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ORIGINAL ARTICLE

A cost-utility analysis for prophylactic central neck dissection in clinically-nodal negative papillary thyroid carcinoma

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SYNOPSIS

Routine prophylactic central neck dissection for low-risk papillary thyroid carcinoma at the time of total thyroidectomy is more cost-effective than total thyroidectomy alone in the long term and it begins to become cost-effective from 9 years onwards.

ABSTRACT

Background

Although prophylactic central neck dissection (pCND) may reduce future locoregional recurrence after total thyroidectomy (TT) for low-risk papillary thyroid carcinoma (PTC), it is associated with a higher initial morbidity. We aimed to compare the long-term cost-effectiveness between TT with pCND (TT+pCND) and TT-alone in the institution's perspective.

Methods

Our case definition was a hypothetical cohort of 100,000 non-pregnant female patients aged 50 year-old with a 1.5cm cN0 PTC within one lobe. A Markov decision tree model was constructed to compare the estimated cost-effectiveness between TT+pCND and TT-alone after a 20-year period. Outcome probabilities, utilities and costs were estimated from the literature. The threshold for cost-effectiveness was set at USD50,000/quality-adjusted life year (QALY). Sensitivity and threshold analyses were used to examine model uncertainty.

Results

Each patient who underwent TT+pCND instead of TT-alone cost an extra USD34.52 but gained an additional 0.323 QALY. In fact, in the sensitivity analysis, TT+pCND became cost-effective 9 years after initial operation. In the threshold analysis, none of the scenarios that could change this conclusion appeared clinically possible or likely. On the other hand, TT+pCND became cost-saving (i.e. less costly and more cost-effective) at 20-year if associated permanent vocal cord palsy was kept ≤1.37%, permanent hypoparathyroidism ≤1.20% and/or postoperative radioiodine (RAI) ablation use was ≤ 73.64%.

Conclusions

In the institution's perspective, routine pCND for low-risk PTC began to become cost-effective 9 years after initial surgery and became cost-saving at 20-year if postoperative RAI use and/or permanent surgically complications were kept to a minimum.

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common type of thyroid carcinoma with its incidence doubled over the last two decades.[1-4] However, despite good prognosis, locoregional recurrence (LR) is relatively common after curative surgery.[5] With recognition of the step-wise progression of metastasis from central (level VI) to lateral compartments (levels II-V), routine prophylactic central neck dissection (pCND) has been advocated at the time of total thyroidectomy (TT) to minimize LR.[6-8] Although central neck dissection (CND) is indicated in clinically-nodal positive disease, it remains controversial in clinically-nodal negative disease (cN0).[9] There is little evidence to suggest patients with cN0 PTC would benefit from pCND at the time of TT (TT+pCND). Although a recent meta-analysis reported a 35% reduction in LR in the TT+pCND group, it was at the expense of higher morbidity.[10]

Given that conducting an adequately-powered prospective, randomized trial comparing outcomes between TT+pCND and TT-alone is unlikely in the near-future and cost-effectiveness is an important outcome measurement between two different procedures or strategies,[11] we aimed to determine which is a more cost-effective strategy in the long-term. To our knowledge, there has only been one study which specifically compared the cost-effectiveness between the two surgical strategies.[12] It concluded that TT+pCND was less cost-effective than TT-alone.[12] However, the literature search was limited and the quality adjustment factors used came from non-thyroid disease. Furthermore, as acknowledged by the authors, some operative complications were omitted and that omission might have favored the TT-alone strategy.[12] Given these findings, we used a decision-tree analysis model to compare the medium to long-term cost-effectiveness between the two strategies, namely TT+pCND and TT-alone in a reference population with biopsy-proven cN0 PTC.

MATERIALS AND METHODS

Case definition

A hypothetical cohort of 100,000 non-pregnant female patients aged 50 year-old with an unifocal intrathyroidal 1.5cm cN0 PTC and with no previous thyroidectomy or neck irradiation was simulated in the model.

The model

A decision tree model using TreeAge Software Pro version 2013 (Treeage Software, Inc., Williamstown, MA, US) was constructed to compare the estimated long-term cost-effectiveness between TT+pCND and TT-alone. Appendix 1 outlines the Markov decision model over one year. Patients underwent one of two surgical strategies, namely TT+pCND or TT-alone, and were followed until death or 70 years-old whichever came earlier. The model included 3 major health states after primary operation, namely disease-free, alive with LR and death. In case of LR involving the central, lateral or central & lateral compartments, a compartment-oriented reoperation and RAI were offered. Patient in either strategy may suffer one of the surgical complications from the primary operation or reoperation.

Probabilities

Estimates of complications from primary operation, postoperative RAI and central and/or lateral recurrences after primary operation came from the available literature.[8,9,18,19,23-29] Studies were limited to those which directly compared outcomes between the two strategies in cN0 PTC. Estimates of complications from reoperation and death from non-thyroid causes came from separate PubMed literature searches.[13-19] Base-case values were derived by pooling the results of all retrieved studies. The annual mortality rate of female patients by 10-year age groups was quoted from the US Centers for Disease Control and Prevention.[20] Table 1 summarizes outcome probabilities used.

Cost data

Our model only looked at the cost of two strategies from an institution's perspective. Total cost included procedural cost, complication cost, and hospitalization. Indirect costs such as loss of productivity and wages were not included. Unit costs of TT and, initial pCND were estimated based on Medicare reimbursement for surgical procedure obtained from public access file from Centers for Medicare and Medicaid Services.[21-23] Unit costs of other surgical procedures (such as reoperative CND and reoperative lateral selective neck dissection), RAI, surgically-related complications and annual routine surveillance were based on data obtained from previous cost-effectiveness analyses.[24,25] For the reoperative cases, the procedural cost already included the cost of fine needle aspiration. Table 1 summarizes the unit costs used.

Effectiveness data

Effectiveness was measured by quality-adjusted life years (QALYs) gained. QALY adjusts the life-expectancy through the multiplication of quality of life adjustment with duration stayed at each health state. The quality of life adjustment is quantified by a utility score ranging from zero to one. Table 1 lists the utility score for each health state.

Assumptions

All pCNDs were assumed unilateral only and surgical resection was the only option for LR involving the different compartments. The LR rates under each strategy were assumed constant throughout the life cycle. Patients were assumed suitable and agreed for reoperation. For simplicity, only a maximum of one LR and one reoperation per patient were allowed. Similarly, only one complication was allowed for each primary operation or reoperation. Reoperative CND was assumed bilateral while reoperative lateral CND was assumed unilateral involving levels II-V. An empirical 3GBq RAI was given after each reoperation. The costs of preoperative assessment and surveillance were assumed the same in both groups. Full compliance was assumed for all kinds of assessment, treatment and surveillance.

Base-case analysis

All the cost and effectiveness were discounted by an annual rate of 3%. This was consistent with the established guideline for cost-effectiveness analysis [26]. The only outcome measurement was the incremental cost-effectiveness ratio (ICER). The ICER was the cost difference between TT+pCND and TT-alone divided by the difference in effectiveness between TT+pCND and TT-alone. A positive incremental cost meant TT+pCND was more costly while a positive effectiveness meant the TT+pCND was more effective. A strategy was said to be "cost-saving" if that strategy cost less and more effective over the other strategy (i.e. that strategy was dominant). The TT+pCND was regarded cost-effective if the ICER was below the threshold of USD50,000 per QALY gained, which was chosen as the threshold for cost-effectiveness based on analysis of the cost of current healthcare resource allocation decisions in the United states.[26].

Sensitivity analysis

Univariate sensitivity analysis was performed to evaluate the impact of various outcome probabilities on the base-case analysis. Each clinical parameter varied from the lowest to the highest values as suggested in the literature while other parameters remained constant. Since TT+pCND would cost more than TT-alone, a negative incremental effectiveness meant TT-alone was dominant. In the multivariate sensitivity analysis, total morbidity was assumed the same between the two strategies. A threshold analysis was undertaken to capture the threshold clinical values at which the ICER of TT+pCND relative to TT-alone became zero (cost equivalence) or infinity (QALY equivalence). The range of threshold analysis was considerably expanded by adopting the theoretical range from 0 to 100%.

RESULTS

Base-case analysis

Table 2 shows the results of base-case analysis. After a 20-year period, each patient in TT+pCND spent an extra USD34.25 but also gained an additional 0.323 QALY over TT-alone. Therefore, following the base-case assumptions and model inputs, the TT+pCND was more costly but was also more effective than TT-alone in the institution's perspective. The ICER of USD105.97 for TT+pCND relative to TT-alone was far below the recommended threshold of USD50,000 per QALY.

Sensitivity analysis

Table 2 shows the univariate and multivariate sensitivity analyses. No change in the conclusion was observed when key parameters such as complication rates and RAI were varied. Varying these parameters still yielded positive ICERs implying TT+pCND remained cost-effective or cost-saving. TT-alone only became cost-effective when annualized central or central & lateral recurrence rates under this strategy decreased to zero or when the annualized central or lateral recurrence rates under the TT+pCND strategy increased to 0.82% and 1.57%, respectively. Varying the number of year-cycles or discount rate did not change the conclusion. Figure 1 shows the changes in ICER for TT+pCND relative to TT-alone over a 50-year period. ICER reached below the threshold of USD 50,000 per QALY starting from 9 years onwards. In the multivariate sensitivity analysis, regardless of the actual value, so long as both strategies had equal total morbidity, TT+pCND was favored. Table 3 shows the results of the threshold analysis. To make TT-alone cost-saving, there were 7 possible scenarios. They were annualized central recurrence in TT-alone reduced from 0.63% to ≤0.17%, annualized central & lateral recurrence in TT-alone reduced 0.56% to ≤0.08%, permanent VCP in TT+pCND increased from 1.70% to ≥6.61%, permanent hypoparathyroidism in TT+pCND increased from 1.47% to ≥6.38%, annualized central recurrence in TT+pCND increased from 0.22% to ≥0.71%, annualized lateral recurrence in TT+pCND from 0.36% to ≥1.03% or annualized central & lateral recurrence in TT+pCND increased from 0.29% to ≥0.94%. On the other hand,

there were many more possible scenarios to render TT+pCND cost-saving. However, in terms of surgical morbidity, TT+pCND became cost-saving if the associated permanent VCP could be kept ≤1.37% or the permanent hypoparathyroidism could be kept ≤1.20%. TT+pCND was also cost-saving when postoperative RAI use was reduced from 76.87% to ≤73.64%.

DISCUSSION

Performing routine pCND at the time of TT for cN0 PTC is controversial and this is reflected in the revised ATA guideline that recommends pCND "may be performed in patients with clinically uninvolved central neck lymph nodes especially for advanced primary tumors (T3 or T4)".[9] Unlike studies that compared surgical outcomes, [27-29] our study aimed to compare the long-term cost-effectiveness between the two strategies. To our knowledge, there has only been one published study that compared cost-effectiveness and in that study, the authors concluded that TT+pCND was more costly and less effective (i.e. less cost-effective) than TT-alone.[12] In contrast, although we did find TT+pCND to be more costly, it was more effective in the longer term. In our base analysis, TT+pCND was more cost-effective than TT-alone at 20 years. The ICER of TT+pCND relative to TT-alone was USD105.97/QALY which was well below the recommended threshold of USD50,000 per QALY and from the sensitivity analysis, the ICER reached below the recommended threshold 9 years after surgery (see Figure 1). These findings could be explained by the fact that patients in TT+pCND suffered less LR over time (see Figure 2) and that led to fewer expensive reoperations, fewer reoperation complications and gain in QALY over time. However, our study had some notable differences from the previous study.[12] Firstly, outcome probabilities were derived from a comprehensive literature search. Secondly, our quality adjustment factors or utility scores were derived from studies on thyroid disease only. Thirdly, to provide a more realistic model, each LR was categorized into one of three locations, namely central, lateral and central & lateral compartments as each compartment-oriented reoperation is associated with its own unique outcomes and costs. Fourthly, instead of assuming the overall life-time recurrence risk as the total recurrence risk over the first 5 years, we annualized recurrence risk based on each of three compartments from previous studies.

Clinical implications

Based on our analyses, there are several implications relevant to clinicians. Firstly, since TT+pCND only becomes cost-effective 9 years after surgery, it is probably not worthwhile to perform pCND

on patients with a life-expectancy < 9 years (such as those in the elderly or with life-limiting co-morbidities) because cost-effectiveness is not going to be achievable. Secondly, our data forces each individual surgeon to consider what difference he or she could achieve by adding pCND at the time of TT. Our model showed that TT+pCND is cost-effective if it could reduce the 10-year LR rate by 7% or 0.7% per year (from 1.57% to 0.87%) and so for a lower risk reduction, TT+pCND would be less or even become not cost-effective. Thirdly, our data suggests that permanent surgical morbidities from TT+pCND play a significant role on the cost-effectiveness of TT+pCND. Based on our analyses, TT+pCND is only cost-effective if the associated permanent VCP could be kept <2.51% or permanent hypoparathyroidism <5.88% and so if any one of these permanent surgical morbidities is higher, TT-alone could become cost-saving (see Table 3).

From the threshold analyses, although there were 7 possible scenarios which could render TT-alone cost-saving, they were either clinically impossible or unlikely to happen. Five of them were considered clinically impossible because all involved having annualized central or central & lateral compartment recurrences in TT-alone less than in TT+pCND (0.17% vs. 0.22% and 0.08% vs. 0.29%, respectively) and vice versa. However, since TT+pCND is already a TT, it could not possibly have a higher LR rate. The other 2 scenarios were clinically possible but unlikely. The first was if permanent VCP rate under the TT+pCND strategy increased from 1.70% to ≥6.61% while under the TT-alone strategy was kept at 1.22%. Although this was possible because pCND involved greater surgical dissection around the recurrent laryngeal nerve (RLN), an experienced surgeon is unlikely to cause a 3.9 times higher RLN injury rate than the same procedure without pCND. Similarly, an experienced surgeon is unlikely to cause a 7.5 times higher permanent hypoparathyroidism rate than the same procedure without pCND (≥6.38% vs. 0.85%).

However, despite these results, we do acknowledge several shortcomings. Firstly, some of the assumptions might have been over-simplified. For example, in many centers, not every patient with proven LR requires treatment and even if treatment is indicated, there are other non-surgical options such as ethanol injection or radiofrequency ablation. Therefore, the actual cost of reoperations

under both strategies might actually be substantially less and that would have favored TT-alone in the long-term. Furthermore, there is data to suggest that the LR rate is probably non-linear and is high only during the initial 5-10 years.[30] Therefore, our model might have over-estimated the difference in LR between the two strategies and favored TT+pCND over time. Another example of over-simplification was to assume one LR followed by one reoperation per patient as up to 10% of patients with first-time LR are expected to require more than one reoperations.[31,32] However, given the higher risk of LR in TT-alone, this would have further favored the TT+pCND strategy. Secondly, despite a comprehensive literature search, selection and publication biases could not be completely ruled out as none of the studies examined were prospective randomized studies.

CONCLUSION

In the institution's perspective, TT+pCND was more cost-effective than TT-alone for low-risk PTC in the long-term. It began to become cost-effective after 9 years from initial operation and this was due to fewer LR and reoperations over time. Although there were 7 possible clinical scenarios which might have rendered TT-alone cost-saving, none were clinically possible. TT+pCND became cost-saving at 20-year if associated permanent vocal cord palsy was ≤1.37%, permanent hypoparathyroidism was ≤1.20% and / or postoperative radioiodine (RAI) ablation use was ≤ 73.64%.

Table 1. Literature-based probabilities, unit cost (USD) for each service component for the care of papillary thyroid carcinoma patients and utility score for each health state in model

Clinical Parameters	**Base case (%)**	**Range for sensitivity analysis (%)**	**Reference**
Complications from the primary operation			
- Temporary vocal cord palsy			
- Total thyroidectomy alone	3.10	0.00 – 6.38	7,8,28,29,33-39
- Total thyroidectomy + prophylactic CND	3.28	0.00 – 7.26	7,8,28,29,33-39
- Permanent vocal cord palsy			
- Total thyroidectomy alone	1.22	0.00 – 2.74	7,8,28,33-38
- Total thyroidectomy + prophylactic CND	1.70	0.0 – 2.51	7,8,28,33-38
- Temporary hypoparathyroidism			
- Total thyroidectomy alone	7.73	4.03 – 33.63	7,8,28,29,33-39
- Total thyroidectomy + prophylactic CND	20.64	8.70 – 42.86	7,8,28,29,33-39
- Permanent hypoparathyroidism			
- Total thyroidectomy alone	0.85	0.00 – 8.11	7,8,29,33-39
- Total thyroidectomy + prophylactic CND	1.47	0.0 – 5.88	7,8,29,33-39
- Hematoma formation requiring reoperation			
- Total thyroidectomy alone	0.99	0.00 – 3.08	7,8,28,29,33,35-37
- Total thyroidectomy + prophylactic CND	1.79	0.00 – 2.50	7,8,28,29,33,35-37
- Total morbidity*			

- Total thyroidectomy alone	13.89		
- Total thyroidectomy + prophylactic CND	28.88		
Complications from reoperative CND			
- Temporary unilateral VCP	4.04	1.59 – 22.22	13-17
- Temporary bilateral VCP / tracheostomy	0.16	0.03 – 4.94	13-17
- Permanent unilateral VCP	2.70	0.00 – 17.78	13-17
- Permanent bilateral VCP / tracheostomy	0.07	0.00 – 3.16	13-17
- Temporary hypoparathyroidism	17.14	6.06 – 42.22	13-18
- Permanent hypoparathyroidism	1.70	0.00 – 5.00	13-18
- Hematoma	1.10	0.00 – 4.35	13-17
- Chyle leakage	1.80	0.00 – 2.22	13-15
- Total morbidity*	28.71		
Complications from lateral selective neck dissection			
- Chyle leakage	5.51	5.8 – 5.83	19,27
Annualized locoregional recurrence rate			
- Central compartment only			
- Total thyroidectomy alone	0.63	0.00 – 1.83	7,8,28,29,33-39
- Total thyroidectomy + prophylactic CND	0.22	0.00 – 0.82	7,8,28,29,33-39
- Lateral compartment only			
- Total thyroidectomy alone	0.38	0.00 – 3.73	7,8,28,29,33-39
- Total thyroidectomy + prophylactic CND	0.36	0.00 – 1.57	7,8,28,29,33-39
- Central and lateral compartments			
- Total thyroidectomy alone	0.56	0.00 – 1.87	7,8,28,29,33-39

- Total thyroidectomy + prophylactic CND	0.29	0.00 – 0.41	7,8,28,29,33-39
- Overall locoregional recurrence rate			
- Total thyroidectomy alone	1.57		
- Total thyroidectomy + prophylactic CND	0.87		
Likelihood of RAI after primary operation			
- Total thyroidectomy alone	53.44	28.01 – 100.00	7,8,29,35-38,40,41
- Total thyroidectomy + prophylactic CND	76.87	58.09 – 100.00	7,8,29,35-38,40,41
Number of deaths per 1000 population			20
-50 – 54	3.1		
-55 – 64	6.4		
-65 – 74	15.3		
-75 – 84	41.4		
-85+	132.2		
Service component for the care of PTC patients	**Unit cost in USD**		**Reference**
Surgical procedure			
- Total thyroidectomy	5500		21-23
- Central neck dissection (initial)	513		21-23
- Central neck dissection (reoperative)	6482		24
- Lateral selective neck dissection (reoperative)	6482		24
RAI ablation	1060		24
- Specialist consult, blood tests (TSH, Tg, Anti-Tg abs),			

recombinant TSH injections, RAI (3.3 Gbq) ablation, hospital stay (2 nights), post-treatment whole body scan		
Complications from primary operation or reoperation		
Temporary VCP+ - Otolaryngology consult, laryngoscopy, follow-up visit, speech therapy	564	24
Permanent VCP# - Otolaryngology consult, laryngoscopy, follow-up visit, speech therapy, vocal cord medialization	10367	25
Tracheostomy for VCP	22049	24
Tracheostomy for permanent VCP (annual cost)	592	24
Temporary hypoparathyroidism+ - Follow-up visits, blood tests, medications	144	25
Permanent hypoparathyroidism (annual cost)# - Follow-up visits, blood tests, medications	863	25
Chyle leak*	15404	24
Hematoma requiring neck re-exploration	5754	21-23
Routine Surveillance (annual cost)	202	24
Health state in model	**Utility Score**	**Reference**
PTC patients -without recurrence and complication	1.00	Assumption

-without recurrence and with permanent complication	0.54	42
-with recurrence and without permanent complication	0.41	42
-with recurrence and complication	0.22	42
Death	0.00	Definition

Abbreviations: CND = central neck dissection; RAI = radioiodine ablation; VCP = vocal cord palsy; TSH = thyroid stimulating hormone; Tg = thyroglobulin; Anti-Tg abs = anti-thyroglobulin auto-antibodies; PTC = papillary thyroid carcinoma;

*patients with more than one complication were counted as one

+ assumed an average of 2-month duration

includes monthly visit for the first 6 months and then thereafter 6-monthly follow-up

* assumed to be managed conservatively

Table 2. Results of Base-case and Sensitivity Analysis

	Cost (in USD) Per Patient	QALYs Per Patient		ICER Per Patient	
Base-case Analysis					
1 TT+pCND	11366.462	14.000		811.899	
2 TT-alone	11332.210	13.677		828.583	
Incremental (1 - 2)	34.252	0.323		105.966	
Univariate Sensitivity Analysis					
Clinical Parameters	Parameter Range (%)	Range for Incremental QALYs		Range for ICER	
TT-alone					
Complications from primary operation					
Temporary VCP	0.00 - 6.38	0.309	0.338	167.445	46.561
Permanent VCP	0.00 - 2.74	0.245	0.420	653.815	Favour pCND
Temporary hypoparathyroidism	4.03 - 33.63	0.306	0.442	129.256	Favour pCND
Permanent hypoparathyroidism	0.00 - 8.11	0.269	0.786	525.017	Favour pCND
Hematoma formation requiring reoperation	0.00 - 3.08	0.319	0.333	286.234	Favour pCND
Complications from reoperative CND					
Temporary unilateral VCP	1.59 - 22.22	0.323	0.323	112.514	57.382
Temporary bilateral VCP	0.02 - 4.94	0.323	0.323	120.771	Favour pCND
Permanent unilateral VCP	0.00 - 17.78	0.316	0.362	243.850	Favour pCND
Permanent bilateral VCP	0.00 - 3.16	0.323	0.331	149.934	Favour pCND
Temporary hypoparathyroidism	6.06 - 42.22	0.323	0.323	113.526	88.854
Permanent hypoparathyroidism	0.00 - 5.00	0.319	0.332	174.218	Favour pCND

Hematoma formation requiring reoperation	0.00 - 4.35	0.323	0.323	135.957	17.358
Chyle leakage	0.00 - 2.22	0.323	0.323	237.345	75.311
Complications from lateral neck dissection					
Chyle leakage	5.21 - 5.83	0.323	0.323	112.958	98.508
Radioiodine ablation after primary operation	28.01 - 100.00	0.323	0.323	939.905	Favour pCND
Annual locoregional recurrence rates					
Central compartment only	0.00 - 1.83	-0.089	1.032	Favour TT	Favour pCND
Lateral compartment only	0.00 - 3.73	0.082	2.061	4768.282	Favour pCND
Central & lateral compartments	0.00 - 1.87	-0.042	1.092	Favour TT	Favour pCND
TT+pCND					
Complications from the primary operation					
Temporary VCP	0.00 - 7.26	0.338	0.305	46.561	185.945
Permanent VCP	0.00 - 2.51	0.435	0.270	Favour pCND	437.836
Temporary hypoparathyroidism	8.70 - 42.86	0.378	0.221	45.108	299.741
Permanent hypoparathyroidism	0.00 - 5.88	0.420	0.033	Favour pCND	18073.707
Hematoma formation requiring reoperation	0.00 - 2.50	0.331	0.320	Favour pCND	234.729
Complications from reoperative CND					
Temporary unilateral VCP	1.59 - 22.22	0.323	0.323	102.998	127.989
Temporary bilateral VCP	0.03 - 4.94	0.323	0.323	99.268	337.839
Permanent unilateral VCP	0.00 - 17.78	0.326	0.306	45.415	466.488
Permanent bilateral VCP	0.00 - 3.16	0.323	0.320	86.406	943.945
Temporary hypoparathyroidism	6.06 - 42.22	0.323	0.323	102.539	113.723
Permanent hypoparathyroidism	0.00 - 5.00	0.325	0.319	76.419	164.344

Hematoma formation requiring reoperation	0.00 - 4.35	0.323	0.323	92.372	146.132
Chyle leakage	0.00 - 2.22	0.323	0.323	46.413	119.862
Complications from lateral neck dissection					
Chyle leakage	5.21 - 5.83	0.323	0.323	98.960	113.440
Radioiodine ablation after primary operation	58.09 - 100.00	0.323	0.323	Favour pCND	864.490
Annual locoregional recurrence rate					
Central compartment only	0.00 - 0.82	0.475	-0.071	Favour pCND	Favour TT
Lateral compartment only	0.00 - 1.57	0.569	-0.434	Favour pCND	Favour TT
Central & lateral compartments	0.00 - 0.41	0.524	0.242	Favour pCND	1090.453
Year Cycle	10 to 50 years	0.047	0.807	6995.449	Favour pCND
Discount rate	0 to 5	0.508	0.239	Favour pCND	599.794

Multivariate Sensitivity Analysis Assuming equivalent total morbidity in primary operation between TT-alone and TT+pCND	Value (%)	Incremental QALYs per patient	ICER per patient
Total Morbidity in TT+pCND	28.88	0.457	Favour pCND
Total Morbidity in TT-alone	13.89	0.460	Favour pCND
Total Morbidity	0.00	0.464	Favour pCND

Abbreviations: TT = total thyroidectomy; pCND = prophylactic central neck dissection; LR = locoregional; RAI = radioiodine; QALYs = Quality-adjusted Life-years; ICER = Incremental cost-effectiveness ratio; VCP = vocal cord palsy

Table 3. Threshold analyses with incremental cost-effectiveness ratio (ICER) becoming zero or infinity

Clinical Parameters	Base-case (%)	Threshold Values (%) at ICER=0 / ∞	Values (%) at ICER>0	Values at which TT-alone became cost-saving	Values at which TT+pCND became cost-saving
TT-alone strategy					
Annualized central recurrence	0.63	0.17 / 0.89	0.17 to 0.89	0.00 to 0.17	0.89 to 100.00
Annualized lateral recurrence	0.38	0.57	0.00 to 0.57	NA	0.57 to 100.00
Annualized central & lateral recurrences	0.56	0.08 / 0.77	0.08 to 0.77	0.00 to 0.08	0.77 to 100.00
TT+pCND strategy					
Permanent VCP	1.70	1.37 / 6.61	1.37 to 6.61	6.61 to 100.00	0.00 to 1.37
Permanent hypoparathyroidism	1.47	1.20 / 6.38	1.20 to 6.38	6.38 to 100.00	0.00 to 1.20
Annualized central recurrence	0.22	0.19 / 0.71	0.19 to 0.71	0.71 to 100.00	0.00 to 0.19
Annualized lateral recurrence	0.36	0.45 / 1.03	0.45 to 1.03	1.03 to 100.00	0.00 to 0.45
Annualized central & lateral recurrences	0.29	0.37 / 0.94	0.37 to 0.94	0.94 to 100.00	0.00 to 0.37
Radioiodine ablation	76.87	73.64	73.64 to 100.00	NA	0.00 to 73.64

Abbreviations: TT = total thyroidectomy; pCND = prophylactic central neck dissection; VCP = vocal cord palsy; NA = Not applicable

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LEGENDS

Figure 1. One way-sensitivity analysis of the incremental cost-effectiveness ratio (ICER) of total thyroidectomy + prophylactic central neck dissection (TT+pCND) over total thyroidectomy alone (TT-alone) as a function of time from primary operation (in years). The dashed line represents the 50,000/QALY threshold for cost-effectiveness. After 9 years, TT+pCND became cost-effective

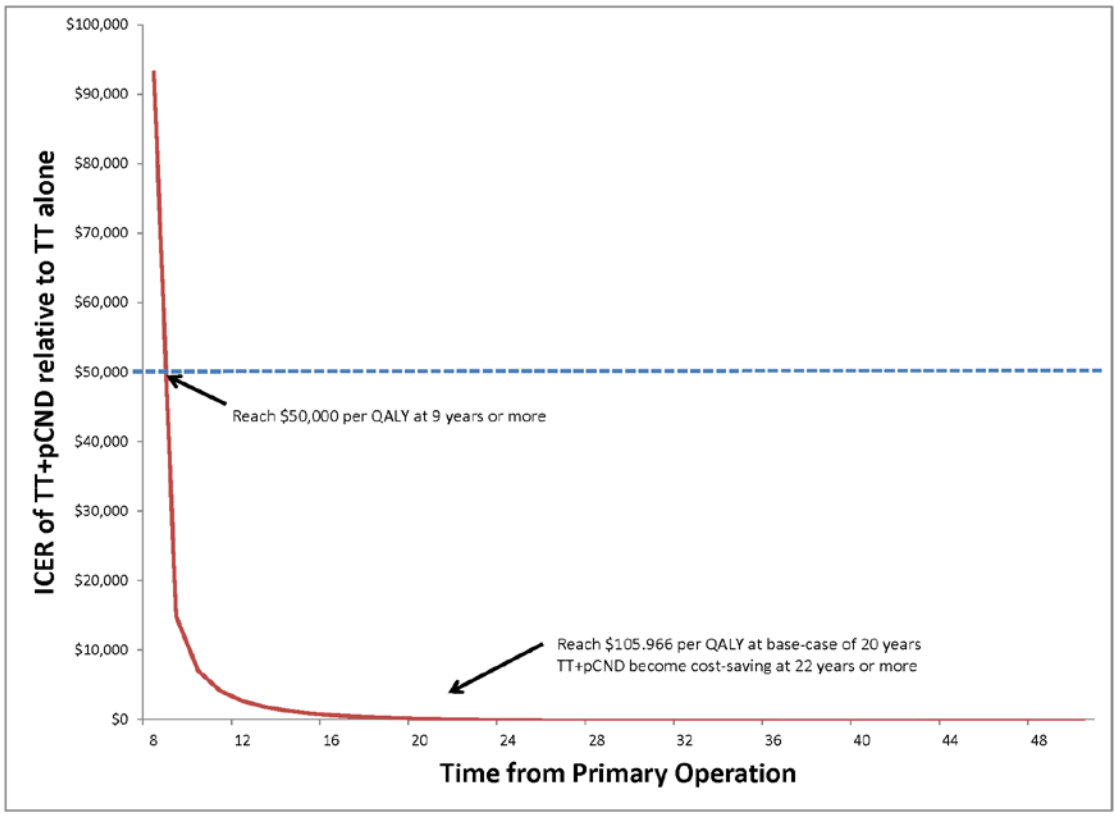
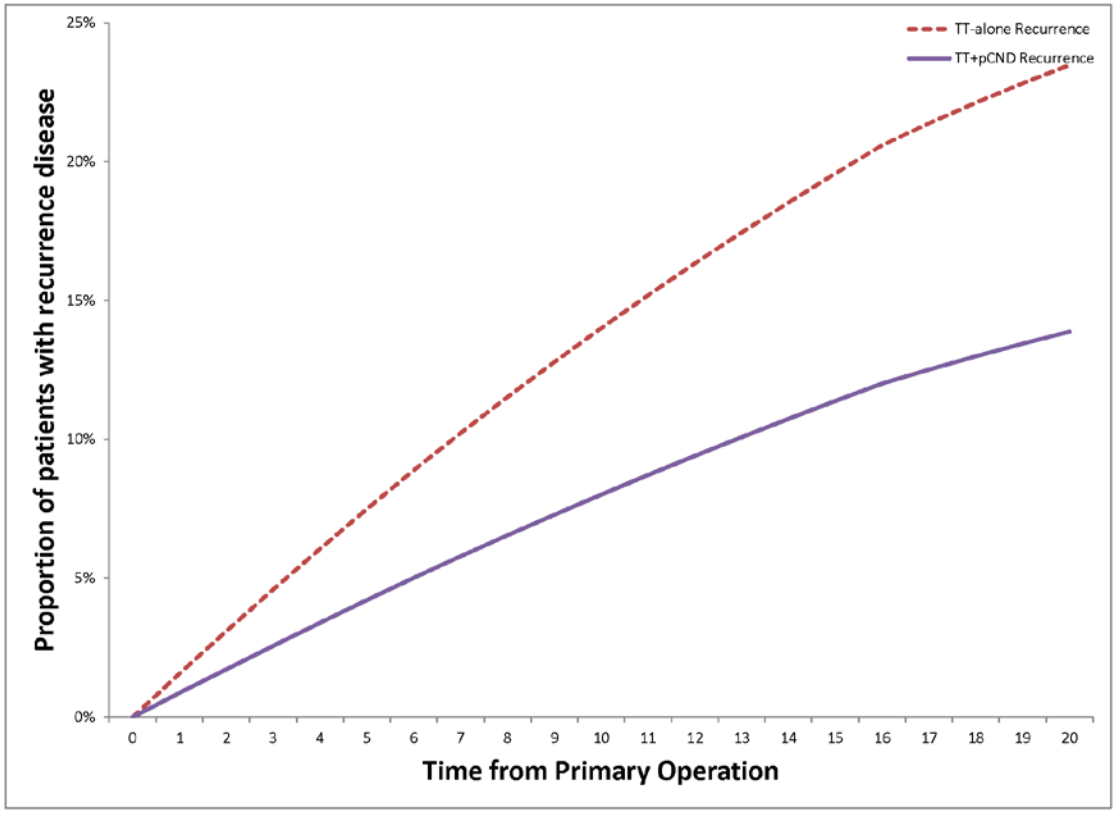


Figure 2. Proportion of patients with recurrent disease (%) as a function of time from primary operation (in years) between total thyroidectomy + prophylactic central neck dissection (TT+pCND) and total thyroidectomy alone (TT+alone)



Appendix 1. The Markov decision tree