Effectiveness of Intensity-Modulated Radiotherapy for Rectal Cancer Patients Treated With Neoadjuvant Concurrent Chemoradiotherapy: A Population-based Propensity Score-matched Analysis

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Abstract. *Background/Aim:* Neoadjuvant concurrent chemoradiotherapy (nCCRT) is the standard of care for locally advanced rectal cancer (LARC) patients treated with neoadjuvant concurrent chemoradiotherapy (nCCRT). The aim of this study was to compare intensity-modulated radiotherapy (IMRT) to 3D conformal radiotherapy (3DCRT) in nCCRT patients. *Patients and Methods:* We identified LARC patients diagnosed from 2007 to 2015 through the Taiwan cancer registry (TCR) and we constructed a propensity score matched cohort to compare IMRT to 3DCRT after balancing observable potential confounders. We compared the hazard ratio (HR) of death as well as other endpoints between the IMRT and 3DCRT. We performed supplementary analysis (SA) when additional potential confounders were considered. *Results:* Our study population consisted of 696 patients. There was no statistical difference when IMRT was compared to 3DCRT (HR for death=1.01, 95%confidence interval(CI)=0.76-1.35, $p=0.93$). There were also no statistical differences for the other endpoints or SA. *Conclusion:* For LARC patients treated with nCCRT, the treatment outcome has no statistically significant benefit between those treated with IMRT or 3DCRT.

Rectal cancer is one of the leading cancers responsible for mortality worldwide (1). Radiotherapy is an important tool for locally advanced rectal cancer (LARC), while neoadjuvant concurrent chemoradiotherapy (nCCRT) has been the common standard of care for decades (2-4).

Intensity-modulated radiotherapy (IMRT) is a 2nd generation advanced radiotherapy technology that allows highly conformal dose distribution (5). IMRT has been advocated for many cancer types, such as head-and-neck cancer, lung cancer, and prostate cancer (6-8), however, its role in rectal cancer was still debated in the current guidelines (9). A review paper published in 2016 stated: "There were no randomized control trials or prospective studies comparing IMRT with three-dimensional conformal radiotherapy (3DCRT) in rectal cancer", and none of the eight clinical studies mentioned in this review were population-based (10). Another systematic review published in 2018 also stated "Due to the sensitivity of IMRT to geometric errors, one might be concerned of the risk of missing the target volume, which can consequently affect oncologic outcomes" (11). This systematic review reported lower toxicity with IMRT (11). However, a landmark single arm phase II study (Radiation Therapy Oncology Group 0822) had reported that the use of IMRT in neoadjuvant chemoradiation for rectal cancer does not reduce the rate of GI toxicity (12). We have found only one relevant population-based study reporting the survival outcome of rectal cancer patients from North America (13). Due to the controversy of IMRT and the lack of population-based studies for rectal cancer, we aimed to compare the outcomes of locally advanced rectal cancer patients treated with neoadjuvant concurrent chemoradiotherapy (with IMRT *versus* 3DCRT) in this large population-based propensity score-matched analysis.

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Key Words: Rectal cancer, neoadjuvant concurrent chemoradiotherapy, intensity-modulated radiotherapy, 3D conformal radiotherapy.

Figure 1. STROBE study flowchart and number of individuals at each stage of the study. ¹We only included those treated (class 1-2) by any single institution to ensure data consistency. ²Cancer staging clinical stage T3-4 N0-2M0 or T1-4N1-2M0. ³Without missing information regarding outcome in the database.

Patients and Methods

Data sources. We collected a study population through the Health and Welfare Data Science Center, from the Ministry of Health and Welfare (HWDC) database. This HWDC database is a set of databases provided by the Bureau of the National Health Insurance (NHI) that gives access to complete information regarding: i) Taiwan cancer registry (TCR) (data until 2015), ii) death registry (data until Dec 31th, 2017), and iii) reimbursement data from NHI (data until Dec 31th, 2016) for the whole Taiwan population (14). The quality of TCR was reported in 2015 to have achieved an excellent level of data quality (15). NHI has also been used in many population-based studies. This study was approved by the research ethics committee of our institute (CMUH104-REC-003).

Study design, setting, study population and variables. Following the STROBE guidelines (16) we constructed our study flow chart, as depicted in Figure 1. From 2007 to 2015, we identified locally advanced rectal adenocarcinoma adult (age 18-75) patients who were not diagnosed with any other cancer, had received nCCRT, and had gone through proctectomy within 4-12 weeks. nCCRT was defined as the concurrent systemic treatment and radiotherapy (RT) (RT by external beam dose 45-50.4Gy at conventional fractionation) before surgery, according to the TCR records. We used the date of diagnosis as the index date, determined the explanatory variable of interest (IMRT or 3DCRT) based on the cancer registry and decided the outcomes: i) overall survival (OS), ii) incidence of local regional recurrence (ILRR), iii) rectal cancer mortality (IRCM), iv) other cancer mortality (IOCM), and v) cardiovascular mortality (ICVM), through

Figure 2. Standardized difference (SDif) via various methods (LR-SAS, LR-R, NN-SAS, and RF-SAS). LR-SAS: propensity score (PS) estimated by logistic regression and PS matched by software SAS; LR-R: PS estimated by logistic regression and PS matched by software R; NN-SAS: PS estimated by neural network and PS matched by software SAS; RF-SAS: PS estimated by random forest and PS matched by software SAS; RT: radiotherapy.

the TCR records or the death registry. We also collected potential confounders, including patient demographic factors (age, gender, and residency region), patient characteristics (social economic status and comorbidity), disease characteristics (clinical T-stage and N-stage), RT delivery using image-guided radiotherapy (IGRT) or other, and time period. All covariates were selected and modified by our experiences in clinical practice and other TCR/NHI related studies (17-21). The definitions of covariates were as follows: i) patient residency was classified as northern Taiwan or elsewhere, ii) socioeconomic status was classified as high (income greater than minimum wage) or not, iii) comorbidity was defined as with or without a modified Carlson comorbidity score ≥ 1 , iv) clinical stage was classified as T1-T2 versus T3-T4 for T-stage and negative versus positive for N-stage, v) RT delivery was classified as IGRT or not, and vi) time period was classified as early (2007-2010) or recent (2011-2015).

Statistical methods and supplementary analyses (SA). In our primary analyses (PA) we used a propensity score method, as advocated in the literature, to balance the measured potential confounders (22, 23). We included the above covariables in the propensity score (PS) model construction using a traditional method: i) logistic regression (LR) and machine learning methods, ii) neural network (NN) and iii) random forest (RF), to estimate the possible PS value (24-27), and then perform PS matching (PSM, 1:1 paired matching). Finally, we accessed the balance of covariate using standardized difference (SDif), as suggested in several review papers (24, 28, 29), and evaluated the effectiveness of IMRT versus 3DCRT. We also calculated the E-value (30), as sensitivity analysis, to evaluate the impact of potentially unmeasured confounder(s).

In the SA we considered more potential confounders regarding prognosis factors, such as the initial carcinoembryonic antigen (CEA) level and the location from anal verge, as well as an

Table I. Patient characteristics of the unmatched and matched study population in primary analysis.

	Unmatched population (n=1466)					Matched study population (n=696)				
	IMRT		3DCRT		SDif [‡]	IMRT		3DCRT		SDif [‡]
	number or mean (SD) [‡]	(%) [‡]	number or mean (SD) [‡]	(%) [‡]		number or mean (SD) [‡]	(%) [‡]	number or mean (SD) [‡]	(%) [‡]	
Age	57.71 (10.31)		56.84 (10.68)		0.083	57.10 (9.92)		56.84 (10.68)		0.025
Gender										
Female	354	(31.7)	111	(31.9)	0.005	113	(32.5)	111	(31.9)	0.012
Male	764	(68.3)	237	(68.1)		235	(67.5)	237	(68.1)	
Residency region										
Non-north	583	(52.1)	195	(56.0)	0.078	196	(56.3)	195	(56.0)	0.006
North	535	(47.9)	153	(44.0)		152	(43.7)	153	(44.0)	
Social economic status										
No more than minimum wage	244	(21.8)	90	(25.9)	0.095	84	(24.1)	90	(25.9)	0.040
Higher	874	(78.2)	258	(74.1)		264	(75.9)	258	(74.1)	
Comorbidity										
Without	729	(65.2)	231	(66.4)	0.025	229	(65.8)	231	(66.4)	0.012
With [†]	389	(34.8)	117	(33.6)		119	(34.2)	117	(33.6)	
T-stage										
T1-T2	92	(8.2)	31	(8.9)	0.024	31	(8.9)	31	(8.9)	0
T3-T4	1026	(91.8)	317	(91.1)		317	(91.1)	317	(91.1)	
N-stage										
negative	250	(22.4)	86	(24.7)	0.055	85	(24.4)	86	(24.7)	0.007
positive	868	(77.6)	262	(75.3)		236	(75.6)	262	(75.3)	
RT delivery										
non-IGRT	841	(75.2)	332	(95.4)	0.595	332	(95.4)	332	(95.4)	0
IGRT	277	(24.8)	16	(4.6)		16	(4.6)	16	(4.6)	
Period										
2007-2010	208	(18.6)	171	(49.1)	0.682	155	(44.5)	171	(49.1)	0.092
2011-2015	910	(81.4)	177	(50.9)		193	(55.5)	177	(50.9)	

3DCRT: 3D Conformal radiotherapy; IMRT: intensity-modulated radiotherapy; IGRT: image-guided radiotherapy; RT: radiotherapy; SD: standard deviation; SDif: standardized difference; [†]Modified Carlson comorbidity score ≥ 1 ; [‡]rounded.

additional outcome involving the pathological complete response (pCR), which has been available on TCR since 2011. In addition to the aforementioned co-variables, we also included the CEA level and location from anal verge in the PS model, to construct a subgroup diagnosed in 2011-2015, and performed the same methods and analyses as in our PA. We used the Cox proportional hazards model with a robust variance estimator during the entire follow-up period (23) to evaluate the hazard ratio (HR) of death. The sub-distribution hazard ratio from the clustered Fine-Gray model was used to evaluate ILRR, IRCM, IOCM, and ICVM (31). When the clustered Fine-Gray model failed to converge, we reported *p*-values using Gray's test instead (31). The binary outcome in the matched pairs was compared using McNemar's test. The softwares SAS 9.4 (SAS Institute, Cary, NC, USA) and R (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria) version 3.5.1 were used for the implementation of our statistical analyses.

Results

Identification of the study population used in the primary analyses. Our initial study population consisted of 1,477

locally advanced rectal adenocarcinoma patients receiving nCCRT. It was divided into an IMRT and a 3DCRT group, as shown in Figure 1. Following the exclusion of the missing data in follow-up, we estimated the PS values using different methods (LR, NN and RF), and then performed PSM using SAS or R. Figure 2 shows the distributions of SDif for all covariates using various methods (LR-SAS, LR-R, NN-SAS and RF-SAS). We found that one of the covariables was moderately out of balance (*i.e.*, SDif >0.25) (25) for PS estimated using NN or RF methods, whereas all covariables could be well-balanced (*i.e.*, SDif ≤ 0.1) (28, 29) for PS estimated using the LR method. When we compared the LR method with PSM using the optmatch package in the R statistical programming environment, we found that PSM using R could achieve a better covariable balance in PSM using R, compared to PSM using SAS, for seven of the nine covariables. For this reason, we adopted the best approach (PS by LR and PSM by R) for our subsequent analysis and included 696 patients as the final study population in the primary analysis (Table I).

Table II. Patient characteristics of the unmatched and matched study population in supplementary analysis.

	Unmatched population (n=374)					Matched study population (n=92)				
	IMRT		3DCRT		SDif [‡]	IMRT		3DCRT		SDif [‡]
	number or mean (SD) [‡]	(%) [‡]	number or mean (SD) [‡]	(%) [‡]		number or mean (SD) [‡]	(%) [‡]	number or mean (SD) [‡]	(%) [‡]	
Age	57.27 (10.73)		56.24 (9.80)		0.100	57.57 (8.21)		56.24 (9.80)		0.147
Gender										
Female	100	(30.5)	13	(28.3)	0.049	11	(23.9)	13	(28.3)	0.099
Male	228	(69.5)	33	(71.7)		35	(76.1)	33	(71.7)	
Residency region										
Non-north	180	(54.9)	20	(43.5)	0.230	18	(39.1)	20	(43.5)	0.088
North	148	(45.1)	26	(56.5)		28	(60.9)	26	(56.5)	
Social economic status										
No more than minimum wage	76	(23.2)	12	(26.1)	0.068	12	(26.1)	12	(26.1)	0
Higher	252	(76.8)	34	(73.9)		34	(73.9)	34	(73.9)	
Comorbidity										
Without	210	(64.0)	30	(65.2)	0.025	32	(69.6)	30	(65.2)	0.093
With [†]	118	(36.0)	16	(34.8)		14	(30.4)	16	(34.8)	
T-stage										
T1-T2	31	(9.5)	8	(17.4)	0.235	8	(17.4)	8	(17.4)	0
T3-T4	297	(90.5)	38	(82.6)		38	(82.6)	38	(82.6)	
N-stage										
negative	54	(16.5)	7	(15.2)	0.034	7	(15.2)	7	(15.2)	0
positive	274	(83.5)	39	(84.8)		39	(84.8)	39	(84.8)	
RT delivery										
non-IGRT	215	(65.5)	43	(93.5)	0.738	43	(93.5)	43	(93.5)	0
IGRT	113	(34.5)	3	(6.5)		3	(6.5)	3	(6.5)	
CEA										
above institution normal limit	133	(40.6)	21	(45.7)	0.103	20	(43.5)	21	(45.7)	0.044
within institution normal limit	195	(59.4)	25	(54.3)		26	(56.5)	25	(54.3)	
Location from anal verge (mm)	62.26	(29.73)	67.76	(27.81)	0.191	65.93	(30.84)	67.76	(27.81)	0.062

3DCRT: 3D Conformal radiotherapy; CEA: Carcinoembryonic Antigen; IMRT: intensity-modulated radiotherapy; IGRT: image-guided radiotherapy; RT: radiotherapy; SD: standard deviation; SDif: standardized difference; [†]Modified Carlson comorbidity score ≥ 1 ; [‡]rounded.

Primary analyses. After a median follow-up of 63 months (range=4-130 months), 191 deaths were observed (91 for the IMRT and 100 for the 3DCRT groups). When IMRT was compared to 3DCRT, there was no statistical difference (HR for death=1.01, 95% confidence interval=0.76-1.35, $p=0.93$). The observed HR could be explained by an unmeasured confounder that was associated with both types of treatment and a live/death risk ratio of 1.09 (E-value). The corresponding Kaplan Meier OS curve is shown in Figure 3. The 5-year OS for the IMRT and 3DCRT groups was 74% and 75%, respectively. The HR for ILRR, IRCM, and IOCM was 1.47 (95% confidence interval (CI)=0.89-2.42, $p=0.13$), 1.3 (95%CI=0.9-1.86, $p=0.16$), and 0.69 (95%CI=0.39-1.19, $p=0.18$), respectively. There was also no statistical difference for ICVM when IMRT was compared to 3DCRT ($p=0.11$).

Supplementary analyses. When additional prognosis factors were taken into consideration, all covariables could

Figure 3. Kaplan-Meier overall survival curve from primary analysis.

still achieve a moderate balance (Table II) in the SA (n=92). The HR for death was not statistically different when IMRT was compared with 3DCRT (HR=0.80, 95%CI=0.28-2.27, $p=0.68$). There was also no statistical difference for ILRR, IRCM, and IOCM, whereas cardiovascular mortality was not observed. The rates of pCR (28% vs 33% for IMRT *versus* 3DCRT groups) were also similar ($p=0.65$).

Discussion

In this large population-based propensity score-matched analysis, we found that for locally advanced rectal cancer patients treated with nCCRT, the treatment outcome was not statistically different between those treated with IMRT *versus* 3DCRT. To our knowledge, this is the first population-based study reporting the survival outcome of these patients outside of North America.

Our results are largely comparable to the aforementioned North American study in that there is no statistical difference in survival using either treatment (13). However, some important potential confounders, such as the CEA level or the distance from the anal verge (which was considered in our SA) were not assessed in this study.

There were several limitations in our study. Firstly, its retrospective nature created issues on unmeasured confounders despite the fact that we had used a propensity score method to deal with measured confounder, as suggested in the literature (22), and considered additional covariables not examined in previous studies. However, some potential confounders, such as surgical intervention, were not considered here, due of data limitation. In addition, some possible outcomes, such as short-term complications (32), long term side effects, or quality of life, were also not compared due to data limitation.

For these reasons, the interpretation of our study should be cautious, and further prospective studies, such as optimally randomized controlled trials (RCT) are needed for clarification.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

CCL, JAL, CYC and TLC contributed equally important to this work. Li CC participated in the conception and design of study, analyzed data, and drafted the manuscript. Liang JA, Chung CY and Chen TL participated in the conception and design of study, interpreted data, and drafted the manuscript. Chien CR participated in the conception and design of study, collected the related researches, analyzed and interpreted data, and drafted the manuscript.

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