

# With versus Without Primary Tumor Radiotherapy in Patients with Unresectable Stage IV Rectal or Rectosigmoid Cancer: A Propensity Score Matching Analysis for Survival

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## Research

**Keywords:** Stage IV Rectal cancer, primary tumor radiotherapy, propensity score matching

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# Abstract

**Background:** To evaluate the impact of primary tumor radiotherapy on survival in patients with unresectable metastatic rectal or rectosigmoid cancer.

**Methods:** From September 2008 to September 2017, 350 patients with unresectable metastatic rectal or rectosigmoid cancer were retrospectively reviewed in our center. All patients received at least 4 cycles of chemotherapy, and were divided into two groups according to with primary tumor radiotherapy or without. 163 patients received primary tumor radiotherapy, and the median radiation dose was 56.69Gy(50.4-60). Survival curves were estimated from the Kaplan–Meier procedure to roughly compare survival among two groups. Subsequently, 18-month survival was used as the outcome variable for this study. This study mainly evaluated the impact of primary tumor radiotherapy on survival of these patients through a series of multivariate Cox regression analyses after propensity score matching (PSM).

**Results:** The median follow-up time was 21 months. All 350 patients received a median of 7 cycles of chemotherapy (range 4-12), 163 (46.67%) patients received primary tumor radiotherapy for local symptoms. The Kaplan–Meier survival curves showed a significant overall survival (OS) advantage for primary tumor radiotherapy group to without radiotherapy (20.07 vs 17.33 months;  $P=0.002$ ). In this study, multivariate Cox regression analysis after adjusted covariates, multivariate Cox regression analysis after PSM, and inverse probability of treatment weighting (IPTW) analysis and propensity score (PS)-adjusted model analysis consistently showed that primary tumor radiotherapy could effectively reduce the risk of death for these patients at 18 months (HR: 0.62, 95% CI 0.40-0.98; HR:0.79, 95% CI:0.93-1.45; HR: 0.70, 95% CI 0.55-0.99 and HR: 0.74, 95% CI:0.59-0.94).

**Conclusion:** Compared with patients with stage IV rectal or rectosigmoid cancer who did not receive primary tumor radiotherapy, received primary tumor radiotherapy reduced the risk of death in these patients. The radical doses of 59.4Gy/ 33 fractions or 60Gy/ 30 fractions of radiation for primary tumors might be considered for unresectable metastatic rectal or rectosigmoid cancer, not just for relieve symptoms. **Keywords:** Stage IV Rectal cancer, primary tumor radiotherapy, propensity score matching.

## Background

In China, the number of newly diagnosed colorectal cancer patient was 376,300 in 2015. Rectal or rectosigmoid cancer accounted for about 50% and 27% of new cases [1–2]. Approximately 25% of colorectal cancer patients present with overt metastases, and an additional 25–35% of patients will develop metastases during the course of their disease [3]. Of which, around 80–90% patients had no chance to conduct a complete surgical removal of all metastatic tumors [3–4]. The prognosis of these patients was extremely poor, and the median survival time of unresectable stage IV rectal cancer was about 5–6 months [5]. At present, systemic chemotherapy is still the preferred treatment for stage IV unresectable colorectal cancer. Radiotherapy or resection of the primary tumor is only recommended for patients with primary tumor progression by the National Comprehensive Cancer Network (NCCN)

guideline. These patients usually have obvious local symptoms such as obstruction, bleeding, pain. Although there is some controversy, most of the studies show that resection of primary tumor without metastasectomy not only relieves pelvic symptoms in patients with metastatic colorectal cancer, but also improves the survival of them [6, 7, 8]. However, there is few studies exploring whether radiotherapy of primary tumor can also improve the survival of these patients. To provide more meaningful clinical evidence to answer this question, in this study, we retrospectively analyzed 350 patients with stage IV unresectable rectal or rectosigmoid cancer using PSM analyses to explore if there were any survival benefits in patients who received primary tumor radiotherapy.

## Methods

We retrospectively reviewed 366 patients who were initially diagnosed with stage IV unresectable rectal or rectosigmoid cancer from September 2008 to September 2017 in our center. All patients received at least 4 cycles of chemotherapy, some of whom had significant local pelvic symptoms received primary tumor radiotherapy. 4 patients' diagnoses were corrected as non-metastatic patients by review, 3 patients underwent emergency resection of the primary tumor because of an acute intestinal obstruction, 4 patients discontinued the primary tumor radiotherapy, and 5 patients were lost to follow-up. The final analysis included 350 patients, and the details of PSM process are demonstrated as Fig. 1. Of 350 patients, 254 were male and 96 were female; 266 were diagnosed with rectal cancer and 84 with rectosigmoid cancer. The number of patients in stage IVa, IVb and IVc were 180, 146 and 24 respectively, according to the 8th edition of the American Joint Commission on Cancer (AJCC) Cancer Staging Manual. The whole group of patients received chemotherapy (FOLFOX4/FOLFOX6), and the average number of chemotherapy cycles was 7 cycles. 74 patients received second-line chemotherapy after disease progression. The response to chemotherapy was assessed by the Response Evaluation Criteria in Solid Tumors (RECIST), and defined partial response (PR) or stable disease (SD) as good response to chemotherapy and progressive disease (PD) as poor response. Because of obvious local pelvic symptoms such as pain, bleeding, and incomplete obstruction, 163 patients received primary tumor radiotherapy while receiving chemotherapy. Intensity-modulated radiotherapy (IMRT) was used in primary tumor radiotherapy, primary tumor included intestinal tumor and metastatic lymph nodes confirmed by pelvic computed tomography (CT) or intensity-modulated radiotherapy (MRI) radiotherapy was administered in doses of 1.8 to 2.0 Gy/day delivered 5 days per week to a total dose of 59.4 to 60 Gy. the pelvic lymph drainage area (presacral, internal iliac, obturator, mesorectum) within 2 cm above and below the primary tumor received 45-50.4 Gy radiotherapy. Patients and treatment characteristics are shown in Table 1.

Table 1

Comparison of clinical and treatment characteristics between the patients with primary tumor radiation and without.

Variable	primary tumor radiotherapy				P-value
	No(187)		Yes(163)		
	Number	%	Number	%	
Age					0.460
< 60 years	90	48.13	72	44.17	
≥ 60 years	97	51.87	91	55.83	
Gender					0.879
Male	136	72.73	118	72.39	
Female	51	27.27	45	27.61	
KPS*					0.037
70–80	120	64.17	122	74.85	
90–100	67	35.83	41	25.15	
Primary Site					0.056
Rectum	134	71.66	132	80.98	
Rectosigmoid	53	28.34	31	19.02	
T Stage					0.043
T2	10	5.35	14	8.59	
T3	86	45.99	90	55.21	
T4	91	48.66	59	36.20	
N Stage					< 0.001
N0	10	5.35	40	24.54	
N1	43	22.99	71	43.56	
N2	44	23.53	42	25.77	
N+	77	41.18	9	5.52	
Nx	13	6.95	1	0.61	

\*KPS: Karnofsky Performance Status

Variable	primary tumor radiotherapy				P-value
	No(187)		Yes(163)		
M Stage					0.880
M1a	98	52.41	82	50.31	
M1b	77	41.17	69	42.33	
M1c	12	6.42	12	7.36	
Differentiation					0.013
Well	20	10.70	8	4.91	
Moderate	94	50.27	104	63.80	
Poor	61	32.62	49	30.06	
Unknown	12	6.42	2	1.23	
Chemotherapy Cycle					0.019
4-8cycle	142	75.94	105	64.42	
9-12cycle	45	24.06	58	35.58	
Second-line Chemotherapy					0.014
No	156	83.42	120	73.62	
Yes	31	16.58	43	26.38	
Chemotherapy Response					0.279
Poor	83	44.39	63	38.65	
Good	104	55.61	100	61.35	
Metastatic Tumor Radiotherapy					0.201
yes	90	48.13	90	55.21	
no	97	51.87	73	44.79	
*KPS: Karnofsky Performance Status					

The follow-up period was defined as the time from the confirmed diagnosis of metastatic colorectal cancer until death or 18 months after confirmed diagnosis at least. Survival time of the two groups was compared with Kaplan-Meier method. The 18-month survival was used as the outcome variable, and whether the primary tumor was treated with radiation as the exposure variable. Screen for covariates that may be related to outcome variables by referring to previous literature, clinical experience, and univariate

Cox regression analysis. Multivariate Cox regression analysis was used to obtain independent effects of exposure variables on outcome variables after adjusting relevant covariates. This study was a retrospective observational study, not an randomized controlled trial (RCT), so selection bias was inevitable. In order to minimize the effect of bias, the propensity score matching (PSM) method can achieve a similar randomization effect, further verifying the previous analysis results. The matching algorithm uses binary logistic regression, and the caliper value is set to 0.05. Given that PSM can cause sample loss, this study uses the inverse probability of treatment weighting (IPTW) as a sensitivity analysis to assess the stability of the results. Moreover, we further verified the result by adjusting the propensity score analysis (PS-adjusted model). Statistical analyses were performed using SPSS software (version 24.0, SPSS, Chicago, IL, USA) and R software.

## Results

The median follow-up time was 21 months. Patients who underwent primary tumor radiotherapy had more cycles of chemotherapy (35.58% vs 24.06%;  $p = 0.019$ ) and more likely to accept second-line chemotherapy (26.38% vs 16.58%;  $p = 0.014$ ). Patients with lower Karnofsky performance status (KPS) score, moderate differentiation and T3 stage constituted a higher percentage in primary tumor radiotherapy group. All of the other characteristics were similar between groups (Table 1).

The Kaplan–Meier survival curves showed a significant overall survival (OS) advantage for primary tumor radiotherapy group to without radiotherapy (20.07 vs 17.33 months;  $P = 0.002$ ; Fig. 2). The 18-months survival rates were 73.01% and 42.25%, respectively, between the groups with and without the primary tumor radiotherapy.

Univariable Cox regression analysis was performed to assess the associations between covariates and 18-months survival, results were displayed in Table 2. Possible protective factors based on univariable Cox regression analysis included elder, more chemotherapy cycles, had second-line chemotherapy, better chemotherapy response, metastatic lesions received radiotherapy, primary tumor received radiotherapy. Possible risk factors included higher T stage, N stage, and M stage. Based on the univariate Cox regression analysis and the distribution of related factors in the two groups of patients, 10 variables (included age, KPS, T stage, N stage, M stage, differentiation, chemotherapy cycle, second-line chemotherapy, chemotherapy response, metastatic tumor radiotherapy) were selected as the covariates that needed to be adjusted for subsequent multivariate Cox regression analysis. After adjusting above covariates in multivariate Cox regression analysis, primary tumor radiotherapy group had a lower risk of death than without primary tumor radiotherapy (HR: 0.62, 95% CI 0.40–0.98; Table 4). The 10 variables were included in propensity score matching. There were 91 matched patients in each group by 1:1 individual matching without replacement. The matching situation was shown in Fig. 3, the clinicopathological features were presented in Table 3. The primary tumor radiotherapy group still shown lower risk of death than without primary tumor radiotherapy group after propensity score matching (HR:0.79, 95% CI:0.93–1.45; Table 4). The sensitivity analyses using propensity score–based IPTW and PS-adjust model yielded similar results (Table 4). Results from our sensitivity analyses were consistent

with our primary analysis findings. Patients treated with primary tumor radiotherapy in this study had a lower risk of death than those treated without radiotherapy (HR: 0.70, 95% CI 0.55–0.99 and HR: 0.74, 95% CI:0.59–0.94).

Table 2

Univariable Cox regression analysis of factors for the whole group of patients 18-months death risk.

Factors	number(%)	HR(95% CI)	P value
Age			
< 60 years	162(46.29)	Reference	
≥ 60 years	188((53.71)	0.98 (0.97, 1.00)	0.0297
Gender			
Male	254 (72.57)	Reference	
Female	96 (27.43)	0.88 (0.62, 1.26)	0.4927
KPS			
70–80	242(69.14)	Reference	
90–100	108(30.86)	1.00 (0.98, 1.03)	0.7220
Primary Site			
Rectum	266(76.00)	Reference	
Rectosigmoid	84(24.00)	1.12(0.53,1.18)	0.6210
T Stage			
T2	24 (6.86)	Reference	
T3	176 (50.29)	2.86 (1.05, 7.83)	0.0406
T4	150 (42.86)	3.16 (1.15, 8.64)	0.0253
N Stage			
N0	50 (14.29)	Reference	
N1	114 (32.57)	0.88 (0.44, 1.75)	0.7192
N2	86 (24.57)	2.03 (1.05, 3.93)	0.0350
N+	86 (24.57)	4.09 (2.21, 7.59)	< 0.0001
Nx	14 (4.00)	7.01 (3.14, 15.66)	< 0.0001
M Stage			
M1a	180 (51.43)	Reference	
M1b	146 (41.71)	1.09 (0.77, 1.54)	0.6163

<b>Factors</b>	<b>number(%)</b>	<b>HR(95% CI)</b>	<b>P value</b>
M1c	24 (6.86)	2.39 (1.46, 3.91)	0.0006
<b>Differentiation</b>			
Well	28 (8.00)	Reference	
Moderate	198 (56.57)	0.28 (0.17, 0.47)	< 0.0001
Poor	110 (31.43)	1.00 (0.61, 1.65)	0.9877
Unknown	14 (4.00)	0.95 (0.22, 4.07)	0.9444
<b>Chemotherapy Cycle</b>			
4-8	247(70.57)	Reference	
9-12	103(29.43)	0.79 (0.69, 0.90)	0.0002
<b>Second-line Chemotherapy</b>			
No	276 (78.86)	Reference	
Yes	74 (21.14)	0.37 (0.22, 0.63)	0.0002
<b>Chemotherapy Response</b>			
Poor	146 (41.71)	Reference	
Good	204 (58.29)	0.82 (0.59, 1.13)	0.0217
<b>Metastatic Tumor radiotherapy</b>			
Yes	180 (51.43)	Reference	
No	170 (48.57)	1.53 (1.11, 2.11)	0.0102
<b>Primary Tumor Radiotherapy</b>			
No	187 (53.43)	Reference	
Yes	163 (46.57)	0.39 (0.28, 0.56)	< 0.0001

Table 3

Clinicopathological features between the two groups after propensity score matching.

Variable	Primary Tumor Radiotherapy				Standardized difference	P value
	No(91)		Yes(91)			
	Number	%	Number	%		
Age					0.0224	1.0000
< 60 years	43	47.3	44	48.4		
≥ 60 years	48	52.7	47	51.6		
KPS						0.1700
70	14	15.4	32	35.2	0.4674	
80	65	71.4	42	46.2	0.5313	
90	12	13.2	14	15.4	0.0628	
100	0	0.0	3	3.3	0.2611	
T Stage						0.1156
T2	10	11.0	5	5.5	0.2008	
T3	43	47.3	56	61.5	0.2898	
T4	38	41.8	30	33	0.1825	
N Stage						0.1250
N0	10	11.0	15	16.5	0.1601	
N1	44	48.4	29	31.9	0.3412	
N2	25	27.5	38	41.8	0.3037	
N+	9	9.9	7	7.7	0.0777	
Nx	3	3.3	2	2.2	0.0673	
M Stage						0.9395
M1a	50	54.9	50	54.9	0.0000	
M1b	37	40.7	36	39.6	0.0224	
M1c	4	4.4	5	5.5	0.0507	
Differentiation						0.3212
Well	7	7.7	6	6.6	0.0427	

Variable	Primary Tumor Radiotherapy				Standardized difference	P value
	No(91)		Yes(91)			
	Number	%	Number	%		
Moderate	53	58.2	52	57.1	0.0222	
Poor	28	30.8	33	36.3	0.1166	
Unknown	3	3.3	0	0	0.2611	
Chemotherapy Cycle						0.0940
4	20	22.0	25	27.5	0.1276	
5	5	3.3	0	0	0.2611	
6	22	24.2	19	20.9	0.0790	
8	20	22.0	14	15.4	0.1698	
10	5	5.5	20	22	0.4932	
12	19	20.9	13	14.3	0.1739	
Second-line Chemotherapy					0.0000	1.0000
No	74	81.3	74	81.3		
Yes	17	18.7	17	18.7		
Chemotherapy Response					0.1562	0.3680
Poor	42	46.2	35	38.5		
Good	49	53.8	56	61.5		
Metastatic Tumor Radiotherapy					0.0880	0.6565
Yes	44	48.4	48	52.7		
No	47	51.6	43	47.3		

Table 4

Various analysis models for two groups of patients 18-months death risk.

Methods	primary tumor radiotherapy		P Value
	No	Yes	
		HR (95% CI)	
COX adjusted*	Reference	0.62(0.40–0.98)	0.0394
PSM model	Reference	0.79(0.93–1.45)	NS
IPTW model	Reference	0.70(0.55–0.99)	0.0436
PS Adjusted**	Reference	0.74(0.50–0.94)	0.0254
* Adjusted Covariates included age, KPS, T stage, N stage, M stage, differentiation, chemotherapy cycle, second-line chemotherapy, chemotherapy response, metastatic lesion radiotherapy.			
** Propensity score were adjusted.			
NS: not significant			

## Discussion

With the application of oxaliplatin and irinotecan combined with fluorouracil regimen, the survival time of stage IV colorectal cancer ranged from 16 to 20 months [9–11]. After entering the era of targeted drugs combined with chemotherapy, the survival time of stage IV colorectal cancer has been significantly improved to 25–35 months [12].

For patients with stage IV colorectal cancer who cannot be cured by radical operation, in general, resection or radiotherapy as a local treatment was used to relieve local obstruction, hemorrhage and pain. More clinical studies focus on the benefits of primary tumor resection alone. Although there are still controversies at present [13, 14], most of the existing clinical studies show that the resection of the primary tumor alone can not only reduce the incidence of local complications [15], but also seem to benefit the survival of patients [7, 16, 17]. However, there are limited data regarding the effect of primary tumor radiotherapy in stage IV unresectable rectal or rectosigmoid cancer, and most of these studies are mainly observing the palliative effect [18–21]. To our knowledge, there have only been a very few studies to explore the effects of primary tumor radiotherapy on survival of metastatic rectal cancer. For clinical researchers, the main reason is that there are many factors that can affect the survival of patients with stage IV rectal cancer, and that have large individual differences. In retrospective observational studies, conventional multivariate regression analysis is difficult to effectively remove the interference of confounding factors and selection bias on the results, which makes the analysis results lack reliability and consistency. At the same time, it is very difficult to implement such randomized controlled trials, for example, two previous trials (NCT01086618 and NCT01978249) were terminated due to recruitment

problems. This study designed a series of analyses based on PSM to minimize the interference of other confounding factors and selection bias on the research results.

In previous clinical studies of primary tumor radiotherapy for metastatic rectal cancer, radiotherapy doses were generally low. Sager et al. reviewed many of studies in which the dose of radiotherapy delivered to primary tumor ranged from 25 to 50 Gy [22]. When the  $\alpha/\beta$  for the tumor was assumed to be 10 Gy for the biologically equivalent dose (BED), the BED of above studies ranged from 37.5 to 53.1 Gy. In this study, the radiation dose of the primary tumor was significantly higher than in previous clinical studies. 78% of patients received a radical dose (59.4 Gy in 33 fractions or 60 Gy in 30 fractions), the average radiation dose was 56.69 Gy and the average BED was 67 Gy. As we all know, the higher radiation doses are closely related to better local tumor control.

In this study, Kaplan-Meier survival analysis showed that the median survival times of the primary tumor radiotherapy group and without radiotherapy group were ( $20.07 \pm 8.98$ ) months and ( $17.33 \pm 7.34$ ) months, respectively. This was consistent with previous studies on the stage IV colorectal cancer who only received chemotherapy (median survival was 16 to 20 months), so we decided to use 18-month survival as the outcome variable of this study. Further, in this study, the priori selection of covariates was based on previous studies and the experience of the authors, but also considered the results of univariate analysis. In the subsequent analysis, multivariate Cox regression analysis after adjusted covariates, analysis after PSM, and IPTW analysis and PS-adjusted model analysis which in order to examine the reliability of the results, all analysis consistently showed that primary tumor radiotherapy could effectively reduce the risk of death for these patients at 18 months. In the analysis results of the above different analysis models, although the hazard ratio (HR) value has increased significantly, the nature of reducing the risk of death has not changed, and the range of the confidence interval has gradually narrowed, our results became more conservative and accurate by IPTW and PS-adjusted model analysis. A retrospective observational study similar to this study shows that palliative radiotherapy could improve the survival of metastatic rectal cancer [23]. However, several deficiencies exist in the study. The study did not further analyze the location of the lesion (primary or metastatic) targeted by palliative radiotherapy, nor did it involve the dose. Chemotherapy, as an important factor affecting the survival of metastatic rectal cancer, was not analyzed in this study. These deficiencies have been corrected in this study.

There are still some shortcomings and limitations in this study: (1) The time range of eligible patients included in this retrospective study was from September 2008 to September 2017. During this period, the price of Bevacizumab and Cetuximab in China were expensive and not included in the local health care insurance, patients who can afford it were rare, so this study did not select patients who received Bevacizumab or Cetuximab. The lack of targeted drugs will definitely reduce the survival benefit of patients and may affect the benefits of radiotherapy for primary tumors. (2) Compared with 12 cycles recommended by the guidelines, the median chemotherapy cycle in this study was relatively low, only 7 cycles. Fewer chemotherapy cycles will reduce the therapeutic efficacy of all patients and may have an uncertain impact on the benefits of primary tumor radiotherapy. (3) This study was a real-world study

(observational clinical study). There might be some confounding factors outside out clinical cognition and previous literature reports that may affect the accuracy of the research results.

## Conclusions

In this study, compared with patients with stage IV rectal or rectosigmoid cancer who did not receive primary tumor radiotherapy, received primary tumor radiotherapy reduced the risk of death in these patients for 18 months. The dose pattern of 59.4 Gy in 33 fractions or 60 Gy in 30 fractions was acceptable during concurrent chemotherapy. The radical doses of radiation for primary tumors might be considered for inoperable metastatic rectal or rectosigmoid cancer, not just for relieve symptoms.

## Abbreviations

AJCC: American joint commission on cancer; BED: Biologically equivalent dose; CT: Computed tomography; Gy: Gray; HR: Hazard ratio; IMRT: Intensity-modulated radiotherapy; IPTW: Inverse probability of treatment weighting; KPS: Karnofsky performance status; MRI: Magnetic resonance imaging; NCCN: National comprehensive cancer network; OS: Overall survival; PD: Progressive disease; PR: Partial response; PS: Propensity score; PSM: Propensity score matching; RCT: Randomized controlled trial; RECIST: Response evaluation criteria in solid tumors; SD: Stable disease;

## Declarations

### Ethics approval and consent to participate

The institutional ethics committee granted the ethics approval in this study (SL-201507004; Guizhou Cancer Hospital, Guiyang, People's Republic of China).

### Consent for publication

All authors consent to the publication.

### Availability of data

The datasets generated and/or analyzed during the current study are not publicly available since the participants did not consent in sharing the data with third parties.

### Competing interests

The authors declare that they have no competing interest.

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## Authors' contributions

Gang Wang, Wen-ling Wang, Hong-Min Dong made substantial contributions to the design of the clinical plan selection protocol and the design of the methods used in this study. Gang Wang delineated all structures. All authors have contributed significantly to the manuscript, have read the manuscript and have given final approval of the version to be published, and take public responsibility for appropriate portions of the content.

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## References

1. Xishan W, Comparison analysis of epidemiological characteristics and prevention-treatment strategy of colorectal cancer in China and the United States. *Chinese Journal of Colorectal Disease* [Electronic Edition]. 2017; 6(06):14-20.
2. Xishan W, Epidemiological characteristics and prevention and control strategies of colorectal cancer in China and American. *Chinese Journal of Colorectal Disease* [Electronic Edition]. 2019; 8(01):7-11.
3. Cutsem EV, Nordlinger B, Adam R, et al. Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. *European Journal of Cancer*. 2006; 42(14):0-2221.
4. Dawood O, Mahadevan A, Goodman KA. Stereotactic body radiation therapy for liver metastases. *European Journal of Cancer*. 2009; 45(17):0-2959.
5. Eadens MJ, Grothey A. Curable metastatic colorectal cancer. *Curr Oncol Rep*. 2011; 13(3): 168-76.
6. Ko-Chao L, Yuche O, Wan-Hsiang H, et al. Meta-analysis of outcomes of patients with stage IV colorectal cancer managed with chemotherapy/radiochemotherapy with and without primary tumor resection. *Oncotargets and Therapy*. 2016; 9:7059-7069.

7. Gulack BC, Nussbaum DP, Keenan JE, et al. Surgical resection of the primary tumor in stage IV colorectal cancer without metastasectomy is associated with improved overall survival compared with chemotherapy/radiation therapy alone. *Diseases of the Colon & Rectum*. 2016; 59(4):299-305.
8. Clancy C, Burke JP, Barry M, et al. A meta-analysis to determine the effect of primary tumor resection for stage IV colorectal cancer with unresectable metastases on patient survival. *Annals of Surgical Oncology*. 2014; 21(12):3900-3908.
9. Cassidy J, Tabernero J, Twelves C, et al. XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. *J Clin Oncol*. 2004; 22(11): 2084-91.
10. Giacchetti S, Perpoint B, Zidani R, et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol*. 2000; 18(1): 136-47.
11. Köhne CH, van Cutsem E, Wils J, et al. Phase III study of weekly high-dose infusional fluorouracil plus folinic acid with or without irinotecan in patients with metastatic colorectal cancer: European Organisation for Research and Treatment of Cancer Gastrointestinal Group Study 40986. *J Clin Oncol*. 2005; 23(22): 4856-65.
12. O'Neil BH, Venook AP. Trying to Understand Differing Results of FIRE-3 and 80405: Does the First Treatment Matter More Than Others. *J Clin Oncol*. 2015; 33(32): 3686-8.
13. Gelsomino F, Spallanzani A, Orsi G, Caputo F, Santini C, Cascinu S. To resect or not to resect: The hamletic dilemma of primary tumor resection in patients with asymptomatic stage IV colorectal cancer. *Crit Rev Oncol Hematol*. 2018; 132: 154-160.
14. Yun JA, Huh JW, Park YA, et al. The role of palliative resection for asymptomatic primary tumor in patients with unresectable stage IV colorectal cancer. *Dis Colon Rectum*. 2014; 57(9): 1049-58.
15. Cellini C, Hunt SR, Fleshman JW, Birnbaum EH, Bierhals AJ, Mutch MG. Stage IV rectal cancer with liver metastases: is there a benefit to resection of the primary tumor. *World J Surg*. 2010; 34(5): 1102-8.
16. Maroney S, de Paz CC, Reeves ME, et al. Benefit of Surgical Resection of the Primary Tumor in Patients Undergoing Chemotherapy for Stage IV Colorectal Cancer with Unresected Metastasis. *J Gastrointest Surg*. 2018; 22(3): 460-466.
17. Lee KC, Ou YC, Hu WH, Liu CC, Chen HH. Meta-analysis of outcomes of patients with stage IV colorectal cancer managed with chemotherapy/radiochemotherapy with and without primary tumor resection. *Onco Targets Ther*. 2016; 9: 7059-7069.
18. Cameron MG, Kersten C, Vistad I, Fosså S, Guren MG. Palliative pelvic radiotherapy of symptomatic incurable rectal cancer - a systematic review. *Acta Oncol*. 2014; 53(2): 164-73.
19. Picardi V, Deodato F, Guido A, et al. Palliative Short-Course Radiation Therapy in Rectal Cancer: A Phase 2 Study. *Int J Radiat Oncol Biol Phys*. 2016; 95(4): 1184-90.
20. Tyc-Szczepaniak D, Wyrwicz L, Kepka L, et al. Palliative radiotherapy and chemotherapy instead of surgery in symptomatic rectal cancer with synchronous unresectable metastases: a phase II study. *Ann Oncol*. 2013; 24(11): 2829-34.

21. Bae SH, Park W, Choi DH, et al. Palliative radiotherapy in patients with a symptomatic pelvic mass of metastatic colorectal cancer. *Radiat Oncol.* 2011; 6: 52.
22. Sager O, Dincoglan F, Demiral S, et al. A Concise Review of Pelvic Radiation Therapy (RT) for Rectal Cancer with Synchronous Liver Metastases. *Int J Surg Oncol.* 2019; 1-11.
23. Qi, Liu, Zezhi, et al. Palliative beam radiotherapy offered real-world survival benefit to metastatic rectal cancer: A large US population-based and propensity score-matched study. *Journal of Cancer,* 2019; 10(5): 1216-1225.

## Figures

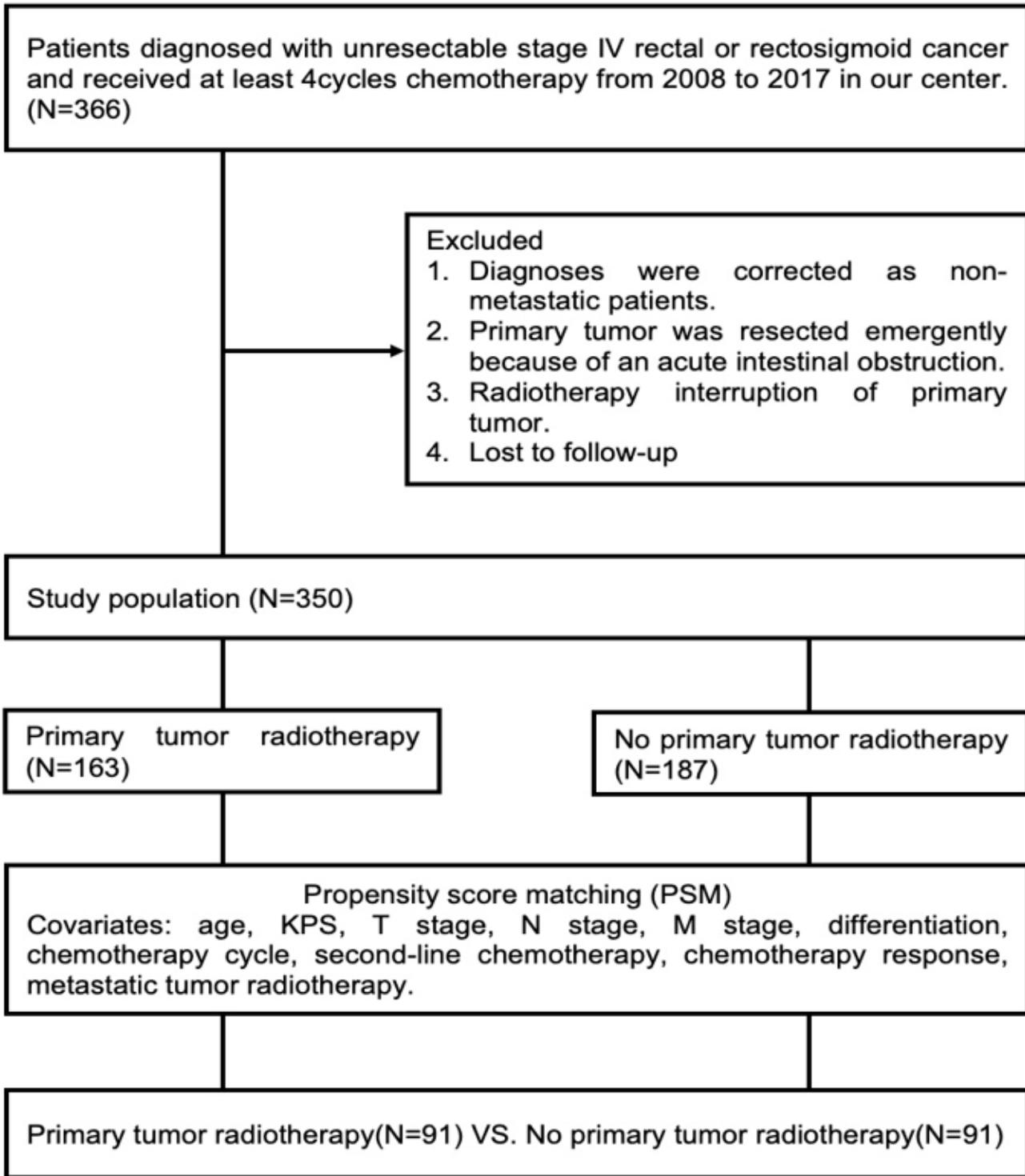
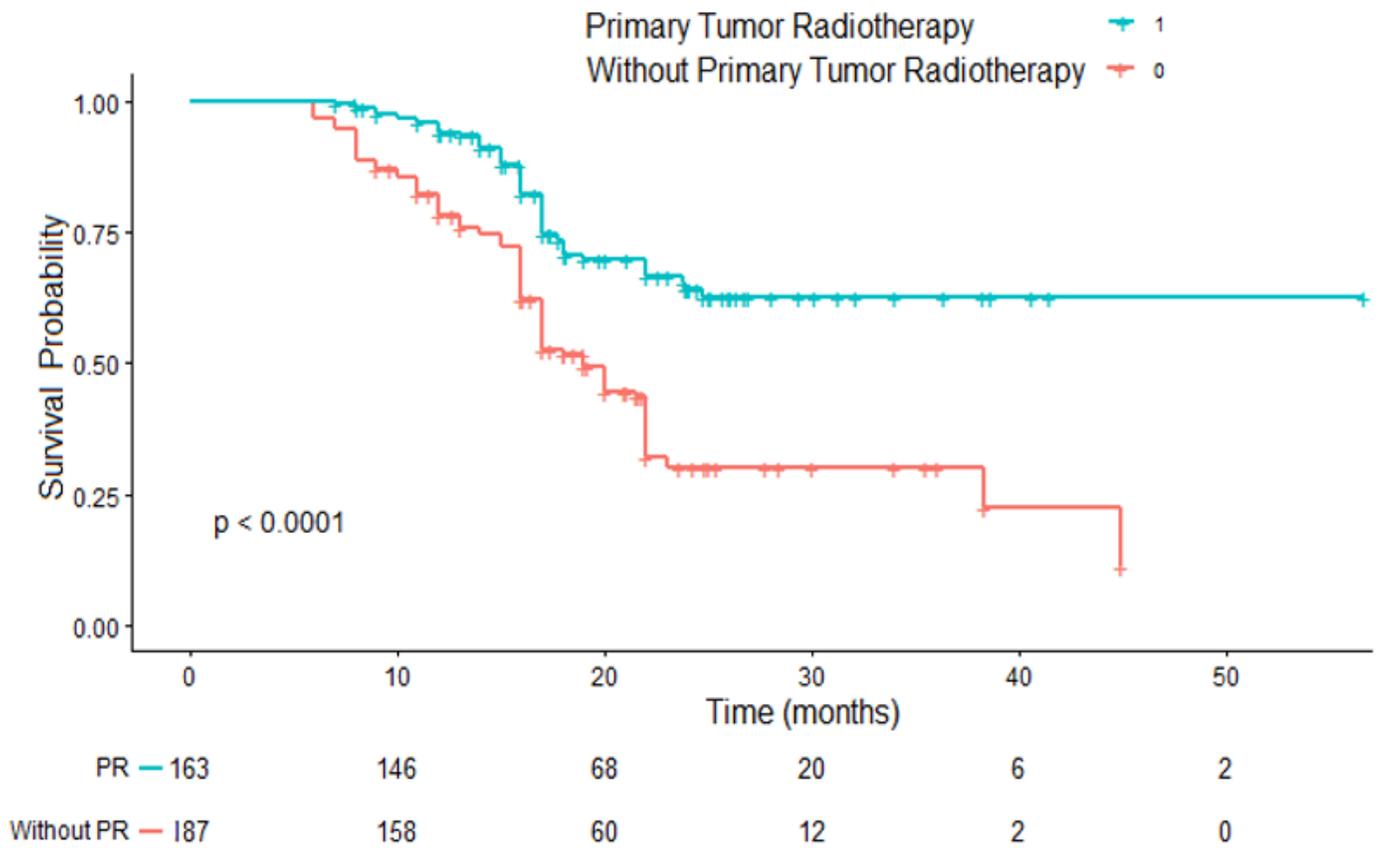


Figure 1

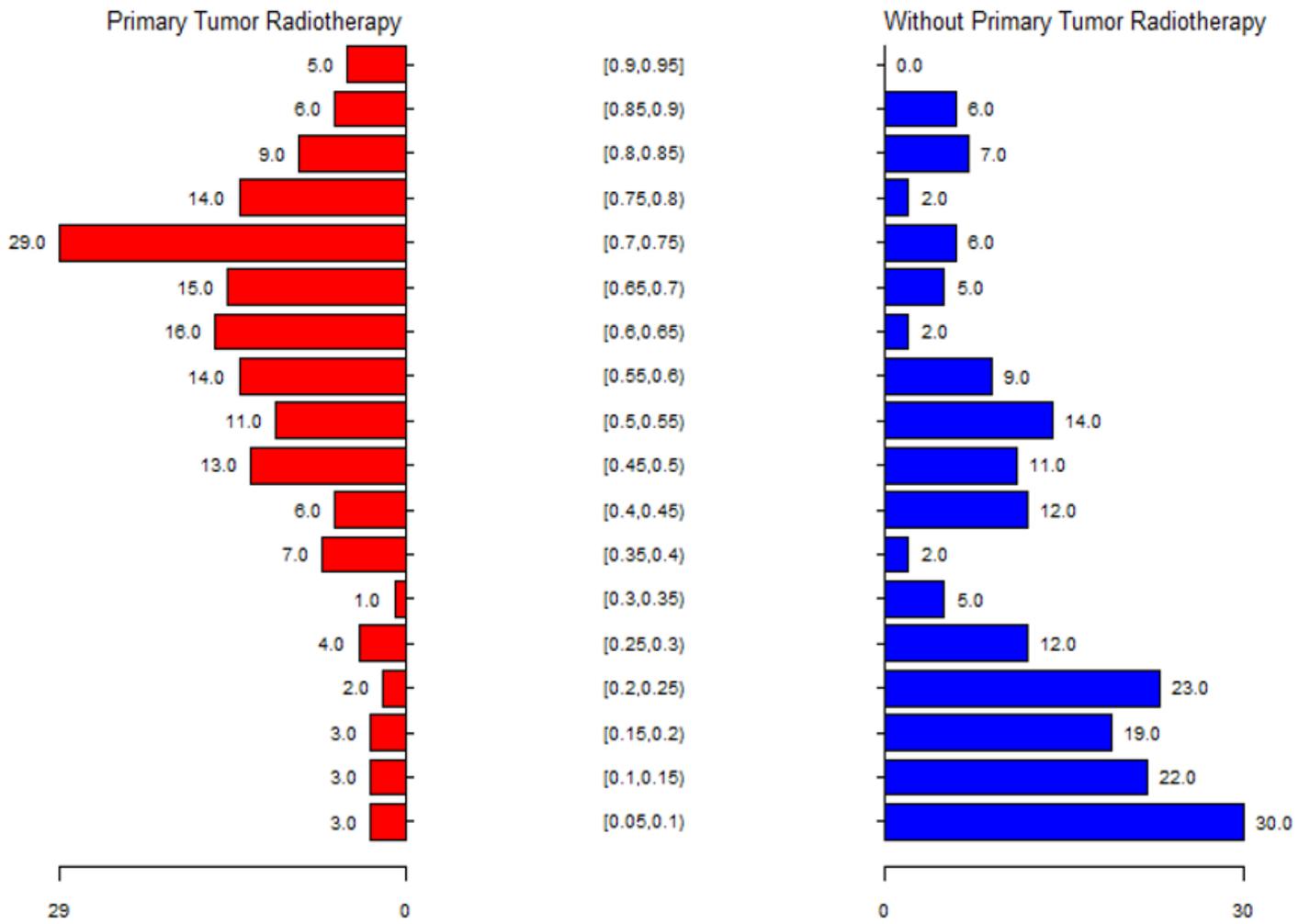
Flow diagram of the PSM process.



**Figure 2**

The Kaplan-Meier curves for primary tumor radiotherapy and without primary tumor radiotherapy.

### Propensity score based on linear model



**Figure 3**

Propensity score based on linear model.