ORIGINAL ARTICLE

A cost-effectiveness comparison between early surgery and non-surgical approach for incidental papillary thyroid microcarcinoma (PTMC)

Running head: Non-surgical approach is always cost-effective

Brian Hung-Hin LANG[1], MS, FRACS

Carlos KH WONG[2], PhD

[1]Division of Endocrine Surgery, Department of Surgery, University of Hong Kong, Pokfulam, Hong Kong SAR

[2]Department of Family Medicine and Primary Care, University of Hong Kong, 3/F Ap Lei Chau Clinic, 161 Main Street, Ap Lei Chau, Hong Kong

Address for Correspondence:

Dr Brian HH Lang

Division of Endocrine Surgery, Department of Surgery,

Queen Mary Hospital,

102 Pokfulam Road,

Hong Kong SAR, China

Tel.: (852) 22554232, Fax No.: (852) 28172291

Email: blang@hku.hk

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ABSTRACT

Background

The issue of whether all incidental papillary thyroid microcarcinoma (PTMC) should be managed by early surgery (ES) has been questioned and there is a growing acceptance that a non-surgical approach (NSA) might be more appropriate. We conducted a cost-effectiveness analysis comparing the two strategies in managing incidental PTMC.

Methods

Our base case was a hypothetical 40 year-old female diagnosed with a unifocal intra-thyroidal 9mm PTMC. The PTMC was considered suitable for either strategy. A Markov decision tree model was constructed to compare the estimated cost-effectiveness between ES and NSA after 20 years. Outcome probabilities, utilities and costs were derived from the literature. The threshold for cost-effectiveness was set at USD50,000/quality-adjusted life year (QALY). A further analysis was done for patients <40 and ≥40 years. Sensitivity and threshold analyses were used to examine model uncertainty.

Results

Each patient who adopted NSA over ES cost an extra USD682.54 but gained an additional 0.260 QALY. NSA was cost-saving (i.e. less costly and more effective) up to 16 years from diagnosis and remained cost-effective from 17 years onward. In the sensitivity analysis, NSA remained cost-effective regardless of patient age (<40 and ≥40 years), complications, rates of progression, year cycle and discount rate. In the threshold analysis, none of the scenarios that could have changed the conclusion appeared clinically likely.

Conclusions

For a selected group of incidental PTMC, adopting NSA was not only cost-saving in the initial 16 years but also remained cost-effective thereafter. This was irrespective of patient age, complication rate or rate of PTMC progression.

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common type of thyroid carcinoma and its age-related incidence has doubled in the last two decades [1]. However, despite this rise, the associated mortality has remained largely unchanged [2,3]. One explanation for this is that this rise has been mainly due to an increased discovery of seemingly-harmless papillary thyroid microcarcinoma (PTMC) (≤1cm) rather than clinically-significant PTCs [2,3]. Autopsy studies have shown that occult PTMCs are present in up to one-third of patients who died of unrelated disease [4]. Therefore, most PTMCs probably never cause any harm or become clinically–significant over one's life-time. This has led to the question of whether all incidental PTMCs should be managed by immediate or early surgery (ES) in the same way as other larger PTCs. To date, two Japanese centers (namely, the Kuma Hospital and Cancer Institute Hospital) have challenged this conventional dogma by conducting non-surgical or observation trials for incidental PTMC for the last 10 years or more [5-8]. Under these trials, patients with cytologically-confirmed PTMC were continuously monitored by regular ultrasound (USG) examination and were offered ES only when the PTMC exhibited signs of progression or spread [5-8]. Their results so far have shown that the great majority (>90%) of PTMCs do not progress with time and more importantly, under the non-surgical approach (NSA), none of the patients developed distant metastasis or die from PTC as a result of delayed surgery [5-8]. Given these findings, NSA has been accepted and adopted by the Japanese Society of Thyroid Surgeons and Japan Association of Endocrine Surgeons as an alternative treatment of PTMC [9]. The feasibility of adopting a similar strategy has been increasingly discussed in the West [10,11]. However, while NSA may serve as an acceptable alternative to ES in the management of incidental PTMC, its cost-effectiveness has rarely been discussed. Although NSA may cost less initially because of fewer operations and less procedural-related complications, it requires life-time surveillance and also over time, more patients are expected to need surgery because of tumor progression. Therefore, we hypothesized that perhaps over time, NSA might become more costly and even less cost-effective than ES from an institution's perspective. The present study aimed to compare the long-term cost-effectiveness between ES and NSA for cytologically-confirmed incidental PTMC based on the published literature.

MATERIALS AND METHODS

A decision tree model using TreeAge Software Pro version 2013 (Treeage Software, Inc., Williamstown, MA, US) was constructed to compare the long-term cost-effectiveness between two strategies, namely NSA and ES, in the management of a cytologically-confirmed incidental PTMC. According to the observation trial protocol, after diagnosis, patients were continuously monitored half-yearly with USG examination until there were signs of tumor progression or spread [5-8]. These included the index tumor enlarging ≥ 3mm from its original size, new appearance of regional nodal metastasis confirmed on fine-needle aspiration cytology (FNAC) and / or the index PTMC enlarging to ≥ 12mm in size [5-8]. For the first and third scenarios, a hemithyroidectomy (HT) + unilateral central neck dissection (CND) was considered sufficient [5-8]. For the second scenario, a total thyroidectomy + unilateral central neck dissection + lateral selective neck dissection (TT+ CND + SND) was necessary because new nodal metastases were mostly found in the lateral compartment [5-8]. In addition, over time, some patients would undergo thyroidectomy for a non-cancerous cause (such as Graves' disease, multinodular goiter or change in patient or physician preference) and in such situations, a TT + CND was usually performed [5,6]. In contrast, under the ES strategy, all patients underwent a HT + CND shortly after diagnosis. Figure 1 outlines the decision-analytic modelling.

Base-case patient

A 40 year-old female who was incidentally diagnosed with a unifocal intra-thyroidal 9mm PTMC in the right lobe. The diagnosis was confirmed on FNAC and the tumor was considered suitable for NSA because it was located far from the trachea or recurrent laryngeal nerve and there was no associated nodal or distant metastasis or history of previous thyroidectomy, familial syndrome or neck irradiation [5-8]. She was managed expectantly for 20 years.

Probabilities

The proportions of PTMCs showing signs of progression or spread (such as interval size enlargement ≥3mm, development of new regional nodal metastasis and PTMC enlarging to ≥12mm) and chance of needing thyroidectomy for a non-cancerous cause over 1 year were derived from data that had spanned for over 10 years [5-8]. Estimate on surgical complications after HT + CND, TT + CND and TT + CND + SND came from relevant studies in the literature [12-14]. 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 [15]. Table 1 summarizes outcome probabilities used.

Cost data

Our model only looked at the cost of NSA and ES 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. For simplicity, the life-time cost of thyroxin replacement was not included as the majority of operations were HT + CND. Unit costs of HT + CND, TT + CND and TT + CND + SND were estimated based on Medicare reimbursement for surgical procedure obtained from public access file from Centers for Medicare and Medicaid Services [16-18]. Unit costs of surgically-related complications and half yearly USG surveillance were based on data obtained from previous cost-effectiveness analyses [13,14]. Table 2 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 surveillance USG examinations were performed by dedicated radiologists using standardized technique with minimal inter-observer variability. The proportion of PTMC showing signs of progression (such as tumor size enlargement, nodal appearance and tumor becoming ≥ 12mm) was assumed to be constant throughout the entire observation period and similar for patients of all ages. All patients in both strategies were assumed cured and disease-free after surgery (i.e. no locoregional recurrence) as these tumors are considered very low risk [19]. A permanent complication resulted from surgery was assumed to be the only factor to impair the health state of patients. Temporary complications and patient anxiety during observation were not accounted for. Full compliance was assumed for all kinds of assessment, treatment and surveillance.

Base-case analysis

This was done according to the established guideline for cost-effectiveness analysis [20]. The incremental cost-effectiveness ratio (ICER) was the only outcome measurement and equaled to [cost of NSA – cost of ES] / [QALYs of NSA – QALYs of ES]. A strategy was "cost-saving" if it was costing less and also more effective over the competing strategy (i.e. that strategy dominated the competing strategy). A strategy was regarded cost-effective over another strategy if the ICER was < USD50,000 per QALY gained. This threshold was chosen based on analysis of the cost of current healthcare resource allocation decisions in the US [20]. Since age was shown to be a critical determinant of tumor progression and spread [6], a subgroup analysis was done for those aged <40 years and those aged ≥40 years.

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 ES would be less effective than NSA (a positive incremental effectiveness), a negative incremental cost meant NSA was a dominant strategy. A threshold analysis was undertaken to capture the threshold clinical values at which the ICER of NSA relative to ES 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 3 shows the results of base-case analysis. After a 20-year period, each patient in NSA spent an extra USD682.54 but also gained an additional 0.260 QALY over ES. Therefore, following the base-case assumptions and model inputs, NSA became more costly but was also more effective than ES in the institution's perspective. The ICER of USD2630.00 for NSA relative to ES was far below the recommended threshold of USD50,000 per QALY. In the subgroup analysis, those aged <40 years had an ICER which was higher than that of those aged ≥40 years (USD 11501.750 vs. USD 1262.696). Nevertheless, both were still far below the threshold of USD 50,000 per QALY.

Sensitivity analysis

Table 3 shows the univariate sensitivity analysis. No change in the conclusion was observed when key parameters such as complication rates and annualized rate of progression under NSA varied. Varying these parameters still yielded positive incremental effectiveness and ICERs implying NSA remained cost-effective or cost-saving. Similarly, varying the number of year-cycles (from 10 to 50 years) or discount rate (from 0 to 5%) did not change the base-case conclusion. The same analysis was performed for the two subgroups, patients <40 years and ≥40 years, but again, despite varying complication rates, year cycle and discount rate, NSA remained cost-effective or cost saving (*data not shown*). Figure 2 shows the changes in average cost for NSA relative to ES over a 50-year period. Relative to ES, NSA was cost-saving up to 16 years and thereafter, became cost-effective.

Table 4 shows the threshold analyses. To make NSA cost-saving relative to ES beyond 20 years, there were 2 possible scenarios. First, the permanent vocal cord palsy (VCP) after HT + CND increased from 0.85% to ≥1.34%. Second, the hematoma rate after HT + CND increased from 0.69% to ≥15.33%. In contrast, to render ES cost-saving relative to NSA, there were 5 possible but unlikely scenarios. They were permanent VCP after TT + CND increased from 1.70% to ≥47.04%, annualized rate of tumor size enlargement increased from 0.84% to ≥88.74%, annualized rate of new nodal metastasis increased from 0.32 to ≥13.95%, annualized rate of becoming clinical disease increased from 0.73% to ≥88.62% and annualized rate of other indications for surgery increased from 1.03% to ≥14.65%.

DISCUSSION

To our knowledge, this is the first study to examine the cost-effectiveness of adopting NSA in the management of incidental PTMC. Our data showed that adopting a strategy of NSA in a well selected group of PTMC was not only cost-saving (i.e. costing less) for the initial 16 years but also more cost-effective (i.e. ICER < USD50,000 per QALY) after 17 years than the ES strategy. However, this finding was not surprising because based on the pooled data, less than 3% of patients under the NSA strategy each year actually required ES (i.e. roughly 2% per year showing signs of tumor progression and 1% per year undergoing surgery for unrelated cause) whereas under the ES strategy, 100% of patients needed upfront surgery. Therefore, the initial cost of the ES strategy would be significantly higher than the NSA strategy. However, with the continuing half-yearly USG examination and the accumulative possibility of more costly "late" surgery and its related complications over time, our data showed that the NSA strategy became more costly over time. In fact, after 17 years, the NSA strategy became more expensive and its total cost continued to rise faster than that of ES (see Figure 2). Therefore, when only cost is considered, observation is only preferable for patients with advanced age or patients with a shortened (≤16 years) life-expectancy while ES is more preferable in younger and healthier patients (with long life-expectancy).

However, in terms of effectiveness as measured by QALY gained, the NSA strategy was more effective than the ES strategy regardless of the length of observation. This was because the former resulted in less procedural-related permanent complications. In fact, in the sensitivity analysis, the incremental QALYs were always positive implying the fact that NSA was always more effective than ES regardless of surgical complications, rate of tumor progression, year cycle or discount rate. Furthermore, the range of ICERs was far below the threshold of USD

50,000 per QALY. Therefore, NSA was always the more cost-effective option. Even when the year cycle was extended to 50 years (i.e. to the time of death), the ICER was still far below the threshold (USD3098.83 per QALY). Therefore, contrary to our initial hypothesis, our study showed that observation was always going to be a cost-saving or cost-effective strategy in the management of incidental PTMC.

From the threshold analyses, although there were 5 possible scenarios which could have rendered the ES strategy cost-saving when compared to NSA, they were clinically unlikely to happen because they all involved dramatically increasing the permanent VCP after TT + CND or annualized base rates of progression. For example, interval size enlargement increased by more than 100 times (from 0.84% to ≥88.74%) or appearance of nodal metastasis increased by more than 40 times (from 0.32% to ≥13.95%). Based on the current knowledge, these increases would seem unrealistic.

However, despite these results, we do acknowledge several shortcomings. First, some of the assumptions were over-simplified. For example, although USG examination remains the best imaging modality for tumor surveillance and monitoring, it is generally more difficult to accurately measure the size of more posteriorly-located tumors and also tumors in a background of chronic thyroiditis [21]. These situations may lead to less reliable monitoring and lower the cost-effectiveness of the NSA strategy. Second, although the present model assumed a constant rate of progression and spread for all patients regardless of age and other clinicopathologic features, recent studies found young age [6] and pregnant patients [22,23] had greater chance of tumor progression and therefore, these factors could potentially lower the cost-effectiveness of the NSA strategy. Third, despite a comprehensive literature search, selection biases could not be completely ruled out as all of these observation trials had been non-randomized. Perhaps, patients who preferred NSA were also those who were less likely to progress or spread over time. Fourth, given that indirect costs such as loss of productivity and wages were not included, we believe their inclusion would have further favored NSA over ES. Last, despite the evidence that most PTMC do not progress or spread over time, when both NSA and ES were equally offered, the majority of patients and physicians might still prefer ES over NSA because of anxiety and uncertainty [5,6,10,11]. Therefore, perhaps the most effective way of lowering cost would be to adopt a policy of avoiding FNAC on nodules <10mm [24].

CONCLUSION

In the institution's perspective, NSA was cost-saving relative to ES in the first 16 years of diagnosis and thereafter, it continued to be a more cost-effective option than ES for a selected group of PTMC. This was regardless of patients aged <40 or ≥40 years. Although there were 5 possible clinical scenarios which could have rendered ES as cost-saving compared to NSA, all seemed clinically unlikely as all involved a significant increase in the published rates of complication and signs of PTMC progression.

Declaration of interest

The authors declare that they have no competing interests

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Authors contributions

Lang / Wong were involved in the review of literature, acquisition of data and drafting and completing the manuscript. Lang / Wong were also involved in the review of literature and drafting the manuscript. Lang / Wong conceived the study, participated in the co-ordination and the acquisition of data and helped to draft the manuscript. All authors read and approved the final manuscript.

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Table 1. Literature-based probabilities

Clinical Parameters	Base-case (%)	Range for sensitivity analysis (%)	References
Surgical complications			
- Temporary vocal cord palsy			
- HT + CND	1.64	0.00 – 3.63	25,26
- TT + CND	3.28	0.00 – 7.26	12-14
- TT + CND + SND	3.28	0.00 – 7.26	12-14
- Permanent vocal cord palsy			
- HT + CND	0.85	0.00 – 1.25	25,26
- TT + CND	1.70	0.00 – 2.51	12-14
- TT + CND + SND	1.70	0.00 – 2.51	12-14
- Temporary hypoparathyroidism			
- TT + CND	20.64	8.70 – 42.86	12-14
- TT + CND + SND	20.64	8.70 – 42.86	12-14
- Permanent hypoparathyroidism			
- TT + CND	1.47	0.00 – 5.88	12-14
- TT + CND + SND	1.47	0.00 – 5.88	12-14
- Hematoma formation			
- HT + CND	0.69	0.00 – 1.50	12-14
- TT + CND	1.29	0.00 – 2.20	12-14
- TT + CND + SND	1.79	0.00 – 2.50	12-14
- Chyle leakage			
- TT + CND + SND	5.81	5.80 – 5.83	27
Proportion of patients showing signs of progression in 1 year under NSA			
- Interval size enlargement (≥3mm)	0.84	0.56 – 0.98	5-8
- < 40 years old	1.60	1.60	6
- ≥ 40 years old	0.81	0.81	6
- Appearance of nodal metastasis	0.32	0.18 – 0.38	5-8
- < 40 years	1.04	1.04	6

- ≥ 40 years old	0.19	0.19	6
- Clinical disease (tumor ≥12mm)	0.73	0.68 – 0.78	5-8
- < 40 years	1.72	1.72	6
- ≥ 40 years	0.52	0.52	6
Other indications for surgery*	1.03	0.58 – 1.15	5,6
Number of deaths per 1000 population			
- 40 – 44		1.4	15
- 45 – 54		3.2	15
- 55 – 64		6.4	15
- 65 – 74		15.3	15
- 75 – 84		41.4	15
- 85+		132.2	15
Healthy state in model		Utility score	
- Alive without permanent complication		1.00	Assumption
- Alive with permanent complication		0.54	28
- Death		0.00	Definition

Abbreviations: HT + CND = Hemithyroidectomy + unilateral central neck dissection; TT + CND = Total thyroidectomy + unilateral central neck dissection; TT + CND + SND = Total thyroidectomy + unilateral central neck dissection + lateral selective neck dissection; NSA = non-surgical approach

* such as patients who developed Grave’s disease or benign multinodular goiter or those who changed their preference (from NSA to ES) over time

Table 2. Unit cost (USD) for each service component for post-thyroidectomy

Cost component	Unit cost (USD)	Reference
Surgical procedure		
- Hemithyroidectomy + central neck dissection	4513	16-18
- Total thyroidectomy + central neck dissection	6013	16-18
- Total thyroidectomy + central neck dissection + selective neck dissection	12495	16-18
Each visit with ultrasound examination	300	16-18
Surgical complications		
- Temporary vocal cord palsy+	564	16-18
- including consultation, laryngoscopy and speech therapy		
- Permanent vocal cord palsy#	10367	16-18
- including consultations, laryngoscopy, speech and medialization		
- Temporary hypoparathyroidism+	144	16-18
- including follow-up visits, blood tests and medications		
- Permanent hypoparathyroidism (annual cost)#	863	16-18
- Follow-up visits, blood tests, medications		
- Hematoma requiring neck re-exploration	5754	16-18
- Chyle leak*	15404	16-18

+ 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 3. Results of base-case and sensitivity analysis

	Cost (in USD) per patient	QALYs per patient		ICER per patient	
Base-case Analysis					
Non-surgical approach (NSA)	7204.33	15.228		473.099	
- < 40 years	8859.86	15.172			
- ≥ 40 years	6862.29	15.238			
Early surgery (ES)	6521.80	14.968		435.703	
- < 40 years	6521.80	14.968			
- ≥ 40 years	6521.80	14.698			
Incremental (NSA – ES)	682.54	0.260		2629.998	
- < 40 years	2338.06	0.203		11501.750	
- ≥ 40 years	340.50	0.270		1262.696	
Univariate Sensitivity Analysis					
Parameters	**Parameter Range (%)**	**Range for Incremental QALYs**		**Range for ICER**	
Surgical complications					
Temporary vocal cord palsy					
HT + CND	0.00 – 3.63	0.260	0.260	2658.878	2594.955

	TT + CND	0.00 – 7.26	0.260	0.260	2621.161	2640.721
	TT + CND + SND	0.00 – 7.26	0.260	0.260	2627.238	2633.347
Permanent vocal cord palsy						
	HT + CND	0.00 – 1.25	0.208	0.284	9003.492	428.543
	TT + CND	0.00 – 2.51	0.269	0.255	1720.515	3087.768
	TT + CND + SND	0.00 – 2.51	0.263	0.258	2338.726	2771.194
Temporary hypoparathyroidism						
	TT + CND	8.70 – 42.86	0.260	0.260	2621.785	2645.283
	TT + CND + SND	8.70 – 42.86	0.260	0.260	2627.433	2634.772
Permanent hypoparathyroidism						
	TT + CND	0.00 – 5.88	0.268	0.234	2488.558	3115.279
	TT + CND + SND	0.00 – 5.88	0.262	0.252	2584.851	2771.097
Hematoma formation						
	HT + CND	0.00 – 1.50	0.260	0.260	2753.961	2484.476
	TT + CND	0.00 – 1.90	0.260	0.260	2694.539	2646.765
	TT + CND + SND	0.00 – 2.50	0.260	0.260	2614.632	2636.093
Chyle leakage						

TT + CND + SND	5.80 – 5.83	0.260	0.260	2629.768	2630.458
Proportion of patients showing signs of progression or spread in the NSA strategy					
Interval size enlargement (≥3mm)	0.56 – 0.98	0.266	0.256	2072.152	2906.217
Appearance of nodal metastasis	0.18 – 0.38	0.265	0.257	1679.260	3032.938
Clinical disease (tumor ≥12mm)	0.68 – 0.78	0.261	0.258	2530.663	2729.381
Other indications for surgery*	0.58 – 1.15	0.275	0.255	1193.891	3042.330
Year Cycle	10 to 50 years	0.077	1.397	Favors NSA	3098.831
Discount rate	0 to 5	0.376	0.206	6496.645	Favors NSA

Abbreviations: QALYs = Quality-adjusted life-years; ICER = Incremental cost-effectiveness ratio; HT + CND = hemithyroidectomy + central neck dissection; TT + CND = total thyroidectomy + central neck dissection; TT + CND + SND = total thyroidectomy + central neck dissection + lateral selective neck dissection

* such as Grave’s disease, benign multinodular goiter or change in patient or clinician preference

Table 4. Threshold analyses with ICER becoming zero or infinity

Parameters	Base-case (%)	Threshold values (%) at ICER=0 / infinity	Values (%) at ICER>0	Values at which NSA became cost-saving	Values at which ES became cost-saving
Complications					
Permanent vocal cord palsy after HT+CND	0.85	1.34	0.00 to 1.34	1.34 to 100.00	NA
Permanent vocal cord palsy after TT+CND	1.70	47.04	0.00 to 47.04	NA	47.04 to 100.00
Hematoma formation after HT+CND	0.69	15.33	0.00 to 15.33	15.33 to 100.00	NA
Proportion of patients showing signs of progression under NSA					
Interval size enlargement (≥3mm)	0.84	88.74	0.00 to 88.74	NA	88.74 to 100.00
Appearance of nodal metastasis	0.32	13.95	0.00 to 13.95	NA	13.95 to 100.00
Clinical disease (tumor ≥ 12mm)	0.73	88.62	0.00 to 88.62	NA	88.62 to 100.00
Other indications for surgery*	1.03	14.65	0.00 to 14.65	NA	14.65 to 100.00
Year cycle	20	17	17 to 50	1 to 16	NA
Discount rate	3.00	4.60	0.00 to 4.60	4.60 to 5.00	NA

Abbreviations: HT + CND = Hemithyroidectomy + central neck dissection; TT + CND = total thyroidectomy + central neck dissection; ICER = incremental cost-effectiveness ratio; NA = not applicable

* such as Grave’s disease, benign multinodular goiter or change in patient or clinician preference

Figure 1

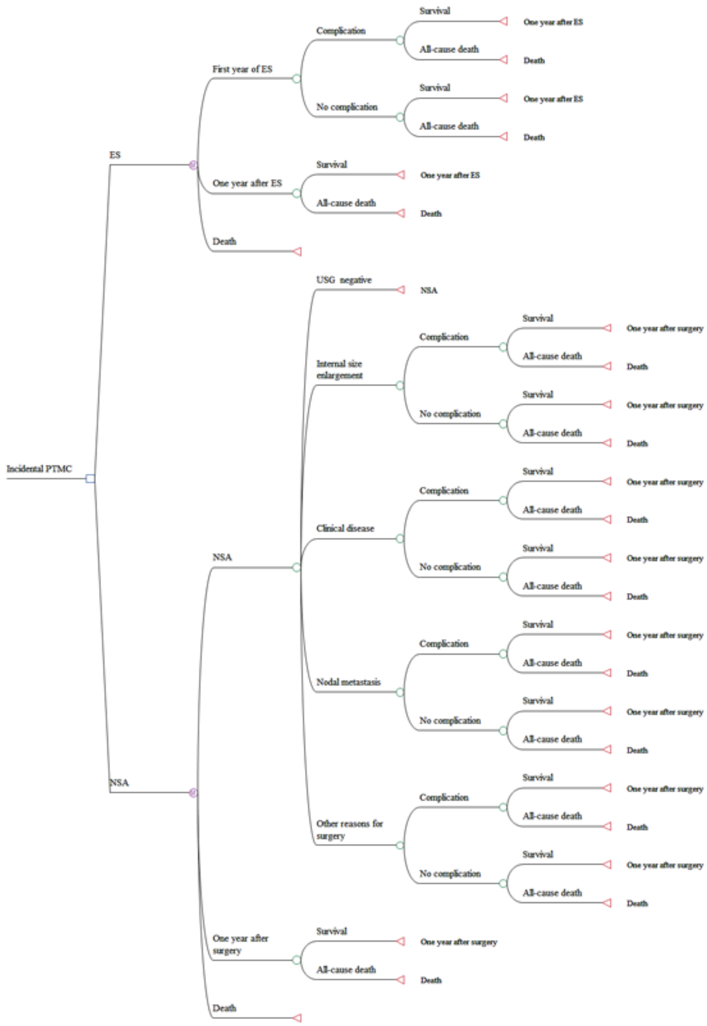
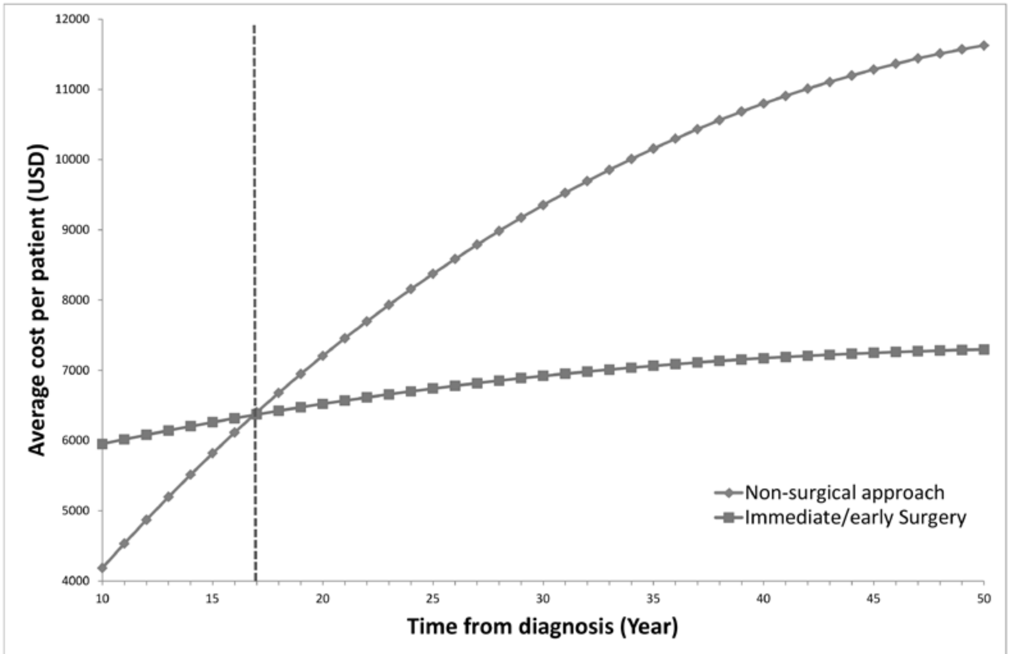

Incidental PTMC
ES
First year of ES
Complication
Survival
One year after ES
All-cause death
Death
No complication
Survival
One year after ES
All-cause death
Death
One year after ES
Survival
One year after ES
All-cause death
Death
Death
NSA
NSA
USG negative
NSA
Internal size enlargement
Complication
Survival
One year after surgery
All-cause death
Death
No complication
Survival
One year after surgery
All-cause death
Death
Clinical disease
Complication
Survival
One year after surgery
All-cause death
Death
No complication
Survival
One year after surgery
All-cause death
Death
Nodal metastasis
Complication
Survival
One year after surgery
All-cause death
Death
No complication
Survival
One year after surgery
All-cause death
Death
Other reasons for surgery
Complication
Survival
One year after surgery
All-cause death
Death
No complication
Survival
One year after surgery
All-cause death
Death
One year after surgery
Survival
One year after surgery
All-cause death
Death
Death

Figure 2.



12000
11000
10000
9000
8000
7000
6000
5000
4000
Average cost per patient (USD)
10
15
20
25
30
35
40
45
50
Time from diagnosis (Year)
Non-surgical approach
Immediate/early Surgery