Cost-Effectiveness Analysis of ^{18}F-FDG PET/CT in Detecting Suspected Recurrence or Metastasis in Well-Differentiated Thyroid Carcinoma Patients with Negative Diagnostic Total Body Scan in Thailand: A Decision Analysis

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Objective: *To evaluate cost-effectiveness analysis of ^{18}F-FDG PET/CT to detect tumor recurrence or metastasis in well-differentiated thyroid cancer patients with high Tg but negative TBS in Thailand.*
Material and Method: *A retrospective literature review of 55 studies published between 1978 and 2010 was done. Decision analysis by TreeAge program showed an evaluation of the most cost-effective treatment and ^{18}F-FDG PET/CT scan in thyroid cancer patients with high Tg but negative TBS. The incremental cost and life years gained associated with seven strategies approached were analyzed by the decision tree model. The first strategy was treatment with empirical high dose ^{131}I therapy. The second to the seventh strategies were using imaging investigations by CT scan of neck and chest, ^{99m}Tc MIBI scan, and ^{18}F-FDG PET/CT scan to identify recurrent, persistent, and metastatic lesions before the specific treatment via curative surgery, external radiotherapy, and high dose ^{131}I therapy. All strategies were adopted using hospital perspective and direct medical cost was estimated based on the reference price of Siriraj Hospital. Deterministic sensitivity analysis was conducted to investigate the effect of the cost of PET/CT scan.*
Results: *The strategy using ^{18}F-FDG PET/CT scan to detect recurrence or metastasis and possible curative surgery in operable cases and high dose ^{131}I therapy in inoperable cases gave the highest life years gained of 27.08 with cost of 90,227.61 Baht (2,926.24 US dollars) and acceptable incremental cost effectiveness ratio (ICER) of 6,936.88 Baht (224.98 US dollars) per life year gained when compared to the least costly strategy using ^{99m}Tc MIBI scan and additional ^{18}F-FDG PET/CT scan in negative MIBI result. Other strategies were dominated by this PET/CT strategy. Deterministic sensitivity analysis (based on the willingness to pay (WTP) 360,000 Baht (11,675.42 US dollars) showed that the cost of PET/CT scan has no impact on the net health benefit.*
Conclusion: *Based on the hospital perspective, the cost-effectiveness of ^{18}F-FDG PET/CT scan in detecting suspected recurrence or metastasis in thyroid carcinoma patients with negative diagnostic TBS but high Tg was first done using ^{18}F-FDG PET/CT scan to identify disease, followed by curative surgery or high dose ^{131}I therapy. Moreover, cost of PET/CT scan did not influence the net health benefit. This PET/CT benefit is helpful for considering the proper PET/CT use for thyroid cancer in Thailand.*

Keywords: *Cost-effectiveness, Thyroid cancer, PET/CT scan*

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Thyroid carcinoma is one of common cancers in Thailand and the incidence of the disease is increasing every year(1). Differentiated thyroid carcinoma undergoing surgery and radioiodine ablation has good prognosis and survival rate. The routine follow-up includes diagnostic ^{131}I total body scan (TBS) and serum thyroglobulin (Tg). The remission of the disease is considered by negative ^{131}I TBS and undetectable serum Tg. Although there is good correlation between ^{131}I TBS and serum Tg, about 10 to 15% of patients who have negative TBS have positive Tg(2). There are many possibilities that complicate the treatment(3-5), of which two main management options are provided for this patient

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group depending on the theory followed[6]. The first option is empirical high dose ^{131}I therapy, because the parameters of the disease activity show improvement[7-13]. The second one is localizing tumor site by imaging modalities such as CT scan, ^{99m}Tc MIBI scan or ^{18}F-FDG PET/CT scan.

^{18}F-FDG PET/CT scan is highly accurate in localizing the disease in patients with discordance between ^{131}I TBS and serum Tg[14-18]. Therefore, this option leads to better treatment planning[19,20]. However, there is limited information on suitable management of these patients. The objective of the present study was to assess the cost-effectiveness of ^{18}F-FDG PET/CT scan in thyroid carcinoma patients with negative diagnostic TBS but high Tg from a health care sector perspective.

Material and Method

Two components of information were required in the present study. The first one was costs, which includes those of CT scan, PET/CT scan, MIBI scan, surgery, high dose ^{131}I therapy, external radiotherapy, and direct expense incurred as cost of adverse event treatment. The second one was probability, which was the diagnostic accuracy of CT scan, PET/CT scan, MIBI scan, and the chance that each clinical incidence will occur, for example, adverse events, probability of complications from surgery, high dose ^{131}I therapy, and external radiotherapy.

Model design

A cost-effective analysis model was used to analyze lifetime cost and life expectancy of thyroid carcinoma patients with negative ^{131}I TBS but high Tg. The assessment of the health economic model was used and input parameters were obtained by systematic reviews of the literatures on the clinical and diagnostic accuracy of investigations in thyroid carcinoma patients with negative ^{131}I TBS but high Tg.

Model structure

A decision tree model was used to analyze the most cost-effective management for thyroid carcinoma patients with negative ^{131}I TBS but high Tg. In developing the decision tree, seven strategies for management are displayed as choice nodes as shown in Fig. 1.

Patient population

A retrospective review of 750 differentiated thyroid cancer patients who were treated in Division of Nuclear Medicine, Faculty of Medicine Siriraj Hospital between 1987 and 1999 was performed. Clinical outcome, cost of treatment, 10-year survival, and various probabilities were recorded and used in decision analysis. The protocol was approved by the Siriraj Ethics Committee for Human Experiment.

Model scenarios

A 40 year-old female patient, diagnosed as papillary thyroid carcinoma with cervical lymph node metastasis, had received total thyroidectomy and radioiodine ablation. The diagnostic TBS at one year after the first radioiodine ablation showed neither residual thyroid tumor nor metastasis. Her serum Tg was undetectable and serum TSH was more than 30 mIU/L. She has received a suppressive dose of thyroxine. During the third year of treatment, her serum Tg rose to 25 ng/ml, so she was sent for diagnostic TBS. The scan showed no evidence of abnormal ^{131}I uptake, but her serum Tg and TSH were high, 51 ng/ml and 108 mIU/L, respectively, and it was assumed that she did not have other underlying diseases. Her complete blood count (CBC) and blood chemistry were normal. Her performance status was good with Karnofsky Performance Status (KPS) scale more than 70. She could receive any course of treatment. The central question of the situation is this: What was the proper management with the most cost-effectiveness? In the present study, there were seven strategies for management.

The first strategy was treatment with high dose ^{131}I treatment (Fig. 2).

The second and third ones were firstly localizing the disease by CT scan of neck and chest. If CT scan did not identify it, the patient would be sent for ^{18}F-FDG PET/CT scan. For the disease that could be operable, a surgeon would remove the tumor or

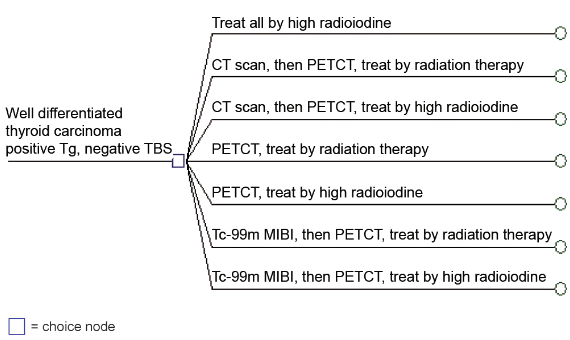

Fig. 1 Decision tree models of 7 strategies of management decision.

metastasis followed by high dose ^{131}I therapy for ablation of micrometastasis. However, if it were inoperable, she would be sent either for radiotherapy for the second strategy or high dose ^{131}I therapy for the third strategy, as shown in the Fig. 3 and 4. If there was no evidence of tumor or metastasis from ^{18}F-FDG PET/CT scan, a physician would follow-up her condition.

The fourth and fifth strategies were localizing the disease by ^{18}F-FDG PET/CT scan. The sixth and seventh strategies were detecting the disease by ^{99m}Tc MIBI scan. However, the ^{18}F-FDG PET/CT scan was using to identify disease if ^{99m}Tc MIBI scan showed negative result. The operable disease would be sent for surgery, followed by ^{131}I therapy while inoperable disease would be treated by radiation therapy for the fourth and sixth strategies or ^{131}I therapy for the fifth and seventh strategies as shown in Fig. 5-8. If PET/CT showed negative result, the physician would follow-up her condition.

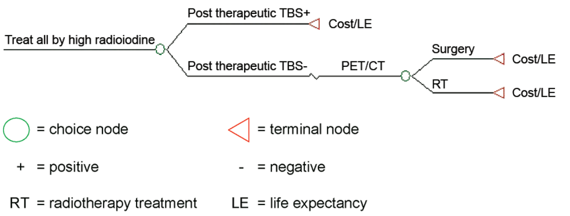

Fig. 2 The 1st strategy in decision tree model for thyroid carcinoma patients with negative ^{131}I TBS but high Tg.

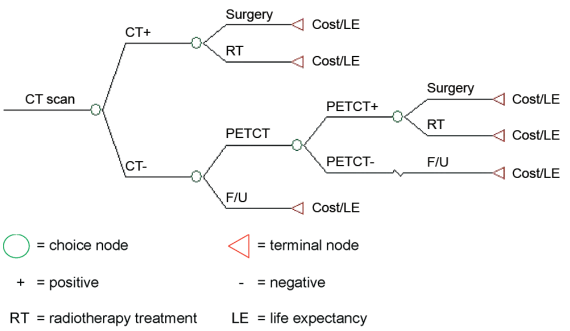

Fig. 3 The 2nd strategy in decision tree model for thyroid carcinoma patients with negative ^{131}I TBS but high Tg.

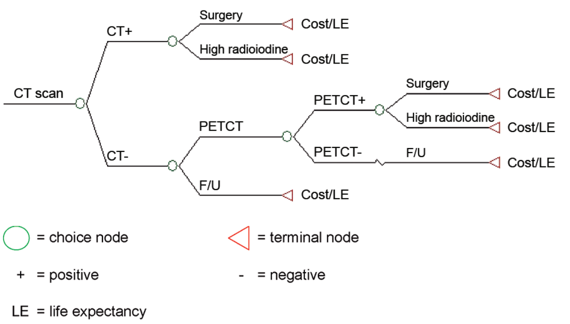

Fig. 4 The 3rd strategy in decision tree model for thyroid carcinoma patients with negative ^{131}I TBS but high Tg.

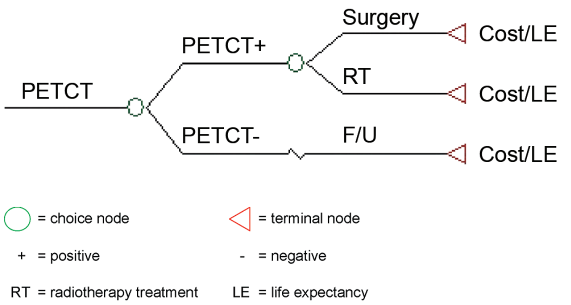

Fig. 5 The 4th strategy in decision tree model for thyroid carcinoma patients with negative ^{131}I TBS but high Tg.

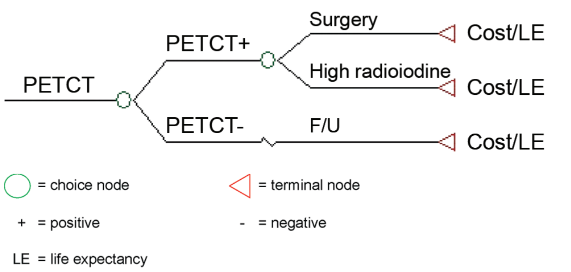

Fig. 6 The 5th strategy in decision tree model for thyroid carcinoma patients with negative ^{131}I TBS but high Tg.

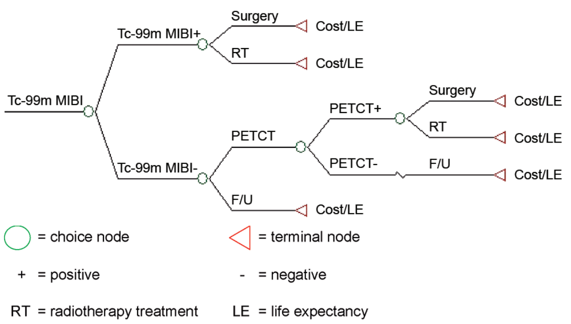

Fig. 7 The 6th strategy in decision tree model for thyroid carcinoma patients with negative ^{131}I TBS but high Tg.

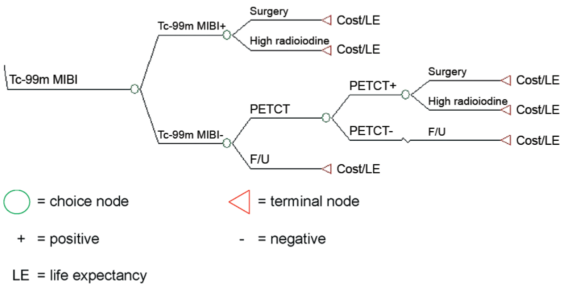

Fig. 8 The 7th strategy in decision tree model for thyroid carcinoma patients with negative ^{131}I TBS but high Tg.

Data and assumption

Transitional probabilities

Transitional probabilities used in the present study were obtained from the literature found in the PubMed database, the Cochrane library, and the Clinical Trials.gov website. Search dates were between January 1, 1978 and December 31, 2010. All searches included the keywords and corresponding MeSH terms for negative total body scan (TBS), high thyroglobulin (Tg), differentiated thyroid carcinoma, empirical high dose radioiodine, CT scan, PET/CT scan, ^{99m}Tc-MIBI, life expectancy, re-surgery of thyroid, radiotherapy treatment, complication, and cost effectiveness. The inclusion and exclusion criteria were as follows:

Inclusion criteria:

-The studies of management for differentiated thyroid cancer with high Tg but negative TBS

-The methodology of the studies was assessed regarding treatment for differentiated thyroid cancer with high Tg but negative TBS

-The studies of outcome, survival rate, and life expectancy of thyroid cancer patients

-The studies of sensitivity and diagnostic accuracy of CT scan, ^{18}F-FDG PET/CT scan, and ^{99m}Tc MIBI in the detection of differentiated thyroid cancer with high Tg but negative TBS

-Side effects of re-operation, radiotherapy, and high dose ^{131}I therapy for thyroid cancer patients

Exclusion criteria:

-No English or Thai full papers were available.

Among 55 potential eligible articles, the 22 excluded articles were eight studies of PET scan, four studies of thyroid surgery including information about the first time of surgery, one study of PET/MRI, and nine studies with different groups of well-differentiated thyroid cancer patients.

From the clinical trial, the compound mortality rate was derived and then the disease specific mortality rate was calculated from the following formula:

$$\mu_C = \mu_D + \mu_{ASR}$$

When, μ_D: diseases specific excess mortality rate (fixed rate)

μ_C: compound mortality rate derived from the studies in the literatures

$$\mu_{ASR} = 1/LE_{ASR}$$

LE_{ASR} (ASR: age, sex, race adjusted life expectancy) was life expectancy of the Thai general population classified by age group (derived from Life Table of Vital Statistics Thailand 2006) as shown in Table 1.

For persistent disease of thyroid cancer, the median standardized survival time was 0.60 (95% CI 0.47-0.72)[21]. The life expectancy of persistent disease was calculated from the equation below.

Mortality rate in persistent thyroid cancer from the literature was 0.102[21] and the expectation for the age and gender matched with median life expectancy was 37.5 years in 1990.

Table 1. Vital statistics Thailand 2006 (LE_{ASR})[22]

Age (female)	LE_{ASR} (years)	Mortality rate (age, sex, race adjusted) = $1/LE_{ASR}$
10-14	64.75	0.015
15-19	59.88	0.017
20-24	55.08	0.018
25-29	50.49	0.020
30-34	46.17	0.022
35-39	41.73	0.024
40-44	37.22	0.027
45-49	32.73	0.031
50-54	28.37	0.035
55-59	24.16	0.042
60-64	20.13	0.050
65-69	16.36	0.061
70-74	12.93	0.077
75-79	9.88	0.101
80-84	7.33	0.136
85-89	5.34	0.187
90-94	3.85	0.260
95-99	2.79	0.358
100+	2.50	0.400

$\mu_C = \mu_D + \mu_{ASR}$

$0.102 = \mu_D + 0.029$

$\mu_D = 0.073$

Diseases specific excess mortality rate = 0.073 and μ_D is a fixed rate so that the compound mortality rate when the age of the female patient was 40 years old was calculated from the same formula:

$\mu_D = 0.073 + 0.027$

$= 0.1$

The life expectancy of persistent disease was calculated from the equation below.

$\mu_D = 1/LE_D$

$LE = 1/0.1$

$= 10$ years

For remission disease of thyroid cancer, the survival pattern was similar to the whole population[21]. The life expectancy for remission disease was 37.22 years[22].

The mortality rates in different age were converted to probability (P) assuming an event occurred at a constant rate (r) over a time period between time zero to sometime beyond, for example a time period between the first and the fifth years was 4 (t):

$P = 1 - \exp\{-rt\}$

= probability of an event over the period t

Then, the probability was converted back to rates to exploit their mathematical features (e.g. changing cycle length)[23,24].

$r = -[\ln(1 - P)]/t$

Model parameters, data sources, and values of transition probability used in the model are presented in the results.

Costs

Cost data in the model is the direct medical costs, which are composed of those of imaging, laboratory investigations, treatments, and treatment complications. The details of each item are

a) Imaging: CT scan of neck and chest, ^{18}F-FDG PET/CT scan and ^{99m}Tc MIBI scan

b) Laboratory investigations before treatment: T4, TSH, Tg, TgAb, CBC, BUN, Cr, total calcium, and electrolyte.

c) Treatments: re-surgery of thyroid, radiotherapy, and high dose ^{131}I therapy

d) Complications:

Re-surgery of thyroid[25,33]: persistent hypoparathyroidism

Radiotherapy[31]: mucositis, pharyngitis, skin toxicity, laryngeal toxicity

High dose ^{131}I therapy[34,35]: acute sialadenitis

The costs of direct and indirect non-medical expenses were not included in the present study. All costs were calculated from the hospital perspective. For an inter-country comparison, they were converted into US dollars using the purchasing power parity exchange rate of 1 US dollar (USD) for 30.834 Thai Baht on February 11, 2011. The values used in the model are shown in Table 2.

Data inputs

Prevalence

The incidence of recurrence or metastasis of well-differentiated thyroid cancer with high Tg but negative TBS was calculated from 110 patients who fit these criteria[25,27]. Eighty-two patients had recurrent tumor for whom the calculated incidence was 0.75.

Cure rate

Nine of twelve patients (75%) with suspected recurrence and negative TBS indicated as disease free in the last follow-up after curative surgery[28].

From the 30 patients treated with high dose ^{131}I therapy, 33.3% showed normalization of serum Tg off L-thyroxine (undetectable Tg) with negative TBS[2].

Data analysis

Decision analysis (decision tree model)[36-38]

Decision analysis is a systematic approach for decision making in an uncertain or difficult condition. It assists a decision maker to identify any available options, predict the outcome of each option, assess the probability and value of outcome and determine the options that give the most cost-effectiveness.

The decision tree model begins with the choice alternatives. A choice node is the point in time when the decision maker chooses one from several options. The possible options will be branched from the initial choice node. The tree will provide the structure for cost-effectiveness analysis. The present study used the decision tree model as shown in Fig. 1-8.

The DATA Professional Economic analysis was used to analyze the data in two aspects, which were cost-effectiveness analysis and incremental cost-effectiveness analysis.

Cost-effectiveness analysis

The cost-effectiveness analysis was analyzed by cost/life expectancy. The incremental

Table 2. Data inputs in the decision tree analysis

Parameter	Value	Reference
Incidence of recurrence or metastasis in well differentiated thyroid cancer with high Tg but negative TBS	0.75	Mirallie et al., 2007[26] Finkelstein et al., 2007[27]
CT; sensitivity, specificity	0.73, 0.71	Freudenberg et al., 2007[28]
^{18}F-FDG PET/CT; sensitivity, specificity	0.95, 0.91	Palmedo et al., 2006[29]
^{99m}Tc MIBI; sensitivity, specificity	0.83, 0.50	Kücük et al., 2006[30]
Cure rate from radiation therapy	0.65	Freudenberg et al., 2007[28] Rosenbluth et al., 2005[31] Schwartz et al., 2009[32]
Cure rate from re-surgery	0.75	Freudenberg et al., 2007[28]
Cure rate from high dose ^{131}I therapy	0.33	Pacini et al., 2001[2]
Life expectancy in cure case	37.22 years	Links et al., 2005[21]
Life expectancy in persistent disease case	10 years	Links et al., 2005[21]
Probability for operable case (true positive, false positive) by PET/CT scan	0.476, 0.75	Finkelstein et al., 2007[27] Freudenberg et al., 2007[28] Palmedo et al., 2006[29]
Probability for operable case (true positive, false positive) by CT scan	0.28, 0.25	Freudenberg et al., 2007[28] Palmedo et al., 2006[29]
Probability for surgical complication	0.07	Ruggiero et al., 2008[25] Kim et al., 2004[33]
Probability for radiation therapy complication	1.00	Rosenbluth et al., 2005[31] Siriraj Hospital, Thailand
Probability for high dose ^{131}I therapy complication (acute sialadenitis)	0.40	Chow, 2005[34] Mazzaferri et al., 2001[35] Siriraj Hospital, Thailand
Direct medical care costs (hospital perspective)		
CT scan of neck and chest	13,200 Baht (428.10 USD)	Siriraj Hospital, Thailand
^{18}F-FDG PET/CT scan	40,000 Baht (1,297.27 USD)	Siriraj Hospital, Thailand
^{99m}Tc MIBI scan	7,000 Baht (227.02 USD)	Siriraj Hospital, Thailand
Laboratory investigations (T4, TSH, Tg, TgAb, CBC, BUN, Cr, calcium and electrolyte)	1,850 Baht (60 USD)	Siriraj Hospital, Thailand
Re-surgery (without complication)	32,500 Baht (1,054.03 USD)	Siriraj Hospital, Thailand
Re-surgery (with complication)	37,500 Baht (1,216.19 USD)	Siriraj Hospital, Thailand
High dose ^{131}I thepary	24,605 Baht (797.98 USD)	Pacini et al., 2001[2] Siriraj Hospital, Thailand
Radiotherapy treatment	93,850 Baht (3,043.72 USD)	Siriraj Hospital, Thailand
Treatment for surgical complication (remission case)	14,400 Baht (467.02 USD)	Siriraj Hospital, Thailand
Treatment for surgical complication (persistent disease case)	53,596.8 Baht (1,738.24 USD)	Siriraj Hospital, Thailand
Treatment for high dose of ^{131}I complication: acute sialadenitis	37.5 Baht (1.22 USD)	Mazzaferri et al., 2001[35] Siriraj Hospital, Thailand
Treatment for radiotherapy complication	765 Baht (24.81 USD)	Siriraj Hospital, Thailand

Tg = thyroglobulin; TBS = total body scan; T4 = thyroxine; TSH = thyroid stimulating hormone; TgAb = thyroglobulin antibody; CBC = complete blood count; BUN = blood urea nitrogen; Cr = creatinine cost-effectiveness ratio (ICER) will express the additional cost per health gain. It was calculated by incremental cost divided by incremental effectiveness.

$$ICER = (C_I - C_N)/(E_I - E_N)$$

When: C_I = intervention cost

C_N = null cost

E_I = intervention effectiveness

E_N = null effectiveness

Sensitivity analysis[36,39,40]

Output data in the present study incur the variation (uncertainty) for many reasons, such as different sources of the inputs from different pooled data sets and unverifiable assumptions. The sensitivity analysis was used for systematically changing parameters to determine the effects of variation. The sensitivity analysis is a technique to ensure the quality of the assessment and sensitivity analysis tries to identify what source of uncertainty weights more on the study's conclusions. The three approaches of sensitivity analysis are 1) one way sensitivity analysis which examines the impact of each variable in the present study, 2) extreme sensitivity analysis which examines the setting of each variable at the same time to select the most optimistic or pessimistic value to generate the best or worst case scenario; 3) probabilistic sensitivity analysis examines the effect of the results when the fundamental variables are allowed to vary across a plausible range according to predefined distributions.

In the present study, a sensitivity analysis was conducted of the cost of PET/CT scan. This will help to determine the suitable cost of PET/CT in thyroid cancer.

Determination of incremental cost effectiveness ratio (ICER)

The incremental cost effectiveness ratio (ICER) was calculated by using incremental cost divided by incremental effectiveness.

$$ICER = (C_I - C_N)/(E_I - E_N)$$

When: C_I = intervention cost

C_N = null cost

E_I = intervention effectiveness

E_N = null effectiveness

Determination of net health benefit (NHB)

NHB is the alternative approach to measure cost-effectiveness. It was calculated by the following formula:

$$NHB = (E_A - E_B) - [(C_A - C_B)/WTP]$$

When: E_A = effectiveness of strategy A

E_B = effectiveness of strategy B

C_A = cost of strategy A

C_B = cost of strategy B

WTP = willingness to pay

The strategy A is appropriate when the NHB value is more than 0 and a high NHB is better than a low NHB.

Results

Cost utility analysis

Based on the hospital perspective, the total costs and life years gained from each treatment option, and the incremental costs per life year gained from management of thyroid carcinoma patients with high Tg but negative TBS are shown in Table 3 and Fig. 9. Based on this perspective, the incremental costs for patients in strategies 1, 2, 3, 4, 5, and 6 compared with strategy 7 were 3,797.88, 12,174.24, 2,508.55, 12,495.14, 5,722.73, and 15,500.76 Baht, respectively. However, the incremental life years gained for strategy 5 was 0.82 years but the incremental life years gained lost for patients in strategies 1, 2, 3, 4, and 6 were 5.42, 4.45, 0.007, 2.53, and 4.72, respectively. The strategy 5 gave the highest life years gained of 27.08 years and an acceptable incremental cost effectiveness ratio (ICER) of 224.98 US dollars per life year gained when compared with strategy 7 as shown in Table 3 and 4. The other strategies were dominated which means they cost more but were less effective, as shown in Fig. 9.

The Tables 5 and 6 showed the incremental costs for patients in strategies 2, 3, 4, 5, 6, and 7

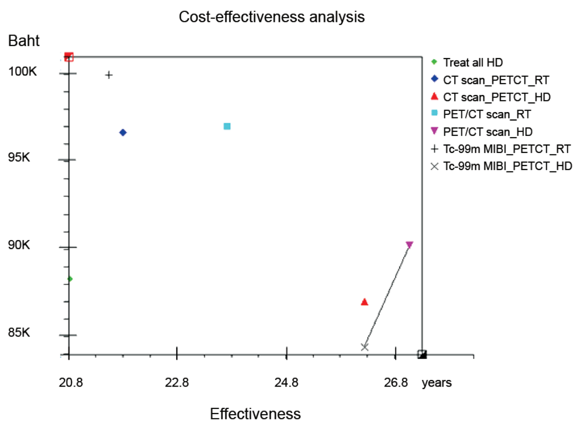

Fig. 9 Cost-effectiveness analyses for thyroid carcinoma patients with high Tg but negative TBS among 7 strategies (hospital perspective).

Table 3. Cost-effectiveness results obtained from the analysis (probabilistic results)

Strategy	Total cost (Baht)	Total effectiveness (life years gained)	Incremental cost (Baht)	Incremental effectiveness (life years gained)	Cost/ effectiveness (C/E)	ICER (Baht/ life year gained)
1	88,302.754	20.836	3,797.876	-5.421	4,237.989	Dominated
2	96,679.119	21.804	12,174.241	-4.453	4,434.008	Dominated
3	87,013.427	26.250	2,508.549	-0.007	3,314.797	Dominated
4	97,000.015	23.729	12,495.137	-2.528	4,087.826	Dominated
5	90,227.608	27.082	5,722.730	0.825	3,331.645	6,936.877
6	100,005.640	21.540	15,500.762	-4.717	4,642.787	Dominated
7	84,504.878	26.257			3,218.375	

Strategy 1: treat all with high dose of radioiodine
Strategy 2: CT scan, then PET/CT scan and treatment by surgery or radiotherapy
Strategy 3: CT scan, then PET/CT scan and treatment by surgery or high dose ^{131}I therapy
Strategy 4: PET/CT scan and treatment by surgery or radiotherapy
Strategy 5: PET/CT scan and treatment by surgery or high dose ^{131}I therapy
Strategy 6: MIBI scan, then PET/CT scan and treatment by surgery or radiotherapy
Strategy 7: MIBI scan, then PET/CT scan and treatment by surgery or high dose ^{131}I therapy
ICER = incremental cost-effectiveness ratio

Table 4. Cost-effectiveness results obtained from the analysis (probabilistic results)

Strategy	Total cost (Baht)	Total effectiveness (life years gained)	Incremental cost (Baht)	Incremental effectiveness (life years gained)	Cost/effectiveness (C/E)
Hospital perspective: all incremental costs calculated relative to the least costly option: strategy 7)					
1	88,302.754	20.836	3,797.876	-5.421	4,237.989
2	96,679.119	21.804	12,174.241	-4.453	4,434.008
3	87,013.427	26.250	2,508.549	-0.007	3,314.797
4	97,000.015	23.729	12,495.137	-2.528	4,087.826
5	90,227.608	27.082	5,722.730	0.825	3,331.645
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Strategy 4: PET/CT scan and treatment by surgery or radiotherapy
Strategy 5: PET/CT scan and treatment by surgery or high dose ^{131}I therapy
Strategy 6: MIBI scan, then PET/CT scan and treatment by surgery or radiotherapy
Strategy 7: MIBI scan, then PET/CT scan and treatment by surgery or high dose ^{131}I therapy

compared with strategy 1 and cost-effectiveness, ordered by the most effectiveness.

Sensitivity analysis

One-way sensitivity analysis based on hospital perspective

Deterministic sensitivity analysis (based on the willingness to pay (WTP) 360,000 Baht) was performed for cost of PET/CT scan between 10,000 and 60,000 Baht. The strategy 5 shows the highest life years gained and an acceptable incremental cost effectiveness ratio (ICER) when compared with the other strategies as shown in Fig. 10. This indicates that the cost of PET/CT scan has no impact on the net health benefit (Fig. 11, 12).

Discussion

There is annually increased incidence of well-differentiated thyroid carcinoma patients in Thailand[1]. The gold standard of treatment is total

Table 5. Cost-effectiveness results obtained from the analysis (probabilistic results)

Strategy	Total cost (Baht)	Total effectiveness (life years gained)	Incremental cost (Baht)	Incremental effectiveness (life years gained)	Cost/effectiveness (C/E)
Hospital perspective: all incremental costs calculated relative to the treatment option: strategy 1)					
1	88,302.754	20.836			4,237.989
2	96,679.119	21.804	8,376.365	0.968	4,434.008
3	87,013.427	26.250	-1,289.327	5.414	3,314.797
4	97,000.015	23.729	8,697.261	2.893	4,087.826
5	90,227.608	27.082	1,924.854	6.246	3,331.645
6	100,005.640	21.540	11,702.886	0.704	4,642.787
7	84,504.878	26.257	-3,797.876	5.421	3,218.375

Strategy 1: treat all with high dose of radioiodine
Strategy 2: CT scan, then PET/CT scan and treatment by surgery or radiotherapy
Strategy 3: CT scan, then PET/CT scan and treatment by surgery or high dose ^{131}I therapy
Strategy 4: PET/CT scan and treatment by surgery or radiotherapy
Strategy 5: PET/CT scan and treatment by surgery or high dose ^{131}I therapy
Strategy 6: MIBI scan, then PET/CT scan and treatment by surgery or radiotherapy
Strategy 7: MIBI scan, then PET/CT scan and treatment by surgery or high dose ^{131}I therapy

Table 6. Cost-effectiveness results obtained from the analysis, ordered by total effectiveness

Strategy	Total cost (Baht)	Total effectiveness (year)	Cost/ effectiveness (C/E)
5	90,227.608	27.082	3,331.645
7	84,504.878	26.257	3,218.375
3	87,013.427	26.250	3,314.797
4	97,000.015	23.729	4,087.826
2	96,679.119	21.804	4,434.008
6	100,005.640	21.540	4,642.787
1	88,302.754	20.836	4,237.989

Strategy 1: treat all with high dose of radioiodine
Strategy 2: CT scan, then PET/CT scan and treatment by surgery or radiotherapy
Strategy 3: CT scan, then PET/CT scan and treatment by surgery or high dose ^{131}I therapy
Strategy 4: PET/CT scan and treatment by surgery or radiotherapy
Strategy 5: PET/CT scan and treatment by surgery or high dose ^{131}I therapy
Strategy 6: MIBI scan, then PET/CT scan and treatment by surgery or radiotherapy
Strategy 7: MIBI scan, then PET/CT scan and treatment by surgery or high dose ^{131}I therapy

thyroidectomy or near total thyroidectomy with follow-up post surgical radioiodine ablation and thyroid hormone suppression of thyroid-stimulating hormone (TSH). The remission of the disease is considered from negative Tg and normal diagnostic TBS. However, either positive Tg or abnormal TBS suggests residual thyroid tumor or metastasis. The patient will then be considered for later doses of radioiodine treatment, if there is evidence of persistent, recurrent or metastatic disease. Nevertheless, about 10 to 15% of thyroid carcinoma patients during the follow-up period[11] show discordance of Tg and diagnostic TBS, especially high Tg but negative TBS. There are several options for management depending on each theory[6]. The first theory is false positive Tg

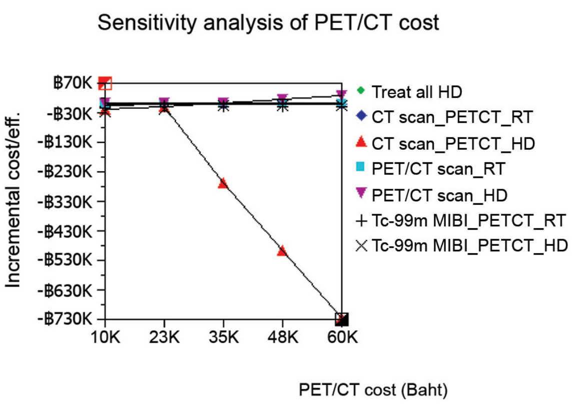

Fig. 10 Sensitivity analyses for PET/CT cost in thyroid carcinoma patients with high Tg, but negative TBS, among 7 strategies showing range of ICER (hospital perspective).

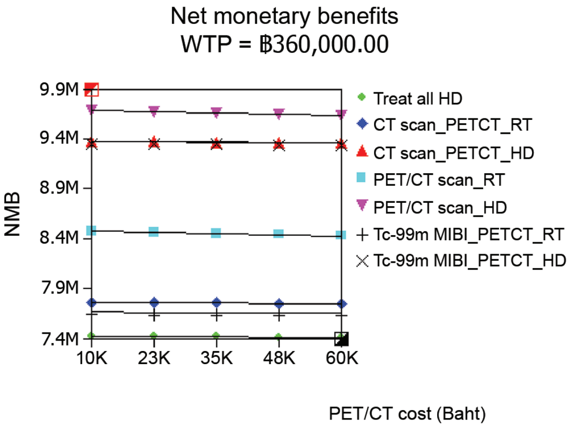

Fig. 11 Sensitivity analyses for PET/CT cost in thyroid carcinoma patients with high Tg, but negative TBS, among 7 strategies showing range of net monetary benefits (hospital perspective).

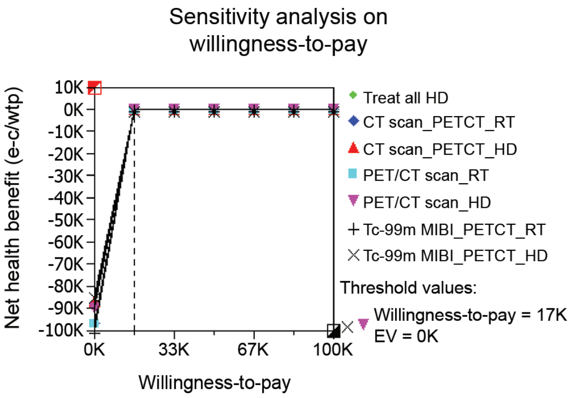

Fig. 12 Sensitivity analyses for PET/CT cost in thyroid carcinoma patients with high Tg, but negative TBS, among 7 strategies showing range of net health benefits (hospital perspective).

but true negative TBS. Some radioimmunoassays (RIAs) that quantify free and Ab-complexed Tg molecules and incorporate separation systems against heterologous antibodies resulted in falsely elevated Tg level and overestimation of Tg[41,42]. The second theory is true positive Tg but false negative TBS. The persistent, recurrent, or metastatic patients who lose iodine uptake ability will show negative TBS but high Tg. The possible causes of this loss are defective iodine-trapping mechanism, loss of differentiation, dispersed microscopic metastases and improper patient preparation for ^{131}I TBS[6]. The defect of iodine-trapping mechanism changes the amount of radioiodine uptake and cause kinetic change of iodine released from cells, leading to the false negative TBS[43,44]. One third of differentiated thyroid carcinoma develops loss of differentiation that increases tumor grading and loss of thyroid specific function[45]. Progressive dedifferentiation of differentiated thyroid carcinoma effects thyroid cells that can synthesize Tg but have lost iodine-concentrating ability, showing negative TBS with high Tg[46].

The treatment for well-differentiated thyroid carcinoma patients with high Tg but negative TBS can be achieved via two main options. The first one is empirical high dose ^{131}I therapy ($\geq$100 mCi). There was much evidence of increase of the sensitivity of post-therapy TBS and the detection rate of neoplastic lesions was not seen from diagnostic ^{131}I TBS[47-49]. Nevertheless, Pacini et al[2] found positive first post-therapy ^{131}I TBS in 30 from 42 (71.43%) differentiated thyroid carcinoma patients using this criteria. Complete remission was found in 10 patients (33%) with a mean number of radioiodine treatment course of 3 (range 1-6). The second option is imaging investigations such as ^{18}F-FDG PET/CT scan, ^{99m}Tc-MIBI scan, CT scan of chest and neck as the first step to direct proper treatment, for example curative surgery, external radiotherapy, high dose ^{131}I therapy or follow-up. However, it stilled uncertain in Thailand which precise imaging modalities should be used because of the cost and accuracy.

As for the results, the optimal strategy for treatment of differentiated thyroid carcinoma patients with high Tg but negative TBS should be considered from the lowest ICER. Strategy 7 gives the least cost of 84,504.878 Baht (2,740.64 US dollars) with total effectiveness (life years gained) of 26.257 years. Strategy 5 provides the highest life years gained of 27.08 years and an acceptable incremental cost effectiveness ratio (ICER) of 224.98 US dollars per life year gained. The other strategies were dominated as compared with the strategy 7. They cost more but were less effective. In 2008, Thai Gross Domestic Product (GDP) per capita was 126,419.4 Baht (4,100 US dollars)[50]. The Macroeconomics and Health Committee suggested choosing interventions that were less than 3 times the gross domestic product (GDP) per capita[51]. The present study indicated that using ^{18}F-FDG PET/CT scan to identify recurrent, persistent, or metastatic disease in well-differentiated thyroid carcinoma patients and determining treatment via curative surgery or high dose ^{131}I for inoperable case is associated with the most cost effectiveness ratio, based on hospital perspective.

The deterministic sensitivity analyses based on the willing to pay (WTP) of 360,000 Baht is presented in terms of cost-effectiveness acceptability curves from hospital perspective for cost of PET/CT scan between 10,000 and 60,000 Baht. The results show that the strategy 5 gives the highest life years gained and an acceptable incremental cost-effectiveness ratio (ICER) when compared with the others. Moreover, the cost of PET/CT scan has no impact on the net health benefit.

Limitation of the study

In the present study, the cost effectiveness of treatment options for well-differentiated thyroid carcinoma patients with high Tg but negative TBS was analyzed. However, some limitations can be pointed as follows:

1) It is a non-randomized, unselected cohort study involving well-differentiated thyroid carcinoma patients with high Tg but negative TBS.

2) Sensitivity, specificity, and accuracy of imaging investigations, outcome, choice of treatment, and data of the patients during follow-up were obtained from retrospective review of the studies performed in other countries.

3) The average costs of imaging, laboratory investigations, treatments, and treatment complications were derived from the realistic data in well-differentiated thyroid carcinoma patients of Siriraj Hospital, but the generalization to other settings should be considered.

4) A large number of well-differentiated thyroid carcinoma patients in the Nuclear Medicine Division between 1987 and 1999 were lost to follow-up. In the present study, only the information on cost of treatment and follow-up were used.

5) The information on life expectancy of well-differentiated thyroid carcinoma patients with high Tg but negative TBS could not be obtained from the literature. In the present study, the life expectancies were calculated based on these of remission and persistent diseases.

6) The costs of direct and indirect non-medical expenses as well as utilities were not included in the present study, because this data was not available.

Generalization

All costs of laboratory investigations, treatments, and treatment complications were calculated from the realistic prices in Siriraj Hospital in 2010, which may be different from the other settings. However, the cost of PET/CT scan was used in the sensitivity analysis. Even though some studies were not randomized and cohort, available suitable information was used in the present study. The results will help physicians make better decisions for this group of thyroid cancer patients.

In summary, based on the experiences and perspective of specialists who take care of well-differentiated thyroid carcinoma patients, it was suggested that localization of the disease, then treatment with curative surgery, is the best way to achieve a remission of disease. However, for an inoperable case, high dose ^{131}I therapy is preferable. If the disease still cannot be cured or improved, radiotherapy treatment is then the next option[52]. However, the life expectancy of these patients is quite long, even though they have persistent disease[53]. Thus, a long-term follow-up of about 5 to 10 years is recommended for thyroid cancer patients.

Conclusion

Nowadays, the proper treatment for well-differentiated thyroid carcinoma with high Tg but negative ^{131}I TBS is still controversial. The management guidelines for patients with thyroid nodules and differentiated thyroid cancer reviewed by the American Thyroid Association Guidelines Taskforce recommend empirical radioactive iodine therapy. In the case of failure to localize for disease, ^{18}F-FDG PET scan should be considered. The goal of treatment for these patients is curative surgery. In the incurable patients, thyroid hormone suppression therapy, external beam radiotherapy, chemotherapy, radiofrequency ablation, chemo-embolization, or monitoring without additional treatment was considered[39]. However, high dose ^{131}I treatment can cause complications[19]. Thus, the second option using imaging investigations was proposed. Among these, ^{18}F-FDG PET/CT scan has high sensitivity, specificity and accuracy to detect the disease[15] and leads to more proper treatment. However, the cost-effectiveness of ^{18}F-FDG PET/CT scan has not been proved in Thailand. Thus, the decision to treat these thyroid cancer patients depends only on the personal practice guidelines that a physician relies on. The findings of the present study showed that if the goal is a WTP of 100,000 to 400,000 Baht (1 to 3 times of GDP per capita in Thailand), ^{18}F-FDG PET/CT scan can be used to identify recurrent, persistent or metastatic disease and determine treatment through curative surgery or high-dose ^{131}I treatment for an inoperable case. This will result in giving the highest life years gained of 27.08 and an acceptable incremental cost effectiveness ratio (ICER) of 224.98 US dollars per life year gained from the hospital perspective. The cost of PET/CT scan has no impact on the net health benefit. These findings can be used to improve the guidelines for appropriate and cost-effective use of FDG PET/CT scan for thyroid cancer. Moreover, it supports the use of health care resources to improve Thai health care system and determine criteria for reimbursement in Thailand.

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Potential conflicts of interest

None.

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การประเมินต้นทุนประสิทธิผลการใช้เอฟดีจี เพ็ท-ซีที เพื่อวินิจฉัยผู้ป่วยมะเร็งไทรอยด์ชนิดเวลดิฟเฟอเรนทิเอทเต็ด ที่สงสัยมีการกลับเป็นใหม่หรือมีการแพร่กระจายของมะเร็งแต่ผลการตรวจสแกนทั้งตัวด้วยไอโอดีนปกติใน ประเทศไทย

เบญจาภา เขียวหวาน, เชิดชัย นพมณีจำรัสเลิศ, ภาวนา ภูสุวรรณ, พงษ์พิชา ตู้จินดา, นภาพร โตจินดา, กฤตยา อุบลนุช

วัตถุประสงค์: *เพื่อประเมินต้นทุนประสิทธิผลการใช้เอฟดีจี เพ็ท-ซีที ในการวินิจฉัยผู้ป่วยมะเร็งไทรอยด์ชนิดเวลดิฟเฟอเรนทิเอทเต็ด ที่สงสัยมีการกลับเป็นใหม่หรือมีการแพร่กระจายของมะเร็ง แต่ผลการตรวจสแกนทั้งตัวด้วยไอโอดีนปกติในประเทศไทย*

วัสดุและวิธีการ: *การทบทวนวรรณกรรม 55 เรื่อง ตีพิมพ์ในปี พ.ศ. 2521 ถึง ปี พ.ศ. 2553 อย่างเป็นระบบ ทำการศึกษาด้วยโปรแกรมทรีอาจ เพื่อหาค่าต้นทุนและปีชีวิตที่เพิ่มขึ้นจำนวน 7 ทางเลือก ได้แก่ ทางเลือกที่ 1 คือการรักษาด้วยไอโอดีนรังสีขนาดสูง ทางเลือกที่ 2 ถึง 7 คือการตรวจด้วยเอกซเรย์คอมพิวเตอร์บริเวณคอ ทรวงอก และปอด ภาพถ่ายเทคนีเชียม-มีบี และภาพถ่ายเอฟดีจี เพ็ท-ซีที แล้วนำไปสู่การรักษาที่เหมาะสมกับโรค เช่น การผ่าตัด การฉายแสง หรือ การให้ไอโอดีนรังสีขนาดสูง และใช้ตัวแปรต้นทุนทางตรง ทางการแพทย์ จากอัตราค่าบริการและราคายาอ้างอิงจากโรงพยาบาลศิริราช ประกอบกับข้อมูลของผู้ป่วยในโรงพยาบาลศิริราช รวมทั้งทำการวิเคราะห์ความไม่แน่นอนสำหรับค่าตรวจภาพถ่ายเพ็ท-ซีที*

ผลการศึกษา: *การใช้ภาพถ่ายเพ็ท-ซีที ตรวจหาโรค ให้การรักษาโดยการผ่าตัดในผู้ป่วยที่ผ่าได้ และไอโอดีนรังสีขนาดสูงในผู้ป่วยที่ผ่าตัดไม่ได้ จะมีต้นทุนส่วนเพิ่มน้อยที่สุดต่อปี ในมุมมองของโรงพยาบาลคือ 27.08 ปี ในจำนวนเงิน 90,227.61 บาท คิดเป็น 6,936.88 บาทต่อปี เมื่อเทียบกับการรักษาจากการตรวจด้วยภาพถ่ายเทคนีเชียม-มีบี และภาพถ่ายเพ็ท-ซีที ในกรณีที่ภาพถ่ายเทคนีเชียม-มีบี ไม่พบความผิดปกติ ให้การรักษาโดยการผ่าตัดในผู้ป่วยที่ผ่าได้และไอโอดีนรังสีขนาดสูงในผู้ป่วยที่ผ่าตัดไม่ได้ ในขณะที่การรักษาทางอื่นจะเพิ่มค่าใช้จ่ายแต่ลดจำนวนปีชีวิต จากการวิเคราะห์ความไว ค่าการตรวจเพ็ท-ซีที ไม่มีผลกระทบต่อต้นทุนประสิทธิผล โดยใช้ความเต็มใจที่จะจ่ายเป็น 360,000 บาท*

สรุป: *การรักษาผู้ป่วยมะเร็งไทรอยด์ที่มีไทโรโกลบูลินสูงแต่ผลการตรวจสแกนทั้งตัวด้วยไอโอดีนปกติ โดยใช้ภาพถ่ายเอฟดีจี เพ็ท-ซีที ตรวจหาโรค ให้การรักษาโดยการผ่าตัดในผู้ป่วยที่ผ่าได้และไอโอดีนรังสีขนาดสูงในผู้ป่วยที่ผ่าตัดไม่ได้ มีความคุ้มค่าที่สุดในมุมมองของโรงพยาบาล และค่าใช้จ่ายการตรวจเพ็ท-ซีที ไม่มีผลกระทบต่อต้นทุนประสิทธิผล ผลการศึกษาดังกล่าวจะเป็นข้อมูลที่ช่วยในการพิจารณากำหนดเกณฑ์การใช้เพ็ท-ซีที สำหรับผู้ป่วยมะเร็งไทรอยด์เพื่อให้เกิดการใช้เพ็ท-ซีที อย่างคุ้มค่าต่อไป*