



The Concept of Economic Evaluation and Its Application in Thyroid Cancer Research

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Economic evaluation is a type of comparative analysis between interventions in terms of both their resource use and health outcomes. Due to the good prognosis of thyroid cancer (TC), the socioeconomic burden of TC patients post-diagnosis is increasing. Therefore, economic evaluation studies focusing on TC are recommended. This study aimed to describe the concept and methods of economic evaluation and reviewed previous TC studies. Several previous studies compared the costs of interventions or evaluated recurrence, complications, or quality of life as measures of their effectiveness. Regarding costs, most studies focused on direct costs and applied hypothetical models. Cost-minimization analysis should be distinguished from simple cost analysis. Furthermore, due to the universality of the term “cost-effectiveness analysis” (CEA), several studies have not distinguished CEA from cost-utility analysis; this point needs to be considered in future research. Cost-benefit analyses have not been conducted in previous TC research. Since TC has a high survival rate and good prognosis, the need for economic evaluations has recently been pointed out. Therefore, correct concepts and methods are needed to obtain clear economic evaluation results. On this basis, it will be possible to provide appropriate guidelines for TC treatment and management in the future.

Keywords: Thyroid neoplasms; Economic evaluation; Cost; Effectiveness; Cost-effectiveness analysis

INTRODUCTION

The incidence of thyroid cancer has markedly increased worldwide in recent decades [1]. In South Korea (hereafter, Korea), the incidence rate of thyroid cancer increased sharply by more than 10 times between 2000 and 2012 (age-standardized inci-

dence rate [ASIR] based on the Korean population in 2000: 7.2 per 100,000 in 2000; 74.8 per 100,000 in 2012), decreased from 2012 to 2015, and then slightly increased again after 2015 [2]. Although the incidence of thyroid cancer in Korea has changed to a pattern of a slow increase since 2015, the incidence in 2018 is still the highest in the world, twice that of the United States

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and three times that of Canada [3].

Thyroid cancer has a 5-year survival rate of almost 100%, irrespective of whether surgery is performed [2]. Furthermore, it has been suggested that the rapid increase of the ASIR of thyroid cancer in Korea may reflect over-diagnosis and over-screening [4]. Collectively, these points call into question the value of thyroid cancer screening. However, there are limitations in making an appropriate choice because no comparative results have been reported. It is also necessary to select appropriate medical services in a resource-limited environment. Economic evaluation methodologies are useful for resolving such issues [5].

With its system of universal coverage through the National Health Insurance Service, Korea is facing a variety of issues, such as providing adequate services to the public, guaranteeing people's right to make choices for their own health, and ensuring efficient compensation for providers [6]. Since thyroid cancer is a disease with a favorable prognosis, the problems in Korea also encompass challenges in screening, diagnosis, treatment, and long-term health care for thyroid cancer, suggesting that an appropriate allocation of limited resources is necessary. Thus, economic evaluation methodology is particularly important because efficient reimbursement in the National Health Insurance Service and people's right to make choices for their own health are both important issues. Therefore, it is vitally important for thyroid cancer research to understand and apply economic evaluation methodology.

The purpose of this study was to introduce the methods of economic evaluation, key elements, and key indicators. To present economic evaluation methodology in an easy-to-understand way for thyroid cancer researchers, we briefly introduce several representative examples of previous thyroid cancer studies using economic evaluation methods. We also present several applicable examples from studies currently in progress at the Korean Thyroid Association.

METHODS

This review focused on illustrating the concept and methods of economic evaluation with examples from thyroid cancer research. First, in order to explain the concept and methods of economic evaluation in an easy-to-understand way for thyroid cancer researchers, textbooks on economic evaluation were selected and summarized based on keywords and main methods [7,8]. Existing thyroid cancer studies applying the economic evaluation methodology were searched up to May 31, 2021 using a

combination of keywords: (“Thyroid Cancer” & [“Cost analysis”, or “Cost-minimization analysis” or “Cost-effectiveness analysis” or “Cost-utility analysis”]) in MEDLINE (PubMed) and Google Scholar. A search was also performed with the same keywords in the Cochrane Database. The resulting 1,323 papers were all searched using the keywords, and after excluding irrelevant papers such as inappropriate literature based on the abstracts and titles, non-English papers, and papers with no access to the full text, 49 papers remained. Among them, we selected examples of straightforward interventions that are easy to understand for thyroid cancer researchers. Four thyroid cancer researchers selected each topic, and one to two examples of each method were selected through discussion and consensus.

RESULTS

Concepts and main methods of economic evaluation

Economic evaluation is a type of comparative analysis between health interventions in terms of both their resource use (costs) and health outcomes [9,10]. Its goal is usually to allocate resources with sufficient efficiency that the maximum outcomes can be expected in a complicated health care environment [9,10].

Based on the methods and outcomes, economic evaluations can be classified into four types: cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), or cost-benefit analysis (CBA) (Table 1) [11]. In these types of economic evaluations, costs are measured in the same way, but the outcomes (cost, effectiveness, utility, and benefit) and their measurement methods are different.

CMA is a method of selecting a more economical intervention by comparing the cost of the interventions when the clinical effects (e.g., in terms of therapeutic effects between generics and patent medicines, safety and tolerability, and quality of life) of each intervention is the same as a prerequisite [12]. It calculates the additional cost of the intervention compared to the comparative intervention for one thyroid cancer case. An assumption of this approach is that the intervention and the comparative intervention have the same effect. A positive number indicates additional cost and a negative number indicates reduced cost. CMA has the benefit of simple and easy interpretation, and it is commonly used to compare generics and patent medicines as standard medications. However, CMA is inappropriate when there are differences in the effects of the intervention and comparison or in the measures and units of the effects.

If the clinical outcome and input cost of the targeted interven-

Table 1. Basic Concepts of Economic Evaluation

Method	Description	Measures	Indicators
Cost-minimization analysis (CMA)	Comparison of costs when the intervention group and comparison group have clearly equivalent clinical effects	Only the cost is measured; the effects are not measured since these are assumed to be equal.	Excess or additional cost per case
Cost-effectiveness analysis (CEA)	Comparison of the relative ratio of cost and effectiveness between an intervention group and a comparison group, which are estimated as different values	This method calculates the cost difference (numerator) of the two interventions per the difference in outcomes (denominator) of the two interventions as the ICER. The ICER indicates the incremental (decreased) cost per 1 unit of increased effectiveness.	ICER
Cost-utility analysis (CUA)	Comparison of different diseases or projects with different units of measure, considering quality of life (health status)	This method calculates the cost per 1-unit increment of the effect on the health status as the ICUR. A life-year at perfect health status is considered as 1 QALY and a life-year at death is 0 QALY.	ICUR
Cost-benefit analysis (CBA)	Method of converting all possible alternatives into monetary values and comparing the benefits per cost (in monetary terms) of the alternatives	Monetary units	BCR

ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; QALY, quality-adjusted life-year; BCR; benefit-cost ratio.

tion and the comparative intervention are different, we calculate the cost difference (numerator) of the two interventions per the difference in outcomes (denominator) of the two interventions, which is the additional cost of the targeted intervention per a 1-unit increment of the outcome. Here, the result of each intervention is clinical effectiveness for CEA and quality of life for the CUA. The incremental cost-effectiveness ratio (ICER), which identifies the incremental (decreased) cost per 1-unit increased effectiveness, is used in the CEA framework [13]. CEA is the main decision-making tool in economic evaluations, and the effectiveness of interventions is measured in “natural units,” such as the recurrence rate, complication-free survival, complication incidence, or life-years [7]. For decision-making, it is necessary to compare the estimated ICER with the maximum acceptable ICER, which represents the maximum amount that society is willing to pay for an additional unit of health outcome [14]. The main advantage of CEA is that measuring outcomes in natural units simplifies the analysis, making it intuitive and facilitating easier communication among physicians. However, CEA faces limitations when comparing different diseases or projects with different measurement units. As another limitation, CEA overlooks quality of life; therefore, CUA has been suggested as an alternative method for analysis [8]. Similar to CEA, CUA uses the incremental cost-utility ratio (ICUR) as the outcome. The ICUR is defined as the incremental (decreased) cost per 1-unit of increased utility (quality of life or quality-adjusted life-year [QALY] due to thyroid cancer treatment or com-

plications). Additionally, some previous studies dealt with quality of life or QALY from cancer treatment and complications as measures of utility [15-17].

CBA is a method of converting all possible alternatives into monetary values and comparing the benefits per cost (in monetary terms) of the alternatives. CBA compares the benefits of two alternatives according to their costs. To choose between alternatives, the costs should be assessed for both alternatives. If the costs of both alternatives are the same, the alternative with the larger benefit would be selected [18]. It is a method of measuring the opportunity cost of investing resources for their efficient allocation. CBA estimates the benefit per cost of a specific intervention, reported as the benefit-cost ratio (BCR). A BCR is greater than 1 indicates that the net present value of the project exceeds zero [19]. The BCR is commonly used in commercial transactions, business or policy decisions, and project investments [20]. When evaluating the economic value of interventions for medical health services, CBA is rarely used because it is difficult to assign a monetary value to clinical results [19]. Therefore, in the latter context, it is recommended to use CEA or CUA.

Of particular note, in economic evaluation, the main economic evaluation method should be selected before constructing the analysis model. The model can be a decision tree or Markov model (Supplemental Fig. S1). A decision tree model consists of decision nodes (squares), chance nodes (circles), probabilities, and outcome nodes (triangles), as shown in Supplemental Fig.

S1A. A decision node is defined as a point where the decision-maker makes a choice. A chance node is defined as a probabilistic event beyond the control of the decision-maker. In addition, each chance node has probability branches, the sum of which should be 1. The probability can be estimated from actual data or a literature review. A Markov model is conducted based on the health status of a study population during an observation period. It has a constant rate of health transition for each health status over time, and it accumulates the cost or quality of life while individuals stay in that health status. The health statuses used in a Markov model should be mutually exclusive, and the model should have as simple a design as possible. Additionally, as shown in Supplemental Fig. S1B, there is a probability of moving to and from each state, which is defined as the transition probability. The sum of the transition probabilities for moving from each health status to other statuses should also be 1 (e.g., probability of moving from mild status to mild status, 0.37; from mild to moderate, 0.49; from mild to severe, 0.11; and from mild to death, 0.03; $0.37+0.49+0.11+0.03=1$).

Costs and outcomes as key elements in economic evaluation

Costs

One of the main challenges in economic evaluation analyses is to decide which costs should be included and how these costs should be measured and valued. Costs can be divided into direct, indirect, and intangible costs (Fig. 1) [21]. Direct costs can be divided into medical and non-medical costs. Direct medical costs are further divided into fixed costs, which must be paid irrespective of treatment (e.g., facility management and building leases), and variable costs, which vary depending on the amount of health care resources used (e.g., inpatient, outpatient, and

pharmaceutical costs). Non-medical costs encompass transportation for outpatient, inpatient, and social services [22]. Because of individuals' personal interest in their health status, it is also necessary to consider health supplements and alternative medicine within the category of complementary and alternative medicine (CAM) [23]. Although CAM is not included as a medical cost, it is relevant for a detailed accounting of non-medical costs. Indirect costs include loss of productivity, the value of the output lost due to a patient's death (converted to monetary value), and inpatient time loss due to a patient's morbidity or injury. Intangible costs are those incurred for psychological damages such as a patient's anxiety and pain (converted to monetary value) [22]. Intangible costs are treated as a type of outcome in CEA and CUA, but as costs in CBA.

The value of current costs and future costs cannot be compared equally. Due to the time preference for the present, the value of future costs (the future monetary value) is lower than that of current costs (the current monetary value) [24]. The discount rate is used to correct for the future value. If the discount rate is 3% and considered 5-year of period the following formula can be applied: $[\text{present value}] = [\text{future value}] \times 1 / (1 + 0.03)^5$. The discount rate is applied in the process of assessing costs and benefits at different times. The discount rate varies depending on the economic status of each country and its health care system, and it should be considered in economic evaluations.

Outcomes

Outcome indicators vary depending on the types of economic evaluation. They can be divided into (1) clinical outcomes, (2) psychosocial outcomes, and (3) economic outcomes. Clinical outcomes consist of complication-free survival, morbidity, mor-

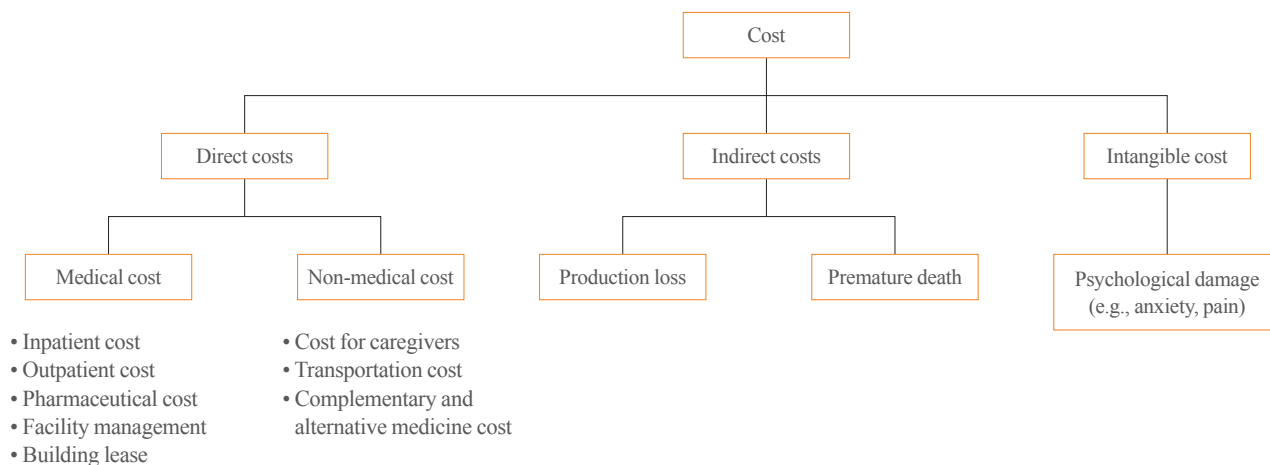


Fig. 1. Main types of costs in economic evaluations.

tality, or complications resulting from interventions for thyroid cancer recurrence. Psychosocial outcomes consist of utility-based quality of life metrics (e.g., QALY). In particular, QALY is a generic measure of the outcome of medical interventions, including both the quality and the quantity of life [25]. The duration of time an individual is likely to spend in a health condition is weighted by a utility score from standard valuations (Fig. 2). Health-related quality of life is generally expressed on a numerical scale ranging from 0 (death) to 1 (perfect health), and it assumes that a year lived in perfect health is worth 1 QALY [25]. QALY is usually used for CUA. Lastly, economic outcomes include productivity loss, such as absence from work and work changes.

In CEA, clinical outcomes are mainly used as indicators of effectiveness, whereas in CUA, psychosocial results that have been adjusted for quality of life are mainly used as indicators of utility. Economic outcomes are generally included as indirect costs when estimating costs. In CBA, the benefit of an investment is estimated by considering the increase or decrease of all the above-mentioned results after the implementation of a specific program.

Examples of economic evaluation in previous thyroid cancer studies

Cost minimization analysis

A previous study conducted in 2014 in Hong Kong sought to determine whether total thyroidectomy or total thyroidectomy with prophylactic central neck dissection was more cost-saving for nodal-negative (cN0) papillary thyroid cancer (PTC) (Table 2) [26]. A hypothetical model was applied based on a decision tree design for 20 years. The reference case was a non-pregnant fe-

male patient aged 50 years with a unifocal intrathyroidal 1.5-cm cN0 PTC. For cost estimation, the study applied an institutional perspective, considering only direct costs. For medical services provided within the national or state health care system, direct cost information was estimated from the government website or its publications. As cost items, workup procedures, complications, hospitalizations, and drugs related to the operation were included and derived from the government database. The probability of death based on reoperation, complications, or non-thyroidal causes following initial surgery was estimated from the literature. A 3% discount rate was applied for cumulative cost calculation, a sensitivity analysis was conducted, and the increased cost per patient was presented as economic evaluation indicators. The CMA analysis suggested that total thyroidectomy alone is less costly than total thyroidectomy with prophylactic central neck dissection in nodal-negative PTC (\$6,702.81 vs. \$10,062.35), with a consistent finding also reported for 20-year cumulative costs (\$19,888.36 vs. \$22,760.86).

Cost-effectiveness analysis

Many previous economic evaluation studies compared interventions to assess which management strategy (e.g., different surgery types) is more appropriate in thyroid cancer patients (Table 2) [27,28]. The two studies selected as examples of CEA compared two thyroid cancer surgical methods by calculating the additional costs per 1-unit increment of the clinical effectiveness of each surgical method relative to each other [27,28]. In a 2007 study, surgical complications, cause-specific mortality, the survival rate, and the recurrence rate were defined as effectiveness metrics for hemi-thyroidectomy and total thyroidectomy (Table 2) [27]. To assess the effectiveness of each intervention, a Markov model was constructed with a 20-year follow-up period. The probability of effectiveness according to the intervention was derived from the literature. For cost estimation, that study applied direct costs, such as diagnostic examinations including ultrasonography or fine-needle aspiration, surgery, and non-surgical treatment based on the New York state government and Medicare cost databases. The value of death resulting from unintentional impairment was also considered. The discount rate was defined as 6%, and the sensitivity analysis suggested acceptable thresholds for various parameters. The researchers concluded that total thyroidectomy was cost-effective compared to hemi-thyroidectomy based on the ICER. Total thyroidectomy was predominantly cost-effective based on overall survival (ICER: total thyroidectomy, \$13,979; hemi-thyroidectomy, \$15,184), recurrence-free survival (ICER: total thyroidectomy,

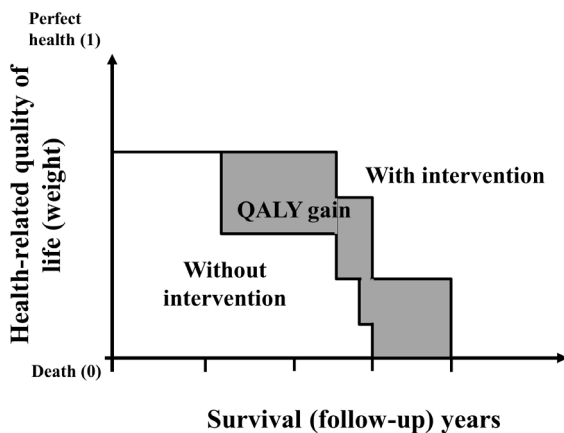


Fig. 2. Basic principle of the quality-adjusted life year (QALY) in economic evaluations.

Table 2. Summary of Previous Studies That Conducted Economic Evaluations Focusing on Thyroid Cancer

Study	Country	Patients	Intervention [I] Comparison [C]	Direct cost [DC] Indirect cost [IC]	Outcomes	Analysis	Results and conclusion
Lang et al. (2014) [26]	Hong Kong	100,000 Hypothetical non-pregnant female patients in a cohort at age 50 years with low-risk PTC (1.5-cm cN0 PTC within one lobe)	[I] TT with pCND [C] TT alone	[DC] 20-Year cumulative cost, including procedural, hospitalizations, annual routine surveillance (hospital costs published in the 2013 Government Gazette) [IC] Not included 3% discount rate	Excess cost per case	Hypothetical model based on decision-tree design	TT+pCND is more expensive in the medium- and long-term in low-risk PTC patients TT: USD 19,888.36 (20-year cumulative cost) TT: USD 19,888.36 (20-year cumulative cost) TT+pCND: USD 22,760.86 (20-year cumulative cost) Incremental cost: USD 2,872.50 Sensitivity analyses: no change
Shrime et al. (2007) [27]	Literature review from PubMed search 940 PTC citations published from January 1, 1966 to January 1, 2007	1 Million hypothetical low-risk PTC cases (age, metastasis, extent, and size of tumor [AMES] score <6, an AGES score <4, or adherence to the Memorial Sloan-Kettering low-risk categories)	[I] HT [C] TT	[DC] Hospital charges for inpatient operative procedure, follow-up costs, complication costs, and recurrence costs from Medicare [IC] Costs for death from unintentional injuries: \$1,130,000 based on the National Safety Council estimates	Cost and ICER for CSM or RFS CSM or RFS under the same cost assumption CSM and RFS were derived from a literature review (31 studies were finally selected)	Monte Carlo microsimulation using the fixed probability estimates of complications and recurrence derived from the 31 eligible studies Sensitivity analyses using a 6% annual discount and cost-to-cost ratio estimated from the 31 eligible studies Threshold analyses: comparison of net monetary benefits obtained from TT and HT using a variable range of WTP values	TT dominates HT as initial treatment for low-risk PTC 20-Year ICER for overall survival: [I] HT, \$15,184; [C] TT, \$13,979 20-Year ICER for RFS: [I] HT, \$15,464; [C] TT, \$20,005 TT is consistently cost-effective in Monte Carlo simulations Sensitivity analyses: HT was sensitive to recurrence rates and follow-up costs Threshold analyses: robust when compared with WTP
Guo et al. (2018) [28]	China	256 PTC patients who underwent TT and BND	[I] TT with simultaneous BND [C] TT with two-stage BND	[DC] Hospital charges for surgery and related charges during hospital stays were obtained [IC] Accommodation, meals, and transportation fees	Cost for DFS during a mean follow-up of 5 years	Cost-effectiveness analysis was performed using a retrospective cohort. Sensitivity analyses: not done Threshold analyses: not done Discount rate was not applied	Simultaneous BND was more cost-effective for the management of PTC patients than two-stage BND Two-stage BND was recommended in cases of internal jugular vein invasion 5-Year cost of surgery: simultaneous BND, \$4,145.32; two-stage BND, \$7,352.53 Cost per DFS: simultaneous BND, \$4,423.34; two-stage BND, \$8,158.25

(Continued to the next page)

Table 2. Continued

Study	Country	Patients	Intervention [I] Comparison [C]	Direct cost [DC] Indirect cost [IC]	Outcomes	Analysis	Results and conclusion
Walgama et al. (2020) [29]	USA	Hypothetical T2N0M0 PTC patients with undiscovered ipsilateral vocal fold paralysis.	[I] Preoperative laryngoscopy prior to TT [C] No preoperative laryngoscopy prior to TT	[DC] Medicare reimbursement data in Medicare from 2019 and the recent medical literature [IC] Not included 3% discount rate	Cost-effectiveness measured by ICER (Δ Cost/ Δ QALY) Ipsilateral and contralateral vocal fold paralysis, as well as hypoparathyroidism over 30 years	Decision tree model with literature-based probabilities Sensitivity analyses: varying the rate of VCP and selected variables. Monte Carlo simulation was performed to determine the overall uncertainty of the model. Threshold analyses: threshold of \$100,000/QALY	Fiberoptic laryngoscopy is cost-effective prior to TT in asymptomatic, low-risk thyroid cancer patients Preoperative laryngoscopy has an ICER of \$45,193/QALY compared to no laryngoscopy Sensitivity analyses: laryngoscopy is cost-effective in 90.9% of cases Threshold analyses: the intervention is cost-effective if the incidence of vocal fold paralysis is at least 0.57%, or when the permissible rate of HT in cases of incidental paralysis is at least 41%
Kuo et al. (2018) [30]	USA	A euthyroid 40-year-old patient with an incidentally discovered thyroid nodule measuring 1 cm. The reference case did not have any clinical or radiologic evidence of cervical nodal metastases, neck surgery, radiation, or family history of thyroid cancer.	[I] Ultrasound surveillance [C] Immediate biopsy	[DC] Medicare reimbursement data in 2016, hospitalization cost data from the Nationwide Inpatient Sample, and a literature review. A 3% annual discount rate was applied to all future costs. [IC] Not included	40-Year quality-adjusted life expectancy measured by ICER (Δ Cost/ Δ QALY) Effectiveness was measured in QALY. Each transition-state in the model was assigned a quality-adjustment factor based on literature and previous work. Event outcomes were natural history of thyroid nodules and thyroid cancer, test performance of thyroid FNA, and surgical outcomes of thyroidectomy and neck dissection.	Markov transition-state model with probabilities obtained from the literature and expert opinion Sensitivity analyses: one-way and two-way sensitivity analyses and a Monte Carlo simulation were performed Threshold analyses: threshold of \$100,000/QALYs	US surveillance is more cost-effective than immediate biopsy for 1.0-cm thyroid nodules with an intermediate-suspicion sonographic pattern US surveillance was \$1,829 less costly and 0.016 QALYs more effective than immediate biopsy Sensitivity analyses: immediate biopsy became cost-effective when the probability of malignancy increased from 15% to 84% or the cost of US increased from \$129 to \$793. Threshold analyses: robust when compared with WTP

PTC, papillary thyroid cancer; TT, total thyroidectomy; pCND, prophylactic central neck dissection; USD, US dollar; AGES, Age Grade Extent Size; HT, hemi-thyroidectomy; ICER, incremental cost-effectiveness ratio; CSM, cause-specific mortality; RFS, recurrence-free survival; WTP, willingness to pay; BND, bilateral neck dissection; DFS, disease-free survival; QALY, quality-adjusted life-year; VCP, vocal cord paralysis; FNA, fine needle aspiration; US, United States.

\$15,464; hemi-thyroidectomy, \$20,005) compared to hemi-thyroidectomy. However, it showed heterogeneity according to the institution in long-term treatment outcomes.

Another study focused on two intervention strategies for bilateral neck dissection (BND): simultaneous and two-stage operations (Table 2) [28]. Patients with bilateral PTC from 2006 to 2012 who did not have a prior history of surgery or radiation exposure comprised the study population. Their pathology records were identified from postoperative clinical data. Surgical and medical expenses including neck dissection, ultrasonography, computed tomography, fine-needle aspiration, and outpatient, inpatient, and postoperative treatment charged by the hospital were considered as medical expenses. As indirect costs, accommodation, meals, and transportation fees were included. Disease-free status was defined as serum thyroglobulin levels of 1 ng/mL after recombinant human thyroid-stimulating hormone (TSH) therapy, negative neck ultrasound findings, and undetectable thyroglobulin antibody. A discount rate was not considered, and sensitivity and threshold analyses were not performed. The simultaneous BND strategy (cost-effectiveness ratio, defined as the cost per disease-free survivor: \$4,423.34) was more cost-effective than the two-stage BND strategy (cost-effectiveness ratio: \$8,158.25). However, two-stage BND was recommended in cases with invasion of the internal jugular vein.

Cost-utility analysis

CUA is a type of CEA used to compare the cost of a target intervention and a comparative intervention for thyroid cancer and the effect on the health status of patients who receive the intervention to determine the cost per 1-unit increment of the effect on health status. A life-year at perfect health status (theoretical life-year) is considered as 1 QALY and a life-year at death is 0 QALY [25]. In thyroid cancer, the meaning of “perfect health” is the status of no complications or no recurrence after primary treatment of thyroid cancer or having the best quality of life after maintenance treatment. The former two scales can estimate QALY as a value distributed between 1 QALY in the optimal state and 0 QALY in the death state using complications or recurrence-free years in the population. When using a health-related quality of life questionnaire such as the 36-item Short-Form Health Survey, the optimal quality of life is 1 QALY and the worst quality of life is 0 QALY [7,8]. QALY values between 0 and 1 can be estimated through the distribution of scores in each questionnaire and the validation of weights in a randomly selected sample population [7,8,25]. However, the conversion method depends on whether QALY is measured as a value at a

single point in time or a cumulative value over several years; therefore, it is necessary to clarify how the results will be operationalized in advance.

A study published in 2020 conducted CUA for fiberoptic laryngoscopy prior to total thyroidectomy in low-risk thyroid cancer patients (T2N0M0 PTC) based on a decision model for 30 years (Table 2) [29]. The study only considered direct costs, which were converted into 2019 direct costs according to public expense data (Medicare) and the literature with a 3% discount rate. The probabilities and health utility values (ipsilateral and contralateral vocal fold paralysis, as well as hypoparathyroidism) in the model were derived from the literature including complication-free survival years and recurrence-free survival years according to the intervention. The threshold for willingness-to-pay was defined as 100,000(\$)/QALY. Given the sensitivity analysis, cost-acceptability curve, and time horizon according to each parameter in CUA, fiberoptic laryngoscopy prior to total thyroidectomy was found to be cost-effective for low-risk thyroid cancer patients (\$45,193/QALY) and acceptable based on the willingness-to-pay threshold. As a sensitivity analysis, laryngoscopy was found to be cost-effective in 90.9% of cases, and the intervention was cost-effective if the incidence of vocal fold paralysis was at least 0.57%.

Another topic of interest is the immediate biopsy and active surveillance of thyroid nodules at 1-cm levels (Table 2) [30]. Therefore, a Markov model was constructed for CUA between immediate biopsy and active surveillance, and the reference case was a 40-year-old woman with 1-cm nodules in 2018. As inclusion criteria, the study considered patients without clinical or imaging evidence of cervical nodal metastases, a history of radiation exposure, or a family history of thyroid cancer. The outcome was defined as the performance and surgical outcomes of fine-needle aspiration, and the probability was derived from the literature. If the probability could not be identified from the literature, it was replaced by expert opinion. The effectiveness of each intervention was measured in QALYs. The time period was 50 years, but the interval of the ultrasound examinations was specifically set according to the nodule condition. For costs, medical and hospitalization fees were considered from the Medicare database or obtained from the literature if they could not be identified from the database, and a 3% discount rate was applied. The threshold value for willingness-to-pay was defined as \$100,000/QALY. Through sensitivity analyses, the dominance point between active surveillance and biopsy was identified, as was the change in ICUR according to the malignancy probability. As a conclusion, active surveillance with ultraso-

nography was more cost-effective than an immediate biopsy (incremental cost, \$1,829; QALY, 0.016), with consistent dominance when the probability of malignancy is less than 84% and if the cost of ultrasonography does not exceed \$793. However, if active surveillance caused considerable anxiety, immediate biopsy was more effective; therefore, quality of life should be considered for each intervention.

Cost-benefit analysis

CBA is generally used as a preliminary feasibility assessment of financial projects or as an analysis comparing the cost-benefit ratio between interventions. For example, rapid-transit railway enterprise and new town developments are domains where CBA has been widely performed. A single intervention can be judged as an economical project if the BCR is greater than 1 or if the net benefit is greater than 0. However, no previous CBA studies have been conducted on thyroid cancer.

DISCUSSION

In this study, the concept and methods of economic evaluation were summarized briefly with a focus on thyroid cancer, and we intended to help readers understand economic evaluation based on examples from previous studies. To conduct an economic evaluation for thyroid cancer, the definitions of several key elements should be discussed and clarified between researchers.

The first points to consider are direct, indirect, and intangible costs [21]. Most previous studies used direct costs, but some studies also used complication costs, the value of death, and indirect costs [26-30]. Previous thyroid cancer studies used discount rates of 3% to 6%, although there were variations across countries and research periods. Costs were most commonly obtained from public expenditure databases such as Medicare or the previous literature, and the probabilities of outcomes according to interventions were derived from previous studies [26-30]. For the economic evaluation analyses, decision tree or Markov models were applied as hypothetical models.

The second point to consider is the outcome. In CMA, it is common to present an excess cost per case or patient, assuming the same effect. However, most previous studies compared costs between interventions, which requires a clear distinction [31-36]. Because of the universality of the term “CEA,” regardless of the study type, numerous CUA studies have been reported as CEA studies, and the indicators were also presented as the ICER, not the ICUR [37-41]. It is possible to evaluate whether the derived ICER or ICUR is socially acceptable compared to

thresholds for decision-making, as social acceptability defines the concept of willingness-to-pay. Socially acceptable marginal costs vary from country to country and over time. In studies in the United States, the cost per QALY is considered socially acceptable if it is lower than *per capita* gross domestic product (GDP). In 2008, the United States *per capita* GDP was about 48,000 dollars, and the United States threshold was therefore \$50,000/QALY [42].

A highlight of recent research on thyroid cancer is the economic evaluation of surgery and active surveillance in patients with low-risk thyroid cancer [33,34,40,43]. Due to the high survival rate and good prognosis of low-risk thyroid cancer, especially papillary thyroid microcarcinoma (PTMC), the American Thyroid Association recommended that immediate surgery is not necessary for patients with low-risk tumors such as PTMC without clinically evident metastases or local invasion [44]. However, active surveillance using ultrasonography also leads to an economic burden in the long term, and patients may also live with the anxiety that cancer might develop. These points need to be considered in an economic evaluation. In this context, a prospective cohort for PTMC patients in Korea (Multi-center Prospective Cohort Study of Active Surveillance on Papillary Thyroid Microcarcinoma [MAeSTro]) was conducted to compare lobectomy and active surveillance in 2016 [45]. MAeSTro is a pragmatic cohort study with the aim of evaluating the evidence regarding whether active surveillance is helpful in reducing unnecessary surgery in patients with small, low-risk thyroid cancer. Thyroid cancer recurrence, complications, and quality of life were compared as measures of effectiveness between the two interventions. Furthermore, researchers at the Korean Thyroid Association launched a practical clinical trial (the Multicenter Randomized Controlled Study for Assessing the Usefulness of Suppressing Thyroid Stimulating Hormone Target Levels after Thyroid lobEctomy in Low to Intermediate Risk Thyroid Cancer Patients [MASTER] study) for thyroid cancer patients who underwent lobectomy for low-risk and intermediate-risk cancer to compare recurrence, quality of life, and complications (including cardiovascular disease, osteoporosis, and metabolic disease, and musculoskeletal disease) [46]. For the first study, if the effects of the two interventions are the same, the economic benefit can be evaluated through CMA. The second study aims to establish evidence about how long TSH levels should be maintained in TSH suppression therapy. The degree of levothyroxine use differs according to the maintenance of TSH levels; thus, TSH suppression therapy has both clinical benefits and risks. Therefore, in addition to CEA, an

evaluation through CUA considering quality of life should be performed.

CONCLUSIONS

In this study, we described the concept and methods of economic evaluation and reviewed previous studies focusing on thyroid cancer. Thyroid cancer has a favorable prognosis, with a high chance of long-term survival. Because of the characteristics of thyroid cancer, it is controversial whether the medical costs administered for thyroid cancer are appropriate. In particular, in countries with a national health insurance system such as Korea, it is necessary to select the most efficient and optimal method to support various medical services in a balanced way within limited financial resources. Economic evaluation is a method for making optimally cost-efficient choices in a resource-limited setting. By understanding and applying the precise concepts and methods of economic evaluation, we can produce comparative results to elucidate controversial issues in an evidence-based manner. Economic evaluation studies are expected to provide appropriate guidelines for thyroid cancer surveillance, diagnosis, and management.

CONFLICTS OF INTEREST

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

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