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ORIGINAL ARTICLE

Cost-effectiveness of neoadjuvant concurrent chemoradiotherapy versus esophagectomy for locally advanced esophageal squamous cell carcinoma: A population-based matched case-control study

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Keywords
Cost-effectiveness analysis; esophageal squamous cell carcinoma; neoadjuvant concurrent chemoradiotherapy; propensity-score matching; Taiwan.

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Abstract

Background: Neoadjuvant concurrent chemoradiotherapy (NCCRT) is often considered for locally-advanced esophageal squamous cell carcinoma (LA-ESCC) patients; however, no data regarding the cost-effectiveness of this treatment is available. Our study aimed to evaluate the cost-effectiveness of NCCRT versus esophagectomy for LA-ESCC at population level.

Methods: We identified LA-ESCC patients diagnosed within 2008–2009 and treated with either NCCRT or esophagectomy through the Taiwan Cancer Registry. We included potential confounding covariables (age, gender, residency, comorbidity, social-economic status, disease stage, treating hospital level and surgeon's experience, and the use of endoscopic ultrasound before treatment) and used propensity score (PS) to construct a 1:1 population. The duration of interest was three years within the date of diagnosis. Effectiveness was measured as overall survival. We took the payer's perspective and converted the cost to 2014 United States dollars (USD). In sensitivity analysis, we evaluated the potential impact of an unmeasured confounder on the statistical significance of incremental net benefit at suggested willingness-to-pay.

Results: Our study population constituted 150 PS matched subjects. The mean cost (2014 USD) and survival (year) were higher for NCCRT compared with esophagectomy (US$91,460 vs. $75,836 for cost; 2.2 vs. 1.8 for survival) with an estimated incremental cost-effectiveness ratio of US$39,060/life-year.

Conclusions: When compared to esophagectomy, NCCRT is likely to improve survival and is probably more cost-effective. Cost-effectiveness results should be interpreted with caution given our results were sensitive to potential unmeasured confounder(s) in sensitivity analysis.

Introduction

Worldwide, esophageal cancer carries high rates of incidence and mortality.[1] Adenocarcinoma incidence is increasing in Europe and North America, whereas squamous cell carcinoma remains the main histology in Asia.[1] For locally advanced stage disease, surgery is the major therapeutic intervention, but a multimodal approach, such as neoadjuvant concurrent chemoradiotherapy (NCCRT), is often considered.[1] In Taiwan, the rate of surgery only for stage II-III esophageal cancer was 11% in 2008 versus 6% in 2011, while the rate of tri-modality therapy was 22% in 2008 versus 32% in 2011.[2,3]

In the literature, neoadjuvant therapy (such as NCCRT) has been associated with improved survival for resectable esophageal cancer when compared to surgery, and may or may not increase the risk of postoperative morbidity.[4–7] Neoadjuvant therapy is also associated with increased cost.[8,9] However, there is a paucity of cost-effectiveness analysis (CEA) regarding NCCRT in esophageal cancer, which is highly desirable in an era of increasing health care costs and the desire for affordable cancer care.[10,11] Using a similar approach as in our previous studies, we performed an extensive literature search in PubMed in January 2015 using (esophageal cancer neoadjuvant chemoradiotherapy) 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 analys*[Title/Abstract] OR cost-benefit analysis [MeSH] OR health care costs[MeSH:noexp])) as keywords, but did not find any relevant CEA.[12,13] Therefore, the aim of our study is to evaluate the cost-effectiveness of NCCRT versus esophagectomy for locally advanced esophageal cancer at the population level from an Asian country (Taiwan), focused on squamous cell carcinoma as it is the major endemic histological type.[1]

Methods

Data source

The Health and Welfare Data Science Center (HWDC) database is a set of databases providing complete information regarding cancer registry, death registration, and reimbursement data for the entire Taiwan population.[14] The Taiwan Cancer Registry (TCR) within HWDC 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.[15] NHI’s reimbursement data files in HWDC provide information regarding the wage range of the insured, details of treatment received, characteristics of health care providers (physicians and hospitals), and charges to the NHI.

Study population and study design

Our study was a population-based matched case-control study. The study population identification and design is depicted in Figure 1. Our target populations were locally advanced esophageal squamous cell carcinoma (LA-ESCC) patients diagnosed within 2008–2009 and treated with either NCCRT or esophagectomy. In brief, the date of diagnosis according to the cancer registry was used as the index date. The duration of interest was three years within the index date. We then decided the interventions of interest (NCCRT vs. esophagectomy) according to recordings in the cancer registry. We also collected other covariables, including: age, gender, residency, comorbidity, social-economic status (SES), disease stage, treating hospital level and surgeon’s experiences, and the use of endoscopic ultrasound before treatment, for adjustment of potential non-randomized treatment selection and cost and effectiveness data from HWDC. Finally, we constructed a propensity score (PS) matched sample, using the covariables to estimate the cost-effectiveness of NCCRT within the duration of interest.[16] We used logistic regression to model the use of NCCRT using all of the covariables and then calculated the PS score as the logit of the estimated probability of receiving NCCRT.[16] Patients were matched on the logit of PS using a caliper of 0.2 standard deviations of the logit of the PS via greedy matching.[16] We used suggestions regarding database approach to CEA to guide our analysis and reporting.[17,18] This study was approved by the Institutional Review Board (CMUH103-REC-005).

Other explanatory covariables

We first searched the literature for potential factors that might influence both the use of NCCRT and the cost. We performed an extensive literature search to fulfill the assumption that no “unobserved confounding” was missed, as suggested in the literature.[17] We identified the use of endoscopic ultrasound before treatment as a potential confounding factor.[19] Secondly, we collected additional factors that might affect both the use and cost of NCCRT for locally advanced esophageal cancer patients based on our clinical and research experiences. In this regard, we also included patient demographic factors (age, gender, and residency), patient characteristics (comorbidity, SES), disease (stage), and health service provider characteristics (treating hospital level and surgeon’s experience) based on our clinical experiences and prior NHI Research Database (NHIRD) and HWDC related studies.[20–26] Patient residency was classified as northern Taiwan or non-north; hospital was classified as medical centers or regional hospitals.

Cost and effectiveness assessment

Our CEA was based purely on a database approach.[27] Our outcomes of interest were mean life-years (LYs) and cost within three years. We identified deaths from the death registry as TCR is a high quality cancer registry.[28] Cost and cost-effectiveness were conducted from the payer’s perspective (i.e. all charges to NHI). All the costs within the duration of interest were summed and expressed as 2014 United States dollars (USD) via conversion by purchasing 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 NCCRT was compared with esophagectomy by applying the following equation in which

Step 1: Initial study population. Using Taiwan Cancer Registry data from 2008-2009[1], we selected clinically locally-advanced stage[2] esophageal squamous cell carcinoma patients who had received either neoadjuvant concurrent chemoradiotherapy (NCCRT) or esophagectomy.[3] We used the date of diagnosis as the index date. (n=104(NCCRT)+280(esophagectomy)=384 after exclusion of missing data)

↓

Step 2: Interventions of interest. NCCRT or esophagectomy and other covariables age, gender, residency region, social-economic status (SES),[4] comorbidity, use of endoscopic ultrasound and clinical stage, and health service provider characteristics,[5] were derived from the cancer registry and reimbursement files.

↓

Step 3: Outcome variables. We used the cancer and death registries to calculate the effectiveness of interest (survival). We also used reimbursement files to calculate charges as the cost of interest after adjustment by consumer price and purchasing power indexes.

↓

Step 4: Final study population after propensity score (PS) matching. We used the covariables to estimate the PS of receiving NCCRT for each subject then constructed our final study population using 1:1 PS matching. (n=150)

↓

Step 5: Analysis. We compared the hazard ratio of death with robust standard errors during the entire follow-up period. We also compared the cost and effectiveness within the duration of interest (3 years within diagnosis). We then estimated the incremental net benefit (INB) of NCCRT versus esophagectomy by applying various willing-to-pay (WTP) thresholds and constructed the cost-effectiveness acceptability curve. In sensitivity analysis, we evaluated the potential impact of an unmeasured confounder on the statistical significance of INB at common WTP.

Figure 1 Study flow chart.[1]: We only included patients treated by any single institution to ensure data consistency.[2]: 6th American Joint Committee on Cancer staging cT2-3N0M0 or cT1-3N1M0.[3]: We only included patients who had visited a single surgeon (among those diagnosed 2008–2009 who had received esophagectomy for esophageal cancer before NCCRT or esophagectomy.[4]: Income higher than minimal wage.[5]: Hospitals were classified as medical center or regional hospital; surgeons were classified as high (had performed at least 28 esophagectomies for esophageal cancer for those diagnosed 2008–2009) or low volume.

an intervention was considered cost-effective if it resulted in a positive net benefit (NB):[30]

$$NB = effectiveness * WTP - cost$$

WTP refers to the amount of money the payer is willing to pay for an outcome. The commonly cited WTP threshold, US$50,000~150,000/LY, means that the payer is willing to pay this amount to gain a year of life and is usually considered as a threshold to decide whether an intervention is cost-effective or not.[31,32] When the incremental NB of an intervention is positive at a specific WTP level, this intervention is associated with positive financial gain and, thus, is also cost-effective at this specific WTP level.

Statistical analysis and sensitivity analysis

Tabulation and standardized difference were used to assess the balance of covariates between PS matched groups. We used standardized differences to assess balancing in covariates across treatment groups, as suggested in the literature.[33] We compared the hazard ratio of death between NCCRT and esophagectomy for the entire follow-up period (censored on 1 January 2013).[34] We used a paired *t*-test to evaluate the probability for INB to be positive, then used this probability to construct the cost-effectiveness acceptability curve (CEAcC) to express the probability at various WTP levels when NCCRT was favored compared with esophagectomy.[30] Although we had used PS matching to adjust for potential bias, our result was still potentially 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 the highest suggested WTP (US$150,000/LY), as proposed by Rosenbaum, as our sensitivity analysis.[35] Under the assumption of "no unmeasured confounder," the probability of receiving either treatment should be the same after PS matching. However, if there was an unmeasured confounder associated with both treatment selection and outcome, then the true probability of receiving treatment might differ for a factor (labelled as Γ), even after PS matching. This sensitivity analysis assessed the extreme statistical significance of the treatment effect that would be observed had this unmeasured confounder been accounted for, at various levels of Γ. Therefore, the robustness of our result could be tested at various levels of violation of the "no unmeasured confounder" assumption. SAS 9.3 (SAS Institute, Cary, NC, USA) and Stata 11 (Stata Corp, College Station, TX, USA) were used for statistical analysis.

Results

Identification of the study cases

As revealed in Figure 1, 384 LA-ESCC patients treated with either NCCRT or esophagectomy were identified as the initial study population. After exclusion of cases with missing data and matching by PS, the final study population included 150 patients. Patient characteristics are listed in Table 1. A good balance in covariables and small standardized differences (<0.1) was seen for all covariables, except moderate standardized difference for gender and hospital (0.119; 0.121), respectively.

Cost and effectiveness

For the entire follow-up period, the hazard ratio of death when NCCRT was compared to esophagectomy was 0.709 (95% confidence interval 0.462~1.087, P = 0.1142). The Kaplan–Meier survival curve is depicted in Figure 2. As seen in Table 2, the mean cost (2014 USD) and survival (year) within three years after diagnosis was higher for NCCRT compared with esophagectomy (US$91,460 vs. $75,836 for cost, variance of incremental cost: $[59147.8]^2$ 2.2 vs. 1.8 for survival LY; variance of incremental effectiveness: 2.25; cova-

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

		NCCRT		Esophagectomy		Standardized difference
		Number	%§	Number	%§	
Gender	Female	5	7	3	4	0.119
	Male	70	93	72	96	
Residency	Non-north	54	72	54	72	0
	North	21	28	21	28	
Social-economic status	Higher than minimal wage	55	73	54	72	0.03
	Others	20	27	21	28	
Comorbidity	Without†	63	84	61	81	0.07
	With	12	16	14	19	
Stage	II	29	39	28	37	0.027
	III	46	61	47	63	
Hospital	Medical center	57	76	53	71	0.121
	Regional hospital	18	24	22	29	
Physician‡	Low case volume	37	49	34	45	0.08
	High case volume	38	51	41	55	
Use of endoscopic ultrasound	No	50	67	49	65	0.028
	Yes	25	33	26	35	

†Carlson comorbidity score <= 1; ‡ had performed at least 28 esophagectomies within 2008–2009; § rounded; ¶ the proportion of senile population (age > = 75) was balanced (<5% in both groups, standardized difference = 0), but the exact numbers were not reported because of a Health and Welfare Data Science Center (HWDC) database center policy to avoid numbers in single cells <= 2). NCCRT, neoadjuvant concurrent chemoradiotherapy.

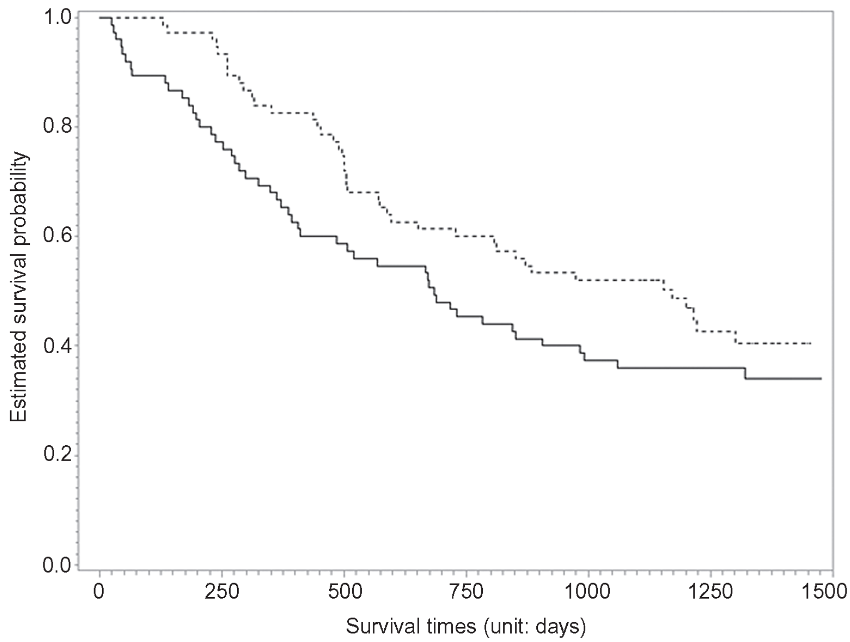

Figure 2 Kaplan–Meier survival curve (NCCRT vs. esophagectomy, in days).nccrt = 1 (dotted line) for neoadjuvant concurrent chemoradiotherapy; nccrt = 0 (solid line) for esophagectomy.

riance of incremental cost and effectiveness: −11533.8). The incremental cost-effectiveness ratio (ICER) was $39,060 (2014 USD/LY). At the common WTP level (US$50,000~$150,000/LY), NCCRT was cost-effective when compared with esophagectomy (INB US$4,376 [WTP US$50,000] or US$44,376 [WTP US$150,000]). The probability for NCCRT to be cost-effective (i.e. positive NB) was high (larger than 50%) at common WTP level (US$50 000~$150 000; Fig. 3).

Sensitivity analysis

Regarding the potential impact of an unmeasured confounder, if there was an unmeasured binary confounder that increased the odds of NCCRT (vs. esophagectomy) of 2.5% instead of zero, our conclusion that NCCRT was cost-effective compared with esophagectomy would remain statistically significant ($P < 0.05$; Table 3). However, if there was an unmeasured binary confounder that increased the odds of NCCRT (vs. esophagectomy) of at least 3%, then the observed cost-effectiveness of NCCRT versus esophagectomy may no longer be statistically significant ($P > 0.05$).

Table 2 Results of cost-effectiveness†

	NCCRT	Esophagectomy
Cost (2014 US Dollars)	91460	75836
Effectiveness (life-year)	2.20	1.80
Incremental cost	15624	reference
Incremental effectiveness	0.4	reference
ICER	39060	reference
INB (WTP = 50 000)	4376	reference
INB (WTP = 150 000)	44376	

† Cost rounded at integral; life-year rounded at second decimal. ICER: incremental cost-effectiveness ratio; INB, incremental net benefit; NCCRT, neoadjuvant concurrent chemoradiotherapy; WTP, willingness-to-pay (in United States dollars/life-year).

Discussion

Our population-based matched case-control study revealed that NCCRT is effective in improving LY survival within three years at 2.2 versus 1.8 for esophagectomy. NCCRT is also probably cost-effective at the common WTP level, with an ICER of US$39,060/LY.

Our results were compatible with previous randomized trials and population-based studies, in that NCCRT was effective in improving survival.[4,5] Our results were also consistent with previous studies in that NCCRT was associated with increased cost.[8,9] Furthermore, to the best of our knowledge, our study is the first to provide an estimate of cost-effectiveness of NCCRT.

The results of our study imply that, along with the increasing use of multimodality treatment for esophageal cancer, this strategy is also cost-effective from the payers' perspective in Taiwan. Whether NCCRT is cost-effective from other perspectives (such as societal) or health care systems deserves further study.

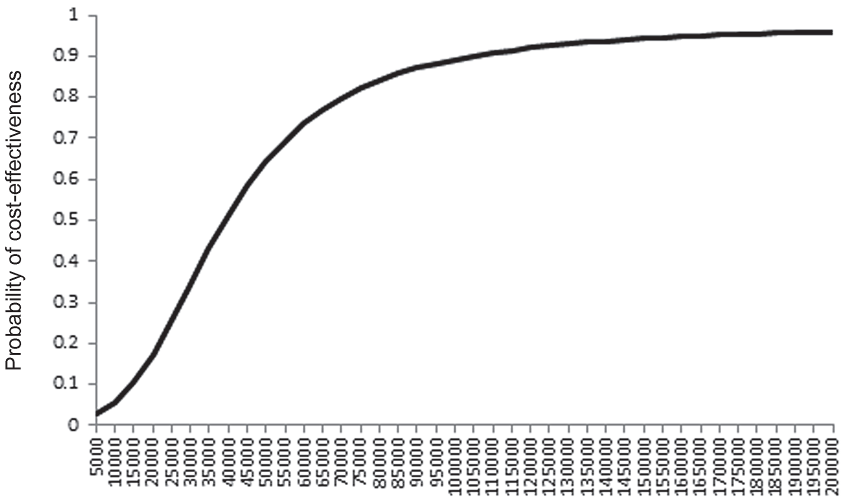

Figure 3 Cost-effectiveness acceptability curve. Vertical axis: probability of neoadjuvant concurrent chemoradiotherapy (NCCRT) to be associated with positive net benefit. Horizontal axis: willingness-to-pay (WTP). LY, life-year; USD, United States dollars.

There were several limitations to our analysis. Firstly, as a retrospective cohort analysis, it is possible that some confounding factors were not considered, although we did perform an extensive literature search and included all available reported factors in our analysis. Secondly, although the long term outcome of locally advanced esophageal cancer was poor, our duration of interest (3 years) might not have been long enough to fully capture the cost-effectiveness of NCCRT compared with esophagectomy. Thirdly, our study sample size was limited.

Conclusions

Our population-based matched case-control study reveals that, when compared with esophagectomy, NCCRT is likely to improve survival and is probably cost-effective at a common WTP level. Our results on cost-effectiveness should be interpreted with caution given these results are sensitive to potential unmeasured confounder(s) in sensitivity analysis. Further studies regarding other perspectives, long term cost-effectiveness, and the impact of new technologies are warranted.

Table 3 Sensitivity analysis

Increased odds of NCCRT (vs. esophagectomy) by unmeasured confounder (%)	Upper end of *P* value† for negative INB when WTP = US$150,000
1.0	0.044
1.5	0.046
2.0	0.048
2.5	0.049
3.0	0.051
3.5	0.053

† Rounded at the third decimal. ICER: incremental cost-effectiveness ratio; INB, incremental net benefit; NCCRT, neoadjuvant concurrent chemoradiotherapy; WTP, willingness-to-pay (in United States dollars/life-year).

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Disclosure

No authors report any conflict of interest.

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