Original Article

Cost and effectiveness of image-guided radiotherapy for non-operated localized lung cancer: a population-based propensity score-matched analysis

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Background: Image-guided radiotherapy (IGRT) is a novel technology to enhance RT delivery accuracy. However, the clinical effectiveness and cost-effectiveness are less clear. The aim of our study is to compare the cost and effectiveness of conventional fractionated RT for non-operated localized lung cancer delivered with vs. without IGRT via this population-based propensity score (PS) matched analysis.

Methods: We identified eligible patients diagnosed within 2007-2010 through a comprehensive population-based database containing cancer, death registries, and reimbursement data in Taiwan. The primary duration of interest (DOI) was 2 years within diagnosis. Effectiveness was measured as survival whereas direct medical cost was measured from the payers' perspective. In supplementary analysis (SA), we estimated the cost-effectiveness in consider of out-of-pocket (OOP) payment and 4 years as DOI.

Results: Our study population constituted 124 patients. Within 2 years, both the mean cost (2014 USD) and survival (life-year, LY) were higher for IGRT ($60,774 *vs.* $60,554; 1.43 *vs.* 1.37). The incremental cost-effectiveness ratio (ICER) when IGRT was compared to non-IGRT was 3,667 (USD/LY). The chance for IGRT to be cost-effective was around 68% & 70% at willingness-to-pay threshold 50,000 USD/LY and 150,000 USD/LY respectively. IGRT remained cost-effective in SA.

Conclusions: We provide the first empirical evidence that when compared to non-IGRT, IGRT was potentially cost-effective.

Keywords: Cost effectiveness analysis; lung cancer; image-guided radiotherapy (IGRT)

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Introduction

Radiotherapy (RT) is one of the treatment modalities in lung cancer treatment, especially in localized non-operated lung cancer (1-4). Image-guided RT (IGRT) is a new technology to enhance RT delivery accuracy via imaging in the treatment room (1,5,6). Although IGRT hold great potential in improving patient outcome, currently there were few available clinical data to prove this concept (5,6). In the field of lung cancer, IGRT had changed the face of lung cancer RT (7). However, in the era of increasing

emphasize on the affordable care (8,9), the cost-effectiveness of a new technology is also important as in the case of IGRT (10). To our knowledge, although IGRT had been reported to be associated with improving pathological response rate for patients receiving neoadjuvant RT in the field of lung cancer (11), the effectiveness of IGRT regarding harder endpoint like survival is less clear in the literature. Therefore, the aim of our study is to compare the cost and effectiveness (survival) of curative conventional fractionated RT for non-operated localized lung cancer delivered with *vs.* without IGRT via this population-based propensity score (PS) matched analysis.

Material and methods

Data source

The Application Center for Health and Welfare statistics database is a set of databases with complete information regarding cancer registry, death registration, and reimbursement data from National Health Insurance (NHI) for the whole Taiwanese population. The cancer registry provides details regarding individual demographics, tumor histology, cancer primary sites, stage of disease, and primary surgical, radiation, and systemic therapy. NHI is a single compulsory payer with universal coverage in Taiwan and provides a comprehensive services package "All medically necessary services are covered. The package covers inpatient, outpatient, dental services, traditional Chinese medicine, etc." (12). NHI's reimbursement data files also provide information including the income of the insured and the characteristics of health care providers.

Study population and study design

Our study flow chart is depicted in *Figure 1*. Our target populations were non-operated localized lung cancer patients received curative conventional fractionated RT, via either with IGRT or without IGRT within 2007-2010. In brief, the date of diagnose was used as the index date. We set the duration of interest (DOI) as 2-year within the index date. We then decided the explanatory variable of interest (IGRT *vs.* non-IGRT) based on the cancer registry record. We collected other covariables for the adjustment of potential non-randomized treatment selection and cost and effectiveness data from the Application Center for Health and Welfare statistics (see next sub-section "other explanatory covariables"). Finally, we constructed a PS matched sample based on PS estimated through the above covariables to compare the cost and effectiveness of IGRT *vs.* non-IGRT within the DOI. In PS analysis, we modeled the use of IGRT (*vs.* non-IGRT) as the dependent variable and the covariables as independent variables, and used logistic regression to model the probability of receiving IGRT as commonly used in the literatures (13,14). We then used the logit of the probability as the PS, as commonly used in the literature (14). This study had been approved by Research Ethics Committee in our institute [CMUH103-REC-005].

Other explanatory covariables

Firstly, we searched the literature regarding potential factors that might influence the cost of lung cancer patients treated with RT. We used the following balanced search filters regarding costs or economics in the PubMed "("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])" as in the literatures (15,16). We combined the above keywords with "(lung cancer) AND ((radiotherapy) OR (radiation therapy))" and found that after the use of positron emission tomography (PET) during peri-diagnostic period was a potential factor (17). Secondly, we collected other factors that were not reported in the literature but that might affect the cost based on our clinical and research experiences. In this regard, we also included patient demographic factors [age, gender, residency region, social-economic status (SES)], patient characteristics (comorbidity), disease characteristics (tumor location, histology, clinical stage & period), treatment (RT method & dose, systemic therapy), and health service provider characteristics (hospital level) based on our clinical experiences and prior NHI and the Application Center for Health and Welfare statistics related studies (18-24). Age was classified as ≥65 years old or not. Patient residency was classified as northern Taiwan or elsewhere. SES was classified as high (income greater than minimal wage) or not. Tumor location was classified as lower *vs.* upper/middle. Histology was classified as small cell or non-small cell. Stage was classified as stage (I-II *vs.* III) while period was classified as 2007-2009 (6^{th} staging edition) *vs.* 2010 (7^{th} edition). Hospital was classified as medical center or not.

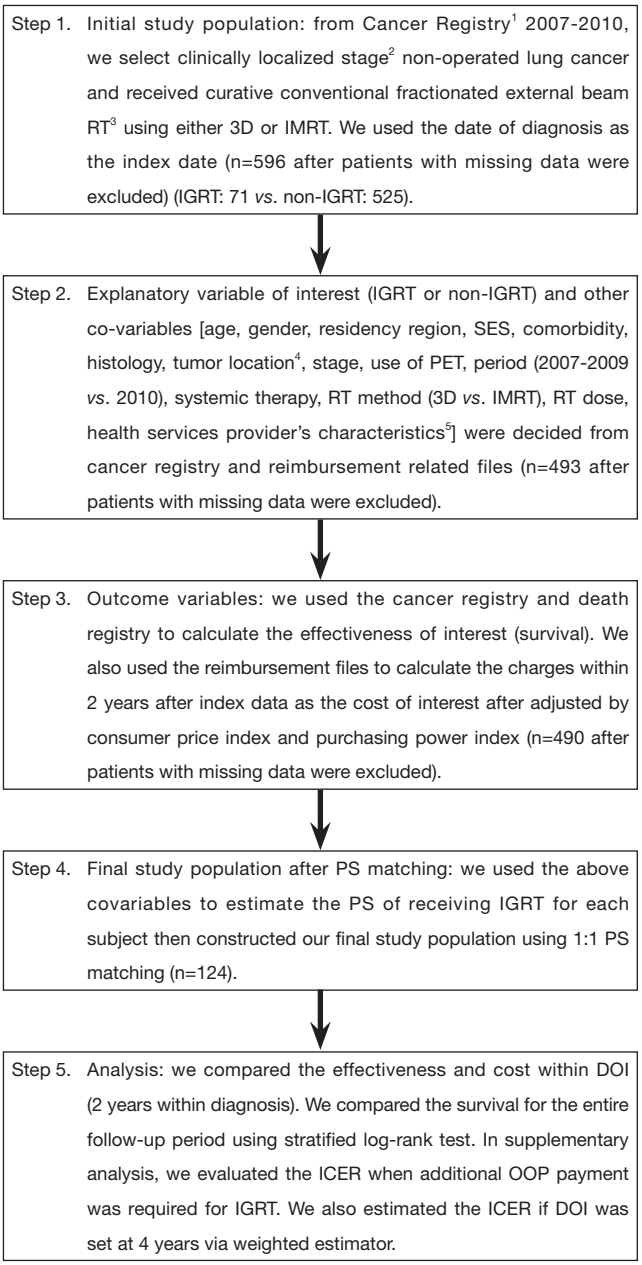

Figure 1 Study flow chart. [1], We only included those treated (class 1-2) by any single institution to ensure data consistency; [2], 6th American Joint Committee on Cancer staging clinical stage I-III (but not cT4NxM0) [2007-2009] or 7th stage I-III [2010]; [3], 50-70 Gy in 1.8-2 Gy/fraction, within +/– 10% in dose and treatment duration; [4], lower lobe *vs.* upper/middle lobe; [5], hospitals were classified as medical center or regional hospital. RT, radiotherapy; IMRT, intensity modulated radiotherapy; IGRT, image-guided radiotherapy; SES, social-economic status; PET, positron emission tomography; PS, propensity score; DOI, duration of interest; ICER, incremental cost-effectiveness ratio; OOP, out-of-pocket.

Cost and effectiveness assessment

We obtained survival status according to the death registry and used survival duration as effectiveness. The cost and cost-effectiveness were conducted from a payers' perspective (i.e., charges to NHI). The cost was converted to 2014 USD by purchasing the power parity and consumer price indexes (25).

Statistical & supplementary analysis (SA)

Tabulation and standardized difference were used to assess the balance of covariates between PS-matched groups. We used the incremental cost-effectiveness ratio (ICER) to evaluate the cost-effectiveness and used the cost effectiveness acceptability curve (CEAcC) to represent the uncertainty of cost-effectiveness at various willing-to-pay (WTP) thresholds (26). We also compared the survival during the entire follow-up period (censored on 1 January 2013) using a robust variance estimator (14). We performed two supplementary analyses to evaluate the robustness of our finding. In the 1st SA (SA-1) we assumed an out-of-pocket (OOP) charge of 3,861 USD (60,000 National Taiwan Dollar by purchasing power parity index (PPP) in 2014, the charge in our hospital for IGRT) and re-calculate the CEAcC. In the 2nd SA (SA-2), we estimated the cost-effectiveness if DOI was set at 4 years via weighted estimator (27). SAS 9.3 (SAS Institute, Cary, NC) was used for all the analysis.

Results

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

As revealed in *Figure 1*, 596 localized lung cancer patients treated with curative RT via either IGRT or non-IGRT were identified as the initial study population. After exclusion of those with missing data and matching by PS, the final study population included 124 patients. The characteristics of these patients are described in *Table 1*. A good balance of covariables and small standardized differences (<0.1) were seen for all covariables except hospital and systemic therapy (0.108; 0.102).

Cost and effectiveness (Figures 2,3 & Table 2)

Within DOI (2-year), both the mean cost (2014 USD) and survival (year) were higher for IGRT ($60,774 *vs.* $60,554; 1.43 *vs.* 1.37). The ICER when IGRT was compared to

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

Variables	Number or mean [SD] (%)*		Standardized difference (rounded)
	IGRT	Non-IGRT	
Age, years			0.035
<65	20 (32.26)	19 (30.65)	
≥65	42 (67.74)	43 (69.35)	
Gender			0.074
Female	15 (24.19)	17 (27.42)	
Male	47 (75.81)	45 (72.58)	
Residency			0.072
Non-north	46 (74.19)	44 (70.97)	
North	16 (25.81)	18 (29.03)	
Stage			0.045
Stage I-II	9 (14.52)	10 (16.13)	
Stage III	53 (85.48)	52 (83.87)	
Period			0
2007-2009	29 (46.77)	29 (46.77)	
2010	33 (53.23)	33 (53.23)	
Histology			0
Non-small cell	59 (95.16)	59 (95.16)	
Small cell	3 (4.84)	3 (4.84)	
RT method			0
3D	3 (4.84)	3 (4.84)	
Intensity-modulated	59 (95.16)	59 (95.16)	
Social-economic status			0
Minimal wage at most	18 (29.03)	18 (29.03)	
Higher	44 (70.97)	44 (70.97)	
Comobidity			0.035
Without	20 (32.26)	19 (30.65)	
With#	42 (67.74)	43 (69.35)	
Hospital			0.108
Medical center	43 (69.35)	46 (74.19)	
Reginal hospital	19 (30.65)	16 (25.81)	
Tumor location (lobe)			0.033
Lower	23 (37.10)	24 (38.71)	
Upper/middle	39 (62.90)	38 (61.29)	
Systemic therapy			0.102
No	8 (12.90)	6 (9.68)	
Yes	54 (87.10)	56 (90.32)	
Use of PET			0.098
No	34 (54.84)	37 (59.68)	
Yes	28 (45.16)	25 (40.32)	
RT dose (Gy)	62.64 [5.36]	62.54 [6.95]	0.017

*, rounded at 2nd; #, Carlson comorbidity score ≥1. IGRT, image-guided radiotherapy; SD, standard deviation; RT, radiotherapy; PET, positron emission tomography.

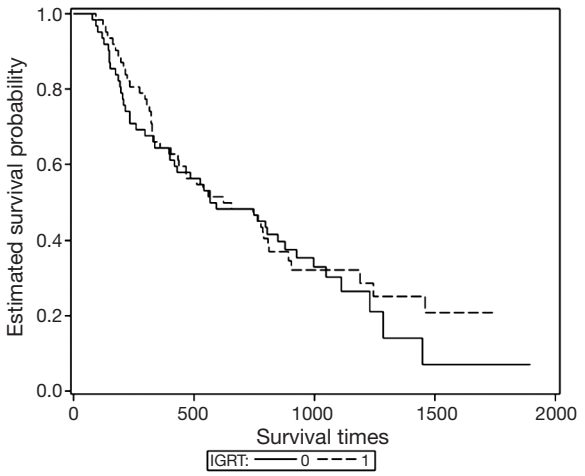

Figure 2 Kaplan-Meier survival curve (in days). IGRT in dotted line *vs.* non-IGRT in solid line. IGRT, image-guided radiotherapy.

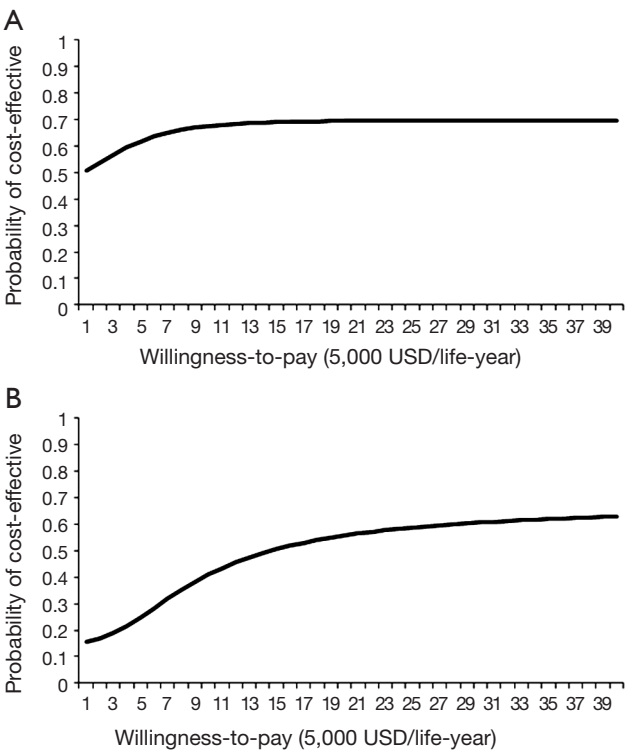

Figure 3 Cost-effectiveness and used the cost effectiveness acceptability curve. (A) Primary analysis; (B) supplementary analysis-1 (take out-of-pocket payment into consideration).

Table 2 Cost-effectiveness results*

Cost & effectiveness	IGRT	Non-IGRT
Cost (2014 US dollars)	60,774	60,554
Effectiveness (life-year)	1.43	1.37
Incremental cost	220	reference
Incremental effectiveness	0.06	reference
ICER	3,667	reference

*, Cost & ICER rounded at integer, life-year rounded at 2nd. IGRT, image-guided radiotherapy; ICER, incremental cost-effectiveness ratio.

non-IGRT was 3,667 [USD/life-year (LY)]. For the entire follow-up period, the survival rate of IGRT group was better but was not of statistical significance (hazard ratio of death =0.903, P value =0.63). The Kaplan-Meier survival curve is depicted in *Figure 2*. The CEAcC in *Figure 3A* revealed that the chance for IGRT to be cost-effective was around 68% & 70% at WTP threshold 50,000 USD/LY and 150,000 USD/LY respectively. In SA-1 as seen in *Figure 3B*, the chance for IGRT to be cost-effective was lower if potential OOP was considered, but was still higher than a half (61%) when the WTP threshold was 150,000 USD/LY. In the SA-2, the estimated incremental cost and effectiveness were 0.11 (LY) and –3,372 (USD). Therefore, if DOI was set as 4-year, IGRT was less costly and more effective, still cost-effective as well.

Discussion

In this population-based PS matched analysis, we found that when used in curative conventional fractionated RT for non-operated localized lung cancer, IGRT was in average cost-effective when compared with non-IGRT.

Our finding was compatible with the literature in that IGRT was associated with higher pathological response rate when used in neoadjuvant RT in lung cancer (11), but that our study provided a more clinically meaningful endpoint (survival) rather than the surrogate endpoint (response rate) in the literature.

The interpretation of our finding is likely to be consistent as in the literature in that IGRT improved the accuracy of RT delivery (5,6). However, our result should also be interpreted with caution given the non-randomized nature of our study and the limit in generalizability to health care systems other than Taiwan.

There were also limitations in our study. Firstly, the intervention in our study was not randomized. Therefore, potential unobserved confounding variable was possible although we had done our best as suggested in the literature (28). In addition, the use of registry in our study was a reasonable alternative to the randomized controlled study as suggested in the literature (29). Secondly, results in our primary endpoints (2-year cost-effectiveness) might be changed in the long term although we had estimated the 4-year results in our supplemental analysis.

Conclusions

In this population-based PS matched cost-effectiveness analysis, we provide the first empirical evidence that when compared to non-IGRT, IGRT was potentially cost-effective in the mid-term (2-year) and probably still cost-effectiveness at longer follow-up (4 years). However, the result should be interpreted with caution given the non-randomized design and the uncertainty regarding applicability in other health care systems.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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