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A Systematic Review of Economic Evaluation of Thyroid Cancer

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Background: This systematic review was conducted to identify and summarize key factors, including economic methods, topics, results, and indicators, within relevant economic evaluation research on thyroid cancer. **Materials and Methods:** A literature search on the economic evaluation of thyroid cancer treatment was conducted using the MEDLINE database up to May 2021. Data on population, intervention, comparison, outcome, time, setting, and study design were extracted from each study. The economic evaluation method in each study was re-classified according to the theoretical criteria defined by the international economic evaluation guidelines. **Results:** A total of 49 studies were included, involving cost analysis (CA, n=9), cost-minimization analysis (CMA, n=3), cost-effectiveness analysis (CEA, n=29), and cost-utility analysis (CUA, n=8). When CEA and CUA were classified as one method, the consistency between the methods of the reviewers based on the theoretical criteria and those from the original studies was 77% (95% confidence interval, 0.63-0.92). Most studies dealt with specific period-related controversial issues including comparison between treatment strategies, and cost-effectiveness of the prophylactic central neck dissection, molecular testing, and rhTSH. Contrasting results have been obtained when different economic evaluation methods were applied for the same topic (e.g., total thyroidectomy [TT] was more dominant than hemithyroidectomy [HT] in CEA, but HT was more dominant than TT in CUA), and different clinical and economic inputs were applied. All studies included direct medical costs, which were mostly derived from Medicare and input probabilities in each economic model, and utility scores for outcomes were mostly based on literature reviews. Few studies included non-medical direct costs and indirect costs. **Conclusion:** Our systematic review provides information on how to design and proceed to overcome the limitations of existing studies and ensure validity.

Key Words: Economic evaluation, Thyroid neoplasm, Economic methods, Economic analysis indicators, Cost effectiveness, Cost utility

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Introduction

The incidence of thyroid cancer has increased more than any other cancer worldwide, while survival has remained relatively stable.[1-4] Owing to its favorable prognosis, there are more than 405,032 thyroid cancer survivors living in Korea.[5] Cancer survivors encounter various economic, psychological, and sociological issues as well as ongoing medical challenges.[6] This context is particularly relevant for thyroid cancer where the number of survivors is increasing.[1,5]

Given resource constraints, the costs of thyroid cancer care have important policy implications.[7,8] In practice, healthcare services that strike a balance between cost-effectiveness and quality-maximization should be selected. Over the last decade, concepts of management for thyroid cancer have evolved rapidly, especially in identifying patients with high- and low-risk of disease recurrence and disease-specific survival and coordinating treatment and follow-up protocols to minimize thyroid cancer risk and treatment morbidity.[9] However, many aspects of thyroid cancer management remain controversial and poorly defined.[10] Therefore, an economic evaluation that allows decision-makers to make evidence-based comparisons of changes or adequately consider controversial issues is likely to help in determining the best treatment strategy.[7,11]

With increasing prevalence and cost, it is essential to identify appropriate and effective strategies for the diagnosis, treatment, and surveillance of patients with thyroid cancer. Studies using economic evaluation methods can provide information on cost-effective choices in resource-limited environments.[7] This systematic review (SR) aims to identify and summarize key factors, including economic analysis methods, topics, results, and economic analysis indicators, derived from economic evaluation studies published on thyroid cancer. The purpose is to provide informed insight into the economic evaluations regarding thyroid cancer.

Materials and Methods

Search Strategy

Based on the PRISMA checklist, a literature search on economic evaluation of thyroid cancer treatment was conducted using the MEDLINE database via PubMed in May 2021 to identify previously published studies. Studies were included if they met the following inclusion criteria: 1) studies that were economic evaluations involving cost analysis (CA), cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), and cost-utility analysis (CUA); 2) studies that involved screening and treatment of thyroid cancer or nodules as an intervention; 3) studies published between January 2000 and December 2020; and 4) studies where the main text was written in English. Studies were excluded if they met the following exclusion criteria: 1) studies in which economic evaluations were not conducted; 2) studies reporting other types of thyroid diseases (e.g., Graves' disease); 3) studies not involving intervention strategies, such as screening or treatment of thyroid cancer or nodules; 4) studies involving cost-benefit analysis (CBA) for evaluating the feasibility of business or policy decisions and project investments; 5) SR, letters to the editor, comments, or editorial studies; 6) studies not presenting a method (e.g., decision tree models or Markov models), outcome measures, or outcome indicators (e.g., cost per case, quality-adjusted life year (QALY), incremental cost-effectiveness ratio (ICER) data); and 7) studies that did not measure costs in monetary units. The search terms for each method of economic evaluation were determined using entry terms taken from the medical subject headings (MeSH) database of PubMed: (Thyroid cancer) AND (Cost analysis), (Thyroid cancer) AND (Cost-minimization analysis), (Thyroid cancer) AND (Cost-effectiveness analysis), and (Thyroid cancer) AND (Cost-utility analysis) (Supplementary Table 1).

Study Selection

The title and abstract of each study were screened and assessed by two reviewers (MK, WL) after which the full text of each potentially eligible study was assessed. Finally, studies meeting population, intervention, comparison, outcome, time, setting, and study design (PICOTS-SD) inclusion criteria were included (Supplementary Table 2). Disagreements were resolved through discussion and further review of the studies.

Data Extraction

The following data were extracted from each study: first author, publication year, study region (country), main title, journal, results, and conclusion. Data on economic evaluation were also extracted: type of existing and alternative intervention strategies (intervention and comparison); type and data source of outcome indicators and measures; number and type of study population (real-world and hypothetical cohort of patients); type of economic evaluation (CA, CMA, CEA, and CUA); number of intervention strategies; type of direct and indirect costs; type and data source of clinical and non-clinical outcomes; type and data source of medical and non-medical costs; method (decision trees and Markov models); and sensitivity analysis.

Study Classification

In classifying the studies by their methods of economic evaluation, each study was evaluated by the two reviewers using classification criteria defined by the international economic evaluation guidelines (Table 1).[7,12] Briefly, the CEA studies classified as such by their authors were re-classified in this study as CUA studies when they met the following criteria: 1) the ICER was calculated by dividing the difference between cost (⊿Cost) by the difference between QALY (⊿QALY); 2) utility weight was applied in the economic evaluation model; and 3) the threshold analysis result was presented in costs per QALY. CUA studies classified as such by their authors were re-classified in this study as CEA studies when they did not present

Table 1. Evidence of economic evaluation article classification

Type of economic evaluation	Cost-minimization analysis	Cost-effectiveness analysis	Cost-utility analysis
Evidence of economic evaluation article classification	1. Total cost of the interventions presented 2. Costs of the interventions presented in the same monetary unit (or currency) 3. Different interventions yielded the same results[a] 4. Cost-minimizing intervention selected as an alternative intervention 5. All expenses related to the interventions considered 6. Indirect comparison between the interventions undertaken if direct comparison was infeasible	1. Costs of the interventions presented in monetary unit (or currency) 2. Outcomes (effect) measured in natural units 3. Results of the evaluation presented in ICER 4. Cost-effectiveness judged by whether the total cost of the alternative intervention was below the threshold 5. Costs of improving additional unit effect presented under the condition that the effect units of alternative interventions were the same, but the improvement rate differed	1. Costs of the interventions presented in monetary unit (or currency) 2. Outcomes (effect) measured in QALY 3. Results of the evaluation presented in ICER 4. Cost-utility judged by whether the total cost of the alternative intervention was below the threshold 5. QoL considered in addition to extended lifespan 6. Cost of improving anadditional QALY formed social consensus
Illustration of the evidence	Comparison between standard intervention vs. A intervention and standard intervention vs. B intervention	Extended lifespan, drop in blood pressure. Additional expenses per additionally extended lifespan	Additional expenses per additionally acquired QALY

ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year, QoL: quality of life
[a]Articles presenting different results between the standard and alternative intervention were classified as "cost analysis."

specific costs per QALY, nor QALYs and utilities as an outcome. Additionally, CA or CEA studies classified as such by their authors were re-classified in this study as CMA studies if they met the following criteria: 1) the effect of the outcome was shown to be the same or similar between the interventions; and 2) a cost-minimized intervention was presented as an alternative intervention. Finally, CMA studies classified as such by their authors were re-classified in this study as CEA studies if they met the following criteria: 1) the outcome was measured in natural units; 2) the ICER was presented as an outcome; and 3) threshold analysis was conducted to evaluate cost-effectiveness. The strength of agreement between the authors and the reviewers was evaluated in terms of overall percentage agreement and the weighted Cohen's Kappa index. Moreover, studies reporting inconsistent results within the same interventions were presented.

Results

Study Selection

The records identified through database searching and screening in PubMed yielded 549 CA studies, 324 CMA studies, 234 CEA studies, and 216 CUA studies. After reviewing the title and abstract of each study, 527 CA studies, 310 CMA studies, 195 CEA studies, and 197 CUA studies were excluded. The remaining 22 CA studies, 14 CMA studies, 39 CEA studies, and 19 CUA studies were given full-text assessment to determine their eligibility, after which 13 CA studies, 11 CMA studies, 10 CEA studies, and 11 CUA studies were excluded for not meeting the inclusion criteria of this study. Finally, 9 CA studies, 3 CMA studies, 29 CEA studies, and 8 CUA studies that met the inclusion criteria were included as economic evaluation studies (Fig. 1).

Economic Methods and Agreement

Based on the classification of each economic evaluation study by the two reviewers using defined criteria, 4 CA studies classified as such by their authors were re-classified in this study as CMA studies, 1 CMA study classified as such by its author was re-classified as a CEA study, 2 CEA studies classified as such by their authors were re-classified as CMA studies, 23 CEA studies classified as such by their authors were re-classified as CUA studies, and 1 CUA study classified as such by its author was re-classified as a CEA study (Table 2). When CUA studies were categorized into CEA studies, the overall percentage agreement was 93.3%, and the weighted Cohen's Kappa index was 0.77 (95% confidence interval [CI], 0.63-0.92), showing good strength of agreement between the authors and the reviewers. However, when the CEA and the CUA studies were distinguished, the overall percentage agreement was 36.7%, and the weighted Cohen's Kappa index was 0.47 (95% CI, 0.33-0.62), showing moderate strength of agreement

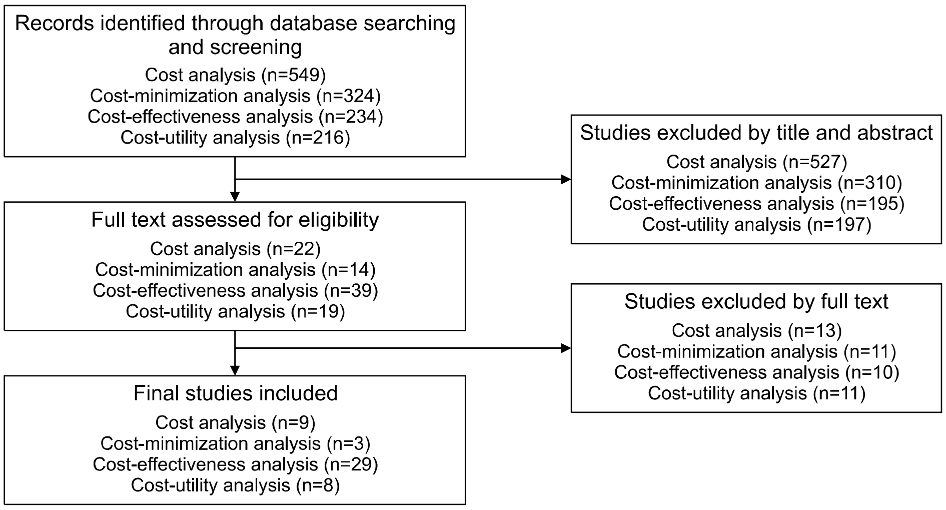

Fig. 1. Flow chart of a systematic review of economic evaluation studies of thyroid cancer.

Table 2. Classification of included economic evaluation studies on thyroid cancer

		Reclassification according to the theoretical method of economic evaluation			
		CA	CMA	CEA (including CUA)	Total
Classification in method of economic evaluation in existing literature	CA	5	4	-	9
	CMA	-	2	1	3
	CEA (including CUA)	-	2	35	37
	Total	5	8	36	49

Agreement=93.3%

Cohen's Kappa index[a] (95% CI)=0.77 (0.63-0.92) p-value=5.36×10^{-25}

		CA	CMA	CEA	CUA	Total
Classification in method of economic evaluation in existing studies	CA	5	4	-	-	9
	CMA	-	2	1	-	3
	CEA	-	2	4	23	29
	CUA	-	-	1	7	8
	Total	5	8	6	30	49

Agreement=36.7%

Cohen's Kappa indexa (95% CI)=0.47 (0.33-0.62) p-value=2.56×10^{-10}

CA: cost analysis, CEA: cost-effectiveness analysis, CI: confidence interval, CMA: cost-minimization analysis, CUA: cost-utility analysis, HT:hemithyroidectomy, ICER: incremental of cost-effectiveness ratio, N: number, PTC: papillary thyroid carcinoma, QALY: quality-adjusted life year, TT: total thyroidectomy

Based on the classification by reviewers, 4 CA articles were re-defined as CMA articles, 1 CMA article was re-defined as a CEA article, 2 CEA articles were re-defined as CMA articles, 23 CEA articles were re-defined as CUA articles, and lastly, 1 CUA article was re-defined as a CEA article.

[a]Weighted index.

between the authors and the reviewers.

Economic Findings according to the Topics and Inconsistent Results within the Same Interventions

We found that 3 out of 9 CA studies were simple cost calculations related to thyroid cancer without providing comparisons, and other topics covered included comparisons between hemithyroidectomy (HT) and total thyroidectomy (TT) (with or without lymph node dissection [LND]), immediate surgery and active surveillance, adjuvant radioiodine therapy (RAIT) and no adjuvant RAIT, and standard thyroidectomy and trans-axillary endoscopic or robotic thyroidectomy (Supplementary Table 3). The CMA studies compared costs between TT with LND versus TT, HT with intraoperative frozen section versus HT, and surgery based on the results of cytology versus diagnostic HT (Supplementary Table 4). Among the 37 CEA or CUA studies, 29 (78.4%) studies were related to surgical extent (n=8), RAIT (n=6), surgical methods (n=6), molecular testing (n=5), and active surveillance (n=4, Supplementary Tables 5 and 6). Table 3 summarizes the major economic findings of the studies that dealt with the most common topics.

1) HT versus TT for Low- to Intermediate-risk Papillary Thyroid Carcinoma (PTC)

Three studies reported on the comparison of HT and TT for low- to intermediate-risk PTC.[13-15] These studies reported inconsistent results on the same subject.[13-15] Shrime et al.[13] reported that TT was substantially preferred over HT as an initial treatment for low-risk PTC, whereas Lang and Wong[14] reported that HT was a more cost-effective long-term option than TT for 1-4-cm PTCs without clinically recognized high-risk features. Al-Qurayshi et al.[15] reported that TT is not just cost-prohibitive but also associated with a lower effectiveness than HT. This inconsistency in the results between the three studies can be explained as follows: Shrime et al.[13] evaluated the ICER for cause-specific mortality or recurrence-free survival

Table 3. Major economic findings of the studies that dealt with the most common topics

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Hemithyroidectomy (HT) versus total thyroidectomy (TT) for low- to intermediate-risk papillary thyroid carcinoma (PTC)								
Shrime (2007) (Literature review from PubMed: 940 PTC papers from 1966/01/01-2007/01/01)	CEA	1 million hypothetical low-risk PTC cases (AMES score <6, and AGES score <4, or adherence to the Memorial Sloan-Kettering low-risk categories)	[I] HT [C] TT	[DC] Hospital charges for inpatient operative procedure, FU cost, complication cost, and recurrence cost [IC] Cost for death from unintentional injuries: $1,130,000 based on National Safety Council estimates of death	Cost and ICER for cause-specific mortality (CSM) or recurrence-free survival (RFS) CSM or RFS under same cost assumption CSM and RFS derived from literature reviews (31 studies finally selected)	- Monte Carlo microsimulation using fixed probability estimates of complications and recurrence derived from 31 eligible studies - Sensitivity analyses using 6% annual discount and cost-to-cost ratio estimated from 31 eligible studies - Threshold analyses: comparison of net monetary benefits obtained from TT and HT using a variable range of willingness-to-pay (WTP) values	- TT dominates HT as initial treatment for low-risk PTC - 20-year ICER: [I] HT, $15,037.58-$15,063.75; [C] TT, $13,896.81-$14,241.24 - 20-year CSM under the same cost assumption: similar HT and TT - 20-year RFS under the same cost assumption: higher in TT (89.9%) than HT (75.2%) - Sensitivity analyses: HT sensitive to recurrence rates and FU costs - Threshold analyses: robust when compared with WTP	Cost, ICER

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Lang (2016) (China)	CUA	Hypothetical cohort of 100,000 non-pregnant women aged 40 years with a unifocal intra-thyroidal 2.5-cm clinically nodal negative PTC but without family history of non-medullary thyroid cancer and neck irradiation	[I] Lobectomy [C] TT	[DC] Costs of surgery, RAI, surgically related complications, and annual thyroxine replacement based on data obtained from Medicare reimbursement data [IC] Not included	QALY gained during 25 years. Estimates of the quality adjustment factor for hypothyroidism needing thyroxine (0.99), uni- and bi-lateral vocal cord palsy (VCP) (0.63, and 0.21, respectively), hypoparathyroidism (0.78), and 1-year recurrence (0.54) derived from the literature	- Markov decision model with literature-based probabilities and utilities - Sensitivity analyses: each clinical parameter varied from lowest to highest values, as suggested in the literature, while other parameters remained constant - Threshold analyses: threshold of $50,000/QALYs	- Initial lobectomy was a more cost-effective long-term option than initial TT for 1 to 4 cm PTCs without clinically recognized high-risk features - After 25 years, lobectomy cost $772.08 more than TT, but gained an additional 0.300 QALY (ICER, $2,577.65/QALY) - Sensitivity analyses: lobectomy began to become cost-effective only after 3 years. Despite varying the reported prevalence of clinically unrecognized high-risk features, complication from surgical procedures, annualized recurrence rates, unit cost of surgical procedure or complication, and utility score, lobectomy remained more cost-effective than TT - Threshold analyses: Lobectomy was regarded as cost-effective if the ICER was below the threshold of the %50,000/QALY	Cost, QALY, ICER

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Al-Qurayshi (2020) (US)	CUA	Base-case scenario, a 40-year-old woman who presented with a 2-cm single thyroid nodule after a pre-operative FNA biopsy that was suspicious for PTC	[I] TT [C] Lobectomy	[DC] Costs of surgery, complications, post-operative surveillance, and drugs retrieved from the literature [IC] Cost of loss of productivity for 2 weeks based on the literature	20-year cost for QALY measured by ICER (⊿cost/⊿QALY) Utility scores for QALY calculation extracted from the literature; absence of complications, 1; hypothyroidism, 0.99; hypoparathyroidism, 0.778; unilateral recurrent laryngeal nerve (RLN) injury, 0.627; and bilateral RLN injury, 0.205	- Markov model with literature-based probabilities (TNM stage categories on surgical pathology, RLN injury, hypothyroidism, hypoparathyroidism) - Sensitivity analyses: varying the risk of PTC stage III or IV, risk of hypoparathyroidism, and risk of RLN injury - Threshold analyses: threshold of \$50,000/QALY	- TT produced an incremental cost of \$2,681.36 and incremental effectiveness of −0.24 QALY compared to lobectomy (−\$11,188.85/QALY) - Sensitivity analyses: TT became cost-effective if the risk of stages III and IV PTC is 82.4% among patients with suspicious PTC on preoperative FNA. Lobectomy was cost-effective and preferred over TT as long as lobectomy complications were less than 50% - Threshold analyses: lobectomy was considered cost-effective if ICER was less than \$50,000/QALY	Cost, QALY, ICER

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Immediate surgery versus active surveillance (AS) for micro-PTC								
Oda (2017) (Japan)	CMA	2153 patients diagnosed with low-risk PTC by ultrasound-guided FNA biopsy From February 2005 to August 2013 at Kuma Hospital (a model was created using patients from a previous study)	[I] Immediate surgery [C] AS	[DC] Costs of the initial diagnosis step, costs of surgeries (including all medical costs of preoperative examinations, surgery, anesthesia, pathological examination, and admission), and costs of follow-up care (Japanese Healthcare Insurance System) [IC] Not included	Medical cost	- A model created from the actual flow of the managements of those 2153 patients with low-risk PTCs	- 10-year simple cost of active surveillance: ¥7,780/patient - Simple cost of immediate surgery: ¥794,770/patient to ¥1,086,070/patient, depending on the type of surgery and post-operative medication - 10-year total cost of active surveillance: ¥225,695/patient when conversion surgeries and recurrence considered - Total cost of immediate surgery: ¥928,094/patient when recurrence considered - 10-year total cost of immediate surgery was 4.1 times expensive than active surveillance	Cost

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Lang (2015) (Hong Kong)	CUA	Base-case scenario, a 40-year-old woman diagnosed with a unifocal intra-thyroidal 9 mm PTC	[I] Non-surgical approach (NSA) [C] Early surgery (ES)	[DC] Costs of surgery (HT+CND, TT+CND, and TT+CND+SND) estimated based on Medicare reimbursement data in 2014 Complication and half yearly ultrasound surveillance costs derived from the literature [IC] Not included	20-year QALY gained measured by ICER (⊿Cost/⊿QALY) Quality of life adjustment is quantified by a utility score ranging from 0 to 1. Utility scores for each health state derived from the literature using the values 1 for alive without permanent complication, 0.54 for alive with permanent complication, and 0 for death	- Markov decision tree model - Sensitivity analyses (+): according to clinical parameters suggested in the literature - Threshold analyses (+): threshold defined as the ICER of NSA to ES became zero or infinity	- After a 20-year period, NSA cost an extra $682.54 but gained an additional 0.260 QALY over NSA - 20-year ICER for NSA relative to ES was $2,630 - NSA was cost saving up to 16 years from diagnosis and remained cost-effective from 17 years - Sensitivity analyses: NSA remained cost-effective regardless of patient age, complications, rates of progression, year cycle, and discount rate - Threshold analyses: none of the scenarios that could have changed the conclusion appeared clinically likely	Cost, QALY, ICER

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Venkatesh (2017) (US)	CUA	Base-case scenario, a 40-year-old patient with a biopsy-proven, unifocal micro-PTC without features that would necessitate immediate HT	[I] AS [C] HT	[DC] Published Medicare reimbursement rates and Healthcare Costs and Utilization Project adjusted to 2015 US$. Cost of thyroid hormone supplementation obtained from the Redbook online database [IC] Not included	20-year cost for QALY measured by ICER (⊿cost/⊿QALY) Health state utility inputs used to calculate QALY obtained from the literature; disutility difference of AS compared to disease-free state post-HT without complication, 0.11; disease-free state after HT without complication, 0.99; disease-free state afterHT with short-term complication, 0.75; disease-free state after HT with long-term complication, 0.63; HT, 0.74; TTLND, 0.55; TTLND with complication, 0.54; Redo LND, 0.56; Redo LND with complication, 0.41; RAI, 0.64; disease-free state after operation and RAI, 0.95; and disease recurrence, 0.54	- Markov model with literature-based probabilities (disease progression during AS, stability of disease after surgery, operative complications, locoregional recurrence) - Sensitivity analyses: range for costs distributed uniformly from 50% to 150% of published data - Threshold analyses: threshold of $100,000/QALY	- 20-year FU, HT was costlier at $13,866 but also afforded patients increased effectiveness of 22.13 QALYs. - For a utility difference of 0.11, the ICER for HT was $4,437/QALY gained - Sensitivity analyses: AS was dominant for a health utility <0.01 below that for disease-free, post HT state, or for a remaining life expectancy of <2 years - Threshold analyses: HT was cost-effectives in 79% of the 100,000 simulations at a WTP threshold of $100,000/QALY	Cost, QALY, ICER

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Lin (2020) (Australia)	CMA	349 micro-PTC patients included from a prospectively collected surgical cohort of patients treated for papillary thyroid cancer between 1985 and 2017	[I] Surgical treatment [C] AS	[DC] Blood test, consult with an endocrinologist/endocrine surgeon, FNA, medications, ultrasound, CND, LND, RAI (anonymized data provided by clinical costing team from the Royal North Shore Hospital and University of Sydney) [IC] Not included	Complications of thyroid surgery, recurrence-free survival, overall survival, and cost of surgical treatment and active surveillance	Papillary thyroid microcarcinoma patients included from a prospectively collected surgical cohort of patients treated for PTC between 1985 and 2017	- Total cost of surgical treatment: $10,226 - Hypothetical AS cost: $756/year. - Estimated cost of surgical micro PTC treatment was equivalent to the cost of 16.2 years of AS - If young Australian patients require more than 16.2 years of follow-up in an AS scheme, surgery may have a long-term economic advantage. - Sensitivity analyses: AS is more cost-efficient over a longer period. It would be less cost-efficient for patients between 20 and 30 years of age to be in an AS program	Cost

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
TT with prophylactic CND (pCND) versus TT for low-risk PTC								
Lang (2014) (Hong Kong)	CEA	100,000 hypothetical non-pregnant female patient cohort at age 50 years with low-risk PTC (1.5-cm cN0 PTC within one lobe)	[I] TT with pCND until death or age 70 years [C] TT until death or age 70 years	DC] 20-year cumulative cost, including procedural cost, RAI ablation, complication cost, hospitalization, annual routine surveillance (Hospital Authority cost published in the 2013 Government Gazette) [IC] Not included	20-year accumulative medical cost. Surgical procedures, complications, and RAI ablation	- A decision-tree model was constructed to compare the estimated long-term cost between TT alone and TT+pCND. Patients underwent one of two strategies, namely TT alone or TT+pCND, and were followed until age 70 years - All the costs were discounted by annual rate of 3% - Sensitivity analysis performed to explore the uncertainty on the clinical parameters of complications, RAI ablation, and annualized recurrence rates	- TT+pCND is more expensive in the medium- and long-term in low-risk PTC patients - TT: US$ 19,888.36 in 20-year cumulative cost - TT+pCND: US$ 22,760.86 in 20-year cumulative cost - Incremental cost: US$ 2,872.50 - Sensitivity analyses: no change	Cost, increment al cost

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Zanocco (2013) (US)	CUA	Base-case scenario, a 40-year-old patient with a 2-cm, non-invasive PTC that was without preoperative or intraoperative evidence of nodal involvement	[I] TT with routine pCND [C] TT alone	[DC] 2010 national Medicare charge limits for surgery, anesthesiology, and pathology services rendered in each strategy. Hospital costs and surgical costs estimated by 2009 Medicare cost-to-charge ratios and 2009 Nationwide Inpatient Samples, respectively. Thyroid hormone-replacement costs based on average US wholesale prices. Costs for complications based on previous studies [IC] Missed patient work due to surgery assigned an hourly cost based on 2010 annual US hourly earnings	Quality-adjusted life expectancy (values based on the literature) for undergoing reoperation for recurrence and complications measured by ICER (Δcost/ΔQALY)	- Markov transition-state model with literature-based outcome probabilities and utilities(risk of recurrence, risk of endocrine complications) - Sensitivity analyses for all variables, including lifetime recurrence after TT alone, recurrence risk reduction with additional pCND, and risk of recurrent laryngeal nerve (RLN) injury and permanent hypoparathyroidism with pCND were performed using 1,000 Monte Carlo iterations - Threshold analyses: threshold of $100,000/QALY	- pCND cost $10,315 and produced an effectiveness of 23,785 QALYs. The addition of routine pCND resulted in an expected incremental cost of $166 and a loss of 0.006 QALYs - Sensitivity analyses: pCND became cost-effective when the probability of recurrence increased from 6% to 10.3%, the cost of reoperation for recurrence increased from $8,900 to $26,120, or added probabilities of RLN injury and hypoparathyroidism due to pCND were less than 0.20% and 0.18%, respectively. - Threshold analyses: pCND was not cost-effective in 97.3% of iterations	Cost, QALY, ICER

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Wong (2014) (Hong Kong)	CUA	100,000 hypothetical non-pregnant female patient cohort at age 50 years with low-risk PTC (1.5-cm cN0 PTC within one lobe)	[I] TT+pCND [C] TT	[DC] operation and reoperation costs, RAI, hospitalization cost, complication cost, and follow-up cost, based on a literature review (Medicare reimbursement data in 2005) [IC] Not included	Disease-free survival, recurrence-free survival, and overall death derived from a literature review (31 eligible studies)	- Markov decision tree model based on literature review of outcome probabilities, utilities, and costs - Sensitivity analyses based on uncertainty model with discount rate of 3% per year - Threshold analyses based on uncertainty model: $50,000/QALY - Monte Carlo microsimulation using the fixed probability estimates of complications and recurrence derived from 31 eligible studies - Sensitivity analyses using 6% annual discount and cost-to-cost ratio estimated from 31 eligible studies	- TT+pCND is more cost-effective than TT along for low-risk PTC in the long-term. It began to become cost-effective after 9 years from the initial operation. - 20-year ICER: TT+pCND, $105.97 relative to TT at threshold of $50,000/QALY - TT+pCND: extra cost of $34.25 but scored 0.323 QALYs) more than TT - Sensitivity analyses: positive ICERs of TT+pCND based on difference parameters. TT+pCND became cost-saving at 20 years if associated permanent vocal cord palsy was ≤1.37%, permanent hypoparathyroidism was ≤1.20%, and/or postoperative RAI ablation use was ≤73.64%. - Threshold analyses: robust when compared with WTP	QALY gain, ICER

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Garcia (2014) (US)	CEA	Base-case scenario, a 40-year-old non-pregnant healthy woman with a biopsy-confirmed 2-cm PTC without clinically or radiologically involved neck lymph nodes (Stage II: T1bN0M0)	[I] TT with routine CND [C] TT alone	[DC] Medicare reimbursement data in 2010 [IC] Opportunity loss based on published US government data. Cost of living determined from the Bureau of Labor Statistics	Lifetime cost-utility measured by ICER (⊿Cost/⊿QALY). Utility scores based on the literature. Health states summed as per the Markov model over all 42 cycles to obtain QALYs. Patients reaching the death state before the 42nd cycle retained in the model to calculate opportunity loss (Patients who developed non-neck recurrence of cancer given a median utility of 0.6 based on the literature)	- Markov model with utilities and outcome probabilities obtained from the literature - Sensitivity analyses: one-way and two-way and Monte Carlo simulation performed - Threshold analyses: not performed	- TT with CND was not a cost-effective strategy in low-risk PTC - TT alone: cost savings of $5,763 per patient with slightly higher effectiveness per patient (0.03 QALY) for a cost savings of $285/QALY - Sensitivity analyses: TT alone offered no advantagewhen RAI became more detrimental to a patient's state of health, when the incidence of non-neck recurrence increased above 5% in patients undergoing TT alone, decreased below 3.9% in patients undergoing TT with CND, or the rate of permanent hypocalcemia rose above 4%	Cost, QALY, ICER

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Molecular test versus no molecular test (standard management or diagnostic lobectomy) for indeterminate thyroid nodules								
Najafzadeh (2012) (US, Canada)	CUA	10,000 patients with an initial indeterminate FNA cytological diagnosis	[I] Molecular diagnostic (DX) test [C] No molecular diagnostic (NoDX) test	[DC] Costs for TT or HT based on results from a previous study [IC] Calculated based on average lengths of hospitalizations subsequent to those surgeries and assuming an average income of $99 per day; calculated average annual income based on US census data and assuming 12% of the patients were men	Simulated outcomes for 10 years: initial and final cytology, occurrence of cancer, type of cancer, HT, TT, completion thyroidectomy, complications, and mortality Health outcomes: QALYs and costs for each patient. A health state utility value derived from short form 36 (SF-36) assigned to each of 10 health states to facilitate the calculation of QALYs	- Patient-level simulation model with literature-based probabilities - Sensitivity analyses conducted by varying the value of model parameters over a viable range on the overall outcomes of the model, and by varying the annual discount rate from 3% to 0% - Threshold analyses: threshold of $50,000/QALY	- DX test strategy appears to be the dominant diagnostic strategy if shown to have a high sensitivity and specificity with a reasonable cost per test - DX test resulted in a gain of 0.046 QALYs and saving of $1,087 in direct cost per patient - Sensitivity analyses: sensitivity of the DX test had a larger influence on the overall outcomes than specificity did. Assuming the DX test could maintain a sensitivity and specificity of 95%, 0.025 QALYs gained at a cost of $291, which is less than that in the NoDX strategy - Threshold analyses: robust when compared with WTP	Cost, QALY gained

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Lee (2014) (US, Canada)	CUA	Low-risk patients with AUS thyroid nodules	[I] Molecular test with i) routine GEC, ii) routine GEC+ selective GMP, iii) routine GMP, or iv) routine GMP+ selective GEC [C] Standard manageme nt without molecular test	[DC] Cost of the GEC and GMP obtained from the respective manufacturers US costs obtained from the Medicare reimbursement data in 2011 and 2013 Canadian costs obtained from Canadian Institute for Health Information case-mix groups and Quebec provincial cost manuals Drug costs based on US and Quebec provincial wholesale costs [IC] Not included	Lifetime costs and QALY. Utilities valued from a scale of 0 (death) to 1 (perfect health). Utilities for each health state taken from three different studies: unilateral RLN palsy, 0.63; bilateral RLN palsy, 0.21; hypoparathyroidism, 0.78; disease-free after HT, 0.99; disease-free after TT and RAI, 0.95; recurrence, 0.54 pre-RAI (post-surgery), 0.55; postRAI 0-4 wk, 0.64; and post-RAI 4-8 wk, 0.82	- Microsimulation model (1 million patients; 1-year cycle length) with literature-based probabilities (risk of mortality, recurrence, and malignancy, complications, and sensitivity and specificity of diagnostic tests) and utilities - Sensitivity analyses: varying one or more variables at a time across a specified range of values - Threshold analyses: cost-effectiveness acceptability curves, representing the proportion of times (out of the total number of simulated patients) that each option is optimal for a given cost/QALY threshold	- From the US perspective, routine GEC+ selective GMP was the dominant strategy - From the Canadian perspective, standard management was most likely to be cost-effective - Sensitivity analyses: the decisions from both perspectives were sensitive to variations in the probability of malignancy in the nodule and the costs of the GEC and GMP - From the US perspective, the routine GEC+ selective GMP strategy would be the least costly only if the cost of a thyroid lobectomy exceeded $6,686 - Threshold analyses: none of the strategies had a probability of cost-effectiveness higher than 35% at any cost/QALY threshold	Cost, QALY, ICER

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Nicholson (2019) (US)	CEA	Base-case scenario, a 40-year-old euthyroid woman with a solitary 2-cm Bethesda III or IV thyroid nodule	[I] Molecular testing using, i) Afirma GSC ii) ThyroSeq ver.3 (TSv3) [C] Diagnostic lobectomy (DL)	[DC] Costs related to management strategy and related surveillance derived from Medicare reimbursement data in 2018 and the literature [IC] Not included	Cost per correct diagnosis (defined as malignant histology after DL or 20 years of nodule stability after negative molecular test)	- Decision tree model with literature-based probabilities (cancer prevalence, molecular test failure, sensitivity and specificity of each test, post-operative complication, and surveillance of molecular test-negative nodule) - Sensitivity analyses performed for costs, pretest probability of malignancy, and performance parameters - Threshold analyses: Not done	- Either of the major molecular test was considerably more cost-effective than DL, although TSv3 was more likely to be cost-effective than GSC - Cost per correct diagnosis: $14,277 for TSv3, $17,873 for GSC, and $38,408 for DL - TSv3 was preferred over both GSC and DL - Sensitivity analyses: One-way sensitivity analysis between TSv3 and GSC demonstrated that the results were robust to variations in cost,cancer prevalence, and length of surveillance. In the two-way sensitivity analysis, TSv3 was preferred over GSC at all considered test costs, and in probabilistic sensitivity analysis, TSv3 was the preferred management strategy in 68.5% of cases	Cost, ICER

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Balentine (2018) (US)	CUA	Base-case scenario, a 40-year-old woman with a 1-cm indeterminate (Bethesda III-IV) nodule	[I] Genetic testing (Afirma) [C] DL	[DC] Medicare reimbursement data in 2016 with a 3% discount rate [IC] Not included	5-year cost forQALYs (⊿Cost/⊿QALY), unnecessary operative procedures, cases requiring long-term hormone replacement, and permanent operative complications. Estimates of utilities drawn from previously published values: post-lobectomy, no hormone replacement required, 0.990; post-lobectomy, hormone replacement required or thyroidectomy, 0.950; distant cancer, 0.700; detected local cancer, 0.950; permanent complications of lobectomy, 0.700; permanent complications of thyroidectomy, 0.650; 6 months before death from distantcancer, 0.350; routine surveillance, 0.980; temporary complications of lobectomy or thyroidectomy, 0.950; surveillance with Afirma, 0.980; and temporary decrease in utility due to lobectomy/thyroidectomy, 0.013.	- Markov decision model with literature-based probabilities and utilities - Sensitivity analyses: Monte Carlo probabilistic sensitivity analysis with 10,000 replications to derive 95% uncertainty intervals for primary and secondary outcomes and ICERs - Threshold analyses: threshold of $100,000/QALYs	- DL dominates genetic testing as a strategy for ruling out malignancy of indeterminate thyroid nodules - During a 5-year, lobectomy was less costly and more effective than Afirma® (lobectomy: $6,100; 4.50 QALYs vs. Afirma®: $9,400; 4.47 QALYs) - Sensitivity analyses using the 2015 guidelines found that an Afirma®-based strategy is slightly more effective than operative thyroidectomy (+0.0017 QALYs) but at considerably greater cost (+$3,130) for an ICER of $1,843,000 - Threshold analyses: in 253 of 10,000 simulations (2.5%), Afirma® showed a net benefit at a cost-effectiveness threshold of $100,000/QALY	Cost, QALY, ICER

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
RAI using rhTSH versus RAI after thyroid hormone withdrawal (THW)								
Borget (2015) (France)	CUA	ESTIMABL trial: 752 patients with thyroid cancer who underwent TT were randomly assigned to one of four strategies, with each strategy combining one TSH stimulation method (rhTSH or THW) and one I-131 activity (1.1 or 3.7 GBq)	[I] TSH stimulation using rhTSH [C] TSH stimulation using THW and [I] 1.1 GBq of I-131 activity [C] 3.7 GBq of I-131 activity	[DC] Fixed and variable costs extracted from the French National Cost Survey, using the diagnosis-related group code, for I-131 administration. Cost of rhTSH was obtained from the French drug database. Transportation costs were estimated using the French health insurance reimbursement tariffs according to the home-hospital distance and the type of transportation used [IC] The value of lost productivity was based on the national added value estimated at €198 per day	8-month total costs, QALY. EuroQoL-5D (EQ-5D) questionnaire used to assess utility and QALYs. Questionnaires collected seven times (at random assignment; immediately before 131I administration; 2, 4, and 6 weeks after radioiodine administration; and at the 3- and 8-month visits) to measure the evolution of utility scores over that period	- Net monetary benefit approach and computed cost-effectiveness acceptability curves used for both TSH stimulation methods and I-131 activities - Sensitivity analyses: reducing the price of rhTSH by 10% and 30% - Threshold analyses: threshold of €50,000/QALY	- rhTSH was more effective than THW in terms of QALYs but more expensive (€474/patient) - The use of 1.1 GBq of I-131 instead of 3.7 GBq reduced per-patient costs by €955 but with slightly decreased efficacy (-0.007 QALY/patient) - Sensitivity analyses: when the rhTSH price was lowered by 30%, the extra cost incurred with rhTSH was reduced and the probability that rhTSH would be cost-effective for a threshold of €50,000/QALY increased to 70% - Threshold analyses: with the threshold of €50,000/QALY, the probability that rhTSH would be cost-effective was 47% and 59% when direct and total costs were considered, respectively. The probability that the lower I-131 activity would be cost-effective was 65% and 77% when direct and total costs were considered	Cost, QALY per patient

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Mernagh (2010) (Canada)	CUA	Hypothetical patients with low-risk thyroid cancer without RAI and exogenous stimulation (i.e., rhTSH), against those prepared with endogenous stimulation (with hypothyroidism resulting from the THW)	[I] RAI using rhTSH [C] RAI after THW	[DC] Canadian resource use and unit costs sourced with a societal perspective. The most up-to-date costs sourced in all instances, with all costs as published in either 2007 or 2008. [IC] Canadian wage rate as a proxy for productivity loss (Statistics Canada 2007)	Incremental cost and benefit for 17 weeks measured by ICER (⊿Cost/⊿QALY). QALYs derived from SF-36 data	- Markov model using the probabilities derived from a pivotal multicenter, randomized, controlled trial - Sensitivity analyses: deterministic one-way and two-way sensitivity analysis - Threshold analyses: considered to be fundable if the cost/QALY is between \$20,000 and \$100,000	- rhTSH use represents a reasonable allocation of costs, with the benefits to patients, hospitals, and society as a whole, obtained at modest cost. - The additional benefits of rhTSH (0.0576 QALY) were obtained with an incremental cost of CDN\$87, generating an incremental cost of CDN\$1,520/QALY - Sensitivity analyses: the results were demonstrated to be robust - Threshold analyses: the results were robust when compared with WTP	Cost, QALY, ICER

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Mernagh (2006) (Germany)	CEA	Hypothetical patients with well-DTC who had undergone thyroidectomy, but had no metastases	[I] RAI using rhTSH [C] RAI after THW	[DC] German setting; takes a societal perspective [IC] Productivity loss using friction-cost method. Lifetime cost of secondary cancer assumed as €48,966	Pre-and post-ablation health states, secondary cancer, recurrence, death, and QALY. Utility weights for the pre- and post-ablation health states that differ between arms obtained from the pivotal controlled clinical trial. SF-36 trial data transformed into utility weights using the SF-6D method. Other utility weights, not different between arms, sourced from the literature, assumptions, and convention	- Lifetime Markov model with inputs derived from a multicenter, randomized controlled trial supplemented with additional information from the literature - Monte Carlo simulation of 100,000 patients used to simulate patients progressing through the various health states at the individual level - Sensitivity analyses: a discount rate of 5% per annual applied to costs and outcomes - Threshold analyses: not undertaken	- rhTSH use prior to RAI represents good value-for-money with the benefits to patient and society obtained at modest net cost - The additional benefits of rhTSH (0.0495 QALY) were obtained with an incremental societal cost of €47, equating to an incremental cost of €958/QALY. - Sensitivity analyses had only a modest impact on cost-effectiveness, with all one-way sensitivity results remaining under €15,000/QALY - Threshold analyses: not undertaken	Cost, QALY, ICER

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Vallejo (2017) (Spain)	CEA	Hypothetical patients newly diagnosed with well-DTC undergoing total or almost TT, comparing rhTSH with THW	[I] RAI using rhTSH [C] RAI after THW	[DC] Costs estimated from hospital charge in Spain, a survey, and the price of commercialized I-131 [IC] Costs of productivity loss: the model assumes that, on average, patients in the THW arm miss 11 working days owing to hypothyroid symptoms while those in the rhTSH arm miss 5.5 days. These costs were analyzed only in the sensitivity test, 17-week cost-utility measured by ICER (⊿Cost/⊿QALY) Utility weights applied in the economic model based on data of SF-36 collected during a pivotal randomized controlled trial	Cost and cost per QALY gained measured by ICER (⊿Cost/⊿QALY). Utility weights applied in the economic model based on data of the SF-36 collected during the pivotal randomized controlled trial	- Markov model with two analysis arms (rhTSHand THW), stratified into high (100mCi/3700 MBq) and low (30mCi/1110 MBq) RAI doses, and using clinical inputs based on published studies and in a treatment survey conducted in Spain - Sensitivity analyses - Threshold analyses: not undertaken	- The use of rhTSH previous to RAI in Spain had cost savings, as well as a series of health benefits for the patient, making it highly cost-effective - RAI preparation with rhTSH was superior to THW, showing additional benefits (0.048 AVAC), as well as cost savings (−€614.16), with an ICER of −€12,795/QALY - Sensitivity analyses showed the result to be robust	Cost, QALY, ICER

Table 3. Continued

First author (year) (Country)	Type of Study	Patients	Intervention [I], Comparison [C]	Direct cost [DC], Indirect cost [IC]	Outcomes	Analysis	Results and conclusion	Economic analysis indicator
Wang (2010) (US)	CUA	Hypothetical population of adult patients with low-risk DTC prepared for ablation by either rhTSH or thyroid hormone withdrawal	[I] Ablation by rhTSH [C] Ablation by thyroid hormone withdrawal	[DC] Physician office visits, imaging studies (ultrasound and 131I), surgery, thyroid hormone, rhTSH, and laboratory tests (2009 Medicare reimbursement schedule) [IC] Lost work days (US Bureau of Labor Statistics 2009)	Cost-utility, measured in US$ per quality-adjusted life-year ($/QALY) PubMed database, (SF-36/Short Form 6D scoring protocol to yield utility weights)	- A Markov decision model constructed to determine the incremental cost-utility - Sensitivity analyses tested the impact of clinical uncertainty around model inputs in the base-case analysis - Threshold analyses based on uncertainty model: $50,000/QALY - A discount rate of 3% per year applied to all costs and outcomes	- Use of rhTSH yielded an incremental cost-utility of $52,554/QALY. - The majority of cost and benefit occurs during the pre-ablation, ablation, and post-ablation period - Differences in cost are due to the cost of rhTSH and differences in productivity loss (days off work). - Sensitivity analyses: the model was most sensitive to changes in time off work, cost of rhTSH, and differences in utilities of health states. - Threshold analyses: robust when compared with WTP	Cost, utility, QALY, ICER

CEA: cost-effectiveness analysis, CMA: cost-minimization analysis, CND: central neck dissection, CUA: cost-utility analysis, FNA: fine needle aspiration, GEC: gene expression classifier, GMP: gene mutation panel, GSC: gene sequence classifier, ICER: incremental cost-effectiveness ratio, LND: lateral neck dissection, QALY: quality-adjusted life year, RAI: radioactive iodine, SND: selective neck dissection whereas Lang and Wong[14] and Al-Qurayshi et al.[15] measured QALY adjusted by utility scores in relation to surgical complications.

2) Immediate Surgery versus Active Surveillance for Micro-PTC

Four recent studies conducted economic evaluation analyses comparing the two strategies in managing micro-PTC. Oda et al.[16] suggested that immediate surgery for micro-PTC is 4.1 times more expensive than AS over a time span of 10 years in Japan. However, Oda et al.[16] did not compare the costs of these strategies after 10 years. Another CMA study in Australia reported that immediate surgery may have a long-term economic advantage for patients with micro-PTC who are likely to require more than 16.2 years of follow-up in an AS scheme.[17] These numbers are concordant with a CUA study from China.[18] Lang and Wong[18] suggested that AS for micro-PTC is cost saving relative to immediate surgery in the first 16 years of diagnosis. Thereafter, it continued to be a more cost-effective option than immediate surgery for a selected group of micro-PTC. However, Lang and Wong[18] assumed patients undergoing AS would have a health utility of 1, which is equivalent to a completely healthy state. Another CUA study from Canada using the utility value for patients undergoing AS of 0.88, and demonstrated that the cost-effectiveness of immediate surgery for micro-PTC is dependent largely on the health utility associated with AS of individual patients, as well as the remaining life expectancy of the patient after diagnosis.[19]

3) TT with Prophylactic Central Neck Dissection (pCND) versus TT for Low-risk PTC

Four studies evaluated cost-effectiveness of the pCND in patients with low-risk PTC compared with TT alone.[20-23] Three of them, the authors concluded that TT plus pCND was more costly and less effective than TT alone.[20-22] In contrast, one CUA study found that TT plus pCND to be more cost-effectiveness after nine years from the initial operation.[23] The main differences of this study from others were outcome probabilities, quality adjusted factors, utility scores, model, and annualized recurrence risk.

4) Molecular Test for Indeterminate Thyroid Nodules

Four studies in United States and Canada conducted economic evaluations of molecular testing for indeterminate thyroid nodules.[24-27] These studies yielded a variety of results, with three of them demonstrating cost saving and improved quality of life,[24-26] while one study has shown the opposite after accounting for the costs of long-term follow-up.[27] There were differences in the cost of molecular test and thyroid surgery, the sensitivity and specificity of molecular test, and the probability of malignancy of the nodule for each study.

5) RAIT Using rhTSH versus RAIT after Thyroid Hormone Withdrawal (THW) for Differentiated Thyroid Carcinoma

Five economic evaluations on the use of rhTSH were conducted in different countries, and they have reported heterogeneous results.[28-32] In the French context, rhTSH avoids the transient THW-induced deterioration of health-related quality of life but is unlikely to be cost effective (€474/patient).[28] Mernagh et al.[29,30] found that rhTSH was cost effective with an ICER of CDN$1,520/QALY and €958/QALY in the Canadian and German perspectives, respectively, using a Markov model and lifetime horizon. In the Spanish context, rhTSH is superior to THW with an ICER of −12,795€/QALY.[31] In the US context, the ICER of rhTSH was $52,554/QALY over a 4-year period, and results were sensitive to potential variations in cost of rhTSH, rates of remnant ablation, time off work, and quality of life.[32] Differences in results may be explained by the clinical and economic inputs included in these economic evaluations.

Data Sources and Types of Costs

Table 4 shows the data sources of costs in each study. Medical direct costs were derived from SR, Medicare reimbursement, raw clinical trial and registry data obtained from medical centers, and combinations of these data sources. Of the 49 economic evaluation

Table 4. Sources in thyroid cancer studies for medical and non-medical costs of economic evaluation

Type of costs	Total N (%)	CA+CMA[a] N (%)	CEA+CUA[b] N (%)
Medical direct costs			
Medicare reimbursement	15 (30.6)	5 (10.2)	10 (20.4)
Medicare reimbursement+Raw data[c]	10 (20.4)	3 (6.1)	7 (14.3)
Raw data	9 (18.4)	4 (8.2)	5 (10.2)
Medicare reimbursement+SR[d]	8 (16.3)	1 (2.0)	7 (14.3)
SR	4 (8.2)		4 (8.2)
SR+Medicare reimbursement+Raw data	2 (4.1)		2 (4.1)
SR+Raw data	1 (2.0)		1 (2.0)
Total	49 (100.0)	13 (26.5)	36 (73.5)
Non-medical direct costs			
Traffic charge	1 (2.0)		1 (2.0)
Not included	48 (98.0)	13 (26.5)	35 (71.4)
Total	49 (100.0)	13 (26.5)	36 (73.5)
Indirect costs			
Productivity loss[e]	12 (24.5)		12 (24.5)
Expenses related to death	3 (6.1)	1 (2.0)	2 (4.1)
Productivity loss+Expenses related to death	1 (2.0)		1 (2.0)
Not included	33 (67.3)	12 (24.5)	21 (42.9)
Total	49 (100.0)	13 (26.5)	36 (73.5)

CA: cost analysis, CEA: cost-effectiveness analysis, CMA: cost-minimization analysis, CUA: cost-utility analysis, N: number, SR: systematic review
[a]CA and CMA studies are presented in a single column, since both evaluation methods compare the costs of the intervention.
[b]CEA and CUA studies are presented in a single column, since both evaluation methods compare the effectiveness of the intervention.
[c]Clinical trial, registry, or single hospital data.
[d]SR for medical direct costs.
[e]Loss of work/revenue/production caused by the unavailability of an employee for any reason.

studies, 15 studies used Medicare reimbursement as a data source of medical direct costs; 10 studies used combinations of Medicare reimbursement and raw data; 9 studies used raw data alone; 8 studies used combinations of Medicare reimbursement and SR; 4 studies used SR; 2 studies used combinations of SR, Medicare reimbursement data, and raw data; and 1 study used SR in combination with raw data. In addition to medical direct cost data sources, reporting of non-medical direct costs was reviewed. Only 1 study among the 49 economic evaluation studies reported non-medical direct costs, involving transportation expenses. Reporting of indirect costs was also reviewed; it included expenses related to death and productivity loss. Productivity loss was reported in 12 studies, expenses related to death were reported in 3 studies, and productivity loss in combination with expenses related to death was reported in 1 study, comprising 16 of the 49 studies. Non-medical direct costs and indirect costs were not measured in most of the studies, and data sources were not presented in most cases.

Data Sources of Clinical and Non-clinical Outcomes

The data sources of clinical and non-clinical outcomes used in the economic evaluation studies are listed in Table 5. Clinical outcomes included complications from thyroid surgery, recurrence-free survival, overall survival, progression-free survival, disease-free survival, cancer-specific mortality, optimal nodule management, long-term treatment/follow-up, hospital stay, surgery time, tumor progression or spread, diagnostic accuracy, successful ablation rate, detection of medullary thyroid carcinoma at early stages, secondary cancer diagnosis, cancer detection rate, recurrence

Table 5. Data sources in economic evaluation studies of clinical outcomes for thyroid cancer

Type of outcomes	CA N (%)	CMA N (%)	CEA N (%)	CUA N (%)
Clinical outcomes				
Non-SR-based literature review	-	-	5 (83.3)	26 (74.3)
Clinical trial	-	-	-	5 (14.3)
Prospective or retrospective cohort	-	1 (12.5)	1 (16.7)	1 (2.9)
Not certified	5 (100.0)	7 (87.5)	-	3 (8.6)
Total	5 (100.0)	8 (100.0)	6 (100.0)	35 (100.0)
Non-clinical outcomes				
Non-SR-based literature review	-	1 (11.1)	4 (44.4)	26 (78.8)
Medicare reimbursement	4 (66.7)	6 (66.7)	3 (33.3)	-
Raw data[a]	1 (16.7)	2 (22.2)	2 (22.2)	5 (15.2)
Expert opinions	-	-	-	1 (3)
Not certified	1 (16.7)	-	-	1 (3)
Total	6 (100.0)[b]	9 (100.0)[b]	9 (100.0)[b]	33 (100.0)[b]

CA: cost analysis, CEA: cost-effectiveness analysis, CMA: cost-minimization analysis, CUA: cost-utility analysis, N: number, SR: systematic review

[a]Clinical trial, registry, or single hospital data.

[b]Total number exceeds the number of studies owing to studies having more than one data source.

with delayed diagnosis, and quality of life. Most of the clinical outcomes were derived from non-SR based literature reviews, followed by clinical trials and prospective or retrospective cohort studies. Non-clinical outcomes included costs, incremental increases in costs, ICERs, cost-effectiveness ratios, utility, incremental cost-utility ratios, and life-year gained and QALY values. Most of the non-clinical outcomes were derived from non-SR based reviews, followed by medical reimbursement data, raw clinical trial, registry, and single hospital data, and expert opinions.

Discussion

The growing economic burden of thyroid cancer justifies the need for economic evaluation in this area. Contributions from the field of economics can support relevant decision-making processes, but economic evaluation studies focusing on the management of thyroid cancer are limited. In this review, we identified 49 thyroid cancer-related economic evaluation studies that showed a wide variety of methodological approaches on various topics. A comprehensive review of these studies found several aspects to consider when conducting or interpreting economic evaluation research on thyroid cancer.

Notably, "CEA" as defined by the authors may include "CUA" in the strictest sense; among the 29-thyroid cancer-related CEA studies defined as such by the authors, 23 were re-classified in this study as CUA studies. This means that most studies classified as CUA studies share the same evaluation methods as studies classified as CEA studies. Based on the authors' definition, the number of CA, CMA, CEA, and CUA studies was 9, 3, 29, and 8, respectively. When the reviewers' definition was applied, a significant number of studies (31/49, 63%) were re-classified, as follows: 5 CA, 8 CMA, 6 CEA, and 30 CUA studies. The traditional classification of economic evaluation includes CMA, CEA, CUA, and CBA.[33] The measurement of costs is similar across all economic evaluation methods, but the outcome variables and their measuring methods differ.[33] CBA is rarely used in healthcare evaluation owing to the difficulty in assigning a monetary value to clinical results, and no studies used CBA in the context of patients with thyroid cancer.[34]

Applying different types of economic evaluation to the same topic can lead to contrasting results.[13-15] The choice of a particular type of economic evaluation depends on the nature of the expected health effects of the interventions under study. For example, if the intervention is expected to have a major effect on health-related quality of life, CUA must be used, where the health outcome is measured in terms of a patient's length of life weighted by a valuation of the health-related quality of life. However, if health-related quality of life is not being assessed as a relevant health effect of the interventions studied, CEA is the required form of economic evaluation where the health outcome is measured by length of life. Shrime et al.,[13] Lang and Wong,[14] and Al-Qurayshi et al.[15] compared the cost-effectiveness of HT and TT for low-risk PTC. Shrime et al.[13] reported that TT was substantially preferred over HT as an initial treatment using CEA, whereas Lang and Wong[14] and Al-Qurayshi et al.[15] reported that HT was more cost-effective than TT in low-risk PTC patients using CUA.[13-15] In this regard, in the process of interpreting and selecting economic evaluation studies for decision-making on controversial issues, it is important to be aware of how outcomes in relation to certain issues are reflected in differing studies and to ensure that the relevant outcomes are identified and considered.

One of the main challenges in economic evaluations is deciding which costs should be included and how these costs should be measured and valued. All the studies in our analysis included direct costs, with 71% of the studies using Medicare reimbursement as a data source. Moreover, 33% of the studies included indirect costs, with most studies focusing on loss of productivity.[11,13,15,21,22,24,28-32,35-39] Productivity loss may be temporary, such as taking time off to undergo treatment, or it may be permanent due to early retirement. While it is an important component in considering the social burden of cancer, the most appropriate methods and instruments for estimating productivity loss remain an area of considerable debate. Our study found that the value of productivity loss in thyroid cancer-related economic evaluation studies was most commonly determined using public statistics, literature reviews, and assumptions (Supplementary Tables 3-6).

We also found that input probabilities for models and utility scores for outcomes were mostly based on literature reviews. For example, Lang and Wong[18] compared cost-effectiveness between early surgery and a non-surgical approach in managing incidental micro-PTC. The probabilities for progression using a non-surgical approach and for recurrence were obtained from four previous observational studies. It is possible that the progression or recurrence rate may change as more validation studies are performed. In addition, in that study, utility scores for healthy status determined using a Markov decision tree model were extracted from a previous study.[18] Probabilities and utility scores depend on clinical settings. Therefore, obtaining these data from a prospective cohort and applying them to analysis is likely to help with establishing cost-effective guidelines for thyroid cancer, considering regional characteristics.

Through this study, we identified 49 thyroid cancer-related economic evaluation studies undertaken over 15 years up to May 2021 and critically evaluated the application of economic analysis to thyroid cancer. Most studies inevitably dealt with specific controversial issues as they arose, with CEA and CUA studies often used without a clear distinction. Direct medical costs were mostly calculated based on Medicare or insurance-based reimbursement data in order to obtain objectiveness in economic evaluation results through excluding the impact on the delivery system or each hospital for each medical institution by country. Input probabilities for models and utility scores for outcomes were mostly based on literature reviews. However, most economic assessment studies on patients with thyroid cancer did not include non-medical direct costs and indirect costs. In particular, they were limited in comparing the economic burden in relation to an intervention involving thyroid cancer patients, because the total illness costs for patients with thyroid cancer could be underestimated if non-medical direct costs are not considered. We also found that contrasting results may be obtained when different economic evaluations, and different clinical and economic inputs are applied for the same topic. Even though CUA and CEA were considered the same method, there was only 77% (weighted Kappa index) consistency across these studies. This finding suggests that it is important to choose an economic assessment method suitable for the precise topic under consideration.

Therefore, our SR provides relevant information on determining research methods and overcoming limitations of existing research. It will also help decision-makers with limited resources in choosing more cost-efficient interventions through facilitating appropriate estimation.

Supplementary Materials

Supplementary data is available at https://doi.org/10.11106/ijt.2022.15.2.74.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conception or design: M.K., W.L., K.K., B.H.K., S.K.P. Acquisition, analysis, or interpretation of data: M.K., W.L., K.K., B.H.K., S.K.P. Drafting the work or revising: M.K., W.L., B.H.K., S.K.P. Final approval of the manuscript: M.K., W.L., K.K., J.S.B., B.J.L., B.S.K., E.K.L., E.J.K., J.Y.C., B.H.K., S.K.P. Obtained funding: B.H.K.

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References

1) Siegel RL, Miller KD, Jemal A. *Cancer statistics, 2018. CA Cancer J Clin 2018;68(1):7-30.*
2) Kitahara CM, Sosa JA. *The changing incidence of thyroid cancer. Nat Rev Endocrinol 2016;12(11):646-53.*
3) Choi YM, Kim WG, Kwon H, Jeon MJ, Han M, Kim TY, *et al*. *Changes in standardized mortality rates from thyroid cancer in Korea between 1985 and 2015: analysis of Korean national data. Cancer 2017;123(24):4808-14.*
4) Yoon J, Park B. *Factors associated with health behaviors in thyroid cancer survivors. J Cancer Prev 2020;25(3):173-80.*
5) Hong S, Won YJ, Park YR, Jung KW, Kong HJ, Lee ES, *et al*. *Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2017. Cancer Res Treat 2020;52(2):335-50.*
6) Krajewska J, Kukulska A, Oczko-Wojciechowska M, Kotecka-Blicharz A, Drosik-Rutowicz K, Haras-Gil M, *et al*. *Early diagnosis of low-risk papillary thyroid cancer results rather in overtreatment than a better survival. Front Endocrinol (Lausanne) 2020;11:571421.*
7) Kim K, Kim M, Lim W, Kim BH, Park SK. *The concept of economic evaluation and its application in thyroid cancer research. Endocrinol Metab (Seoul) 2021;36(4):725-36.*
8) Bae JM. *Strategies for appropriate patient-centered care to decrease the nationwide cost of cancers in Korea. J Prev Med Public Health 2017;50(4):217-27.*
9) 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):1-133.*
10) Tuttle RM. *Controversial issues in thyroid cancer management. J Nucl Med 2018;59(8):1187-94.*
11) Lubitz CC, Kong CY, McMahon PM, Daniels GH, Chen Y, Economopoulos KP, *et al*. *Annual financial impact of well-differentiated thyroid cancer care in the United States. Cancer 2014;120(9):1345-52.*
12) Ngorsuraches S. *Defining types of economic evaluation. J Med Assoc Thai 2008;91 Suppl 2:S21-7.*
13) Shrime MG, Goldstein DP, Seaberg RM, Sawka AM, Rotstein L, Freeman JL, *et al*. *Cost-effective management of low-risk papillary thyroid carcinoma. Arch Otolaryngol Head Neck Surg 2007;133(12):1245-53.*
14) Lang BH, Wong CKH. *Lobectomy is a more cost-effective option than total thyroidectomy for 1 to 4 cm papillary thyroid carcinoma that do not possess clinically recognizable high-risk features. Ann Surg Oncol 2016;23(11):3641-52.*
15) Al-Qurayshi Z, Farag M, Shama MA, Ibraheem K, Randolph

GW, Kandil E. *Total thyroidectomy versus lobectomy in small nodules suspicious for papillary thyroid cancer: cost-effectiveness analysis. Laryngoscope 2020;130(12):2922-6.*
16) Oda H, Miyauchi A, Ito Y, Sasai H, Masuoka H, Yabuta T, *et al*. *Comparison of the costs of active surveillance and immediate surgery in the management of low-risk papillary microcarcinoma of the thyroid. Endocr J 2017;64(1):59-64.*
17) Lin JF, Jonker PKC, Cunich M, Sidhu SB, Delbridge LW, Glover AR, *et al*. *Surgery alone for papillary thyroid microcarcinoma is less costly and more effective than long term active surveillance. Surgery 2020;167(1):110-6.*
18) Lang BH, Wong CK. *A cost-effectiveness comparison between early surgery and non-surgical approach for incidental papillary thyroid microcarcinoma. Eur J Endocrinol 2015;173(3):367-75.*
19) Venkatesh S, Pasternak JD, Beninato T, Drake FT, Kluijfhout WP, Liu C, *et al*. *Cost-effectiveness of active surveillance versus hemithyroidectomy for micropapillary thyroid cancer. Surgery 2017;161(1):116-26.*
20) Lang BH, Wong CK. *A cost-minimization analysis comparing total thyroidectomy alone and total thyroidectomy with prophylactic central neck dissection in clinically nodal-negative papillary thyroid carcinoma. Ann Surg Oncol 2014;21(2):416-25.*
21) Zanocco K, Elaraj D, Sturgeon C. *Routine prophylactic central neck dissection for low-risk papillary thyroid cancer: a cost-effectiveness analysis. Surgery 2013;154(6):1148-55; discussion 54-5.*
22) Garcia A, Palmer BJ, Parks NA, Liu TH. *Routine prophylactic central neck dissection for low-risk papillary thyroid cancer is not cost-effective. Clin Endocrinol (Oxf) 2014;81(5):754-61.*
23) Wong CK, Lang BH. *A cost-utility analysis for prophylactic central neck dissection in clinically nodal-negative papillary thyroid carcinoma. Ann Surg Oncol 2014;21(3):767-77.*
24) Najafzadeh M, Marra CA, Lynd LD, Wiseman SM. *Cost-effectiveness of using a molecular diagnostic test to improve preoperative diagnosis of thyroid cancer. Value Health 2012; 15(8):1005-13.*
25) Lee L, How J, Tabah RJ, Mitmaker EJ. *Cost-effectiveness of molecular testing for thyroid nodules with atypia of undetermined significance cytology. J Clin Endocrinol Metab 2014;99(8): 2674-82.*
26) Nicholson KJ, Roberts MS, McCoy KL, Carty SE, Yip L. *Molecular testing versus diagnostic lobectomy in Bethesda III/IV thyroid nodules: a cost-effectiveness analysis. Thyroid 2019;29(9): 1237-43.*
27) Balentine CJ, Vanness DJ, Schneider DF. *Cost-effectiveness of lobectomy versus genetic testing (Afirma(R)) for indeterminate thyroid nodules: considering the costs of surveillance. Surgery 2018;163(1):88-96.*
28) Borget I, Bonastre J, Catargi B, Deandreis D, Zerdoud S, Rusu D, *et al*. *Quality of life and cost-effectiveness assessment of radioiodine ablation strategies in patients with thyroid cancer: results from the randomized phase III ESTIMABL trial. J Clin Oncol 2015;33(26):2885-92.*
29) Mernagh P, Suebwongpat A, Silverberg J, Weston A. *Cost-effectiveness of using recombinant human thyroid-stimulating hormone before radioiodine ablation for thyroid cancer: the Canadian perspective. Value Health 2010;13(2):180-7.*
30) Mernagh P, Campbell S, Dietlein M, Luster M, Mazzaferri E, Weston AR. *Cost-effectiveness of using recombinant human TSH prior to radioiodine ablation for thyroid cancer, compared with treating patients in a hypothyroid state: the German perspective. Eur J Endocrinol 2006;155(3):405-14.*
31) Vallejo JA, Muros MA. *Cost-effectiveness of using recombinant human thyroid-stimulating hormone before radioiodine ablation for thyroid cancer treatment in Spanish hospitals. Rev Esp Med Nucl Imagen Mol 2017;36(6):362-70.*
32) Wang TS, Cheung K, Mehta P, Roman SA, Walker HD, Sosa JA. *To stimulate or withdraw? A cost-utility analysis of recombinant human thyrotropin versus thyroxine withdrawal for radioiodine ablation in patients with low-risk differentiated thyroid cancer in the United States. J Clin Endocrinol Metab 2010;95(4):1672-80.*
33) Goldsmith LJ, Hutchison B, Hurley FJ. *Economic evaluation across the four faces of prevention. Hamilton, Ontario: Centre for Health Economics and Policy Analysis, McMaster University; 2004.*
34) Sculpher MJ, Price M. *Measuring costs and consequences in economic evaluation in asthma. Respir Med 2003;97(5):508-20.*
35) Wilson L, Huang W, Chen L, Ting J, Cao V. *Cost effectiveness of lenvatinib, sorafenib and placebo in treatment of radioiodine-refractory differentiated thyroid cancer. Thyroid 2017;27(8): 1043-52.*
36) Zanocco K, Heller M, Elaraj D, Sturgeon C. *Cost effectiveness of intraoperative pathology examination during diagnostic hemithyroidectomy for unilateral follicular thyroid neoplasms. J Am Coll Surg 2013;217(4):702-10.*
37) Rocke DJ, Goldstein DP, de Almeida JR. *A cost-utility analysis of recurrent laryngeal nerve monitoring in the setting of total thyroidectomy. JAMA Otolaryngol Head Neck Surg 2016; 142(12):1199-205.*
38) Lee WS, Palmer BJ, Garcia A, Chong VE, Liu TH. *BRAF mutation in papillary thyroid cancer: a cost-utility analysis of preoperative testing. Surgery 2014;156(6):1569-77; discussion 77-8.*
39) Leiker AJ, Yen TW, Cheung K, Evans DB, Wang TS. *Cost analysis of thyroid lobectomy and intraoperative frozen section versus total thyroidectomy in patients with a cytologic diagnosis of "suspicious for papillary thyroid cancer". Surgery 2013; 154(6):1307-13; discussion 13-4.*