ORIGINAL ARTICLE

Cost-effectiveness of chemotherapy combined with thoracic radiotherapy versus chemotherapy alone for limited stage small cell lung cancer: A population-based propensity-score matched analysis

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Keywords

Cost-effectiveness analysis; limited stage small cell lung cancer; population-based; propensity-score matching; thoracic radiotherapy.

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Abstract

Background: The addition of thoracic radiotherapy improves the outcome of limited stage small cell lung cancer (LS-SCLC), however, the cost-effectiveness of this process has never been reported. We aimed to estimate the short-term cost-effectiveness of chemotherapy combined with thoracic radiotherapy (C-TRT) versus chemotherapy alone (C/T) for LS-SCLC patients from the payer's perspective (Taiwan National Health Insurance).

Methods: We identified LS-SCLC patients diagnosed within 2007–2009 through a comprehensive population-based database containing cancer and death registries, and reimbursement data. The duration of interest was one year within diagnosis. We included potential confounding covariables through literature searching and our own experience, and used a propensity score to construct a 1:1 population for adjustment. We used a net benefit (NB) approach to evaluate the cost-effectiveness at various willingness-to-pay (WTP) levels. Sensitivity analysis regarding potential unmeasured confounder(s) was performed.

Results: Our study population constituted 74 patients. The mean cost (2013 USD) and survival (year) was higher for C-TRT (42 439 vs. 28 357; 0.94 vs. 0.88). At the common WTP level (50 000 USD/life-year), C-TRT was not cost effective (incremental NB – 11 082) and the probability for C-TRT to be cost effective (i.e. positive net benefit) was 0.005. The result was moderately sensitive to potential unmeasured confounder(s) in sensitivity analysis.

Conclusions: We provide evidence that when compared to C/T, C-TRT is effective in improving survival, but is not cost-effective in the short-term at a common WTP level from a payer's perspective. This information should be considered by clinicians when discussing thoracic radiotherapy with their LS-SCLC patients.

Introduction

Chemotherapy (C/T) is the cornerstone of treatment for small cell lung cancer (SCLC), but optimally added thoracic radiotherapy (TRT) improves long-term survival with high toxicity, especially for limited stage SCLC (LS-SCLC).^{1–3} In two meta-analyses, chemotherapy combined with TRT (C-TRT) had been reported to lead to an improved overall

survival rate by around 5%.^{4,5} However, this strategy is also associated with higher treatment related death with a reported odds ratio of 2.54.⁴

Although this strategy (C-TRT) is effective in improving treatment outcome, the uptake of C-TRT is not universal, as reported in several studies.^{6–8} In addition, in an era when affordable cancer care becomes a worldwide issue,^{9,10} the cost-effectiveness of C-TRT should also be considered because a

consideration of cost will possibly affect patients' access to cancer treatment.¹¹ As stated in the recent Institute of Medicine recommendation "Provide patients and their families with understandable information about cancer prognosis, treatment benefits and harms, palliative care, psychosocial support, and COSTs," discussing cost information is an essential part of quality cancer care nowadays.¹⁰ Even if a treatment may improve patient outcome to the point of survival, it might still be denied in some health care systems.¹¹ Existing treatments that were reimbursed in the past may also be denied after regular re-evaluation as has been evidenced in Oregon, USA, in which "The Prioritized List of Health Services determines which services the OHP (Oregon Health Plan) may cover. Once a patient's condition has been diagnosed, providers must use the list to find out whether the condition and treatment fall between Line 1 and the CURRENTLY funded line number."¹² However, to our knowledge, this information (cost-effectiveness) has not been reported in the literature. Therefore, the aim of our study is to estimate the short-term (one year) cost-effectiveness of C-TRT versus (C/T) alone for LS-SCLC patients from the payer's perspective via this population-based retrospective cohort analysis.

Methods

Data source

The Collaboration Center of Health Information Application (CCHIA) database is a set of databases providing complete information regarding cancer and death registration, and reimbursement data for the whole Taiwanese population.¹³ The cancer registry within CCHIA provides information regarding individual demographics, tumor histology, cancer primary sites, stage of disease, and primary surgical, radiation, and systematic treatment. National Health Insurance (NHI) is a single compulsory payer with almost universal coverage in Taiwan.¹⁴ NHI provides a comprehensive services package "All medically necessary services are covered. The package covers inpatient, outpatient, dental services, traditional Chinese medicine, and maintains a very long list of nearly 20 000 items of prescription drugs."¹⁴ NHI's reimbursement data files at the CCHIA provide information regarding the occupations of the insured, details of treatment received, and the characteristics of health care providers.

Study population and study design

Our study population identification and design are depicted in Figure 1. Our target populations were LS-SCLC patients diagnosed within 2007–2009 and treated with either C-TRT (either concurrent or sequential) or C/T. In brief, the date of diagnosis according to the cancer registry was used as the

Figure 1 Study flow chart.

¹We only included those treated by any single institution to ensure data consistency.

²Defined as 6thAmerican Joint Committee on Cancer clinical staging I-III, but T4NxM0 is excluded.

³1.8-2Gy/fraction, five days/week as it is the common practice in Taiwan.

⁴We used the occupational types of the insured as the surrogate for SES and classified SES as white collar, blue collar, and others.

⁵Diagnosed before or after 1 July 2008 (the middle within 2007–2009).

⁶Hospitals (that delivered initial chemotherapy): medical center versus regional hospital.

index date. We set the duration of interest (as commonly used in patient-level data based cost-effectiveness analysis¹⁵) as one year within the index date. Given the known efficacy of C-TRT, and that our duration of interest is longer than the usual treatment period, so as to include potential cost for complication or recurrence, we set our study as a cost-effectiveness analysis, rather than a cost-minimization analysis. We then decided the explanatory variable of interest (C-TRT vs. C/T) based on the cancer registry. We also col-

lected other covariables for the adjustment of potential non-randomized treatment selection and cost and effectiveness data from the CCHIA. Finally, we constructed a propensity-score (PS) matched sample based on PS estimated through the above covariables,¹⁶ to estimate the cost-effectiveness of C-TRT within the duration of interest. We used the use of C-TRT (vs. C/T) as the independent variable and the covariables as dependent variables, and used logistic regression to model the probability of receiving C-TRT. We then used the logit of the probability as the PS, as commonly used in the literature.¹⁶ Identifying patient details were removed from the CCHIA datasets. There was a further restriction of data usage in cases where the patients had less than three specific characteristics. There was also a central review of data analysis by the CCHIA. Therefore, it is impossible for the subjects to be identified.¹³ This study was exempt from Institutional Review Board review because the Collaboration Center of Health Information Application contains de-identified person identifiers and is publicly available through the proper application process.¹⁷

Other explanatory covariables

Firstly, we searched the literature regarding potential factors that might influence the use of TRT. After a search in PubMed¹⁸ using: ([small cell lung cancer] NOT [non small cell lung cancer]) AND ([thoracic radiotherapy]) AND ([use] OR [pattern] OR [associated] OR [association] OR [receipt] OR [uptake]) as keywords, we identified that factors of age (≥ 70 years old) and treatment period might affect the use of C-TRT in SCLC.^{19,20} Secondly, we collected other factors that were not reported in the literature, but that might affect the use of C-TRT based on our clinical and research experience. In this regard, we also included patient demographic factors (gender), patient characteristics (social-economic status [SES]), disease status, and health service provider characteristics (treating hospital level) based on our clinical experiences and prior NHI and CCHIA related studies.^{21–28} Patient residency was classified as northern Taiwan or elsewhere. We used the occupational types of the insured as the surrogate for SES and classified SES as white collar, blue collar, and others. The treatment period was classified as recent (diagnosed after 1 July 2008 [the middle within 2007–2009]) or otherwise. Disease status was classified as locally advanced (stage III) or early (stage I–II). The treatment facility was classified as a medical center or regional hospital.

Cost and effectiveness assessment

We obtained survival status according to the death registry. The cost and cost-effectiveness were conducted from a Taiwan NHI perspective (i.e. charges to NHI). The cost was limited to the duration of interest (1 year within the index

date) then converted to 2013 USD by purchasing the power parity and consumer price indexes.²⁹ We then applied various thresholds of willingness-to-pay (WTP) to calculate the incremental net benefit (INB) when C-TRT was compared to C/T³⁰ by applying the following equation:

$$\text{INB} = \text{incremental effectiveness} * \text{WTP} - \text{incremental cost.}$$

WTP refers to the amount of money the payer is willing to pay for an outcome. A commonly cited WTP threshold (50 000 USD/life year [LY]) means that the payer is generally willing to pay 50 000 USD to gain a year of life and this was considered a threshold to decide whether an intervention was cost-effective or not.³¹ When the INB of an intervention is positive at a specific WTP level, this means that this intervention is associated with a positive net monetary gain, so it is also cost-effective at this specific WTP level.

Statistical analysis & sensitivity analysis

Tabulation and standardized difference were used to assess the balance of covariates between PS-matched groups. We used a stratified log-rank test to compare the survival of C-TRT versus C/T for the entire follow-up period (censored on 1 January 2012).³² We used the paired *t* test to evaluate the statistical significance of the INB, then constructed the cost-effectiveness acceptability curve (CEAC).³⁰ Although we had used PS matching to adjust for potential bias, our result was still vulnerable to the assumption of “no unobserved confounding.” Therefore, we evaluated the potential impact of an unmeasured confounder on the statistical significance of INB at common WTP (50 000 USD/LY), as proposed by Rosenbaum, as our sensitivity analysis.³³ SAS 9.3 (SAS Institute, Cary, NC) and Stata 11 (Stata Corp, College Station, TX) were used for statistical analyses.

Results

Identification of the study cases (Figure 1 & Table 1)

As revealed in Figure 1, 144 LS-SCLC patients treated with either C-TRT or C/T were identified as the initial study population. After exclusion of those with missing data and matching by PS, the final study population included 74 patients. Other patients were not included in the final analysis because of the 1:1 matching study design or if no matched control was available. The characteristics of these 74 patients are described in Table 1. A good balance of covariables and small standardized differences (<0.1) were seen for all covariables, except a moderate standardized difference for hospital level and residency region, with standardized differences of 0.12 & 0.11, respectively.

Table 1 Patient characteristics of the propensity-score matched final study population

		C-TRT		C/T		Standardized difference (rounded)
		Number	Percentage (rounded)	Number	Percentage (rounded)	
age	<70 y/o	18	49	18	49	0.00
	≥70 y/o	19	51	19	51	
gender	male	34	92	34	92	0.00
	female	3	8	3	8	
residency	north	16	43	18	49	0.11
	non-north	21	57	19	51	
social-economic status	white collar	9	24	11	30	0.07
	blue collar	18	49	16	43	
	others	10	27	10	27	
Comorbidity	without	16	43	16	43	0.00
	with	21	57	21	57	
stage	I-II	9	24	10	27	0.06
	III	28	76	27	73	
	IV	1	3	1	3	
hospital	medical center	25	68	27	73	0.12
	regional hospital	12	32	10	27	
Period	early	19	51	20	54	0.05
	recent†	18	49	17	46	

†Diagnosed after 1 July 2008 (the middle within 2007–2009). C/T, chemotherapy; C-TRT, chemotherapy combined with thoracic radiotherapy.

Cost and effectiveness

For the entire follow-up period, the survival rate of C-TRT was better than C/T (1 year: 81% vs. 72%, $P = 0.39$), but was not of statistical significance. The Kaplan-Meier survival curve is depicted in Figure 2. The mean cost (2013 USD) and survival (year) within one year after diagnosis was higher for C-TRT versus C/T (42 439 vs. 28 357; 0.94 vs. 0.88) (Table 2). The incremental cost-effectiveness ratio (ICER) was 234 700 (2013 USD) (Table 2). At the common WTP (50 000 USD/LY), C-TRT was not cost-effective when compared to C/T

Figure 2 Kaplan-Meier survival curve (in days). C-TRT = 1 (dotted line) for chemotherapy combined with thoracic radiotherapy & C-TRT = 0 (solid line) for chemotherapy; $P = 0.39$.

(INB −11 082) (Table 2). The probability for C-TRT to be cost-effective (i.e. positive net benefit) was 0.005 & 0.07 at WTP 50 000 & 100 000, respectively (Fig. 3).

Sensitivity analysis

Regarding the potential impact of an unmeasured confounder, we can see in Table 3 that if there was an unmeasured binary confounder that increased the odds of C-TRT (vs. C/T) for 20% or 40%, instead of the zero by our assumption, our conclusion that C-TRT was “not cost effective” versus C/T would remain statistically significant ($P < 0.05$). However, if there were an unmeasured binary confounder that increased the odds for at least 48%, then the observed “not cost effective” at common WTP (50 000 USD/LY) would no longer be statistically significant ($P > 0.05$).

Table 2 †Cost-effectiveness results

	C-TRT	C/T
Cost (2013 USD)	42439	28357
Effectiveness(life-year)	0.94	0.88
Incremental cost	14082	reference
Incremental effectiveness	0.06	reference
ICER	234700	reference
INB‡	−11082	reference

†Cost rounded at integral; life-year rounded at second decimal. ‡At willingness-to-pay 50 000 US dollar (USD)/life-year. C/T, chemotherapy; C-TRT, chemotherapy combined with thoracic radiotherapy; ICER, incremental cost-effectiveness ratio; INB, incremental net benefit.

Figure 3 Cost-effectiveness acceptability curve.

Discussion

In this population-based propensity-score matched cost-effectiveness analysis, we provide the first empirical evidence that C-TRT is effective versus C/T in improving survival, but is not cost-effective versus C/T in the short-term (1 year) at a common WTP level from a payer's perspective.

In general, there were two approaches (and their combinations) for this cost-effectiveness analysis: patient-level data based or model based.³⁴ Given the availability of patient-level data, we preferred this approach to avoid assumptions needed in modeling. We searched PubMed in January 2014 using the following keywords, as modified from our previous studies, to realize which cost issue(s) of SCLC had been reported in the literature: ([small cell lung cancer] NOT [non-small cell lung]) AND ([“costs and cost analysis”{MeSH}] OR costs[Title/Abstract] OR cost effective*[Title/Abstract]) OR (cost*[Title/Abstract] OR “costs and cost analysis” [MeSH:noexp] OR cost benefit analysis*[Title/Abstract] OR cost-benefit analysis[MeSH] OR health care costs MeSH:noexp).³⁵ We found that various issues, including work-up

modality, chemotherapy intensity, prophylactic cranial irradiation, granulocyte colony-stimulating factor, prophylactic antibiotics, second line treatment, new drugs, and overall cost, had been reported since 2000.^{36–47} However, the cost-effectiveness of C-TRT in LS-SCLC had never been reported. Our result did, however, reflect similar results in the literature that C-TRT versus C/T is associated with improved overall survival.^{4,5}

There were several potential limitations in our study. Firstly, as a retrospective cohort analysis, it is possible that some confounding factors were not included. For example, we did not consider the response after initial treatment ($\pm$ prophylactic cranial irradiation) and pulmonary function status because of data limitation in the cancer registry. However, we had done an extensive literature search and included all reported covariables in our analysis. In addition, our sensitivity analysis showed that our result (C-TRT not cost effective) was moderately sensitive to potential omitted variable(s). Secondly, although the long-term outcome of LS-SCLC was not positive, our short duration of interest (one year) might not be long enough to fully capture the cost-effectiveness of C-TRT versus C/T.

Our result should not be interpreted as a suggestion that C-TRT should not be considered for LS-SCLC patients, but rather that the payer should take cost-effectiveness into consideration. The results should also be interpreted with caution because the duration of interest was short and the result is moderately sensitive to sensitivity analysis. In addition, the impact of modern technology may also potentially affect our conclusion in the future. For example, we did not consider the impact of potential staging migration because of positron emission tomography (not reimbursed by NHI during our study period).⁴⁸ We also did not consider oral chemotherapy alone, such as etoposide,⁴⁹ because the current cornerstone of the chemotherapy regimen is still intravenous chemotherapy, such as cisplatin or carboplatin.¹ The impact of the introduction of new radiation technology, such as intensity modulated radiotherapy (IMRT), also has potential, but is debatable.^{24,50,51} In addition, the cost might be increased for IMRT, which would make C-TRT even less cost-effective.

Conclusions

In this population-based propensity-score matched cost-effectiveness analysis, we provide the first empirical evidence that when compared to C/T alone, C/T combined with C-TRT is effective in improving survival, but is not cost-effective in the short-term (1 year) at a common willingness-to-pay level from a payer's perspective. This information should be considered by clinicians when discussing TRT with LS-SCLC patients. Further studies are needed to clarify the long-term cost-effectiveness.

Table 3 Sensitivity analysis

Increased odds of C-TRT (vs. C/T) by unmeasured confounder	Upper end of p-value for negative INB when WTP = 50 000
0.20	0.015
0.40	0.038
0.47	0.049
0.48	0.051
0.60	0.072
0.80	0.120
1.00	0.180

C/T, chemotherapy; C-TRT, chemotherapy combined with thoracic radiotherapy; INB, incremental net benefit; WTP, willingness-to-pay (in US dollars/life-year).

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Disclosure

No authors report any conflict of interest.

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