Determination of the Best Treatment Option in Stage III, Resectable, Non-small Cell Lung Cancer Patients by Decision Analysis Method

M. Bahadır Berktaş[1], Ergun Karaağaoğlu[2]

[1]Atatürk Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları , Ankara, Turkey
[2]Department of Biostatistics, Hacettepe University Faculty of Medicine, Ankara, Turkey

Abstract

The aim of this study was to determine the best treatment strategy in stage III, resectable non-small cell lung cancer (NSCLC) patients by decision analysis method. A decision tree was prepared with data collected from randomized clinical trials containing the treatment in this group of patients. Treatment outcomes were evaluated by life expectancy measure. "Quality- adjusted life expectancy" measure and Markov models were used to evaluate the effects of treatment methods on patient quality of life. Baseline utility values were estimated from similar studies and sensitivity analyses were conducted with a broad range of values. The predictions reached by these models were in agreement with the present treatment preferences. If quality of life was excluded, neoadjuvant, concurrent chemoradiotherapy provides 0.21 year more life expectancy than immediate surgery and adjuvant therapy. Concurrent chemoradiotherapy provides 0.97 year more life expectancy than sequential chemoradiotherapy. As a neoadjuvant treatment, chemoradiotherapy obtains 1.74 years longer life expectancy than chemotherapy alone. But when decision analysis was calculated by "quality- adjusted life expectancy" measure or Markov models, the strategy consisting of immediate surgery and postoperative chemotherapy was the best treatment strategy (but with only 0.05 year longer quality-adjusted life expectancy). Both of these models were found sensitive to utility values. If utility values of patients could be established confidently and accurately, the decision analysis method can be used successfully for the determination of the best treatment option.

Keywords: lung cancer, treatment, non-small cell, stage III, neoadjuvant, chemotherapy, radiotherapy, decision analysis, decision tree, Markov models

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INTRODUCTION

Locally advanced non-small cell lung cancer (NSCLC) is a major cause of morbidity and mortality. Based on the collected series of 5,230 patients with NSCLC seen from 1975 to 1988 at the M.D. Anderson Cancer Center, 30% of all patients have locally advanced disease at initial presentation. In this group of patients, stage IIIA group forms the most therapeutically challenging and controversial subset of patients with lung cancer, with a published five-year survival of only 23% [1]. These patients have been the subjects of a wide variety of clinical trials incorporating various combinations of chemotherapy, radiotherapy, and surgery. Despite the large amount of clinical research, it remains unclear how patients with stage III NSCLC should be managed [2]. This status is further complicated by differential adoption of clinical trial results [3] and demonstrated diversity in patterns of practice [4,5].

Decision analysis, used in medicine for more than three decades, has been promoted as useful when the clinical or policy decision complex and information are uncertain [6-8]. As stage III NSCLC has a large public health impact, substantial practice variation, and controversy over treatments, decision analysis might be useful [9].

Brundage and colleagues used decision analysis to bring clarity to the choice of combined chemotherapy plus radiation versus radiation alone [10]. The two models they developed worked reasonably well and they demonstrated that decision analysis has the potential to guide therapy in locally advanced NSCLC. We also evaluated this potential, but we included a resectable subgroup of stage III NSCLC patients in our study, so we incorporated surgery as an option in treatment choices. Additionally, we analyzed more recent data from clinical trials, especially studies using a neoadjuvant approach.

The aim of this study was to determine the best treatment option in stage III, resectable NSCLC patients by decision analysis method. Neoadjuvant treatment approach was compared directly with surgery for this purpose. Chemotherapy, radiotherapy and chemoradiotherapy choices as adjuvant and neoadjuvant strategies were evaluated. Also, concurrent chemoradiotherapy approach was compared with sequential chemoradiotherapy approach in neoadjuvant treatment.

Decision analysis was also undertaken to define the most important parameters involved in this decision-making process. The threshold values that would lead to a change recommendation in the decision were determined.

Corresponding Author: M. Bahadır Berktaş, Atatürk Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları, Ankara, Turkey,
E-mail: bahadir.berktas@gmail.com

Table 1. Probabilities used in decision analysis

Probabilities	Baseline probability	Accepted range of probability	Source
Complete resection of tumor with neoadjuvant chemotherapy	0.650	0.510-0.680	Memorial Hospital [19,20] Toronto [21], LCSG 881 [22]
Fatal toxicity with neoadjuvant chemotherapy	0.065	0.031-0.067	Darwish [23] Depierre [24], Date [25], CALGB 8935 [26]
Complete resection of tumor with neoadjuvant, concurrent chemoradiotherapy			
By standard fraction radiotherapy	0.710	0.520- 0.710	SWOG 8805 [27] LCSG 852 [28], Ahn [29]
By hyperfraction radiotherapy	0.530	0.530-0.920	Eberhardt [30],Choi [31]
Fatal toxicity with neoadjuvant concurrent chemoradiotherapy			
By standard fraction radiotherapy	0.080	0.040- 0.170	SWOG 8805 [27] Faber [32], Langer [33]
By hyperfraction radiotherapy	0.064	0.050-0.120	Eberhardt [30] Taylor [34], Rice [35]
Complete resection of tumor with neoadjuvant, sequential chemoradiotherapy	0.770	0.770-0.880	Takamori [36], Skarin [37]
Fatal toxicity with neoadjuvant sequential chemoradiotherapy	0.030	0.017-0.087	Pisch [38] Comella [39], Elias [40]
Completely resection of tumor with immediate surgery	0.860	0.860-0.880	Depierre [41] Quoix [42]
Death with immediate surgery	0.045	0.045-0.120	Depierre [41], Harpole [43]
Death with adjuvant chemotherapy	0.000	0.000-0.022	Ohta[44]
Death with adjuvant chemoradiotherapy	0.016	0.016-0.087	Keller[45], Dautzenberg[46]
Death with adjuvant radiotherapy	0.013	0.013-0.039	Dautzenberg[46], Dautzenberg[47]

MATERIALS AND METHODS

Information resources

The identification of relevant health states, their probabilities of occurrence with each treatment, and their associated utilities are needed for the development of decision models. A computer literature search with MEDLINE and CANCERLIT was used to gather information for decision analysis. References that included the keyword "non-small cell lung cancer" were retrieved. We then selected data from randomized clinical trials and metaanalyses containing the treatment of stage III, NSCLC. Moreover, the reference lists of each retrieved report as well as lists from recent meetings of a related topic were scanned for potential eligible reports.

Decision analysis model

We used two-step approaches. Life expectancy as a utility measure (treatment outcomes) was used in the first step. Quality-adjusted life expectancy measure and Markov models were used in second step for the evaluation of effects of quality of life on treatment preferences. For this reason, both quality and quantity of life were considered when preparing decision models. We used a "declining exponential approximation of life expectancy (DEALE)" [11] similar to that of other published decision analyses in oncology [10,12-16]. In the DEALE model, the percent of patients surviving (S) in time (t) was defined by the exponential function $S = 100\ (e^{-\lambda t})$ %, where λ is the annual mortality rate. Life expectancy for a patient under this model is equal to $1/\lambda$. Validated survival functions for patients with resectable, stage III NSCLC have not yet been developed even though more complex survival functions have been proposed [17,18]. The quality of life multiplier Q is then applied to this life expectancy to consider differences in survival quality between treatment approaches. Quality-adjusted life expectancy (QALE) is equal to "Q/λ", and gives a measure of quality-adjusted life-years (QALYs). We used a cohort of 60-year–old, stage III, resectable, NSCLC patients immediately after diagnosis. Base mortality rates were taken from life tables for both genders of the country of the study population.

Probabilities

Baseline probabilities and life expectancy values used in our models were obtained from published data [19-58] (Tables 1, 2). Reasonable ranges of probabilities and life expectancy values for sensitivity analyses were taken from maximum and minimum values reported in comparable studies. Well-designed and peer-reviewed studies and studies based on a large number of patients were chosen as a data source. At least one-third of the study population included stage III, NSCLC patients evaluated for decision analysis.

Assignment of utilities

We used life expectancy and QALE as a utility scale in our analysis and we assigned a value for life expectancy of zero for early deaths that result from adverse effects of treat-

Table 2. Life expectancy data used in decision analysis

Patient subsets	Life expectancy (year)	Accepted range (year)	Source
Patients with completely resected tumor after neoadjuvant chemotherapy	2.822	1.864 - 4.894	Memorial Hospital [19,20], Roth [48,49], Rosell[50]
Patients with incompletely resected tumor after neoadjuvant chemotherapy	2.822	1.864 - 4.894	Memorial Hospital [19,20], Roth [48,49], Rosell[50]
Patients with completely resected tumor after neoadjuvant concurrent chemoradiotherapy	5.151	2.383 - 5.151	Eberhardt[30], Ahn[29]
Patients with incompletely resected tumor after neoadjuvant concurrent chemoradiotherapy	3.415	2.023 – 5.029	Eberhardt[30], Ahn[29], Choi[31]
Patients with completely resected tumor after neoadjuvant sequential chemoradiotherapy	3.608	3.208 – 3.808	Takamori[36]
Patients with incompletely resected tumor after neoadjuvant sequential chemoradiotherapy	3.142	1.166 - 3.345	Takamori[36], Comella[39], Pisch[38]
Patients with completely resected tumor by surgery alone and treated by BSC postoperatively	3.011	1.669 - 5.457	van Rens[51]
Patients with incompletely resected tumor by surgery alone and treated by BSC postoperatively	1.905	1.001 – 3.443	LCSG[52], Miller[53], Soorae[54]
Patients treated with adjuvant chemotherapy	4.763	4.763 - 6.090	Ohta[44], Xu[55]
Patients treated with adjuvant chemoradiotherapy	3.011	2.822 - 4.689	Dautzenberg[46], Keller [45], Pisters [56]
Patients treated with adjuvant radiotherapy	4.153	4.119 – 5.908	Dautzenberg[47], Mayer[57], Feng[58]

BSC: Best supportive care.

ment. The adjustments for the quality of life were made by multiplying life expectancy with quality multiplier. Chemotherapy and radiotherapy increase quality of life in patients by decreasing symptomatology despite their toxicities. Paesmans reviewed randomized trials using quality of life as an endpoint and comparing best supportive care with or without chemotherapy and stated that most of the selected trials showed an improvement in quality of life in various components in the chemotherapy arm [59]. Thus, we used a higher value for quality multiplier to these treatments than best supportive care. A lower value was estimated for chemoradiotherapy than for chemotherapy or radiotherapy alone because of combined toxicities augmenting a negative effect on quality of life. Quality multiplier values used in decision analyses are shown in Table 3.

Decision tree

Decision analysis uses a decision tree to consider all the available options and their possible outcomes systematically in solving a problem. We constructed a decision tree (Figure 1) to illustrate treatment alternatives for stage III, resectable NSCLC patients. There were two main strategies of neoadjuvant treatment or direct surgery. Following a decision of neoadjuvant treatment, chemotherapy or chemoradiotherapy approach could be chosen for the neoadjuvant setting. Neoadjuvant radiotherapy option was not included in the tree. This treatment approach was evaluated from 1970-1975 and results of these studies were all negative, so radiotherapy alone as a neoadjuvant treatment has not been utilized thereafter [60,61]. After neoadjuvant treatment and surgery were completed, some tumors could be resected completely and others could not. There was also a probability of death caused by adverse effects of the treatment. These situations were depicted as a chance node (circular node in decision tree). Chemotherapy, radiotherapy, combined chemotherapy and radiotherapy or best supportive care may be followed after direct surgery. All of them had their own treatment-related mortality rates. Life expectancies or QALE's of surviving patients were used as values for utilities for final outcome.

Assumptions and limitations of models

We did not consider short-term morbidity of surgery while developing the QALE model. As both of the main treatment alternatives contributed a similar morbidity risk of surgery, it did not change the result of the decision analysis.

We assumed that the probability of a transition among any given health state of NSCLC patients is independent of the prior transitions, and also that the probabilities of transition are constant over time. We did not take age of patients into account in the Markov model, because mortality rate of stage III, NSCLC patients is so high that the increasing mortality rate with age does not play an important role in the estimation of life expectancy.

We did not directly determine utility values from NSCLC patients, but rather estimated them from comparable health states in published decision and cost effectiveness analyses in oncology [10,62-64]. To our knowledge, there are no published data that compare radiotherapy

Table 3. Utility values (quality of life multiplier) employed in the calculation of quality-adjusted life expectancy

	Utility value	Range tested by sensitivity analysis
Chemotherapy	0.60	0.4 - 0.8
Radiotherapy	0.60	0.4 - 0.8
Chemoradiotherapy	0.55	0.35 - 0.75
Best supportive treatment	0.53	0.33 - 0.73
Incomplete resection	0.45	0.25 - 0.65

with chemotherapy regarding deleterious effect on quality of life. We used the same utility value estimate for radiotherapy and chemotherapy as we assumed that amplitudes of these effects are the same. Also, the magnitudes of toxicities of concurrent and sequential chemoradiotherapy were assumed to be equal.

When constructing the decision tree, we excluded some of the branches from the tree. "Open and close" surgery branch was omitted at the surgery decision node, as these patients should be managed as unresectable patients and this group was not included in our study. The patients with stage IIIA tumor have substantial heterogeneity in clinical presentation, treatment and prognosis. Survivals of patients with T3, N0-1 disease were much better than in patients with N2 tumor after surgical resection [65]. We did not separate these groups of patients, as there was not sufficient data regarding outcome measures and probabilities as required for separate decision analysis of these subgroups.

We evaluated only cisplatin-based chemotherapies as adjuvant or neoadjuvant settings. Studies that used source of data for decision analysis were dispersed over the last three decades. Earlier studies have a number of problems, including inconsistent staging, lack of effective therapeutic agents until recently, and the poor tolerance to chemotherapy in an era lacking strong antiemetic agents [66]. Use of earlier and recent studies together in decision analysis could affect the results.

Markov models

A Markov process is a modeling technique used for a condition in which the prognosis is described by a series of chance events, and the value of these outcomes depends on whether and when they occur [67]. Figure 2 illustrates Markov chains used in the Markov model of prognosis that we used. Markov chains' schemes were adapted from the study of Brundage and colleagues [10]. We reorganized the structure of the Markov chain so that surgery was included at different time points in neoadjuvant and adjuvant treatments. For this reason, objective response rate, survival at two years, early date and two-year disease-free survival parameters were taken from neoadjuvant and adjuvant treatment studies. These data were used to define the Markov model transitions for each treatment strategy.

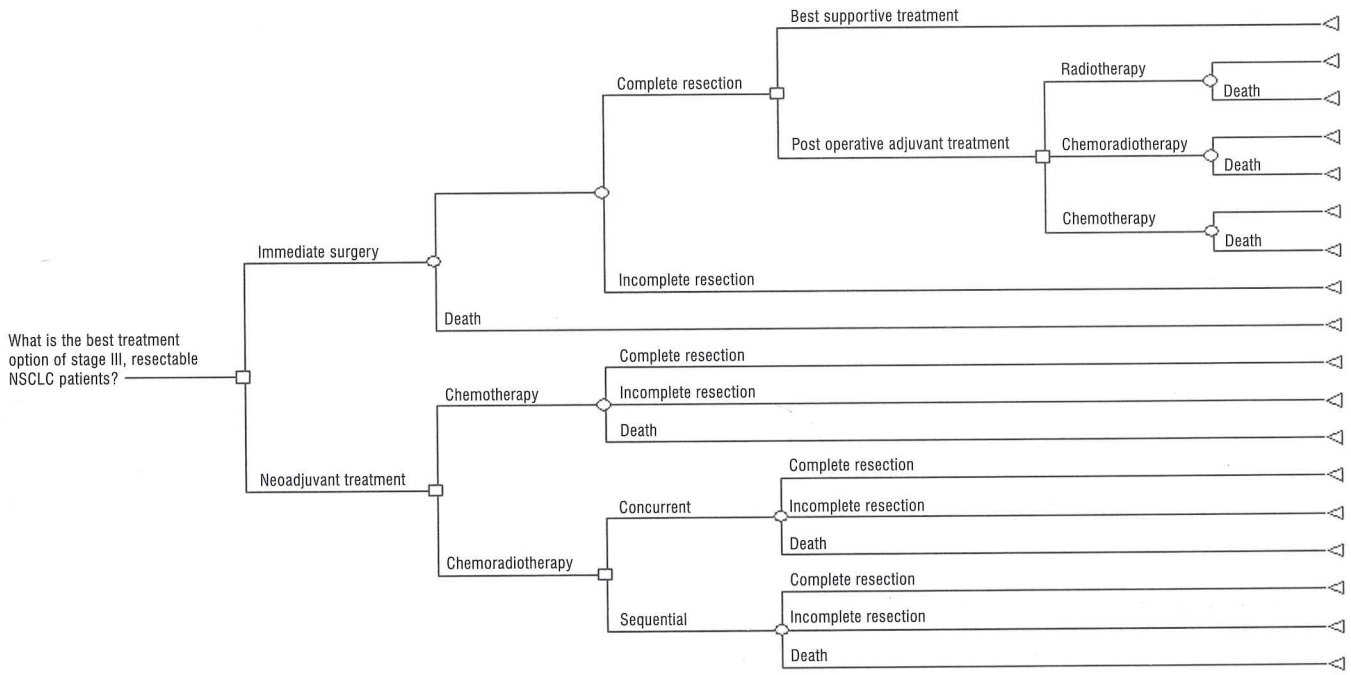

Figure 1. A decision-tree diagram illustrating treatment strategies in resectable, stage III NSCLC patients. The square nodes denote the decision; branches emanating from them represent treatment alternatives. Circular nodes represent chance events that may follow each choice. Triangles represent final outcomes. Values for utilities for final outcomes are expressed as life expectancy or quality-adjusted life expectancy according to the model. Circular nodes on the far right were replaced with Markov chains while calculating life expectancies with the Markov model.

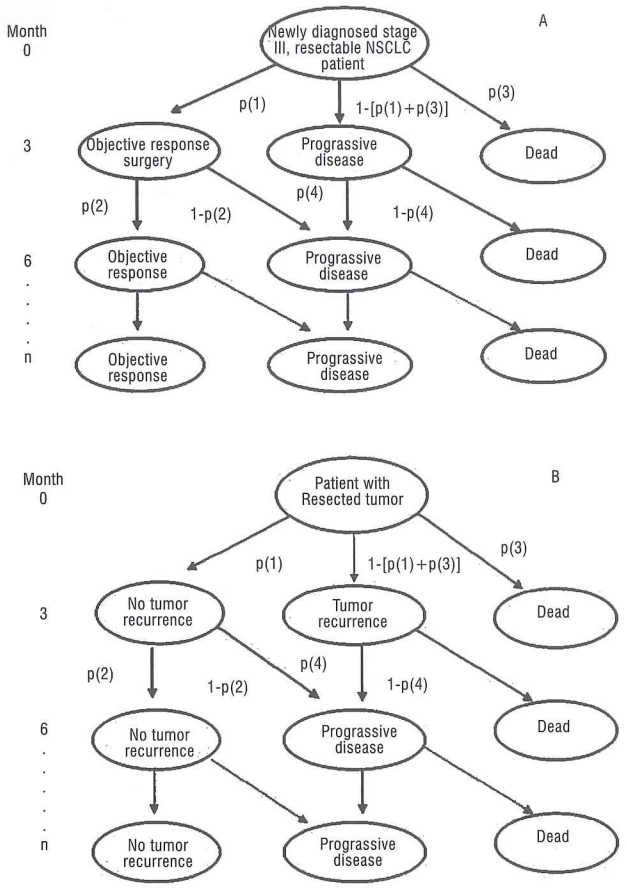

Figure 2. Abbreviated scheme of the Markov chains used in the Markov model of study. (A) Shows three-month Markov cycles for neoadjuvant treatment. All patients start with newly diagnosed, stage III, resectable tumor and symptomatic disease. (B) Shows Markov chain scheme for adjuvant treatment. In this strategy all patients begin Markov cycles after resected tumor and postoperative period. Cancer could recur during any cycle. The probability of recurrence was reduced with adjuvant treatment (from reference 10).

This Markov process is similar to that used in decision analysis in oncology [10,63,68,69]. The figure shows important health states in the natural history of stage III NSCLC. "Health states", a part of the Markov vocabulary, describe defined categories of health or disease that apply to a person for a finite period of time. Time-dependent probabilities determined how the patients moved from one state to another. We selected three months as a length of cycle that determines when transitions to and from the various health states will be allowed.

In the Markov chain used in neoadjuvant treatment strategy for the Markov model, all patients were newly diagnosed, symptomatic stage III resectable NSCLC. After the first cycle (three months), objective response may be obtained with neoadjuvant treatment and surgery is done. Another probability is that objective response could not be obtained and surgery is not considered. Or patients may have died within this period. After the second cycle, objective response states may be sustained or the disease progresses and death can occur within this period. In the Markov chain for adjuvant treatment strategy, all patients began in the postoperative period with resected tumor. After the first cycle tumor, recurrence may be observed or the disease-free state persists. Some patients may die within this period. The model was run until 99.5% of the cohort died.

Calculations

Calculations for the QALE and Markov model were analyzed by DATA 4.0 software (TreeAge Software Inc., Cambridge, MA). First, the expected utilities for each strategy were calculated using the baseline values for probabilities and utilities. Calculations were then repeated as necessary for threshold and sensitivity analyses.

RESULTS

Base-case analysis

We first used crude life expectancy (unadjusted for quality of life) measure for utilities. When radiotherapy with standard fractions was used in concurrent chemoradiotherapy, neoadjuvant treatment was the preferred strategy compared with direct surgery and adjuvant treatment. The magnitude of life expectancy benefit associated with neoadjuvant treatment strategy was 0.21 years longer than with adjuvant treatment strategy. But when radiotherapy with hyperfractions was used instead of standard fractions in concurrent chemoradiotherapy, neoadjuvant treatment lost this advantage against direct surgery with adjuvant treatment. However, life expectancy difference was only 0.05 years in this situation.

Chemoradiotherapy as a neoadjuvant approach was the preferred treatment compared with neoadjuvant treatment as chemotherapy alone. Chemoradiotherapy gained 1.74 years more crude life expectancy than chemotherapy alone in induction therapy. In chemoradiotherapy, concurrent approach added 0.97 years more crude life expectancy compared with sequential approach.

When we used QALE for utility values, preferred treatment choice changed. Direct surgery and adjuvant treatment with chemotherapy was the preferred strategy. The magnitude of the QALE benefits associated with this approach was 0.10 years longer than with neoadjuvant treatment strategy. Chemotherapy alone as an adjuvant treatment was the preferred choice compared with chemoradiotherapy or radiation alone. Adjuvant chemotherapy gained 1.26 years more QALE than best supportive care.

Direct surgery and adjuvant treatment with chemotherapy was also the preferred treatment strategy in Markov analysis. When Markov prognosis model was used, 4.05

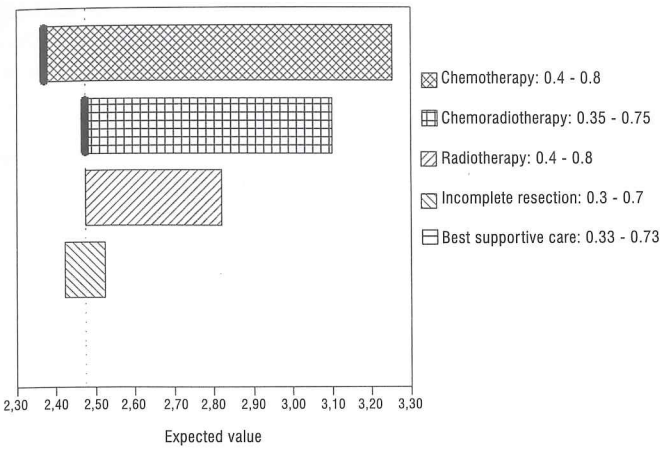

Figure 3. The results of a one-way sensitivity analysis. This graph of the results of a one-way sensitivity analysis presents all the variables to which the tree of QALE model is sensitive and the plausible range of these variables (Most sensitive = top, least sensitive = bottom). Vertical bars represent the base-case scenario.

years QALE was gained by direct surgery and adjuvant chemotherapy and 3.54 years QALE was gained by neoadjuvant chemotherapy. Chemotherapy alone was the best adjuvant and neoadjuvant treatment approach when quality of life was considered.

Sensitivity analysis

Sensitivity analyses were performed to examine the effect of varying probabilities and utility estimates (over a range shown in Tables 1 and 2). When crude life expectancy is considered, "probability of complete resection of tumor" and "probability of fatal toxicity with neoadjuvant chemotherapy" did not affect the preferred treatment choice of neoadjuvant strategy, in one-way sensitivity analyses. Decision of preferred approach in neoadjuvant strategy as a chemoradiotherapy was robust over sensitivity analyses. Furthermore, variation in the surgical mortality rates and complete resection rate after direct surgery did not affect model outcome.

However, when QALE was considered, both QALE decision model and Markov prognosis model were found to be sensitive to utility values (quality of life multiplier). The most influential parameters are depicted in Figure 3. Utility values of best supportive care did not affect decision. Direct surgery and adjuvant treatment strategy was the preferred choice under threshold of 0.578 chemoradiotherapy utility value. Above this value, neoadjuvant strategy was the preferred choice. Chemoradiotherapy approach was the selected choice among alternatives of neoadjuvant approaches over sensitivity analyses. Concurrent chemoradiotherapy achieved more QALE than sequential approach within ranges of sensitivity analyses. Adjuvant radiotherapy was the preferred treatment approach in adjuvant strategy only above 0.70 threshold value of utility. Under this threshold, chemotherapy gained more QALE than other approaches of adjuvant treatment.

DISCUSSION

Stage III, NSCLC has a large public health impact. Due to substantial practice variation and controversy over treatments, treatment decision in these patients becomes more complex [9]. Our models can offer an explicit and systematic approach to decision making based on the premise of rationality. The acknowledgment of choices and their associated uncertainties are positive steps towards improving the process of decision making between patients and professionals. Decision analysis potentially enhances patient autonomy because the patients influence the decision-making process by contributing their own values [70]. In our study, QALE decision model has also shown the influence of utility values on final decision.

Our crude life expectancy model has shown that neoadjuvant treatment strategy including concurrent chemoradiotherapy should be preferred compared with surgery alone or adjuvant treatments. Bimodality therapy with chemotherapy and radiotherapy as an induction therapy was preferred treatment compared with neoadjuvant treatment by chemotherapy alone. These outcomes of the model agree well with recent evidence-based lung cancer guidelines [65]. However, the benefit versus toxicity of combined modality treatments for stage III disease has made them controversial. Therefore, decision analysis that would effectively quantify the benefits, risks and quality of life facilitates weighing the alternatives.

The QALE model of our study has shown that when quality of life was considered, there was minor difference between gained QALEs of neoadjuvant and adjuvant strategy (representing a toss-up decision). Adjuvant chemotherapy obtained only 0.1 year more QALE than neoadjuvant treatments. Estimated utility value of chemoradiotherapy was lower than chemotherapy alone due to combination of toxicities of chemotherapy and radiotherapy. Induction with combined chemotherapy and radiotherapy gained cruder life expectancy than chemotherapy alone. However when QALE was calculated, chemoradiotherapy lost this advantage due to its lower utility value. This effect of quality of life multiplier on decision analysis can be neutralized with 18% increase in three-year survival. This example thus highlights the importance of the patient's utility value on the final decision. Adjuvant chemotherapy was also found better than adjuvant chemoradiotherapy when QALE was calculated.

However, the life expectancy model becomes complicated when incorporating quality of life considerations. It requires a single number to represent quality of life, and

there remains no one simple number to adequately encompass health status of patients, side effects, postponed death, etc. despite studies related to this issue [71]. We tried to use Markov model to overcome this problem. In Markov analysis, the difference between expected value of direct surgery and adjuvant treatment with chemotherapy strategy and expected value of neoadjuvant chemoradiotherapy strategy was more prominent. Direct surgery and adjuvant treatment with chemotherapy gained 0.5 years more QALE. We cannot know whether addition of other health states (symptomatic improvement, local disease control, severity of treatment toxicity, etc.) to those considered in our Markov analyses would improve confidence in the model results. However, estimation of transition probabilities between these health states is problematic due to lack of information in the literature.

Decision analyses in NSCLC, like in our study, are extremely useful in identifying what information is missing. These areas with omissions of information make construction of valid decision analyses difficult. However, these limitations are less-related with the method than with the data incorporated into the model. Physicians already make decisions against these uncertainties in their daily clinic practice [9]. Thus, well-structured decision analyses are still useful in facilitating the decision-making process.

The major deficiency in our analysis is in the utility values, which have not been derived directly from NSCLC patients. Lung cancer studies rarely collected and reported utilities from patients [72]. The utility values of other seriously ill patients are higher than expected, do not agree with those offered by surrogates, and get higher over time despite continued illness [73]. We used sensitivity analyses with a broad range of utility values to decrease this disadvantage. Sensitivity analyses demonstrated that the preference of treatment is sensitive to the utilities of the health states considered. These utility values can change treatment choice easily so they become the most important parameters involved in this decision-making process. Therefore, effort should be given to finding ways to describe influencing health states and methods to obtain valid quality-of-life modifiers.

CONCLUSION

If utility values of patients could be established confidently and accurately, the decision analysis method can be used successfully in determination of the best treatment option.

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