ENDORAMA

'RAPIDLY ENLARGING THYROID GLAND'

Kelvin Memeh MD, MRCS
Fellow, Endocrine Surgery.
Jan 30, 2020

THE UNIVERSITY OF CHICAGO ENDOCRINE SURGERY

LEARNING OBJECTIVES

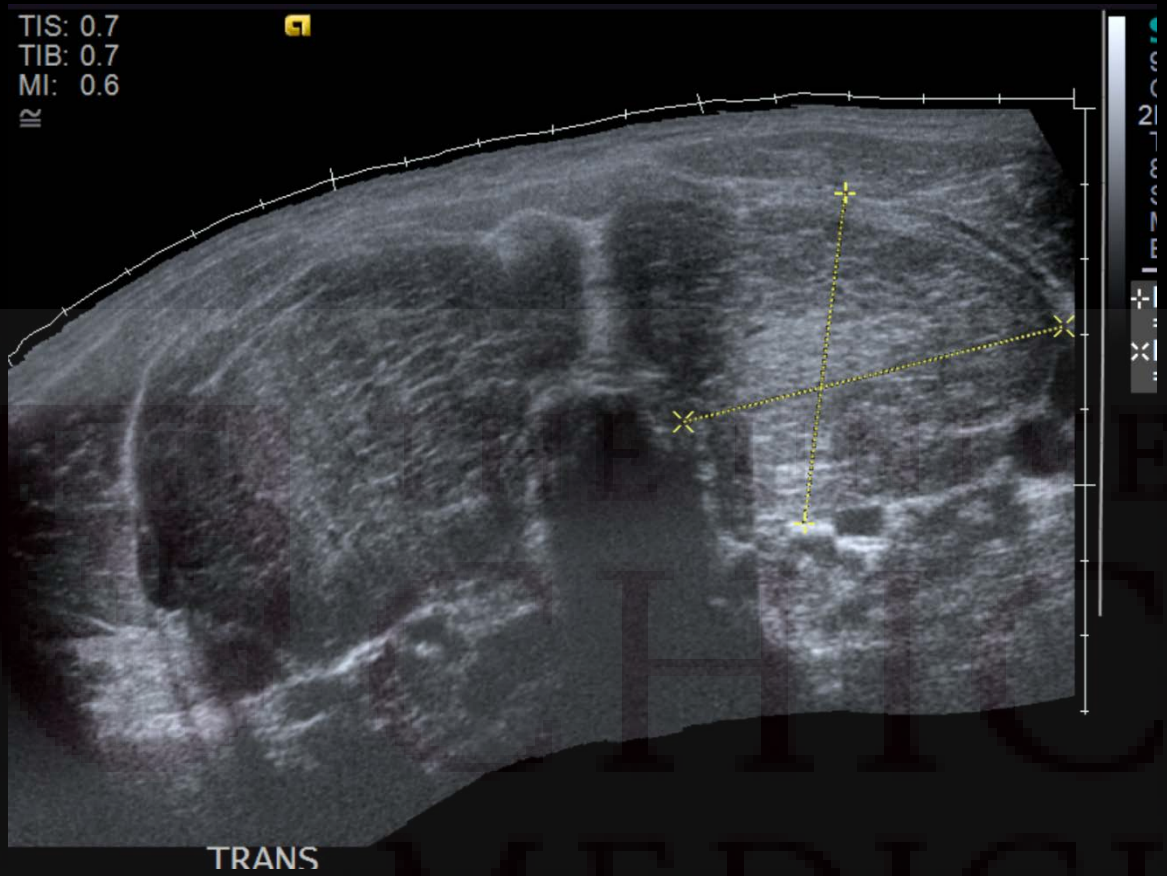
- Review differential diagnosis of rapidly enlarging thyroid mass.
- Review the role of surgery in the diagnosis and treatment of the rapidly enlarging thyroid.
- A brief review of the indication for thyroidectomy in Hashimoto thyroiditis.
- Brief discussion of research in section of Endocrine Surgery

Case: History

55 y/o M who presented to Endo surgery clinic with symptomatic goiter.

Background hx

- Diagnosed with hypothyroidism in 2017 and has been on levothyroxine since then.
- Thyroid US done at the time of diagnosis showed diffusely enlarged thyroid. No discrete nodules.
- Developed worsening dysphagia and choking sensation when lying flat on his back starting late 2018.
- Past Med : HTN, HLD, DM, Obesity, OSA.
- No hx of exposure to radiation.
- No family history of thyroid cancer/ problems



Thyroid US : Jan 2019

Diffusely enlarged heterogeneous thyroid.

Right lobe

11.2 x 5.1 x 6.1 cm (previously 7.7 x 4.1 x 4.9 cm in Dec 2017)

Volume 228 cm^3(previously 102cm^3)

Left Lobe

9.4 x 4.5 x 5.2 cm (previously 7.2 x 3.7 x 4.0 cm in Dec 2017)

Volume 149 cm^3 (previously 77cm^3)

CASE: WORK UP

- **Labs**:
- TSH 7.03.
- Anti-thyroglobulin > 1000

- **Core Needle biopsy 1/28/19:**
- Thyroid tissue with atrophic follicles, diffuse infiltrate and stromal fibrosis
- Flow/PCR clonal B- cell gene re-arrangement suspicious for ***B cell lymphoma***

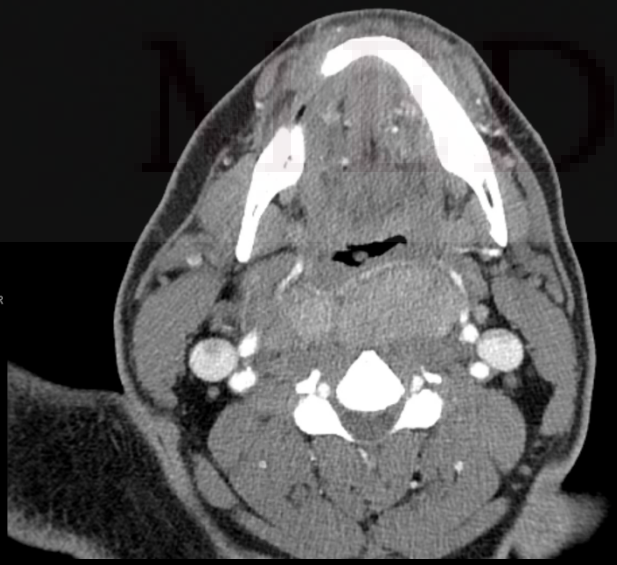
* Path recommended open biopsy for further evaluation

- **Open thyroid biopsy Feb 2019**
- Chronic sclerosing thyroiditis
- ↑IgE4 raising suspicion for ***Riedel thyroiditis***
- Positive plasma cells with features suspicious for ***B cell lymphoma***

Consult - > Hem/ Onc

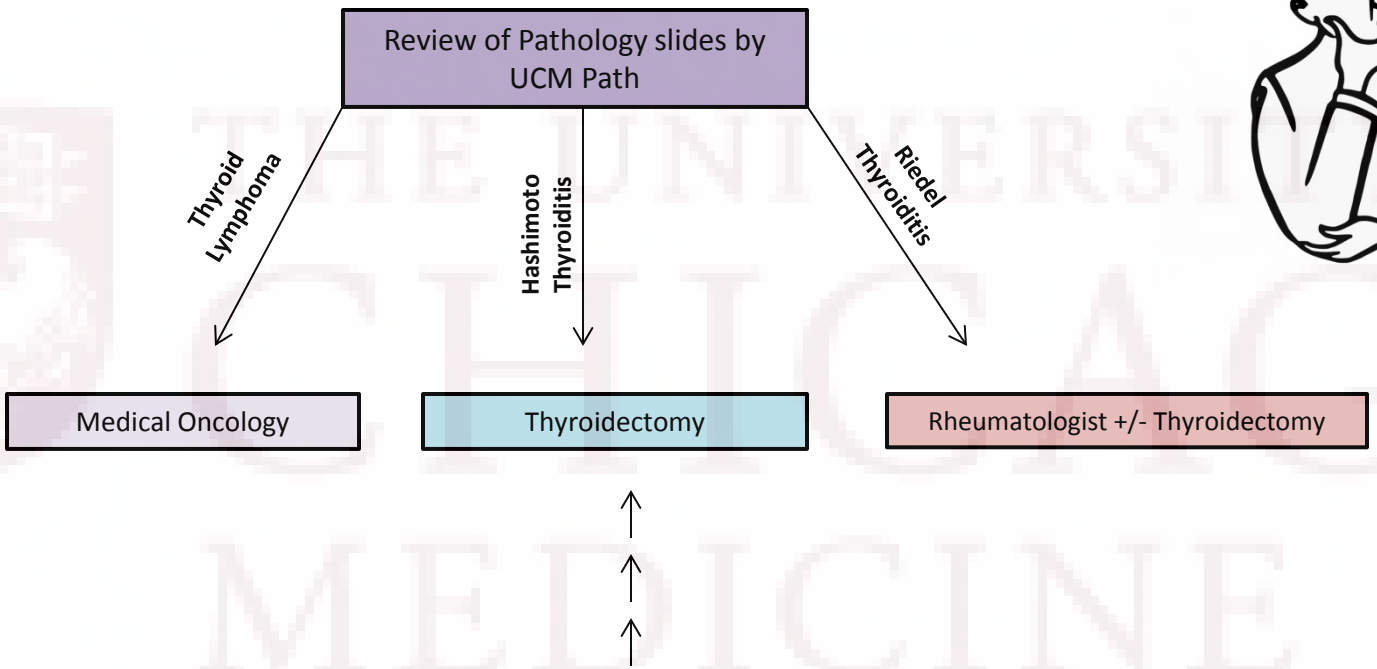

55.1 mm
58.1 mm
R
A


R


R

- Hem/Onc consult:
- CT Chest abdomen and pelvis ; negative for disease elsewhere.
- Assessment likely focal thyroid lymphoma. Recommended Rituximab.

Referred to UChicago Medicine for 2nd opinion



UCM Path Review : Chronic sclerosing thyroiditis

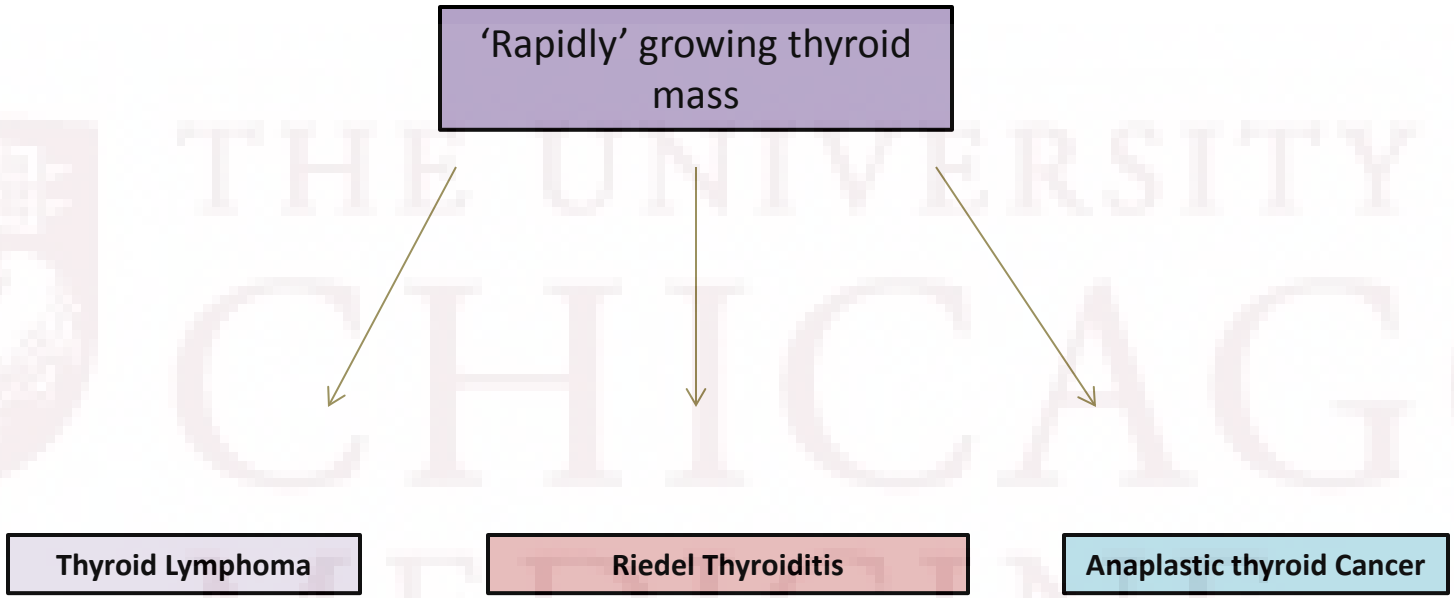
OR:SEPT 2019

THE UNIVERSITY OF CHICAGO ENDOCRINE SURGERY

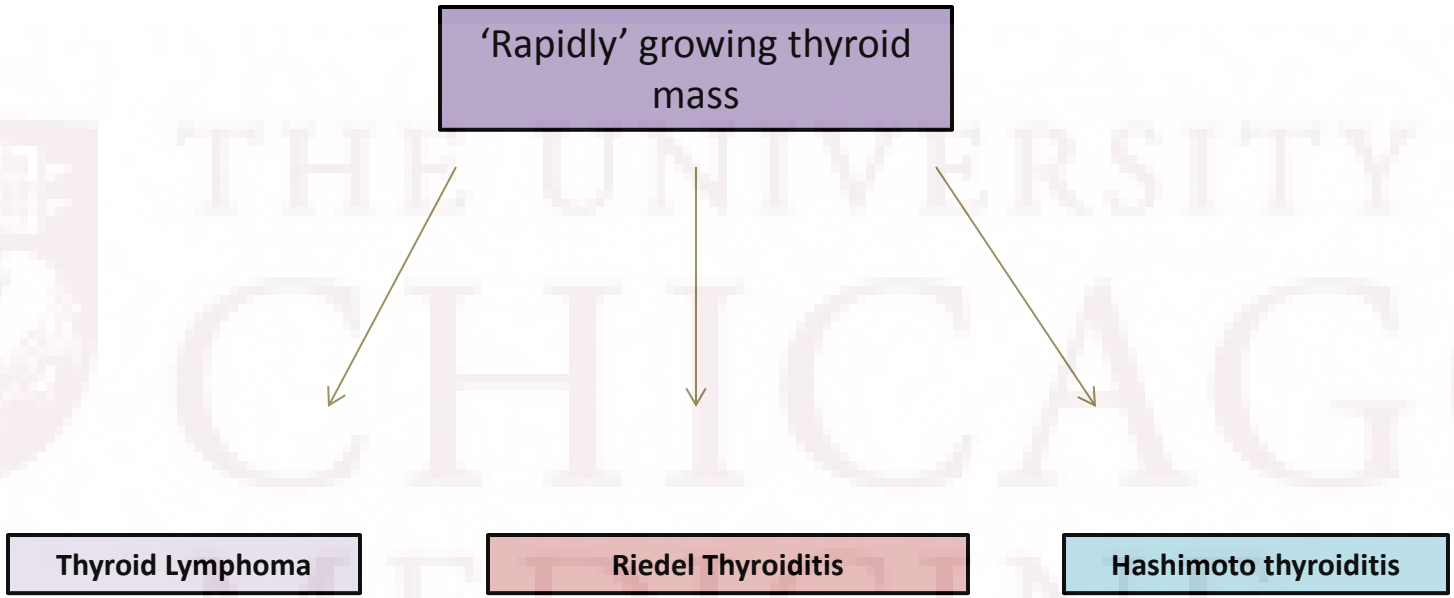
Final Path:

- Fibrosing variant of Hashimoto thyroiditis
- Four reactive lymph nodes.
- No atypical B cells infiltrates

Discussion



Discussion



THYROID LYMPHOMA

Epidemiology & Diagnosis

- Primary thyroid lymphomas(PTL) are rare.
  - 1-5% of all thyroid tumors.
  - 2 % of all extra-nodal lymphoma
- 4:1 female predominance
- Hashimoto thyroiditis confers 60 – 80 time ↑risk of developing PTL .
  - 60 -90% of PTL arise in the setting of thyroiditis
  - 0.5% of HT give rise to PTL
- Females with Hashimoto thyroiditis are about 20x more likely to develop PTL
- Typically presents with a 'rapidly' enlarging painless goiter with associated cervical LN.
- Most patients will have obstructive symptoms ; dysphagia, SOB/dyspnea/stridor, hoarseness, facial swelling
- ~ 10% of patients will have B symptoms (weight loss, night sweats, fever etc) [3]

THYROID LYMPHOMA

- **Three main variants of PTL**

- Diffuse Large B Cell (DLBC): most common, most aggressive

- Mucosa-associated lymphoid tissue(MALT) : good prognosis. Most commonly associated with Hashimoto thyroiditis

- Follicular lymphoma : least common, least aggressive.

- **Staging(Lugano Modification of Ann Arbor classification)**

Stage	Involvement	Extranodal status(E)
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	
IV	Additional non-contiguous extralymphatic involvement	

THYROID LYMPHOMA

Diagnosis

- Core needle biopsy for path and immunocytochemistry.

- Imaging not very useful for diagnosis but cross-sectional image helps for extent of disease, & monitoring response to therapy.

  - FDG: Hashimoto and PTL are FDG avid. But MALT is FDG negative
  - Radio iodine uptake scan: PTL does not take up radio-iodine

Treatment

- PTL are highly radio and chemo-sensitive: therapy is a combination of chemotherapy and radiotherapy.
- CHOP- R (cycophospamide, hydoxydaunoxorubucin, oncovin and prednisone) - Rituximab

- Older data showing no difference in OS or DFS between surgical resection/debulking vs surgical biopsy and definitive chemo-radiation.

- Surgery is mostly diagnostic in most center.

THYROID LYMPHOMA

Treatment

- Thyroidectomy/debulking surgery.
  - Severe relatively rapid airway compromise :

    CHOP-R vs Tracheostomy.

  - Newer data suggest survival benefit after thyroidectomy in early stage disease (stage IE).

  - Delineating intra-thyroidal disease from disease with node involvement

    Surgery with adjuvant radiation vs beam radiation + CHOP-R

Cureus

Open Access Original Article

DOI: 10.7759/cureus.4088

Primary Thyroid Lymphoma: An Analysis of the National Cancer Database

Victoria Vardell Noble [1], Daniel A. Ermann [2], Emily K. Griffin [1], Peter T. Silberstein [3]

1. Internal Medicine, Creighton University School of Medicine, Omaha, USA 2. Internal Medicine, Creighton University Medical Center, Omaha, USA 3. Hematology-Oncology, Creighton University School of Medicine, Omaha, USA

3466 PTL patents diagnosed btw 2004 and 2015 in the NCDB database

Aim:

- Clinical and epidemiological features.
- Association of treatment modalities and overall survival.

Multivariate analysis of management options affecting survival:

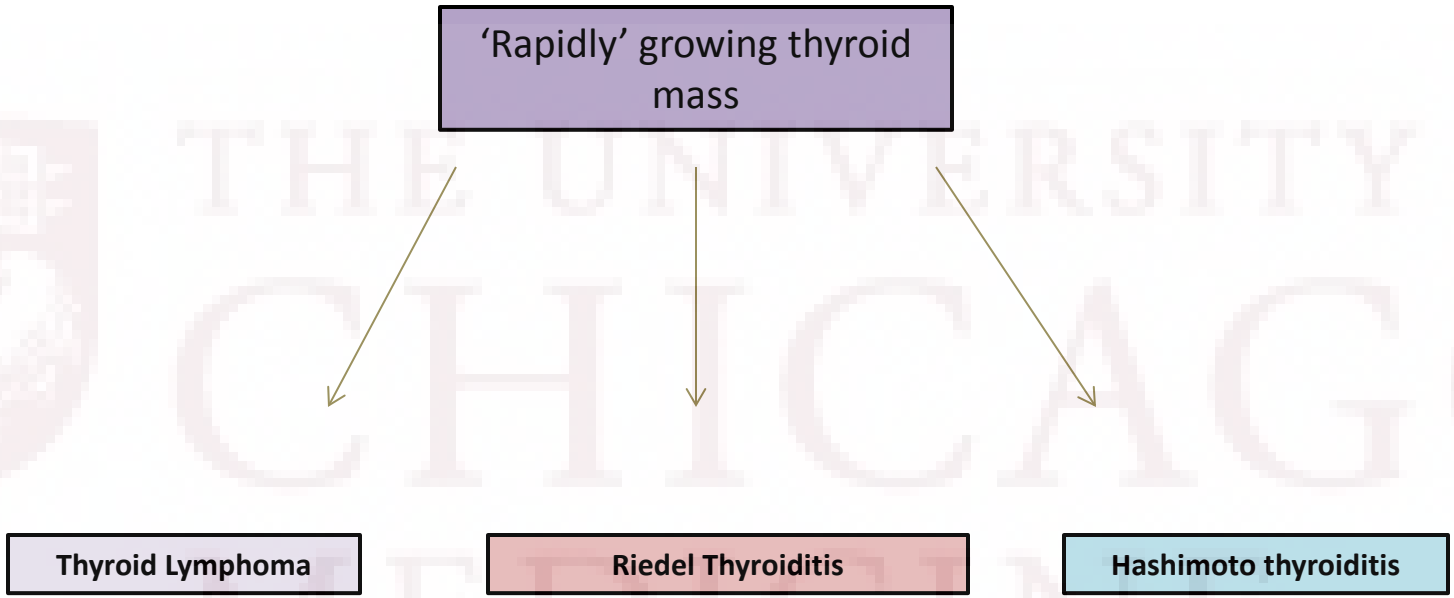
- ↑survival with all types of surgery vs no surgery.
  - lobectomy (HR: 0.52).
  - total or subtotal thyroidectomy (HR: 0.49).
- ↑ survival with beam radiation vs no radiation
  - radiation (HR: 0.61)
  - adjuvant radiation following surgery (HR: 0.48).
- Chemotherapy (multi-agent) had a benefit vs no chemotherapy (HR: 0.71).

Mean overall survival by treatment method for primary thyroid lymphoma, from the NCDB, 2004-2015

* Reference; NS, not statistically significant (p >0.05); NCDB: National Cancer Database

Mean Survival		Years	P value
Surgical Treatment (n = 3423)			
	None	8.0	*
	Partial lobectomy/ local excision	8.4	NS
	Lobectomy	9.9	<0.001
	Total/ Subtotal Thyroidectomy	9.7	<0.001
Radiation Therapy (n = 3421)			
	None	8.3	*
	Beam Radiation	9.8	<0.001
	Radioisotopes	7.3	NS
Chemotherapy (n = 3263)			
	None	8.2	*
	Single-agent Chemotherapy	7.7	NS
	Multiagent Chemotherapy	9.2	<0.001

Discussion



RIEDEL THYROIDITIS

- Riedel's thyroiditis (RT), is a rare, chronic inflammatory disease of the thyroid gland.
- First reported by Professor Bernhard Riedel in 1883, RT is characterized by a dense fibrosis that replaces normal thyroid parenchyma.
- Female predilection (4:1). Mean age at diagnosis 47 years.
- RT can involve one or both thyroid lobes.
- ~ 30% of patients will have extra-cervical fibro-sclerosing disease. ? primarily a systemic disease.
- Cause and pathogenesis is not fully understood

- Fibro-sclerotic theory

  Vs

- Auto-immune theory

RIEDEL THYROIDITIS

- Current thoughts is that RT is part of IgG4 -related systemic disease.
- IgG4-RSD are characterized by lymphoplasmacytic infiltrates containing IgG4-positive plasma cells.
- These cells induced a chronic inflammatory process that leads to fibrosis.

Schema of pathogenesis:

RIEDEL THYROIDITIS

- Clinical presentation:
- Hx of enlarging thyroid gland typically painless and stony hard.

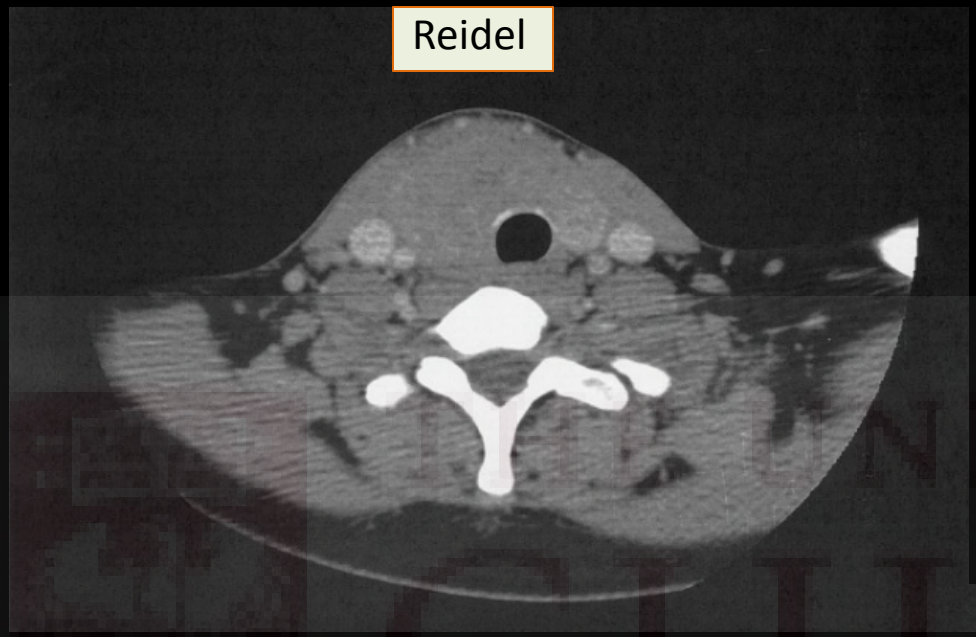
- Local compression: Dysphagia, dysphonia, dyspnea, neck tightness and pressure

- Symptoms from systemic sclerosis: Retroperitoneal fibrosis, sclerosing cholangitis, mediastinal fibrosis, lacrimal and parotid sclerosis.

- Most patients are euthyroid ; up to 30 % maybe hypothyroid at diagnosis

- Diagnosis:
- CT Imaging:
  a. Extension beyond the thyroid may help differentiates RT from the Fibrosing variant of Hashimoto thyroiditis.
  b. Absence of Cervical lymphadenopathy

Reidel



Hashimoto

RIEDEL THYROIDITIS

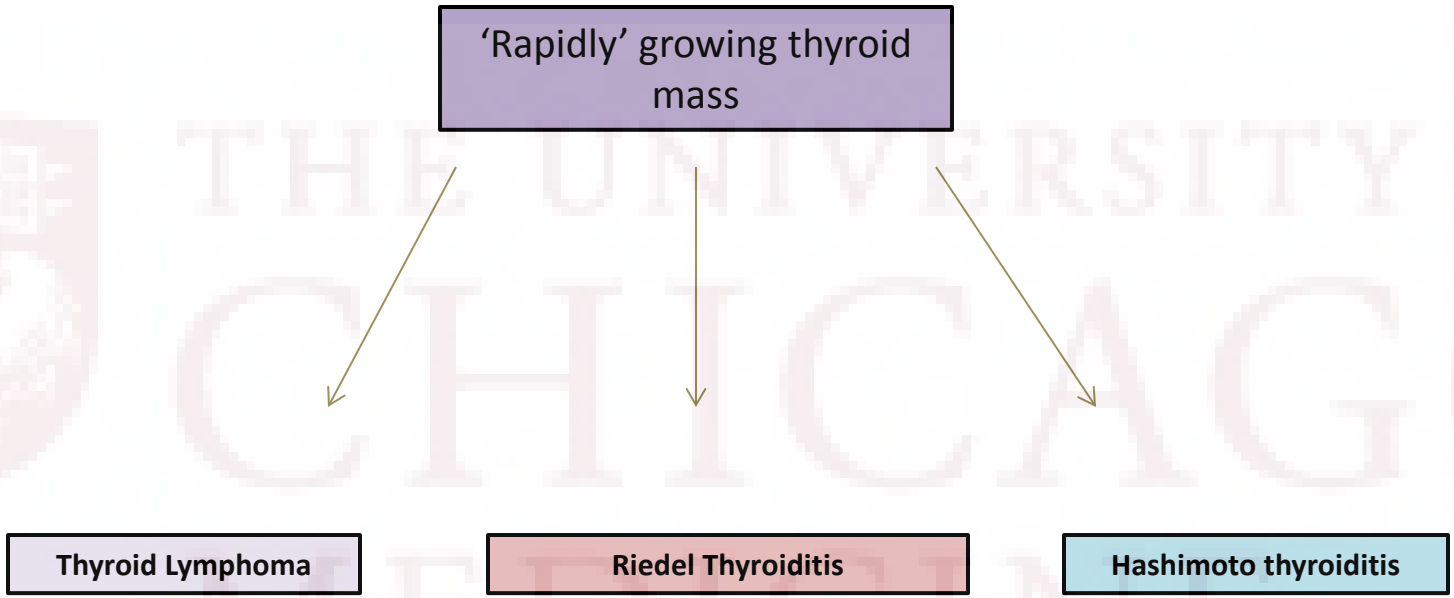
- Diagnosis/Labs

- TFT usually normal in most people.
- IgG4 levels ↑in about 95% of cases.
- Core or open biopsy is the definitive diagnostic test.

- Treatment & Prognosis

- Typically self –limiting but need supportive therapy.
- Frequently surgical intervention is required due to the compressive/invasive nature

Discussion



HASHIMOTO THYROIDITIS

Epidemiology

- Hashimoto disease is the most prevalent auto-immune disorder worldwide.
- Hashimoto thyroiditis (HT) is the most common cause of hypothyroidism in the US
- Pathogenesis is not fully understood but thought to be autoimmune with lymphocyte infiltration and fibrosis as typical features.
- Hashimoto thyroiditis confers 60 – 80 fold ↑risk of developing PTL .

Clinical presentation

- Depends on the phase of disease.
- Hypo vs hyper vs euthyroid

HASHIMOTO THYROIDITIS

Diagnosis

- Symptoms; goiter, hypothyroid symptoms
- Anti-thyroid antibody- anti-thyroid peroxidase (anti-TPO) antibody and anti-thyroglobulin.
  * up to 10% maybe antibody negative

Treatment

- The main therapy in HT is thyroid hormone replacement and most patients will respond well to thyroid hormone replacement.

- Subgroup of HT patients will continue to experience persisting (hypothyroidism-like) symptoms despite been euthyroid . ?auto-immune mediated inflammation of other tissues

  - Thyroid hormone replacement while euthyroid dose not relieve the persisting symptoms

  - Selenium supplementation; inconsistent data vs does not work

Annals of Internal Medicine ORIGINAL RESEARCH | 2 APRIL 2019

Thyroidectomy Versus Medical Management for Euthyroid Patients With Hashimoto Disease and Persisting Symptoms

A Randomized Trial

Ivar Guldvog, MD, PhD; Laurens Cornelus Reitsma, MD*; Lene Johnsen, MD*; Andromeda Lauzike, MD; Charlotte Gibbs, MD; Eivind Carlsen, MD; Tone Hoel Lende, MD; Jon Kristian Narvestad, MD; Roald Omdal, MD, PhD; Jan Terje Kvaløy, PhD; Geir Hoff, MD, PhD; Tomm Bernklev, PhD†; and Håvard Søiland, MD, PhD†

Trial Structure

- 150 patients randomized to surgery vs medical therapy
- Baseline QoL using validated questionnaires

Results

- A significant improvement in the general health score after thyroidectomy compared to medical therapy alone.
- ↓TPO antibody titres in the thyroidectomy group vs no difference in med therapy group

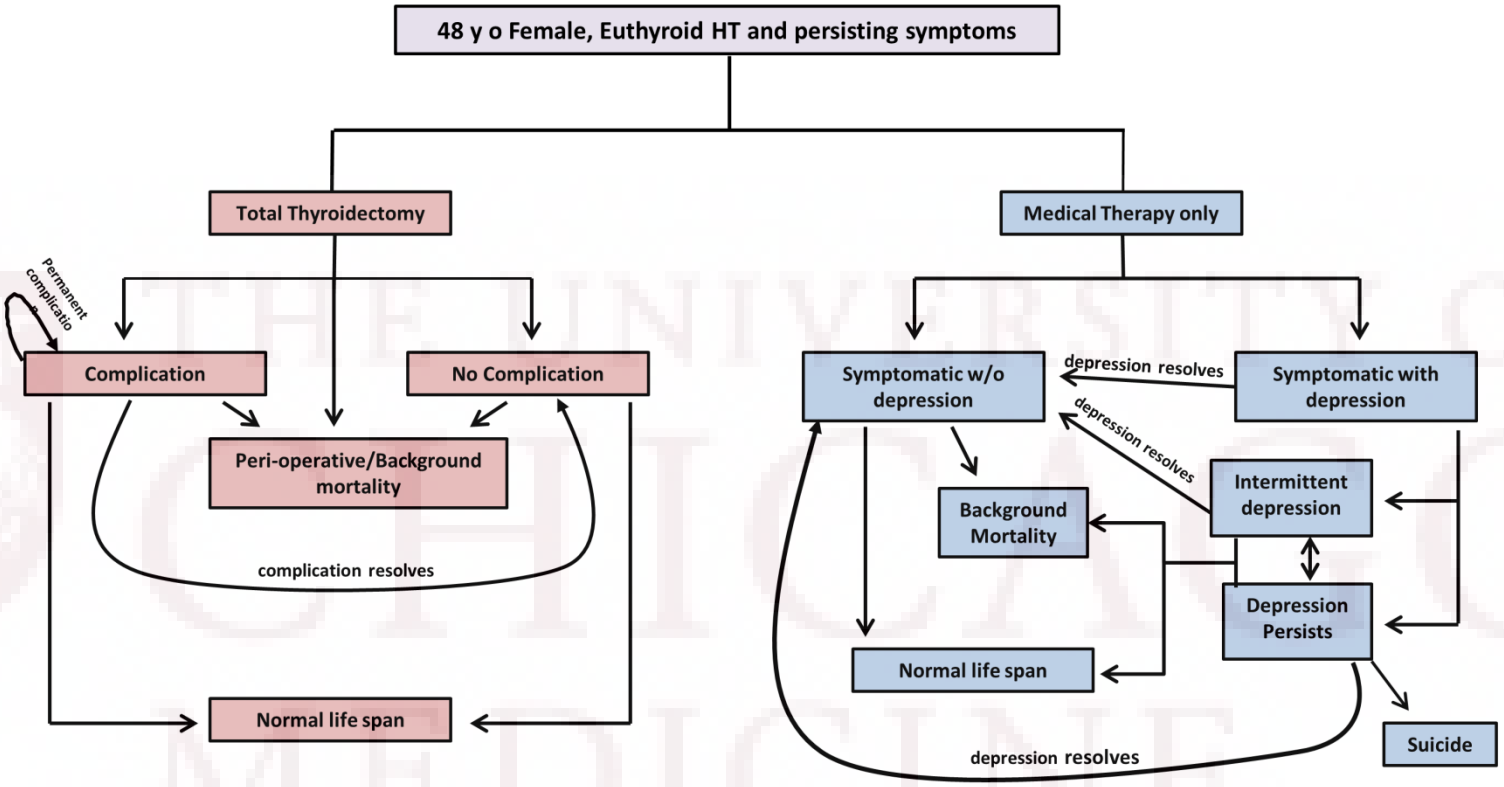
- Higher than expected thyroidectomy complication rate.

** similar to reported in retrospective studies.

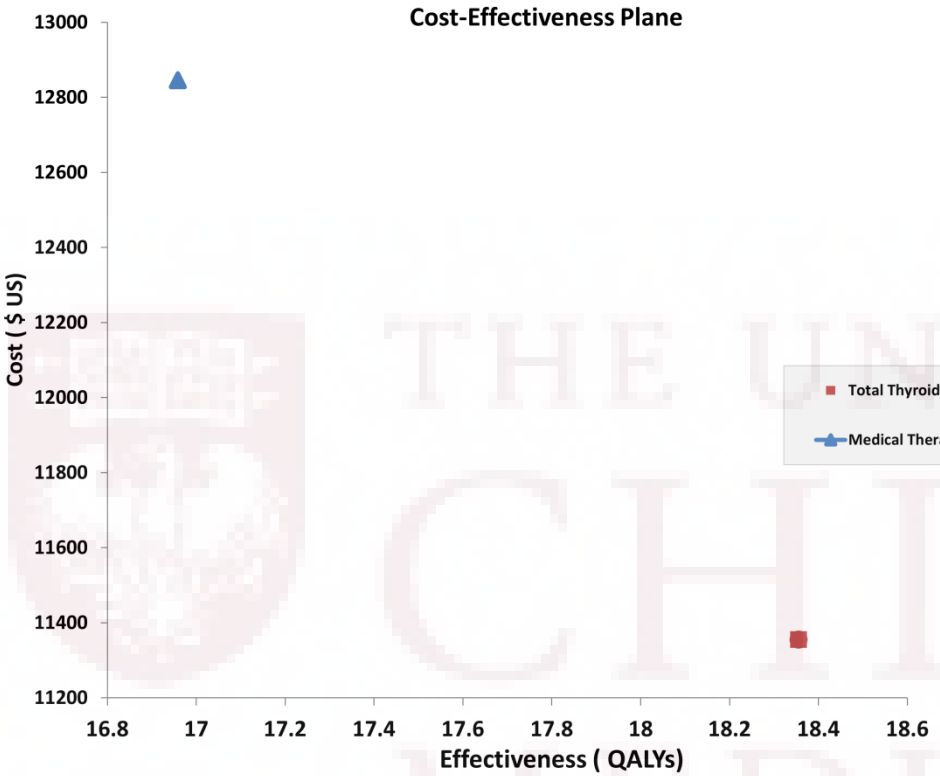
Surgical Complication	Trial Frequency	Frequency from other indication
Surgical wound infection	4.1%	<1%
Bleeding/wound hematoma	0%	1-2%
Hypoparathyroidism? permanent	4.1%	1-2%
Unilateral recurrent Laryngeal Nerve injury(temporary)	5.5	1-2%

- **Question: Is surgery for Hashimoto thyroiditis with persistent symptoms cost-effective?**

Cost effectiveness analysis: Model Structure

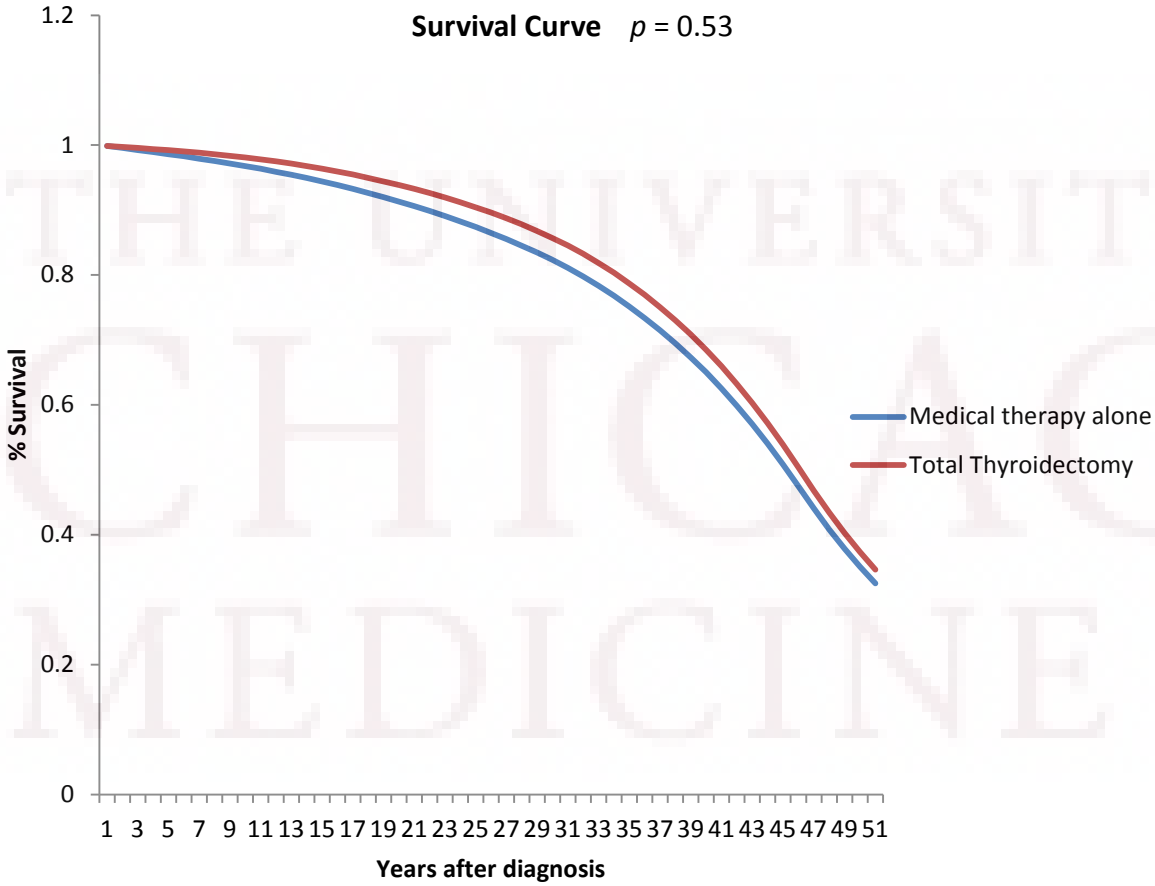


Cost effectiveness analysis: results



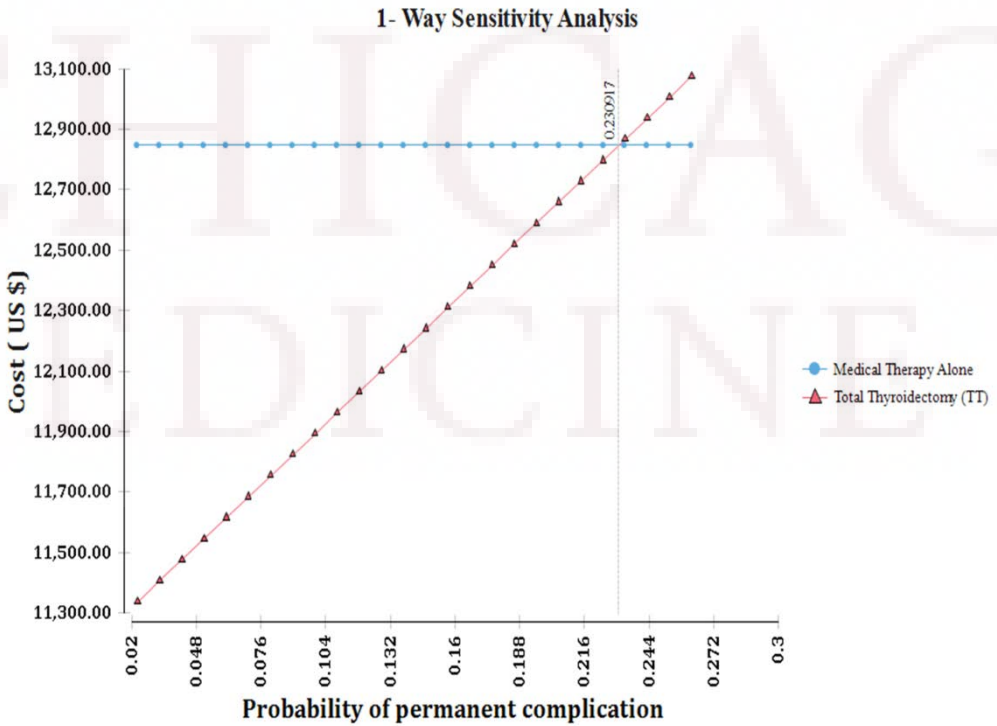
Base Case Analysis (WTP $100,000/ QALY)			
	Cost	**Effectiveness**	**Strategy status**
Total Thyroidectomy	$ 11,195	18.36 QALYs	Dominant
Medical therapy alone	$ 12,845	16.96 QALYs	Dominated
Incremental cost and QALY	- $ 1,490	1.4 QALYs	
Total thyroidectomy is less costly, more effective and so the dominant strategy			

COST EFFECTIVENESS ANALYSIS: RESULTS



COST EFFECTIVENESS ANALYSIS: RESULTS

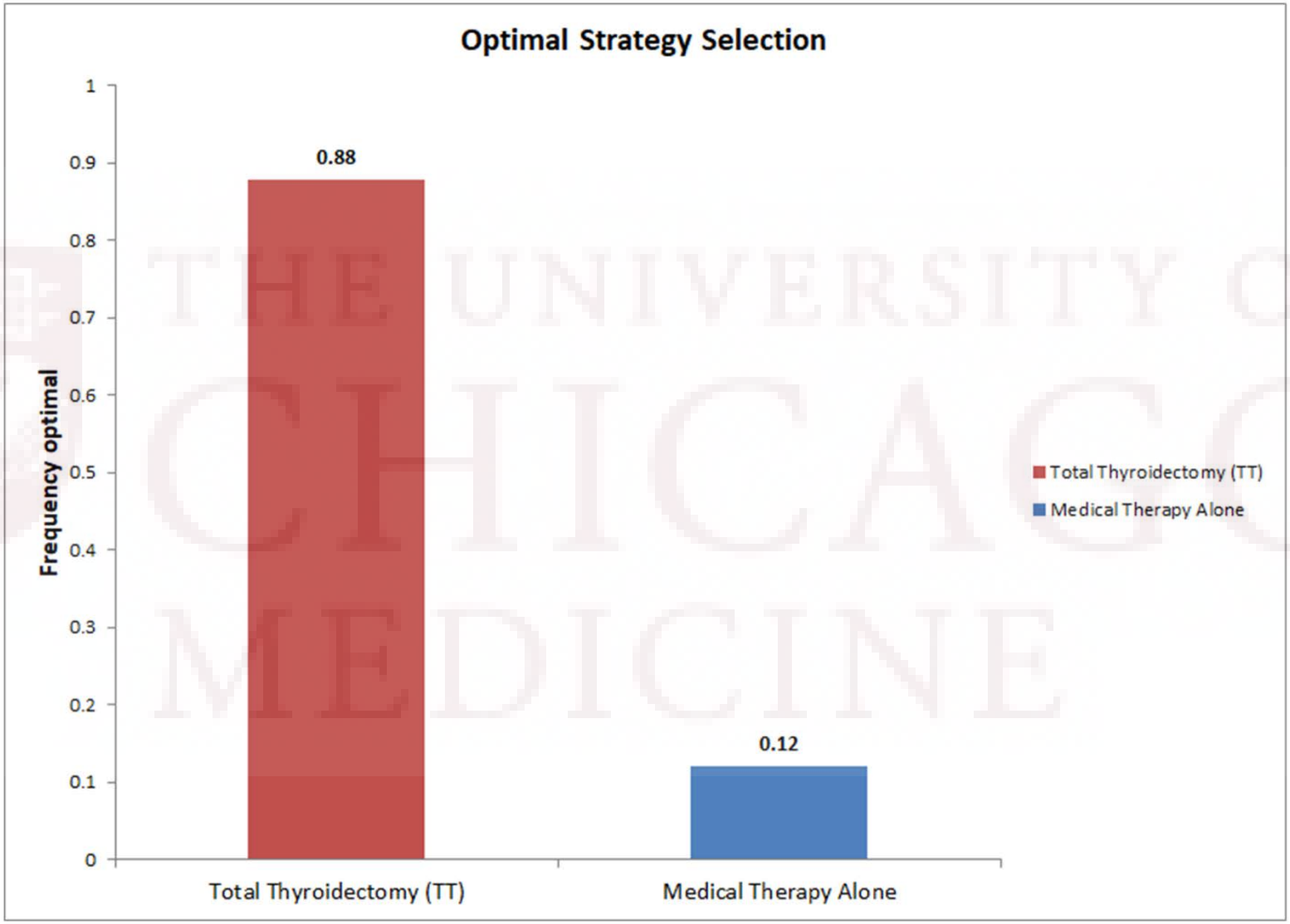
Parameter	Base Case Value	Cost effectiveness threshold	Order of Magnitude from base case value
Risk of any permanent complication after thyroidectomy	2.5%	23.1%	↑9.2x
Cost of uncomplicated thyroidectomy	$6,154	$8,035	↑1.3x
Annual cost of treating depression in HT patient	$8,089	$3,425	↑2.36x
Age at Diagnosis	48 yrs	69.9 years	↑1.46x



Thyroidectomy no longer cost effective if permanent complication rate 9 fold (2.5% to 23.1%)

THE UNIVERSITY OF CHICAGO ENDOCRINE SURGERY

COST EFFECTIVENESS ANALYSIS: RESULTS



REFERENCE

1. Logue JP, Hale RJ, Stewart AL, Duthie MB, Banerjee SS. Primary malignant lymphoma of the thyroid: a clinicopathological analysis. *International Journal of Radiation Oncology Biology Physics*. 1992;22(5).
2. Kumar R, Khosla D, Kumar N, Ghoshal S, Bera A, Das A, et al. Survival and failure outcomes in primary thyroid lymphomas: a single centre experience of combined modality approach. J Thyroid Res. 2013;2013:269034.
3. Chai YJ, Hong JH, Koo DH, et al. Clinicopathological characteristics and treatment outcomes of 38 cases of primary thyroid lymphoma: a multicenter study. Ann Surg Treat Res. 2015;89:295.
4. Vardell Noble V, Ermann DA, Griffin EK, Silberstein PT. Primary Thyroid Lymphoma: An Analysis of the National Cancer Database. *Cureus*. 2019;11(2):e4088. Published 2019 Feb 18. doi:10.7759/cureus.4088.
5. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al; American Thyroid Association Task Force on Thyroid Hormone Replacement. Guidelines for the treatment of hypothyroidism: Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. Thyroid. 2014;24:1670-751. DOI:10.1089/thy.2014.0028.
6. Ott J Promberger R Kober F Neuhold N Tea M Huber JC & Hermann M 2011. Hashimoto's thyroiditis affects symptom load and quality of life unrelated to hypothyroidism: a prospective case-control study in women undergoing thyroidectomy for benign goiter. Thyroid 21 161–167 doi.org/10.1089/thy.2010.0191.
7. Chiovato L, Latrofa F, Braverman LE, Pacini F, Capezzone M,Masserini L, et al. Disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. Ann Intern Med. 2003; 139:346-51. DOI 10.7326/0003-4819-139-5_part_1-200309020-00010.
8. M. Djurovic, A.M. Pereira, J.W.A. Smit, O. Vasovic, S. Damjanovic, Z. Jemuovic, D. Pavlovic, D. Miljic, S. Pekic, M. Stojanovic, M. Asanin, G. Krljanac, M. Petakov, Cognitive functioning and quality of life in patients with Hashimoto thyroiditis on long-term levothyroxine replacement. Endocrine **62**(1), 136–143 (2018). DOI:10.1007/s12020-018-1649-6.
9. Zivaljevic VR, Bukvic Bacotic BR, Sipetic SB, Stanisavljevic DM,Maksimovic JM, Diklic AD, et al. Quality of life improvement in patients with Hashimoto thyroiditis and other goiters after surgery: a prospective cohort study. Int J Surg. 2015;21:150-5. doi:10.1016/j.ijsu.2015.08.001.
10. Promberger R, Hermann M, Pallikunnel SJ, Seemann R, Meusel M, Ott J. Quality of life after thyroid surgery in women with benign euthyroid goiter: influencing factors including Hashimoto's thyroiditis. Am J Surg. 2014;207:974-9. doi:10.1016/j.amjsurg.2013.05.005.
11. Guldvog I, Reitsma LC, Johnsen L, Lauzike A, Gibbs C, Carlsen E, et al. Thyroidectomy Versus Medical Management for Euthyroid Patients With Hashimoto Disease and Persisting Symptoms: A Randomized Trial. Ann Intern Med. [Epub ahead of print 12 March 2019]170:453–464. doi: 10.7326/M18-0284.
12. McManus C, Luo J, Sippel R et al (2012) Is thyroidectomy in patients with Hashimoto thyroiditis more risky? J Surg Res 178:529–532. doi: 10.1016/j.jss.2012.09.017