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Estimation of loss of quality-adjusted life expectancy (QALE) for patients with operable versus inoperable lung cancer: Adjusting quality-of-life and lead-time bias for utility of surgery

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ABSTRACT

Objectives: This study attempts to quantify the difference in loss of quality-adjusted life expectancy (QALE) for patients with operable and inoperable non-small-cell lung cancer (NSCLC).
Patients and methods: A cohort consisting of 1652 pathologically verified NSCLC patients with performance status 0–1 was monitored for 7 years (2005–2011) to obtain the survival function. This was further extrapolated to lifetime, based on the survival ratios between patients and age- and sex-matched referents simulated from the life tables of the National Vital Statistics of Taiwan. Between 2011 and 2012, EuroQol 5-dimension questionnaires were used to prospectively measure the quality-of-life (QoL) of a 518 consecutive, cross-sectional subsample. We adjusted the lifetime survival function by the utility values of QoL for the cancer cohort to obtain the QALE, while that for the age and sex-matched referents were adjusted to the values collected from the 2009 National Health Interview Survey, and the difference between them was the loss-of-QALE.
Results: The QALE for patients with operable and inoperable NSCLC were 11.66 ± 0.18 and 1.43 ± 0.05 quality-adjusted life year (QALY), with the corresponding loss-of-QALE of 5.25 ± 0.18 and 14.24 ± 0.05 QALY, respectively. The lifetime utility difference for patients with operable and inoperable NSCLC was 9.00 ± 0.18 QALY, after adjustment for QoL and lead-time bias.
Conclusion: The utility gained from surgical operation for operable lung cancer is substantial, even after adjustment for lead-time bias. Future studies should compare screening programs with treatment strategies when carrying out cost-utility assessments to improve patients' values.

1. Introduction

Over the past two decades, the mortality attributed to lung cancer has increased and it is now the leading cause of cancer deaths [1]. Late diagnosis is a fundamental obstacle to improving the outcomes of lung cancer, with more than 70% of new cases presenting too late for curative treatment to be attempted [2]. Owing to the development of new chemotherapeutic agents, the costs of care for inoperable lung cancer are growing rapidly [3]. Therefore, it is worth examining the lifetime utility difference for patients with operable and inoperable lung cancer, which emphasizes the importance of early diagnosis of lung cancer.

For the assessment of lifetime utility difference, both survival and quality-of-life (QoL) should be taken into consideration, and thus, the quality-adjusted life year (QALY) unit is more suitable than estimating survival alone for comparison of various types of healthcare services [4]. Quality-adjusted life expectancy (QALE) can be estimated via adjusting the survival function with the mean QoL at each time point, t, using the following equation [5–7]:

$$\mathrm{QALE} = \int E\left[\mathrm{QoL}\left(t/x\right)\right] S\left(t/x\right) dt$$

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$E[\mathrm{QoL}(t/x)]$ denotes the expected value of health state (QoL) for patients with condition x at time t and $S(t/x)$ denotes the survival function for condition x at time t.

Previous studies discussing the benefits of surgery mostly focused on survival alone, and usually did not take lead-time bias into consideration [8]. Based on a 7-year follow-up cohort, this study aims to quantify the difference in loss-of-QALE for patients with operable and inoperable non-small-cell lung cancer (NSCLC). In other words, we attempt to estimate the utility difference after adjustment for QoL and lead-time bias, which might be regained through future screening initiatives.

2. Patients and methods

The Institutional Review Board of the National Cheng Kung University Hospital (NCKUH) approved the study before commencement (ER-100-079), and every interviewed patient provided written, informed consent. We abstracted a NSCLC cohort from the NCKUH database of lung cancer for survival analysis, applied the national life tables to extrapolate the survival function to lifetime, prospectively collected the QoL data from a cross-sectional subsample of the cohort, and integrated the lifetime survival with the QoL to estimate the QALE and loss-of-QALE of NSCLC patients using the QALY unit.

2.1. The 7-year follow-up cohort for estimation of the survival

All patients with NSCLC and free from other malignancies during the period from January 2005 to December 2011 were recruited from the NCKUH lung cancer database. The diagnosis of NSCLC and its pathological subtypes were based on histology or cytology. We defined the tumor stage of each patient by tumor-node-metastasis classifications [9,10]. Patients with tumor stages I, II, IIIA, and IIIB were assessed by experienced thoracic surgeons for tumor operability. Subjects who underwent pulmonary resections as the curative treatment were recruited as the operable patients, while the others belonged to the inoperable group. The thoracic surgeons decided whether to perform pulmonary resections or not, according to the practice guidelines [11] as well as each patient's pulmonary reserve and co-morbidities. We used the Eastern Cooperative Oncology Group score to classify the performance status of each patient [12]. The score runs from 0 to 5, with 0 denoting fully active and 1–5 denoting restricted in physical strenuous activity, <50% in bed during the day, >50% in bed, bedbound, and dead, respectively. To avoid selection bias in the operable group, only patients with performance status 0–1 were evaluated, however, a sensitivity analysis for subjects with performance status 0–4 was also performed. The survival status for each patient was verified by follow-up from the day of diagnosis till the end of 2011.

2.2. Extrapolating the survival to lifetime

After obtaining the survival function of the cohort through Kaplan–Meier estimate, a method proposed by Huang and Wang was used to extrapolate the survival function beyond the end of the follow-up period [13]. This approach assumed that NSCLC generated a constant excess hazard after the initial follow-up period, and its calculation comprised three steps. First, we borrowed the hazard functions from the life tables of the National Vital Statistics of Taiwan to generate an age- and sex-matched reference population by the Monte Carlo method and estimated its survival function. Second, we calculated the survival ratio between the NSCLC cohort and the reference population at each time t and performed a logit transformation of the ratio. Third, the logit transformations of the ratios were fitted by simple linear regression up to the end of the follow-up period. The estimated regression line, together with survival function of the reference population beyond the follow-up limit, was used to extrapolate the lifetime survival function of the NSCLC cohort. The life expectancy of the NSCLC cohort (up to 600 months) after diagnosis was thus estimated. The expected years of life lost of the NSCLC cohort was defined as the survival difference between the cohort and the reference population. The method described above has been demonstrated by computer simulation [13] and proven mathematically [14]. It has also been corroborated by several examples of cancer cohorts [15,16]. An open access software, the iSQoL statistical package, was used for the computation [17].

2.3. Prospectively measuring the QoL from a cross-sectional subsample

From May 2011 to April 2012, all consecutive patients with NSCLC from the outpatient oncology, chest surgery, and chest medicine departments of NCKUH were invited to participate in this study. To minimize any magnitude of overestimation of the QoL, we also consecutively screened patients admitted to the wards between November 2011 and January 2012. The inclusion criteria were realization of a lung cancer diagnosis by each participant, the absence of malignancy at another site, and each subject's ability to understand and answer the questionnaire. In some individuals, measurements were performed repeatedly; however, each measurement was taken at least 3 months after the previous one.

The 5-dimension EuroQol questionnaire (EQ-5D) [18], the Taiwanese version of which has been validated in a previous work [19], was used with face-to-face interviews to estimate the utility values of QoL. The five dimensions assessed by the EQ-5D are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each of which has three levels of severity. Using the scoring function from Taiwan, these health state parameters were transformed into a utility value ranging from 0 to 1, in which 0 represented death and 1 indicated full health.

The duration-to-date for each measurement was defined as the period between the date of NSCLC diagnosis and the date of interview. A kernel-smoothing (i.e., the moving average of the nearby 10%) method was used to estimate the mean QoL function [6,7]. The utility values of QoL beyond the follow-up period were assumed to be the same as the average of the last 10% of patients near the end of follow-up.

2.4. Estimating the QALE and loss-of-QALE

The lifetime survival function of the NSCLC cohort was adjusted by the corresponding mean QoL function to obtain a quality-adjusted survival curve, in which the sum of the area under this curve was the QALE of NSCLC patients [6]. We borrowed the EQ-5D utility values of the age- and sex-matched general population from the 2009 National Health Interview Survey in Taiwan. After adjusting the utility values with the survival function of the age- and sex-adjusted referents, the loss-of-QALE of NSCLC patients was calculated by subtracting the area under the quality-adjusted survival curve of NSCLC patients from that of the referents. Since the referents were age- and sex-matched with every NSCLC case, the loss-of-QALE would be the expected lifetime utility loss from developing the disease, and the difference between that of operable and inoperable NSCLC patients would be the expected lifetime utility difference after adjustment for lead-time bias.

We further performed a stratified analysis among patients with stage IIIA NSCLC using the above methods. The lifetime utility difference between operable and inoperable stage IIIA patients was also estimated.