11.5% (N = 6)	8.3% (N = 1)	16.2% (N = 6)

Figure 1: PTH and S-Ca levels in the surgery group (subjects deemed disease-free after surgery, N = 50), untreated group (patients without medical therapy or surgery, N = 37), and bisphosphonate-treated group (patients on anti-resorptive treatment with bisphosphonates, N = 52).

PTH displayed a significant difference (ANOVA P<0.05) etween patients deemed disease-free after surgery and those without any therapy (a); regarding S-Ca, significant differences (ANOVA P = 0.001) emerged between patients deemed disease-free after surgery and those without therapy (a) and between patients deemed disease-free after surgery and those on bisphosphonate therapy (b).

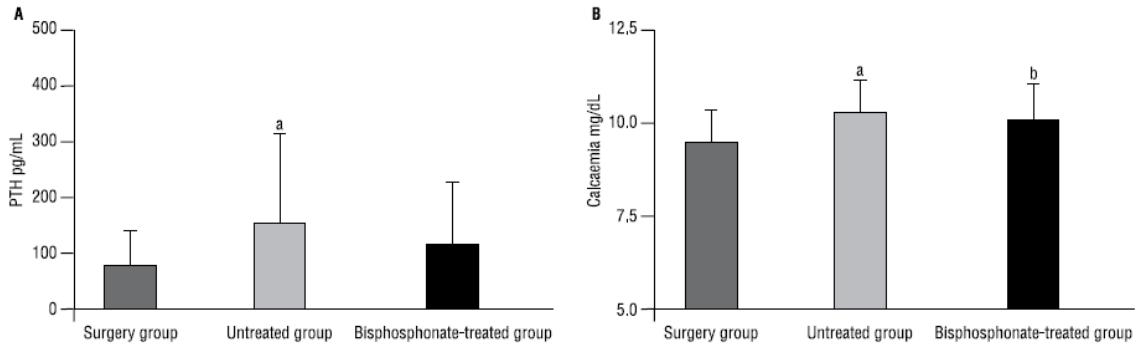


Figure 2: Evaluation of pre- and post-surgery QoL by means of SF-36 scores in the three groups of subjects studied.

A statistically significant difference was seen only in the surgery group (patients deemed disease-free after surgery).

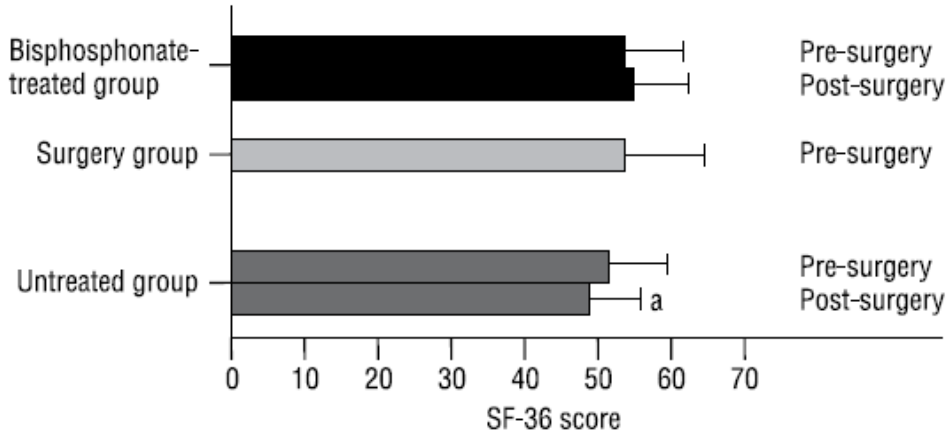
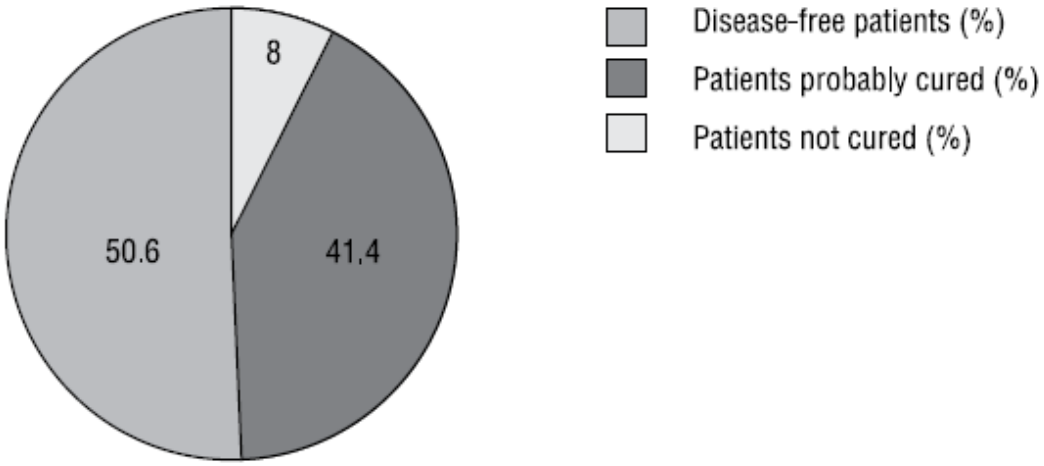


Figure 3: Distribution of prognoses in PHPT patients who underwent surgery.

Both S-Ca and PTH concentrations normalised postoperatively in only 50.6%. In patients who underwent surgery, the clinical course and S-Ca levels prompted us to define the 8% of patients with hypercalcemia as 'not cured'. In many patients (41.4%), S-Ca reverted to the normal range, while serum PTH concentration remained elevated.



CHAPTER 7

Other papers

Primary hyperparathyroidism in pregnancy treated with cinacalcet: a case report and review of the literature.

Vera L, Oddo S, Di Iorgi N, Bentivoglio G, Giusti M.

J Med Case Rep. 2016; 10: 361.

Background

Primary hyperparathyroidism (PHPT) is typically a disease of middle-aged and older women. A recent analysis of a large health system database reported the incidence of PHPT to be 4.7 to 6.2 cases per 100,000 person-years in women of reproductive age (20 to 39 years) [1]. PHPT usually runs a relatively benign clinical course. By contrast, during pregnancy PHPT may have serious clinical implications [2], with rates of maternal complications, fetal complications, and fetal/neonatal mortality being estimated at 67 %, 80 % and 30 %, respectively [2, 3]. It is therefore important to recognize this pathology during pregnancy. This is not simple, however, owing to its aspecific presentation [3]. The most frequent complications are hyperemesis, pre-eclampsia, nephrolithiasis, pancreatitis, hypercalcemic crisis, intrauterine growth retardation, preterm labor, neonatal tetany, and neonatal death [2–4]. Although the pregnancy may develop uneventfully, severe fetal/neonatal complications have been reported even in cases of mild PHPT. The optimal management of PHPT during pregnancy needs to be individualized. Most authors advocate parathyroidectomy (PTx)

as the treatment of choice [2]. Surgery should be performed in the second trimester [3]. The safety of surgery in the first and third trimesters is debated because of the associated risks for the fetus [5]. The efficacy and safety of various modes of medical treatment for PHPT in pregnancy are largely unknown. So far, only hydration and calcitonin have emerged as safe treatments [5], although both will lower serum calcium (S-Ca) only temporarily. Bisphosphonates cross the placenta; they should therefore only be used in emergencies as a short-term intervention prior to surgery [6]. Calcimimetics are effective in reducing S-Ca in PHPT; however, they have rarely been used in pregnancy [7]. We describe a case of PHPT in pregnancy that was treated with cinacalcet.

Case presentation

We report the case of a 34-year-old white woman with a 5-year history of nephrolithiasis, who was referred to the Department of Endocrinology after having undergone a previous endoscopic treatment. A biochemistry evaluation revealed elevated S-Ca and parathyroid hormone (PTH) levels, consistent with severe PHPT. All data from the basic evaluation are reported in Table 1. She had no family history of hypercalcemia or other factors suggestive of multiple endocrine neoplasia (MEN) syndrome. Given her young age, genetic testing was performed, which excluded MEN1 mutation. On examination, no mass was palpable in her neck. Neck imaging revealed no pathological parathyroid tissue: neck ultrasound, technetium-99m (99mTc) sestamibi scan, and single-photon emission computed tomography-computed tomography (SPECT-CT). Neck ultrasound showed a small nodule of 10 mm in her right thyroid lobe. Her bone density is below the expected range (Z-scores of −1.2 and −1.3 at her spine and total hip, respectively). An abdominal ultrasound confirmed the bilateral presence of kidney stones. Oral hydration, cholecalciferol (600 U/day), vitamin C, and cinacalcet were started, but calcimimetic therapy was poorly tolerated. She became pregnant 17 months later while on therapy.

Given the unknown teratogenic effects of cinacalcet in pregnancy, the calcimimetic was discontinued. Cholecalciferol was continued to 1200 U daily. During pregnancy, she presented two to three times per week for saline infusions administered intravenously (sodium chloride, NaCl, 0.9 % 1000 ml two to three times per week) associated with oral hydration at home, but her S-Ca level was not controlled. Conversely, her PTH levels decreased (Table 2). Parathyroid re-exploration was

performed in her tenth week of gestation. A nodular area was found at the inferior pole of the left lobe; the location and the sonographic appearance were typical of parathyroid adenoma. Fine-needle washing after aspiration biopsy (PTH-FNAB) was therefore carried out on both nodules. A cytological examination of the left nodules was not diagnostic, but the PTH-FNAB confirmed the thyroidal nature of the nodules: thyroglobulin-fine-needle aspiration biopsy (FNAB) 41334.0 µg/l, calcitonin-FNAB 6.8 ng/l, and PTHFNAB 4.0 ng/l. The right nodule was a colloid nodule, which was classified according to the British Thyroid Association as Thy2: thyroglobulin-FNAB 23690.0 µg/l, calcitonin-FNAB 6.3 ng/l, and PTH-FNAB 4.0 ng/l. Exploratory surgery was proposed in her second trimester of pregnancy, but was refused and postponed to the postpartum period. Options for medical management were therefore explored. In her 24th week of gestation, daily treatment with cinacalcet (15 to 30 mg/day orally) was restarted, but nausea and hyperemesis ensued.

The combination of calcimimetic and intravenously administered hydration resulted in a small decrease in her S-Ca (Table 2). However, in her 25th week, an episode of renal pain due to left nephrolithiasis occurred. Her renal function was normal, as was her electrocardiogram-monitored cardiac function. She was hospitalized in her 30th week of pregnancy for a non-serious spontaneous rupture of the membranes. A preterm delivery was decided upon. In her 32nd week of pregnancy, a cesarean section was carried out, and a baby boy was delivered. Postpartum, she discontinued cinacalcet in order to start breastfeeding. She was discharged on postoperative day 3, as is normal. A blood test 8 weeks after her cesarean section revealed elevated S-Ca and PTH levels, as noted in her prepregnancy period. Breastfeeding was discontinued and cinacalcet

was restarted. The time-course of her S-Ca during pregnancy and her puerperium are reported in Fig. 1.

One year after delivery, she underwent surgical exploration of her neck without further localization studies. Ten minutes after surgical removal of her left upper parathyroid gland (1.2 cm), her level of intraoperative PTH was 22 pg/ml. One day after PTx, her S-Ca levels were 2.22 mmol/L. Histology confirmed the diagnosis of adenoma of the parathyroid gland.

The neonate

Ultrasound scans in her first and second trimesters revealed normal fetal development. Immediately after delivery, the baby boy (weight 2.03 kg; length 45.0 cm; head circumference 31.7 cm, Apgar score 8 to 9) was transferred to our neonatal intensive care unit. The baby boy had hyperphosphatemia with serum phosphorous (S-P) of 7.94 mmol/l, hypocalcemia with ionized calcium (Ca++) of 1.12 mmol/l, and low PTH (17.0 ng/l); a picture compatible with hypoparathyroidism due to maternal hyperparathyroidism. Therefore, oral calcium gluconate 10 % (3 ml×7/day = 100 mg/kg) and vitamin D (ergocalciferol, two drops/day and alfacalcidol, two drops/day) in milk feed were started. A mild episode of neonatal tetany occurred in week 4. After 6 weeks, calcium supplementation was stopped and serum Ca++ was stable (Ca++ 1.13 mmol/l; S-Ca 3.61 mmol/l). His PTH (38.0 ng/l) and S-P (7.12 mmol/l) were in the normal range. The time-course of Ca++ (in the first 30 days postpartum) is reported in Fig. 2.

Discussion

During pregnancy, the calcium metabolism is altered in order to supply calcium to the fetus. Although S-Ca may decrease owing to lower levels of albumin, Ca++ remains constant. In order to meet fetal needs, intestinal calcium absorption doubles under mediation by calcitriol, prolactin, and placental lactogen. There is a compensatory increase in renal calcium excretion, which allows the mother to remain eucalcemic. By contrast, in our case, S-Ca increased considerably, while urinary calcium remained in the normal range, probably owing to a dilution effect induced by forced hydration. Changes in PTH, PTH-related protein (PTHrP), calcitonin, and calcitriol may occur throughout pregnancy, but typically do not produce clinically significant perturbations in calcium balance [8].

Pathologic alterations in calcium metabolism during pregnancy are uncommon, but include PHPT, milkalkali syndrome or PTHrP-mediated hypercalcemia [9].

During pregnancy and the puerperium, sources of PTHrP include underlying malignancy, placenta, and mammary tissue during lactation: cases have been reported of hypercalcemic crises attributable to each of these sources [10]. Since PTH levels are not proportionately high, the poor control of hypercalcemia may be partly a result of PTHrP. After delivery, hypercalcemia may acutely worsen owing to loss of placental shunting of calcium away from the maternal circulation; alternatively, S-Ca levels may decrease if the placenta was a source of PTHrP, which may have been a factor in our case.

As demonstrated by our patient, PHPT may put the mother and fetus at risk of more severe complications; this case also illustrates the fact that maternal hypercalcemia

can cause neonatal hypoparathyroidism, which are manifested in only 12 % of neonates [11].

Considerations on imaging The usual techniques for detecting parathyroid adenomas or hyperplasias are not recommended in pregnancy. Technetium (Tc) and 99mTc sestamibi scintigraphy should be avoided, owing to the risk of ionizing radiation for the fetus. The effects of fetal irradiation are divided into deterministic effects (caused by damage to a number of cells in tissues) and stochastic effects (caused by mutations in cells). McMullen et al. [12] have described the use of functional imaging in pregnancy while appropriately shielding the fetus; in our case, however, such an approach would have been very unlikely to yield a positive result, as the SPECT-CT performed shortly before the pregnancy was negative. In addition, McMullen et al. [12] claimed that 99mTc sestamibi imaging may be used safely to visualize the parathyroid glands only after negative cervical explorations, which our patient had refused. Thus, neck ultrasound is currently the first-line investigation for locating parathyroid diseases during pregnancy (sensitivity of 69 %, specificity of 94 %) [3, 13]. The failure of imaging is most unusual in patients with S-Ca levels higher than 3 mmol/L, as in our case. In our case, an ultrasonography examination was supplemented by PTH-FNAB. The use of this type of examination in the diagnosis of PHPT is debated [14]. In the present case, however, it was necessary in order to tackle the differential diagnosis between PHPT and thyroid nodules and then to decide whether to undertake mini-invasive surgery (recommended) or exploratory surgery (more invasive and therefore not recommended in pregnancy) [12]. Sometimes a mediastinal parathyroid adenoma is the culprit, but pre-pregnancy SPECT-CT had excluded this in our patient.

Finally, computed tomography (CT) and MRI were not performed because when they are used alone they are relatively insensitive in detecting normally located and ectopic parathyroid adenomas [12]. In Italy, positron emission tomography (PET) with methionine has only recently been proposed for the localization of parathyroid glands, and was therefore not performed in our patient before pregnancy.

Considerations on treatment

Surgery is the first choice of treatment in patients with symptomatic PHPT. Minimally invasive approaches have gained progressive acceptance as an alternative safe and effective technique over the past two decades, owing to the use preoperative imaging to suggest the position of the parathyroid glands [15]. Although negative imaging studies would not preclude neck exploration in a young woman with moderately severe hypercalcemia and recurrent nephrolithiasis, our patient chose to postpone neck exploration with the more invasive techniques required for PTx; medical treatment was therefore initiated. However, bone anti-reabsorptive therapy was not started because her bones had not been significantly compromised.

There are no guidelines for the treatment of PHPT in pregnancy. The options are a conservative approach or surgery [3]. Both approaches carry the risk of drug related side effects and procedure-related side effects, although the risk imposed by hypercalcemia is sometimes greater. PTx is the only curative treatment, but is recommended only when medical treatment is insufficient [3]. If surgery is deferred, as in our case, it should be undertaken as soon as possible after delivery, to prevent a hypercalcemic crisis.

Conservative management has been shown to significantly reduce maternal and fetal complications [3].

Intravenously or orally administered rehydration, with or without forced diuresis, is the first line of treatment [11].

In our case, we first started hydration without forced diuresis because the patient was hypotensive (her mean arterial pressure was 65 to 70 mmHg). However, as saline therapy administered intravenously is very unlikely to have a lasting benefit in any patient, close maternal and fetal monitoring are necessary in order to prevent clinical or biological deterioration. As calcitonin alone is considered ineffective for long-term S-Ca control, it was not administered in this case. As bisphosphonates are embryotoxic [16], they are not recommended. The use of cinacalcet during pregnancy is debated [3]. However, as S-Ca levels were still very high in our patient, cinacalcet seemed the best choice. Unfortunately, our case seems to indicate that the use of cinacalcet to treat PHPT in pregnancy is not effective in the acute control of S-Ca. In fact, evidence for a true benefit of cinacalcet in our case is very weak. Moreover, we do not know whether this caused a premature decline in S-Ca or compromised fetal calcium metabolism. Before considering cinacalcet treatment, we extensively discussed the pros and cons, as its use in pregnancy has been scantly reported.

Review of the literature

Since the first case of PHPT in pregnancy was reported in 1932 [4], about 200 cases have been published in the medical literature. Moreover, only three cases of PHPT in

women on cinacalcet therapy in pregnancy [8, 17, 18] and two cases in puerperium [17, 19] have been published.

Horjus et al. [17] first described a case of PHPT, while Edling et al. [8] described a case of parathyromatosis and Nadarasa et al. [18] reported a case of carcinoma.

In the first two cases, therapy was initiated during the third trimester, whereas in our case we decided to start at the end of the second trimester, given the lack of control of S-Ca. In the third case, pregnancy was initiated while the patient was on calcium-lowering therapy, as in our case. In the cases previously reported, tolerance was variable, whereas in our case it was poor, thus precluding administration at higher doses. In our case, unlike those reported in the literature, it was not possible to perform PTx. Therefore, cinacalcet was restarted in the puerperium [17, 19].

Conclusions

Only three cases of PHPT in women on cinacalcet therapy in pregnancy have been published in the medical literature.

Hydration was useful in controlling S-Ca, and cinacalcet therapy also helped to control S-Ca, although it was dangerously high. However, in the present case, evidence for a true benefit of cinacalcet is very weak. In our case, cinacalcet tolerance was very poor, which precluded the administration of higher doses. It remains unclear whether PTH levels in pregnancy were reduced owing to a possible role of placental PTHrP.

References

1. Yeh MW, Ituarte PH, Zhou HC, Nishimoto S, Liu IL, Harari A, et al. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. J Clin Endocrinol Metab. 2013;98:1122–9.

2. Schnatz PF, Curry SL. Primary hyperparathyroidism in pregnancy: evidence based management. Obstet Gynecol Surv. 2002;57(6):365–76.

3. Dochez V, Ducarme G. Primary hyperparathyroidism during pregnancy. Arch Gynecol Obstet. 2015;291:259–63.

4. Bevere L, Sorrentino B. Contributo allo studio dell'osteite fibrocystica generalizzata. Riforma Med. 1932;48:313–8.

5. Goodman S. Anesthesia for nonobstetric surgery in the pregnant patient. Semin Perinatol. 2002;26:136–45.

6. Phitayakorn R, McHenry CR. Hyperparathyroid crisis: use of bisphosphonates as a bridge to parathyroidectomy. J Am Coll Surg. 2008;206:1106–15.

7. Peacock M, Bilezikian JP, Klassen PS, Guo MD, Turner SA, Shoback D. Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. J Clin Endocrinol Metab. 2005;90:135–41.

8. Edling KL, Korenman SG, Janzen C, Sohsman MY, Apple SK, Bhuta S, et al. A pregnant dilemma: primary hyperparathyroidism due to Parathyromatosis in Pregnancy. Endocr Pract. 2014;20(No.2):e14–7.

9. Simmonds CS. Role of parathyroid hormone (PTH) and PTH-related protein (PTHrP) in regulating mineral homeostasis during fetal development. Crit Rev Eukaryot Gene Expr. 2010;20(3):235–7.

10. Eller-Vainicher C, Ossola MW, Beck-Peccoz P, Chiodini I. PTHrP-associated hypercalcemia of pregnancy resolved after delivery: a case report. Eur J Endocrinol. 2012;166:753–6.

11. Norman J, Politz D, Politz L. Hyperparathyroidism during pregnancy and the effect of rising calcium on pregnancy loss: a call for earlier intervention. Clin Endocrinol. 2009;71:104–9.

12. McMullen TP, Learoyd DL, Williams DC, Sywak MS, Sidhu SB, Delbridge LW. Hyperparathyroidism in pregnancy: options for localization and surgical therapy. World J Surg. 2010;34(8):1811–6. doi:10.1007/s00268-010-0569-2.

13. Vitetta GM, Neri P, Chiecchio A, Carriero A, Cirillo S, Mussetto AB, et al. Role of ultrasonography in the management of patients with primary hyperparathyroidism: retrospective comparison with technetium-99m sestamibi scintigraphy. J Ultrasound. 2014;17(1):1–12.

14. Giusti M, Dolcino M, Vera L, Ghiara C, Massaro F, Fazzuoli L, et al. Institutional experience of PTH evaluation on fine-needle washing after aspiration biopsy to locate hyperfunctioning parathyroid tissue. J Zhejiang Univ Sci B. 2009;10(5):323–30.

15. Udelsman R, Åkerström G, Biagini C, Duh QY, Miccoli P, Niederle B, et al. The Surgical Management of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99:3595–606.

16. Djokanovic N, Klieger-Grossmann C, Koren G. Does treatment with bisphosphonates endanger the human pregnancy? J Obstet Gynaecol Can. 2008;30(12):1146–8.

17. Horjus C, Groot I, Telting D, van Selten P, van Sorge A, Kovacs CS, et al. Cinacalcet for Hyperparathyroidism in Pregnancy and Puerperium. J Pediatr Endocrinol Metab. 2009;22:741–749.

18. Nadarasa K, Bailey M, Chahal H, Rajo O, Bhat R, Gayle C, et al. The use of cinacalcet in pregnancy to treat a complex case of parathyroid carcinoma. Endocrinol Diabetes Metab Case Rep. 2014;2014:140056.

19. Baretić M, Tomić Brzac H, Dobrenić M, Jakovčević A. Parathyroid carcinoma in pregnancy. World J Clin Cases. 2014;2:151–156.

Table 1: Laboratory findings on diagnosis, during pregnancy, and postpartum (median values are reported).

GFR glomerular filtration rate, Ca(U) urinary calcium, S-Ca serum calcium, S-P serum phosphorous, PTH parathyroid hormone, 25OHvitD 25hydroxyvitamin D.

	Diagnosis	Pregnancy	Puerperium	Normal range
Creatinine (mg/dl)	0.7	0.8	0.8	0.5–1.3
GFR (ml/minute/1.73m^2)	>60.0	107.0	107.0	>60.0
Ca(U) (g/24 hours)	0.46	0.35	–	0.05–0.40
S-Ca (mmol/l)	3.15	3.025	3.0	2.12–2.75
S-P (mg/dl)	1.6	1.9	1.9	2.5–4.5
PTH (ng/l)	109.0	44.0	124.0	6.5–36.5
25OHvitD (ng/ml)	20.1	21.0	13.5	>30.0

Table 2: The time-course of serum calcium and parathyroid hormone levels and treatment in a patient with primary hyperparathyroidism.

i.v. intravenous, NaCl sodium chloride

Time	Treatment	Serum calcium (mmol/l)	Parathyroid hormone (ng/L)
1st trimester	NaCl 0.9 % 1000 ml i.v. 2/week	3.025–3.775	48.0
2nd trimester	NaCl 0.9 % 1000 ml i.v. 3/week	2.800–3.325	44.0–62.0
3rd trimester	Cinacalcet 15–30 mg/day	2.775–3.125	–
Postpartum	No therapy	2.900–3.000	46.0–124.0

Figure 1: Serum calcium levels in the patient.

The graph shows the effect of treatments on the patient's serum calcium levels during pregnancy and puerperium. i.v. intravenous, S-Ca serum calcium.

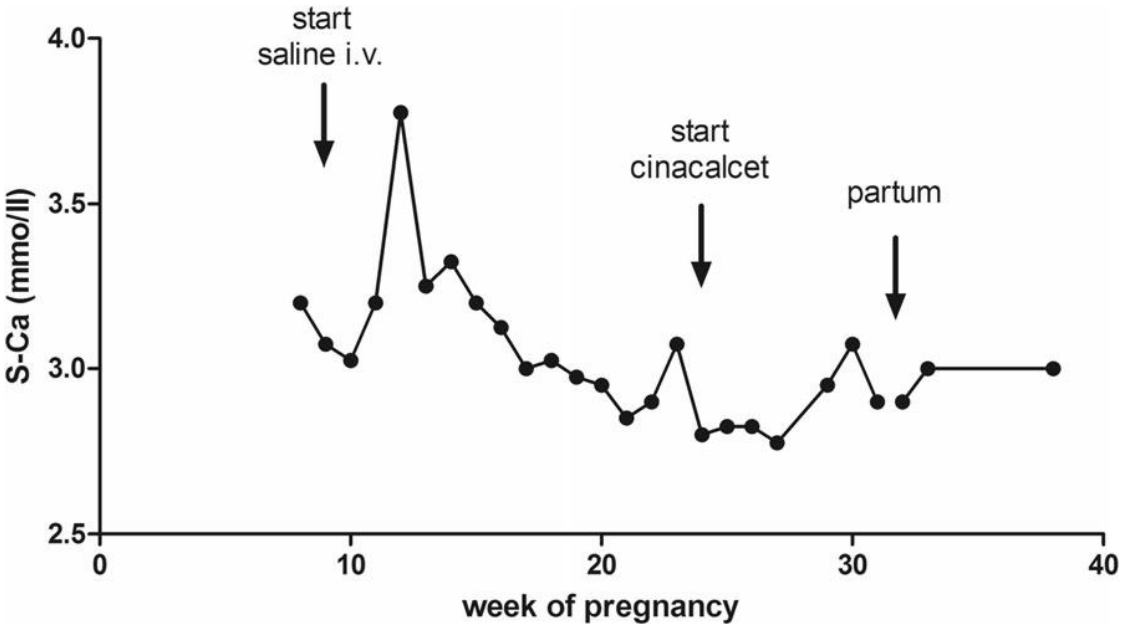
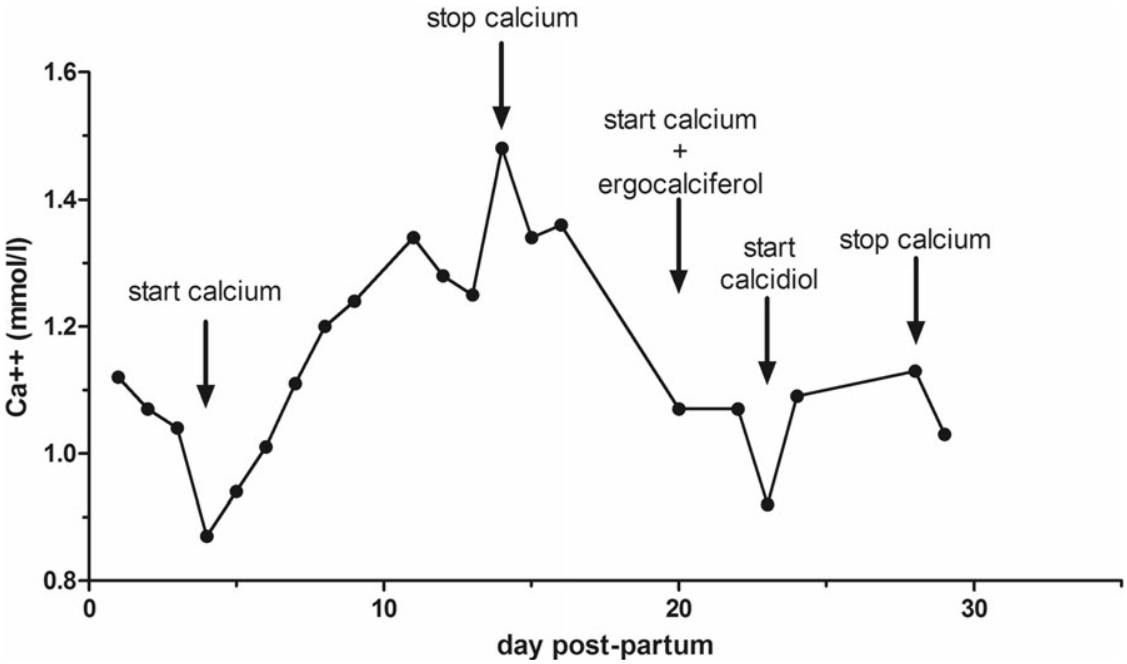


Figure 2: Serum calcium levels in the baby boy.

The graph shows the effect of treatments on serum ionized calcium levels in the baby boy in the first 30 days postpartum. Ca++ ionized calcium.



CHAPTER 8

Conclusions

Minimally invasive techniques have become known in Italy only in recent years. The first European papers about LA on benign thyroid nodules dates back to 2000 while those about RFA to 2007.

They were born and were developed in the Korea to remedy the surgery for purely aesthetic-cultural reasons (the scars on the neck and on the face are a sign of impurity) and then, expanded in Europe because they are effective, safe and more accepted by patients than surgery; they are also cheaper than surgery, both total and partial. Since 2010 the guidelines include RFA e LA among the possible therapies of benign thyroid nodules.

My thesis reports our personal experience in minimally-invasive techniques, RFA e LA, in many years of work.

We perform RFA from January 2012 and we had performed PLA from September 2014 to December 2015. For a year we were one of few centers in Europe to be able to practice both techniques.

In our work published in 2016 we reported our case studies on 32 benign thyroid nodules (between 14 and 76 mL) treated with RFA, performing the procedures according to international guidelines.

Procedures lasted between 2:45 and 15:00 minutes, with a delivery energy between 349 – 3171 J/ml; the duration of thyroid RFA in our hands was lower than that

reported in the literature and this difference can be ascribed to the personal choice of the operator, whose main objective was to prevent severe side effects.

RFA were preceded by local subcutaneous anaesthesia; in literature is described that subcapsular anaesthesia could increase the percentage of adverse events, but no data are reported about subcapsular anaesthesia. The volumetric reduction of the nodules was -30% a sixth month and -45% at 2 years. There was no significant correlation between percentage volume reduction and joules administered during the procedure, baseline nodule volume or years since diagnosis. A significant correlation between better reduction and patient age was found; we might hypothesize a different intracellular content in older patients, which could facilitate necrosis after thyroid RFA. In literature, none described this correlation before and none has confirmed this data until now.

Our RFA-treated patients did not have any serious complications during or after the procedure (hoarseness, dysphagia, nodule rupture, major bleeding or infections), conversely described, albeit rarely in literature; the only reported symptoms were: discomfort in the neck, little pain, haematoma and oedema in the neck in the same percentage that in literature. These symptoms did not require any kind of medication and resolved spontaneously.

We report, however, a case of thyroid cancer on the track of the electrode 30 months after RFA in a 74-year-old woman with negative oncological history and a symptomatic multi-nodular goiter with a predominant nodule of 34 mL with two fine-needle aspiration biopsy, which revealed a colloid nodular hyperplasia. Thirty months after RFA, an ultrasound scan revealed a hypoechoic extra-thyroid jugular median supra-

fascial lesion of about 14. FNAB on that lesion showed a hyperplastic, hypercellular with focal cytological atypia. The histologic diagnosis of the RFA-treated nodule was of a follicular carcinoma with a minority component of papillary carcinoma.

We suppose that the extra-thyroid lesion was a dissemination of the follicular component of the thyroid carcinoma. In conclusion, we suppose that RFA could have caused seeding of malignant cells from the nodule. This data is the first reported in literature and it needs eventually a confirmation.

In our paper thyroid functional parameters do not changed after RFA (f-T4 and thyroglobulin levels were significantly increased at the first week but they had returned to baseline levels by the month-1 follow-up examination). This data are similar to data reported in literature and it is one of the reasons why patients often prefer minimally invasive technique to surgery.

As described in literature, 75% of our patients reported an improvement in symptoms by means of VAS score. Our patients displayed a significant improvement in VAS at follow-up examinations; however, the significance seemed to shrink with time: this borderline significance was lost after the 12^{th} month, probably because of the decrease in the number of patients at the subsequent time-points of the study.

In our study, none of the scores on the single ThyPRO scales changed significantly from the baseline to the last evaluation. However, the overall score was significantly lower at the month-3 evaluation, and this reduction persisted over time.

To our knowledge, no data on QoL evaluated by means of ThyPRO in patients treated with RFA for thyroid nodules have ever been reported.

We perform LA just for one year in 14 patients with benign nodules from 5 to 55 mL.

LA lasted from 13 to 19 minutes, a time comparable to that reported in literature.

As for RFA, LA were preceded by local subcutaneous anaesthesia; in literature is described that subcapsular anaesthesia could increase the percentage of adverse events, but no data are reported about subcapsular anaesthesia.

After LA, we found a progressive important reduction in nodule volume similar or slightly lower than those observed in other centers (-50% at 6^{th} month, -60% at one year). At one year, we observed a reduction of > 50% in 86% of the treated patients.

As in RFA-treated patients, LA-treated patients did not have any serious complications during or after the procedure (hoarseness, dysphagia, nodule rupture, major bleeding or infections); the only reported symptoms were: discomfort in the neck, little pain, haematoma and oedema in the neck, in the same percentage that in literature. These symptoms did not require any kind of medication and resolved spontaneously.

As in RFA and as reported in literature, thyroid functional parameters do not changed after LA.

The VAS score improved in 100% of patients treated with LA. The scale of “goiter symptoms” and the scale of “general score” of ThyPRO improved after LA.

To our knowledge, no data on QoL evaluated by means of ThyPRO in patients treated with RFA and LA for thyroid nodules have been reported before; this is the specificity of our studies.

In addition, we participated to an Italian multicenter study of a comparison of laser with radiofrequency ablation for the treatment of benign thyroid nodules. In literature there are few paper that compare the two techniques. A systematic review tried to compare the results of RFA and LA from the data of the published literature; it

concluded that RFA appears to be superior to LA in reducing benign solid thyroid nodule volume. A more recent paper compared results of LA and RFA performed by the same equip of operators, and found no significant differences among the two techniques, suggesting that the two techniques might be similarly effective when performed by operators with the same expertise.

Our work is the first large retrospective cohort study to date which compares safety and technique efficacy of RFA and LA in the percutaneous treatment of benign solid thyroid nodules by using propensity score matching with power analysis and statistically simulating randomized controlled trials.

This study leads to some interesting considerations:

1. both percutaneous thermal ablation procedures were highly effective in inducing a significant decrease in thyroid nodule volume; both techniques were equally effective in small and medium size nodules (confirmed by propensity score adjustment), while the LA showed a slightly greater efficacy than RFA in nodules larger than 30 ml (probably due to simultaneous use of multiple laser sources in large nodules, with a more homogeneous distribution of heat energy in the target area and due to the trans-isthmic approach of RFA that might be more difficult to treat the deeper part of large nodules);
2. the role of the operator experience is determining for the efficacy and the extent of nodule volume reduction, regardless of whether laser light or radiofrequency energy was used. This problem underscores the importance of appropriate training and learning curve;

3. to achieve a comparable volume reduction in small and medium size nodules, the operators used more energy (about ten times more) with the radiofrequency technique than with laser technology; this data, however, do not seem to be relevant in clinical practice because they are inherent to the technique used but do not cause the undesired effects on thyroid tissue;
4. the two procedures appeared both safe and well tolerated, with a similar complications rate;
5. the easiness of use of techniques seems to be subjective and in most cases is dependent on the clinical circumstances and on the devices available in the institution where the operators work;
6. taking into account the rental of generators in both techniques, the cost of a single laser applicator is about U.S.$250 per session (in most cases two applicators are needed) while the cost of an RFA electrode is about U.S.$800 per session. Both treatments may be performed on outpatients by an operator and a nurse. In both procedures, the cost of dressings, including local anesthetics and pain-killers, is quite low.

Finally, we proposed that some patients that don't respond to RFA can be treated in a second chance with LA. Generally, when the first session therapy is not successful, another session of the same ablation may be proposed. This choice is probably determined by the availability of LA or RFA in each centre.

In our centre, however, we had the possibility to perform both RFA and LA. We chose to perform LA after unsuccessful RFA because in our cohort of patients, we had already observed two cases in which the repetition of RFA had failed to yield significant results

in nodules that had previously undergone an unsuccessful RFA procedure. We conjectured that certain nodules might be intrinsically resistant to necrosis when one ablation technique is undertaken, but might respond to the other ablation technique. In our opinion, there are no data in literature about this topic. This data must be confirmed with a study in a large cohort of patients.

From our studies we can conclude that RFA and LA are efficient to reduce the volume of benign thyroid nodules and to reduce symptoms at the neck.

RFA and LA are safe (major adverse events are rare and minor adverse events are often asymptomatic and resolve spontaneously).

RFA and LA do not cause thyroid function alterations in contrast to surgery.

RFA and LA must be performed by a trained operator, able in minimally invasive techniques, to obtain better results and to limit adverse events.

Follow-up with US-scan is essential to exclude long-term adverse events; in particular, we suggest that the regrowth of treated nodule should be followed by a cytological examination.

RFA and LA are cheaper than total and subtotal thyroidectomy and it is very important in a period of spending review.

As suggested by guidelines, minimally invasive techniques should be proposed only to patients that have comorbidities that contraindicated surgery or refuse thyroidectomy. We agree with guidelines because we think that we can't produce adverse events, even if rare, in treating a *benign* thyroid nodule and this is the same reason why we choose to be less invasive performing RFA and LA, thus obtaining less results in nodules reduction than other centres.

More studies are necessary to confirm our data and more studies are necessary to understand which nodules can reduce better with RFA or with LA or what nodules will not respond, despite more sessions of minimally invasive technique.

Secondary I participated to the drafting of two papers about primary hyperparathyroidism, that was my main interest before 2012 and that was the topic of my graduation thesis in 2009. PHPT is a disorder characterized by inappropriately high secretion of PTH by an adenoma or a hyperplasia or rarely by a cancer. It is a common disease and 80–85% of cases are asymptomatic.

Therapy may involve medical or surgical treatment: parathyroidectomy is the treatment of choice for patients with symptomatic hypercalcemia or evidence of target organ damage; conservative management has been favored in asymptomatic patients or in some cases surgery fails, in some it is contraindicated, and in others it is refused. At the most recent International Workshop, the guidelines pointed out that there was no data to support the medical treatment of patients with mild PHPT. In general, it is recommended that patients who do not meet surgical criteria be monitored closely. However, the validity of medical treatment is unanimously recognized. The prognosis of PHPT patients depends on the time-line of the diagnosis.

In our five-year study, we evaluated 157 patients with PHPT during the course of different types of treatment: patients with therapy, patients without therapy and patients treated with surgery; moreover, we evaluate QoL in PHPT subjects by means of several instruments, both self-rated and physician-administered.

Half of our patients underwent surgery and, according to literature, a parathyroid adenoma in histology was discovered in most cases; as described in literature after

surgery patients have lower levels of PTH and S-Ca than medically-treated group or untreated group.

The untreated group and the bisphosphonate-treated group showed similar reductions in S-Ca and PTH concentrations over the five-year follow-up, higher than patients who underwent surgery, as reported in literature.

In the bisphosphonate-treated group, PTH levels tended to remain stable. A slight, non-significant increase in PTH levels was found in the untreated group.

In many patients, PTH concentration remained elevated; these findings are in line with those of the literature, although this is usually only seen in 20% of patients or less. It is also possible that some of these patients may have been suffering from vitamin D deficiency.

In our study BMD at the spinal level was not significantly different among the three groups of subjects, despite bisphosphonates are known to be effective in reducing bone turnover in PHPT patients; this data is different from literature that instead suggest use of bisphosphonates in PHPT patients with bone impairment.

In our study, no significant differences in QoL scores emerged among the three groups of subjects. In the surgery group, however, QoL improved significantly after parathyroidectomy. In semi-structured interviews of 28 subjects, the psychiatric evaluation performed did not detect any improvement in psychopathology. In the majority of cases in which psychopathology was present, this was minor (anxiety, anxiety-depression, reactive depression) and was more frequent in women.

No significant differences emerged between anti-resorptive therapy and observation only.

One obstacle to evaluating illness perception in patients with PHPT is the current lack of developed questionnaires in literature.

Finally, we reported a case of 34-year-old woman with a not-localized PHPT associated to hypercalcemia treated with cinacalcet during pregnancy because she refused exploratory surgery and calcium levels were not controlled by saline infusion. Only three cases of PHPT in women on cinacalcet therapy in pregnancy have been published in the medical literature: in two cinacalcet was started in the last trimester, in one it was started before, as in our paper.

In our case the maternal outcome resulted in a preterm delivery at 32nd week of pregnancy; the neonatal outcomes were a hyperphosphatemia, hypocalcemia: a picture compatible with transitory hypoparathyroidism due to maternal hyperparathyroidism with a mild episode of neonatal tetany. In the case described in literature there were no adverse maternal outcomes and hypocalcaemia in the newborn.

There are no guidelines for the treatment of PHPT in pregnancy. The options are a conservative approach or surgery. Both approaches carry the risk of drug related side effects and procedure-related side effects, although the risk imposed by hypercalcemia is sometimes greater. Conservative management has been shown to reduce maternal and fetal complications. Intravenously or orally administered rehydration, with or without forced diuresis, is the first line of treatment, calcitonin alone is considered ineffective for long-term S-Ca control and bisphosphonates are embryotoxic. The use of cinacalcet during pregnancy is debated but as S-Ca levels in our patient were still very high and it seemed the best choice.

Further studies are necessary to understand what are the best therapies to improve clinical data and long-term clinical signs of PHPT patients in the reason of the frequent mild clinical presentation and, in particular cases, as pregnancy, where is mandatory to pondering the risk-benefit.